NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report & appendix** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **Patient Expert Statement** – statement submitted by patient expert on this technology
8. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
9. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Document cover sheet

Assessment report: GID-MT568 Magtrace and Sentimag

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EAC sign-off: Andrew Sims

Version number	Brief description of changes	Author/reviewer (e.g. J Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
0.01	Creation of report, adding technology and clinical evidence content	R Parker K Keltie	19/01/2022	
0.02	Adding outcomes from literature search, critical appraisal QA	R Parker K Keltie	01/02/2022	
0.03	Adding content for adverse events and QA	K Keltie, R Parker	08/02/2022	
0.04	Adding economic content and QA	R Parker, K Keltie	15/02/2022	
0.05	Critical appraisal of single arm studies, adding clinical evidence content	K Keltie, R Parker	22/02/2022	
0.06	Meta-analysis, review Outlining EAC basecase	AJ Sims K Keltie	22/02/2022 23/02/2022	
0.07	Critical appraisal, adding economic evidence	K Keltie	24/02/2022	

0.08	Draft pre-submission checks	J Davison	28/02/2022	
0.09	Clean version of report, adding literature search strategy, QA of critical appraisal	R Parker, K Keltie, H Abdul-Razakq	01/03/2022	
1.00	Clean version of report for draft submission to NICE, adding feedback from Clinical experts	R Parker, K Keltie	02/03/2022	02/03/2022
1.01	Adding conclusions and QA of economic evidence	R Parker	03/03/2022	
1.02	Adding EAC basecase	K Keltie	03/03/2022	
1.03	Report review	AJ Sims	07/03/2022	
1.04	Addressing comments, adding content to Clinical evidence QA of critical appraisal, adding economic evidence	R Parker K Keltie	09/03/2022	
1.05	Review and sign off	AJ Sims	11/03/2022	
1.06	Addressing comments	K Keltie	14/03/2022	
1.07	Pre-submission checks	R Parker	14/03/2022	
1.08	Final review	K Keltie AJ Sims	14/03/2022	
2.0	Clean version for final submission to NICE	K Keltie	15/03/2022	15/03/2022
2.1	Tracked changes in response to Company Factcheck	R Parker	18/03/2022	
2.2	Tracked changes in response to Company Factcheck review and sign off	AJ Sims	21/03/2022	
3.0	Clean version of report for submission to NICE	R Parker	22/03/2022	22/03/2022

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

External Assessment Centre report

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Date completed: 15/03/2022

Contains confidential information: No

Number of attached appendices: 4

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the Company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None.

Acknowledgements

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AE	Adverse events
ALND	Axillary lymph node dissection
ALNS	Axillary lymph node sampling
ARSAC	Administration of Radioactive Substances Advisory Committee
BCS	Breast conserving surgery
BNMS	British Nuclear Medicine Society
CC	Clinical coding
CESM	Contrast enhanced spectral mammography
CI	Confidence interval
DCIS	Ductal carcinoma in situ
EAC	External Assessment Centre
ECOG	Eastern Cooperative Oncology Group
EORTC-QoL	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires
FDA	Food and Drug Administration
HRG	Healthcare resource group
IFU	Instructions for use
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MTAC	Medical Technology Advisory Committee
MTEP	Medical Technologies Evaluation Programme
NICE	National Institute for Health and Care Excellence
NICE CG	NICE Clinical Guideline
NICE MTG	NICE Medical Technology Guidance
NICE QS	NICE Quality Standard
NIHR	National Institute for Health Research
NIHRIO	National Institute for Health Research's Innovation Observatory
NMPCE	Northern Medical Physics and Clinical Engineering
NN	Number of nodes
NR	Not reported
nRCT	Non-randomised controlled trial
NuTH	Newcastle upon Tyne Hospitals NHS Foundation Trust
OPCS	Office of Population Censuses and Surveys classification of Interventions and Procedures
OSNA	One Step Nucleic Acid Amplification
PRESS	Peer reviewed economic search strategy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs	Patient reported outcome measures
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services

Executive summary

In this assessment report, “Company” refers to Endomag. “EAC” refers to the Newcastle External Assessment Centre, the authors of this assessment report. “Clinical experts” refers to individuals, approved by NICE, who advised the EAC in the preparation of this report.

The Magtrace and Sentimag system (Endomag) is a dual tracer system intended to help locate sentinel lymph nodes (SLNs) during sentinel lymph node biopsy (SLNB) procedures for cancer staging. Magtrace is a dark brown liquid containing superparamagnetic iron oxide (SPIO) with a carboxydextran coating that can be identified with the use of a handheld Sentimag magnetic sensing probe. The dark brown-black colouration of Magtrace also assists visual identification. Currently in the NHS, a dual tracer comprising a radioisotope (Technetium-99m with a half-life of 6 hours) and blue dye is used with a handheld gamma probe to identify SLNs during SLNB. The benefits of the Technology claimed by the Company include improved efficiency in the use of NHS facilities and staff resources due to the lack of reliance on Nuclear Medicine departments and prolonged injection window associated with Magtrace (which can occur up to 30 days prior to the SLNB procedure).

The Company identified 31 papers from their literature search; the EAC considered 10 of these out of scope and identified an additional 15 papers from an independent search. In total, 36 publications (18 non-randomised controlled trials, 16 cohort, 1 paired and 1 validation study), 9 of which were available in abstract form only, were included. A total 4,202 patients were included across the 36 included studies, with sample sizes ranging from 10 to 371 patients. Four papers were from the SentiMAG study based in the UK and the Netherlands. Only one abstract was UK-based. Study comparators were varied with dual tracer (N=4), radioisotope alone (N=11), and a combination of dual tracer and radioisotope alone with outcomes not reported exclusively (N=6). The majority of comparative evidence studies used Magtrace and the radioisotope technique in the same patients (N=18). Fourteen non-comparative studies were included for adverse events and patient reported outcomes.

The EAC identified there is evidence supporting the non-inferiority of Magtrace with Sentimag to the current dual tracer standard of care for detection of SLNs including those that are malignant. There is a lack of robust comparative evidence to

determine the impact of the use of Magtrace on the SLNB procedure time. Meta-analysis performed by the EAC did not identify significant evidence to suggest that the number of nodes excised differs between methods. The EAC identified no published evidence that directly compares skin staining outcomes of Magtrace with blue dye although note that published evidence and opinion from Clinical experts does not identify skin staining as a significant problem for patients. There are no significant safety concerns relating to the technology, although the EAC identified six published studies that reported imaging artefacts associated with the use of SPIO.

The Company developed a cost-minimisation analysis, which estimated that use of Magtrace would lead to a cost-saving of £105 per procedure (Magtrace £240 versus dual technique £345); driven by the inclusion of opportunity costs. The EAC considered that the Company base case analysis was developed from the perspective of a hospital without on-site Nuclear Medicine only, did not consider risk of anaphylaxis in the comparator arm, and did not consider the costs associated with the SLNB procedure. The EAC formulated the Company economic model into a decision tree structure to permit additional sensitivity analysis. The EAC base case found Magtrace to be cost-saving by £78.90; with cost-savings representing 3% of the cost of a SLNB procedure, Magtrace £2,488.83, Dual technique £2,567.73; also driven by the inclusion of opportunity costs. Univariate threshold analysis conducted by the EAC highlighted that the economic case is sensitive to changes in parameters: including the setting of the Magtrace injection, the proportion of hospitals realising one additional SLNB procedure weekly (opportunity costs). EAC modelling confirmed that high SLNB volume centres are likely to experience lower cost-savings (600 procedures annually saving £33 per procedure). Results from limited PSA, in which only three parameters were varied due to lack of available data confirmed Magtrace to be cost-saving at £79.51 [95%CI -£119.92 to -£41.02]. However, removal of opportunity costs results in Magtrace being cost-incurring when compared to dual technique. The EAC considers that opportunity costs associated with additional procedures may not be realised at all NHS hospitals conducting breast surgery, and that Nuclear Medicine facilities will continue to be required to deliver standard of care (dual tracer) to patients contraindicated to Magtrace. Special considerations may be required for patients where future MRI for routine surveillance is likely, due to the potential risk of Magtrace masking imaging.

1 Decision problem

The Company has not proposed any variation to the decision problem specified in the final scope (NICE MT568 Final Scope, 2021), Table 1.

Table 1: Scope of the decision problem

Decision problem	Scope	Proposed variation in Company submission
Population	People with high-grade ductal carcinoma in-situ or invasive breast cancer having a sentinel lymph node biopsy.	No variation.
Intervention	Magtrace and Sentimag.	No variation.
Comparator(s)	Technetium-99m in combination with blue dye.	No variation.
Outcomes	The outcome measures to consider include: • sentinel lymph node detection rate • mean number of sentinel lymph nodes retrieved perprocedure • time taken for SLNB procedure • patient-reported outcome measures • device-related adverse events.	No variation, Company clarified: • Detection rate: the per-patient proportion of SLNB operations in which one or more sentinel lymph nodes successfully identified and resected. • Number of nodes: the per-patient mean number of sentinel nodes identified and resected during SLNB procedure. • Procedure time: per-patient mean time taken to complete the SLNB procedure.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties inthe model parameters.	No variation
Subgroups to be considered	Not applicable.	No variation.

Special considerations, including those related to equality	People with cancer are protected under the Equalities Act 2010. People who may experience anaphylaxis as an adverse reaction to blue dye would currently be given Technetium-99m only or a four-node axillary sample. Magtrace and Sentimag could offer analternative treatment option for this group. Known contraindications include people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or in the chest. This may be recognised as an equality issue as some people may be excluded from treatment with the technology. Magtrace and Sentimag may improve access to healthcare services as it could be used in smaller sites where there is not access to nuclear medicine. Currently, healthcare settings must have systems in place to handle, store and dispose of radioactivesubstances. The broader timing for the injection of Magtrace, between 1 and 30 days before surgery, may improve management of healthcareresources related to the procedure. Outcomes relevant to service delivery, efficiency gains and resource use could also be considered as part of the economic model. Technetium-99m is not always available and is usually preparedand used on the same day as the procedure. Where there is a shortage of Technetium-99m, blue dye is used alone. The dual technique has been shown to improve the rate of identification of SLNs.		No variation.
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No.	No variation.

	Are there any changes that need to be considered inthe scope to eliminate unlawful discrimination and topromote equality?	No.	No variation.
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No.	No variation.
	No specific equality issues have been identified relating to usingthe device.		No variation.
Any other special considerations	When injected directly into the bloodstream, the presence of Magtrace may cause image artefacts to present during Magnetic Resonance Imaging (MRI) of the injection and drainage site.		No variation.
Abbreviations: MRI, magnetic resonance imaging; SNLB, sentinel lymph node biopsy; SLNs, sentinel lymph nodes;			

The EAC has made the following clarifications on other aspects of the scope:

- Intervention: Evidence relating to previous versions of Magtrace (Sienna+, Sienna XP) and Sentimag (Sentimag Generation 1) is relevant to the decision-making within this report. The Magtrace Instructions for Use (IFU) advises on the use of 1.0 ml or 2.0 ml to be administered pre-operatively within 30 days of the procedure or 2.0 ml injected intraoperatively followed by 5 minutes of vigorous massage at the injection-site. Any study or subgroup that included a dosage or administration of Magtrace outside of the technology IFU (for example, 0.5 ml or 1.5 ml; 1.0 ml intraoperatively) were considered out of scope and were excluded from this review. Superparamagnetic iron oxide (SPIO)-enhanced MRI is also considered out of scope if this assessment report.

- Comparator: Technetium-99m (Tc-99m) in combination with blue dye (dual technique) represents standard of care in the NHS (NICE NG101) and is most relevant to the decision problem. However, additional evidence comparing to Tc-99m alone will be summarised as potential subgroup (relevant to patients

with allergy to blue dye). The EAC note that there is no blue dye currently licensed for human use in SLNB in the UK and this is considered off-label use of the technology (MHRA). Patent Blue V, manufactured by Guerbet, is approved for use in Canada to label lymphatic vessels, arterial territories, and lymph nodes prior to biopsy in some cancers (DrugBank). Methylthioninium chloride (formerly called methylene blue) is approved for the management of drug-induced methaemoglobinaemia in adults; other uses are not covered by the product license (MHRA). Five manufacturers have Isosulfan Blue products that are currently approved for use by the FDA. Studies comparing Magtrace to blue dye alone are considered out of scope for this assessment due to evidence that the use of blue dye alone as a mapping agent can result in high false negative rates (Li *et al.* 2018, EAC Correspondence Log, 2022) and is inferior to the dual technique (He *et al*. 2016; Hung *et al*. 2005). The Clinical experts also report that very few patients decline the use of radioisotopes (EAC Correspondence Log, 2022).

2 Overview of the technology

The system, manufactured by Endomag, comprises tracer (Magtrace) and a handheld magnetic sensing probe (Sentimag). Both are class IIa medical devices intended to help locate sentinel lymph nodes (SLNs) during sentinel lymph node biopsy (SLNB) procedures for cancer staging. The system has valid CE certification provided by a Notified Body until 26 May 2024.

Magtrace is a dark brown liquid containing superparamagnetic iron oxide (SPIO) with a carboxydextran coating. Magtrace is injected into subareolar or peritumoural interstitial tissues. The superparamagnetic particles are then absorbed into lymphatic vessels and become trapped in SLNs. Magtrace serves as both a magnetic marker and a visual dye due to the dark colour of the particles.

During surgery, the Sentimag probe detects the tracer trapped in the lymph nodes and guides the surgeon to remove them for biopsy. Sentimag uses sounds of different pitches and a visual reading to indicate how close the surgeon is to the tracer. The nodes often appear dark brown or black in colour, which also helps identification.

Magtrace can be injected in the operating theatre 20 minutes before an SLNB or up to 30 days before surgery (Magtrace IFU, EAC Correspondence Log, 2022). Recommended dosage, up to the maximum of 2 ml, depends on the timing of administration. From the IFU, if using intraoperatively or on the day of surgery the maximum 2 ml dose should be administered via subcutaneous injection into either subareolar or peritumoural interstitial tissue followed with a five minute vigorous massage of the injection-site. For subareolar injection, surgeons should wait at least 20 minutes from injection before attempting transcutaneous measurement of the axilla while peritumoural injection may require a longer wait. If administering pre-operatively, the day before surgery or earlier, a 1 or 2 ml dose of Magtrace can be injected into subareolar or peritumoural interstitial tissue without need for massage (Magtrace IFU). Each Magtrace vial contains 2 ml of Magtrace fluid. Intermediate dosages (for example, 0.5 or 1.5 ml) are recognised in research only (EAC

Correspondence Log, 2022). Magtrace may leave a brown bruise-like colouration around the area of injection in some people, which may fade (partially or completely) over time.

Previous versions of both the probe and tracer were available; the former Sentimag (Generation 1) was launched in 2011 prior to the release of Sentimag (Generation 2) in September 2012. Alterations in the latest version include a longer probe cable, increased probe sensitivity, probe holder and smaller probe diameter (Company Clinical Submission). Magtrace had two previous versions, Sienna+ and Sienna XP, released in 2011 and 2013 respectively. The earliest version of Magtrace was diluted at time of surgery whereas the later versions were pre-formulated (FDA Summary of Safety and Effectiveness Data 2018; Sienna+ IFU). The Company state that there is no difference in the iron nanoparticles in any of the iterations of Magtrace (EAC Correspondence Log, 2022). The Company did not provide any direct evidence for diagnostic accuracy equivalence between models additional to that reported in the literature.

Following the administration of Magtrace, MRI studies of the injection and drainage sites can be altered and this effect may be long-term (Magtrace IFU; EAC Correspondence Log, 2022). The Company report that there are no associated problems or specific considerations for patients receiving Magtrace using body scanners typically found at airports (EAC Correspondence Log, 2022).

The Company reports that as Magtrace is regulated as a medical device, it was not required to undergo pharmacological studies. Magtrace was tested for safety and biocompatibility (against EN ISO 10993-1 biological evaluation of medical devices) and the Company claims that there are no associated cytoxicity, sensitisation, irritation or intracutaneous reactivity, systemic toxicity, subacute or subchronic toxicity or genotoxicity associated with Magtrace (EAC Correspondence Log, 2022).

3 Clinical context

SLNBs help to stage cancer that has spread to the lymph nodes. An SLN is defined as the first lymph node to which cancer cells are most likely to spread from a primary cancer. Sometimes there can be more than one SLN. SLNB is a surgical procedure to remove one or more of the nodes. It is used in people who have already been diagnosed with cancer.

NICE has published guidance on the use of SLNB for the management of breast, skin and early oral cavity cancer. Specifically, SLNB is recommended by NICE for the following groups:

- people with invasive breast cancer who had no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy
- people with stage 1B to 2C melanoma with a Breslow thickness of more than 1 mm (considered out of scope for this assessment report)
- people with early oral cavity cancer (T1 to T2, N0), unless cervical access is needed at the same time (considered out of scope for this assessment report)

In current practice, a dual technique using both a radioactive isotope (Tc-99m) and blue dye are commonly used to mark SLNs during SLNB. This aligns to the NICE guideline on early and locally advanced breast cancer, which recommends that the dual technique with radioisotope and blue dye should be used when performing SLNB.

The following publications have been identified as relevant to this care pathway:

- NICE guideline on early and locally advanced breast cancer: diagnosis and management
- NICE guideline on melanoma: assessment and management
- NICE guideline on cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over

The EAC contacted the Administration of Radioactive Substances Advisory Committee (ARSAC) who confirmed (on 14/03/2022) that there are 163 NHS sites with current employer licences under Ionising Radiation (Medical Exposure) Regulations. ARSAC confirmed that this included both Nuclear Medicine and Brachytherapy services and does not include sites who may still be operating in accordance with authorisations under the previous Medicines Administration of Radioactive Substances Regulations (2006). ARSAC were unable to release the names of these NHS sites, therefore the EAC are unable to identify the proportion of NHS hospitals conducting breast surgery who also have on-site access to nuclear medicine (EAC Correspondence Log, 2022). Patients under the care of NHS Trusts without on-site Nuclear Medicine facilities, are required to travel to centres where Tc-99m is administered, or Tc-99m is transported to the site where the SLNB procedure is planned (EAC Correspondence Log, 2022). The Clinical experts note that few patients decline radioisotopes and current NICE guidance (NG101) does not identify any specific contraindications to the use of Tc-99m (EAC Correspondence Log, 2022). Currently, where radioisotopes are not used patients may undergo SLNB with blue dye alone, or axillary lymph node dissection (ALND) (EAC Correspondence Log, 2022). The use of blue dye alone as a mapping agent is considered inferior in terms of detection (He *et al*. 2016; Hung *et al*. 2005) and some patients experience severe anaphylaxis with blue dye. Compared to SLNB, ALND is less cost-effective (Perrier *et al.* 2004; Verry *et al.* 2012) and is associated with higher rates of morbidity (Schrenk *et al*. 1999; Schulze *et al.* 2006; Veronesi *et al.* 2010) and post-surgical side effects (Peintinger *et al.* 2003).

Special considerations, including issues related to equality

According to the Magtrace IFU, the technology is contraindicated in patients with known hypersensitivity to iron oxide or dextran compounds, or have iron overload disease. Iron overload disease, also known as Haemochromatosis (US National Institutes of Health), is an inherited condition where iron levels in the body slowly build up over many years; this build up of iron (known as iron overload) can cause damage to other parts of the body such as the liver, joints, pancreas and heart (NHS, 2022). According to Haemochromatosis UK,

genetic haemochromatosis is found in 1 in 150 people in England and Wales, and in 1 in 113 people in Scotland and Northern Ireland. The British Liver Trust reports that genetic haemochromatosis is underdiagnosed with only 1 in 5,000 people being diagnosed. A review by the UK National Screening Committee in 2021 identified insufficient evidence to support routine national screening for Haemochromatosis in UK adults. The Clinical experts agreed that they do not routinely screen for iron overload disease in patients receiving Magtrace, although have not encountered any issues with the use of Magtrace in clinical practice (EAC Correspondence Log, 2022).

According to the Sentimag IFU, the technology is contraindicated in patients with a metal implant in the axilla or in the chest and the Sentimag probe should not be placed 15 mm in proximity to a working pacemaker.

Breast cancer is rare in men accounting for around 1% of newly diagnosed invasive cases in the UK each year (Cancer Research UK). The Clinical experts did not identify any particular barriers or benefits of Magtrace and Sentimag compared with standard care in male or transgender patients and three experts had experience in using the technology in male patients (EAC Correspondence Log, 2022). One Clinical expert noted that if a patient had previous breast surgery this might lead to a disruption of the lymphatics (EAC Correspondence Log, 2022); this is a consideration independent of the tracer type used.

The prevalence of breast carcinoma during pregnancy is rare occurring in approximately 1 in 3,000 pregnancies (Middleton *et al.* 2003; Cancer Research UK). The Company submission and Magtrace IFU do not identify any studies relating to pregnant women, breastfeeding mothers or paediatric patients. The Clinical experts identified that the use of Magtrace and Sentimag could be used in pregnant women although a four-node axillary sample may be favoured (EAC Correspondence Log, 2022). The use of Tc-99m is labelled as pregnancy category C (FDA Tc-99m Prescribing Information, 2011) as there is not enough adequate well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. The Clinical experts note that radioisotopes

can be used in pregnant women, however patients but would require local risk assessment and senior lead approval (EAC Correspondence Log, 2022). There was consensus from the Clinical experts that breast surgery is generally avoided in breastfeeding mothers and that lactation is stopped prior to any surgery (EAC Correspondence Log, 2022). There was also consensus from the Clinical experts that blue dye should not be used in pregnant patients (EAC Correspondence Log, 2022).

Following the administration of Magtrace, MRI studies of the injection and drainage sites can be altered and this effect may be long-term (Magtrace IFU; EAC Correspondence Log, 2022). The Clinical experts note that Magtrace should not be considered in patients who require routine MRI follow-up after surgery (EAC Correspondence Log, 2022). Patients under the age of 40 years when diagnosed with breast cancer or those with lobular carcinoma where the tumour is mammographically occult are more likely to require routine MRI surveillance (EAC Correspondence Log, 2022).

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The Company search strategy was critiqued using the Peer Review of Electronic Search Strategies (PRESS) tool (McGowan *et al.* 2016), Appendix A1. The strategy submitted was inadequate; both in terms of the sources scrutinised and the search terms utilised. Subject (thesaurus) headings were not included, and proximity operators were not used, although it was appropriate to do so. The Company search risked excluding relevant articles due to its composition and execution.

A literature search was developed by the EAC, using the concepts: breast cancer AND sentinel lymph nodes AND (Magtrace or magnetic tracers). The search strategy was developed in Medline; MeSH thesaurus headings were identified in various ways. Terms relating to breast cancer were identified by the information specialist and cross referenced with terms used in the DG34 (NICE DG34, 2018) search strategy. The review by (Huxley *et al.* 2015)

included broader terms relating to lymph nodes as well as terms specific to sentinel lymph node biopsy, so these were added to this search strategy. The papers included in the Company submission were used to identify useful MeSH headings relating to the Magtrace element – a number of MeSH terms were used for this element.

A previous search strategy on this topic that was conducted by NICE for a Medtech Innovation Briefing (NICE MIB263, 2021) was also used to identify relevant thesaurus and free text terms.

The strategy was then translated into other relevant databases (Appendix A2). The searches were run on 01/02/2022 on Medline (Ovid), Embase (Ovid), CINAHL (EBSCOhost), Cochrane Database of Systematic Reviews (CDSR) and CENTRAL (Cochrane Library via Wiley), Scopus, INA HTA, Clinicaltrials.gov, and NHS Economic Evaluation Database (NHSEED), DARE and HTA databases (CRD). A total of 804 results were initially retrieved, of which, 506 remained after deduplication.

The title and abstract of each were sifted according to the population, intervention, comparator and outcomes (PICO) defined in the final scope (NICE MT568 Final Scope, 2021), by a single reviewer (KK). Full papers were retrieved and reviewed by a single reviewer. Comparative studies comparing against blue dye alone were excluded. Single arm studies were only included if they reported on adverse events or patient reported outcome measures (PROMs). Additional papers were excluded based on study design (reviews, editorials); however their references were reviewed for completeness. Included papers were reviewed by a second reviewer (RP). The study selection process is illustrated as a PRISMA diagram in Appendix A3.

4.2 *Included and excluded studies*

The Company identified 31 papers; 22 studies and 9 conference abstracts they considered were relevant and were in scope of the decision problem. The EAC excluded ten of these (Table 2). Two full papers were excluded as the volume or administrative timing of SPIO was inconsistent with the Magtrace IFU and dosage recommended for clinical practice (EAC

Correspondence Log, 2022). One full single-arm paper did not report adverse events or patient reported outcomes. Seven conference abstracts were excluded; two did not report on adverse events or patient reported outcomes; one did not explicitly report breast cancer as inclusion criteria; and one had a full publication. The remaining three excluded conference abstracts used interventions or comparators deemed out of scope of this review; one compared with blue dye alone and two did not report on the volume of SPIO used.

Six studies were included in NICE MIB263 comprising of one systematic review and meta-analysis (Zada *et al.* 2016), three non-inferiority studies (Alvarado *et al.* 2019; Ghilli *et al.* 2017; Anninga *et al.* 2016) , one non-randomised study (Shams *et al.* 2020) , and one prospective cohort study (Karakatsanis *et al.* 2017). The study by Anninga *et al.* (2016) was conducted exclusively in patients with melanoma and so is considered out of scope for this review. The primary evidence from Zada *et al.* (2016) was retrieved and assessed within this review along with three other papers identified by the EAC that included a review of the literature (Ahmed *et al.* 2014a; Mak *et al.* 2019; Treshome *et al*. 2016) Appendix A4.

A total of 36 papers are included in this assessment report, Appendix A3. The EAC identified an additional 15 papers that were relevant to the scope, comprising 9 additional peer-reviewed publications and 6 additional conference abstracts relevant to the decision problem, of which 7 single-arm studies, reported in 5 full papers and 2 conference abstracts, were included for patient reported outcomes and adverse events. The independent search by the EAC identified 20 of 21 studies identified by the Company; missing only 1 conference abstract in a German journal (Munawwar *et al.* 2021).

Of the 36 included studies, 5 compared Magtrace and Sentimag with Tc-99m and blue dye (dual technique), Table 3a, 11 studies used Tc-99m alone as the comparator, Table 3b, and 6 studies used the dual technique and radioisotope tracer alone but did not report these exclusively, Table 3c. Of the remaining studies, 14 were single-arm and included for patient reported outcomes and adverse events only, Table 3d.

Table 2: Studies included by Company and excluded by the EAC (N=10)

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Ahmed *et al.* 2015 UK MagSNOLL trial [ISRCTN68689512; UKCRN 14979]	Feasibility study, prospective non-randomised controlled trial, patients received both the intervention and comparator, (n=32 patients, 33 procedures due to 1 patients having bilateral breast cancer) Intervention (n=32): Sienna+ (0.5 ml, 24 hours before surgery) intratumoural injection and Sentimag, and placement of non-ferromagnetic coil under ultrasound guidance and skin marking directly overlying the lesion. ☒☑ Comparator (n=32): radioisotope (timing of injection not reported) and Patent Blue V dye and gamma probe ☑	Inclusion criteria: Patients with histologically confirmed invasive breast cancer visible on ultrasound imaging and suitable for SLNB (normal, or indeterminate or abnormal preoperative axillary ultrasonography and benign fine-needle aspiration or core biopsy) recruited between 4 August 2013 and 8 June 2014. Predefined minimum of 10 of the first recruited had to be palpable breast cancer, all patients had to be available for minimum 12 month follow-up. Exclusion criteria: patients with intolerance or hypersensitivity to iron or dextran compounds, who could or did not receive radioisotope for SLNB, suffered from iron overload disease, had pacemaker or other implantable devices in the chest wall were excluded. ☑ Setting: multi-centre (N=2)	Primary: successful localisation of breast cancer within excised specimens. Secondary: excised specimen margin status (inadequate excision of invasive cancer of incidental in situ disease defined by margins of less than 2 mm at study outset, changed to less than 1mm for invasive and less than 2mm for in situ disease from March 2014, and same at second site), volume of excised specimens, calculated resection ratio (defined as total resection volume/optimal resection volume), and sentinel lymph node identification. ☑	Excluded due to 0.5ml of Magtrace; against IFU. Change in definition of inadequate excision part way (7 months) into the study. Addition of non-ferromagnetic coil placed with ultrasound guidance.
Hersi *et al.* 2019 Sweden	Feasibility study, prospective cohort (n=32). Intervention: Magtrace (1 to 2ml injected on dorsal surface of the tumour or divided in four doses	Inclusion criteria: Consecutive patients with non-palpable, screening-detected breast lesion with a core cut biopsy diagnostic for breast cancer with planned breast conserving surgery and	Primary: successful lesion localisation and excision (Magseed) and successful node detection (Magtrace).	Large variation in SPIO injection time (2-50 minutes), concomitant to Magseed lesion localisation procedure, total procedure time reported (tumour excision and SLNB),

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	at the periphery of the lesion in cases with microcalcifications, larger lesions seated in the breast of lesions with diffuse growth pattern; timing of injection 0 to 25 days prior to surgery, median 3 days). Combination of Magseed with Magtrace (n=32), with addition of blue dye (n=8, injected intraoperatively) at surgeon's discretion. Mammography conducted to confirm successful localisation. ☒☑ Comparator: N/A ☒	SLNB. Recruitment period not reported. Exclusion criteria: hypersensitivity to dextran compounds or SPIO, iron overload disease, pregnancy, unable to give informed consent. ☑ Setting: multi-centre (N=2)	Secondary: Magseed migration, median number of nodes retrieved, localisation time, excision time, calculated resection ratio, physician experience. ☒☑	blue dye added in 8 patients but results not reported exclusively. Excluded due to single arm study, PROMs and AEs not reported. Information included as reference to implementation in NHS considerations.
Karakatsanis *et al.* 2019 Sweden SentiNot study [ISRCTN18430240]	Prospective cohort study (n=40) Intervention: SPIO, Endomagnetics (2 ml interstitial injection) on day of initial surgery with Sentimag probe. Patients diagnosed with invasive breast cancer following first surgery underwent second SLNB surgery with addition of Tc-99m and blue dye. ☒☑ Comparator: N/A ☒	Inclusion criteria: Female patients with preoperative diagnosis of DCIS where SLND planned; nuclear grade 3 or nuclear grade 2 and preoperative size large than 20 mm on imaging; mass effect on imaging or clinical examination; any DCIS planned for mastectomy. Recruitment period started on 1 June 2015, end date not reported. Only patients undergoing SLNB with anxillary signal were included in analysis. Exclusion criteria: suspected or verified microinvasion on core biopsy, intolerance or hypersensitivity to iron or dextran	Primary: reduction in SLND procedures required by using intervention at primary breast operation and performing SLND in second session only if invasive breast cancer identified from the first procedure. Secondary: number of procedures avoided; predictive value for invasive breast cancer of factors considered to relate to high-risk DCIS; SLN detection rate on reoperation; costs; adverse events. ☒☑	Patients without signal detection were excluded from study. If invasive breast cancer was identified at subsequent specimen pathology, a secondary SLND was performed in a separate operation. If SLND failed, the protocol stated that axillary lymph node dissection (ALND) or axillary lymph node sampling could be performed based on the surgeon's discretion. May not be easily generalisable to NHS – aim is to reduce the number of secondary SLNB performed.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
		compounds; iron overload disease; and pregnancy or lactation. ☑ Setting: multi-centre (N=5); university hospitals (N=3), regional hospitals (N=2)		Excluded due to the subgroup of patients considered in scope (undergoing SLNB injected with Magtrace) were administered 9-46 days prior to procedure, outside of IFU window.
†Karakatsanis *et al.* 2020 Sweden SentiDose trial [ISRCTN11156955]	Non-inferiority, prospective non-randomised controlled trial (n=330). Intervention: Cohort 1: Magtrace (1.5 ml periareolar injection on day of surgery) with Sentimag alongside radioisotope and blue dye (n=163). ☒ Cohort 2: Magtrace (1.0 ml periareolar or peritumoral injection 1 to 7 days prior to surgery) with Sentimag alongside radioisotope and blue dye (n=159) ☑ Comparator: (Data from Nordic trial, Karakatsanis *et al.* 2016 used) Sienna+ (2 ml) injected on day of surgery with Tc-99m injected on day of surgery or the day before and blue dye (1 to 2 ml) injected on day of surgery	Inclusion criteria: not reported Exclusion criteria: not reported Recruitment period: not reported Setting: multi-centre (N=6) ☑	Primary: proportion of successful SLNB procedures (per-patient detection rate). Secondary: number of nodes, discoloration rates ☑	Results later published in full paper (Hersi *et al.* 2021)

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	with Sentimag and gamma probe (n=206) ☒☑			
†Mullapudi *et al.* 2020 UK SMART trial [NCT02739425]	Prospective paired comparison study, patients received both intervention and comparator (n=109) Intervention: Sienna+ (dosage and injection timing not specified) with Sentimag. ☑ Comparator: Tc-99m ☒☑	Patients undergoing SLNB. Recruitment period not reported. Inclusion/exclusion criteria not reported. ☒☑ Setting: NR	Primary: proportion of SLNs detected by each technique Secondary: total number of sentinel nodes removed, LN retrieval per patient, concordance between techniques, detection rate per patient. ☑	Does not explicitly state use in breast cancer patients (may include melanoma patients). Author affiliations are UK, stated comparator is standard of care, however only reports use of Tc-99m; EAC assumes blue dye was not used (no corresponding author details available to check with authors). Overlap with Sukumar *et al.* (2020) abstract included by EAC.
†Qureshi *et al.* 2021 ǂUK	Cohort, prospective database (n=214) Intervention: Magtrace (volume not reported, 4 subgroups based on timing of injection A: <24h pre-op, B: EAC assumed ≥24h pre-op, C: <7 days pre-op, D: EAC assumed ≥7 days pre-op). Use of Sentimag not reported; no other probe licenced for use with Magtrace reported by Company (EAC Correspondence Log, 2022). ☑	Patients receiving Magtrace for sentinel node biopsy, with subsequent histological or intraoperative analysis. Database established in August 2019. Exclusion criteria: NR ☑ Setting: NR	Intraoperative node detection, mean number of sentinel nodes retrieved, nodal positivity rate (macro and micrometastases), block dissection rate ☑	Excluded due to single arm study with adverse events & PROMs not reported. Abstract states that Magtrace is licensed for use up to 7 days before surgery. EAC confirmed with the Company that Magtrace can be used up to 30 days prior to surgery in line with the Magtrace IFU (EAC Correspondence Log, 2022). Poor reporting of number of

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	Comparator: N/A ☒			patients, and time interval within each subgroup.
†Raus and Faridova, 2020 ǂCzech Republic	Cohort with retrospective comparator Intervention (n=137): Magtrace (2ml, within 24h prior to surgery) with Sentimag ☑ Comparator (n=approximately 600): Sienna+ ☒	Patients with biopsy verified invasive breast cancer or high-grade DCIS. Lumpectomy or mastectomy with SLNB were performed in all patients. Recruitment between April to August 2019. Retrospective comparator group recruited between September 2017 and April 2019. Exclusion criteria: NR ☑ Setting: single-centre	Detection of SLN, mean number of SLNs retrieved per patient ☑	Historical comparator of SPIO intervention- treat as single-arm. Adverse events and patient reported outcomes not reported.
†Rubio *et al.* 2016 Spain	Non-randomised comparator trial Intervention (n=92): SPIO (volume not reported, intraoperatively) and Tc99 (day before surgery) ☒☑ Comparator (n=188): Tc99 alone (day before surgery) ☒☑	Breast cancer patients T1-3, N0-1 before neoadjuvant chemotherapy, all patients had clinically or ultrasound negative axilla before the SLNB procedure. Exclusion criteria: NR ☒☑ Setting: NR	Median number of SLNs, detection rates, false negatives poorly reported (Note: patients who were N0 pre and post-neoadjuvant therapy did not undergo an axillary lymph node dissection (except for initial validation patients), while patients who were N1 pre-neoadjuvant chemotherapy and N0 post-neoadjuvant chemotherapy underwent SLN and anxillary node dissection).☒☑	Intervention out of scope.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Scally *et al.* 2020 ǂUK	Retrospective cohort, patients received the intervention and comparator (n=45) Intervention: Sienna and Magtrace (dosage and timing of administration not reported) ☑ Comparator: Patent blue dye ☒☑	Inclusion and exclusion criteria not reported. Recruitment period not reported. ☒ Setting: NR	Detection of sentinel nodes, mean number of nodes ☑	Does not explicitly state use in breast cancer patients (may include melanoma patients). Comparator (blue dye alone) out of scope.
†Syahkal *et al.* 2019 ǂUK	Service evaluation: retrospective case review (n=347 procedures) Intervention: SLNB with Sentimag probe (tracer type, dosage and timing of administration not reported) with blue dye (n=134) Comparator: Axillary node sampling with blue dye (n=208) or Sentimag (n=1; tracer type, administration timing, and dosage not specified), or no tracer (n=1) ☒☑	All breast cancer patients undergoing axillary staging surgery for one year prior to the introduction of Sentimag (1st April 2016 to 31st March 2017) and one year after the introduction of Sentimag (1st October 2017 to 30th September 2018). Exclusion criteria not reported. ☑ Setting: single centre	Reasons for not using Sentimag (previous surgery, poor renal function); number of lymph nodes excised with each procedure. ☒☑	Comparator and intervention out of scope.

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; †Conference abstract or poster; ǂ assumed from author affiliations (not explicitly stated in paper).

Abbreviations: DCIS, ductal carcinoma in situ; EAC, External Assessment Centre; ECOG, Eastern Cooperative Oncology Group; NR, not reported; PROMs, patient reported outcome measures; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SLND, sentinel lymph node dissection; SPIO, superparamagnetic iron oxide; Tc-99m, Technetium-99m radioisotope;

Table 3a: Studies selected by the EAC as the evidence base with dual technique comparator (N=5)

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Alvarado *et al.* 2019 USA SentiMagIC trial [NCT02336737]	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator, (n=146) Intervention: Sienna XP (2 ml injected intraoperatively, at least 20 minutes prior to SNLB), and Sentimag ☑ Comparator: Tc-99m radioisotope (injected on the day of surgery or the day before) and isosulfan blue dye (injected following Sienna XP injection) ☑	Inclusion criteria: Patients with a diagnosis of primary invasive breast cancer or ductal carcinoma in situ scheduled for surgical intervention with SLNB part of surgical plan. Participants aged 18 years or older, with ECOG grade 0-2, clinically node negative (T0-3, N0, and M0). Patients recruited between January 2015 and December 2015. Exclusion criteria: Pregnancy or lactation; intolerance or hypersensitivity to isosulfan blue dye, iron, dextran compounds or Magtrace; previous axillary surgery, reduction mammoplasty or impaired lymphatic function (surgeon's judgment); previous radiation to the affected breast or axilla; a recent injection of ferumoxytol; iron overload disease; or implantable device in the chest wall, such as a pacemaker. ☑ Setting: multi-centre (N=6)	Primary: lymph node detection rate (number of lymph nodes identified by a specific method as a proportion of the total number of nodes detected), adverse events Secondary: number of nodes excised per patient, nodal concordance ☑	Some study methodology information gained from trial registration. Only histologically confirmed nodes were included in analysis. Follow up carried out between 6 and 22 days post-procedure. Reports outcomes against Tc-99m+blue dye, and Tc-99m separately.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Karakatsanis *et al.* 2017 Sweden The MONOS study [ISRCTN14097881]	Prospective non-randomised controlled trial, n=338 Intervention (n=183): Sienna+ (2 ml injected on the day of surgery, or 1-4 weeks before surgery) with Sentimag probe. Patent blue dye was administered interstitially at the areolar border (10 minutes before skin incision) only if the transcutaneous signal was deemed inadequate by the operator. Comparator (n=155): Tc-99m (day before or morning of surgery) with gamma probe. Patent blue dye (1-2 ml) injected on the day of or day before surgery.☑	Inclusion criteria: Consecutive patients with early breast cancer scheduled for primary surgery with SLNB. Patients with T1-T3 invasive breast cancer or DCIS without clinical suspicion of metastasis on axillary ultrasound imaging. Recruitment period between September 2014 and June 2015. Exclusion criteria: Pregnant or lactating. Intervention arm only: pacemaker or implantable metallic device in chest, allergy or intolerance to dextran compounds, haemochromatosis. Setting: multi-centre (N=2; one centre intervention, one centre comparator) ☑	Primary: node detection rate with intervention alone and in combination with blue dye and with comparator, detection rate per case. Secondary: size and fading of staining (intervention arm only), patient survey on staining (Likert scale), evaluate feasibility of preoperative injection of intervention; number of nodes identified and retrieved with each technique; cost-analysis; malignancy rate; adverse events.☑	Includes subgroup analyses; SPIO with or without blue dye; timing of tracer administration. Contains some cost-analysis. Different patients in intervention and comparator arms. Some study methodology information gained from trial registration.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Karakatsanis *et al.* 2018 Sweden MagPilot study	Prospective feasibility study, n=12, patients received the intervention and comparator Intervention: Sienna+ (2 ml injected during pre-operative outpatient visit 3 to 15 days prior to surgery, median 8 days) with Sentimag probe. ☑ Comparator: Tc-99m and blue dye with gamma probe. ☑	Inclusion criteria: Consecutive patients 18 years and older, diagnosed with invasive breast cancer and DCIS with negative axilla in clinical examination and ultrasound. All patients had to be available for post-operative follow-up. A single adult healthy volunteer was recruited to assess the magnetic signal over 6 weeks. Recruitment period between September 2014 and October 2014. Exclusion criteria: hypersensitivity to dextran compounds, iron, or Sienna+, iron overload disease, pregnancy, pacemaker or other implantable metallic devices in the chest wall, inability to provide written consent. ☑ Setting: single-centre ☑	Feasibility of preoperative SPIO injection, detection rate, concordance, adverse events, median number of nodes retrieved, metastases, ferromagnetic signal curve in healthy volunteer ☑	A single adult healthy volunteer was recruited to assess magnetic tracing for 6 weeks.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Pouw *et al.* 2015 UK & the Netherlands SentiMAG study MRI subprotocol [NTR3283]	Feasibility prospective cohort study, patients received the intervention and comparator (n=11) Intervention: 1.5 T MRI performed with SENSE Breast-7 coil (n=8) or SENSE body coil (n=3) in situ. Sienna+ (2 ml) injected either before (n=9) or after (n=2) radioisotope injection whilst within the scanner. The first two patients did not receive massage to the injection-site [reason not specified]. Pre- and post-contrast imaging performed. Sentimag probe and MRI. ☒☑ Comparator: Tc-99m (two 0.5ml injections administered the day before surgery), gamma camera (2 hours after injection), and SPECT-CT imaging. Patent Blue V dye administered on day of surgery. Gamma probe. ☒☑	Inclusion criteria: Patients with histologically confirmed breast cancer who were clinically and radiologically node negative scheduled to undergo SLNB. Recruitment period between July 2012 and March 2013. Exclusion criteria: Known intolerance to iron or dextran compounds, iron overload disorder and standard MRI exclusion criteria. Patients scheduled for 1-day protocol were excluded for logistical reasons. ☑ Setting: Not explicitly reported.	Primary: Number of SLNs identified by SPIO on MRI compared with those excised during SLNB; SLNs resected per patient; adverse events. ☒☑	Outcomes reported for SPIO with MRI for localisation of SLNs (research use) are out of scope but reported separately. Overlap with Douek 2014 (excluded), is a sub-protocol of the SentiMAG study. In 9 of 11 patients the magnetic tracer was administered first, in 2 of 11 the radioisotope was administered first.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Sreedhar *et al.* 2021 New Zealand	Retrospective non-randomised controlled trial (n=116) Intervention (n=45): Magtrace (2 ml injected the day before surgery) with Sentimag probe, and blue dye ☑ Comparator (n=71): Tc-99m with lymphoscintigram the day before, and blue dye ☑	Inclusion criteria: consecutive patients with breast cancer requiring localisation of impalpable breast lesion or SLNB. Recruitment period between January 2013 and January 2020. Exclusion criteria: patients with previous breast or axillary surgery, patients were eligible for Magtrace only if Magseed was not required. ☑ Setting: single-centre	SLN detection with each technique independent and combined, malignancy, cost-evaluation, adverse events. ☑	First 10 patients of Magtrace also had Tc-99

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; †Conference abstract/poster; ǂ assumed from author affiliations (not explicitly stated in paper).

Abbreviations: ACR BI-RADS, American Collect of Radiology Breast Imaging-Reporting and Data System; DCIS, ductal carcinoma in situ; EAC, External Assessment Centre; ECOG, Eastern Cooperative Oncology Group; NR, not reported; PROMs, patient reported outcome measures; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SLND, sentinel lymph node dissection; SPIO, superparamagnetic iron oxide; Tc-99m, Technetium-99m radioisotope;

Table 3b: Studies selected by the EAC as the evidence base with Tc-99m alone as comparator (N=11)

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Ahmed *et al.* 2014b UK & the Netherlands SentiMAG trial [ISRCTN35827879; NTR3283]	Validation study, participants received both the intervention and comparator (n=347) Intervention: Sienna+ (2 ml periareolar subcutaneous injection intraoperatively) and Sentimag ☑ Comparator: radioisotope (timing of injection administered to local protocols and documented in medical notes) and gamma probe. ☑☒	Inclusion criteria: Patients with breast cancer (including DCIS) scheduled for SLNB, clinically and radiologically node negative (via normal ultrasound, or indeterminate or abnormal ultrasound with benign fine-needle aspiration or core biopsy). Male breast cancer patients and pregnant women were suitable as long as they were scheduled to undergo SLNB with radioisotope. All patients had to be available for 12 month follow-up. Exclusion criteria: Known intolerance or hypersensitivity to iron, dextran compounds, magnetic tracers, SPIOs, blue dye; patients who could or did not received radioisotope, iron overload disease; pacemaker; chest wall implantable device. ☑ Setting: multi-centre (N=7 high-volume practices >300 cases of newly diagnosed breast cancer patients per annum); UK (N=6), the Netherlands (N=1)	SLN detection for intervention and comparator, distribution counts for nodes with each technique, false negative rates. ☑	Inclusion and exclusion criteria not explicitly reported, identified from SentiMAG trial registration. Overlap with Douek *et al.* 2014 although includes more patients. Study does not report on the use of blue dye although Douek *et al.* 2014 includes patients with dual technique but does not report these exclusively. Focus of abstract is validation of 10% rule.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Castillo-Berrio *et al.* 2015 łSpain	Prospective non-inferiority, non-randomised controlled trial, patients received intervention and comparator, (n=22) Intervention: Sienna+ (2 ml injected intraoperatively) with Sentimag probe. ☑ Comparator: Tc-99m injection with lymphoscintigraphy day before surgery. ☑☒	Patients with breast cancer and axilla clinically and radiologically negative. Recruitment period between March and April 2014. Exclusion criteria: NR ☑ Setting: NR	SLN detection with each technique independently and combined, number of malignant nodes. ☑	
Ghilli *et al.* 2017 Italy	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator, n=193 patients (197 SLNs due to four patients with bilateral disease) Intervention: Sienna+ (2 ml not reported, injected immediately before procedure) and Sentimag ☑ Comparator: Tc-99m (day before surgery) ☒☑ Note: One Step Nucleic Acid Amplification (OSNA) used intraoperatively to assess sentinel nodes.☒☑	Inclusion criteria: Female patients who were candidate for SNB after a clinical and imaging negative axillary assessment, with invasive carcinoma (ductal or lobular) or DCIS at the pre-operative biopsy only if there was a high probability of invasive component in the final histology (high grade DCIS, DCIS in the biopsy associated with palpable lumps or suspicious invasive tumour at the ultrasound; finally, extensive DCIS requiring a mastectomy). Recruitment between October 2012 and January 2014. Exclusion criteria: patients with allergy to iron or dextran compounds, iron metabolism disease, pregnancy, pacemaker or other ferrous devices near the breast. ☑ Setting: multi-centre (N=3; 2 with nuclear medicine and 1 without)	Primary: detection of sentinel nodes Secondary: number of nodes per patient, adverse events ☑	

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Giménez-Climent *et al.* 2021 Spain IMAGINE-II trial [Research Registry 7050]	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator (n=89) Intervention: Sienna+ (2 ml on day of surgery) and Sentimag ☑ Comparator: radioisotope tracer only (day before surgery) and gamma probe ☒☑ Note: One Step Nucleic Acid Amplification (OSNA) used intraoperatively to assess sentinel nodes.☒☑	Inclusion criteria: Patients aged 18 years or older, histologically confirmed diagnosis of invasive carcinoma, and clinically and radiologically negative nodes before neoadjuvant therapy Consecutive recruitment between June 2016 and October 2018. Exclusion criteria: Clinically or radiologically positive nodes after neoadjuvant therapy, intolerant or hypersensitive to iron or dextran compounds, administration of a radioisotope for SLNB contraindicated, disorders associated with abnormal iron levels (haemosiderosis, haemochromatosis, iron deficiency anaemia), pacemaker or other partial or totally metallic thoracic implant. ☑ Setting: multi-centre (N=5)	Detection of sentinel nodes by procedure combined and independent. ☑	Recruitment period listed as starting in June 2016 and September 2016, poorly reported.
†Granados *et al.* 2015 łSpain	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator (n=29) Intervention: Sienna+ (2 ml, periareolar injection on day of surgery) and Sentimag ☑ Comparator: radioisotope tracer only (mainly intra- or peritumoural the day before surgery) with lymphoscintigraphy and gamma probe. ☒☑	Patients with breast cancer scheduled for SLNB. Exclusion criteria: NR ☑ Setting: NR	Detection of sentinel nodes by procedure combined and independent, mean operating time. ☑	Abstract states use of 5 ml Sienna+, however EAC assumes author used 2 ml and diluted to 5 ml (including 3 ml of 0.9% sterile saline) in line with IFU.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Munawwar *et al.* 2021 ŧGermany	Retrospective comparative cohort (n=55) Intervention (n=29): Magtrace with Sentimag (1 ml injected periareolar or peritumoral, injection timing not specified) ☑ Comparator (n=26): Tc-99m (subcutaneously) ☒☑	Patients with early breast cancer aged between 24 and 80 years undergoing SLNB with breast conserving surgery (n=42), mastectomy (n=6), nipple-sparing mastectomy (n=7). Recruitment period not reported. Exclusion criteria not reported. ☑	SLN detection and median number of nodes reported for each technique (no statistical comparison), surgeon reported outcomes reported. ☒☑	Only reports use of Tc-99m; EAC assumes blue dye was not used. Reports on surgeon experience.
Pelc *et al.* 2022 ŧPoland	Propensity score matched analysis cohort study, (n=124 after propensity matching) Intervention (n=62 propensity matched): Sienna+ 2 ml injected 18-24 hours pre-operatively (dosage and administration timing specified from Kurylcio *et al.* 2021) with Sentimag probe) ☑ Comparator (n=62 propensity matched): Tc-99m only (periareolar intradermal infection) with gamma probe. Lymphoscintigraphy performed 2-3 hours prior to surgery. ☒☑	Study group comprised of 508 patients who underwent SLNB after neoadjuvant chemotherapy for non-recurrent, non-metastatic ycT1-4, N0, M0 breast cancer between 2013 and 2021 in two high volume centres. 62 patients were included from each group after propensity score matching considering age, post neoadjuvant therapy T and N stage and biological subtype. Exclusion criteria: NR ☑ Setting: multi-centre (N=2)	SLN detection, number of nodes retrieved, nodal malignancy rates ☑	

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Rubio *et al.* 2015 Spain	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator, (n=120) Intervention: Sienna+ (2ml, intraoperatively) with Sentimag ☑ Comparator: Tc99 only (20-24 hours before surgery) ☒☑	Patients diagnosed with breast cancer, clinically node negative axilla, T1-3, N0 who were evaluated for SLN. Axilla evaluated by clinical examination and axillary ultrasound in all patients. Recruitment between July 2013 and March 2014. Exclusion criteria: patients with hypersensitivity or intolerance to iron oxide or dextran compounds, iron overload disease, pacemakers or other implantable devices in the chest wall, pregnant. ☑ Setting: single-centre	Detection of sentinel node, concordance between tracers, time between injection to axillary incision, mean number of SLNs excised per patient, false negatives, adverse events ☑	Surgeon was blinded to results of lymphoscintigraphy until detection of axillary lymph node by hand held magnetometer.
Rubio *et al.* 2020 Spain SUNRISE	Non-inferiority, prospective randomised controlled trial (n=135), consecutive randomisation to 3 groups (1:1:1) based on dose, all patients also received radioisotope tracer. Intervention: Group 1 (n=45): Sienna XP (1ml subareolar, intraoperatively) with Sentimag Group 2 (n=45): Sienna XP (1.5ml subareolar, intraoperatively) with Sentimag Group 3 (n=45): Sienna XP (2ml subareolar, intraoperatively) with Sentimag ☒☑ Comparator: Tc-99m (day before surgery) with gamma probe ☒☑	Patients diagnosed with early-stage breast cancer cT1-3, N0, planned to have conservative breast surgery plus SLNB. Recruitment between October 2016 and August 2018. Exclusion criteria: female patients with intolerance or hypersensitivity to iron, dextran compounds or Sienna+, iron overload disease, pacemaker or implantable device in chest wall, pregnant women. Patients needing mastectomy after breast conservation for positive margins also excluded (and new patient randomised) ☒☑ Setting: single-centre	Detection of SLN, concordance, time between injection to axillary incision, number of SLN excised, adverse events, surgeon assessment of skin discolouration, PROMs (post-op and 6, 12, 24 months) ☑	Does not report use of blue dye. Cohort 1 uses 1 ml of Sienna XP intraoperatively (against IFU and outside scope of review). Cohort 2 uses 1.5 ml Sienna XP, also against IFU and outside scope of review.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Shams *et al.* 2021 Germany	Non-randomised controlled trial (surgeon choice) pilot (n=59) Intervention (n=30): Magtrace (2 ml, injected at preoperative visit, 3 days before surgery (n=5), the day before surgery (n=23), or intraoperatively (n=2)) with Sentimag probe (n=30) ☑ Comparator (n=29): Tc-99m (injected on day of surgery (n=17) or the day before (n=12)) and gamma probe ☑	Inclusion criteria: female patients undergoing breast-conserving surgery or mastectomy and SLNB for invasive breast cancer (cT1-T3, cN0, cM0). Recruitment period between May 2019 and January 2020. Exclusion criteria: Patients under the age of 40 years, BRCA 1 or 2 mutation, breast composition level C or higher according to ACR BI-RADS 5th Ed., high likelihood of a breast MRI required in next 5 years, hypersensitivity to iron oxide or dextran compounds, haemochromatosis, metal implants in the axilla or chest. ☑ Setting: single-centre	Primary: SLN detected, median number of retrieved SLN, care pathway duration; total duration of SLNB procedure; operation time from probe use until sentinel extraction. Secondary: Pain; treatment costs. ☑	Different patients in intervention and comparator arms. Patients excluded if likely to need MRI in next 5 years.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Thill *et al.* 2014a ŧGermany, Poland & Switzerland Central-European SentiMag study	Non-inferiority, prospective non-randomised controlled trial. Patients received the intervention and comparator (n=150) Intervention: Sienna+ (2 ml, intraoperative subareolar injection) with Sentimag probe. ☑ Comparator: Tc-99m (following 1 or 2 day protocol). Blue dye not used in any patients. ☒☑	Inclusion criteria: Patients with histopathologically verified breast cancer, planned for SLNB with clinically and ultrasonographically node-negative invasive breast carcinoma or extended DCIS. Axillary lymph node status was preoperatively examined by palpation and ultrasonography with or without lymph node fine needle aspiration cytology or true cut core biopsy. Recruitment period between November 2012 and June 2013. Exclusion criteria: allergy to iron or dextran compounds, iron overload disease, pacemaker or ferrous metal-containing devices in chest wall, pregnancy and lactation. ☑ Setting: multi-centre (N=NR)	Primary: proportion of successful SLNB. Secondary: proportion of SLN detected, mean number of nodes excised per patient, proportion of pathologically positive results (malignancy rate), concordance between techniques used, adverse events, surgeon experience. ☑	Associated comment (Barranger and Ihrai 2014) and response (Thill *et al.* 2014b) discuss: technology learning curve (3-4 patients), incision enlargement and need for magnometer, detection of the probe, non-magnetic surgical instruments, requirement for regular calibration during use lengthening surgery length.

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope;
†Conference abstract or poster; ŧ assumed from author affiliations (not explicitly stated in paper).

Abbreviations: ACR BI-RADS, American Collect of Radiology Breast Imaging-Reporting and Data System; DCIS, ductal carcinoma in situ; EAC, External Assessment Centre; ECOG, Eastern Cooperative Oncology Group; NR, not reported; PROMs, patient reported outcome measures; SLN, sentinel lymph node SLNB, sentinel lymph node biopsy; SPIO, superparamagnetic iron oxide; Tc-99m, Technetium-99m radioisotope; SLND, sentinel lymph node dissection;

Table 3c: Studies selected by the EAC as the evidence base with dual technique and Tc-99m alone as comparator (N=6)

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Douek *et al.* 2013 UK & the Netherlands SentiMAG trial [ISRCTN35827879; NTR3283]	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator, (n=347) Intervention: Sienna+ (2 ml periareolar subcutaneous injection intraoperatively) and Sentimag ☑ Comparator: radioisotope (timing of injection administered to local protocols and documented in medical notes) with and without Patent Blue V dye (injected following Sienna+ injection where used; blue dye not used in all cases) and gamma probe. ☒☑	Inclusion criteria: Patients with breast cancer (including DCIS) scheduled for SLNB, clinically and radiologically node negative (via normal ultrasound, or indeterminate or abnormal ultrasound with benign fine-needle aspiration or core biopsy). All patients had to be available for 12 month follow-up. Recruitment period specific to this abstract not reported. Exclusion criteria: Known intolerance or hypersensitivity to iron, dextran compounds, magnetic tracers, Sienna+ or blue dye, patients who cannot or did not receive radioisotope for SLNB, iron overload disease; pacemaker; chest wall implantable device. ☑ Setting: multi-centre (N=7); UK (N=6), the Netherlands (N=1)	Primary: node detection rate with each technique; number of successful procedures for each technique (defined by detection of at least one node); mean number of nodes excised. ☑	Inclusion and exclusion criteria not explicitly reported in abstract (extracted from trial registration). Full data set for Ahmed *et al.*2014 & Douek *et al.* 2014.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Douek *et al.* 2014 UK & the Netherlands SentiMAG trial [ISRCTN35827879; NTR3283]	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator, (n=160) Intervention: Sienna+ (2 ml periareolar subcutaneous injection intraoperatively) and Sentimag ☑ Comparator: radioisotope (timing of injection administered to local protocols and documented in medical notes) and Patent Blue V dye (injected following Sienna+ injection where used; blue dye not used in all cases) and gamma probe. ☑☒	Inclusion criteria: Patients with breast cancer (including DCIS) scheduled for SLNB, clinically and radiologically node negative (via normal ultrasound or indeterminate/abnormal ultrasound with benign fine-needle aspiration or core biopsy). Male breast cancer patients and pregnant women were suitable as long as they were scheduled to undergo SLNB with radioisotope. All patients had to be available for 12 month follow-up. Patients recruited between 29 February 2012 and 3 October 2012. Exclusion criteria: Known intolerance or hypersensitivity to iron, dextran compounds, magnetic tracers, SPIOs, blue dye; patients who could or did not received radioisotope, iron overload disease; pacemaker; chest wall implantable device. ☑ Setting: multi-centre (N=7 high-volume practices >300 cases of newly diagnosed breast cancer patients per annum); UK (N=6), the Netherlands (N=1)	Primary: node detection rate with each technique; number of successful procedures for each technique (defined by detection of at least one node); mean number of nodes excised. Secondary: complication rate and morbidity from SLNB. ☑	Of the 7 centre, 5 used combined radioisotope and blue dye, 1 used radioisotope alone, and 1 used blue dye in some patients. Total of number of patients with blue dye used not reported. Timing and administration of radioisotope may have varied across centres. Subset of Ahmed *et al.* 2014 and Douek *et al.* 2013.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Houpeau *et al.* 2016 France French Sentimag study [NCT01790399]	Feasibility, prospective non-randomised controlled trial, patients received both the intervention and comparator, n=108 Intervention: Sienna+ (2 ml injected intraoperatively into periareolar area) and Sentimag. ☑ Comparator: Tc-99m (injected in the periareolar area on the day of surgery or the day), including lymphoscintigraphy within 2-3 hrs (blinded from surgeon) and gamma probe. Blue dye was injected intraoperatively following Sienna+ in n=45 patients. ☑	Inclusion criteria: Female patients aged 18 years or older, T0-T2 breast cancer proven by histopathology or cytology, clinically or radiologically node-negative and scheduled for SLNB. Participants recruited between February 2013 and December 2013. Exclusion criteria: Patients with T3-T4 breast cancer or with multifocal tumours, intolerance or hypersensitivity to iron-dextran compounds or patent blue dye, iron overload disease, unable to receive radioisotope or patients with pacemaker or other implantable device in chest wall. ☑ Setting: multi-centre (N=4)	Primary: successful node identification rate per patient by intervention and comparator (success defined as detection of at lead one sentinel node). Secondary: concordance of SLN detected by each technique (per patient and per node), adverse events. ☑	Female patients only. One of the four centres do not routinely use patent blue, but only inject it in case of no scintigraphic fixation which is communicated to the surgeon by the nuclear medicine department prior to the surgery. Intraoperative SLN analysis conducted with OSNA or histopathologic analysis.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Karakatsanis *et al.* 2016 Sweden & Norway Nordic SentiMag [no trial ID reference found]	Prospective non-randomised controlled trial, patients received both the intervention and comparator, n=206 patients Intervention: Sienna+ (2 ml injected subareolarly on day of surgery shortly before or after induction of anaesthesia) with Sentimag probe. ☑ Comparator: Tc-99m (injected subareolarly, subdermally or subcutaneously on day of surgery or the day before) and gamma probe, with Patent Blue V dye (1 to 2 ml injected intraoperatively) being used in n=127 patients. ☑	Inclusion criteria: Patients aged 18 years or older with invasive breast cancer or DCIS, clinically and ultrasonographically negative axilla scheduled for SLNB. All patients had to be available for post-operative follow-up (time period undefined). Patients identified from case presentation in the multidisciplinary rounds. Exclusion criteria: Hypersensitivity to dextran compounds, iron or Sienna+, isotope intolerance, iron overload disease, pregnancy, pacemaker or other implantable metallic device close to axilla, unable to give informed consent. ☑ Setting: multi-centre (N=7); Sweden (N=5), Denmark (N=2)	Primary: proportion of successful SNB (detection rate per patient) with either technique. Secondary: proportion of SN detection (nodal detection rate) and malignancy rate per patient and per node by either techniques (combined and independent), concordance, adverse events.☑	Lymphoscintigraphy was not performed routinely. All (frozen section) nodes examined with haematoxylin-eosin staining, and where no metastases found immunohistochemistry was used.
Pinero-Madrona *et al.* 2015 Spain IMAGINE study	Non-inferiority, prospective non-randomised controlled trial, patients received both the intervention and comparator, (n=181) Intervention: Sienna+ (2 ml injected in the subareolar area, on day of surgery) and Sentimag probe. ☑ Comparator: radioisotope tracer and optional addition of methylene blue dye (proportion not reported) with gamma probe. ☒☑	Inclusion criteria: patients aged 18 years and older scheduled for SLNB, preoperatively clinically and radiologically node negative. Patients recruited consecutively between November 2013 and June 2014. Exclusion criteria: received neoadjuvant therapy, intolerant to iron or dextran compounds, contraindicated to receive radioisotope, disorders implying high iron concentration, pacemaker or other metallic device in chest wall. ☑ Setting: multi-centre (N=9).	Primary: ex-vivo detection per patient by both techniques, independent and combined. Secondary: time between intervention injection and start of SLNB procedure; number of nodes assessed and number of positive nodes per patient; adverse events. ☑	Blue dye not used exclusively in this cohort. Ex-vivo analysis by OSNA or histologically.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
†Sukumar *et al.* 2020 ǂUK SMART trial [NCT02739425]	Prospective non-randomised controlled trial, patients received both the intervention and comparator (n=113) Intervention: Sienna+ (dosage and administration timing NR) with Sentimag ☑ Comparator: Tc-99m with or without blue dye (proportion not reported) with gamma probe. ☒☑	Patients over the age of 18 years with primary breast cancer T1-T3, N0, M0. ☑ Exclusion criteria: NR Setting: multi-centre (N=NR)	Detection per patient, node retrieval per patient, concordance, malignancy rates. ☑	

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope;
†Conference abstract/poster; ǂ assumed from author affiliations (not explicitly stated in paper).

Abbreviations: ACR BI-RADS, American Collect of Radiology Breast Imaging-Reporting and Data System; DCIS, ductal carcinoma in situ; EAC, External Assessment Centre; ECOG, Eastern Cooperative Oncology Group; NR, not reported; PROMs, patient reported outcome measures; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SPIO, superparamagnetic iron oxide; Tc-99m, Technetium-99m radioisotope; SLND, sentinel lymph node dissection;

Table 3d: Single-arm studies selected by the EAC as the evidence base for patient reported and adverse events outcomes only (N=14)

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Bazire *et al.* 2019 ǂFrance	Retrospective cohort (n=288) Intervention: Sienna+ (2 ml periareolar injection on the day of surgery) with Sentimag. The first 30 patients also received Tc-99m, outcomes not reported. Patients also received postoperative radiotherapy ☑ Comparator: N/A ☒	Indicated for SLNB based on negative axillary lymph node status (physical examination, ultrasound scan and if necessary node needle aspiration cytology or true cut core biopsy). Consecutive patients with early-stage breast cancer (cT0-T2, N0) without any neoadjuvant treatments, who underwent adjuvant radiotherapy. Recruitment period between October 2013 and December 2016. Exclusion criteria: NR ☑ Setting: single-centre	Tolerance of adjuvant radiotherapy, toxicity measured by radiodermatitis and fibrosis, adverse events. ☑☒	First 30 patients also had radioisotope, then only magnetic procedure was performed. Results not reported separately (therefore detection of sentinel lymph nodes excluded as outcome measure).
Chapman *et al.* 2020 ǂUSA	Retrospective cohort (n=16) Intervention: Sienna+ or Magtrace (2-5ml, injected intraoperatively) ☑ Comparator: N/A ☒	Patients who had previously undergone conservative breast cancer surgery (lumpectomy) with use on an SPIO tracer between 1st January 2015 and 1st May 2020. Each patient had a diagnosis of invasive breast carcinoma or DCIS. MRI reports, images and relevant oncology and surgical history were collected. Exclusion criteria: NR ☑ Setting: single-centre	Impact of SPIO-related artefact on MRI interpretation, adverse events. ☑☒	21 MRIs conducted in 16 patients (median 10.8, range 3 to 18 months).

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Gutesa *et al.* 2016 ŧCroatia	Retrospective cohort (n=128) Intervention: Sienna+ (2ml intraoperative injection under nipple areola) with Sentimag ☑ Comparator: N/A ☒	Patients with early breast cancer (T1-T2) axillary lymph node negative tumours on imaging (either ultrasound or MRI) with primary tumour confirmed by cytology or core biopsy. Patients with invasive breast cancer who underwent SLNB with SPIO and breast conservative surgery (segmentectomy). Exclusion criteria: previous breast surgery or irradiation of breast or axillary region, hypersensitivity to iron products or dextrate, iron overload disease. ☑ Setting: NR	SLN identification, mean nodes excised, malignancy, SLN retrieval rate, adverse events. ☑	Limited AEs/PROMs reported in Discussion section of paper.
†Hannebicque *et al.* 2017 France Subset from French Sentimag study [NCT01790399]	Retrospective cohort (n=47) Intervention: Sienna+ (2 ml injected intraoperatively) with Sentimag. Patients also received Tc-99m ± for SLN detection. Cohort investigated for skin staining outcomes relating to Sienna+ only. ☑☒ Comparator: N/A ☒	Patients who had participated in the Sentimag study who had undergone breast conservative surgery. Retrospective note review between January 2015 and April 2015, 1.5 to 2 years after surgery. Exclusion criteria: patients who had undergone mastectomy. ☑ Setting: single-centre	Skin discolouration due to Sienna+ 1.5 to 2 years post-surgery. ☑☒	Subset of Houpeau *et al.* 2016.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Hersi *et al.* 2021 Sweden SentiDose trial [ISRCTN11156955]	Non-inferiority, prospective non-randomised controlled trial (n=534). Intervention: Cohort 1 (n=163): Magtrace (1.5 ml periareolar injection on day of surgery within 20 minutes of procedure) and Sentimag, with radioisotope, blue dye and gamma probe. Cohort 2 (n=165): Magtrace (1.0 ml subareolar or peritumoural injection into the interstitial tissue without massage 1 to 7 days prior to surgery and Sentimag, with radioisotope, blue dye and gamma probe. ☒☑ Comparator: Data from Nordic Sentimag trial, Karakatsanis *et al.* 2016 used (n=206); Sienna+ (2 ml, injected on day of surgery), Tc-99m (injected on day of surgery or the day before) and blue dye (1 to 2 ml injected on day of surgery) with Sentimag and gamma probe. ☑	Inclusion criteria: breast cancers graded cT0–2, cN0, cM0, ECOG performance status 0 to 2. Consecutive recruitment: cohort 1 between August 2017 and April 2018, and cohort 2 between May 2018 and September 2019. Comparator data from Karakatsanis *et al.* (2016); recruitment period not reported. Exclusion criteria: previous ipsilateral breast or axillary surgery, radiation, neoadjuvant chemotherapy. ☑ Setting: multi-centre (N=6)	Primary: proportion of successful SLNB procedures (per-patient detection rate; successful if respective tracer if at least one SLN was identified and retrieved). Secondary: nodal detection rate with each technique; average number of nodes excised; malignancy rate; concordance of Magtrace and radioisotope, adverse events, skin discolouration up to 6 months post-surgery. ☑	All endpoints were analysed at two different cut-off points with regards to the Sentimag® signal of the SLN, >0 and 20. Overlap with Karakatisanis *et al.* (2016) however reported explicitly. Use of radioisotope not used as comparator, include in adverse events only. **EXCLUDE cohort 1 (1.5ml Magtrace against IFU)**

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Jazrawi *et al.* 2021 Sweden MagUS study	Prospective cohort study (n=79) Intervention: Magtrace (2 ml injected 1 to 14 days prior to MRI protocol). Axillary ultrasound performed in a separate session. Sentimag was used to localise SLNs during SLND. ☑ Comparator: N/A ☒	Inclusion criteria: adult patients with clinically and ultrasound node-negative early breast cancer (cN0) planned for SLND. Diagnostic breast MRI performed prior to SPIO injection where required. Recruitment period between September 2017 and December 2020. Exclusion criteria: patients with hypersensitivity to dextran compounds or SPIO, iron overload disease or planned for neoadjuvant therapy and monitored with breast MRI for tumour response. ☑ Setting: single-centre	Primary: MagUS detection rate (imaging protocol). Secondary: malignancy, sensitivity, specificity, adverse events. ☑	Of 79 included patients, 48 had early breast cancer and underwent upfront surgery, 12 underwent neoadjuvant therapy, and 19 had recurrent breast cancer after previous breast and axillary surgery.
Kurylcio *et al.* 2021 Poland	Feasibility study: cohort, prospective database (n=74) Intervention: Sienna+ (2ml 18-24 hours prior to surgery) with Sentimag. ☑ Comparator: N/A ☒	Patients operated on with early breast cancer between February 2013 and December 2020. Patients received neoadjuvant chemotherapy. HER2-positive patients additionally received HER2-targeted therapy. Exclusion criteria: not reported ☑ Setting: single-centre	Proportion of patients with surgical margin achieved, sentinel node detection, time to lymph node retrieval, number of resected sentinel nodes, adverse events ☑	Operation time for SLNB reported but excluded from outcomes due to lack of comparative data. No comparator, include in adverse events only.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Lorek *et al.* 2019 Poland	Cohort (n=303) Intervention: Sienna+ (2 ml administered 1-2 cm under areola of the mammary gland, administered 1-12 hours prior to surgery) with Sentimag ☑ Comparator: N/A ☒	Patients with primary operative breast cancer who had received SLNB procedure in combination with wide local excision or simple mastectomy, or had autonomous SLNB prior to induction treatment based on the Sentimag method between January 2014 and September 2017. Prior to sentinel lymph node identification all patients had their regional lymph nodes assessed by ultrasound. In cases of doubt, a fine-needle aspiration biopsy of the lymph node was performed under ultrasound control. Only cN0 (no signs of cancer in the lymph nodes) were included. Exclusion criteria: patients not attending follow-up consultations at outpatient clinic. ☑ Setting: single-centre	SLN detection rate, number of dissected SLN per procedure, adverse events including sensory disturbance (paresthesias including hyperesthesia on the skin of the arm), restricted range of motion in the upper limb (more than 20 degrees in comparison with other limb treated as significant), presence of lymphedema (defined as 10% difference between limbs, ranked as minimal <20%, moderate 20-40%, and severe >40%), discolouration of the skin of the breast (diameter in cm, and colour intensity). ☑	Patients followed for average of 25.5 (range 5-42) months.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Man *et al.* 2019 ǂHong Kong	Retrospective cohort (n=328) Intervention: Sienna XP (2ml subareolar injection the night prior to surgery) with Sentimag ☑ Comparator: radioisotope (subareolar region) in first 22 patients. No blue dye used in any patients. ☒☑	All adult female patients with clinical and radiological node-negative breast cancers were invited between August 2016 and December 2017. All recruited patients received triple assessment to establish diagnosis of breast cancers. Exclusion criteria: pregnant or lactating patients, patients with known hypersensitivity to dextran compounds, patients with an iron-overload disease, and patients with pacemaker or other implantable devices on chest wall. ☑ Setting: NR	Detection of sentinel node, number of sentinel nodes, median number of sentinel nodes removed, adverse events ☑	Blue dye not used in this cohort. Gamma probe used only in 2/22 patients, not reported exclusively.
†Paepke *et al.* 2020 ǂGermany	Retrospective cohort (n=50) Intervention: Magtrace (2 ml, injected on the day of surgery peritumoural or periareolar) with Sentimag probe. ☑ Comparator: N/A ☒	Patients undergoing breast conserving surgery, mastectomy or nipple-sparing mastectomy. Recruitment period assumed by EAC between May 2019 and October 2019. Exclusion criteria: not reported ☑ Setting: single-centre.	Node detection rate, operation time and adverse events reported. ☑	Operation time for SLNB reported but excluded from outcomes due to lack of comparative data. Abstract only, no comparator.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Pohlodek *et al.* 2018 Slovakia	Pilot cohort study (n=10) Intervention: Sienna+ (2 ml, injected subareolarly at least 20 minutes before SLNB) with Sentimag probe. Magseed used for tumour localisation with Sentimag probe. ☑ Comparator: N/A ☒	Inclusion criteria: patients with core biopsy-proven early cT1 invasive breast cancer or DCIS, atypical ductal hyperplasia with clinically and ultrasound negative axilla (cN0) undergoing SLNB for which breast conserving surgery was planned. Exclusion criteria: pacemaker or implantable device in chest wall, iron or nickel allergy, Sienna allergy, pregnancy or lactation. ☑ Setting: single-centre.	Mean number of SLN detected per patient, proportion of patients with metastatic nodes, adverse events. ☑	Magseed (with confirmatory mammography) used for tumour localisation. Single arm.
†Szynglarewicz *et al.* 2019 ǂPoland	Prospective cohort study (n=132) Intervention: Sienna+ (2 ml injected pre-operatively timing not reported) with Sentimag ☑ Comparator: N/A ☒	Consecutive patients with invasive breast cancer or high-risk DCIS (extensive lesions, high nuclear grade, comedonecrosis). All underwent breast conserving surgery with SLNB. ☑ Setting: NR	Skin staining at 1, 3, 6 and 12 months post SLNB procedure. ☑	
Vural and Yilmaz 2020 Turkey Turkish SentiMAG	Feasibility, prospective cohort study (n=104) Intervention: Sienna+ (2 ml, 20 minutes before surgery or within four weeks of surgery; injected into the retro-areolar area or in the peritumoral area for non-palpable tumours,) with Sentimag probe. ☑ Comparator: N/A ☒	Inclusion criteria: Adult female patients with clinical T0-T2 early breast cancer proven by histopathology, clinically or radiologically node-negative and scheduled for SLNB. Patients recruited during 2013 to 2017. Exclusion criteria: Patients with T3-T4 breast cancer, hypersensitivity to iron or dextran compounds, pacemakers or metal implants, neoadjuvant therapy. ☑ Setting: single-centre.	Primary: proportion of successful procedures for SLN detection per patient. Secondary: number of nodes retrieved, malignancy rate, adverse events. ☑	Study does not report the proportion of patients injected with Magtrace on the day of surgery, or the distribution of time between injection and surgery.

Author (year) and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Wärnberg *et al.* 2019 Sweden Subgroup from the MONOS study [ISRCTN14097881]	Prospective cohort study (n=337; 258 patients included in qualitative outcome data) Intervention: Sienna (2 ml injected up to 4 weeks pre-operatively, retroareolar injection between April 2014 and October 2016, peritumoral injection between November 2016 and November 2017) with Sentimag probe ☑ Comparator: N/A ☒	Female patients undergoing breast conserving surgery or mastectomy who underwent SPIO procedure between April 2014 and November 2017. Patients undergoing mastectomies analysed for detection rates only (no PROMs). Exclusion criteria: NR ☑ Setting: single-centre.	Skin staining after retroareolar and peritumoural injections and different injection techniques, intensity of staining classified by patient using Likert scale. Secondary: SLN detection, SLN retrieval. ☑	Subgroup analysis by injection type (retro-areolar, peritumoral) which changed over time. SLN detection outcomes not considered by the EAC due to lack of comparative evidence and overlap with Karakatsanis *et al.* 2017 cohort.

Key: ☑ aspect of study in scope; ☒ aspect of study not in scope; ☑☒ aspect of study partially in scope, or elements of this are not in scope; †Conference abstract/poster; ǂ assumed from author affiliations (not explicitly stated in paper).

Abbreviations: ACR BI-RADS, American Collect of Radiology Breast Imaging-Reporting and Data System; DCIS, ductal carcinoma in situ; EAC, External Assessment Centre; ECOG, Eastern Cooperative Oncology Group; NR, not reported; PROMs, patient reported outcome measures; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SLND, sentinel lymph node dissection; SPIO, superparamagnetic iron oxide; Tc-99m, Technetium-99m radioisotope

Table 4: Papers included by Company and EAC

#	Author (year)	Included by Company	Included by EAC
1.	Ahmed *et al.* 2014	No	Yes
2.	†Ahmed et al. 2015	Yes	No
3.	Alvarado *et al.* 2019	Yes	Yes
4.	Bazire *et al.* 2019	No	*Yes
5.	†Castillo-Berrio *et al.* 2015	No	Yes
6.	Chapman *et al.* 2020	No	*Yes
7.	†Douek *et al.* 2013	No	Yes
8.	Douek *et al.* 2014	Yes	Yes
9.	Ghilli *et al.* 2017	Yes	Yes
10.	Giménez-Climent *et al.* 2021	Yes	Yes
11.	†Granados *et al.* 2015	No	Yes
12.	Gutesa *et al.* 2016	No	*Yes
13.	†Hannebicque *et al.* 2017	No	*Yes
14.	Hersi *et al.* 2019	Yes	No
15.	Hersi *et al.* 2021	Yes	*Yes (excl. cohort 1)
16.	Houpeau *et al.* 2016	Yes	Yes
17.	Karakatsanis *et al.* 2016	Yes	Yes
18.	Karakatsanis *et al.* 2017	Yes	Yes
19.	Karakarsanis *et al.* 2018	No	Yes
20.	Karakatsanis *et al.* 2019	Yes	No
21.	†Karakatsanis *et al.* 2020	Yes	No
22.	Jazrawi *et al.* 2021	No	*Yes
23.	Kurylcio *et al.* 2021	Yes	*Yes
24.	Lorek *et al.* 2019	Yes	*Yes
25.	Man *et al.* 2019	Yes	*Yes
26.	†Mullapudi *et al.* 2020	Yes	No
27.	†Munawwar *et al.* 2021	Yes	Yes
28.	†Paepke *et al.* 2020	Yes	*Yes
29.	Pelc *et al.* 2022	No	Yes
30.	Pinero-Madrona *et al.* 2015	Yes	Yes
31.	Pohlodek *et al.* 2018	Yes	*Yes
32.	Pouw *et al.* 2015	Yes	Yes
33.	†Qureshi *et al.* 2021	Yes	No
34.	†Raus and Faridova 2020	Yes	No
35.	†Rubio *et al.* 2016	Yes	No
36.	Rubio *et al.* 2015	Yes	Yes
37.	Rubio *et al.* 2020	Yes	Yes (excl. cohorts 1 & 2)
38.	†Scally *et al.* 2020	Yes	No
39.	Shams *et al.* 2021	Yes	Yes
40.	Sreedhar *et al.* 2021	No	Yes
41.	†Sukumar *et al.* 2020	No	Yes
42.	†Syahkal *et al.* 2019	Yes	No
43.	†Szynglarewicz *et al.* 2019	No	*Yes
44.	Thill *et al.* 2014	Yes	Yes
45.	Vural and Yilmaz 2020	Yes	*Yes
46.	Wärnberg *et al.* 2019	No	*Yes

†Conference abstract
*Include as single-arm study reporting on adverse events and patient reported outcome measures only.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC included 36 studies with the following study designs:

- 18 non-randomised controlled trial, (12 non-inferiority; 3 prospective; 1 retrospective; 1 feasibility; 1 pilot)
- 16 cohort (7 retrospective; 6 prospective; 1 feasibility; 1 pilot; 1 propensity-matched)
- 1 prospective, paired comparison
- 1 validation study

The 36 studies including a total 4,202 patients where Magtrace and Sentimag were used. Nine of the studies were reported in conference abstracts only.

Comparators included the dual technique (radioisotope in combination with blue dye) and radioisotope alone. Five studies compared the combination technique with Magtrace and Sentimag exclusively (Alvarado *et al.* 2019; Karakatsanis *et al.* 2017; Karakatsanis *et al.* 2018; Pouw *et al.* 2015; Sreedhar *et al.* 2021) and are considered most relevant to the decision problem in line with the relevant NICE clinical guideline and Clinical experts (EAC Correspondence Log, 2022). 11 studies compared Magtrace and Sentimag with radioisotope alone and 6 studies included both the dual technique and radioisotope only and did not report outcomes exclusively. The remaining 14 non-comparative studies were included in the context of patient reported outcomes and adverse events.

5.2 *Critical appraisal of studies and review of Company's critical appraisal*

The 36 studies included 18 non-randomised controlled trials and 17 cohort studies. 14 non-comparative studies (study size ranging from 10 to 371 patients) were only included in the EAC review due to their reporting on patient outcomes or adverse events; 9 of these 14 reported on SLN detection

rates, however these outcomes have not been tabulated due to the lack of comparative data. No study reported exclusively on male patients; two studies reported patient gender characteristics and seven studies excluded men.

Non-randomised controlled trials where the intervention and comparator arms included different patients were appraised using the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) checklist, Appendix B1. Studies where the intervention and comparator were conducted in the same patients, and detection concordance reported were appraised using the STAndards for the Reporting of Diagnostic accuracy studies (STARD) checklist, Appendix B2. Single-arm studies included for adverse events and patient reported outcomes were appraised using the NIH National Heart, Lung and Blood Institute Cohort tool, Appendix B3. Nine of the included studies were reported in conference abstracts only and therefore were not critically appraised by the EAC.

Only one study was conducted exclusively in a UK or NHS setting (Sukumar *et al*. 2020). The SentiMAG study was based in the UK and the Netherlands and four associated papers have been included in this review (Ahmed *et al.* 2014b; Douek *et al.* 2013; Douek *et al.* 2014; Pouw *et al.* 2015). Four studies were set outside of Europe; Alvarado *et al.* (2019) and Chapman *et al.* (2020) in USA; Man *et al*. (2019) in Hong Kong; Sreedhar *et al.* (2021) in New Zealand. The remaining 27 studies were set in European locations comprising:

- six in Spain (Castillo-Berrio *et al*. 2015; Granados *et al.* 2015; Pinero-Madrona *at al.* 2015; Rubio *et al.* 2015; Rubio *et al.* 2020; Gimenez-Climent *et al*. 2021),
- five in Sweden (Karakatsanis *et al.* 2017; Karakatsanis *et al.* 2018; Wärnberg *et al.* 2019; Hersi *et al.* 2021; Jazrawi *et al.* 2021),
- four in Poland (Lorek *et al.* 2019; Kurvlcio *et al.* 2021; Szynglarewicz *et al.* 2019; Pelc *et al.* 2022),

- three in France (Houpeau *et al.* 2016; Hannebicque *et al.* 2017; Bazire *et al.* 2019),
- three in Germany (Paepke *et al.* 2020; Munawwar *et al.* 2021; Shams *et al.* 2021),
- one in Italy (Ghilli *et al.* 2017),
- one in Slovakia (Pohlodek *et al.* 2018),
- one in Turkey (Vural and Yilmaz 2020),
- one in Sweden and Norway (Karakatsanis *et al.* 2016),
- one in Germany, Poland and Switzerland (Thill *et al.* 2014),
- one in Croatia (Gutesa *et al.* 2016).

Only four studies were conducted exclusively in patients with invasive breast cancer (Shams *et al.* 2021; Houpeau *et al.* 2016; Giménez-Climent *et al.* 2021; Pelc *et al.* 2022). The majority of studies included patients with ductal carcinoma in-situ and invasive breast cancer; none reported outcomes separately by subgroup. Studies included patients with a range of tumour grades, tumour sizes, oestrogen, progesterone, Ki67 receptor and HER2 status, previous surgery status, undergoing conservative breast surgery or mastectomy; none reported outcomes separately by subgroup.

Ten studies included lymphoscintigraphy imaging with the radioisotope comparator (Castillo-Berrio *et al.* 2015; Thill *et al*. 2014; Pouw *et al.* 2015; Rubio *et al*. 2015; Houpeau *et al.* 2016, Karakatsanis *et al.* 2018; Ghilli *et al*. 2017; Shams *et al*. 2021; Pelc *et al.* 2022; Granados *et al.* 2015). The Clinical experts report that the use of lymphoscintigraphy in the UK is varied and many centres do not routinely use this in patients with breast cancer (EAC Correspondence Log, 2022).

The majority of studies reported the administration of Magtrace intraoperatively with only five studies (two comparative) including patients

injected with Magtrace prior to surgery (Karakatsanis *et al.* 2017; Karakatsanis *et al.* 2018; Hersi *et al.* 2021; Jazrawi *et al.* 2021; Warnberg *et al.* 2019). The Clinical experts report that Magtrace is injected in a routine clinical visit within 30 days of surgery and not injected intraoperatively due to an improved visual and magnetic signal during surgery from earlier administration of Magtrace (EAC Correspondence Log, 2022). The Clinical experts note that intraoperative Magtrace injection is performed during the learning curve with the technology to allow the refinement of technique to reduce pain and skin staining outcomes (EAC Correspondence Log, 2022). Karakatsanis *et al.* (2017) excluded three patients from analysis owing to a lack of Magtrace during one week of the study period. No study reported exclusion of patients due to the lack of radioisotope availability.

Studies reporting SLN detection outcomes in patients receiving both Magtrace and the radioisotope comparators were considered of higher quality than an RCT comparing SLN detection comparing different tracer methods in different patients. SLNB procedure timing, when reported in patients receiving Magtrace compared with different patients receiving a radioisotope comparator, was considered of higher quality.

Metastatic status of excised nodes was identified using a range of techniques, including: OSNA, histopathology, frozen section. The Clinical experts report that histopathology assessment is standard of care in the UK (EAC Correspondence Log, 2022).

5.3 *Results from the evidence base*

The EAC cross-tabulated the 36 included studies against the outcomes listed in the final scope (NICE MT568 Final Scope, 2021), Table 5.

Table 5: Cross-tabulation of included studies against outcomes (N=36).

					Patient Group		Outcomes				
Comparator	Trial name	Author (year)	Study design (n=total no. of patients)	Volume of Magtrace used (ml)	Ductal carcinoma in-situ	Invasive breast cancer	Sentinel lymph node detection rate	Mean number of sentinel lymph nodes retrieved per procedure	Time taken for SLNB procedure	Patient-reported outcome measures	Device-related adverse events
Tc-99m and blue dye (dual technique) (N=5)	SentiMagIC	Alvarado *et al.* 2019	Non-inferiority, nRCT (n=146)	2.0	✓	✓	✓	✓			✓
	MONOS	Karakatsanis *et al.* 2017	nRCT (n=338)	2.0	✓	✓	✓	✓			✓
	MagPilot	Karakatsanis *et al.* 2018	nRCT (n=12)	2.0	✓	✓	✓	✓			✓
	SentiMAG (MRI subprotocol)	Pouw *et al.* 2015	pCohort (n=11)	2.0	✓	✓	✓	✓			✓
		Sreedhar *et al.* 2021	nRCT (n=116)	2.0	✓	✓	✓				✓
Tc-99m alone (N=11)	SentiMAG	†Ahmed *et al.* 2015 ↿	nRCT (n=347)	2.0	✓	✓	✓				
		†Castillo-Berrio *et al.* 2015	Non-inferiority, nRCT (n=22)	2.0		✓	✓	✓			
		Ghilli *et al.* 2017	Non-inferiority, nRCT (n=193)	NR	✓	✓	✓	✓			✓
	IMAGINE-II	Giménez-Climent *et al.* 2021	Non-inferiority, nRCT (n=89)	2.0		✓	✓				
		†Granados *et al.* 2015	Non-inferiority, nRCT (n=29)	2.0		✓	✓		✓		
		†Munawwar *et al.* 2021	rCohort (n=55)	1.0	NR	NR	✓				
		Pelc *et al.* 2022	Propensity matched cohort (n=124)	2.0		✓	✓	✓			
		Rubio *et al.* 2015	Non-inferiority, nRCT (n=120)	2.0	✓	✓	✓	✓			✓
	SUNRISE	Rubio *et al.* 2020	Non-inferiority, RCT (n=45ł)	2.0	✓	✓	✓	✓		✓	✓
		Shams *et al.* 2021	nRCT pilot (n=59)	2.0	✓	✓	✓	✓	✓	✓	✓
	Central-European SentiMag	Thill *et al.* 2014	Non-inferiority, nRCT (n=150)	2.0	✓	✓	✓	✓			✓
Mixture of dual technique and Tc-99m alone (N=6)	SentiMAG	†Douek *et al.* 2013	Non-inferiority, nRCT (n=347)	2.0	✓	✓	✓	✓			
		Douek *et al.* 2014↿	Non-inferiority, nRCT (n=160)	2.0	✓	✓	✓	✓			✓
	French Sentimag	Houpeau *et al.* 2016	nRCT (n=108)	2.0		✓	✓				✓
	Nordic SentiMag	Karakatsanis *et al.* 2016	nRCT (n=206)	2.0	✓	✓	✓				✓
	IMAGINE	Pinero-Madrona *et al.* 2015	Non-inferiority, nRCT (n=181)	2.0	✓	✓	✓	✓			✓
	UK SentiMag (SMART)	†Sukumar *et al.* 2020	nRCT (n=113)	NR		✓	✓	✓			
Single-arm studies included for AEs or PROMS only (N=14)		Bazire *et al.* 2019	rCohort (n=288)	2.0	✓	✓					✓
		Chapman *et al.* 2020	rCohort (n=16)	2.0	✓	✓					✓
		Gutesa *et al.* 2016	rCohort (n=128)	2.0		✓	✓	✓			✓
	French Sentimag	†Hannebicque *et al.* 2017*	rCohort (n=47)	2.0		✓					✓
	SentiDose	Hersi *et al.* 2021	Non-inferiority, nRCT(n=371ł)	1.0	✓	✓	✓	✓			✓
		Jazrawi *et al.* 2021	pCohort (n=79)	2.0		✓	✓				✓
		Kurylcio *et al.* 2021	Cohort feasibility (n=74)	2.0	NR	NR	✓	✓	✓		✓
		Lorek *et al.* 2019	rCohort (n=303)	2.0	✓	✓	✓	✓			✓
		Man *et al.* 2019	rCohort (n=328)	2.0	✓	✓	✓	✓			✓
		†Paepke *et al.* 2020	rCohort (n=50)	2.0	NR	NR	✓		✓		✓
		Pohledek *et al.* 2018	Cohort pilot (n=10)	2.0	✓	✓	✓				✓
		†Szynglarewicz *et al.* 2019	pCohort (n=132)	2.0	✓	✓					✓
	Turkish SentiMAG	Vural and Yilmaz 2020	pCohort (n=104)	2.0	✓	✓	✓	✓			✓
	MONOS	Wärnberg *et al.* 2019	pCohort (n=258)	2.0		✓				✓	✓

Abbreviation: NR, not reported; nRCT, non-randomised controlled trial; rCohort, retrospective cohort; pCohort, prospective cohort; AEs, adverse events; PROMs, patient reported outcome measures; Tc-99m, Technetium-99m; SLNB, sentinel lymph node biopsy

†Conference abstract; ŧEAC has removed patients where the dose or administration timing of Magtrace was outwith IFU (0.5ml, 1.5ml); ↿Overlap with Douek *et al.* (2013); *Subset of Houpeau *et al.* (2016)

Sentinel lymph node detection rate

The majority of studies compared SLN detection with the different tracers in the *same* patient (N=18). Four comparative studies compared SLN detection rates with Magtrace and radioisotope-based tracers in *different* patient groups. Studies reporting SLN detection outcomes in patients receiving both the intervention and comparator were considered of higher quality than an RCT comparing SLN detection comparing different methods in different patients. It is noted that there may be bias as to the extent to which the accuracy of each device was affected by the other during the concurrent use of both Sentimag and the standard gamma technique during surgery and lack of blinding. 11 of these 18 studies were designed as non-inferiority trials.

Per patient detection rate

Per patient SLN detection rate comparing Magtrace and Tc-99m with and without blue dye in the same patient was reported in 18 studies with Alvarado *et al.* (2019) reporting detection rates with both dual technique and the radioisotope tracer alone. The detection of SLNs with Magtrace ranged from 89.7% to 100.0% per patient with four studies reporting 100.0% detection rates (Table 6a). The detection of SLNs with Tc-99m with blue dye ranged from to 83.3% to 100.0%, with five papers reporting 100.0% detection rates (Table 6a). Only four studies (three non-randomised controlled trials, one propensity matched cohort) statistically compared detection between techniques; no study reported a significant difference in per patient detection rates between techniques. Per patient concordance between Magtrace and Tc-99m with and without blue dye ranged from 89.7% to 100.0% with seven studies reporting 100.0% concordance.

Per node detection rate

Nodal detection rate comparing Magtrace and Tc-99m with and without blue dye in the same patient was reported in 15 studies (Table 6b). Nodal detection with Magtrace ranged from 77.5% to 100.0% (Castillo-Berrio *et al.* 2015; Pouw *et al.* 2015). Nodal detection with Tc-99m with and without blue dye ranged from 67.2% to 98.0% (Castillo-Berrio *et al.* 2015; Sukumar *et al*.

2020). Three studies reported p values for per node detection rates between Magtrace and standard technique. Two studies reported no statistically significant difference in per node detection rates; Karakatsanis *et al.* (2018) (p=1.0) and Karakatsanis *et al.* (2016) (p=0.34). Houpeau *et al.* (2016) reported a significant difference with Magtrace identifying additional nodes (p=0.0041) (Table 6b). Per node concordance between Magtrace and Tc-99m with and without blue dye ranged from 88.7% to 100.0% (Pinero-Madrona *et al*. 2015; Karakatsanis *et al.* 2018; Pouw *et al*. 2015).

Further comparative evidence detection rates

Two comparative studies reported the detection rate in patients receiving Magtrace compared to a different group of patients receiving Tc-99m with blue dye (Karakatsanis *et al.* 2017; Sreedhar *et al.* 2021). Karakatsanis *et al.* (2017) compared patients receiving Sienna+ (n=183) with patients receiving Tc-99m with blue dye (n=155) reporting per patient detection rate as 93.5% (95% CI 89.5 to 96.1%) and 90.3% (95% CI 86.3 to 93.3%) and per node detection rate as 95.6% and 96.9% respectively, although the total number of nodes retrieved were not reported. Sreedhar *et al*. (2021) reported the detection rate was higher in those receiving Magtrace (n=45) with 91.1% and 71.8% for patients receiving the standard dual technique (n=71). Shams *et al.* (2021) reported detection rate per patient using Magtrace in 30 patients as 90.0% and Tc-99m alone in a different group of 29 patients as 89.6%, per node detection rates were not reported.

Table 6a: Summary of comparative studies (N=18) reporting number of sentinel lymph nodes identified by Magtrace and either dual technique (Tc-99m and blue dye), Tc-99m only or a combination, *per patient*, including concordance where reported.

		Per patient								
Comparator	Author (year)	No. of patients	I+/C- %	I+/C+ %	I-/C+ %	I-/C- %	Detection rate: Intervention, % [95%CI]	Detection rate: Comparator, % [95%CI]	p-value	Concordance, % [95% CI]
Dual Tc-99m and blue dye (exclusively)	Alvarado *et al.* (2019)	146	0.7	98.6	0.0	0.7	99.3 [98.0-100.0]	98.6 [96.7-100.0]	-	100.0
	Karakatsanis *et al.* (2018)	12	16.7†	83.3	0.0	0.0	100.0	83.3	0.5	100.0
	Pouw *et al.* (2015)	11	0.0†	100.0†	0.0†	0.0†	100.0†	100.0†	-	100.0†
Dual Tc-99m and blue dye (not exclusively)	‡Douek *et al.* (2013)	347	-	-	-	-	91.9	96.3	-	90.5†
	Douek *et al.* (2014)*	160	3.1	91.3	3.8	1.9	94.4	95.0	-	93.1†
	Houpeau *et al.*(2016)	108	2.8	94.4	0.9	1.9	97.2 [92.1-99.4]	95.4 [89.5-98.5]	0.6250	99.0 [94.7-100.0]
	Karakatsanis *et al*. (2016)	206	2.4†	95.1†	1.9†	0.5†	97.6 [94.1-99.1]	97.1 [93.5-98.8]	0.76	98.0 [94.6-99.3]
	Pinero-Madrona *et al*. (2015)	181	0.6†	96.7†	1.1†	1.7†	97.2	97.8	-	98.3
	‡Sukumar *et al.* (2020)	113	-	-	-	-	97.2	97.2	-	-
Tc-99m (exclusively)	Douek *et al.* (2014)*	160	-	-	-	-	-	90.6	-	-
	Alvarado *et al.* (2019)	146	3.4	95.9	0.0	0.7	99.3 [98.0-100.0]	95.9	-	100†
	‡Castillo-Berrio *et al.* (2015)	22	4.5	95.4	0.0	0.0	95.4	100.0	-	-
	Ghilli *et al.* (2017)	193	1.0†	96.9†	2.1†	0.0	97.9 [95.9-99.9]	99.0 [97.5-100.0]	-	97.9 [95.9-99.9]
	Gimenez-Climent *et al.* (2021)	89	0.0	97.8†	0.0	2.2†	97.8	97.8	-	100.0
	‡Granados *et al.* (2015)	29	0.0	89.7†	10.3†	0.0	89.7†	100.0†	-	89.7†
	‡Munawwar *et al.* (2021)	55	-	-	-	-	96.6¶	85.2¶	-	-
	Pelc *et al.* (2022)	124	-	-	-	-	100.0	100.0	-	100.0
	Rubio *et al.* (2015)	120	4.2†	94.1†	1.7†	0.0	98.3	95.7	0.35	98.2
	Rubio *et al.* (2020) (*Cohort 3*)	45	-	-	-	-	100.0	100.0	-	100.0
	Thill *et al.* (2014)	150	1.3	96.7	0.7	1.3	98.0 [94.8-99.4]	97.3 [93.9-99.1]	-	99.3 [96.8-99.9]

†Calculated by the EAC; *Detection rates were taken ex vivo, additional nodes analysed; ¶EAC assumption per patient reporting, detection rate given per number of patients.

Abbreviations: NR, not reported; Tc-99m, Technetium-99m radioisotope; I±/C±, intervention and comparator positive or negative comparison

Table 6b: Summary of comparative studies (N=15) reporting number of sentinel lymph nodes identified by Magtrace and either dual technique (Tc-99m and blue dye), Tc-99m only or a combination, *per node*, including concordance where reported.

		Per node								
Comparator	Author (year)	No. of nodes	I+/C- %	I+/C+ %	I-/C+ %	I-/C- %	Detection rate: Intervention, % [95%CI]	Detection rate: Comparator, % [95%CI]	p-value	Concordance, % [95% CI]
Dual Tc-99m and blue dye (exclusively)	Alvarado *et al.* (2019)	369	6.0	88.3	5.1	0.5	94.3 [91.9-96.7]	93.5 [91.0-96.0]	-	94.5 [92.1-96.9]
	Karakatsanis *et al.* (2018)	16	0.0	81.3	0.0	18.8†	81.25	81.25	1.0	100.0
	Pouw *et al.* (2015)	22	13.6†	86.4†	0.0†	0.0†	100.0†	86.4†	-	100.0†
Dual Tc-99m and blue dye (not exclusively)	‡Douek *et al.* (2013)	825	-	-	-	-	NR	76.0	-	-
	Douek *et al.* (2014)*	404	13.6†	66.3†	7.2†	12.9	79.9†	74.0	-	90.2
	Houpeau *et al.*(2016)	214	9.3†	87.9†	2.3†	0.5†	97.2†	90.2†	0.0041	97.4 [94.1-99.2]
	Karakatsanis *et al*. (2016)	403	5.7†	87.6†	3.7†	3.0†	93.3 [90.3-95.5]	91.3 [88.0-93.8]	0.34	95.9 [93.2-97.6]
	Pinero-Madrona *et al*. (2015)	319	7.2†	85.3†	4.1†	3.4†	92.5	89.3	-	88.7
	‡Sukumar *et al.* (2020)	NR	-	-	-	-	98.0	98.0	-	-
Tc-99m (exclusively)	Alvarado *et al.* (2019)	369	7.9	86.4	5.1	0.5	94.3 [91.9-96.7]	91.6 [88.8-94.4]		94.3†
	‡Ahmed *et al.* (2014)	855	-	-	-	-	87.4†	92.9†	-	-
	‡Castillo-Berrio *et al.* (2015)	58	-	-	-	18.9	77.5	67.2	-	-
	Ghilli *et al.* (2017)	380	5.3†	90.5†	4.2†	0.0	95.8 [93.8-97.8]	94.7 [92.5-97.0]	-	95.6 [93.4-97.7]
	Gimenez-Climent *et al.* (2021)	129	6.2†	93.0†	0.8†	0.0	99.2	93.8	-	93.0
	Rubio *et al.* (2015)	287	-	-	-	-	92.0†	80.1†	-	-
	Thill *et al.* (2014)	291	6.9	90.4	1.4	1.4	97.3 [94.9-98.7]	91.8 [88.2-94.5]	-	98.5 [96.5-99.5]

†Calculated by the EAC
*Detection rates were taken ex vivo, additional nodes analysed
¶EAC assumption per patient reporting, detection rate given per number of patients.

Abbreviations: NR, not reported; Tc-99m, Technetium-99m radioisotope; I±/C±, intervention and comparator positive or negative comparison

Detection rates in malignant nodes

The proportion of patients with malignant nodes ranged from 15.1% to 42.6% (Alvarado *et al.* 2019; Houpeau *et al.* 2016). It is anticipated that 20% to 30% of SLNs excised from SLNB will contain metastases depending on patient population and tumour size (British Nuclear Medicine Society, BNMS 2009).

Per patient detection rate

Per patient malignant node detection rate comparing Magtrace and Tc-99m with and without blue dye in the same patient was reported in nine studies (Table 7a). The per patient detection rate for malignant lymph nodes with Magtrace ranged from 91.7% to 100.0% (Pinero-Madrona *et al.* 2015; Gimenez-Climent *et al*. 2021). The per patient detection rate for malignant lymph nodes with Tc-99m with and without blue dye ranged from 88.3% to 98.3% (Pinero-Madrona *et al.* 2015; Ghilli *et al.* 2017). Only one study statistically compared the per patient detection rates between techniques (Houpeau *et al.* 2016) and reported no difference between techniques. Per patient concordance between Magtrace and Tc-99m with and without blue dye ranged from 90.5% to 100.0% with three studies reporting 100.0% concordance.

Per node detection rate

Per malignant node detection rate comparing Magtrace and Tc-99m with and without blue dye in the same patient was reported in nine studies (Table 7b). The per node detection rate for malignant lymph nodes with Magtrace ranged from 90.8% to 100.0% (Pinero-Madrona *et al.* 2015; Gimenez-Climent *et al.* 2021). The detection rate for malignant lymph nodes with Tc-99m with and without blue dye ranged from 88.2% to 96.0% (Pinero-Madrona *et al.* 2015; Alvarado *et al.* 2019). Only one study statistically compared the per node detection rates between techniques (Houpeau *et al.* 2016) and reported no difference between techniques. Per malignant node concordance between Magtrace and Tc-99m with and without blue dye ranged from 91.3% to 100.0% (Rubio *et al.* 2020; Thill *et al.* 2014) with four studies reporting 100% concordance.

The lowest per patient and per node detection rates across the included studies were reported by Pinero-Madrona *et al.* 2015 (91.7% for Magtrace, 88.3% for Tc-99m with and without blue dye); however, authors only reported the *ex-vivo* detection rates for malignant nodes retrieved.

Table 7a: Summary of comparative studies (N=9) reporting number of malignant sentinel lymph nodes identified by Magtrace and either dual technique (Tc-99m and blue dye), Tc-99m only or a combination, *per patient*, including concordance where reported.

		Per patient								
Comparator	Author (year)	No. of patients with positive nodes (n/% of total patients)	I+/C- %	I+/C+ %	I-/C+ %	I-/C- %	Detection rate: Intervention, % [95%CI]	Detection rate: Comparator, % [95%CI]	p-value	Concordance, % [95% CI]
Dual Tc-99m and blue dye (exclusively)	Alvarado *et al.* (2019)	22 (15.1%)	0.0	95.5	0.0	4.5	95.5 [86.8-100.0]	95.5 [86.8-100.0]	-	100.0
Dual Tc-99m and blue dye (not exclusively)	Houpeau *et al.*(2016)	46 (42.6%)	4.3†	93.5†	2.2†	0.0	97.8 [88.4-99.9]	95.7 [85.2-99.5]	1.000	97.7 [88.9-99.9]
	Karakatsanis *et al*. (2016)	54 (26.2%)	0.0	96.3†	1.9†	1.9†	96.3 [86.2-99.4]	98.1 [88.8-99.9]	-	98.1 [88.8-99.9]
	Pinero-Madrona *et al*. (2015)*	60 (33.1%)	5.0†	86.7†	1.7†	6.7†	91.7	88.3	-	98.1†
	‡Sukumar *et al.* (2020)	NR	-	-	-	-	NR	NR	-	100.0
Tc-99m (exclusively)	Ghilli *et al.* (2017)	57 (29.5%)	1.8†	94.7†	3.5†	0.0	96.5 [91.7-100.0]	98.3 [94.8-100.0]	-	96.4†
	Gimenez-Climent *et al.* (2021)	21 (23.6%)	9.5†	90.5†	0.0	0.0	100.0	90.5	-	90.5
	Rubio *et al.* (2015)	36 (30.5%)	5.6†	88.9†	2.8†	2.8†	94.4†	91.7†	-	97.0†
	Thill *et al.* (2014)	34 (22.7%)	5.9	91.2	0.0	2.9	97.1 [87.1-99.7]	91.2 [78.3-97.5]	-	100.0

†Calculated by the EAC
*Detection rates were taken ex vivo, additional nodes analysed
‡Abstract only

Abbreviations: CI, confidence interval; NR, not reported; Tc-99m, Technetium-99m radioisotope; I±/C±, intervention and comparator positive or negative comparison

Table 7b: Summary of comparative studies (N=9) reporting number of malignant sentinel lymph nodes identified by Magtrace and either dual technique (Tc-99m and blue dye), Tc-99m only or a combination, *per node*, including concordance where reported.

		Per node							
Comparator	Author (year)	No. of positive nodes	I+/C-	I+/C+	I-/C+	I-/C-	Detection rate, Intervention % [95% CI]	Detection rate, Comparator % [95% CI]	p-value	Concordance, % [95% CI]
Dual Tc-99m and blue dye (exclusively)	Alvarado *et al.* (2019)	25	0.0	96.0	0.0	4.0	96.0 [88.3-100.0]	96.0 [88.3-100.0]	-	100.0
Dual Tc-99m and blue dye (not exclusively)	Houpeau *et al.*(2016)	61	11.5†	86.9†	1.6†	0.0	98.4†	88.5†	0.0703	98.1 [90.1-100.0]
	Karakatsanis *et al.* (2016)	68	2.9†	88.2†	4.4†	4.4†	91.2 [81.1-96.4]	92.6 [83.0-97.3]	-	95.2 [85.6-98.8]
	Pinero-Madrona *et al.* (2015)*	76	5.3†	85.5†	2.6†	6.7†	90.8	88.2	-	97.0†
	‡Sukumar *et al.* (2020)	NR	-	-	-	-	NR	NR	-	100.0
Tc-99m (exclusively)	Ghilli *et al.* (2017)	77	6.5†	88.3	5.2†	0.0	94.8 [89.9-99.8]	93.5 [88.8-99.0]	-	94.4†
	Gimenez-Climent *et al.* (2021)	23	8.7†	91.3†	0.0	0.0	100.0	91.3	-	91.3
	Rubio *et al.* (2020) (*Cohort 3*)	NR	-	-	-	-	NR	NR	-	100.0
	Thill *et al.* (2014)	45	4.4	91.1	0.0	4.4	95.6 [86.5-99.1]	91.1 [80.2-96.9]	-	100.0

†Calculated by the EAC
*Detection rates were taken ex vivo, additional nodes analysed

Abbreviations: CI, confidence interval; NR, not reported; Tc-99m, Technetium-99m radioisotope; I±/C±, intervention and comparator positive or negative comparison

Mean number of sentinel lymph nodes retrieved per procedure

The mean or median number of sentinel lymph nodes retrieved per SLNB procedure was reported in ten comparative studies. Of these, eight studies reported the number of lymph nodes retrieved that were identified as Magtrace or Tc-99m with and without blue dye in the same patient (Table 8). Studies that did not report the mean or median number of lymph nodes retrieved by intervention type were not tabulated. Pouw *et al.* (2015) reported the removal of all magnetic SLNs, compared to seven studies that did not remove SLNs with less than 10% of the maximum count number. Sukumar *et al.* (2020) (conference abstract) did not report the method used.

Three studies compared the number of SLN retrieved in patients receiving Magtrace to patients receiving Tc-99m with and without blue dye (Karakatsanis *et al.* 2017; Pelc *et al.* 2022; Shams *et al.* 2021).

Shams *et al.* (2021) and Pelc *et al.* (2022) compared and statistically analysed two non-randomised cohorts of patients receiving Magtrace or Tc-99m alone. Pelc *et al.* (2022) identified a higher number of SLNs retrieved in patients receiving Magtrace with 3.0 SLNs compared with 2.0 SLNs in patients receiving the Tc-99m comparator ($p<0.0001$). Shams *et al.* (2021) reported the median number of SLNs retrieved as 1.0 in each arm; however, multiple lymph nodes were excised in 9 of 30 patients receiving Magtrace whereas a single lymph node was removed in all 29 control patients receiving Tc-99m alone. The range of SLNs retrieved in patients receiving Magtrace was one to seven nodes resulting in a statistical difference between SLN retrieval across arms ($p<0.0001$). In this study, the lymph node with the highest tracer signal was removed and additional extraction continued if a tracer signal at least 10% higher than the signal of the initially retrieved lymph node was detected in the axilla. Reasons for this were not explicitly discussed.

Karakatsanis *et al.* (2017) compared the number of SLNs excised in patients receiving Magtrace (n=183) compared to those receiving Tc-99m and blue dye (n=155). A higher number of SLNs were retrieved in patients receiving Magtrace compared to the dual technique with a mean of 1.35 (95% CI 1.24 to 1.46) and 1.26 (95% CI 1.15 to 1.37) SLNs respectively. The authors also

reported on subgroups by intervention administration timing; patients receiving Magtrace on the day of surgery (n=76) had a mean 1.43 (95% CI 1.28 to 1.58) SLNs retrieved compared with 1.03 (95% CI 0.89-1.17) nodes excised when Magtrace was administered 16 days (range 2 to 27 days) prior to surgery (n=107). No other study reported on this outcome by administrative timing and the timing methods used were in line with Magtrace IFU. Statistical analysis was not performed.

The mean number of SLNs in retrieved patients receiving both the Magtrace and Tc-99m with and without blue dye ranged from 1.0 to 2.4 in both arms (Karakatsanis *et al.* 2018; Alvarado *et al.* 2019). Rubio *et al.* (2015) was the only study to statistically compare the number of SLNs retrieved in patients receiving both Magtrace and Tc-99m and reported the use of Magtrace yielded a higher number of SLNs for excision with 2.2 and 1.9 nodes respectively (p=0.001).

Table 8: Summary of comparative studies (N=11) reporting number of sentinel lymph nodes retrieved per procedure, reported as mean (SD), median [IQR], or median {range}.

Comparator	Author (year)	Study design (n)	Intervention, nodes retrieved	Comparator, nodes retrieved	p-value
Tc-99m and blue dye (dual technique) (exclusively) (N=3)	Alvarado *et al.* (2019)	nRCT (n=146)	2.4 (1.19)	2.4 (1.34)	NR
	Karakatsanis *et al.* (2018)	nRCT (n=12)	1 [1-2]	1 [1-3]	NR
	Pouw *et al.* (2015)	pCohort (n=11)	2.00† (NR)	1.73† (NR)	NR
Tc-99m and blue dye and Tc-99m alone (not exclusively) (N=4)	Karakatsanis *et al.* (2018)	nRCT (n=12)	1 [1-2]	1 [1-2]	NR
	¶Douek *et al.* (2013)	nRCT (n=347)	1.83 (NR)	1.80 (NR)	NR
	Douek *et al.* (2014)⊥	nRCT (n=160)	2.02 (NR)	1.86 (NR)	NR
	¶Sukumar *et al.* (2020)	Paired comparison (n=113)	1.75	1.79	NR
Tc-99m alone (exclusively) (N=4)	Pelc *et al.* (2022)	Cohort-propensity matched (n=124)	3 [2-4]	2 [2-2]	<0.0001
	Rubio *et al.* (2015)	nRCT (n=120)	2.20 [NR]	1.90 [NR]	0.001
	Shams *et al.* (2021)	nRCT (n=59)	1 [1-7]	1 [1-1]	<0.0001
	Thill *et al.* (2014)	nRCT (n=150)	1.9 {1-9}	1.8 {1-9}	NR

*Number of patients receiving dual technique (Tc-99m and blue dye) not reported exclusively.
†Calculated by the EAC, only study to report removal of all magnetic SLNs; all other studies did not remove nodes with less than 10% of the maximum SLN count number.
¶Abstract only
⊥Subset from Douek *et al.* (2013)

Abbreviations: NR, not reported; Tc-99m, Technetium-99m radioisotope

Time taken for SLNB procedure

One study reported SLNB procedure duration in patients receiving Magtrace (n=30) compared with a different group of patients receiving Tc-99m alone (n=29) (Shams *et al.* 2021). One study reported SLNB procedure duration in patients receiving both Magtrace and Tc-99m only (Granados *et al.* 2015).

The non-randomised comparative trial by Shams *et al.* (2021) reported that there was no significant difference in the duration of the SLNB procedure between patients receiving Magtrace (n=30) and those receiving Tc-99m alone (n=29) with a median [IQR] duration of 9 [4 to 15] minutes and 10 [IQR 7 to 15] minutes respectively (p=0.412), Table 9.

Shams *et al.* (2021) also considered the mean (SD) time taken in the full pre-operative care pathway identifying a significant difference favouring the intervention arm with 5.4 (1.3) minutes compared with 82 (20.0) minutes with radioisotope only. One of the reasons for the longer pathway in the comparator arm was the need for patients injected with Tc-99m to undergo lymphoscintigraphy as per standard care protocols. The Clinical experts have advised that lymphoscintigraphy following radioisotope injection is not standard practice within the NHS (EAC Correspondence Log, 2022). With lymphoscintigraphy procedure time removed, the pathway length reported by Shams *et al. (*2021) reduced to 54.4 (SD 13.6) minutes, however remained significantly longer than the Magtrace arm. Additional time in the comparator arm was associated with patients requiring attendance in a different clinic for administration of Tc-99m injection and included the time between leaving and returning to the department. Furthermore, as Magtrace was injected within the same clinic, only the injection time was considered. Magtrace (2 ml) was injected the day before surgery in 23 patients, 3 days before surgery in 5 patients and intraoperatively in 2 cases. In the comparator arm, 17 patients received Tc-99m injection on the day of surgery and 12 patients received Tc-99m the day before. The two compared patient groups also had a different procedures (breast conserving surgery, mastectomy and SLNB only); whilst the proportions were not significantly different between groups, this may have influence the range of total procedure times.

The remaining comparative study by Granados *et al.* (2015) reported the mean operating time for Magtrace as longer than that for radioisotope tracer alone with 44 and 38 minutes respectively (no statistical analysis was reported), however this is likely influenced by Magtrace detecting a higher number of sentinel lymph nodes. As all patients in this study received both the intervention and comparator, it is not clear to the EAC how procedural duration was measured for the intervention and comparator separately.

Two non-comparative cohort studies reported SLNB procedure time for patients receiving Magtrace (Paepke *et al.* 2020; Kurylcio *et al*. 2021). The single-arm study by Kurylcio *et al.* (2021), which included 74 patients, reported the median [IQR] duration of lymph node resection as 20 [18.7 to 25.0] minutes, when excising a median [IQR] of 4 [3 to 5] sentinel lymph nodes. The abstract by Paepke *et al.* (2020), which included 50 patients, reported the median SLNB time of 8 minutes (range 3 to 28) minutes, however the number of sentinel lymph nodes excised was not reported.

Table 9: Summary of studies (N=1) reporting procedure duration in minutes, reported as either median [IQR]

Author (year)	Study design (n)	Intervention	Duration, minutes	Comparator	Duration, minutes	p-value
Shams *et al.* (2021)	Pilot, nRCT (n=59)	Magtrace (n=30)	9 [4-15]	Tc-99m only (n=29)	10 [7-15]	0.412
*Time from the first and definite use of the probe until removal of the last marked lymph node Abbreviations: nRCT, non-randomised controlled trial; Tc-99m, Technetium 99m radioisotope						

The Clinical experts identified the preferred administration timing of Magtrace, after overcoming the technology learning curve, as during a routine outpatient clinic visit within 30 days of surgery (EAC Correspondence Log, 2022). However, none of the included studies reporting use of Magtrace before the day of surgery reported procedure duration as an outcome. There is a lack of robust comparative evidence to determine the difference in SLNB procedure time between Magtrace and standard care (dual technique). Additionally, the evidence reported only on the SLNB duration between the first use of the

detection probe (Sentimag or gamma) and the last retrieved SLN and did not consider the intraoperative time taken for the administration of Magtrace, including injection time, 5 minute massage and 20 minute period for lymphatic drainage.

Patient-reported outcome measures

Quality of Life

No study reported quality of life (QoL) measures in patients receiving Magtrace compared with a different cohort of patients receiving radioisotope with and without blue dye. Rubio *et al.* (2020) reported patient outcomes with patients completing the EORTC-QoL and breast specific questionnaires postoperatively at 6, 12 and 24 months. Patients received different dosages of Magtrace (1.0, 1.5 and 2.0 ml) and the Tc-99m radioisotope tracer comparator. In breast-specific outcomes, significantly different future perspectives were seen at one month post-surgery between groups with higher scores in the 1 ml arm (p=0.004) although these were not sustained; no differences were reported at six months post-surgery across all breast outcomes. Significant difference in cognitive function was reported at one month after surgery (p=0.004), however it was unclear whether this was across all three groups or the direction of the effect although this difference was not seen at six months post-surgery.

Pain

Shams *et al.* (2021) compared patient pain scores in patients receiving Magtrace and patients receiving Tc-99m only using the Quality Improvement in Post Operative Pain Management (QUIPS) pain questionnaire. The median pain level in the radioisotope arm was 0 [IQR 0-1] and all patients in the Magtrace arm reported no pain, however a significant difference was identified in the number of respondents across each treatment arm with 28 (96.5%) and 22 (73.3%) patients respectively (p=0.026).

Alvarado *et al.* (2019) reported that 5 of 146 patients (3.4%) experienced pain, however authors did not report how this was measured and study patients received both Magtrace and dual technique.

Karakatsanis *et al.* (2017) injected 2 ml Sienna+ mixed with 3 ml of local anaesthetic rather than sterile saline, however did not report pain outcomes. This was the only study to use this method and reasons for this were not explicitly reported.

The Company and identified clinical evidence report on the incidence of lymphoedema and reduced upper limb mobility following SLNB. The EAC consider these adverse events an associated risk from the procedure rather than associated with the use of a tracer to identify the lymph nodes in line with published and information provided by Cancer Research UK and the US National Cancer Institute. The published evidence highlight a number of factors associated with the risk of developing lymphoedema or reduced shoulder mobility including the number and type of breast surgeries, the number of SLNs removed, BMI, concomitant therapy and medication, and prior injuries to the area (Isik *et al.* 2021; Golshan *et al*. 2003; Norman *et al.* 2010; Breast Cancer Org). No study reported on these outcomes comparing different patients receiving Magtrace with those receiving dual technique (radioisotope and blue dye).

Skin staining

No study compared skin staining between Magtrace and blue dye.

Karakatsanis *et al.* (2017) and Warnberg *et al.* (2019) reported skin staining outcomes using the Likert scale in patients enrolled on the MONOS trial. Warnberg *et al.* (2019) assessed patient reported skin staining outcomes using the Likert scale up to 36 months postoperatively. Patients who underwent breast-conserving surgeries were invited to classify the cosmetic outcome of the staining according to a scale of zero to five, ranging from not a problem to an important problem, based on a pictographic scale given to each participant. Size of skin staining was recorded three weeks post-surgery and reviewed by telephone every three months. Patients were reported by those receiving retroareolar (n=110) and peritumoural (n=148) injections with significant differences in skin staining reported between groups in both size and long-term cosmetic outcomes. Patients who underwent retroareolar

Magtrace injection were more likely to experience skin staining compared with those who underwent peritumoural Magtrace injection with 67.3% and 37.8% incidence reported at 3 weeks respectively (p<0.001). The mean size of the skin staining at 3 weeks between those receiving retroareolar and peritumoural injections was 24.2 cm^2 and 17.9 cm^2 respectively (p=0.02). Skin staining at 36 months was seen in 46.2% of patients following retroareolar injection compared with 9.4% of patients receiving peritumoural injection (p<0.001). Self-reported cosmetic outcomes were better in patients who underwent a peritumoural injection at 12 (p<0.001) and 24 (p=0.02) months post-operatively; although this difference was not sustained at 36 months (p=0.49) or when only comparing patients with residual skin staining at each time point. Authors also note that age and injection-site were statistically significantly related to staining in uni- and multivariate analysis.

Rubio *et al.* (2020) also investigated the size and intensity of skin staining outcomes with Likert scale questionnaires completed by the patient and surgeon. Size was measured from 0, less than 3 cm, and greater than 3 cm. Intensity was evaluated through a scale from 1 (mild) to 7 (very intense). At one month postoperatively 83 of 118 (70.3%) patient respondents reported skin staining; group 3 experienced a higher prevalence (p=0.042) and size (p=0.047) of skin staining out of the three cohorts 3 weeks postoperatively. In group 3, 73.2% of patients did not report the skin staining being a problem postoperatively; 4.9% of patients reported it as an important problem.

Adverse events

Skin staining:

Skin staining was identified as a higher risk in patients undergoing breast conserving surgery compared with those undergoing mastectomy surgery. Karakatsanis *et al.* (2018) and Karakatsanis *et al*. (2016) reported that 97% (p<0.001) and 95.6% (p=0.001) of patients presented with skin staining having undergone breast conserving surgery respectively. Lorek *et al.* (2019) also noted discolouration was predominantly seen in patients after wide local excision compared with those undergoing mastectomy surgery, however did not report the proportions or perform statistical analysis. Six papers did not

report skin staining outcomes in patients receiving mastectomy surgery (Rubio *et al.* 2020; Chapman *et al.* 2020; Hannebicque *et al.* 2017; Hersi *et al.* 2021; Szynglarewicz *et al.* 2019; Warnberg *et al.* 2019). Seven papers included patients who had undergone mastectomy or breast conserving surgery but did not report the incidence of skin staining by surgery type (Rubio *et al.* 2015; Houpeau *et al.* 2016; Bazire *et al.* 2019; Kurylcio *et al.* 2021; Paepke *et al.* 2020; Vural and Yilmaz 2020).

The post-operative follow-up period for studies reporting skin staining outcomes ranged from 22 days to 30 months. Injection-site and methods were varied across studies; patients received retroareolar or peritumoural injections between 30 days prior to surgery and intraoperatively, with results not reported exclusively. Although depth of injection was not reported, some authors noted the use of a deeper injection to reduce skin staining outcomes, which is also in line with opinion from Clinical experts (Kurylcio *et al.* 2021; Paepke *et al.* 2020; EAC Correspondence Log, 2022). No study reported the skin staining outcomes from the use of blue dye.

Skin staining in patients receiving Magtrace and dual technique

One comparative study reported skin staining in patients receiving Magtrace compared with patients receiving Tc-99m with blue dye; Karakatsanis *et al.* (2017) identified skin staining in 73 of 184 patients receiving Magtrace reducing to 66 patients at 15 months post-operatively, however do not identify how staining was attributed to Magtrace rather than the blue dye.

Skin staining in patients receiving Magtrace and Tc-99m only

Three comparative studies reported on skin staining in patients receiving Magtrace and Tc-99m tracers without blue dye (Rubio *et al*. 2015; Rubio *et al.* 2020; Ghilli *et al.* 2017).

Rubio *et al.* (2020) compared the size and intensity of skin staining using patient and surgeon reported measures including questionnaires post-operatively across three groups of patients receiving different Magtrace doses (1.0, 1.5 and 2.0 ml). On univariate analysis magnetic tracer dose, age,

menopause status and mammographic density were statistically significant for skin staining. In multivariate analysis there were no differences between 1 and 1.5 ml doses and only the dose of 2 ml was statistically significant for skin staining. Surgeon reported skin staining was noted in 102 of 135 patients (75.6%) with 38 of 45 (84.4) patients in group 3, 3 weeks postoperatively. At six months postoperatively, no significance decrease in skin staining was seen with 35 of 45 (83.3%) of patients presenting with skin staining. Patient reported outcomes are reported in the previous section.

Ghilli *et al.* (2017) reported brown-coloured skin pigmentation at the injection-site in 71 of 193 patients (47.3%). Skin pigmentation was reassessed at 5.9 month follow up in 150 patients with a complete resolution in 21.1%, reduction in 70.4%, unchanged in 7.1%, and enlargement of the pigmentation area in 1.4%.

Rubio *et al.* (2015) reported 20 patients (19%) who developed a 'grayish breast tattoo' following injection of Magtrace and Tc-99m tracers, which began to fade after 6 months.

Skin staining in patients receiving Magtrace and dual technique or Tc-99m

Three comparative studies reported the incidence of skin staining and breast discolouration following Magtrace and Tc-99m with and without blue dye. It is not clear how authors attributed skin discolouration to Magtrace or blue dye (where used) (Alvarado *et al.* 2019; Karakatsanis *et al.* 2016; Houpeau *et al.* 2016).

Alvarado *et al.* (2019) report discolouration and hyperpigmentation occurrence in 23 of 146 patients (16.3%) although patients were only followed up until 22 days post-surgery. Participants received both Magtrace and dual technique tracers with only one patient having discolouration and hyperpigmentation associated with the use of blue dye.

Karakatsanis *et al*. (2016) reported an incidence of skin discolouration in 35.5% of patients between 0 to 3 months following surgery reducing to 21% of patients at 12 months and 8.6% at 15 months.

Houpeau *et al.* (2016) noted brown dermopigmentation among 22 of 108 patients (20.4%) at post-operative follow-up within 30 days of SLNB procedure only. The authors did not report long-term follow up or whether these patients also received blue dye.

Skin staining in patients receiving Magtrace only

Ten single-arm studies evaluated skin staining as an outcome including Warnberg *et al.* (2019) that has been described earlier due to the use of patient reported outcome measures.

Chapman *et al.* (2020) report a single case of 21 patients who experienced skin discolouration associated with Magtrace. The impact, severity and duration of this was not reported.

Hannebicque *et al.* (2017) evaluated dermopigmentation outcomes after 20.2 (range 14.4 to 25.9) months post-operatively in 47 patients who underwent breast conservative surgery. Of 47 patients, 17 presented with skin discolouration ranging from grade 1 (light yellowing) to grade 3 (dark browning). 14 patients presented with grade 1 to 2 and 3 patients presented with grade 3. Authors note that no patients reported that the persistent staining was a cosmetic or psychological problem; however it is not clear how this was evaluated. Some patients within the study cohort also received blue dye (number not specified) and skin staining relating to blue dye was not reported.

Hersi *et al.* (2021) reported on the incidence and size of skin staining in 141 patients at 6 months following breast conserving surgery. Skin staining was observed in 26 (18.4%) patients with mean size of 11.2 cm^2.

Paepke *et al.* (2020) injected Magtrace peritumoural or periareolar in about 15 mm depth under the skin and reported no incidence of skin staining in all 50 patients as a result of using this technique.

Lorek *et al.* (2019) evaluated the incidence and progression of skin discolouration following administration of Sienna+ in 303 patients.

Disolourations were observed in 47 (15.5%) patients between surgical intervention and at 4 months post-operatively. Discolouration resolved in 36 patients at the end of the 30 month follow-up schedule and a gradual decrease in diameter and intensity of the discolouration was observed during consecutive follow-up examinations in those presenting with skin staining.

Szynglarewicz *et al*. (2019) reported the incidence and duration of skin staining following Sienna+ injection in 132 patients. Dark-brown staining at the injection-site developed in 83% of patients with complete resolution in all patients after 12 post-operative months. The median (range) size of the skin staining was 60 (30 to 90) mm. The depth of SPIO injection at retroareolar tissue site was not reported.

Bazire *et al.* (2019) reported the incidence of skin staining in patients receiving Magtrace and adjuvant radiotherapy (n=288). Only 27.8% of cases (n=80) had skin staining resolution outcomes reported and residual pigmentation disappeared between six and nine months post-surgery. The total number of patients experiencing skin pigmentation was not reported.

Kurylcio *et al.* (2021) reported the use of a deeper subareolar interstitial tissue injection at least 18 to 24 hours prior to SLNB procedure in order to avoid skin staining, however did not report occurrence or skin staining outcomes.

Vural and Yilmaz (2020) reported brown dermopigmentation outcomes however, the figures were poorly reported and equated to more than the number of participants and less than the number of procedures, so it is unclear to the EAC how to interpret the skin staining outcomes reported by this study.

Complication rates

Sreedhar *et al.* (2021) compared the number of Clavien-Dindo Grade III complications in patients receiving Magtrace (n=45) and patients receiving Tc-99m with blue dye (n=71). The complication rate was similar with four cases in the Magtrace group (8.4%) and six patients in the comparator group (8.2%) (p=0.957), however, the nature of the complications identified were not

explicitly reported. Alvarado *et al.* (2019) report the occurrence and type of adverse events, however patients received both Magtrace and standard of care (dual technique) and so complications cannot be attributed per technique.

Douek *et al*. (2014) reported 3 adverse events in 160 patients relating to the use of blue dye only; 2 patients presented with a blue rash without systemic reaction, 1 patient presented with a transient drop in blood pressure during surgery and a rash. No adverse events associated with Magtrace were reported.

Houpeau *et al.* (2016) reported no serious adverse events with patent blue dye or Magtrace. Post-operative complications were recorded at a follow-up visit within 30 days of the SLNB procedure with results not shown or reported in the paper.

Lorek *et al.* (2019) reported complication incidence in patients who underwent SLNB with concomitant mastectomy or wide local incision. Lymphedema, paresthesias, and restricted upper limb range of movement incidence were reported in these patients; however, the authors attributed these outcomes to the full surgical procedures (SLNB with mastectomy compared to SLNB with wide local excision).

An additional ten studies, including a total of 1,325 patients, reported no allergic, irritations, complications, or adverse events relating to the injection of Magtrace (Ghilli *et al.* 2017; Thill *et al.* 2014; Chapman *et al.* 2020; Hersi *et al.* 2021; Jazrawi *et al.* 2021; Kurylcio *et al.* 2021; Man *et al.* 2019; Pohlodek *et al.* 2018; Vural and Yilmaz 2020).

Surgical and technical complications

Ghilli *et al.* (2017) reported that non-ferrous surgical tools (retractor, forceps and grips) were necessary during SNB with Sentimag probe to avoid interference. The Company note that some clinicians use metallic instruments during SLNB with Magtrace, however move them away when using Sentimag to reduce signal interference (EAC Correspondence Log, 2022). The

Company also note that titanium instruments are metallic but non-ferrous so cause less interference with the Sentimag probe and the option of lightweight carbon fibre instruments is being explored in the USA but not currently available in the NHS. The Company and Clinical experts note that polymer instruments can also be used for SLNB procedure with Magtrace and Sentimag and are supplied free of charge by the distributor (EAC Correspondence Log, 2022).

Karakatsanis *et al.* (2017) and Chapman *et al.* (2020) both excluded one patient each from analysis due to technical problems with the probe; one probe malfunction and one reporting 'technical reasons'. Gutesa *et al.* (2016) reported inconsistent probe readings in patients with high BMI, vascular diseases, smokers, diabetics, and elderly patients. No study reported outcomes by comorbitity subgroup and no specific subgroups were identified within the NICE MT568 Final Scope, 2021.

Pinero-Madrona *et al.* (2015) reported technical complications in 11 patients relating to the failure of one or both gamma and Sentimag probe transcutaneous detection attempts or a discrepancy of probe identification results. Six technical complications were related to Sentimag only, two complications related to gamma probe only and three related to both devices.

Chapman *et al.* (2020) report one occasion where SLNs were not removed due to a lack of axillary magnetic signal detection due to technical reasons.

Magtrace and adjuvant radiotherapy toxicity

Bazire *et al.* (2019) considered toxicity of postoperative radiotherapy following Magtrace through the evaluation of radiodermatitis and post-therapeutic fibrosis occurrence. Patients who received Magtrace and adjuvant radiotherapy (n=288) were followed-up for 16 months (range of 1 to 42 months). Grade 0 to 2 radiodermatitis was identified in 95.8% of patients grade 3 was identified in 1% of patients; no patients presented with grade 4 or higher. 19.4% of patients developed grade 1 to 2 post-therapeutic fibrosis; no patients presented with grade 3 or higher. No increase in toxicity was

observed. This study is non-comparative and authors acknowledge that no other study has assessed the tolerance of radiotherapy in this context.

6 Adverse events

The Company identified no adverse events associated with their technology from regulatory databases. The EAC searched the MAUDE (FDA) database on 20/01/2022 using the search terms ‘Magtrace’; ‘Sentimag’; ‘Sienna’; ‘Endomag’ and identified no adverse event reports between 01/01/2011 (from the introduction of the technology) and 31/12/2021. The Medicines and Healthcare Products Regulatory Agency (MHRA) records were also searched with the same four search teams with no alerts, recalls and safety information identified.

The Company acknowledged within their conducted meta-analysis the adverse event of skin staining or discolouration. Studies reporting on this outcome have been summarised in Section 5.

Magtrace is not intended for intravenous injection (Magtrace IFU); occurrences of intravenous administration were not reported within the identified literature and two Clinical experts with experience of using Magtrace did not report any incidents of this (EAC Correspondence Log, 2022).

7 Evidence synthesis and meta-analysis

The Company conducted meta-analyses for a number of outcome measures, Table 10, using the meta package in R (version 3.5.3). Page 41 of Company’s Clinical submission states identification rate, number of nodes and complication rates from the dual technique, however it is unclear to the EAC where these values have been derived from as the literature search strategy for identifying evidence on the comparator was not presented in the Economic Submission, and therefore is subject to uncertainty.

Table 10: Tabulation of results from the Company's meta-analysis

	Magtrace			Dual technique			Relative risk			EAC comment
Outcome	Studies (total patients)	Random effects	I^2	Studies (total patients)	Random effects	I^2	Studies (total patients)	Random effects	I^2	
Staining complication	N=3 (542)	0.33 [0.08 to 0.73]	98%	N=5 (669)	0.49 [0.20 to 0.78]	96%	-	-	-	Comparison of different studies, overlap of confidence intervals.
Identification rate	N=21 (2969)	0.97 [0.96 to 0.98]	51%	-	-	-	-	-	-	Proportion represents weighted average across 21 studies (EAC excluded 1 study and 2 subgroups from clinical evidence base).
Number of nodes	N=17 (2793)	2.04 [1.67 to 2.48]	98%	-	-	-	-	-	-	Meta-analysis represents the number of nodes per patient. Relevance of single arm analysis unclear.
Complication rate	N=5 (577)	0.03 [0.01 to 0.04]	0%	-	-	-	-	-	-	4/5 studies had 0 complication rate. Relevance of single arm analysis unclear.
Nodal retrieval rate	-	-	-	-	-	-	N=9 (2798)	0.04 [0.02 to 0.07]	58%	Comparator varied across studies, only 1 compared Magtrace to dual technique exclusively (Tc-99m and blue dye).
Nodal concordance	-	-	-	-	-	-	N=8 (2228)	0.96 [0.94 to 0.97]	73%	Comparator varied across studies, only 1 compared Magtrace to dual technique exclusively (Tc-99m and blue dye).

* Taking a conservative approach, the use of random effect analysis is most appropriate (Nikolakopoulou *et al.* 2014).
† I2 value is a measure of inter-study heterogeneity. It can be interpreted as follows: 0% to 40%, might not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins *et al.* 2019).

7.1 Staining complication rate (SCR)

The Company defined the Staining Complications Rate (SCR) as the probability that a patient will present with post-operative dermatological staining following the SLNB procedure. Due to the difficulty of separating the effects of staining due to blue dye from staining due to Magtrace, this meta-analysis should include cohorts where either blue dye or Magtrace, but not both, were administered to each patient.

The Company provided a meta-analysis of SCR for three studies that used Magtrace and five that used blue dye. They found considerable heterogeneity in the studies. The EAC repeated the meta-analysis in R (version 4.1.2) (R Core Team, 2022) using the *meta* package (version 5.2-0) (Balduzzi *et al.* 2019) for staining due to Magtrace only, using included studies. Within the *meta* package, the 'metaprop' function was used for pooling one proportion from a number of studies, and the 'metabin' function used for pooling paired proportions from a number of studies. There were no comparative studies, conducted in different groups of patients that reported on staining of Magtrace and blue dye separately. One paper, Karakatsanis *et al.* (2017) reported skin staining outcomes, however all patients received Magtrace and blue dye and it is not clear how skin staining outcomes were attributed to the intervention. Due to this, the EAC included studies that report subgroups of patients that only had Magtrace or Magtrace with radioisotope (that is, did not use blue dye) and that reported staining outcomes. Ten studies met these criteria and the meta-analysis is shown in Figure 1. By Egger's test, there was some evidence of publication bias (p=0.05), Figure 2.

Figure 1: EAC meta-analysis for skin staining (Magtrace arm only)

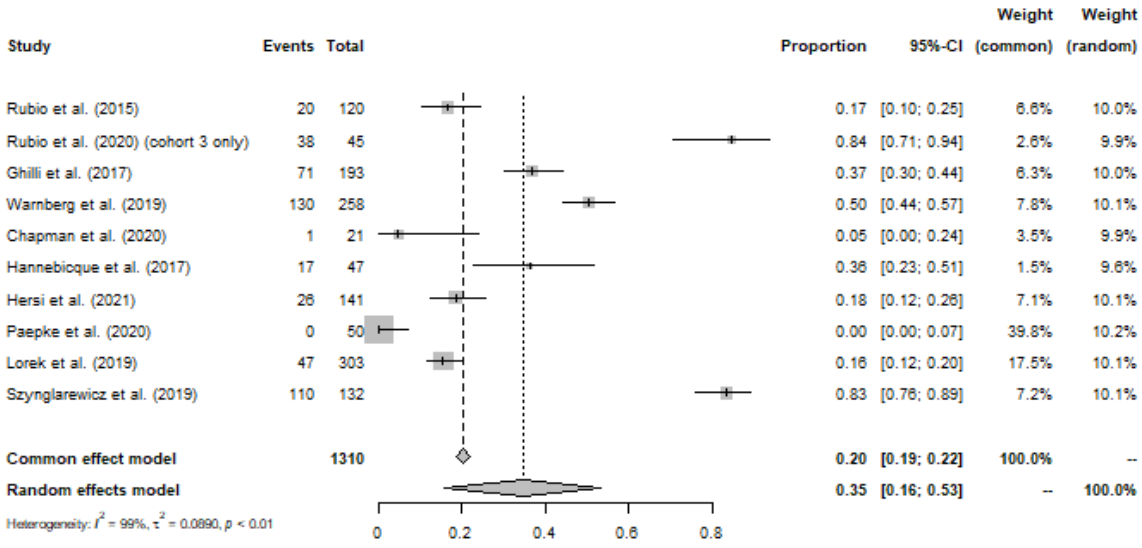
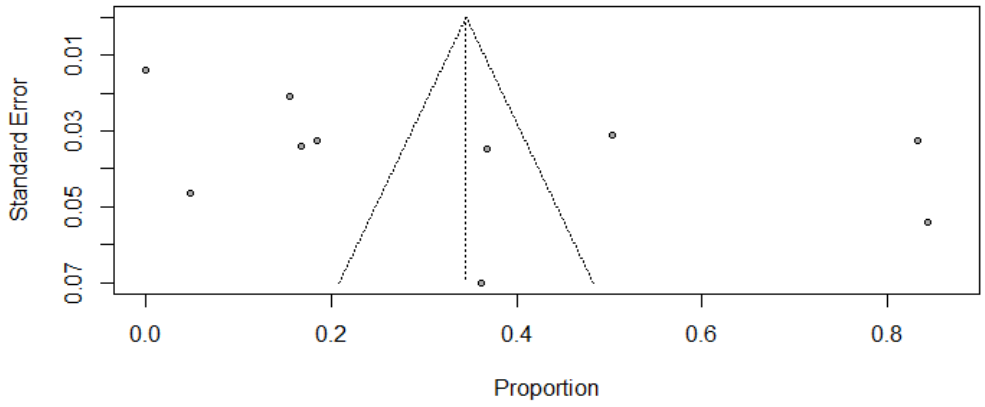


Figure 2: Funnel plot for publication bias



The results agree with the Company in that there is significant heterogeneity in SCR. The EAC cannot replicate an equivalent meta-analysis for SCR due to blue dye, because studies only involving standard care were out of scope of the literature search.

The EAC notes that in the included studies, the type of breast surgery (mastectomy or breast conserving), follow-up time points, injection techniques and injection depths varied across studies and were not always reported. The

number of patients at each follow-up time point were also poorly reported. For its meta-analysis, the EAC has used the first reported time point, although notes that this ranged from 0.75 to 25 months.

The EAC considers that meta-analysis of SCR for Magtrace adds little to the evidence base, due to the heterogeneity of the included studies arising mainly from differences in assessing and classifying the staining, and because there are no eligible comparative studies to provide a pooled comparison of effect.

7.2 Identification rate (IR)

The Company defined Identification Rate (IR) as the per-patient proportion of surgical SLNB operations performed in which one or more sentinel lymph nodes are successfully identified and resected.

The principal difficulty with the application of meta-analysis to IR arises from its definition and, in particular, the absence of a diagnostic reference standard ("gold standard") for identifying sentinel lymph nodes. That is, both Magtrace with Sentimag and standard care (dual technique) are imperfect diagnostic methods, and are known to be discordant in some patients.

IR, as defined here, is subject to incorporation bias. In comparative diagnostic studies (in which each patient receives both Magtrace with Sentimag and standard care), the IR for Magtrace and Sentimag is the number of patients with at least one SLN detected by Magtrace and Sentimag divided by the number with at least one SLN detected by either method. A corresponding definition applies to IR for standard care. This form of incorporation bias, in which an index test is included in a composite outcome, is known to bias the estimate of the sensitivity of the index test.

The absence of a diagnostic reference standard also rules out the possibility of applying meta-analysis to diagnostic test studies (for example with R package *mada*) to compare the pooled diagnostic test performance of Magtrace and Sentimag with a reference standard, and an equivalent approach is similarly ruled out for standard care.

In their meta-analysis of IR (p39), the Company has pooled information from 21 studies. Some included studies were excluded by the EAC and vice-versa. The comparator test varied between studies (that is, some use radioisotope and blue dye, some use radioisotope only and some use a mixture). For these reasons, and due to the fundamental problem of incorporation bias, the EAC considers that a meta-analysis of IR does not contribute meaningful new information to the assessment, at worst may be misleading, and should not be considered further by Committee.

7.3 Number of nodes (NN)

The Company defined Number of Nodes (NN) as the per-patient mean number of sentinel nodes identified and resected during the SLNB surgical procedure using Magtrace and Sentimag. The denominator includes all patients in a study, even those from whom no nodes were retrieved.

The Company included 17 studies in their meta-analysis. Some included studies were excluded by the EAC and vice-versa. Some included studies were comparative studies in which patients received both methods. In these cases, the Company have used information on the number of nodes identified by Magtrace (for example in Alvarado *et al.* (2019), Magtrace with Sentimag identified 348 nodes in 146 SLNB procedures, from a total of 369 nodes identified by both methods).

The Company used the R *meta* package function ‘metarate’ to estimate the node retrieval rate (nodes identified and excised per procedure) for the Magtrace and Sentimag arms of studies, and used the number of procedures as a proxy for person time at risk. Although this leads to a numerical estimate of the mean number per procedure (such as a weighted mean), it may be misleading because *meta* treats the value as an incidence rate, and takes no account of the variation in the number of nodes excised per person.

The EAC considers that making a pooled estimate of nodes identified per procedure is reasonable but it is not comparative, and the EAC is unable to conduct a similar calculation for standard care alone, because studies only involving standard care were out of scope of the literature search. Further, the

meta-analysis is limited by the ability of surgeons to ascertain which, or both, methods identified each excised node.

The EAC replicated the meta-analysis for NN using included comparative studies only to assess, subject to methodological limitations, whether there was a difference in the number of nodes identified and excised between the techniques. The EAC estimated the pooled rate for nodes identified by both methods separately, via function 'metamean', which requires the standard deviation of the number of nodes (or range, inter-quartile range) as well as the mean. Figure 3 shows the results for Magtrace with Sentimag, for those studies reporting results in sufficient detail, and the pooled rate for the comparator is shown in Figure 4. The comparator included studies that used the dual technique, radioisotope only, and a mixture. Both meta-analyses showed the presence of significant heterogeneity between studies; the estimate of the NN rate for Magtrace and Sentimag was 2.03 and that of the comparator was 1.83.

Figure 3: EAC meta-analysis for number of nodes; Magtrace and Sentimag

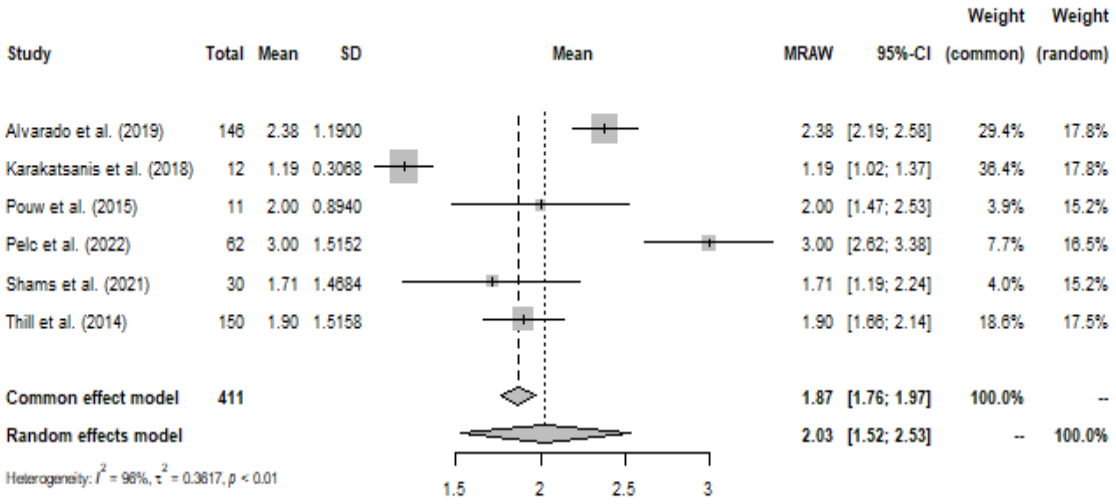
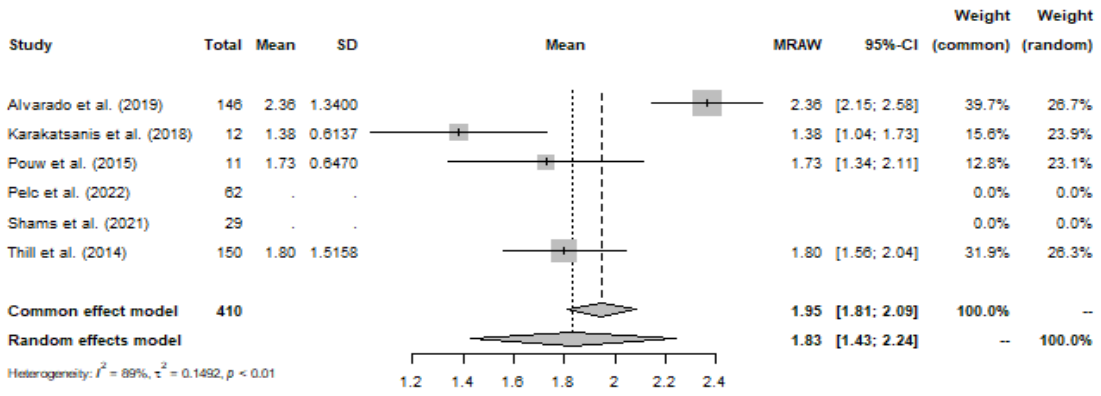
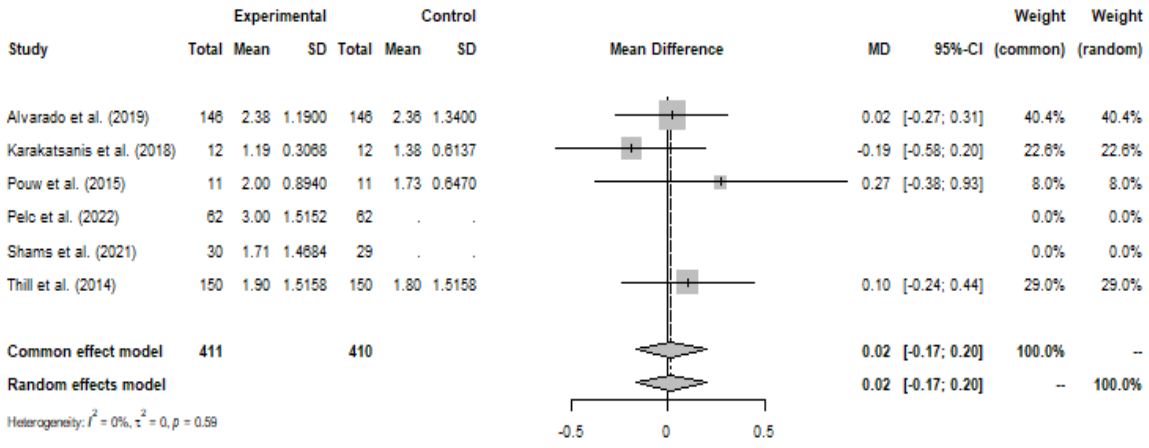


Figure 4: EAC meta-analysis for number of nodes; comparator



Separate pooled estimates of NN for each method do not account for within-study similarities; that is, the identification and retrieval rates for each method in the two arms of the same study (including when both techniques were used in the same patients) are likely to be correlated. The EAC repeated the meta-analysis using function 'metacont', which pools the ratios of means between arms, across studies. The EAC notes that this assumes the participants in the arms of each study are independent, which is not the case in practice. Despite this limitation, the paired method accounts for between-study variation (as evident from Figures 3 and 4). The results are shown in Figure 5. There is little evidence to suggest that NN differs between methods.

Figure 5: EAC meta-analysis for number of nodes; paired



7.4 Sentimag-versus-Gamma nodal retrieval rate (NRR)

The Company defined this as the per-node proportion of surgically retrieved nodes that are successfully identified by Sentimag and Magtrace compared to the corresponding (that is the same study) per-node proportion of surgically retrieved nodes that are successfully identified by gamma probe and radiotracer.

As with IR, the nodal retrieval rate (NRR) is subject to incorporation bias because the denominator (number of nodes identified and excised) depends on the index test (such as some excised nodes were identified by Magtrace only).

The Company included nine comparative studies which included different variants of the comparator (some included blue dye and some did not, for example). For this reason, and due to the fundamental problem of incorporation bias, the EAC considers that a meta-analysis of NRR does not contribute meaningful new information to the assessment, at worst may be misleading, and should not be considered further by committee.

Incidentally, the EAC notes that the Company appears to have swapped the labels of “gamma” and “Sentimag” in their results on page 40. By their definition, radioisotope should have a lower “risk” as it identifies fewer nodes.

7.5 Sentimag to Gamma nodal concordance rate (NCR)

The Company defined the Sentimag-to-Gamma Nodal Concordance Rate (NCR) as the per-node proportion of gamma probe and radiotracer detected nodes that are also detected (such as in the same study) by Sentimag and Magtrace. The EAC notes that the other form of concordance (such as the per-node proportion of nodes identified by Sentimag and Magtrace that are also identified by radioisotope) may also be important.

The EAC replicated the meta-analyses for both types of concordance using the included comparative studies that reported sufficient details to calculate the proportions. Pooled concordances of each type were calculated with separate meta-analyses. The EAC notes that the studies included comparators that were standard care, radioisotope only, and a mixture.

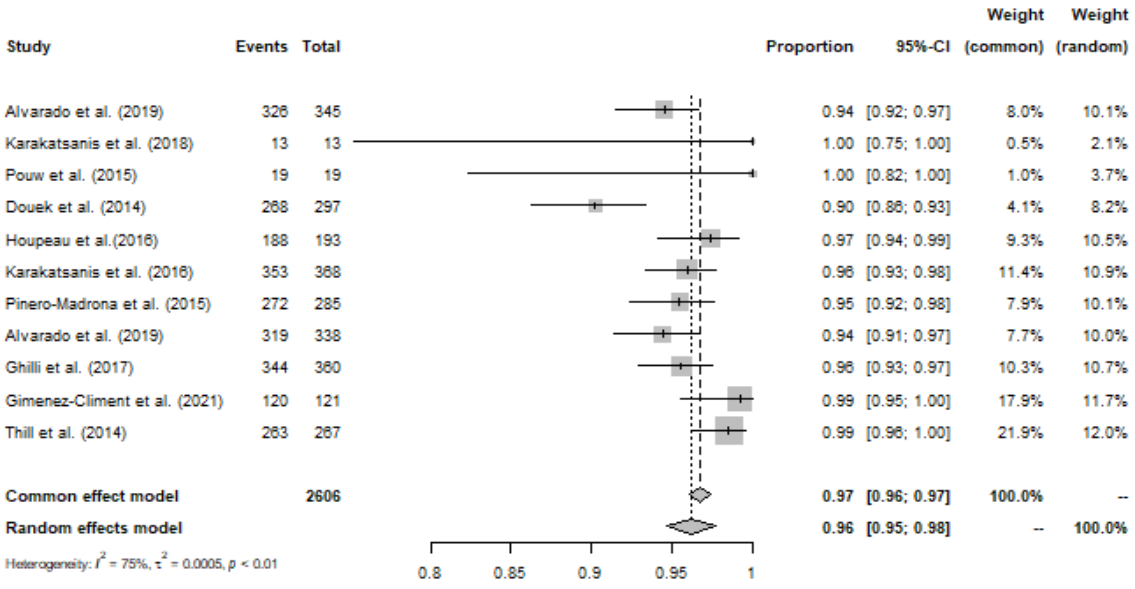
Studies not including blue dye as a comparator are likely to have a lower detection rate than those with.

Sentimag with Magtrace to radioisotope

The EAC estimated the pooled proportion of nodes that were detected by radioisotope (including dual technique, radioisotope alone or combination) that were also detected by Magtrace and Sentimag as 0.96 [95%CI 0.95 to 0.98], I^2=0.75, from 11 studies, Figure 6, using the R meta package function metaprop. This replicates the Company's analysis using included studies, with similar results. The EAC notes that only three of these studies (Alvarado *et al.* 2019, Karakatsanis *et al*. 2018; Pouw *et al.* 2015) reported dual technique (radioisotope and blue dye) exclusively, four reported radioisotope only, and four reported a combination, therefore the generalisability of this analysis to the NHS is unclear. Alvarado *et al.* (2019) included nodal detection rates for both the dual technique and radioisotope alone.

Incidentally, the EAC notes that the Company has included the ex-vivo detection from the Pinero-Madrona *et al.* (2015) study. The EAC has selected the intraoperative detection reported in the study to align with the approach taken across the remaining studies.

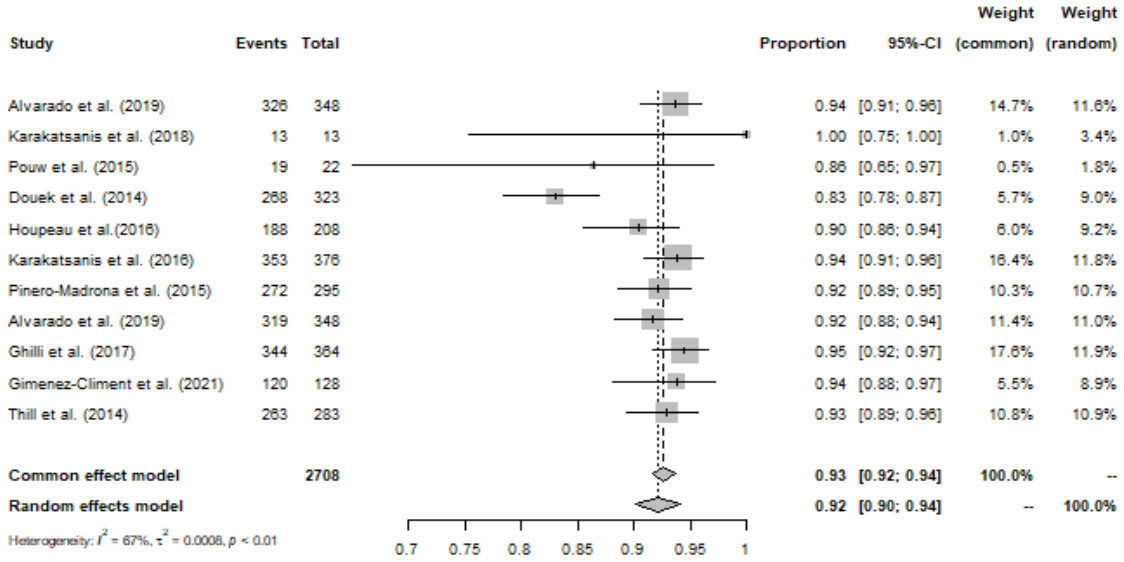
Figure 6: EAC meta-analysis of the proportion of nodes that were detected by radioisotope that were also detected by Magtrace and Sentimag (N=11)



Radioisotope to Sentimag with Magtrace

The EAC estimated the pooled proportion of nodes that were detected by Magtrace and Sentimag that were also detected by radioisotope (including dual technique, radioisotope alone, or combination) as 0.92 [95% CI 0.9 to 0.94], I^2=0.67, from the same 11 studies, Figure 7, using the R meta package function metaprop.

Figure 7: EAC meta-analysis of the proportion of nodes that were detected by Magtrace and Sentimag that were also detected by comparator (including dual technique, radioisotope alone and combination) (N=11)



7.6 Paired nodal concordance

The EAC also made a paired pooled estimate, in which the nodal concordance proportions for each arm of the 11 included studies were compared pair-wise. The EAC notes that this approach is based on the assumption that in each study, the two concordances are independent. This is not the case, and the results should be treated with caution. However, the approach does account for within-study similarities. It is reported as a risk ratio, that is, the ratio of the two concordances.

Noting the limitations, the results suggest that Magtrace and Sentimag may identify around 4% more nodes than standard care, Figure 8. However, the EAC notes that only three of these studies (Alvarado *et al.* 2019, Karakatsanis *et al.* 2018, Pouw *et al.* 2015) reported dual technique (radioisotope and blue

dye) exclusively, four reported radioisotope only, and four reported a combination, therefore the generalisability of this analysis to the NHS is unclear. Alvarado *et al.* (2019) included nodal detection rates for both the dual technique and radioisotope alone.

Finally, the EAC repeated the meta-analysis, limiting the studies to those in which the comparator was standard care (Figure 9). There was no evidence for a difference in detection rates between the methods.

Figure 8: EAC meta-analysis of the paired nodal concordance between experimental (Magtrace and Sentimag) and control (comparator including dual technique, radioisotope alone and combination) across N=11 studies

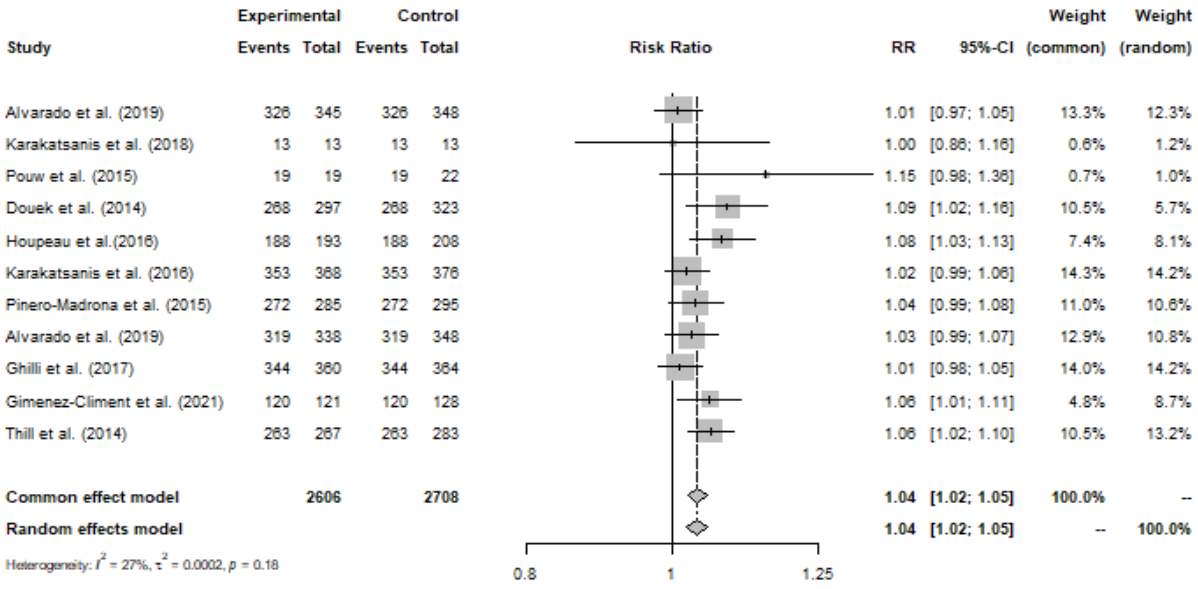
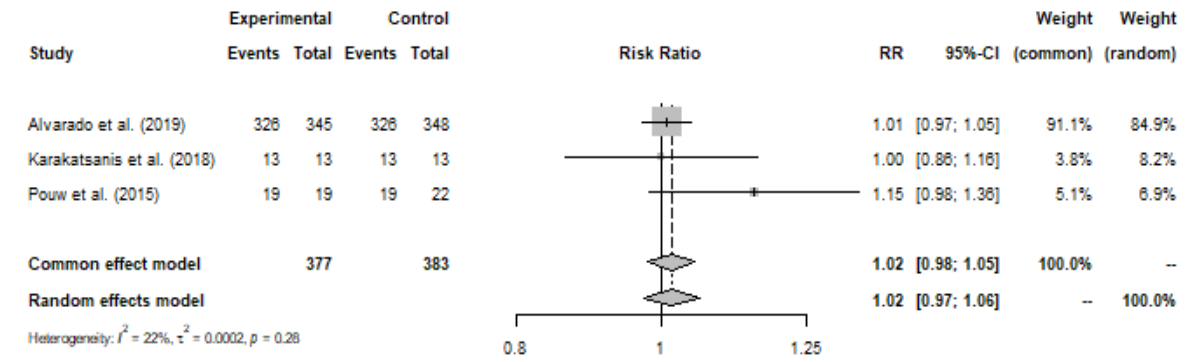


Figure 9: EAC meta-analysis of the paired nodal concordance between experimental (Magtrace and Sentimag) and control (comparator including dual technique exclusively) across N=3 studies



8 Interpretation of the clinical evidence

The EAC considered a total of 36 studies as relevant to the decision problem, including 22 comparative studies (9 of which were conference abstracts). Of these, 5 studies compared Magtrace with the standard care (dual technique) exclusively; 11 studies used Tc-99m radioisotope only as a comparator, and 6 studies included dual technique and Tc-99m alone as comparators but did not report outcomes exclusively. Studies comparing Magtrace to blue dye alone are considered out of scope for this assessment due to high false negative rates (Li *et al.* 2018, EAC Correspondence Log, 2022) and known inferiority when compared to the dual technique (He *et al*. 2016; Hung *et al*. 2005).

Of the 22 comparative studies, only 4 studies compared Magtrace with Tc-99m with and without blue dye in different cohorts of patients. Fourteen non-comparative studies were included for patient reported outcomes and adverse events only. Only one study, reported in a conference abstract, was conducted exclusively in a UK NHS setting (Sukumar *et al*. 2020) and the SentiMAG study, with four associated included publications, was based in the UK and the Netherlands.

Of the 36 included studies, 18 administered Magtrace intraoperatively or on the day of surgery; 6 did not report injection timing and only 5 included patients injected prior to 3 days before surgery. Clinical experts advised that Magtrace injected during a prior routine clinic visit provides visual colouration of nodes with clinical benefit when compared to intraoperative injection (EAC Correspondence Log, 2022). From the available published literature, there is no evidence to support earlier Magtrace administration affects the detection rate.

The published evidence for the detection rates of Magtrace with Sentimag to standard care with the dual technique is based on non-inferiority trials. Twelve studies were statistically powered to show non-inferiority; only one of which reported the dual technique outcomes exclusively (Karakatsanis *et al.* 2018). The evidence supports the non-inferiority of Magtrace with Sentimag to standard care with the dual technique for detection of sentinel lymph nodes

including for malignant lymph nodes. The *per patient* and *per node* detection rates for Magtrace ranged from 89.7% to 100.0% and 77.5% to 100.0% respectively, compared to detection rates with Tc-99m with and without blue dye with 83.3% to 100.0% and 67.2% to 98.0% respectively. *Per patient* detection rates for malignant lymph nodes for Magtrace and Tc-99m with and without blue dye were also comparable with ranges of 91.7% to 100% and 90.8 to 100.0% respectively. *Per node* detection rates for malignant lymph nodes for Magtrace and Tc-99m with and without blue dye were 88.3% to 98.3% and 88.2% to 96.0% respectively.

There is a lack of robust comparative evidence to determine the impact of the use of Magtrace rather than standard of care (dual technique) on procedure duration.

There are no significant concerns relating to the safety of the technology, although 6 studies have noted future imaging (6 MRI, 1 mammography – see Integration into the NHS section) being impacted by artefacts up to 5 years after Magtrace administration. There is currently no longitudinal evidence to determine the impact of this on future diagnoses or treatment. Alternative tests are available for diagnostic assessment where MRI, or possibly mammography, interpretation is not feasible, however these may not be readily available across all services and may have higher associated costs. There is consensus from Clinical experts that Magtrace would not be advised for patients who are anticipated to require MRI within three months of SLNB procedure (EAC Correspondence Log, 2022).

The main safety concern relating to the use of Magtrace is the incidence of skin staining although the literature and opinions from Clinical experts suggest that deeper injections reduces this occurrence. There is no comparative evidence reporting the difference in skin staining associated with Magtrace compared to blue dye. A small number of studies investigating patient reported outcomes do not identify skin staining as a significant problem to patients.

8.1 *Integration into the NHS*

Summary of Training Requirements

There was consensus from the Clinical experts and the Company that there is a learning period associated with the technology with peer support. The Company suggest a minimum of five cases to ensure competency with the technology. The length of the learning curve was varied across the Clinical experts suggesting a range of 10 to 50 cases is required for a surgeon to become familiarised with Magtrace and Sentimag and the learning curve can take around a year (EAC Correspondence Log, 2022). Three of the surgical Clinical experts reported the use of blue dye with Magtrace to assist with SLN detection during the learning period (EAC Correspondence Log, 2022).

Thill *et al.* (2014) highlighted the difference in probe size compared with a gamma probe used with the current standard of care; "the diameter of the SentiMag probe is slightly larger (6 mm) than that of the gamma probe, however larger incisions were not required and SLNB could be performed via the same incision the breast tumour was resected from, if desired". A response from Barranger and Ihrai (2014) noted that there is a minimum learning curve for surgeons and that larger incisions are required to enable insertion of the Sentimag probe to identify the magnetic SLN. The respondents also note that the regular calibration during usage lengthens surgery duration. Barranger and Ihrai (2014) did not report the requirements relating to the learning curve, additional incision length or surgery duration.

Future Imaging Considerations

Following the administration of Magtrace, MRI studies of the injection and drainage sites can be altered and this effect may be long-term (Magtrace IFU; EAC Correspondence Log, 2022).

One included study reported MRI outcomes in 16 patients following Magtrace injection (Chapman *et al*. 2020). Across the patient cohort, 21 MRI examinations were performed with 13 patients undergoing single MRI; 2 patients undergoing 2 MRIs, and 1 patient undergoing 4 MRIs. MRI examinations were undertaken between 3 and 18 months (mean 10.8

months) after Magtrace administration, with 85.7% of the imaging being performed at 3 T strength and the remainder at 1.5 T. MRI quality was impaired in all 21 studies with the presence of SPIO residue and associated artefacts. Five patients had non-diagnostic MRI results with one patient undergoing follow-up MRI four months later (ten months post-operatively) that was deemed limited. Timing of imaging deemed non-diagnostic or limited due to the extent of artefact with a mean (range) time ranged from 5 to 16 and 3 to 63 months postoperatively respectively. In one patient, despite the presence of artefact limiting interpretation of a portion of the breast, several enhancing masses were seen and invasive ductal carcinoma was diagnosed following further biopsy. Authors did not report on other patient specific outcomes or interventions that were impacted from the limited interpretation of the MRI studies.

Houpeau *et al.* (2016) noted that potential ionising effects of an external radiation due to temporary occurrence of intra-tissue nanoparticles are not known and may require consideration.

The EAC identified an additional three papers and two conference abstracts that were considered out of scope for the assessment report, which reported on MRI outcomes following Magtrace injection (Forte *et al*. 2019; Krischer *et al.* 2017; Aribal *et al.* 2021; Huizing *et al.* 2015; Shrotria *et al.* 2020).

A study by Krischer *et al.* (2017) evaluated MRI performed 42 (range 40.6 to 46.5) months following Magtrace injection in a sample of 25 patients. Imaging interpretation was not restricted in 12 cases (48%), impaired in 10 cases (40%), and not possible in 3 cases (12%) due to Magtrace residues.

A paper by Forte *et al.* (2019) reports a case study with MRI following the use of Sienna+. Authors note that artefacts were severe and predominant when using higher magnetic imaging strength in the early post-operative period, within 6 months of surgery, however decreased at 12 and 18 months post-operatively. Images were impaired at all visits although still readable.

Aribal *et al.* (2021) reported MRI in 36 patients who received Magtrace for SLNB. Susceptibility artefact in the patient MR images due to iron-oxide

particles was classified with a 4-scale evaluation; 0: no artefact (n=11, 30.6%); 1: focal area of signal void artefact (less than 5 mm) (n=14, 38.9%); 2: segmental area of signal void artefact (n=3, 8.3%); 3: regional signal void artefact (n=8, 22.2%). The mean time between Magtrace administration and MRI examination was 20 months. Three patients underwent a second MRI at 36, 38 and 41 months post-surgery; two patients showed no change in artefact and one patient showing a relatively smaller artefact compared with the first MRI 14 months prior. Authors also reported on mammography outcomes in 69 patients. Three patients (4.4%) presented with artefacts due to the iron oxide particle accumulation that presented as dense irregular and ill-defined lesions, mimicking malignant features on mammograms.

Huizing *et al.* (2015) reported postoperative breast MRIs for ten imaging reports in six patients recruited to the SentiMAG study at two UK sites. Patients received a 2 ml Magtrace periareolar injection. All MRI studies showed void artefacts with a mean (SD) size of 60.3 (14) by 37.8 (13) mm in the axial plane in the breast. Artefacts were seen at 25 months, and another study showed no decrease in size when comparing 3 consecutive studies spanning a period of 10 months. None of the artefacts were reported as incidents or as having impacted clinical management.

Another UK-based abstract from Shrotria *et al.* (2020) evaluated the extent of the requirement for postoperative MRI in patients with breast cancer during follow-up. This study included 221 patients undergoing surgery for breast cancer (including 160 wide local excision, 61 mastectomy), of which 14 patients required MRI within 3 years. The study reports that of these 14 patients, 3 *would have been* affected by the use of Sienna+, although it was not clear how this was evaluated. The EAC contacted the corresponding author for clarification on 07/03/2022 with no response received by 14/03/2022.

The Clinical experts report few patients require post-surgery MRI, however one expert noted an increasing number of surveillance MRI beyond one year postoperatively. Two Clinical experts report the combined use of MRI and mammography in patients undergoing subsequent imaging. An additional

Clinical expert advised on the routine surveillance using mammography; MRI is used only in patients under the age of 40 years when diagnosed with breast cancer or in rare cases of lobular carcinoma where the tumour is mammographically occult (EAC Correspondence Log). Shams *et al.* (2021) excluded patients under the age of 40 years or likely to require MRI in the 5 years following SLNB.

The Company and three Clinical experts agree that Contrast Enhanced Digital Mammography or gadolinium-enhanced MRI could be used in addition to or as alternative imaging techniques in these patients, however are associated with higher radiation and higher costs and may not be readily available across NHS hospitals.

A Swedish multicentre trial is currently underway (POSTMAG MRI ISRCTN85167182) to understand the impact of SPIO particle injection on postoperative MRI up to five years following SLNB, with publication anticipated in January 2024.

Magtrace Administration Timing

The majority of included studies administered Magtrace intraoperatively and only five included studies reported patients where Magtrace was administered more than three days prior to surgery (Hersi *et al.* 2021, Karakatsanis *et al.* 2017; Karakatsanis *et al*. 2018; Warnberg *et al.* 2019; Jazrawi *et al*. 2021). The Clinical experts note that injecting Magtrace at least seven days prior to surgery results in better tracer visualisation (EAC Correspondence Log, 2022). Karakatsanis *et al.* (2017) note a higher tracer-specific SLN detection rate with preoperative administration of Magtrace compared with perioperative administration, with 95.3% and 86.0% respectively (p=0.031). The Clinical experts note that earlier administration of Magtrace does not result in higher number of SLNs being retrieved or tracer spreading to secondary lymph nodes (EAC Correspondence Log, 2022).

A later paper by Karakatsanis *et al.* (2018) reported the transcutaneous axillary ferromagnetic signal curve in a healthy volunteer injected with Magtrace over a period of 42 days. The ferromagnetic signal increased from

injection and was greatest at 21 days post administration before reducing until no signal was detected by Sentimag at 42 days.

Hersi *et al*. (2019) reported the axillary magnetic signal detection in all 32 patients receiving Magtrace injected between 0 and 25 days.

Magtrace with Concomitant Magseed Use

Two of the included studies reported the use of Magtrace alongside Magseed for tumour localisation (Pohlodek *et al*. 2018; Sreedhar *et al.* 2021). Both are located using the Sentimag probe. The Clinical experts advised that 30% of breast surgery with SLNB would use a Magseed and that caution should be exercised where Magseed placement is within the same quadrant of the breast as Magtrace and local practice is to ensure Magseed placement is at least 3 cm away from the SLNs (EAC Correspondence Log, 2022). The Company broadly estimated 50% of breast cancer cases would involve the use of Magtrace and Magseed and around 20% of patients would undergo mastectomy surgery and therefore would require Magtrace only.

Pohlodek *et al.* (2018) reported on ten patients who underwent Magtrace for SLN localisation and Magseed for localisation of non-palpable breast lesions. In all cases, there was no interferences in magnetic probe measurements due to the presence of both markers in the same breast. Authors did not report the location of Magseed in relation to the SLNs in any of these cases.

Sreedhar *et al.* (2021) reported a single case where Magseed and Magtrace were used in the same patient where the seed placement was masked by the magnetic tracer leading to the first wide excision biopsy to be done in the incorrect location and a second wide excision biopsy was required.

An additional study included by the Company, but excluded by the EAC, reported on 32 patients who underwent SLNB and breast conserving surgery with Magtrace and Magseed (Hersi *et al*. 2019). A survey on the physicians' views on the techniques were collected with all participants would recommend the combined technique to others. The authors note that the operation theatre coordinators experienced that the combined method was an improvement,

allowing for more flexibility in the mammography unit and theatre list schedules.

Histopathological sampling considerations

A conference abstract reporting a single UK-based case study by Davies *et al.* (2020) noted an abundance of pigment-laden macrophages within the sinuses and a prominence of eosinophils within the excised nodes on histopathological evaluation. The authors note an importance for histopathologists to be aware of the nodal changes associated with Magtrace if it is used more frequently during clinical practice.

Hersi *et al*. (2019) reported that the use of Magtrace did not affect specimen pathology.

8.2 *Ongoing studies*

The NICE MIB263 highlighted three ongoing studies; two now have published results (Karakatsanis *et al.* 2019; Hersi *et al.* 2021) and one is still ongoing (Appendix C2). The Company identified four ongoing studies (Appendix C2). The EAC identified an additional two ongoing studies (Appendix C2) from their independent searches. None of the seven ongoing studies are conducted in a UK setting.

The EAC also identified two completed studies with no publication of results (Appendix C1), and one discontinued study (MAGnetic versus STAndard technique for sentinel node biopsy in breast cancer compared in a Randomised controlled trial (MAGSTAR); EudraCT 2015-000549-21) which was cancelled before going active with no results or data available.

A Swedish multicentre trial is currently underway (POSTMAG MRI ISRCTN85167182) to understand the impact of SPIO particle injection on postoperative MRI up to five years following SLNB, with publication anticipated in January 2024.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The Company did not conduct a separate literature search, but instead identified three published studies reporting costs, which were included in the Company Economic Submission. The EAC considered two relevant to the decision problem (Karakatsanis *et al.* 2017; Shams *et al.* 2021); the remaining study only reported a single sentence regarding costs in the Discussion section (Man *et al.* 2019) and was excluded by the EAC.

The EAC would have identified all economic evidence within the EAC's clinical evidence search (Appendix A2), and therefore did not conduct a separate economic search. The EAC identified an additional one study that was relevant to the decision problem (Sreedhar *et al.* 2021).

Published economic evidence review

A summary of the three studies reporting on costs associated with Magtrace and Sentimag are summarised in Table 11. The focus of all three was clinical comparison of tracer identification techniques; all were included in clinical evidence and were critically appraised during the assessment of clinical evidence (the EAC did not reappraise these papers for the context of reporting additional cost information). None included formal economic modelling, none included the complete SLNB procedure, all device, procedure or adverse event costs, and none looked at post-operative outcomes. One reported on purchase costs only, one reported on reimbursement costs to hospital using routine data, one reported on purchase costs and speculated on hotel and travel costs for the patient. The Company did not use any parameters from the included economic studies to inform their *de novo* model.

Table 11: Summary of results from published studies reporting on costs.

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
Karakatsanis *et al.* (2017) Sweden (N=2)	Prospective non-randomised controlled trial (n=338) One centre delivered Technetium (injected on the day of the surgery or the day before). Second centre delivered Magtrace in an outpatient clinic before surgery. Swedish healthcare perspective.	Patients with early breast cancer (T1 to T3 or DCIS) undergoing SLNB.	MagTrace injected before surgery during pre-op outpatient clinic (1-4 weeks before surgery) or immediately before surgery (n=183). Magtrace mixed with 3ml Xylocaine at least 20 mins before removal of sentinel node. Blue dye was also used if the signal recognised by the SentiMag was poor (blue dye used in 92 procedures). Technetium injected on the day of the surgery or the day before in Nuclear Medicine (n=155). Blue dye was injected routinely in the isotope arm.	Cost of tracer, preoperative visit and administration of injection delivery. Cost parameters based on Swedish crowns and converted to Euros based on the exchange rate on 20/12/2016.	Cost of tracer and injection: €225 for MagTrace, €252 for Technetium; resulting in Magtrace being cost-saving by €27. Preoperative injection of SPIO saved an additional minimum 20 min of operating theatre time (for SPIO to migrate to axilla), saving €352 when compared to perioperative injection of SPIO.	Total cost per SLNB not reported, adverse events not included. Cost savings driven by removal of preop nuclear medicine visit. Discussion reports pre-operative injection of SPIO reduced need for blue dye. Additional benefit that SPIO resides in tissue means that cancellation or rescheduling of the operation does not require another injection (as is the case with isotope).

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
Shams *et al.* (2021) Germany	Non-randomised controlled trial pilot (n=59) Group allocation to Magtrace or radioisotope was by the surgeon's choice. Breast conserving surgery was performed by five different surgeons. Additional lymph nodes were extracted if a positive signal was demonstrated. Perspective of German diagnosis-related group 2019 system.	Females who underwent breast cancer surgery and lymph node biopsy. One patient had a sentinel lymph node biopsy only.	Tc-99m was administered either on the day of the surgery or the day before (n=29). MagTrace (2 ml) was administered intraoperatively or up to 3 days before the operation (n=30).	All patients (both groups) received their breast cancer surgery during an inpatient visit with an overnight hospital admission. Final diagnosis-related group (used for hospital reimbursement purposes, using German grouping 2019 system) were compared between arms.	Use of Magtrace did not affect diagnosis-related group outcome, and reimbursement remained the same independent of the tracer method.	Authors acknowledge that the use of reimbursement costs based on diagnostic and operation codes does not account for variation in patient complexity (flat rate applied). It is unclear if cost of Magtrace solution and probe were included in the established German Diagnostic-related group system.

Study reference	Methods and perspective	Population	Intervention(s)	Clinical and cost parameters	Summary results	EAC comments
Sreedhar *et al.* (2021) New Zealand	Retrospective non-randomised controlled trial (n=116). Data from patient notes, digital and paper. New Zealand rural hospital perspective (including purchase and reimbursement costs).	Consecutive patients undergoing SLNB or localisation of an impalpable tumour.	Intervention (n=45): Magtrace (2 ml injected the day before surgery) with Sentimag probe, and blue dye Comparator (n=71): Tc-99m with lymphoscintigram the day before, and blue dye	Financial data collected from administrative staff via receipts and invoices of purchases to the hospital. Conjecture was taken to illustrate estimations of costs of detection modality and no formal analysis has been undertaken.	Cost of SLNB with radioisotope colloid $1418.00 (breakdown: $600 injection, $588 CT-SPECT, $130 transport, $100 hotel). Cost with Magtrace $557.70. Magtrace cost-saving by $860.30 per procedure.	Authors acknowledge that the upfront cost of Sentimag probe and gamma probes were excluded from calculations. Appendix of paper shows that costs in Magtrace arm did not include staff time for injection. Costs were driven by transport and accommodation associated with 7 hour round trip by road to receive radioisotope injection.

Abbreviations: CT, computed tomography; DCIS, ductal carcinoma in situ; SLNB, sentinel lymph node biopsy, SPECT, single-photon emission computed tomography, SPIO, super paramagnetic iron oxide, Tc-99m, Technetium-99m radioisotope.

Results from the economic evidence

None of the three included studies reporting on costs associated with Magtrace and Sentimag were explicitly, or assumed to be, from the perspective of the UK NHS. Karakatsanis *et al.* (2017), conducted in Sweden, reported use of Magtrace to be cost-saving by €27 per person (including cost of tracer and injection time only), and reported larger savings of €352 per person if Magtrace was injected in a prior clinic (saving 20 minutes of theatre time). Shams *et al.* (2021), conducted in Germany, reported that reimbursement was unaffected by choice of localisation method, however it is unclear if the cost of Magtrace solution and probe were included in the diagnosis-related group tariffs. Sreedhar *et al.* (2021), conducted in New Zealand, reported Magtrace to be cost-saving by $860.30 per procedure when including patient car travel and hotel expenses, but acknowledged that costs of Sentimag and gamma probes were not included in the calculation.

9.2 *Company de novo cost-analysis*

Economic model structure

In the absence of published studies, which directly addressed the decision problem defined by the final scope, the Company developed a *de novo* cost-minimisation analysis from an NHS and PSS perspective in an executable Excel spreadsheet, described across three worksheets. The EAC critically appraised the *de novo* model and its narrative description in the Company's Economic Submission using the Drummond checklist (Drummond *et al.* 1996), Appendix D1. The model included 17 parameters and 7 costs, and compared the use of Magtrace and Sentimag against the use of dual technique (radioisotope and blue dye).

Population

The Company defined the population, in line with the scope, as patients undergoing sentinel lymph node biopsy with breast cancer. The Clinical experts advised that all breast cancer patients would be assessed by ultrasound, indeterminate or suspicious nodes would undergo core biopsy, and that patients with no abnormalities detected on ultrasound would proceed to SLNB (EAC Correspondence Log, 2022). The Clinical experts estimated that between 60-80% of breast cancer patients are lymph node negative and

routed for SLNB. The Clinical experts advised that SLNB is rarely indicated in patients with ductal carcinoma in-situ (DCIS) undergoing breast conserving surgery. The Clinical experts also stated that all patients with invasive carcinoma and a subgroup of patients with DCIS undergoing mastectomy, would undergo breast surgery and SLNB within the same theatre session (EAC Correspondence Log, 2022).

Intervention and Comparator

The Company defined the intervention and comparator with no deviation from the published scope: Magtrace and Sentimag compared with dual technique (radioisotope Tc-99m and blue dye) for the localisation of the sentinel lymph nodes during SLNB surgery. However, the timing and hospital setting of each tracer injection was not explicitly stated within the model.

The Company have confirmed that polymer tools are provided by the distributor alongside the Sentimag system free of charge, including retractors and grasping (Debakey forceps, Allis and Babcok) instruments (EAC Correspondence Log, 2022). Two Clinical experts advised that with experience plastic instruments are not required; metal instruments can be used and simply removed from when using the probe to locate Magtrace (EAC Correspondence Log, 2022). The Sentimag IFU notes that for best results during baseline set up, the probe head should be at least 0.5 metre away from any metallic or magnetic objects and care should be taken when using the probe in the proximity of any extraneous metallic or magnetic objects including surgical tools.

The model does not include any costs for local anaesthesia (in Magtrace or dual technique arms), which may be used if the tracer was injected at a clinic appointment prior to the SLNB procedure. The model does not account for patients contraindicated to Magtrace (hypersensitivity to iron oxide, dextran compounds, iron overload disease, metal implant close to the expected sentinel lymph node location) requiring standard of care. The Clinical experts advised that routine screening would not be carried out in patients undergoing Magtrace injection, however estimated that the total proportion of patients with any contraindication would be rare; less than 1% (EAC Correspondence Log,

2022). The Clinical experts discussed that radioisotope tracer did not have these contraindications; and that Tc-99m would still be considered in pregnant patients but would require local risk assessment and senior lead approval (EAC Correspondence Log, 2022).

Outcomes

The cost-minimisation analysis includes the cost of the vial for each of the tracers (Magtrace, radioisotope and blue dye), delivery costs (radioisotope only) and staff time for injection (Magtrace: 1 nurse 20 minutes, dual technique: 2 staff 40 minutes), and theatre time lost (dual technique arm only). The model does not include device costs for the Sentimag probe for detecting Magtrace. The Company justifies this as "hospitals who have adopted Magseed will already have the probe, and for most other hospitals the probe will be provided as part of an annual contract at no extra costs". The EAC queried the length and volume of contract with the Company who advised that NHS Trusts who enter a consumable commitment (100 to 120 consumable units per annum) receive the system free of charge; the Sentimag probe is £24,900 to purchase outside of this contract with a minimum expected device lifetime of 5 years (EAC Correspondence Log, 2022). The EAC notes that the model does not include device costs of the gamma probe for detecting the radioisotope. This may be due to an assumption that detection with a gamma probe is included within the SLNB Health Resource Group (HRG) code, or may be due to gamma probes being used for a range of procedures in a hospital and therefore the per-procedure use may be regarded as negligible. However, the reason for excluding the gamma probe costs from the model has not been reported explicitly as an assumption by the Company in their submission. As dual technique represents the standard of care, and includes blue dye which is injected after induction of anaesthesia (due to risk of anaphylaxis), the EAC would assume that the costs associated with blue dye injection (material and staff time) are included within the bundled HRG code associated with SLNB procedure.

The cost-minimisation analysis does not include costs associated with patient travel or patient satisfaction. However, the Company has included two separate opportunity costs in the comparator arm to account for theatre time

lost due to supply disruption or shortage of Nuclear Medicine staff and theatre time lost due to time required for Tc-99m injection on the day of surgery. The EAC notes that the values for these opportunity costs only came from only one NHS hospital that does not have an embedded Nuclear Medicine department. The Clinical experts also advised the EAC that delays due to radioisotope were unlikely; that delays would be mitigated by changes to theatre scheduling, and that the SLNB procedure could proceed with blue dye alone, or with four-node random sampling (EAC Correspondence Log, 2022). A number of published studies included in the clinical evidence reported injection of radioisotope the day prior to surgery. Additionally, the majority of published evidence reported injection of Magtrace intraoperatively, where subareolar injection requires a 20 minute wait before attempting transcutaneous measurement of the axilla (in line with the Magtrace IFU). The IFU for Magtrace also states that "peritumoural injection may require a longer wait"; however this is not quantified. Therefore, the EAC considers that the opportunity costs included in the Company cost-minimisation analysis may not be realised by all NHS hospitals in practice (particularly those with on-site access to Nuclear Medicine, or those injecting Magtrace intraoperatively), and should be subjected to sensitivity analysis. One Clinical expert advised that Magtrace was injected intraoperatively when initially implementing the superparamagnetic tracer in their hospital. However, two Clinical experts advised that earlier injection of Magtrace (for example, at prior clinic) also leads to better visualisation (via brown-black colouration of the tracer) alongside magnetic detection with the Sentimag probe. Different scenario analyses should be conducted to address the different settings of Magtrace injection.

Time horizon

The Company states in Table 4 of Economic Submission that the time horizon of the model is "from the time the patient attends the hospital for SLNB to the end of the procedure". The justification the Company provides for this is that the choice of tracer has no long-term implications for patient outcomes or costs. Due to the short-term nature of the study no discounting was applied. However, the cost-analysis provided by the Company only formally considers

the duration of injection. Pathway costs prior to the SLNB (for example, Magtrace injections at previous clinic, radioisotope injection at different hospital), duration of SLNB procedure, the cost of the SLNB procedure itself and adverse events following the tracer injection or SLNB procedure are not included in the model. Whilst the majority of evidence in the Clinical Evidence Submission demonstrated non-inferiority of SLN detection, the EAC would consider that the intervention and comparator may be different in terms of safety. The rare but serious adverse events associated with blue dye are well documented. A recent systematic review and meta-analysis reported 61 episodes of anaphylaxis in 40,268 SLNB procedures, with an (adjusted) anaphylaxis risk of 0.083% in breast cancer patients (Perenyei *et al.* 2021). This is broadly in line with results from the NEW START and ALMANAC study group where grade III reactions (severe hypotension requiring vasopressor support, change or abandoning planned procedure or HDU or ITU admission) were noted in 5 out of 7,917 patients (0.063%) undergoing SLNB in breast cancer (Barthelmes *et al.* 2009). Additionally the EAC has identified a number of published studies which have documented the long-term impact of Magtrace in producing artefacts on future MRI up to 5 years after injection (see Section 8), which may alter the modes of imaging as part of the patient's routine surveillance. However, there is a lack of comparative long-term data to determine the clinical impact of this. The EAC would recommend modelling long-term implications of MRI masking with Magtrace in scenario analysis.

Assumptions

The Company summarised the assumptions made in their *de novo* model, in Table 3 of the Company Economic Submission, summarised by the EAC in Table 12.

Table 12: Assumptions made by the Company to support the *de novo* model

Assumption (from Company submission)	Company justification	Company source	EAC comment
The costing relates to a hospital carrying out 250 SLNB procedures annually:	Estimating annual costs requires an assumption about volumes. The relative cost-	Source reported in economic Excel worksheet. Lower end estimate of data provided by	The EAC did not identify any UK national audit data related to SLNB. EAC consulted with Clinical experts; 4 responded who stated the number of SLNB procedures

Assumption (from Company submission)	Company justification	Company source	EAC comment
approximately 5 procedures in a single surgery list weekly for 50 weeks.	effectiveness of a tracer does not depend on the annual volume of procedures	2 NHS trusts in England.	in a year ranging between 200 and 600 (EAC Correspondence Log, 2022).
The hospital receives one delivery weekly of two vials of Tc-99m.	The radioactive isotope requires specialist delivery with associated costs. The number of weekly deliveries depends on the number of planned procedures. One vial of Tc-99m is typically used for 2-3 procedures, hence 2 vials is assumed for 5 procedures. Unused material cannot be stored.	Source obtained from Excel worksheet. Lower end estimate of data from 3 NHS trusts in England.	One Clinical expert advised that the number of patients treated from a vial will vary depending on order and decay of the product (EAC Correspondence Log, 2022).
Magtrace and blue dye can be ordered in bulk and stored until required. The shelf-life of Magtrace is approximately 2 years. No special delivery or storage arrangements are necessary. One vial of each is required per SLNB procedure.	Not reported	Not reported	Storage, replacement, waste costs not applied to any arm. Delivery charge of £25 applied to each radioisotope delivery (no delivery charge applied to Magtrace or blue dye). EAC assumes that the cost for radioisotope delivery would be included within HRG for radioisotope injection.
The opportunity cost of theatre time lost through delays to surgery is measured by the number of SLNB procedures forgone, valued at the HRG tariff.	An alternative approach would be to value theatre time at a cost per hour (£1200).[7] This approach is less likely to represent the true opportunity cost.	Source obtained from Excel worksheet. NHS Tariff JA43B (which aligns to Unilateral intermediate breast procedures with CC score 0-2).	The EAC considers that delay to surgery may not occur across all hospitals. Clinical experts from hospitals with on-site nuclear medicine confirmed that shortage of radioisotope would not result in delay of SLNB as patients would be given priority. Four Clinical experts advise that between 20-50% of patients are injected with radioisotope the day before SLNB. Clinical experts also advised that delays

Assumption (from Company submission)	Company justification	Company source	EAC comment
			to surgery due to lack of radioisotope are rare. If isotope was unavailable the surgical team may proceed with blue dye alone, or random four-node sample (unlikely that surgery would be cancelled) (EAC Correspondence Log, 2022).The EAC notes that the Company has not considered within their economic model that intraoperative injections of Magtrace would add 20 minutes to total theatre time. The EAC considers that there may be an opportunity of additional surgeries as a consequence of lack of Nuclear Medicine and the short half-life of Tc-99m not permitting morning surgery on some days (for example Nuclear Medicine is not open at weekends and bank holidays which may impact surgeries the next day). However, the EAC would consider this a planned impact on scheduling (for example, if SLNB are not scheduled for mornings immediately after weekends or bank holidays, then the theatre is likely to be used for another procedure). With efficient theatre scheduling and radioisotope inject the day prior, the EAC would consider that opportunity for additional surgeries are unlikely for the majority of weekdays. Therefore, the EAC will consider realisation of this opportunity cost within sensitivity analysis, as additional procedures may not be realised in all centres.
OPCS code T87.3 relates to SLNB performed as a surgical procedure. T87.3 maps to HRG JA43 “unilateral intermediate breast procedures”	A note on coding. OPCS code T91.1 “biopsy of sentinel lymph node” relates to a radiological procedure which maps to HRG code YJ04. Since 2020, the coding has been	Company shared link to the 2020 update from the ABS Clinical Practice & Standards Committee.	The Clinical experts have advised that SLNB would rarely be conducted in isolation, and would like be included with breast surgery (EAC Correspondence Log, 2022). Clinical Coding has advised that a number of HRG codes include SLNB procedures (OPCS: T87.3 Excision or biopsy of axillary lymph node + O14.2 Sentinel

Assumption (from Company submission)	Company justification	Company source	EAC comment
	refined to differentiate a surgical sentinel lymph node biopsy, which is coded as T87.3 "excision or biopsy of axillary lymph node". T87.3 maps to HRG JA43 "unilateral intermediate breast procedures".		lymph node) and would depend on the concomitant procedures conducted during the same admission. - HRG: "JA20F Unilateral major breast procedures with CC score 0-2", would include SLNB and mastectomy, SLNB and lumpectomy (NHS Reference Costs 2019/20; £2782, activity: 27,996 procedures) - HRG: JA43B Unilateral intermediate breast procedures with CC score 0-2, would include SLNB and breast biopsy, SLNB with no breast procedure (NHS Reference Costs 2019/20; £1113, activity: 16,371). Weighted average of these two HRG codes, based on annual activity of 2019/20, is £2193.02 The cost of the SLNB procedure should be applied to all patients (Magtrace and dual technique) to represent the patient pathway cost; this is not the case in the Company model. The EAC notes that costs associated with these core bundled HRG codes will also include blue dye injection, costs associated with anaphylaxis care, and gamma probe detection.
A SLNB procedure takes 30-45 minutes.[8] The opportunity cost of forgone procedures assumes only 50% of potential additional procedures could be realised	There will be constraints other than theatre time on the potential number of procedures which can be performed		Clinical experts advised that lack of radioisotope would rarely result in cancelling of SLNB procedure. No robust clinical evidence reported on duration of procedure with Sentimag and dual technique. Use of Magtrace intraoperatively may add 20 minutes (as the tracer needs time to drain to the axilla). The EAC considers that opportunity costs may not be realised in all hospitals (those with and without on-site nuclear medicine, and may depend on centre volume of SLNB procedures). The percentage of hospitals receiving this opportunity cost should be varied in sensitivity analysis.

Assumption (from Company submission)	Company justification	Company source	EAC comment
Magtrace is appropriate in 100% of patients	Not expliticlty listed in assumptions, but implied in model.	N/A	Magtrace is contraindicated in patients with hypersensitivity to iron oxide or dextran compounds, patients with iron overload disease, and patients with a metal implant close to the expected sentienel lymph node location. The Clinical experts stated that patients with these characteristics were rare. The experts advised that they would not routinely screen for iron overload disease or iron oxide or dextran hypersensitivity, however that they had not encountered any cases so far. The Clinical experts have also advised that these contraindications do not occur with radioisotope (EAC Correspondence Log, 2022). Therefore, the EAC would recommend that provision of standard of care (dual technique) in patients with a contraindication to Magtrace is considered in scenario analysis.

Abbreviations: EAC, external assessment centre;; HRG, healthcare resource group; OPCS, Office of Population Censuses and Surveys classification of Interventions and Procedures; SLNB, sentinel lymph node biopsy

Validation of the economic model

The Company did not include any conceptual or technical validation of the economic model within their Economic Submission. Data was provided by three NHS Trusts (the majority provided by two NHS Trusts), none of which have on-site access to Nuclear Medicine and therefore may not be representative of care across the NHS.

Economic model parameters

Clinical parameters and variables

No clinical outcomes were included in the Company cost-minimisation analysis.

Resource identification, measurement and valuation

The Company reported the values for the clinical parameters and variables used in the model in Table 4 of the Company Economic Submission, as

summarised in Table 13. Some of the parameters were sourced from up to three NHS hospitals, none of which have an on-site Nuclear Medicine department.

Table 13: Clinical parameters used in the Company's model and any changes made by the EAC

Variable	Company value	Source	EAC comment
Tc-99m	£100 per vial £25 per delivery (assuming two vials per delivery)	Total cost per procedure (including delivery time) provided by 3 NHS Trusts.	Two Clinical experts stated that this cost was appropriate. Two Clinical experts advised that each vial costs approximately £60. One Clinical expert stated that 5 patients can be injected from the same vial if in the same session, however is dependent on patient mix. Another Clinical expert advised that the number of patients treated from a vial will vary depending on the order, and decay of the product (EAC Correspondence Log, 2022). One Clinical expert advised that hospitals with on-site Nuclear Medicine may pay substantially more (up to £160 per delivery) due to delivery of larger quantities, however that £25 may be representative of hospitals without on-site nuclear medicine. This cost would likely be shared with delivery of other radiopharmaceuticals for other procedures and other patient groups. An additional Clinical expert felt that the delivery charge may not be applicable to all hospitals (for example, hospitals with in-house radiopharmacy), however that some hospitals receive vials from external sites for which a delivery charge was applicable. This expert felt that delivery cost of £25 was reasonable. The cost of an additional clinic appointment for radioisotope injection is represented by the Health Resource Group (HRG) code: RN19Z "Sentinel Lymph Node Scan" £239 (NHS Reference Costs 2019/20). This HRG includes lymphoscintigraphy, and will not be

Variable	Company value	Source	EAC comment
			specific to a breast cancer population, but using an HRG enables a consistent approach across all NHS hospitals. However, one Clinical Expert stated that this HRG likely represents an underestimate (EAC Correspondence Log, 2022). The EAC confirms that this HRG code is an unbundled, and that additional costs such as staff time for documentation, waste management, may not be included.
Nuclear Medicine time to prepare and administer Tc-99m	Two Band 6 staff, 40 mins each to prepare and administer injection to a patient, complete documentation and handle radioactive waste	Time provided by 2 NHS Trusts.	The EAC assumes that staff time to deliver the radioisotope injection is incorporated within the unbundled HRG code above.
Nurse time to administer Magtrace injection	1 Band 5 nurse, 20 minute routine appointment	Time provided by 2 NHS Trusts.	Assumes that Magtrace is delivered at a prior routine appointment (within 30 days of the SLNB procedure), therefore no additional appointment costs. For the base case will assume 20 minutes (total time including consent, preparation and injection) of Band 5 nurse in line with the company estimatation. In line with Magtrace IFU, for perioperative subareolar injections, surgeons should wait 20 minutes before attempting transcutaneous measurement of the axilla. The EAC would assume that a consultant surgeon would conduct the injection perioperatively. As an upper estimate, an additional 20 minutes could be added to theatre time (which would include room and staff costs) in enable drainage to axilla. However, as SLNB are usually conducted with concomitant procedures (mastectomy, breast conserving surgery), the wait time will be varied in sensitivity analysis.
Blue dye	£25 per vial	Cost range provided by 2 NHS Trusts.	One Clinical expert confirmed that the cost of £25 per blue dye injection was approapriate; four

Variable	Company value	Source	EAC comment
			were unable to comment (EAC Correspondence Log, 2022). Dual technique (radioisotope and blue due) are considered standard of care. However, due to the risk of anaphylaxis, blue dye is routinely injected after induction of anaesthesia. Therefore, the EAC would assume that blue dye injection is incorporated within the HRG code for the SLNB procedure.
Magtrace	£226 per vial	Company	The Company has not included the cost of the Sentimag probe that is required to detect the Magtrace. The EAC has queried this with the Company who advised that NHS Trusts who enter a consumable commitment (100 to 120 consumable units per annum) receive the system free of charge; the Sentimag probe is £24,900 to purchase outside of this contract (EAC Correspondence Log, 2022). Company also confirmed that there is a delivery charge associated with Magtrace £10.65 per delivery (EAC Correspondence Log, 2022). However as Magtrace has a long shelf life, hospitals could buy a larger number of vials within a single delivery. The EAC assumes that the inclusion of delivery of Magtrace to "per-procedure" costs would be negligible and therefore can be omitted from the economic model.
Cost, Band 6 hospital scientific and technical staff	£55 per hour	PSSRU 2021	The Company model assumes that 2 Band 6 staff are involved in the injection of the radioisotope. Four Clinical experts have advised that a band 6 or 7 staff nurse, nuclear medicine technologist, or radiographer would conduct the injection. The EAC notes that PSSRU 2020/21 Hospital based scientific and professional (Band 6) assumed equivalent to radiographer are £54 per hour. However, the HRG code associated with radioisotope injection at previous clinic (RN19Z)

Variable	Company value	Source	EAC comment
			will include cost of radioisotope and staff time for the injection.
Cost, Band 5 hospital nurse	£41 per hour	PSSRU 2021	The EAC confirmed this cost was in line with that published in PSSRU 2020/21 (Band 5 hospital nurse includes staff nurse, theatre nurse).
Operating theatre time per SLNB procedure	45 minutes	The Company states the source is NHS Trust experience, however the EAC was unable to verify this (not included in the economic model spreadsheet).	One clinical expert stated that 45 minutes was representative of a SLNB procedure (EAC Correspondence Log, 2022).
SLNB HRG tariff	£1208	HRG JA43B combined day-case and ordinary elective spell. NHS Tariff Payment System 2021/22	Using NHS Reference Costs 2019/20 and a weighted average of HRG codes JA43B and JA20F: - HRG: "JA20F Unilateral major breast procedures with CC score 0-2", would include SLNB and mastectomy, SLNB and lumpectomy (NHS Reference Costs 2019/20; £2782, activity: 29,996 procedures) - HRG: JA43B Unilateral intermediate breast procedures with CC score 0-2, would include SLNB and breast biopsy, SLNB with no breast procedure (NHS Reference Costs 2019/20; £1113, activity: 16,371). Weighted average of these two HRG codes, based on annual activity of 2019/20, is £2193.02 However, the EAC notes that a proportion of this HRG code will include blue dye injection, gamma probe detection of radioisotope associated with SLNB and treatment of adverse events associated with anaphylaxis.
Theatre time lost to supply disruption and/or shortage of Nuclear Medicine staff	20% of procedures delayed by average of 30 minutes	This was only declared by a single NHS hospital in the economic model spreadsheet.	The Company has incorporated this into the cost analysis as 20% of 250 annual procedures (per hospital) are delayed by 30 minutes. The total length of time (*i.e.* 25 hours) is equivalent to 33 SLNB procedures (assuming 45 minutes per procedure). The

Variable	Company value	Source	EAC comment
			Company has assumed that this will be realised in 50% of cases (*i.e.* opportunity cost of 16 SLNB procedures is added to the per-procedure cost in the dual technique arm). The EAC considers that delay to theatre may not occur across all hospitals. Clinical experts from Nuclear Medicine have confirmed that national supply chain issues have been rare, and have not resulted in delay of SLNB as patients would be given priority. Clinical experts also advised that 20-50% of patients would have radioisotope injection the day before SLNB procedure, which would include patients on the morning surgery list, and therefore would not incur delay (EAC Correspondence Log, 2022). Clinical experts also advised that delays to surgery due to lack of radioisotope are rare. If isotope was unavailable the surgical team may proceed with blue dye alone, or random 4 node sample (unlikely that surgery would be cancelled) (EAC Correspondence Log, 2022). The EAC notes that this is not standard of care. The EAC notes that the Company has not considered that intraoperative subareolar injection of Magtrace may add 20 minutes to total theatre time (in line with device IFU to give the tracer time to drain to the axilla, IFU also states that peritumoural injection may require a longer wait). The EAC would recommend removing this opportunity cost.
Theatre time lost because of time required for Tc-99m injection on the day of surgery	1 additional procedure each week (realised in 50% of cases)	The Company confirmed that this value was derived from communication with 3 NHS hospitals, assuming theatre lists for SLNB unable to start until	Delay to theatre due to radioisotope may differ between NHS Hospitals with and without access to on-site Nuclear Medicine. Additionally the EAC notes that from the Clinical evidence that many SLNB procedures can be combined with mastectomy and breast conserving surgeries in breast cancer patients. Therefore, it

Variable	Company value	Source	EAC comment
		10:30am, with injection of radioisotope occurring at 9:00am. Resulting in 1.5 hours per session, however if 50% was realised then 45 minutes (equivalent to 1 extra SLNB) could be added each week (assuming one theatre session each week).	is unlikely that time associated with radioisotope injection could result in additional theatre slots (as this will depend on the patient and surgery type mix). Two experts (both from hospitals with on-site Nuclear Medicine) stated their access to radioisotope was not a rate limit factor. One expert stated that use of Magtrace could provide flexibility in theatre scheduling, however that the number of patients per theatre session was determined by theatre availability and the other concomitant breast surgery procedures undertaken alongside SLNB. One Clinical expert was unsure if Magtrace would facilitate more SLNB procedures (EAC Correspondence Log, 2022). The EAC considers that an opportunity cost is possible with Magtrace with regards to an additional surgery possible on a morning SLNB theatre list. Clincial experts have advised that Nuclear Medicine departments do not inject radioisotope at weekends, which may cause delays on a Monday; or following a bank holiday. Use of Magtrace (for example, injected the Friday before) would enable sufficient drainage to the axilla, and may also give enough time to promote brown staining to assist with visual detection. However, the EAC would consider this opportunity cost may not be realised in all hospitals; as with effective theatre scheduling the morning theatre list may include other procedures. However, realisation of this opportunity cost could be considered in sensitivity analysis.
Abbreviations: EAC, external assessment centre; HRG, healthcare resource groups; NHS, National Health Service; SLNB, sentinel lymph node biopsy; Tc-99m, Technetium 99-m radioisotope;;			

Sensitivity analysis

The Company described univariate sensitivity analysis within the Economic Submission across a number of parameters:

- decreasing the number of vials of radioisotope used per theatre list;
- radioisotope vial cost greater or less than 50%;
- reducing the number of staff required to inject radioisotope;
- Nuclear Medicine staff time to inject radioisotope greater or less than 20 minutes;
- nurse time to inject Magtrace greater or less than 10 minutes;
- value of theatre time cost at £1,200 per hour;
- proportion of lost time realised 30%, 60%;
- earlier start time realised in 30%.

The Company states that the individual parameters were varied within a realistic range, however the range does not reflect the range of responses gained by the three NHS hospitals they consulted (listed in the Excel spreadsheet of their cost-minimisation analysis). The EAC considers that the sensitivity analysis applied in the Company analysis were not applied consistently across the intervention and comparator arms, and did not address the main areas of uncertainty (for example, variation in patient pathway, differences between hospitals with and without on-site Nuclear Medicine department, adverse events).

9.3 *Results from the economic modelling*

Base case results

In the Company's base case, the use of Magtrace and Sentimag was £240 per procedure, compared with £345 per procedure using dual technique (radioisotope and blue dye), resulting in an overall cost-saving per procedure of £105, Table 14. Cost savings were driven by opportunity costs, particularly

those associated with the ability to conduct additional surgeries in the Magtrace arm.

Table 14: Summary of base case results

	Company estimate, per procedure*		
	Magtrace and Sentimag	Dual technique (Tc-9m and blue dye)	Incremental cost (Magtrace and Sentimag minus dual technique) †
Tracer acquisition costs	£226	£70	£156
Tracer administration costs	£14	£73	-£59
Theatre time lost due to supply or staff shortage	£0	£81	-£81
Theatre time lost due to Tc-99m injection on day of surgery	£0	£121	-£121
Total (per patient)	**£240**	**£345**	**-£105**
* Taken from Table 5 of Company's Economic Submission. † Negative values (shaded green) indicate a cost saving.			

Sensitivity analysis results

In the Company's univariate deterministic sensitivity analysis, all showed Magtrace and Sentimag to be cost-saving when compared with dual technique, Table 15.

Table 15: Results of Company's univariate deterministic sensitivity analysis

			Cost per procedure*		
Parameter	Basecase	Value used in sensitivity analysis	Magtrace and Sentimag	Dual technique (Tc-9m and blue dye)	Incremental cost (Magtrace and Sentimag minus dual technique) †
Basecase	**-**	**-**	**£240**	**£345**	**-£105**
No. of radioisotope vials per week	2	1	£240	£325	-£85
Cost per radioisotope vial	£225	£113	£240	£322	-£82
		£338	£240	£367	-£127
No. of nuclear medicine staff required per injection	2	1	£240	£308	-£68
	40	60	£240	£381	-£142

Nuclear medicine staff time per radioisotope injection, min		20	£240	£308	-£68
Nurse time per Magtrace injection, min	20	30	£247	£345	-£98
		10	£233	£345	-£112
Value of theatre time	£1,208 per SLNB procedure	£1,200 per hour	£240	£324	-£84
Lost time realised	50%	30%	£240	£312	-£73
		60%	£240	£361	-£121
Earlier start time realised	50%	30%	£240	£296	-£57
*Taken from Table 6 of Company's Economic Submission † Negative values (shaded green) indicate a cost saving.					

Additional analysis

The EAC was able to replicate the Company's base case. The EAC conducted a number of univariate changes to the Company economic analysis to determine the impact on procedure costs, Table 16.

Table 16: EAC univariate changes to the Company economic analysis

			Cost per procedure*		
Parameter	Basecase	Value used in sensitivity analysis	Magtrace and Sentimag	Dual technique (Tc-9m and blue dye)	Incremental cost (Magtrace and Sentimag minus dual technique) †
Basecase	**-**	**-**	**£240**	**£345**	**-£105**
Removing opportunity cost associated with theatre time lost due to supply or staff shortage [SA calculations!M8=0]	£80.53	£0.00	**£240**	**£264**	**-£24.47**
Removing opportunity cost associated with theatre time lost due to Tc-99m injection on day of surgery [SA calculations!M21=0]	£120.80	£0.00	**£240**	**£224**	**+£16**
Adding 20 minutes theatre time to SentiMag arm when injected intraoperatively (based on direct theatre cost per hour from Public Health Scotland 2019/20 for General surgery RX142X:	£0.00	£357.33	**£597**	**£345**	**+£252**

£1,072 which would include staff time)					
† Negative values (shaded green) indicate a cost saving.					

EAC base case

The EAC reformulated the Company's base case into a decision tree to define its own base case, Figure 10. The decision tree embodies the decision problem in a conventional form, and incorporates the Company's base case for a particular set of values of the model variables. The decision tree structure also enables probabilisitic sensitivity analysis.

Model structure

Intervention (Magtrace and Sentimag) and comparator (dual tracer technique) remain in line with final scope. However, to represent the current care pathway across the NHS, the EAC considers three arms in the decision to represent the different timing and setting of the tracer injections:

- Magtrace injected intraoperatively (20 minutes before SLNB following administration of anaesthesia);
- Magtrace injected at a separate clinic (up to 30 days before SLNB);
- radioisotope injected at separate clinic (up to 1 day before SLNB, or 1 hour before). Note that due to anaphylaxis risk, blue dye is usually injected after induction of anaesthesia for SLNB procedure and therefore would be included within the Health Resource Grouping (HRG) cost for the procedure.

All patients in the comparator arm incur separate Nuclear Medicine clinic appointment for Tc-99m injection. Note that the timing of injection (including day before, at a different hospital or a few hours prior to the SLNB procedure) all incur same cost based on the unbundled HRG code (RN19Z). Two Clinical experts confirmed that patients would not have Tc-99m injected during the SLNB theatre session (EAC Correspondence Log, 2022).

All patients in the intervention arm (Magtrace and Sentimag) arm incur £226 per injection as sourced from the Company, with additional costs associated with staff time depending on the location of the injection. Patients injected at a routine prior appointment only incur cost of staff time (20 minutes of a Band 5 nurse) which will include time for an informed consent process and delivering the injection. Patients injected intraoperatively incur the theatre costs (which includes staff time) plus an additional 20 minutes of general surgery theatre time. A minimum of 20 minutes is required following Magtrace administration to allow lymphatic drainage before attempting transcutaneous measurement of the axilla (in line with the Magtrace IFU), with the published evidence confirming the SLNB did not start until at least 20 minutes had elapsed following Magtrace administration when used intraoperatively (Karakatsanis *et al.* 2016; Alvarado *et al.* 2019; Ghilli *et al.* 2017; Thill *et al.* 2014). The EAC assumes that the 20 additional minutes will include 5 minutes of breast massage to promote drainage to the axilla. The EAC assumes that intraoperative injection of blue dye (which occurs after induction of anaesthesia) also requires five minutes of breast massage to promote drainage to the axilla prior to SLNB procedure. The EAC assumes no delay to surgery for drainage to axilla related to the radioisotope as it is injected the day prior or at an appointment several hours before the SLNB theatre session. The cost of the Sentimag probe and reusable tools are not included, as confirmed by the Company that these would be provided free of charge to centres committing to a minimum annual contract of 100 to 120 vials of Magtrace tracer.

All patients across all arms incur cost associated with the SLNB procedure, represented by an HRG code. The cost associated with this HRG will include blue dye injection (which occurs after anaesthesia induction), gamma probe detection and costs associated with anaphylaxis. The EAC micro-costed blue dye injection and costs of anaphylaxis care, and removed these costs from the HRG at the appropriate branches of the decision tree (see Figure 10). This approach enabled the EAC to more accurately cost the complete patient pathway for SLNB. The EAC assumed that costs associated with gamma probe detection of the radioisotope during surgery are negligible, due to use

of the device across a number of procedures and patient groups (not specific to SLNB or breast cancer).

The EAC did not identify any published events of anaphylaxis associated with Magtrace. Therefore, the model will assume that anaphylaxis only occurs in the comparator arm (associated with blue dye). The proportion of patients experiencing severe anaphylaxis was derived from meta-analysis (Perenyei *et al.* 2021) including papers conducted exclusively in patients with breast cancer undergoing SLNB. The EAC assumed that severe anaphylaxis will result in a critical care admission, which is supported by opinion from Clinical experts (EAC Correspondence Log, 2022).

The EAC assumed that injection of blue dye is included in the total HRG cost for the SLNB procedure. Therefore, blue dye costs were removed from the SLNB cost in the Magtrace and Sentimag arms. The EAC has included only the technology costs associated with blue dye, at £25 per injection, in line with Company submission. The EAC also assumes that blue dye incurs 5 minutes staff time to conduct the injection and conduct breast massage before the SLNB procedure can begin.

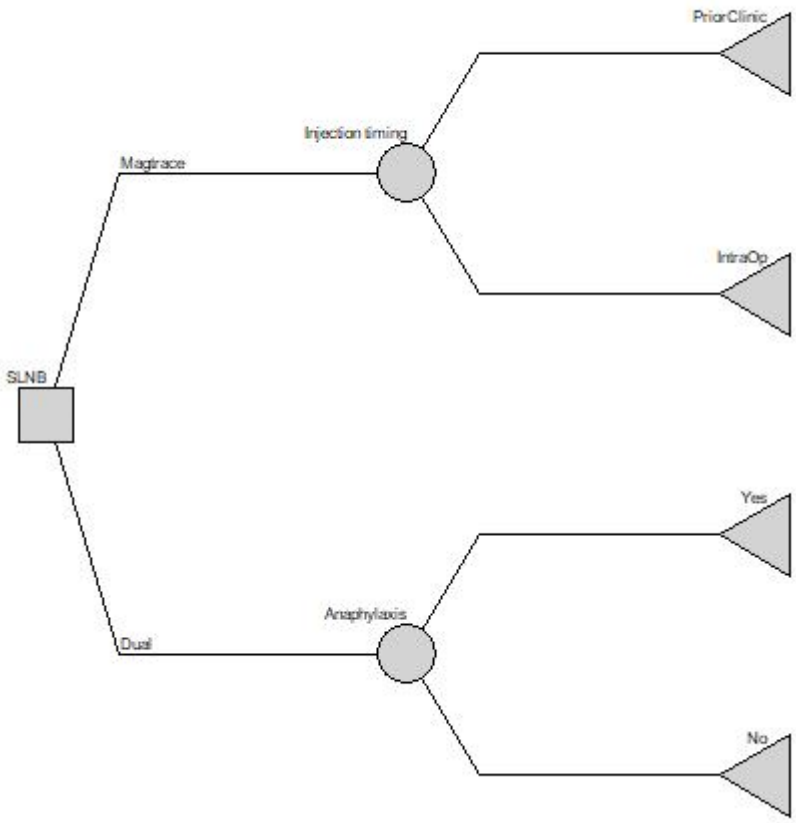
The EAC has not included opportunity costs associated with lack of availability of radioisotope. Clinical experts from hospitals with on-site Nuclear Medicine have advised that this was not an issue as SLNB patients would be given priority (EAC Correspondence Log, 2022). Clinical experts from hospitals without on-site Nuclear Medicine have advised that SLNB procedures would still go ahead using blue dye only or four-node axillary sampling, although a small proportion may have their procedure rescheduled (EAC Correspondence Log, 2022).

Clinical experts report delays to surgery due to lack of radioisotope are rare, and if unavailable the surgical team may proceed with blue dye alone or random four node sample. In addition to this, Clinical experts noted that 20 to 50% of patients receive radioisotope injection the day before SLNB procedure, which would include patients on the morning surgery list and would not incur delay (EAC Correspondence Log, 2022). The EAC has

included opportunity costs associated with one additional SLNB procedure being added to a morning theatre list, when using Magtrace. This is a direct consequence of lack of Nuclear Medicine availability at weekends and bank holidays, and the radioisotope can only be injected on the day of surgery due to half life of Tc-99m. The base case will consider one additional SLNB procedure each week, assuming 400 procedures conducted annually at each hospital; which represents the mid-point of annual estimates from the Clinical experts; 200 to 600 (EAC Correspondence Log, 2022). The EAC considers that additional SLNB surgeries may not be possible across all hospitals, and therefore has assumed that opportunity costs are achieved in 50% of hospitals, in line with the assumption made by the Company. However, the EAC will include the number of additional procedures and the proportion of hospitals realising this opportunity cost within sensitivity analysis due to the large uncertainty in both.

The EAC acknowledges that patient costs (associated with travel, waiting time) may be different between hospitals with and without on-site Nuclear Medicine facilities. The EAC contacted the Administration of Radioactive Substances Advisory Committee (ARSAC) to determine the proportion of NHS hospitals with access to on-site Nuclear Medicine. ARSAC advised that there are currently 163 licenced NHS sites in England, however as ARSAC were unable to share the names of these sites, the EAC is unable to determine the proportion of NHS hospitals conducting breast surgery who also have on-site Nuclear Medicine facilities. However, the cost of the radioisotope injection is incorporated in the economic model as an HRG code, and the cost associated is unaffected if injected the day prior to or few hours before the SLNB procedure. Therefore, the EAC considers that the costs to the NHS will not be different between hospitals with and without on-site Nuclear Medicine facilities. The EAC does acknowledge that patient travel and wait times may differ between hospitals with and without on-site Nuclear Medicine facilities, however these are not incorporated into the economic model.

Figure 10: EAC base-case represented by a decision tree



HRG SLNB (remove ITU care, blue dye) add 20 minutes staff time for Magtrace injection only

HRG SLNB (remove ITU care, blue dye) add 20 minutes to total theatre time

HRG Tc-99m, HRG SLNB

HRG Tc-99m, HRG SLNB (remove ITU care associated with anaphylaxis)

Model parameters (clinical and cost)

All model parameters used in the EAC base case are listed in Table 17.

Table 17: EAC base case model parameters

Parameter	Value	Source
Cost per SLNB procedure	£2,193.02	Using NHS Reference Costs 2019/20 and a weighted average of HRG codes JA43B and JA20F, which includes SLNB procedures conducted alone, or alongside mastectomy, lumpectomy, breast biopsy.
Cost of Tc-99m injection	£239.00	HRG: RN19Z Sentinel Lymph Node Scan (NHS Reference Costs 2019/20, activity: 16,686), as advised by two Clinical experts.
Cost of blue dye (per vial)	£25.00	Same value as used by Company, verified by one clinical expert. The EAC assumed that blue dye contributes £25 to the total HRG cost for each SLNB procedure. This cost will be deducted from Magtrace branches.
Cost of Magtrace (per vial)	£226.00	Company. Assume one vial per patient.
Blue dye (time): drainage time to axilla (delay to surgery when injected in theatre)	5 minutes	Assumed by EAC to incorporate breast massage duration only.
Magtrace (time): drainage time to axilla (delay to surgery when injected in theatre)	20 minutes	Magtrace Instructions for Use recommend that for subareolar injections that surgeons wait at least 20 minutes before attempting measurement of axilla. IFU state that longer may be required for peritumoural injection.
Magtrace (time): duration of staff time for informed consent and injection in outpatient clinic setting	20 minutes	Same assumption as made in Company model, confirmed as appropriate by the Clinical experts.
Magtrace: cost staff per hour	£41.00	Band 5 hospital-based nurse (PSSRU 2019/20). Assume that Magtrace injected at prior routine clinic (irrespective of whether the day before or 30 days before) only adds additional staff time to an existing appointment.
Percentage of patients experiencing anaphylaxis due to blue dye	0.083% PSA: Beta (α=61, β=40,207)	Meta-analysis by Perenyei *et al.* (2021) which included 59 studies of patients exclusively with breast cancers (61 events in 40,268 patients). This is applied to the comparator arm only (associated with blue dye only).
Cost per critical care stay	£1,634.90	NHS Reference Costs 2019/20: HRG code for surgical adult patients (unspecified specialty) CX05Z “Adult Critical Care, 2 Organ Supported”. The EAC assumes that anaphylaxis contributes £1.36 to the total HRG cost for each SLNB procedure (such as 0.083% incurring £1,634.90). This cost will be removed from approximate branches

		(Magtrace and dual technique where no anaphylaxis is experienced).
Theatre costs per hour	£1,072.00	Public Health Scotland 2019/20 for General surgery RX142X (this includes staff time). For intraoperative Magtrace injection and in line with Magtrace IFU, waiting for 20 minutes after Magtrace injection before conducting SLNB procedure (to enable time for tracer to drain to axilla) would result in additional theatre costs of £357.33.
Percentage of patients experiencing delay due to unavailability of radioisotope	0%	EAC has excluded this opportunity cost.
Percentage of patients receiving Magtrace injection at prior routine appointment	50% PSA: Beta (α=200, β=200)	Assume patients injected at prior routine appointment only incur cost of staff time to inject the tracer. Patients injected intraoperatively incur additional theatre costs (per minute costs, which include room and staff time) for the same duration, 20 minutes. The majority of published clinical evidence uses intraoperative injection, however lack of generalisability to NHS. Two Clinical experts advised they started with intraoperative injection, but now inject at prior clinic having passed the learning curve.
Opportunity cost associated with additional surgeries	1 per week	One additional procedure each week, assuming surgery is conducted across 50 weeks of the year. Assume each hospital conducts 400 SLNB procedures each year (midpoint of estimates from Clinical experts, 200-600; EAC Correspondence Log, 2022). The opportunity cost will be attributed to the standard of care arm.
Percentage of hospitals realising opportunity costs	50% PSA: Beta (α=50, β=350)	Same percentage applied in Company model. EAC has applied PSA analysis on this variable.
Abbreviations: EAC, external assessment centre; HRG, Healthcare Resource Group; IFU, instructions for use; NHS, National Health Service; PSA, probabilistic sensitivity analysis; SLNB, sentinel lymph node biopsy; Tc-99m, Technetium-99m radioisotope;		

Results

The EAC model was used replicate the Company base case model, with the same results; Magtrace: £239.67, Dual: £344.67, with associated cost savings of £105 per procedure.

Results from the EAC base case are presented in Table 18, showing Magtrace and Sentmag costing £2,488.83 per procedure, dual technique costing £2,567.73, resulting in Magtrace and Sentimag being cost-saving of £78.90 per patient (cost-savings representing 3% of the total cost of the SLNB procedure).

Table 18: EAC base case

	Intervention (Magtrace & Sentimag)	Comparator (dual technique)	Cost difference (Intervention-Comparator)
Cost of tracer (incl. staff time for injection)	£411.50	£239.00	**+£172.50**
Cost associated with SLNB	£2077.33	£2191.66	**-£114.33**
Opportunity cost (associated with being able to conduct one additional SLNB procedure per week)	£0	£137.06	**-£137.06**
Total	**£2488.83**	**£2567.73**	**-£78.90**

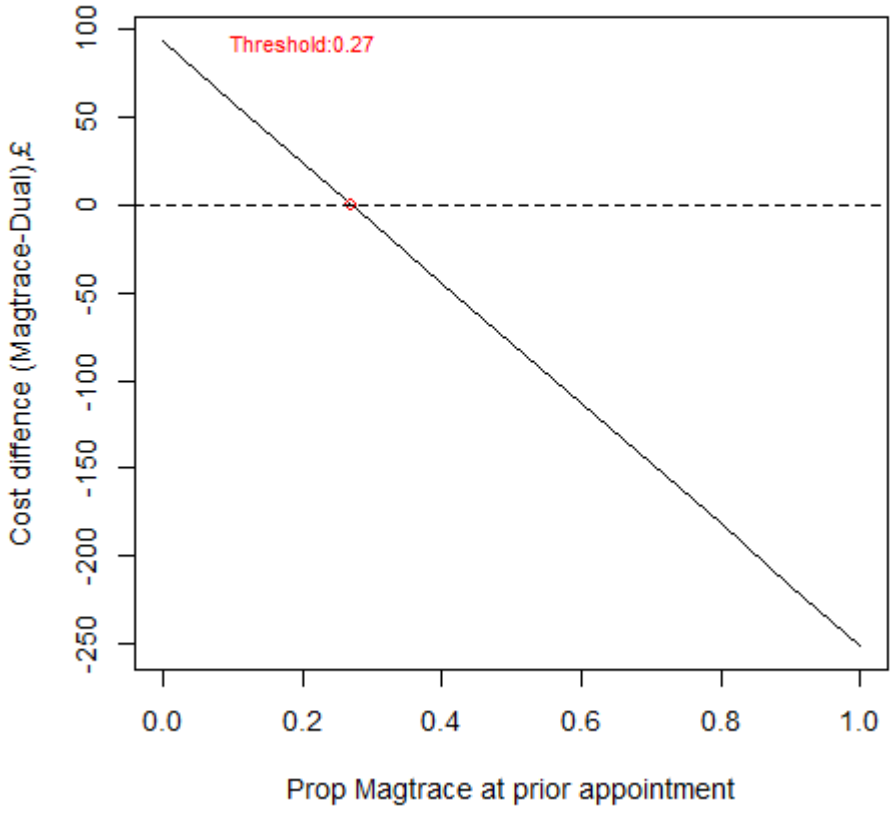
Sensitivity analysis

Due to lack of national audit data (with numerator and denominator) the EAC conducted various univariate sensitivity across parameters and scenario analysis, informed from the feedback of Clinical experts.

The EAC conducted univariate analysis to determine the impact of the proportion of Magtrace injections conducted at a prior appointment on total costs, Figure 11. The higher the proportion conducted at a prior appointment the larger the cost-saving associated with Magtrace; the threshold at which Magtrace becomes cost-saving is 0.27 (base case was 0.50). The EAC notes

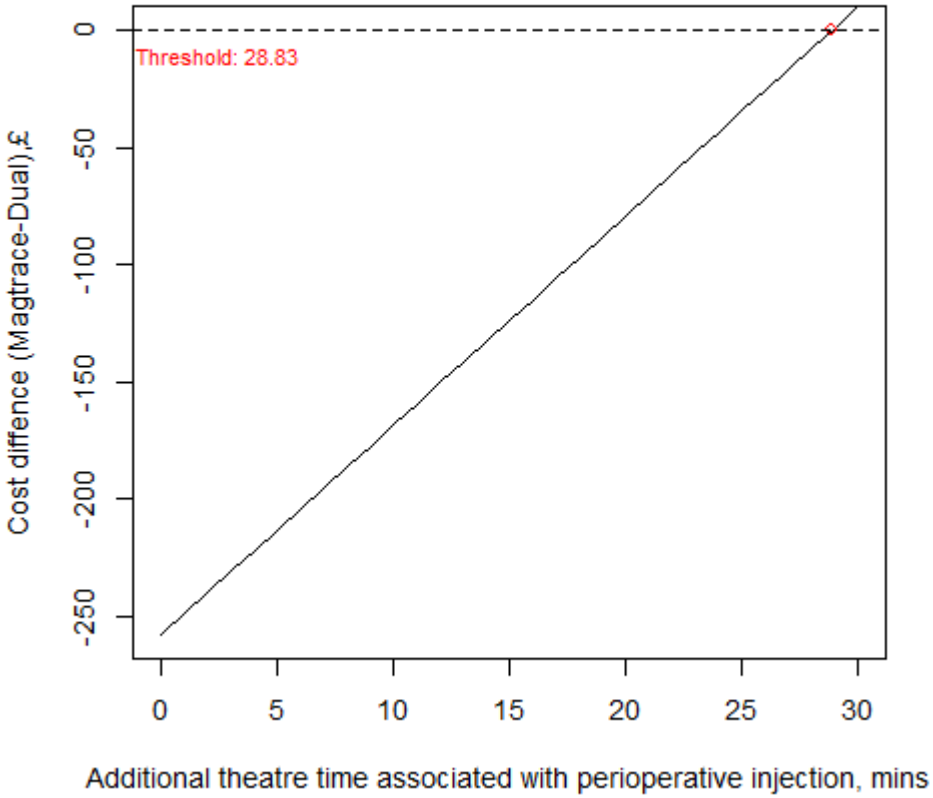
that the Clinical experts advised that Magtrace injections were initially all injected intraoperatively (in theatre, immediately before SLNB), however after getting over the learning curve (correct depth to reduce skin staining, ability to do without local anaesthesia) that injections occur at a prior routine clinical appointment (EAC Correspondence Log, 2022). The Clinical experts also noted that a longer interval between Magtrace injection and detection with the Sentimag probe may be beneficial as the Magtrace is brown in colouration and gives the surgeon a visual, as well as magnetic indicator, from earlier injection to the procedure; therefore injection at prior appointment has clinical benefit (EAC Correspondence Log, 2022). The EAC notes that from the IFU the indicated use of Magtrace suggest prior injection can occur *up to* 30 days before procedure.

Figure 11: Univariate analysis on EAC base case: change in proportion of Magtrace injections conducted at prior routine appointment.



The model was sensitive to changes in total theatre time in the Magtrace arm (due to delay associated with intraoperative subareolar injection of Magtrace to permit drainage to axilla in line with device IFU). A reduction in additional theatre time resulting in an increased cost saving for Magtrace, Figure 12. From threshold analysis, the additional theatre time waiting for drainage to axilla using Magtrace would need to exceed 29 minutes before it was considered cost-incurring (base case: 20 minutes).

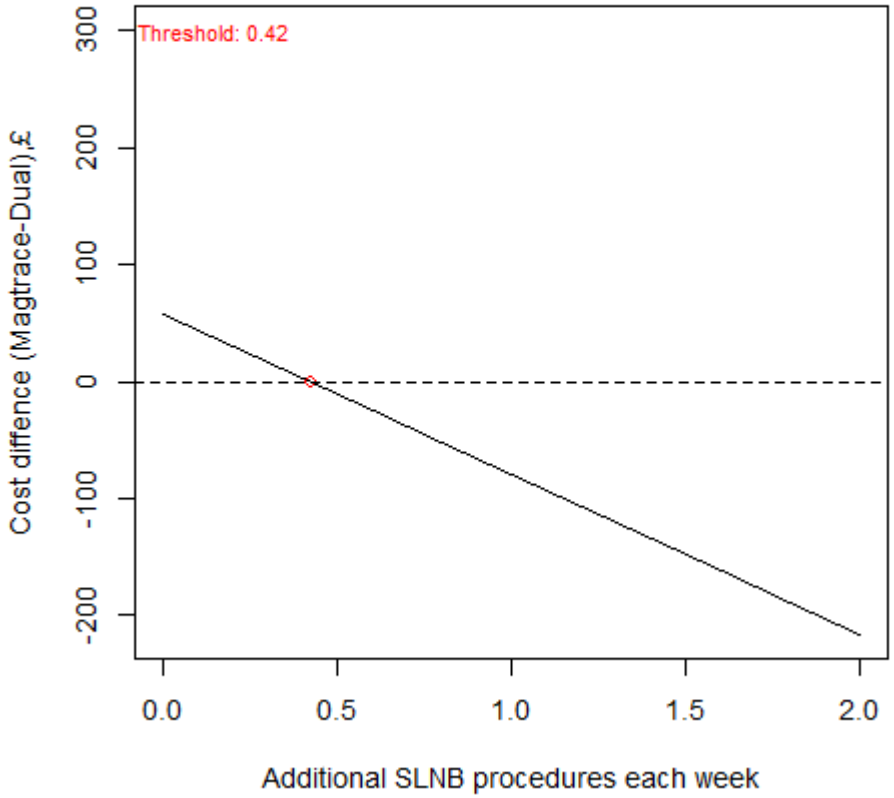
Figure 12: Univariate analysis on EAC base case: Additional theatre time associated with periopereative injection of Magtrace



The model was also sensitive to changes in the number of additional SLNB procedures conducted each week, for example a procedure that could be added to a morning theatre list (as a result of lack of Nuclear Medicine facilities at weekends and bank holidays) as an opportunity cost. The threshold at which Magtrace became cost-incurring was 0.42 additional

procedures per week (base case: 1 procedure), Figure 13. The EAC notes that if a hospital was unable to realise any additional procedures in a week (thus removing this opportunity cost) that Magtrace would be cost-incurring by £58.17 per procedure.

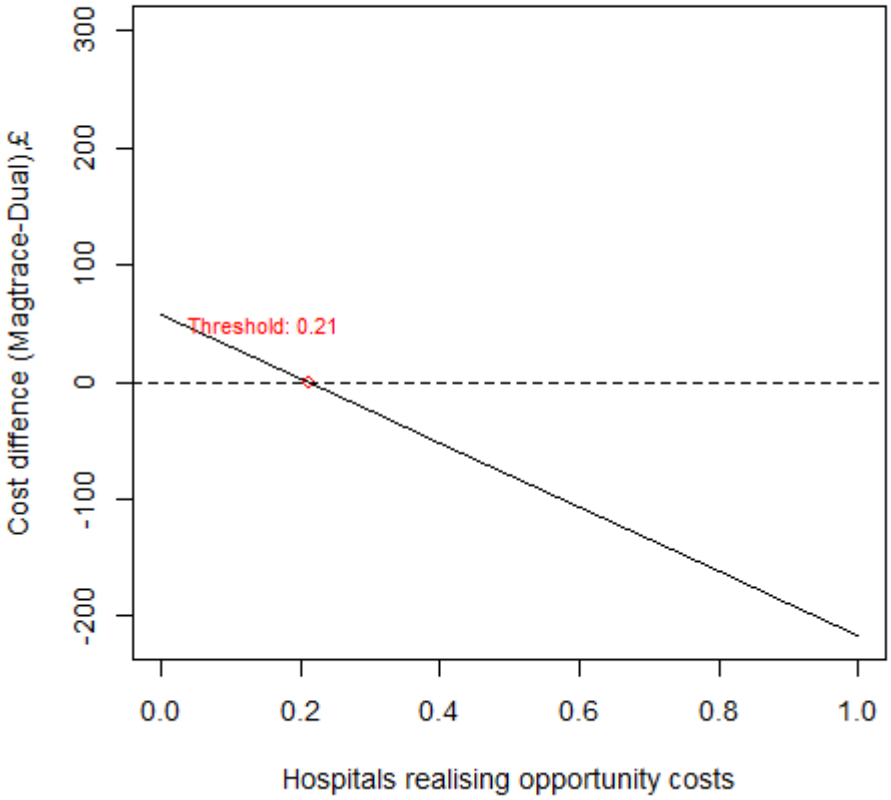
Figure 13: Univariate analysis on EAC base case: Additional SLNB procedures added to theatre list each week, added as opportunity cost in comparator (dual technique) arm only.



An alternative approach is to vary the proportion of centres that will realise the opportunity costs associated with ability to conduct one additional SLNB procedure each week. In the base case (50% of hospitals achieving 1 additional SLNB procedure with Magtrace) was cost-saving by £78.90 per procedure. This represents a 6.25% non-attendance rate (50 additional procedures a year, realised in 50% of centres conducting 400 SLNB procedures each year). However, the model is sensitive to changes in the proportion realising this opportunity cost, Figure 14. The threshold at which

Magtrace become cost-incurring is if 21% of hospitals can conduct 1 additional SLNB additional procedure. The EAC notes that if no centre was able to realise the opportunity cost associated with one additional SLNB procedure per week, that Magtrace would become cost-incurring by £58.17 per procedure.

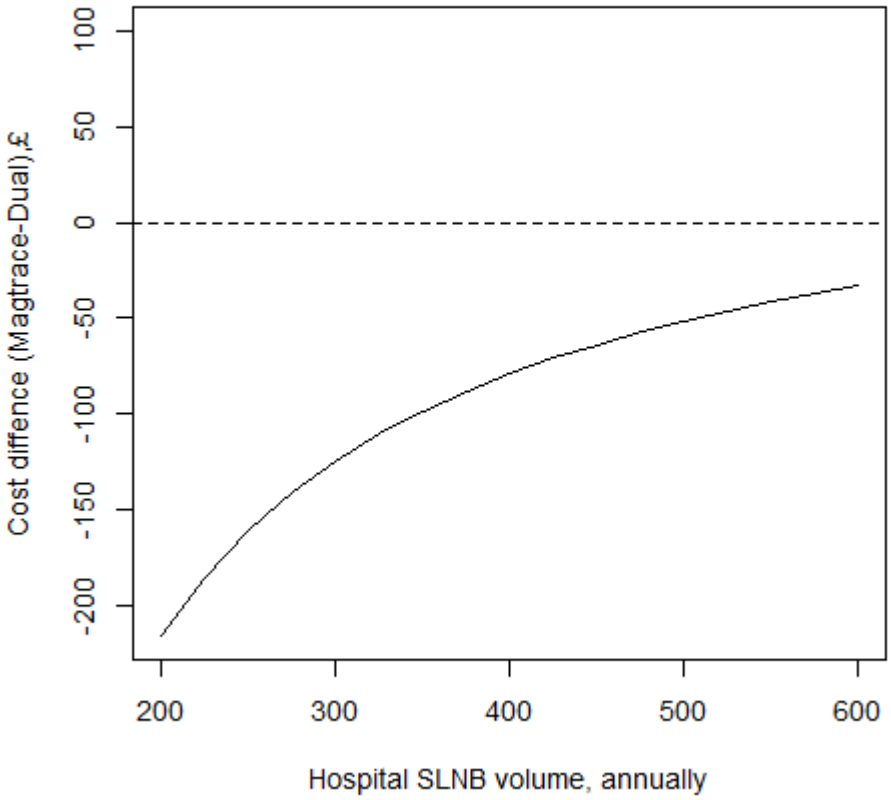
Figure 14: Univariate analysis on EAC base case: Proportion of hospitals realising opportunity costs associated with one additional SLNB procedure each week



The model is also sensitive to the hospital volume of SLNB procedures conducted annually, Figure 15. Whilst the base case included the mid-point estimate from the Clinical experts (400 SLNB annually), lower volume centres may achieve larger cost-savings with Magtrace (200 SLNB per year: cost saving £215.96 per patient), whereas higher volume centres may achieve

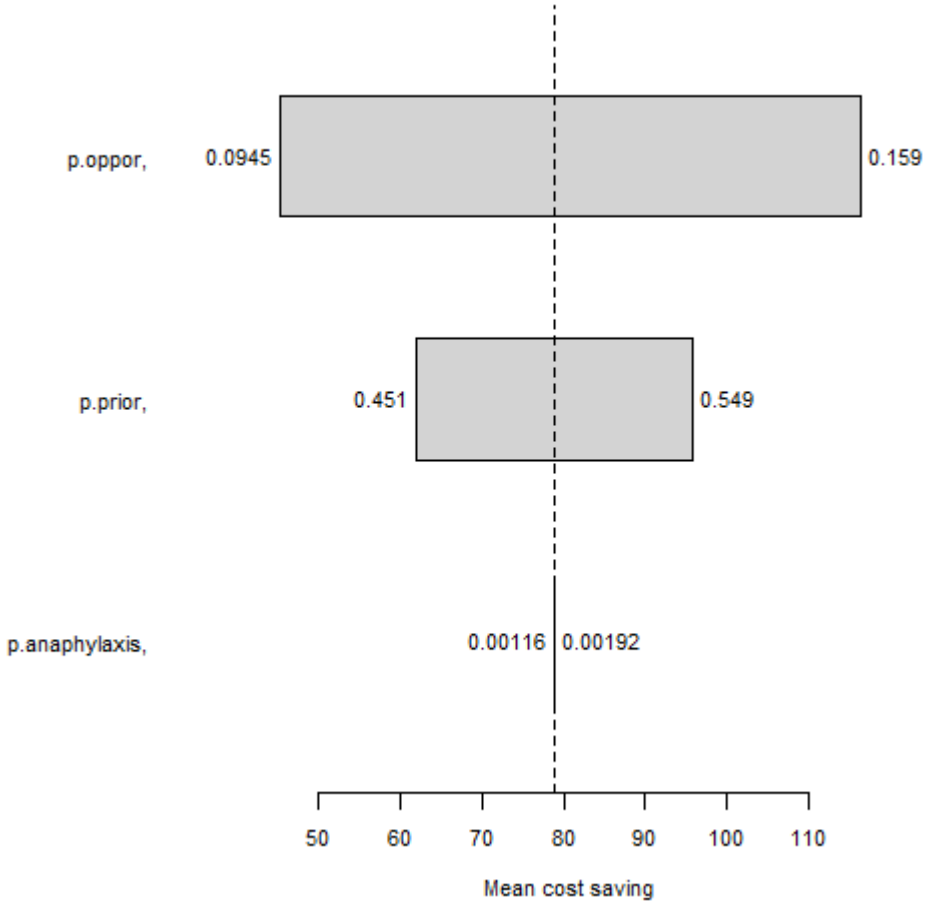
smaller cost-savings with Magtrace (600 SLNB per year: cost-saving £33.21 per patient), assuming 1 session per week is wasted in each case.

Figure 15: Univariate analysis on EAC base case: annual SLNB centre volume



The EAC illustrated the multiple univariate sensitivity analysis of three parameters (probability of centres realising opportunity costs associated with gaining one additional SLNB per week, proportion of SLNB procedures where Magtrace was injected at a prior clinic, and probability of anaphylaxis due to blue dye) in tornado diagram is shown in Figure 16. Each parameter was varied over their corresponding 95% confidence interval, with the rest of the variables set to their point estimates due to a lack of robust published data.

Figure 16: Tornado diagram



The mean cost difference from probabilistic sensitivity analysis (varying three parameters as above) between Magtrace and dual technique was -£79.41 (95% CI -£117.88 to -£43.89) per patient, with 100% simulations being cost-saving.

Scenario analysis:
A range of scenario analysis was conducted, Table 19.

Due to the sensitivity of the model to additional minutes of theatre time, the EAC modelled a scenario where Magtrace was instead injected at a prior non-routine outpatient clinical oncology appointment (thus incurring an additional appointment cost of NHS Reference costs 2019/20, consultant-led: £151, without occurring 20 minute delay in theatre associated with awaiting drainage to axilla). In this scenario, cost savings associated with Magtrace increased to £182.07 per procedure: Magtrace: £2,385.66, Dual: £2,567.73.

Additional scenarios were modelled to account for patients contraindicated to Magtrace that would require standard of care (dual tracer). When assuming 0.5% contraindicated (Clinical experts stated that this is a rare event), Magtrace remains cost-saving by £78.50 per procedure. The EAC notes that if the proportion of patients contraindicated to Magtrace increased (from 0.5% to 1.0%) then Magtrace remains cost-saving at £78.11 per procedure; low impact due to rarity of contraindication.

Published clinical evidence (Chapman *et al.* 2020; Forte *et al.* 2019; Krischer *et al.* 2017; Aribal *et al.* 2021; Huizing *et al.* 2015; Shrotria *et al.* 2020) and Magtrace IFU suggest that patients injected with Magtrace can present with artefacts in future MRI. Timing of MRI following Magtrace injection varied from 3 to 63 months across the literature with some patients undergoing multiple MRIs. The Clinical experts advise that a small proportion of breast cancer patients require MRI after breast surgery as part of their routine surveillance conducted alongside mammography. Two Clinical experts advised that this would include patients aged less than 30 to 40 years, and those with mammography occult cancers (EAC Correspondence Log, 2022). Two Clinical experts stated that the need for post-surgery MRI should be considered prior to injecting Magtrace and another expert noted the increasing number of MRI for surveillance from one year post-operatively.

The Company have confirmed that the amount of Magtrace residue will depend on a number of factors including physiology of the patients (age, BMI), quality of post-injection massage, time lapsed before SLNB is commenenced, number of nodes removed, and extent of surgical tumour removal (EAC Correspondence Log, 2022). Due to this, the EAC had developed an additional scenario analysis, which will assume a proportion of all patients require additional diagnostic imaging during routine follow-up, across intervention and comparator arms, as advised by Clinical experts (EAC Correspondence Log, 2022). In the standard of care arm we assume that this proportion of patients all undergo standard MRI (unbundled HRG outpatients: RD01A “Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over”, £143.72). In the intervention arm would assume that the

same proportion of patients undergo standard MRI, but that a small proportion are uninterpretable and thus will require an additional Gadolinium enhanced MRI instead (unbundled HRG outpatients: RD02A “Magnetic Resonance Imaging Scan of One Area, with post-contrast only, 19 years and over”, £144.29). The Company also advised that patients undergoing Magtrace injection may require further imaging with contrast-enhanced spectral mammography (CESM). Four Clinical experts stated that CESM imaging would be appropriate in this patient group, however as this is a relatively new diagnostic imaging technique it does not have an associated HRG code and therefore is omitted from the EAC scenario analysis.

It is not possible to establish the proportion of uninterpretable MRI due to Magtrace from the existing published literature, due to the lack of denominator, variability in follow-up duration and inconsistent reporting of the diagnostic impact of Magtrace artefact on MRI. However, the additional contrast enhanced MRI in the Magtrace arm has little impact on total costs due to this being applicable to a small proportion (5% uninterpretable of 1% requiring future MRI). However, this analysis does not take into account clinical outcomes associated with potential missed diagnoses of cancer recurrence due to masking on MRI.

Table 19: Summary of scenario analysis conducted on EAC base case.

Scenario	Magtrace & SentiMag	Radioisotope & Blue dye	Cost difference (%)
Base case	£2488.83	£2567.73	-£78.90 (3.1%)
Magtrace not injected in theatre, injected at additional outpatient appointment	£2385.66	£2567.73	-£182.07 (7.1%)
0.5% patients contraindicated to Magtrace and require dual technique	£2489.22	£2567.73	-£78.50 (3.1%)
1.0% patients contraindicated to Magtrace and require dual technique	£2489.62	£2567.73	-£78.11 (3.0%)
Assume 1% of patients in both arms require future MRI, and that 5% of those in Magtrace arm are uninterpretable and require contrast enhanced MRI	£2490.34	£2569.16	-£78.82 (3.1%)
Abbreviations: MRI, magnetic resonance imaging			

Limitations of EAC economic model

The EAC acknowledges a number of limitations in the economic modelling:

- The lack of available data has limited the variables subject to deterministic and probabilistic sensitivity analysis.
- Removal of opportunity costs (associated with the ability to conduct additional SLNB procedures when using Magtrace) results in Magtrace becoming cost-incurring in both the Company and EAC basecase models.
- The costs associated with radioisotope injection at a prior clinic appointment, represented by the unbundled HRG code RN19Z, do not include Nuclear Medicine infrastructure costs associated with quality checks, documentation, waste management or training. However, in hospitals with Nuclear Medicine facilities it is difficult to attribute these costs solely to SLNB procedures. However, the EAC acknowledges that due to the exclusion of costs for these additional activities associated with radioisotope management that the cost savings with Magtrace reported in the EAC basecase may represent a lower estimate.
- The number of SLNB procedures including random four node sampling (due to lack of availablility of tracer, or lack of detection), was not incorporated into the model as no published comparative evidence (comparing Magtrace with dual technique) reported on this outcome.
- The EAC did not include comparison of Magtrace with blue dye alone as this does not represent standard of care in the NHS, and is known to have inferior detection when compared with radioisotope alone.
- Injection of Magtrace at a prior appointment may require cost of local anaesthesia. However, this was not incorporated into the model as there was no data to inform the proportion of Magtrace injections where this was necessary. Additionally, there was uncertainty whether local

anaesthesia would be required in all cases if centres had established an injection technique (likely after the learning curve) which reduced staining and pain.

9.4 *The EAC's interpretation of the economic evidence*

Three clinical studies incorporated reporting of costs within their publications; none were conducted in a UK NHS setting. One conducted in New Zealand reported Magtrace to be cost-saving (by $860 per procedure) when incorporating patient car travel and hotel exepsnses, one conducted in Sweden reported Magtrace to be cost-saving (€27 per person), one reported no difference in German hospital reimbursement between Magtrace and standard care.

The Company's cost minimisation model, estimated that use of Magtrace would lead to a cost-saving of £105 per patient (£240 with Magtrace, £345 with dual tracer technique). The Company model was applicable to the decision problem, however it did not include adverse event costs associated with the comparator (anaphylaxis with blue dye). The EAC considered that two important assumptions in the Company's model were subject to uncertainty. Firstly, the Company assumed that the comparator included a cost associated with delays to radioisotope availability due to supply issues or staff shortages (calculated as a cost of £81 per procedure). Secondly, that the comparator included a cost due to delays to surgery associated with patients having a radioisotope injection on the day of the procedure (£121 per procedure). The Company calculated these values by assuming the time wasted using radioisotopes woud be translated into additional SLNB procedures if Magtrace was used instead. The EAC considers it uncertain whether these opportunity cost savings would be realised in practice in the NHS. The EAC base case found Magtrace to be cost-saving by £78.90 per patient, which represents 3% of the cost of the procedure (Dual: £2,568), however the model was sensitive to changes in additional theatre time, location of Magtrace injection, the proportion of hospitals realising opportunity costs, and the number of additional SLNB that may be realised on a weekly basis when implementing Magtrace over standard of care. Use of Magtrace was more cost-saving if injected at a prior routine clinic, or prior additional clinic appointment, than if injected in theatre. The Clinical experts confirmed additional clinical benefit of earlier Magtrace injection was the brown-black visual indicator alongside magnetic detection. However, the EAC notes from

the Clinical expert with experience of using Magtrace, that NHS hospitals may only move to Magtrace injection at a prior clinic when passing the learning curve (to determine depth and location of injection to reduce skin staining and pain). The EAC identified that high volume centres may achieve lower cost savings, when implementing Magtrace, than lower volume centres (with lower volume centres being highly influenced by the proportionate increase in opportuntity costs associated with one extra procedure per week). Neither the Company nor the EAC model accounted for costs associated with patient travel, waiting times, or theatre rescheduling. The cost implication associated with a small proportion of patients requiring contrast enhanced imaging, due to potential of Magtrace to mask MRI or mammography during routine surveillance, is minimal. However, due to lack of long-term data, the clinical consequences of Magtrace producing artefact on, or precluding, future imaging are unclear.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The Company identified 31 papers, of which the EAC considered 10 out of scope. An independent search by the EAC identified an additional 15 papers. A total of 27 peer-reviewed publications and 9 available in abstract form only were included in the EAC assessment. Within the included evidence, 14 non-comparative studies were included for adverse events and patient reported outcomes only. The majority of evidence was set outside of the UK and NHS limiting generalisability to this setting. The EAC identified a high level of heterogeneity across the published evidence with differences in the population included (patients with invasive breast cancer and ductal carcinoma in situ, tumour grade and hormone receptor status, with a range of co-morbidities and different proportion of patients undergoing mastectomy or breast conserving surgery). The administration of Magtrace and radioisotope tracer also differed across studies with variations in injection-site, depth, timing, dosage, and imaging protocols used. The included evidence also represented variations in comparators with 5 papers comparing Magtrace with the dual technique, 11 using radioisoptope only and 6 using the dual technique and radioisotope alone without reporting outcomes exclusively.

The EAC identified evidence supporting the non-inferiority of Magtrace with Sentimag to the current dual tracer standard of care for detection of SLNs, including those that are malignant. There is a lack of robust comparative evidence to determine the impact of the use of Magtrace compared with the standard of care dual tracer on the SLNB procedure time. Meta-analysis performed by the EAC did not identify significant evidence to suggest that the number of nodes excised differs between methods. The EAC identified no published evidence that directly compares skin staining outcomes of Magtrace with blue dye.

There are no significant safety concerns relating to the technology. However, the EAC identified six published papers which reported artefacts on surveillance imaging in breast cancer patients following Magtrace injection for SLNB. The proportion of patients that this affects, and the impact of this on

patient and clinical care is not fully understood. Standard of care may be more appropriate for patients who are required or anticipated to undergo routine MRI following SLNB.

The risks associated with axillary lymph node dissection as well as the inferiority and safety risks of using blue dye as an independent tracer are well known. The EAC notes that particular consideration should be given to patients unsuitable for Magtrace and are under services no longer providing isotope-based tracer options; standard of care should continue to be provided where Magtrace is not appropriate or used.

10.2 *Conclusions from the economic evidence*

The Company developed a cost-minimisation analysis, which estimated that use of Magtrace would lead to a saving of £105 per procedure (Magtrace £240 versus dual technique £345). The EAC considered that the Company analysis was developed from the perspective of a hospital without on-site access to Nuclear Medicine only, did not consider adverse events in the comparator arm, and did not consider the costs associated with the procedure itself therefore did not cost the complete patient pathway. The EAC reformulated the Company economic model into a decision tree structure to permit additional sensitivity analysis. The EAC base case found Magtrace to be cost-saving by £78.90 per procedure; Magtrace £2,488.83, Dual technique £2,567.73; driven by the inclusion of opportunity costs associated with time delays associated with the comparator. Univariate threshold analysis conducted by the EAC highlighted that the economic case is sensitive to changes in parameters. If the proportion of SLNB procedures involving an injection of Magtrace at a prior clinic appointment is below 0.27 then Magtrace would be considered cost-incurring. Similarly, in centres conducting SLNB procedures, if the proportion realising the opportunity cost associated with gaining one extra procedure a week drops below 0.21, Magtrace would be considered cost-incurring. EAC modelling confirmed that high SLNB volume centres are likely to experience lower cost savings than low volume centres. Results from limited PSA, in which only three parameters were varied (probability of anaphylaxis, probability having Magtrace injection at prior appointment and probability of centres realising opportunity costs) confirmed

the cost saving at £79.51 [95%CI -£119.92 to -£41.02]. However, removal of opportunity costs (for example, in centres with efficient theatre scheduling) may result in Magtrace being cost-incurring when compared with standard of care.

11 Summary of the combined clinical and economic sections

The EAC has identified evidence to support the non-inferiority of Magtrace and Sentimag to the standard of care dual technique in the detection of SLNs including malignant nodes. The EAC identified a lack of robust comparative evidence to determine the impact of the use of Magtrace on the SLNB procedure time and patient quality of life, pain and staining outcomes compared to the dual technique. Meta-analysis conducted by the EAC found no evidence to suggest that the number of nodes excised differs between Magtrace and the dual technique. The EAC have not identified any immediate or short-term safety concerns relating to the use of Magtrace and Sentimag, although note that the long-term impact of the associated MRI artefact on clinical and patient care are currently not known. Economic modelling suggests that Magtrace could be cost-saving when considering the SLNB costs, however is sensitive to hospital setting, location of Magtrace injection and the ability of centres to realise opportunity costs associated with extra procedures each week. Magtrace and Sentimag may offer an alternative non-inferior tracer option in SLNB procedures, which may alleviate some logistical difficulties faced by healthcare providers and patients who cannot easily access Nuclear Medicine facilities. However, for centres with established Nuclear Medicine facilities or effective theatre scheduling, where opportunity costs associated with additional SLNB procedure may not be realised, implementing the new technology may not be cost-saving. Particular consideration should be given for patients who are contraindicated to Magtrace and those under the care of hospitals without access to radioisotope-based tracer options. Standard of care options should remain available due to the inferiority of blue dye as an independent tracer and associated safety risks.

12 Implications for research

Dual technique is currently considered standard of care in line with NICE Guidance NG101, however there is limited evidence exclusively reporting the use of Magtrace when compared with dual technique as a comparator, particularly in a UK NHS setting, limiting the generalisability of the results. There is a lack of comparative evidence evaluating the incidence and severity of skin staining (between Magtrace and blue dye), total SLNB procedure times and number of wasted SLNB theatre slots (between Magtrace and dual technique). These outcomes could be obtained from audit data, preferably in UK NHS setting.

There is a lack of longitudinal data investigating the impact of the administration of Magtrace on future imaging and diagnostics. The POSTMAG MRI study is currently underway at two Swedish sites investigating MRI outcomes up to five years following SLNB with Magtrace. The target sample size is relatively small (n=93) with no UK based sites. The impact of Magtrace on the quality of MR imaging in terms of the possible requirement for additional imaging in both clinical and economic outcomes is currently unknown.

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14 Appendices

Appendix A: Clinical literature search

Appendix A1: PRESS checklist for search strategy peer review

Question	Y/N	Notes
Translation of the research question		
Does the search strategy match the research question/PICO?	Query	The search terms used could be more precise for the population group. There may be additional terms for the technology also.
Are the search concepts clear?	Yes	
Are there too many or too few PICO elements included?	Okay	
Are the search concepts too narrow or too broad?	Query	It would be better to search for sentinel node biopsy separately to breast cancer and then combine them
Does the search retrieve too many or too few records? (Please show number of hits per line.)	Query	The search was not reported line by line. In the PRISMA diagram 264 results are retrieved altogether. 134 were excluded before screening due to duplication, being non-peer reviewed and non-English language which should leave **130** results. **133** were reported as being screened.
Are unconventional or complex strategies explained?	N/A	The search was very simple
Boolean and proximity operators (these vary based on search service)		
Are Boolean or proximity operators used correctly?	Query	They are not used incorrectly, but adjacency operators or phrase searching would be more appropriate for the population terms.
Is the use of nesting with brackets appropriate and effective for the search?	N/A	
If NOT is used, is this likely to result in any unintended exclusions?	N/A	
Could precision be improved by using proximity operators (eg,	Yes	Yes, adjacency or phrase searching should be used for “sentinel node

adjacent, near, within) or phrase searching instead of AND?		biopsy" or sentinel adj3 biopsy – it can be described as sentinel node biopsy, or sentinel lymph node biopsy.
Is the width of proximity operators suitable (eg, might adj5 pick up more variants than adj2)?	N/A	
Subject headings (database specific)		
Are the subject headings relevant?	N/A	Subject headings are not used, but should be
Are any relevant subject headings missing; for example, previous index terms?	Yes	Yes, all subject headings are missing
Are any subject headings too broad or too narrow?	N/A	
Are subject headings exploded where necessary and vice versa?	N/A	
Are major headings ("starring" or restrict to focus) used? If so, is there adequate justification?	N/A	
Are subheadings missing?	N/A	
Are subheadings attached to subject headings? (Floating subheadings may be preferred.)	N/A	
Are floating subheadings relevant and used appropriately?	N/A	
Are both subject headings and terms in free text (see the following) used for each concept?	No	Only free text is used
Text word searching (free text)		
Does the search include all spelling variants in free text (eg, UK vs. US spelling)?	Query	Check for US alternatives for superparamagnetic iron oxide
Does the search include all synonyms or antonyms (eg, opposites)?	Query	The terms for SLNB and breast cancer could be broadened, also ductal carcinoma in situ (DCIS) should be added. Additional terms for the Magtrace device may be available.
Does the search capture relevant truncation (ie, is truncation at the correct place)?	No	No truncation is used

Is the truncation too broad or too narrow?	N/A	
Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?	Yes	The acronym SPIO is appropriate and is an acronym for superparamagnetic iron oxide
Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?	Query	The use of the AND operator rather than proximity or phrase searching makes the population keywords too broad.
Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded (database specific)?	Query	The field TS is used, this is the topic field in Web of Science, no fields are shown for the PubMed search
Should any long strings be broken into several shorter search statements?	Yes	Breast cancer should be searched separately to SLNB
Spelling, syntax, and line numbers		
Are there any spelling errors?	No	
Are there any errors in system syntax; for example, the use of a truncation symbol from a different search interface?	No	
Are there incorrect line combinations or orphan lines (ie, lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?	No	
Limits and filters		
Are all limits and filters used appropriately and are they relevant given the research question?	Query	No limits were used in the search, but exclusions were made before screening based on language and peer review status which may have been filters applied to search results.
Are all limits and filters used appropriately and are they relevant for the database?	Query	The limits used as above are not specified for each database
Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too	No	No publication type filter is used, but the results are few, so it would not be necessary to use one

narrow? Can any limits or filters be added or taken away?		
Are sources cited for the filters used?	N/A	

Further comments:
This search is inadequate, both in terms of sources searched (PubMed and Web of Science only) and the search terms used. The search structure I would recommend is (sentinel lymph node biopsy) AND (breast cancer or DCIS) AND (MagTrace OR magnetic tracers). Adding proximity or phrase searching to the sentinel lymph node element may reduce the number of results, but is more appropriate. Searching a range of databases, e.g. Medline, Embase, Cochrane library (CENTRAL and CDSR), Cinahl, HTAi and Scopus would be more appropriate.

Appendix A2: Literature search conducted by EAC

Database and years covered by the search (where applicable)	Dates of coverage	Date of search	Number of Results
Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions®	1946 to January 31, 2022	1st February 2022	241
Embase (via Ovid)	1974 to January 31, 2022	1st February 2022	263
CINAHL (via EBSCO)	1981 to January 2022	1st February 2022	26
DARE/NHS EED/HTA (via CRD Database website)	From inception (for all) and, for NHS EED and DARE up to and including 31 December 2014, and for HTA up to 31 March 2018, when active updating of these databases ended.	1st February 2022	6
Cochrane Library (via Wiley) - Cochrane Database of Systematic Reviews	From inception to Issue 12, December 2021	1st February 2022	0
Cochrane Library (via Wiley) - CENTRAL	From inception to January 31, 2022	1st February 2022	32
INAHTA	1989 to present	1st February 2022	8
Scopus	1970 to present	1st February 2022	206
Clinicaltrials.gov	From inception to present	1st February 2022	22
Total number of records retrieved from all sources			804
Total number of records after de-duplication			506

Source: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 31, 2022.
Interface/URL: OvidSP

Database coverage dates: 1946 to present

Search date: 01/02/2022

Retrieved records: 241

#	Searches	Results
1	exp Breast Neoplasms/	319645
2	exp breast/ and exp neoplasms/	30652
3	((breast* or mammar*) adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti,ab,kw.	393594
4	exp "Neoplasms, Ductal, Lobular, and Medullary"/	43459
5	Carcinoma, Ductal, Breast/	16569
6	("ductal carcinoma in situ" or DCIS).ti,ab,kw.	8581
7	or/1-6	473045
8	exp Lymph Nodes/	94937
9	(lymph* adj3 node*).ti,ab,kw.	225794
10	Sentinel Lymph Node Biopsy/	12293
11	(sentinel adj4 (biopsy or identification or dissection or detection)).ti,ab,kw.	11199
12	(sentinel adj3 node*).ti,ab,kw.	16283
13	(snb or slnb or slnd).ti,ab,kw.	4641
14	(sn adj3 detect*).ti,ab,kw.	534
15	or/8-14	266300
16	7 and 15	34534
17	exp Magnetic Iron Oxide Nanoparticles/	9757
18	exp Ferric Compounds/	40961
19	exp Magnetics/	25881
20	exp Iron Compounds/	67765
21	exp Magnetic Phenomena/	494670
22	exp Metal Nanoparticles/	51692
23	exp Magnets/	2760
24	exp Magnetometry/ or magnetometry.ti,ab,kw.	11398
25	(Magtrace* or Sienna* or Endomag* or Sentimag*).ti,ab,kw.	108
26	"magnetic tracer*".ti,ab,kw.	95

27	("superparamagnetic iron oxide" or SPIO).ti,ab,kw.	4540
28	((Magnet* or liquid*) adj4 (device* or system* or probe* or tech* or trace* or nanoparticle*)).ti,ab,kw.	64231
29	("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996").tw.	461
30	or/17-29	678092
31	16 and 30	388
32	exp animals/ not exp humans/	4951717
33	31 not 32	362
34	limit 33 to (english language and yr="2011 -Current")	241

Source: Ovid Embase 1974 to January 31 2022.

Interface/URL: OvidSP
Database coverage dates: 1996 to present
Search date: 01/02/2022
Retrieved records: 263

#	Searches	Results
1	exp breast tumor/	588401
2	exp breast/ and exp neoplasm/	79762
3	((breast* or mammar*) adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti,ab,kw.	550848
4	exp breast adenocarcinoma/	15143
5	("ductal carcinoma in situ" or DCIS).ti,ab,kw.	14626
6	or/1-5	690450
7	exp lymph node/	188551
8	(lymph* adj3 node*).ti,ab,kw.	326245
9	exp sentinel lymph node biopsy/	18777
10	(sentinel adj4 (biopsy or identification or dissection or detection)).ti,ab,kw.	18146
11	(sentinel adj3 node*).ti,ab,kw.	26384
12	(snb or slnb or slnd).ti,ab,kw.	7880

13	(sn adj3 detect*).ti,ab,kw.	817
14	or/7-13	379472
15	6 and 14	56413
16	magnetic iron oxide nanoparticle/ or exp iron oxide nanoparticle/ or exp magnetic nanoparticle/	19475
17	exp ferric ion/	19973
18	exp ferric oxide/	8198
19	ferromagnetic material/	2356
20	exp superparamagnetic iron oxide nanoparticle/	4052
21	exp metal nanoparticle/	95016
22	magnetometer/ or exp magnetometry/	4064
23	exp magnetism/	81601
24	iron derivative/	4317
25	(Magtrace* or Sienna* or Endomag* or Sentimag*).ti,ab,kw.	235
26	"magnetic tracer*".ti,ab,kw.	147
27	("superparamagnetic iron oxide" or SPIO).ti,ab,kw.	5727
28	((Magnet* or liquid*) adj4 (device* or system* or probe* or tech* or trace* or nanoparticle*)).ti,ab,kw.	71348
29	("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996").tw.	929
30	or/16-29	256450
31	15 and 30	347
32	exp animals/ not exp humans/	4894742
33	31 not 32	308
34	limit 33 to (english language and yr="2011 -Current")	263

Source: CINAHL®

Interface/URL: EBSCOhost Web
Database coverage dates: 1981 to present
Search date: 01/02/2022
Retrieved records: 26

#	Query	Results
S33	S29 NOT S30 limited to 2011 onwards	26
S32	S29 NOT S30 limited to English language only	27
S31	S29 NOT S30	27
S30	(MH "Animals+") NOT (MH "Humans+")	98,966
S29	S16 AND S28	28
S28	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	15,466
S27	TI (("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996")) OR AB (("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996"))	24
S26	TI (((Magnet* or liquid*) N4 (device* or system* or probe* or tech* or trace* or nanoparticle*))) OR AB (((Magnet* or liquid*) N4 (device* or system* or probe* or tech* or trace* or nanoparticle*)))	5,223
S25	TI (("superparamagnetic iron oxide" or SPIO)) OR AB (("superparamagnetic iron oxide" or SPIO))	335
S24	TI "magnetic tracer*" OR AB "magnetic tracer*"	15
S23	TI ((Magtrace* or Sienna* or Endomag* or Sentimag*)) OR AB ((Magtrace* or Sienna* or Endomag* or Sentimag*))	31
S22	TI magnetometry OR AB magnetometry	37
S21	(MH "Magnets")	512
S20	(MH "Iron Compounds+")	5,347
S19	(MH "Magnetics+")	4,845
S18	(MH "Ferric Compounds+")	2,054
S17	(MH "Iron Oxide Nanoparticles")	15

S16	S7 AND S15	6,348
S15	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	30,573
S14	TI (sn N3 detect*) OR AB (sn N3 detect*)	58
S13	TI ((snb or slnb or slnd)) OR AB ((snb or slnb or slnd))	820
S12	TI (sentinel N3 node*) OR AB (sentinel N3 node*)	3,421
S11	TI ((sentinel N4 (biopsy or identification or dissection or detection))) OR AB ((sentinel N4 (biopsy or identification or dissection or detection)))	2,459
S10	(MH "Sentinel Lymph Node Biopsy")	2,856
S9	TI (lymph* N3 node*) OR AB (lymph* N3 node*)	26,246
S8	(MH "Lymph Nodes+")	9,608
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	117,965
S6	TI (("ductal carcinoma in situ" or DCIS)) OR AB (("ductal carcinoma in situ" or DCIS))	2,364
S5	(MH "Carcinoma, Ductal, Breast")	2,979
S4	(MH "Neoplasms, Ductal, Lobular, and Medullary+")	5,901
S3	TI (((breast* or mammar*) N5 (neoplasm* or cancer* or tumo#r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) OR AB (((breast* or mammar*) N5 (neoplasm* or cancer* or tumo#r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))	91,567
S2	(MH "breast+") AND (MH "neoplasms+")	4,998
S1	(MH "Breast Neoplasms+")	91,542

Source: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)

Interface/URL: Cochrane Library, Wiley
Database coverage dates: 1995 to present
Search date: 01/02/2022
Retrieved records:
CDSR: 0
CENTRAL: 32

ID	Search	Hits
#1	MeSH descriptor: [Breast] explode all trees	813
#2	MeSH descriptor: [Neoplasms] explode all trees	85789
#3	#1 and #2	385
#4	MeSH descriptor: [Breast Neoplasms] explode all trees	14135
#5	(((breast* or mammar*) NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))):ti,ab,kw	40822
#6	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees	660
#7	MeSH descriptor: [Carcinoma, Ductal, Breast] explode all trees	371
#8	(("ductal carcinoma in situ" or DCIS)):ti,ab,kw	739
#9	(National Institute for Health and Care Excellence, -#8)	41031
#10	MeSH descriptor: [Lymph Nodes] explode all trees	861
#11	((lymph* NEAR/3 node*)):ti,ab,kw	12307
#12	MeSH descriptor: [Sentinel Lymph Node Biopsy] explode all trees	295
#13	((sentinel NEAR/4 (biopsy or identification or dissection or detection))):ti,ab,kw	1229
#14	((sentinel NEAR/3 node*)):ti,ab,kw	1540
#15	((snb or slnb or slnd)):ti,ab,kw	534
#16	((sn NEAR/3 detect*)):ti,ab,kw	23
#17	{OR #10-#16}	12648
#18	#9 and #17	3615
#19	MeSH descriptor: [Magnetic Iron Oxide Nanoparticles] explode all trees	39
#20	MeSH descriptor: [Ferric Compounds] explode all trees	1362
#21	MeSH descriptor: [Magnetics] explode all trees	301
#22	MeSH descriptor: [Iron Compounds] explode all trees	2474
#23	MeSH descriptor: [Magnetic Phenomena] explode all trees	3901
#24	MeSH descriptor: [Metal Nanoparticles] explode all trees	58

#25 MeSH descriptor: [Magnetometry] explode all trees 195

#26 (magnetometry):ti,ab,kw 10

#27 ((Magtrace* or Sienna* or Endomag* or Sentimag*)):ti,ab,kw 31

#28 ("magnetic tracer*"):ti,ab,kw 15

#29 (("superparamagnetic iron oxide" or SPIO)):ti,ab,kw 82

#30 (((Magnet* or liquid*) NEAR/4 (device* or system* or probe* or tech* or trace* or nanoparticle*))):ti,ab,kw 1746

#31 (("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996")) 10

#32 {OR #19-#31} 8524

#33 #18 and #32 with Publication Year from 2011 to 2022 32

Source: Scopus

Interface/URL: Elsevier
Database coverage dates: 1966 to present
Search date: 01/02/2022
Retrieved records: 206

((TITLE-ABS-KEY (((breast* OR mammar*) W/5 (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR dcis OR ductal OR infiltrat* OR intraductal* OR lobular OR medullary)) OR ("ductal carcinoma in situ" OR dcis))) AND (TITLE-ABS-KEY ((lymph* W/3 node*) OR (sentinel W/4 (biopsy OR identification OR dissection OR detection)) OR (sentinel W/3 node*) OR (snb OR slnb OR slnd) OR (sn W/3 detect*)))) AND ((TITLE-ABS-KEY (magnetometry OR magtrace* OR sienna* OR endomag* OR sentimag* OR "magnetic tracer*" OR "superparamagnetic iron oxide" OR spio)) OR (TITLE-ABS-KEY ((magnet* OR liquid*) W/4 (device* OR system* OR probe* OR tech* OR trace* OR nanoparticle*))) OR (TITLE-ABS-KEY (("Ami 25*" OR "Aim25" OR eudorem* OR feridex* OR ferridex* OR ferixan* OR ferrixan* OR ferumoxide* OR "win39996" OR "win39996")))) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011))

Source: ClinicalTrials.gov

Interface/URL: https://clinicaltrials.gov/ct2/home
Database coverage dates: From inception to present
Search date: 01/02/2022
Retrieved records: 22

Search	No of results
Breast cancer and sentinel and magnetic	17
Breast cancer and sentimag	10
Breast cancer and magtrace	3
Breast cancer and sienna	7
Breast cancer and spio	3
Breast cancer and superparamagnetic iron oxide	6
Total found	46
Remaining after pre 2011 results removed	45
Remaining after duplicates removed	22

Source: INAHTA

Interface/URL: INAHTA
Database coverage dates: 1989 to present
Search date: 01/02/2022
Retrieved records: 8

((("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996")) OR (((Magnet* or liquid*) and (device* or system* or probe* or tech* or trace* or nanoparticle*))) OR (("superparamagnetic iron oxide" or SPIO)) OR ("magnetic tracer*") OR ((Magtrace* or Sienna* or Endomag* or Sentimag*)) OR (magnetometry) OR ("Magnetometry"[mhe]) OR ("Magnets"[mhe]) OR ("Metal Nanoparticles"[mhe]) OR ("Magnetic Phenomena"[mhe]) OR ("Iron Compounds"[mhe]) OR ("Magnetics"[mhe]) OR ("Ferric Compounds"[mhe]) OR ("Magnetic Iron Oxide Nanoparticles"[mhe])) AND ((((sn and detect*)) OR ((snb or slnb or slnd)) OR ((sentinel and node*)) OR ((sentinel and (biopsy or identification or dissection or detection))) OR ("Sentinel Lymph Node Biopsy"[mhe]) OR ((lymph* and node*)) OR ("Lymph nodes"[mhe])) AND ((("ductal carcinoma in situ" or DCIS)) OR ("Carcinoma, Ductal, Breast"[mhe]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ((((breast* or mammar*) AND (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))) OR ("Breast Neoplasms"[mhe]) OR (("Neoplasms"[mhe]) AND ("Breast"[mhe]))))

Source: NHS EED/DARE/HTA via the CRD website

Interface/URL: https://www.crd.york.ac.uk/CRDWeb/
Search date: 01/02/2022
Database coverage dates: From 2014 to present

Retrieved records: 6
Search strategy:

Line	Search	Hits
1	MeSH DESCRIPTOR Breast EXPLODE ALL TREES	97
2	MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES	12016
3	#1 AND #2	65
4	MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES	1798
5	(((breast* or mammar*) adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))	2413
6	MeSH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES	65
7	MeSH DESCRIPTOR Carcinoma, Ductal, Breast EXPLODE ALL TREES	26
8	(("ductal carcinoma in situ" or DCIS))	45
9	#3 OR #4 OR #5 OR #6 OR #7 OR #8	2436
10	MeSH DESCRIPTOR Lymph Nodes EXPLODE ALL TREES	152
11	((lymph* adj3 node*))	702
12	MeSH DESCRIPTOR Sentinel Lymph Node Biopsy EXPLODE ALL TREES	119
13	((sentinel adj4 (biopsy or identification or dissection or detection)))	141
14	((sentinel adj3 node*))	149
15	((snb or slnb or slnd))	20
16	((sn adj3 detect*))	1
17	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	712
18	#9 AND #17	210
19	MeSH DESCRIPTOR Magnetic Iron Oxide Nanoparticles EXPLODE ALL TREES	6
20	MeSH DESCRIPTOR Ferric Compounds EXPLODE ALL TREES	33
21	MeSH DESCRIPTOR Magnetics EXPLODE ALL TREES	23
22	MeSH DESCRIPTOR Iron Compounds EXPLODE ALL TREES	66
23	MeSH DESCRIPTOR Magnetic Phenomena EXPLODE ALL TREES	217
24	MeSH DESCRIPTOR Metal Nanoparticles EXPLODE ALL TREES	8
25	MeSH DESCRIPTOR Magnets EXPLODE ALL TREES	3
26	MeSH DESCRIPTOR Magnetometry EXPLODE ALL TREES	11

27 (magnetometry) 0

28 ((Magtrace* or Sienna* or Endomag* or Sentimag*)) 2

29 ("magnetic tracer*") 0

30 (("superparamagnetic iron oxide" or SPIO)) 6

31 (((Magnet* or liquid*) adj4 (device* or system* or probe* or tech* or trace* or nanoparticle*)))78

32 (("Ami 25*" or "Aim25" or Eudorem* or Feridex* or Ferridex* or Ferixan* or Ferrixan* or Ferumoxide* or "win39996" or "win39996")) 1

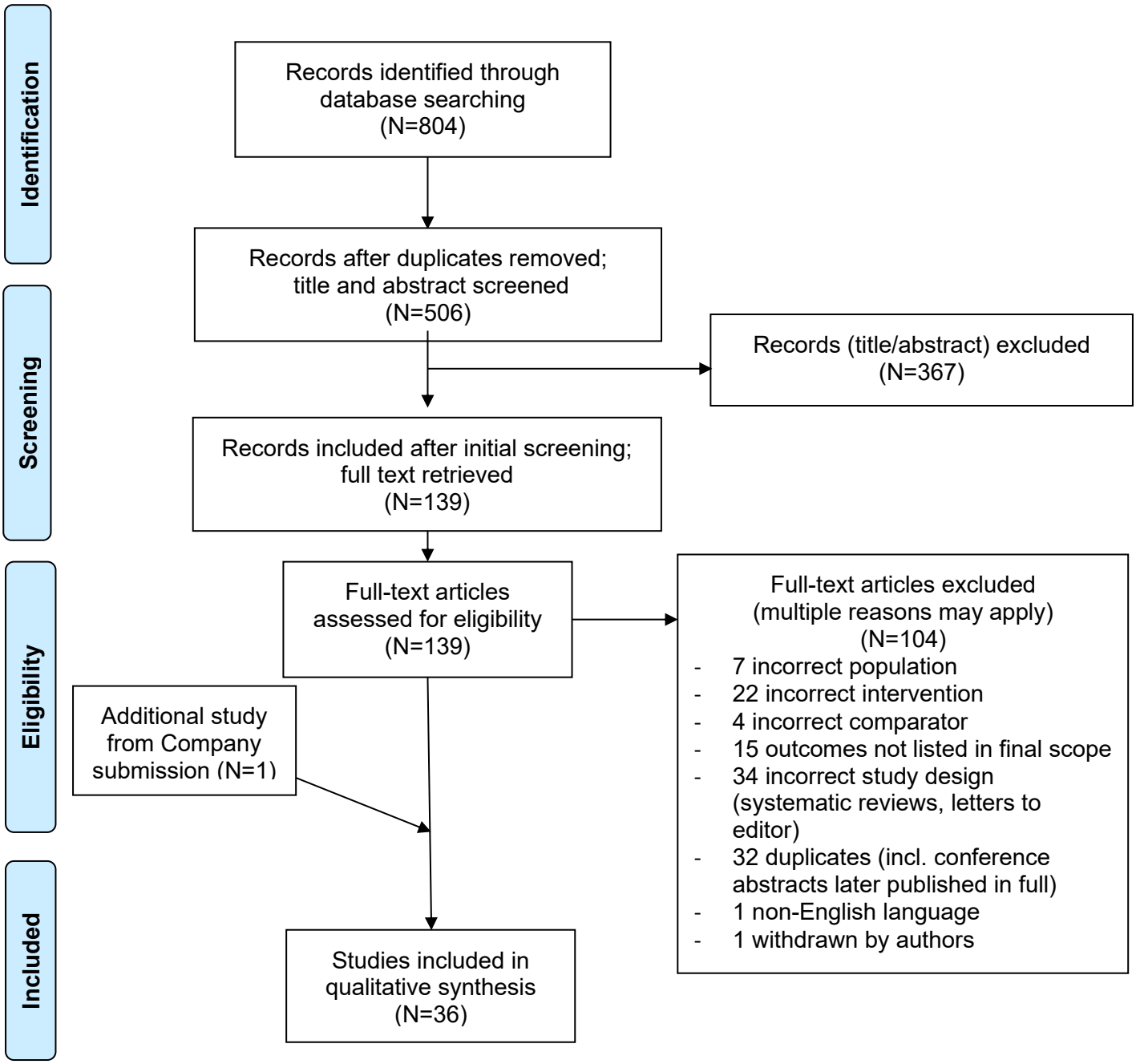
33 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 392

34 #18 AND #33 7

35 #34 AND 2011- 6

Appendix A3: PRISMA diagram illustrating EAC literature search

[From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097]



Appendix A4: Summary of identified systematic reviews (N=5)

Author (journal, year)	MIB263 (2021); N=5	Ahmed *et al.* (2014a); N=2	Mok *et al.* (2019); N=8	Teshome *et al.* (2016); N=5	Zada *et al.* (2016); N=7
Anninga *et al.* (Ann Surg Oncol, 2016)	✓				
Alvarado *et al.* (Ann Surg Oncol,2019)	✓				
Douek *et al.* (Ann Surg Oncol, 2014)		✓	✓	✓	✓
Ghilli *et al.* (Eur J Cancer Care, 2017)	✓		✓	✓	✓
Houpeau *et al.* (J Surg Oncol, 2016)			✓		✓
Karakatsanis *et al.* (Br Cancer Res Treat, 2016)			✓		✓
Karakatsanis *et al.* (Br J Surg, 2017)	✓				
Pinero-Madrona *et al.* (Eur J Surg Oncol, 2015)			✓	✓	✓
Rubio *et al.* (Eur J Surg Oncol, 2015)			✓	✓	✓
Shams *et al.* (Ann Surg Oncol, 2021)	✓				
*Shiozawa *et al.* (Breast Cancer, 2013)		✓	✓		
Thill *et al.* (Breast, 2014)			✓	✓	✓
*incorrect interventions, includes competitor product (Risovist) not Magtrace/Sienna					

Appendix B: Critical appraisal of clinical evidence

Appendix B1: Non-randomised controlled trials (TREND)

Karakatsanis *et al*. 2017 (n=338, prospective non-randomised controlled trial)
First reviewer: RP Second reviewer: KK

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	✓	Abstract- one centre recruiting to intervention arm, one to comparator.
		• Structured abstract recommended	✓	Abstract- background, methods, results and conclusion.
		• Information on target population or study sample	✓	Title- patients with breast cancer undergoing SLNB.
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	Introduction, paragraphs 1-4; availability and legislation of Tc-99m, non-inferiority of Magtrace previously published
		• Theories used in designing behavioral interventions	N/A	
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels inrecruitment/sampling plan (e.g., cities, clinics, subjects)	✓	Inclusion and exclusion criteria in Methods paragraph 6: "All consecutive patients with early breast

				cancer scheduled for primary surgery with SNB were included between September 2014 and June 2015 at the two trial sites in Sweden."
		Method of recruitment (e.g., referral, self-selection), including thesampling method if a systematic sampling plan was implemented	Partly	Methods paragraph 5-6, consecutive patients from outpatient clinics and multidisciplinary rounds from two centres (recruitment from one centre to intervention arm, one centre to comparator arm). Number of patients invited/declining participation not reported, no figure illustrating data flow.
		Recruitment setting	✓	Methods paragraph 5; two Swedish hospitals.
		Settings and locations where the data were collected	✓	Methods paragraph 5; two Swedish hospitals.
Interventions	4	• Details of the interventions intended for each study condition and howand when they were actually administered, specifically including:	✓	Tracer Injection and Operative Technique sections:
		○ Content: what was given?	✓	Sienna+ 2 ml mixed with 3ml of local anaesthetic (intervention) or Tc-99m with blue dye (comparator)
		○ Delivery method: how was the content given?	✓	Within 4 weeks of surgery (intervention: interstitially) or the day before/the day of surgery (comparator: interstitially)
		○ Unit of delivery: how were the subjects grouped during delivery?	✓	Intervention arm in one hospital, comparator arm in another hospital.
		○ Deliverer: who delivered the intervention?	Partly	Injections peri- or intra-operatively. Injection of Tc-99m within nuclear medicine department.

		○ Setting: where was the intervention delivered?	✓	Injections performed perioperaatively (outpatient clinic 1-4 weeks before surgery) or 1 hour (or at least 20 minutes) before operation. Injection of Tc-99m within nuclear medicine department on day of surgery or day before.
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	One-time intervention and comparator for SLNB procedure. Adverse events reported up to median [IQR] 398 [356-440] days post-operatively.
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	Partly	One-time intervention and comparator for SLNB procedure, length of time for each injection not reported, intervention injection was followed by 5 minute massage to injection-site.
		○ Activities to increase compliance or adherence (e.g., incentives)	✗	None reported
Objectives	5	• Specific objectives and hypotheses	✓	Abstract Background; use of SPIO as sole tracer and efficacy of tracer in pre-operative setting.
Outcomes	6	• Clearly defined primary and secondary outcome measures	✓	Primary and secondary aims reported in Introduction paragraph 5.
		• Methods used to collect data and any methods used to enhance thequality of measurements	✓	Operative Technique and Tracer Injection sections document outcomes relating to primary objective. Additional outcomes reported in Follow-up, Cost-Analysis
		• Information on validated instruments such as psychometric and biometricproperties	✓	Detection rate considered against existing evidence and reference standard. Likert scale used in absence of relevant validated

				patient questionnaire for skin staining.
Sample Size	7	How sample size was determined and, when applicable, explanation of anyinterim analyses and stopping rules	✓	Statistical Analysis; sample size calculation and justification provided; non-inferiority.
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g.,individual, group, community)	✓	One centre recruiting to intervention arm, one centre recruiting to comparator arm, inclusion/exclusion criteria applied to both groups.
		Method used to assign units to study conditions, including details of anyrestriction (e.g., blocking, stratification, minimization)	×	Lack of randomisation, but pragmatic approach.
		Inclusion of aspects employed to help minimize potential bias induced dueto non-randomization (e.g., matching)	✓	Methods section; same geographical region with populations of similar demographics and clinical characteristics and levels of procedural experience. Methodology evaluated with PRECIS-2 tool.
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment;if so, statement regarding how the blinding was accomplished and how it was assessed.	✓	No blinding used. Assumed not possible to blind surgeon from intervention and outcomes due to equipment used, handling of radioactive substances protocols and removal of SLNs.
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assessintervention effects (e.g., individual, group, or community)	✓	Per SLN detection rates (per patient and per patient node).
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	✓	Statistical Analysis.

Statistical Methods	11	• Statistical methods used to compare study groups for primary methodsoutcome(s), including complex methods of correlated data	✓	Statistical Analysis.
		• Statistical methods used for additional analyses, such as a subgroupanalyses and adjusted analysis	✓	Statistical Analysis. Separate calculations performed where nodal metastasis was present.
		Methods for imputing missing data, if used	×	Not reported, assumed not applicable to detection rate; nodes removed without detection of either intervention/comparator reported as per detection rates.
		Statistical software or programs used	✓	Statistical Analysis, SPSS used
Results				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (adiagram is strongly recommended)	Partly	Diagram not provided; patients allocated to each arm with consecutive recruitment, timing of injection and exclusion due to probe malfunction reported in Results, Influence of timing of SPIO injection. Follow-up also reported in Results section.
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	×	Not reported, no data flow diagram.
		○ Assignment: the numbers of participants assigned to a study condition	✓	One centre recruiting to intervention arm, one centre recruiting to comparator arm.
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	✓	Results section reports the number of patients and procedures in each arm and exclusions due to lack of SPIO or probe malfunction.

		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	×	Not reported.
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	Results & tables 1-3
		• Description of protocol deviations from study as planned, along with reasons	✓	Results section reports the number of patients and procedures in each arm and exclusions due to lack of SPIO or probe malfunction.
Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	Methods; recruitment between Sept 2014-Jun 2015. Results, Follow-up; 398 (IQR 356-440) days.
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	Table 1. Tables 2-3 also report on characteristics of subgroups.
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	Disease status integral to inclusion/exclusion criteria; hormonal status, surgery type and tumour status/grades reported in Tab 1-3.
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	Not reported.
		Comparison between study population at baseline and target population of interest	Partly	Not explicitly reported, target population integral to inclusion criteria (stage of breast cancer undergoing SLNB). Table 1-3 also report on characteristics of subgroups with malignant SLNs reported.
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	Where there were differences in characteristics between the study arms, multinomial logistic regression was performed for the relevant outcomes, and the

				exponentiated coefficient (expB) was calculated with 95 percent confidence intervals.
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	Absolute numbers for each group and subgroup reported in Results and Tab 1-3 with p numbers.
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	✓	1 exclusion in SLNB arm due to technical problems with probe.
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	✓	Results section, timing of intervention, detection rates, node retrieval, skin staining reported in narrative and Tab 1-3 with p values/CIs where appropriate
		• Inclusion of null and negative findings	✓	Results section, Tab 1-3
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	N/A	
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✓	Subgroup analysis of intervention timing, site, and costings reported in Results section narrative and Tab2-3.
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	Partly	Skin staining discussed and follow-up. Probe malfunction discussed but patient excluded. No additional reporting of AEs.
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses,	✓	Discussion; fewer nodes removed with intervention. Lack of randomization and methodological considerations also reported.

		and other limitations or weaknesses of the study		
		Discussion of results taking into account the mechanism by which theintervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	Discussion, reliability of intervention compared to treatment and impact on clinical care pathway.
		Discussion of the success of and barriers to implementing the intervention,fidelity of implementation	✓	Discussion; authors address skin staining, future MRI and timing of intervention.
		Discussion of research, programmatic, or policy implications	✓	Restrictions for research methodology considered, implications for using intervention in practice also considered.
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into accountthe study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	Partly	Not explicitly stated or considered, authors aim to account for variations in study population during statistical analysis as well as considering cost implications from healthcare payers perspective. Authors declared no conflict of interest. Listed in clinical trials registry: The MONOS study [ISRCTN14097881]
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory	✓	Discussion, final paragraph.

Pelc *et al.* 2021 (n=62, propensity matched cohort) First reviewer: RP Second reviewer: HAR

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	Partly	Abstract, Methods; consecutive cases recruited, Magtrace used where possible, not explicit how patients were allocated. No further information in Methods sections.
		• Structured abstract recommended	✓	Abstract- background, methods, results and conclusions.
		• Information on target population or study sample	Partly	Title- Introducing Sentimag in a rural setting, population and sample not explicit. Number of patients within each cohort not stated. No mention of bi-institutional
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	Introduction; Paragraphs 1-4.
		• Theories used in designing behavioral interventions	✓	Introduction; Sentimag system offers techniques to overcome difficulties in patient care due to geographic isolation and also minimises radiation exposure. Paper also describes current literature and justifies the reasons for undertaking the study.
Methods				

Participants	3	• Eligibility criteria for participants, including criteria at different levels inrecruitment/sampling plan (e.g., cities, clinics, subjects)	✓	Methods, Data & Analysis, Surgical Considerations; inclusion and exclusion criteria provided in narrative.
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	Partly	Propensity score matching was used- but only 62 patients in each cohort. Methods, Study Design; patients attending clinic meeting inclusion criteria included. Consecutive sampling. Allocation to intervention not explicitly reported.
		Recruitment setting	✓	Methods, Data collection & analysis; two high volume centres
		Settings and locations where the data were collected	✓	Methods, Data collection & analysis; single hospital setting- although mentions bi-institutional cohort without any explanation as to what this means.
Interventions	4	• Details of the interventions intended for each study condition and howand when they were actually administered, specifically including:	✓	Methods, Tracer Injection and Surgery sections:
		○ Content: what was given?	✓	Magtrace 2 ml (intervention) or Tc-99m (comparator)
		○ Delivery method: how was the content given?	✓	Within 3 days of surgery (intervention) or the day before/the day of surgery (comparator)
		○ Unit of delivery: how were the subjects grouped during delivery?	✓	Methods Study Design; single centre. Propensity Score Matching Analysis.
		○ Deliverer: who delivered the intervention?	✓	Injections performed by the surgical team pre- or intra-operatively. Injection of Tc-99m injected in nuclear medicine department.
		○ Setting: where was the intervention delivered?	✓	Injections performed by the surgical team pre- or intra-operatively. Injection of Tc-99m performed in

				nuclear medicine department.
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	One-time intervention and comparator for SLNB procedure. Adverse events reported up to 440 days post-operatively.
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	Partly	One-time intervention and comparator for SLNB procedure, length of time for each injection not reported, intervention injection was followed by 5 minute massage to injection-site. Time taken for patients attending nuclear medicine department reported.
		○ Activities to increase compliance or adherence (e.g., incentives)	×	Not reported
Objectives	5	• Specific objectives and hypotheses	Partly	Last sentence at the end of introduction. Authors did not declare any hypotheses.
Outcomes	6	• Clearly defined primary and secondary outcome measures	✓	Primary and secondary analyses reported in section 2.4
		• Methods used to collect data and any methods used to enhance the quality of measurements	Partly	Propensity Score Matching analysis was used to enhance quality of measurements. No mention of methods used to collect data.
		• Information on validated instruments such as psychometric and biometric properties	✓	Detection rate considered against existing evidence and reference standard. Chemotherapy administered based on Polish National Guidelines
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	✓	Methods, Statistical Analysis; sample size calculation and justification provided.
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	×	No mention on how a patient was assigned to either SPIO or radioactive isotope.

		Method used to assign units to study conditions, including details of anyrestriction (e.g., blocking, stratification, minimization)	×	Not reported
		Inclusion of aspects employed to help minimize potential bias induced dueto non-randomization (e.g., matching)	×	Not reported
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment;if so, statement regarding how the blinding was accomplished and how it was assessed.	✓	No blinding used. Assumed not possible to blind surgeon from intervention and outcomes due to equipment used, handling of radioactive substances protocols and removal of SLNs.
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assessintervention effects (e.g., individual, group, or community)	✓	Per SLN detection rates (per patient and per patient node).
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	✓	Statistical Analysis; groups independently evaluated and reported.
Statistical Methods	11	• Statistical methods used to compare study groups for primary methodsoutcome(s), including complex methods of correlated data	✓	Methods, Statistical Analysis.
		• Statistical methods used for additional analyses, such as a subgroupanalyses and adjusted analysis	×	Not performed.
		Methods for imputing missing data, if used	✓	Not reported, assumed not applicable to detection rate; nodes removed without detection of either intervention/comparator reported as per detection rates.
		Statistical software or programs used	✓	MedCalc Statistical Software version 20.009
Results				

Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (adiagram is strongly recommended)	✓	Narrative provided in Methods, Study Design and Results, Fig 1 shows diagram of patient flow.
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	✓	Narrative provided in Methods, Study Design and Results, Fig 1 shows diagram of patient flow.
		○ Assignment: the numbers of participants assigned to a study condition	✓	Fig 1.
		○ Allocation and intervention exposure: the number of participantsassigned to each study condition and the number of participants who received each intervention	✓	Fig 1.
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	✓	Fig 1.
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	Results, Fig 1, & tables 1-2.
		• Description of protocol deviations from study as planned, along withreasons	Partly	Not explicitly stated, Fig 1 shows patients excluded from analysis due to procedure failure, reasons for failure not reported exclusively.
Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	Methods, Study Design; recruitment between 2013to 2021. No long term follow up reported.
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	Table 1.
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	Disease status integral to inclusion/exclusion criteria; hormonal status, surgery type and tumour status/grades reported in Tab 1.

		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	Not reported.
		Comparison between study population at baseline and target population of interest	Partly	Not explicitly reported, target population integral to inclusion criteria (stage of breast cancer undergoing SLNB).
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	Partly	Propensity Score Matching analysis- no information on how this was done
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	Absolute numbers for each group and subgroup reported in Results and Tab 1.
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	N/A	
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	✓	Results section, timing of intervention, detection rates, node retrieval, reported in narrative and Tab 1-3 with p values/OR/CIs where appropriate
		• Inclusion of null and negative findings	✓	Results section, last paragraph
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	N/A	
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✓	Results, Other clinical variables that may have affected outcome were analysed

Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	×	Not reported
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	Discussion; includes clinical considerations. Limitations include selection bias, small sample size, non-randomised design, additional PROMs not investigated.
		Discussion of results taking into account the mechanism by which theintervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	Discussion, reliability of intervention compared to treatment and impact on clinical care pathway.
		Discussion of the success of and barriers to implementing the intervention,fidelity of implementation	✓	Paragraphs 5 and 6 in the discussion section
		Discussion of research, programmatic, or policy implications	✓	Restrictions for research methodology considered, implications for using intervention in practice also considered.
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into accountthe study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	Partly	Not explicitly stated or considered.
Overall Evidence	22	• General interpretation of the results in the context of current evidenceand current theory	✓	Conclusions

Shams *et al.* 2021 (n=59, non-randomised controlled trial) First reviewer: RP Second reviewer: HAR

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	✓	Abstract- surgeon's choice.
		• Structured abstract recommended	✓	Abstract- background, methods, results and conclusions.
		• Information on target population or study sample	✓	Title- patients with breast cancer undergoing SLNB.
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	Paragraphs 1-4.
		• Theories used in designing behavioral interventions	✓	Paragraphs 1-5.
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels inrecruitment/sampling plan (e.g., cities, clinics, subjects)	✓	Methods, Study Design; inclusion (paragraph 6) and exclusion (paragraph 7) criteria reported.
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	Methods, Study Design; patients attending clinic meeting inclusion criteria offered inclusion, specific sampling not reported, assumed systematic and consecutive. Allocation based on surgeon choice.
		Recruitment setting	✓	Methods Study Design, paragraph 6; single German breast centre.
		Settings and locations where the data were collected	✓	Methods Study Design, paragraph 6;

				single German breast centre.
Interventions	4	• Details of the interventions intended for each study condition and howand when they were actually administered, specifically including:	✓	Methods, Tracer Injection and Surgery sections:
		○ Content: what was given?	✓	Magtrace 2 ml (intervention) or Tc-99m (comparator)
		○ Delivery method: how was the content given?	✓	Within 3 days of surgery (intervention) or the day before/the day of surgery (comparator)
		○ Unit of delivery: how were the subjects grouped during delivery?	✓	Allocated by surgeon's choice and equally allocated to a study arm
		○ Deliverer: who delivered the intervention?	✓	Injections performed by the surgical team pre- or intra-operatively. Injection of Tc-99m injected in nuclear medicine department.
		○ Setting: where was the intervention delivered?	✓	Injections performed by the surgical team pre- or intra-operatively. Injection of Tc-99m performed in nuclear medicine department.
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	One-time intervention and comparator for SLNB procedure. Adverse events reported up to 440 days post-operatively.
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	Partly	One-time intervention and comparator for SLNB procedure, length of time for each injection not reported, intervention injection was followed by 5 minute massage to injection-site. Time taken for patients attending nuclear medicine department reported.
		○ Activities to increase compliance or adherence (e.g., incentives)	×	Not reported
Objectives	5	• Specific objectives and hypotheses	✓	Paragraph 5.
Outcomes	6	• Clearly defined primary and secondary outcome measures	✓	Methods, Outcomes; primary and secondary aims reported.

		• Methods used to collect data and any methods used to enhance thequality of measurements	×	Not reported
		• Information on validated instruments such as psychometric and biometricproperties	✓	Detection rate considered against existing evidence and reference standard. Validated German pain questionnaire used.
Sample Size	7	How sample size was determined and, when applicable, explanation of anyinterim analyses and stopping rules	✓	Methods, Statistical Analysis; sample size calculation and justification provided.
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g.,individual, group, community)	✓	Methods, Study Design; Individual allocation based on surgeon choice.
		Method used to assign units to study conditions, including details of anyrestriction (e.g., blocking, stratification, minimization)	✓	Methods, Study Design; surgeon choice.
		Inclusion of aspects employed to help minimize potential bias induced dueto non-randomization (e.g., matching)	×	Not reported
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment;if so, statement regarding how the blinding was accomplished and how it was assessed.	✓	No blinding used. Assumed not possible to blind surgeon from intervention and outcomes due to equipment used, handling of radioactive substances protocols and removal of SLNs.
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assessintervention effects (e.g., individual, group, or community)	✓	Per SLN detection rates (per patient and per patient node).
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	✓	Statistical Analysis; groups independently evaluated and reported.
Statistical Methods	11	• Statistical methods used to compare study groups for primary methodsoutcome(s), including complex methods of correlated data	✓	Methods, Statistical Analysis.

		• Statistical methods used for additional analyses, such as a subgroupanalyses and adjusted analysis	×	Not performed.
		Methods for imputing missing data, if used	✓	Not reported, assumed not applicable to detection rate; nodes removed without detection of either intervention/comparator reported as per detection rates.
		Statistical software or programs used	✓	Statistical Analysis, SPSS used
Results				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (adiagram is strongly recommended)	✓	Narrative provided in Methods, Study Design and Results, Fig 1 shows diagram of patient flow.
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	✓	Narrative provided in Methods, Study Design and Results, Fig 1 shows diagram of patient flow.
		○ Assignment: the numbers of participants assigned to a study condition	✓	Fig 1.
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	✓	Fig 1.
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	✓	Fig 1.
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	Results, Fig 1, & tables 1-2.
		• Description of protocol deviations from study as planned, along withreasons	Partly	Not explicitly stated, Fig 1 shows patients excluded from analysis due to procedure failure, reasons for failure not reported exclusively.

Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	Methods, Study Design; recruitment between May 2019-Jan 2020. No long term follow up reported.
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	Table 1.
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	Disease status integral to inclusion/exclusion criteria; hormonal status, surgery type and tumour status/grades reported in Tab 1.
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	Not reported.
		Comparison between study population at baseline and target population of interest	Partly	Not explicitly reported, target population integral to inclusion criteria (stage of breast cancer undergoing SLNB).
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	×	Statistical power calculated to assume normal distribution.
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	Absolute numbers for each group and subgroup reported in Results and Tab 1.
		• Indication of whether the analysis strategy was “intention to treat” or, if not, description of how non-compliers were treated in the analyses	N/A	
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	✓	Results section, timing of intervention, detection rates, node retrieval, skin staining reported in narrative and Tab 1-3 with p values/CIs where appropriate
		• Inclusion of null and negative findings	✓	Results section, Tab 1-3

		Inclusion of results from testing pre-specified causal pathways throughwhich the intervention was intended to operate, if any	N/A	
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restrictedanalyses, indicating which are pre-specified or exploratory	✓	Results, Economic Analysis; costing analysis performed.
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	✓	Results, Pain Levels; Pain levels reported with each groups although statistically fewer respondents across arms.
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	Discussion; includes clinical and economic considerations. Limitations include small sample size, non-randomised design, additional PROMs not investigated.
		Discussion of results taking into account the mechanism by which theintervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	Discussion, reliability of intervention compared to treatment and impact on clinical care pathway.
		Discussion of the success of and barriers to implementing the intervention,fidelity of implementation	✓	Discussion; authors address learning curve of surgeons, MRI considerations, skin staining.
		Discussion of research, programmatic, or policy implications	✓	Restrictions for research methodology considered, implications for using intervention in practice also considered.
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into accountthe study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	Partly	Not explicitly stated or considered, authors aim to account for variations in study population during statistical analysis as well as considering cost implications from healthcare payers perspective.
Overall Evidence	22	• General interpretation of the results in the context of current evidenceand current theory	✓	Discussion, final paragraph.

Sreedhar *et al.* 2021 (n=116, non-randomised controlled trial) First reviewer: RP Second reviewer: HAR

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	✓	Abstract- Prospective collection of data by operative surgeon
		• Structured abstract recommended	✓	Abstract- background, methods, results and conclusions.
		• Information on target population or study sample	✓	Abstract- (1) any patient who needed localisation of an impalpable breast lesion; (2) any patient who needed a sentinel lymph node biopsy
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	Paragraphs 1-4. Overcome difficulties in patient care due to geographical location- rural hospital
		• Theories used in designing behavioral interventions	✓	Paragraphs 1-5.
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels inrecruitment/sampling plan (e.g., cities, clinics, subjects)	✓	Methods, paragraph 11. Patients were eligible for SLNB using Magtrace if they did not require placement of a Magseed. Patients who had previously undergone breast or axillary surgery. No other exclusions took place.

		Method of recruitment (e.g., referral, self-selection), including thesampling method if a systematic sampling plan was implemented	Partly	Patients recruited sequentially by the surgeon, however specific sampling not reported
		Recruitment setting	Partly	Gisborne Hospital- Rural Hospital in New Zealand. No information on whether recruitment occurred at outpatient appointment or on the day of SLNB.
		Settings and locations where the data were collected	✓	Gisborne Hospital- all information collected on a single database with access limited to the authors.
Interventions	4	• Details of the interventions intended for each study condition and howand when they were actually administered, specifically including:	×	Retrospective collection of data, therefore no true intervention was given in the study. Retrospective review of the different localisation techniques for either breast or the axilla, staging, lymph node status, lymph node detection rates, financial data and complications were collected
		○ Content: what was given?	×	Retrospective collection of data.
		○ Delivery method: how was the content given?	×	Retrospective collection of data.
		○ Unit of delivery: how were the subjects grouped during delivery?	×	Retrospective collection of data.
		○ Deliverer: who delivered the intervention?	×	Surgeon performing either the SLNB or localisation of an impalpable tumour.
		○ Setting: where was the intervention delivered?	×	Gisborne Hospital
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	Partly	Retrospective review of 5-year data. Authors did not state why this time-frame was chosen.

		○ Time span: how long was it intended to take to deliver the intervention to each unit?	Partly	Retrospective review of 5-year data. Authors did not state why this time-frame was chosen.
		○ Activities to increase compliance or adherence (e.g., incentives)	×	Not reported
Objectives	5	• Specific objectives and hypotheses	×	Not reported
Outcomes	6	• Clearly defined primary and secondary outcome measures	×	Not reported
		• Methods used to collect data and any methods used to enhance thequality of measurements	✓	Single database. Financial data was collected via receipts and invoices of purchases to the hospital.
		• Information on validated instruments such as psychometric and biometricproperties	×	Not reported
Sample Size	7	How sample size was determined and, when applicable, explanation of anyinterim analyses and stopping rules	×	Not reported
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g.,individual, group, community)	✓	All patients underwent either Magtrace, Magseed or hookwire. Magtrace was used whenever possible.
		Method used to assign units to study conditions, including details of anyrestriction (e.g., blocking, stratification, minimization)	✓	Methods- implied that it was surgeon's choice
		Inclusion of aspects employed to help minimize potential bias induced dueto non-randomization (e.g., matching)	×	Not reported
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment;if so, statement regarding how the blinding was accomplished and how it was assessed.	✓	No blinding used. Assumed not possible to blind surgeon from intervention and outcomes due to equipment used and removal of SLNs.
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assessintervention effects (e.g.,	✓	Individual, for different localisation techniques for either

		individual, group, or community)		the breast or the axilla. Financial costs were based on per case.
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	N/A	
Statistical Methods	11	• Statistical methods used to compare study groups for primary methodsoutcome(s), including complex methods of correlated data	✓	Methods (paragraph 7) Statistical Analysis.
		• Statistical methods used for additional analyses, such as a subgroupanalyses and adjusted analysis	✗	Not performed.
		Methods for imputing missing data, if used	✗	Not reported
		Statistical software or programs used	✓	JASP Statistical Package
Results				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (adiagram is strongly recommended)	Partly	Narrative provided in first two paragraphs. No diagram given.
		○ Enrollment: the numbers of participants screened for eligibility,found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	Partly	Narrative provided in first two paragraphs. No diagram given.
		○ Assignment: the numbers of participants assigned to a study condition	✓	Paragraph 2-3. 23 cases has a magnetic seed insertion, 15 underwent a hookwire insertion. 116 cases underwent SLNB. 45 cases used Magtrace. 71 cases used Tc-99m.
		○ Allocation and intervention exposure: the number of participantsassigned to each study condition and the	✓	Paragraph 2-3.

		number of participants who received each intervention		
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	Partly	No Follow-up done despite the study lasting at least 5 years.
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	Results, Table 1.
		• Description of protocol deviations from study as planned, along with reasons	Partly	Not explicitly stated. Retrospective review of data, although there appears to be no missing data?
Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	January 2013. Few cases were included in 2013 or 2014 with the large majority of cases performed in 2015-2020.
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	Table 1.
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	Table 2-3.
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	Not reported.
		Comparison between study population at baseline and target population of interest	×	Not reported.
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	×	Not reported.
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different	✓	Absolute numbers for each group and subgroup reported in Results Table 2 and 3.

		outcomes; statement of the results in absolute numbers when feasible		
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	N/A	
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	Partly	Results section, staging, lymph node status, localisation techniques, lymph node detection rate, financial data and complications were reported. Confidence intervals and estimated effect size was not calculated.
		• Inclusion of null and negative findings	✓	Results section
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	N/A	
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✓	Results, financial data for case by case basis.
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	✓	Results, Clavien-Dindo Grade III complication
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	Discussion; includes clinical and economic considerations. Limitations include surgeons unable to perform both Magtrace and Magseed due to lack of

				training
		Discussion of results taking into account the mechanism by which theintervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	Discussion, Sentimag is non-inferior to radioactive colloid use.
		Discussion of the success of and barriers to implementing the intervention,fidelity of implementation	✓	Discussion; authors address learning curve of surgeons, skin staining, using Magseed, impalpable breast lesions, complications regarding hookwires, and financial implications
		Discussion of research, programmatic, or policy implications	✓	Study showed that Sentimag in a rural hospital is cost-effective, and not only beneficial in large academic institutions.
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into accountthe study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	✓	Extrapolated financial data to the next 100 cases- Table 5.
Overall Evidence	22	• General interpretation of the results in the context of current evidenceand current theory	✓	Conclusion

Appendix B2: Studies reporting concordance (STARD)

Alvarado *et al.* 2019 (n=146, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)

First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; non-inferiority of SPIO to standard care (Tc-99m and blue dye) for SLN detection.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; includes background, methods, results and conclusions.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Paragraphs 1-5; current clinical and scientific background discussed. Standard of care involves radioactive material with short half-life which may impact scheduling, risk of anaphylaxis with blue dye.
	4	Study objectives and hypotheses	Paragraph 6; establish alternative intervention to the standard of care to support adoption in the USA.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Materials and Methods, Study Design and Patients, paragraph 7; prospective paired comparison study. Order of testing not explicitly stated, patients injected with Tc-99m and blue dye and SPIO interventions, blue dye reported as subgroup; unclear how this group evaluated.
Participants	**6**	Eligibility criteria	Materials and Methods, Study Design and Patients, paragraph 8, inclusion and exclusion criteria stated.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Study Design and Patients, paragraph 8, patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Abstract, Methods; identified the setting. Results section reports recruitment dates Jan-Dec 2015.

	9	Whether participants formed a consecutive, random or convenience series	Not specified. Number of patients approached and declining participation not reported. Withdrawal rates reported in Results. Patients received intervention and comparator
Test methods	**10a**	Index test, in sufficient detail to allow replication	Procedures, paragraph 11.
	10b	Reference standard, in sufficient detail to allow replication	Procedures, paragraph 10; limited detail, established test following local protocol across 6 centres.
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A, reference standard considered standard of care.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Procedures, paragraph 12; index test ability to detect SLNs using probe (magnetism) and visual confirmation (brown colouration).
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Procedures, paragraph 12; reference standard ability to detect SLNs using probe (radioactivity) and visual confirmation (blue colouration).
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Procedures, paragraph 12; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded).
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Procedures, paragraph 12; index test also performed by the surgeon identifying lymph nodes for retrieval (not blinded).
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Statistical Analysis, paragraph 13-14; ability of index and reference standard to detect the SLNs independently and in combination.
	15	How indeterminate index test or reference standard results were handled	Procedures, paragraph 12; Detection rate reported as binary value (detected/not detected) so indeterminate results N/A. SLNs identified by the surgeon as clinically suspicious were also retrieved.
	16	How missing data on the index test and reference standard were handled	Procedures, paragraph 12; only SLNs with histologically confirmed node status included in the analysis.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Statistical Analysis, paragraph 14-15; study powered for non-inferiority for error rates for detection.
	18	Intended sample size and how it was determined	Statistical analysis, paragraph 15; sample size power calculations reported.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Results section provides narrative, Fig 1 provides flow diagram.
	20	Baseline demographic and clinical characteristics of participants	Results, paragraphs 16-17, Tab 1; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Tab 1 reports the diagnostic status of the participants, not referenced to expected population statistics. Disease status integral to inclusion criteria.

	21b	Distribution of alternative diagnoses in those without the target condition	Results, Detection Rates for Positive Nodes; detection rates for positive nodes and patients reported but not referenced to expected population statistics.
	22	Time interval and any clinical interventions between index test and reference standard	Procedures, paragraph 11-12; order of test analysis reported, index test and reference standard performed concomitantly.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results, Patient Detection Rates; results shown in Fig 2 and Tab 2.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results, Patient Detection Rates and Detection Rates for Positive Nodes sections.
	25	Any adverse events from performing the index test or the reference standard	Narrative reported in Results, Safety Results; results also provided in Tab 3.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Limitations, sources of bias and statistical uncertainty not reported. Discussion of index test timing in Discussion, paragraph 35.
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion of service implementation reported in Discussion, paragraphs 33-37.
OTHER INFORMATION			
	28	Registration number and name of registry	Materials and Methods, Study Design and Patients, paragraph 7; NCT reference reported.
	29	Where the full study protocol can be accessed	Full protocol not provided; additional information available from clinicaltrials.gov (NCT02336737)
	30	Sources of funding and other support; role of funders	Acknowledgment (correction published in Ann Surg Oncol 2020; 27: S979); Study sponsored by index test manufacturer which provided funding to the institutions of all authors. Additional travel support provided to one author.

Douek *et al.* 2014 (n=160, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; SLNB with magnetic tracer (index test) vs standard technique (reference standard). Abstract states discordance.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; structured with background, methods, results and conclusions.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Paragraphs 1-5 (no heading); provides scientific and clinical background. Fig 1 demonstrates features of the index test. Drawbacks of combined technique: radiation exposure to patients and healthcare workers, heavily controlled legislation (training for operators and subsequent disposal of surgical waste), poor preoperative spatial resolution on lymphoscintigraphy.
	4	Study objectives and hypotheses	Paragraph 5; comparison of index test with standard reference for identification of sentinel nodes.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Methods, Trial Design; prospective (assumed from trial registration) non-randomised paired equivalence trial.
Participants	**6**	Eligibility criteria	Methods, Patient Recruitment; inclusion and exclusion criteria reported. Patients with breast cancer (including DCIS), scheduled for SLNB and who were clinically and radiologically node negative (pre-op ultrasound results were normal or indeterminate/abnormal and had benign fine-needle aspiration or core biopsy). Patients with male breast cancer and pregnant women were suitable as long as they were scheduled to undergo SLNB with radioisotope. All patients had to be available for at least 12 months. Patients with known intolerance or hypersensitivity to iron or dextran compounds, magnetic tracers, SPIO, blue, who did not receive radioisotope, with iron over load

			disease, with pacemaker or other implantable devices in chest wall were excluded.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Methods, Patient Recruitment; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Methods, Patient Recruitment & Surgery sections; setting and recruitment dates (29 February 2012 to 3 October 2012). Locations reported in Methods (6 centres in UK, 1 in the Netherlands, all experienced with SLNB from both teaching and district general hospitals with relatively high-volume practice >300 cases of newly diagnosed breast cancer per annum)
	9	Whether participants formed a consecutive, random or convenience series	Not explicitly reported. Number of patients invited to participate or those declining participation not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Methods, Surgery. 2ml Sienna+ diluted with 3ml saline, injected periareolar subcutaneously intraoperatively (after induction of anaesthesia), followed by 5 minute massage. Magnetic tracer injected before blue dye (when it was used). All metal retractors were removed from the surgical field while the magnetometer (Sentimag) were used.
	10b	Reference standard, in sufficient detail to allow replication	Methods, Surgery; local protocols used for standard technique, very little detail provided (e.g. no timing or location of injection provided for radioisotope injection). Subgroup of patients receiving blue dye not reported exclusively. Variability amongst reference standard: "Of seven centres, five used the combined technique, one used radioisotope alone, and another used selective blue dye on some patients."
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction states gold standard for SLNB being the combined technique using both blue dye and radioisotope injection.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Methods, Surgery; index test ability to detect SLNs using probe (magnetism) and visual indicator (black/brown colouration). "Any node with a count of 10 % or more of the node with the highest count (with the handheld magnetometer and then gamma probe) was excised. Beyond four sentinel nodes, surgeons noted the background count (with both devices) and excised additional nodes only at their discretion. Any palpable nodes were also removed."
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Methods, Surgery; reference standard ability to detect SLNs using probe (radioactivity) and visual indicator (blue colouration). "Any node with a count of10 % or more of the node with the highest count (with the handheld magnetometer and then gamma probe) was excised. Beyond four sentinel

			nodes, surgeons noted the background count (with both devices) and excised additional nodes only at their discretion. Any palpable nodes were also removed."
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Methods, Surgery; Sentimag used first, gamma probe used to confirm (not blinded), blue tracts not followed until after handheld magnetometer was used to locate and excise sentinel nodes.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Methods, Surgery; Sentimag used first, gamma probe used to confirm (not blinded)
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Materials and Methods, Study Objectives and Statistical Analyses; ability of index and reference standard to detect the SLNs independently and in combination.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected). However surgeons removed additional nodes (beyond 4 sentinel nodes) at their discretion. Any palpable nodes were also removed.
	16	How missing data on the index test and reference standard were handled	Methods, Surgery & Primary End Points; all SLNs identified by either method retrieved and palpable SLNs not picked up by either technique also retrieved.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Methods, Statistical Analysis; detection concordance.
	18	Intended sample size and how it was determined	Methods, Statistical Analysis; sample size justification reported assuming 97% detection by standard care, proportion discordance of 0.052. Non-inferiority margin of 5%, 80% power.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	No flow diagram provided. Number of patients withdrawn or invited not reported.
	20	Baseline demographic and clinical characteristics of participants	Results, Patient Characteristics, Tab 1; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Tab 1 reports the diagnostic status of the participants (nodal status by largest metastasis, lymphovascular invasion, tumour size, grade, type, estrogen, receptor and HER2 status), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive nodes and patients reported in Results, Histopathology, but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Methods, Surgery; order of test analysis reported (Sentimag first, gamma probe/blue tracts after)

Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results; clear 2x2 in Table 2 for detection rate, and Table 3 for number of nodes removed.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; discordance with only CI upper limit reported in Tab 2.
	25	Any adverse events from performing the index test or the reference standard	Methods: "Any adverse events, complications, or reactions were noted during surgery and postoperatively. Patients were followed up at a postoperative visit and also at 3 months." Results, Sentinel Lymph Node Biopsy: "Three dye-related reactions were observed. Of these, 2 were related to blue dye (blue rash without systemic reaction); 1 was indeterminate but related to dye injection (transient drop in blood pressure during surgery and rash in a patient with dark skin)."
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Not reported. Limitations of technique with regards to false-negative staging reported in Discussion.
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion & Conclusion; recommendations for randomised controlled trial to validate the magnetic technique, and to evaluate the independent magnetic identification rate and procedure-related morbidity.
OTHER INFORMATION			
	28	Registration number and name of registry	Trial registration and reference with links provided on cover page (ISRCTN35827879, NTR3283)
	29	Where the full study protocol can be accessed	Full protocol not provided. Appendix listing SentiMAG trialist group (study collaborators).
	30	Sources of funding and other support; role of funders	Funding; study sponsored by index test manufacturer; role of funder not reported. NIHR support in recruiting patients (UK), and Clinical Research Coordinator (the Netherlands).

Ghilli *et al.* 2017 (n=193, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; valid alternative in SLNB for breast cancer. Non-inferiority, detection rate, concordance all mentioned in abstract.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; study overview provided, design, methods, results and conclusions broadly described but not in explicit sections.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction, paragraphs 1-7; current clinical and scientific background discussed. Major limitation is necessity of nuclear medicine unit which may not be present in small and medium sized breast units. Radiation exposure of patients and staff.
	4	Study objectives and hypotheses	Introduction, paragraph 8; comparison of Sentimag with superparamagnetic iron oxide tracer with standard reference for SLNB localization in breast cancer patients in larger Italian sample.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Materials, Study Design and Patients, paragraph 9; paired non-inferiority comparison study. Prospective only mentioned in abstract. From methods section: Data were collected by surgical staff using ad hoc forms after the operation and transmitted to an independent statistical and methodological unit for analysis.
Participants	**6**	Eligibility criteria	Methods, Study Design and Patients, paragraph 10, inclusion and exclusion criteria stated. Inclusion: Women who were candidate for SNB after a clinical and imaging negative axillary assessment, invasive carcinoma (ductal or lobular), or DCIS at the pre-operative biopsy only if there was a high probability of invasive component in final histology. Contraindications: allergy to iron or dextran compounds, iron metabolism disease, pregnancy, pacemaker or other ferrous devices near the breast.

	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Methods, Study Design and Patients, paragraph 9; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Methods, Study Design and Patients, paragraph 9; setting, location and recruitment dates reported: three Italian breast centres (Pisa University Hospital, Rome IFO-IRE University Hospital and Sanremo Civic Hospital) between October 2012 and January 2014.
	9	Whether participants formed a consecutive, random or convenience series	Results, paragraph 16; consecutive patients recruited. Number of patients approached and declining participation not reported. Withdrawal rates also reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Methods, Intraoperative Procedures, paragraph 12-13: subareolar injection for SPIO, 5 mins massage, at least 20 mins after injection the localization of the sentinel node was identified with magnetometer, and confirmed with gamma probe.
	10b	Reference standard, in sufficient detail to allow replication	Methods, Intraoperative Procedures, paragraph 12-13: periareolar or peritumoural-subdermal sites of Tc-99m injection (no mention of blue dye), day before or 1-day protocol (after a public holiday). Lymphoscintigraphy performed in all patients.
	11	Rationale for choosing the reference standard (if alternatives exist)	Abstract and Introduction claims standard of care is Tc-99m with or without blue dye.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Methods, Intraoperative Procedures, paragraph 12-13; index test ability to detect SLNs using probe (magnetism): cut-off for stopping SNB was 10% of maximum count for both methods.
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Methods, Intraoperative Procedures, paragraph 12-13; reference standard ability to detect SLNs using probe (radioactivity): cut-off for stopping SNB was 10% of maximum count for both methods.
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Methods, Intraoperative Procedures, paragraph 12-13; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded). Sentimag first and then confirmed with gamma.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Methods, Intraoperative Procedures, paragraph 12-13; index test also performed by the surgeon identifying lymph nodes for retrieval (not blinded). Sentimag first and then confirmed with gamma.
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Methods, End Points & Statistical Analysis, paragraph 13-14; ability of index and reference standard to detect the SLNs independently and in combination. Concordance per patient, reverse concordance – defined.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected). 0 were not detected by I/C

	16	How missing data on the index test and reference standard were handled	Methods, End Points, paragraph 13; only patients with SLN identified by one or both methods included for analysis.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	No exploratory analysis on thresholds.
	18	Intended sample size and how it was determined	Methods, Statistical Analysis, paragraph 14; sample size power calculations reported; assumed 97% detection rate for control and 98% in experimental arm, true difference of 1%.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Results section provides narrative, no patient flow diagram provided.
	20	Baseline demographic and clinical characteristics of participants	Results, paragraphs 15-17, Tab 1; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Table 1 reports the diagnostic status of the participants (tumour stage, grade, estrogen, progesterone, Ki67 receptor and HER2 status), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Results, paragraphs 21-22; detection rates for positive (malignant) nodes and patients reported but not referenced to expected population statistics.
	22	Time interval and any clinical interventions between index test and reference standard	Methods, Intraoperative Procedures, paragraph 12-13; order of test analysis reported, index test and reference standard performed concomitantly.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	No explicit 2x2 table, however narrative provided in Results section, additional results shown in Fig 1.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section with 95% confidence intervals.
	25	Any adverse events from performing the index test or the reference standard	Narrative reported in Results, paragraph 23. No allergic or inflammatory reaction was registered. Reported slightly brown skin pigmentation at site of injection. Skin pigmentation attenuated in 70.4%, vanished in 21.1%, enlarged in 1.4%, unchanged in 7.1%.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Limitations discussed in Discussion, paragraph 25. Sources of bias and statistical uncertainty not reported. Discussion of index test timing in Discussion, paragraph 25. States brief learning curve of 25 patients.
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion of service implementation reported in Discussion, paragraph 25-26.

OTHER INFORMATION			
	28	Registration number and name of registry	Not reported.
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Funding; Study sponsored by index test manufacturer (who provided the Sentimag devices and the tracer Sienna for the period of the study). The Company had no involvement in collecting and interpreting the data or the decision to publish. Author Contributions and Disclosure highlights role of funders and authors.

Giménez-Climent *et al.* 2021 (n=89, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; comparative non-inferiority study using magnetic tracer versus standard technique.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; introduction, materials and methods, results and conclusion. Reports 5 centres
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	1. Introduction, paragraphs 1-4; current clinical and scientific background discussed. Limitations: exposing patients to radiation, heavily controlled by legislation, requires nuclear medicine, intraop blue dye can obscure surgical field, blue dye can leave permanent skin residue, allergic reaction.
	4	Study objectives and hypotheses	1. Introduction, paragraph 5; specifically designed to evaluate the non-inferiority of Sentimag compared with gamma probe for detection of sentinel lymph nodes in post-neoadjuvant breast cancer patients.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Abstract, Materials and Methods; reading taken transcutaneously, intra-operative and ex-vivo (prospective study).
Participants	**6**	Eligibility criteria	2.1 Materials Methods, Study Subjects, paragraph 6; inclusion and exclusion criteria stated: aged 18 years and older, histologically confirmed diagnosis of invasive carcinoma, clinically and radiologically negative nodes before NAT. Excluded if clinically or radiologically positive nodes after NAT< if they were intolerant or hypersensitive to iron or dextran compounds present in the magnetic tracer, the administration of a radioisotope for SLNB was contraindicated, had disorders associated with abnormal iron levels, pacemaker, or other partial or totally metallic thoracic implants.

	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	2.1 Materials Methods, Study Subjects, paragraph 6 & 2.3 Data Collection and Study Outcomes, paragraph 1 ; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	2.1 Study subjects; setting, location reported. Recruitment dates reported (5 centres: Jun 2016-Oct 2018) in 3.1 Results, Patient Characteristics.
	9	Whether participants formed a consecutive, random or convenience series	3.1 Results, Patient Characteristics; consecutive patients recruited. Number of patients approached and declining participation not reported. Withdrawal rates also reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	2.2 Preoperative Procedures and SLN Detection Methods: 2ml Sienna diluted with 3ml saline, injected into subareolar area (after anaesthesia), 5 mins massage, at least 20 min after injection then transcutaneous detection attempted with bboth techniques before incision.
	10b	Reference standard, in sufficient detail to allow replication	2.2 Preoperative Procedures and SLN Detection Methods, very limited information provided with procedure according to local protocols. Timing of tracer injection provided in 3.2 SLN Detection Procedure: injections performed day before surgery and mainly periareolar, dose average 122.2 Mbq. Although permitted, no combined technique with blue dye was conducted at any site.
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction reports standard of care involving injection of radioisotope alone or in combination with blue dye.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	2.2 Preoperative Procedures and SLN Detection Methods; index test ability to detect SLNs using probe (magnetism) and visual indicator (brown colouration). After incision, intraoperative detection within the axilla was attempted with SM, and positive spots were also measured intraoperatively using GP. All nodes with a positive reading with SM or GP were excised as long as their reading was superior to 10% of the node with the highest SM or GP reading.
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	2.2 Preoperative Procedures and SLN Detection Methods; reference standard ability to detect SLNs using probe (radioactivity). All nodes with a positive reading with SM or GP were excised as long as their reading was superior to 10% of the node with the highest SM or GP reading.
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	2.2 Preoperative Procedures and SLN Detection Methods; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded).

	13b	Whether clinical information and index test results were available to the assessors of the reference standard	2.2 Preoperative Procedures and SLN Detection Methods; index test also performed by the surgeon identifying lymph nodes for retrieval (not blinded).
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	2.3 Data Collection and Study Outcomes; ability of index and reference standard to detect the SLNs independently and in combination. 2.5 Statistical analysis: McNemars test.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable. However 2x2 table (Table 2 & 3) does report 0 cases not picked up by either technique.
	16	How missing data on the index test and reference standard were handled	Not explicitly reported, method of SLN detection for each method reported. SLNs removed and detected by neither test reported in Tab 2 & 3.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	2.5 Statistical Analysis, calculations for non-inferiority with error rates for detection included.
	18	Intended sample size and how it was determined	5% non-inferiority, Bonnet-Price test.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Results sections 3.1 Patient Characteristics and 3.2 SLN Detection Procedure provides narrative, no patient flow diagram provided.
	20	Baseline demographic and clinical characteristics of participants	3.1 Patient characteristics, Tab 1; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Tab 1 reports the diagnostic status of the participants (tumour location, detection, stage, grade, estrogen, progesterone, Ki67 receptor and HER2 status) not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	3.1 Patient Characteristics & 3.2 SLN Detection Procedure; detection rates for positive nodes and patients reported but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	3.2 SLN Detection Procedure; order of test analysis reported, index test and reference standard performed concomitantly.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in 3.2 SLN Detection Procedure and 3.3 Pathological Analysis of SLNs; results also reported clearly in Tables 2-3 (including 2x2 table information) including against multiple studies.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results sections and reported in Tab 2-3; CI only provided for overall detection rate differences.

	25	Any adverse events from performing the index test or the reference standard	Not explicitly reported; safety of index procedure reported in Discussion.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Limitations of study discussed in Discussion (pragmatic settings regarding reference technique; non-use of blue dye, small patient numbers). Sources of bias and statistical uncertainty not reported. Generalisability not reported.
	27	Implications for practice, including the intended use and clinical role of the index test	Service implementation in units with and without nuclear medicine units raised in Discussion.
OTHER INFORMATION			
	28	Registration number and name of registry	Registration of Research Studies; registration code reported: GES-SEN-2015-01
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Sources of Funding; study sponsored by index test manufacturer and role of funder reported (without participating in study design, analysis of data, or preparation of manuscript). Author Contribution reports role of authors.

Houpeau *et al.* 2016 (n=108, feasibility, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; SLN identification with SPIO (index test) vs radioisotope (reference standard). Abstract states detection rate and concordance.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; structured with background and objectives, methods, results and conclusions.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction; provides scientific and clinical background. Disadvantages of standard care: blue dye can cause severe anaphylaxis, blue dye alone has low identification rate, radioisotope is associated with pre=operative lymphoscintigraphy often day before surgery, coordination with other teams, radiotracer availability, radioactive waste, waiting time for patients.
	4	Study objectives and hypotheses	Introduction, Abstract Background and Objectives; "evaluated, in a French multicenter prospective trial, the feasibility, reliability, and safety of the magnetic method Sentimag/Sienna+ alongside standard method."
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Materials and Methods, Patients; prospective non-randomised paired feasibility trial.
Participants	**6**	Eligibility criteria	Methods, Patient Recruitment; inclusion and exclusion criteria reported. All adult female patients with clinical T0-T2 breast cancer proven by histopathology or cytology, clinically or radiologically node-negative and scheduled for sentinel node biopsy. Excluded patients with T3-T4 breast cancer or with multifocal tumours, intolerance or hypersensitivity to iron-dextran compounds or Patent blue dye, who could not receive radioisotope, with

			chronic iron overload disease, with pacemaker or other implantable device in chest wall.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Patients; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Materials and Methods, Patients; setting, location (4 French cancer centres) and recruitment dates (February 2013 to December 2013) reported.
	9	Whether participants formed a consecutive, random or convenience series	Not explicitly reported. Number of patients invited to participate or those declining participation (as informed consent required) not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Sentinel Node Mapping and Identification. 2ml Sienna+ diluted with 3ml saline injected subcutaneously in periareolar area, 5 min massage.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Sentinel Node Mapping and Identification; Tc-99m injected in periareolar area either day before surgery or day of surgery, lymphoscintigraphy performed at least 2-3 hours after injection, but results not shared with surgeon to avoid bias of sentinel localization. Four centres using colorimetric method, 2ml Patent blue dye was injected after Sienna+ (number of patients where blue dye used not reported).
	11	Rationale for choosing the reference standard (if alternatives exist)	Study endpoints: standard of care reported as isotopes with or without patent blue.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Materials and Methods, Sentinel Node Mapping and Identification; index test ability to detect SLNs using probe (magnetism) and visual indicator (brown colouration). “Magnetic or radioactive nodes were removed until the background signal was less than 10% of the highest magnetic or radioactive node.”
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Materials and Methods, Sentinel Node Mapping and Identification; reference standard ability to detect SLNs using probe (radioactivity) with and without visual indicator (blue colouration). Lymphoscintigraphy also used to assist with radioisotope localisation. “Magnetic or radioactive nodes were removed until the background signal was less than 10% of the highest magnetic or radioactive node.”
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Materials and Methods, Sentinel Node Mapping and Identification; results from lymphoscintigraphy blinded until surgical use of gamma probe for localisation. “Intraoperative SLN identification was firstly performed using the Sentimag device and then with the gamma-probe.” Surgeons not blinded.

	13b	Whether clinical information and index test results were available to the assessors of the reference standard	As above.
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Materials and Methods, Study Endpoints; ability of index and reference standard to detect the SLNs independently and in combination. Statistical analysis: overall concordance, standard of care concordance, inverse standard of care concordance, overall discordance.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable.
	16	How missing data on the index test and reference standard were handled	Materials and Methods, Sentinel Node Mapping and Identification; SLNs identified by either method retrieved. Table 3 shows some patients did not have nodes detected by either technique, so assume that palpable SLNs were also retrieved by surgeon (but not explicitly reported).
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Materials and Methods, Statistical Analysis; Difference definitions of concordance/discordance reported.
	18	Intended sample size and how it was determined	Power calculation based on 95% feasibility rate with 95% confidence limit of length 8%.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	No flow diagram provided: 115 enrolled, 108 analysed. Number of patients withdrawn or invited not reported. 2 patients with protocol deviations, and 5 with insufficient intraoperative data.
	20	Baseline demographic and clinical characteristics of participants	Results, Patient Characteristics, Tab 1; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Tab 1 reports the diagnostic status of the participants (tumour side, size, histological type, node status, estrogen, progesterone, Ki67 receptor and HER2 status), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive (malignant) nodes and patients reported in Results and Tab 3 and 4, but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Materials and Methods, Sentinel Node Mapping and Identification; order of test analysis reported, index test and reference standard performed in parallel. Results from lymphoscintigraphy blinded from surgeon until after reference standard and index test performed.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results; results also reported in Table 3 (per patient) and Table 4 (per node).

	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; concordance with CI intervals reported under Tab 3 and 4.
	25	Any adverse events from performing the index test or the reference standard	Results; "No serious adverse event was observed with patent blue (when applied) or with Sienna+." Dermopigmentation was noted at 30 day follow-up in 22 patients; however unclear if caused by Sienna or blue dye.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	"Although the study mandated detection, at each stage of the dissection, first by the hand-held magnetometer Sentimag, and then by the gamma probe, the presence of a simultaneous magnetic and isotopic signal could potentially influence and help the surgeon even in the absence of known lymphoscintigraphy (the surgeon was blinded). Only a randomized trial could answer this question."
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion & Conclusions; feasible method and possible alternative to isotope. States technical improvement still needed (in progress). But proposes Sienna as a solution for institutions without nuclear medicine units.
OTHER INFORMATION			
	28	Registration number and name of registry	Trial registration reported in Materials and Methods (NCT01790399)
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Acknowledgement; study sponsored by index test manufacturer; assumed funded activities of Centre Oscar Lambret (France): protocol drafting, study insurance, ethic committee submission, patient inclusions, clinical research technicians, data manager, statistician works.

Karakatsanis *et al.* 2016 (n=206, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; SLN identification with SPIO (index test) vs radioisotope and blue dye (reference standard). Abstract reports concordance rates.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; not structured with headings.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction, paragraphs 1-3; provides scientific and clinical background. Drawbacks of standard of care: need for nuclear medicine departments, hazards to patients and staff, legislation and restrictions in handling and disposal, all limit access.
	4	Study objectives and hypotheses	Introduction, paragraph 4; "The aims of the present study were to compare detection rate with SPIO versus conventional technique, to describe the frequency and duration of discolouration, and to perform meta-analysis of published data on detection and concordance between the different techniques."
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Materials and Methods, Study Design; prospective (Nordic SentiMag study)
Participants	**6**	Eligibility criteria	Materials and Methods, Patient Selection; inclusion and exclusion criteria reported. Patients aged more than 18 years, diagnosed with breast cancer of DCIS, with clinically and ultrasonographically negative axilla, scheduled for SLNB. Exclusions: hypersensitivity to dextran compounds, iron or Sienna+, isotope intolerance, iron overload disease, pregnancy, pacemaker or other implantable metallic devices close to the axilla, or mental condition rendering

			patient incapable of giving informed consent. All patients had to be available for postoperative follow-up.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Patient Selection; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Materials and Methods, Study Design & Patient Selection; setting and location reported (5 Swedish, 2 Danish hospitals with experience in SLNB). Recruitment period not explicitly defined.
	9	Whether participants formed a consecutive, random or convenience series	Not explicitly reported (unclear reporting in Table 1 for Nordic study). Number of patients invited to participate or those declining participation not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Operative Protocol. 2ml Sienna+ diluted with 3ml saline, injected subareolarly either shortly before or after induction of anaesthesia, massage 5 mins, and the operation was not to start until at least 20 minutes had elapsed.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Operative Protocol; Tc-99m injected subareolarly, subdermally or subcutaneously above tumour according to local standards, either on day of surgery or day before. Lymphoscintigraphy was not performed routinely. Patent blue dye (1-2ml) injected after onset of anaesthesia. However number of centres using blue dye not reported. Typographical error noted: [Blue was used in 127 patients (61.7%)] – assumed to refer to blue dye, cases not reported exclusively in any subgroup analysis.
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction: standard of care reported as combination of radioactive tracer and blue dye.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Materials and Methods, Operative Protocol; index test ability to detect SLNs using probe (magnetism) and visual indicator (brown colouration). “All SNs wwere excised until the counts were lower than 10% of the highest count or maximum of hour nodes per patient were removed.”
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Materials and Methods, Operative Protocol; reference standard ability to detect SLNs using probe (radioactivity) with and without visual indicator (blue colouration). “All SNs wwere excised until the counts were lower than 10% of the highest count or maximum of hour nodes per patient were removed.”
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Materials and Methods, Operative Protocol; Sentimag first, then confirmed with gamma probe (not blinded).
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Materials and Methods, Operative Protocol; Sentimag first, then confirmed with gamma probe (not blinded).

Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Materials and Methods, Statistical Methods: Study Endpoints; ability of index and reference standard to detect the SLNs independently and in combination; detection rate for malignant nodes also explored. Detection per patient and per node.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable.
	16	How missing data on the index test and reference standard were handled	Materials and Methods, Operative Protocol & Statistical Methods: Study Endpoints; all SLNs identified by either method retrieved and palpable SLNs not picked up by either technique also retrieved (assumed from results in Table 5; although not explicitly reported).
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Materials and Methods, Statistical Methods: Study Endpoints; study powered for non-inferiority and detection concordance.
	18	Intended sample size and how it was determined	Materials and Methods, Statistical Methods: Study Endpoints; sample size justification reported. Total number of cases included below the required sample size for statistical analysis (206 of 214), assuming 97% detected by reference and index test, limit of difference for equivalence of -4%, and expected difference between proportions detected under both arms as 0%.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	No flow diagram provided. Number of patients withdrawn or invited not reported.
	20	Baseline demographic and clinical characteristics of participants	Results, Table 2; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Table 2 reports the diagnostic status of the participants (pT, pN, grade and Ki67 status reported), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive (malignant) nodes and patients reported in Results and Table 3-6, but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Materials and Methods, Operative Protocol; order of test analysis reported (Sentimag first, then confirmed with gamma), index test and reference standard performed in parallel.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results; results also reported in Tab 3-7. Results from other studies (mate-analysis) also included in tables 3-6, figures 3-10 and narrative.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; concordance and reverse concordance with CI intervals reported under Table 7 and Figures 7-10.

	25	Any adverse events from performing the index test or the reference standard	Discussion; narrative for both techniques. Staining persisted to 15 months in 8.6% patients. Discolouration rates for index test only reported in Fig 2.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Not explicitly reported. Study includes meta-analysis of other published studies. Difficulty in quantifying presence of ink. Some nodes would have been difficult to find if using SPIO alone due to size of probe (however acknowledges slimmer version of probe now available).
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion; impact of test adoption in routine care considered as an alternative in the absence of nuclear medicine facilities.
OTHER INFORMATION			
	28	Registration number and name of registry	No trial reference stated or identified.
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Final sentence in paper reports index test probe and tracer were provided by the Company however specific funding and role of funders not explicitly reported. Authors declared no conflicts of interest.

Karakatsanis *et al.* 2018 (n=12, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Not explicitly stated in title or abstract (feasibility mentioned)
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; includes purpose, methods, results and conclusion.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Paragraphs 1-4; current clinical and scientific background discussed. Disadvantages of SN tracing: half-life of radioisotope, allergy to blue dye, need for injection after induction of anaesthesia.
	4	Study objectives and hypotheses	Paragraph 6, Study Aim and Design; prospective comparative cohort study to assess the feasibility of the preoperative injection of SPIO.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Paragraph 6, Study Aim and Design; prospective comparative cohort study.
Participants	**6**	Eligibility criteria	Patient Selection; inclusion and exclusion criteria stated. Patients aged over 18 years, diagnosed with invasive breast cancer [or] DCIS, with negative axilla in clinical examination and ultrasound. Exclusion criteria: hypersensitivity to dextran compounds, iron or Sienna+, iron overload disease, pregnancy, pacemaker, or other implantable metallic devices, in the chest wall, or inability to provide written informed consent. All patients had to be available for postoperative follow-up.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Not explicitly reported; symptoms and disease status integral to inclusion criteria.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Study Aim and Design; breast department of Uppsala University Hospital. Results; recruitment period September 2014 to October 2014.

	9	Whether participants formed a consecutive, random or convenience series	Results; consecutive patients. Number of patients assessed for eligibility, number excluded (with reasons) explicitly reported in Fig 1 flow chart.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Tracer Injection-Operative Protocol. 2ml Sienna+ diluted with 3ml local anaesthesia, injected subareolarly during pre-operative visit in outpatient clinic. Days between SPIO injection and operation, median 8 days reported in Table 1. Sentimag used first, results confirmed with gamma probe.
	10b	Reference standard, in sufficient detail to allow replication	Tracer Injection-Operative Protocol. Tc-99m injected subareolarly either on day of surgery or day before. Lymphoscintigraphy not performed. Patent Blue V (1-2ml) injected after onset of anaesthesia. Sentimag used first, results confirmed with gamma probe.
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction states established method of SN tracing using radioisotope and blue dye, with detection rate as high as 99%.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Tracer Injection-Operative Protocol; index test ability to detect SLNs using probe (magnetism) and visual confirmation (brown colouration). "All sentinel nodes were excised until the counts were lower than 10% of the highest count or a maximum of four nodes per patient were removed."
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Tracer Injection-Operative Protocol; reference standard ability to detect SLNs using probe (radioactivity) and visual confirmation (blue colouration). "All sentinel nodes were excised until the counts were lower than 10% of the highest count or a maximum of four nodes per patient were removed."
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Tracer Injection-Operative Protocol; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded).
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Tracer Injection-Operative Protocol; index test also performed by the surgeon identifying lymph nodes for retrieval (not blinded).
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Statistical Analysis; ability of index and reference standard to detect the SLNs independently and in combination. Correlation via Spearman. Comparison of detection via McNemar's.
	15	How indeterminate index test or reference standard results were handled	Statistical Analysis; Detection rate reported as binary value (detected/not detected) so indeterminate results N/A.
	16	How missing data on the index test and reference standard were handled	Tracer Injection-Operative Protocol, Statistical Analysis, and Results; only SLNs with histologically confirmed node status included in the

			analysis. Not explicitly report that suspicious nodes (not detected by either tracer) were removed by surgeon.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Statistical Analysis; statistical analysis performed for non-inferiority for error rates for detection, concordance defined.
	18	Intended sample size and how it was determined	Sample size power calculations not reported, pilot study design (feasibility reported)
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Results section provides narrative, Figure 1 provides flow diagram.
	20	Baseline demographic and clinical characteristics of participants	Characteristics presented in Table 1.
	21a	Distribution of severity of disease in those with the target condition	Table 1 reports the diagnostic status of the participants (multifocality, tumour size, histological type, nuclear grade, receptor status, T-stage) not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Results; detection rates for positive (malignant) nodes and patients reported but not referenced to expected population statistics and poorly reported particularly in relation to the detection rates with the index and reference tests.
	22	Time interval and any clinical interventions between index test and reference standard	Tracer Injection-Operative Protocol; order of test analysis reported (Sentimag then gamma probe), index test and reference standard performed concomitantly.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative concordance provided in Results; results shown in Tab 1 (median, range nodes); no cross-tabulation provided
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results with p values (no 95% CI reported)
	25	Any adverse events from performing the index test or the reference standard	Narrative reported in Results. Decline in magnetic signal in single volunteer plotted (Figure 4). States that 15 days after the injection, the volunteer passed a metal detector (Ceia02PN20) at an airport without detection of ferromagnetic signal. “No side effects were reported by the patients or the volunteer. Data on the long-term follow-up of SPIO-induced skin staining will be reported elsewhere.”
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Discussion; limitations including feasibility/pilot design and small numbers of patients with very specific disease status. States that larger numbers are required to document that SPIO performance is not compromised by factors such as axillary metastases, previous surgery, or

			primary systemic treatment. Authors acknowledge that this small pilot is unable to address costs issues.
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion of service implementation, specifically considerations for index test injection timing, reported in Discussion. "As far as cost issues are concerned, compared to the intraoperative injection of SPIO, preoperative injection is advantageous as one could spare the 5-min massage at the injection-site as well as the 20 min required as minimum for SPIO to migrate to the axilla, thus sparing operative time."
OTHER INFORMATION			
	28	Registration number and name of registry	Not reported.
	29	Where the full study protocol can be accessed	Full protocol not provided. Supplementary material available (CONSORT checklist)
	30	Sources of funding and other support; role of funders	Funding; study sponsored by the study site (Uppsala University). No declarations of conflicting interests reported.

Piñero-Madrona *et al.* 2015 (n=181, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; SLN identification with SPIO (index test) as a tracer for SLNB, comparative, non-inferiority study. Abstract: detection rate and concordance reported.
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; structured with aims, methods, results and conclusions.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction, paragraphs 1-3; provides scientific and clinical background. Disadvantage of gold standard is exposure of patients and physicians to radiation, short half-life of radioisotope, availability, handling and disposal.
	4	Study objectives and hypotheses	Introduction, paragraph 4; "The study was designed to show the non-inferiority of [Sentimag] as compared to the [gamma probe] technique, for the detection of SLN in breast cancer patients in whom a SLN biopsy is indicated."
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Prospective/retrospective not explicitly stated. Patients provided informed consent to participate in the study (prospective design assumed).
Participants	**6**	Eligibility criteria	Materials and Methods, Study Subjects; inclusion and exclusion criteria reported. Breast cancer patients aged 18 years or older, scheduled for SLNB, pre-operatively node negative, clinically and radiologically. Exclusions: had received neoadjuvant therapy, were intolerant to iron or dextran compounds, administration of radioisotope contraindicated, disorders implying high iron concentration, pacemaker or other metallic device implanted in thorax wall.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Study Subjects; eligible patients identified from existing clinical pathway.

	8	Where and when potentially eligible participants were identified (setting, location and dates)	Materials and Methods, Study Subjects; setting and location reported (9 Spanish hospitals with extensive experience in SLNB). Recruitment period reported in Results, Patient Characteristics (November 2013 to June 2014).
	9	Whether participants formed a consecutive, random or convenience series	Results, Patient Characteristics; consecutive recruitment, number meeting study selection criteria reported. Number of patients invited to participate or those declining participation not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Preoperative Procedures and SLN Detection Methods. On day of surgery, 2ml Sienna+ diluted in saline to final volume 5ml, injected subcutaneously in the subareolar area (after anaesthesia, but before blue dye, if used). Intradermal injection must be avoided in order to prevent skin pigmentation. 5 min massage, and 20 mins after injection, transcutaneous detection attempted with both devices before incision.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Preoperative Procedures and SLN Detection Methods; poorly reported. Injection of radioisotope tracer and optionally an injection of methylene blue as per "standard protocol of each centre". Number of centres and patients using/receiving blue dye not reported, subgroup analysis not performed.
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction states gold standard as combined technique (radioisotope and blue dye) with gamma probe.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Materials and Methods, Preoperative Procedures and SLN Detection Methods; index test ability to detect SLNs using probe (magnetism) and visual indicator (brown colouration) also noted. "All nodes with positive reading with [Sentimag] were excised as long as their reading was superior to 10$ of the node with the highest [Sentimag] reading."
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Materials and Methods, Preoperative Procedures and SLN Detection Methods; reference standard ability to detect SLNs using probe (radioactivity) with and without visual indicator (blue colouration) noted. "All remaining nodes positive with GP were excised as long as their reading was superior to 10% of the node with the highest GP reading."
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Materials and Methods, Preoperative Procedures and SLN Detection Methods & Data Collection and Outcomes; Sentimag first, then gamma probe; surgeon identifying lymph nodes for retrieval (not blinded).
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Materials and Methods, Preoperative Procedures and SLN Detection Methods & Data Collection and Outcomes; Sentimag first, then gamma probe; surgeon identifying lymph nodes for retrieval (not blinded).
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Materials and Methods, Data Collection and Outcomes & Statistical Analysis; ability of index and reference standard to detect the SLNs independently and

			in combination; detection rate for malignant nodes also explored. Detection rate per patient and per node.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable.
	16	How missing data on the index test and reference standard were handled	Materials and Methods, Data Collection and Outcomes; all SLNs identified by either method retrieved and palpable SLNs not picked up by either technique also retrieved (as reporting in Table 2). [Missing data in patient characteristics explicitly reported – footnote]
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Materials and Methods, Statistical Analysis: difference in detection rates computed using the Wald method.
	18	Intended sample size and how it was determined	Non-inferiority was declared if a pre-defined advantage of 5% (or higher) of the gamma probe device over the Sentimag device could be ruled out.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	No flow diagram provided.
	20	Baseline demographic and clinical characteristics of participants	Results, Patient Characteristics, Tab 1; narrative and tabulated overview of patient characteristics. One male patient included but not reported exclusively.
	21a	Distribution of severity of disease in those with the target condition	Table 1 reports the diagnostic status of the participants (tumour side, single/multiple tumours, size, grading, hsitological type, progesterone, estrogen, Ki67 receptor, and HER2 status), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive nodes and patients reported in Results, SLN Detection of Histopathologically Positive Nodes and Table 3 but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Materials and Methods, Preoperative Procedures and SLN Detection Methods; order of test analysis reported, timing of radioisotope not explicitly reported.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results, Preoperative Procedures and SLN Detection and SLN Detection of Histopathologically Positive Nodes; results also reported in Tables 2 and 3. Results from other studies also included in Table 4 and narrative provided in Discussion.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; one-sided 95% CI reported in Tables 2 and 3.
	25	Any adverse events from performing the index test or the reference standard	Results, Technical Complications & Extraaxillary Detection; narrative for index test and reference standard provided. Complications in 11 patients (6 in Sentimag, 2 with gamma probe, 3 with both), related to failure of the initial

			transcutaneous detection attempt, or disprepancy of results between detection devices. No difference in patient characteristics between those with and without technical complications were found.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Discussion; non-standardised reference standard (varied by centre) however authors consider this a pragmatic trial thus improving external validity of the results; surgical investigators members of the same group (Spanish Society of Senology), no other limitations, statistical uncertainty or generalisability discussed. Authors acknowledge new thinner Sentimag probe, and that the calibration process does not imply a significant difference with isotopic techniques. Also mentioned is possible interference of surgical instrumentation thus need for plastic tools when using Sentimag.
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion; "The fact that the SentiMag/Sienna system is noninferior to the current standard for SLNB procedure implies that it should be considered as a solid alternative. This is of special interest to hospitals without in-house nuclear medicine department, whose clinicians and patients can benefit from the logistic advantages while keeping a standard-like performance."
OTHER INFORMATION			
	28	Registration number and name of registry	No trial reference stated or identified.
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Reports no conflicts of interest. "no significant financial support for this work that could have influenced its outcome".

Pouw *et al.* 2015 (n=11, feasibility, prospective cohort. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Not reported, study is a subprotocol of larger trial (SentiMAG), assumes non-inferiority of index test to standard reference. Abstract states "equal performance"
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; includes objectives, methods, results, conclusion and advances in knowledge.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Paragraphs 1-3; current clinical and scientific background discussed. Limitations of radioisotopes: exposes patients and medical staff to radiation, governed by stringent legislation.
	4	Study objectives and hypotheses	Paragraph 4; feasibility of MRI for pre-operative localisation of SLNs in breast cancer with index procedure as an alternative to lymphoscintigraphy or SPECT-CT imaging.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Not explicitly stated, assumed prospective as informed consent was given prior to interventions.
Participants	**6**	Eligibility criteria	Materials and Methods, Patients, paragraph 5; inclusion and exclusion criteria stated. Patients with histologically confirmed breast cancer who were clinically and radiologically node-negative and scheduled to undergo SLNB. Exclusion criteria were known intolerance to iron or dextran compounds, iron overload disorder and the standard MRI exclusion criteria. Furthermore, patients scheduled for a 1-day protocol were excluded for logistical reasons.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Patients, paragraph 5; patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Setting not explicitly stated. Materials and Methods, Patients, paragraph 5; recruitment dates Jul 2012-Mar 2013.

	9	Whether participants formed a consecutive, random or convenience series	Not specified. Number of patients approached and declining participation not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Superparamagnetic Iron Oxide MRI section. Sienna+ 2ml + 3ml saline, periareolar subcutaneous injection. In 9/11 patients the magnetic tracer was administered after radioisotope, in 2/11 it was before. In first two patients, injection-site was not massaged, in the remaining 9/11 injection-site was massaged for 3-5 min to promote lymphatic drainage. Post-contrast imaging of the breast and axillary region was started approx. 5 mins after injection.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Planar Lymphoscintigraphy and Single Photon Emission CT-CT. Limited details with 'as per standard practice' reported. Blue dye administration detailed in Materials and Methods, Surgery section. Blue dye administered periareolarly intraoperatively after induction of anaesthesia. A gamma probe was used for subsequent confirmation of magnetometer results.
	11	Rationale for choosing the reference standard (if alternatives exist)	Abstract and discussion refer to "standard combined technique".
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Methods, Surgery; index test ability to detect SLNs using probe (magnetism). "Any iron-containing and/or radioactive and/or blue SLNs were removed."
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Methods, Surgery; index test ability to detect SLNs using probe (magnetism). "Any iron-containing and/or radioactive and/or blue SLNs were removed."
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Methods, Surgery; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded). Gamma probe used for subsequent confirmation – assume not blinded.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Methods, Surgery; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded). Gamma probe used for subsequent confirmation – assume not blinded.
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Methods, Surgery; ability of index and reference standard to detect the SLNs independently and in combination. Concordance reported (between LS and SPECT-CT). No. of magnetic and radioactive nodes resected for each patient tabulated in Table 1.
	15	How indeterminate index test or reference standard results were handled	Methods, Surgery; Detection rate reported as binary value (detected/not detected) so indeterminate results N/A. Assume that the surgeon did not remove any clinical suspicious (but non-radioactive and non-magnetic) nodes

	16	How missing data on the index test and reference standard were handled	Methods, Surgery; only SLNs retrieved included in the analysis, method of identification compared (imaging, index test, reference standard).
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not reported, feasibility trial but explored SLNs on MRI and LS/SPECT-CT
	18	Intended sample size and how it was determined	Not reported, feasibility trial
RESULTS			
Participants	**19**	Flow of participants, using a diagram	No narrative, no flow diagram provided.
	20	Baseline demographic and clinical characteristics of participants	Results section provides limited narrative (proportion of invasive carcinoma and DCIS, age), no tabulation of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Proportion of invasive and DCIS only.
	21b	Distribution of alternative diagnoses in those without the target condition	Results; histopathological analysis and detection rates for positive nodes reported for 2 patients, not referenced to expected population statistics. Very small sample size.
	22	Time interval and any clinical interventions between index test and reference standard	Gamma probe used for subsequent confirmation.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results, Tab 1 reports the number of nodes identified with each method (imaging, index test, reference standard) – unclear whether these agree (no 2x2 table provided).
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results sections including patients with histopathologically positive nodes, small sample size without statistical analysis. Detection rates able to be calculated from Tab 1.
	25	Any adverse events from performing the index test or the reference standard	Not reported. Does mention histopathologically node-negative patients were falsely classified as metastatic.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Discussion section, limitations include small sample size (patients could participate in the surgical trial without participating in this imaging subprotocol) and low number of metastatic SLNBs in cohort.
	27	Implications for practice, including the intended use and clinical role of the index test	Conclusion section. Further research needed for evaluation of MRI characterization of LN involvement using subcutaneous injection of magnetic tracer.
OTHER INFORMATION			
	28	Registration number and name of registry	Introduction, paragraph 4; SentiMAG trial registration and number reported, study is subprotocol of this, NTR (trialregister.nl): NTR3238
	29	Where the full study protocol can be accessed	Full protocol not provided; additional information from main SentiMAG protocol available from trial registration.

	30	Sources of funding and other support; role of funders	Acknowledgments & Funding; Study sponsored by Dutch Technology Foundation STW (part of Netherlands Organisation for Scientific Research (NOW). NIHR BRC funding scheme. Research was supported by an unrestricted Educational Grant from manufacturer (Endomagnetics Ltd, UK). Role of funders not explicitly reported.

Rubio *et al.* 2015 (n=120, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; method equivalence. Abstract: measure concordance between superparamagnetic iron oxide and radiotracer
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; introduction, materials and methods, results and discussion.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction, paragraphs 1-2; current clinical and scientific background discussed. Drawbacks of standard technique: radiation exposure, dependency on nuclear medicine, controversy on the need for lymphoscintigraphy, allergy to blue dye mild to severe in 0.4% patients.
	4	Study objectives and hypotheses	Introduction, paragraph 3; investigate the use of SPIO for the SLN detection compared to the radioisotope method in clinically node negative breast cancer patients.
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Abstract, Materials and Methods; prospective study.
Participants	**6**	Eligibility criteria	2.1 Materials Methods, Study Subjects, paragraph 6; inclusion and exclusion criteria stated. Patients diagnosed with breast cancer and clinically node negative axilla Tis, T1-T3, N0, evaluated for SLN. Axilla evaluated by clinical examination and axillary ultrasound in all patients. Exclusion criteria: patients with hypersensitivity or intolerance to the iron oxide or dextran compounds with iron overload disease, with pacemakers or other iron implantable devices in the chest wall, or pregnancy.
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Study Design; eligible patients identified from existing clinical pathway.

	8	Where and when potentially eligible participants were identified (setting, location and dates)	Materials and Methods, Breast Surgical Oncology Unit at the Hospital Universitario Vall d'Hebron. Study Design; setting, and location reported. Recruitment dates reported in Results section (July 2013-March 2014).
	9	Whether participants formed a consecutive, random or convenience series	Not explicitly stated. Number of patients approached and declining participation not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Surgery. 2ml Sienna+, 3ml saline, massage 5 mins, 20 mins wait count on the breast and axilla with Sentimag before incision.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Study Design, paragraph 6 & continued in Materials and Methods, Surgery. Tc-99m day before with lymphoscintigraphy and SPECT-CT. No blue dye used.
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction states gold standard technique as radioisotope.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Materials and Methods, Surgery; index test ability to detect SLNs using probe (magnetism) and visual indicator (brown colouration). Sentinel nodes were excised until the counts were <10% of the highest count and this applied to Tc-99m and SPIO.
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Materials and Methods, Surgery; reference standard ability to detect SLNs using gamma probe (radioactivity). Sentinel nodes were excised until the counts were <10% of the highest count and this applied to Tc-99m and SPIO.
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Materials and Methods, Surgery; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded) however results from lymphoscintigraphy (conducted at Tc-99m injection on the day before) blinded to surgeon.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Materials and Methods, Surgery; index test also performed by the surgeon identifying lymph nodes for retrieval. States surgeon was blinded to the results of the lymphoscintigraphy (assumed to be the lymphatic mapping conducted day prior with Tc-99m injection). Sentimag first then gamma probe.
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Materials and Methods, Study Objectives; ability of index and reference standard to detect the SLNs independently and in combination.
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable. Sentinel nodes was considered if it was radioactive, magnetic or palpable node.

	16	How missing data on the index test and reference standard were handled	Not explicitly reported, method of SLN detection for each method reported. SLNs removed and detected by neither test reported.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Materials and Methods, Statistical Analysis; detection by Tc-99m only, Sienna+ only, both techniques.
	18	Intended sample size and how it was determined	5% non-inferiority assuming 95% detection rate.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Narrative provided in Methods and Materials and Results sections, no patient flow diagram provided.
	20	Baseline demographic and clinical characteristics of participants	Results, Tab 1; narrative and tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Tab 1 reports the diagnostic status of the participants (tumour grade, type, estrogen, progesterone, Ki67 receptor and HER2 status, type of surgery, intraoperative ultrasound), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive nodes and patients reported in Results section but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Materials and Methods, Surgery; order of test analysis reported, index test and reference standard performed concomitantly. Results from lymphoscintigraphy (from day before when Tc-99m injected) blinded from surgeon.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results; results also reported in Tables 2 for positive SLNs only.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; CI not reported. P-values for number of SLNs reported.
	25	Any adverse events from performing the index test or the reference standard	Results section; only AEs relating to index test reported. “There were no allergic reactions to the SPIO injection. Twenty patients (19%) developed a grayish breast tattoo that started to fade after 6 months.”
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Limitations of study not explicitly stated. Sources of bias from influences from each method reported in Discussion section. Statistical uncertainty not reported. Generalisability not reported.
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion; surgical learning curve, adverse events reported (compared to inclusion of blue dye that was not used as a comparator) reported.
OTHER INFORMATION			

	28	Registration number and name of registry	Not reported.
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Source of Funding; study sponsored by index test manufacturer and role of funder reported (no role in study design, analysis or interpretation of the data). Authors declare no conflicts of interest.

Rubio *et al.* 2020 (n=135 total – only cohort 3 aligns with device IFU (n=45), non-inferiority, prospective randomised controlled trial. Participants received both the intervention and comparator.)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; comparison of different tracer doses for SLNB in breast cancer. Abstract: mentions non-inferiority, and concordance
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; introduction, methods, results and conclusion.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction, paragraphs 1-4; current clinical and scientific background discussed. Drawbacks of radioisotope: radiation exposure, dependency on nuclear medicine, need for lymphoscintigraphy in some cases, allergy to blue dye. Study also investigating the impact of different doses of index test noting that Sienna XP particles are smaller than the 60 nm previous version (Sienna+).
	4	Study objectives and hypotheses	Introduction, paragraph 5; "this randomised study has been designed to assess the accuracy of intraoperative detection of the SLN with Sienna XP (Magtrace), using different doses of the magnetic tracer to evaluate its non-inferiority compared to the conventional techniques and to assess the presence of skin staining".
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Methods, Patients; "The study was a prospective randomised study"
Participants	**6**	Eligibility criteria	Methods, Patients, paragraph 6; inclusion and exclusion criteria, gender not listed in inclusion but is applied in listed exclusion criteria: "Patients were eligible if they were diagnosed with early-stage breast cancer cT1-3, N0, and were planned to have breast conservative surgery plus SLN biopsy. Women with intolerance or [hypersensitivity] to iron, dextran compounds or Sienna+,

			iron overload disease, carrying pacemaker or implantable devices in the chest wall, and pregnant women were excluded."
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Methods, Patients; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Methods, Patients; setting, and location reported. Recruitment dates reported in Abstract, Methods section (at the Breast Surgical Unit of the Hospital Universitario Vall d'Hebron: October 2016 to August 2018).
	9	Whether participants formed a consecutive, random or convenience series	Methods, confirms patients were consecutively randomised. Number of patients approached and declining participation not reported. "In case a patient needed a mastectomy after breast conservation for positive margins, she was excluded from the study and a new patient was randomized."
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Surgery. The day of surgery, after induction of anaesthesia, subareolar injection, 5 min massage, after 20 min SLN located transcutaneously in axilla. Once SLN located with hand held magnetic probe, the removal and checking of the counts and the measurement of radioactivity were done.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Study Design, paragraph 6 & continued in Materials and Methods, Surgery. Day before surgery Tc-99m diluted in 0.2cm saline, subareolar injection. No mention of blue dye.
	11	Rationale for choosing the reference standard (if alternatives exist)	Standard of care reported in Introduction as radioisotope, blue dye, combination of both techniques.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Methods, Procedures; index test ability to detect SLNs using probe (magnetism). "the residual activity in the armpit was checked with the gamma probe and the hand held manometer to ensure that all radioactive and/or ferromagnetic nodes were removed."
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Methods, Procedures; reference standard ability to detect SLNs using probe (radioactivity) "the residual activity in the armpit was checked with the gamma probe and the hand held manometer to ensure that all radioactive and/or ferromagnetic nodes were removed."
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Methods, Procedures; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded), magtrace and then gamma probe.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Methods, Procedures; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded), magtrace conducted first.
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Methods, Procedures; ability of index and reference standard to detect the SLNs independently and in combination. Statistical analysis: concordance.

	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable. No reported cases of negative by both techniques.
	16	How missing data on the index test and reference standard were handled	Not explicitly reported, method of SLN detection for each method reported. Table 3 SLN negative and SLN positive do not add to 45 for Group 1 and 2.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Methods, Statistical Analysis; detection concordance.
	18	Intended sample size and how it was determined	Methods, Statistical Analysis; sample size calculation reported for non-inferiority margin 10%, assuming 10% loss of cases.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Narrative provided in Methods and Results sections, no patient flow diagram provided. Not all patients accounted for in groups 1 and 2 (Table 3).
	20	Baseline demographic and clinical characteristics of participants	Results, Tables 1 & 2; narrative and tabulated overview of patient characteristics. Significant difference in age, mammographic density and histology between groups.
	21a	Distribution of severity of disease in those with the target condition	Table 1 reports the diagnostic status of the participants, not referenced to expected population statistics. Disease status integral to inclusion criteria. Tumour size, grade, estrogen, progesterone, Ki67 receptor and HER2 status, T1-T3, N0-N1. Includes patients with known lymph node involvement.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive nodes and patients reported in Results, Sentinel Node Identification section and Tab 3, but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Methods, Procedures; order of test analysis reported (magtrace first), index test and reference standard performed concomitantly (same surgery).
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results; results also reported in Table 3 (no 2x2 table)
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; CI not reported, concordance with p values reported.
	25	Any adverse events from performing the index test or the reference standard	Results, Skin Staining, EORTC questionnaires reported.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Limitations of study not explicitly stated. Baseline differences between groups reported with limited impact on outcomes. Comparison with Nordic study in conclusions. Sources of bias not explicit. Statistical uncertainty not reported. Generalisability not reported.

	27	Implications for practice, including the intended use and clinical role of the index test	Discussion; surgical learning curve, adverse events reported (compared to inclusion of blue dye that was not used as a comparator) reported.
OTHER INFORMATION			
	28	Registration number and name of registry	Not reported.
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Source of Funding; study sponsored by index test manufacturer and role of funder reported (no role in study design, analysis or interpretation of data). Authorship contribution statement included.

Thill *et al.* 2014a (n=150, non-inferiority, prospective non-randomised controlled trial. Participants received both the intervention and comparator)
First reviewer: RP Second reviewer: KK

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title; SLNB with SPIO vs radioisotope (reference standard). Abstract reports "non-inferiority"
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	Abstract; formal structure with headings not provided.
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	Introduction; history of detection methods provided, brief discussion to drawbacks and need for alternative options (radiation exposure of patients and healthcare personnel, strong legislative control, limitations in tracer availability, dependency on nuclear medicine units and allergic reactions to blue dye). Clinical context of breast cancer not specified.
	4	Study objectives and hypotheses	Introduction, paragraph 3; " The aim of our study was to investigate the potential equivalency of the SentiMag technique in comparison to the gold standard of SLNB."
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	Materials Methods, Trial Design and Patient Recruitment; prospective non-randomised paired equivalence study.
Participants	**6**	Eligibility criteria	Materials and Methods, Trial Design and Patient Recruitment; inclusion and exclusion criteria reported. Included 150 patients with histopathologically verified breast cancer. Planned for SLNB, with clinically and ultrasonographically node-negative invasive breast carcinoma or extended DCIS were eligible. Exclusion criteria: allergy to iron r dextran compounds, iron overload disease, pacemaker or ferrous metal-containing devices in chest wall, pregnancy or lactation.

	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	Materials and Methods, Trial Design and Patient Recruitment; eligible patients identified from existing clinical pathway.
	8	Where and when potentially eligible participants were identified (setting, location and dates)	Materials and Methods, Trial Design and Patient Recruitment; recruitment dates reported: November 2012 to June 2013. States multicenter and multinational, but specific location not specified. Conclusion states 4 Central-European centres.
	9	Whether participants formed a consecutive, random or convenience series	Not explicitly reported. Number of patients invited to participate or those declining participation not reported.
Test methods	**10a**	Index test, in sufficient detail to allow replication	Materials and Methods, Intraoperative Proceedings. After induction of anaesthesia 2ml Sienna+ diluted to 5ml with saline, injected subareolar interstitial tissue at least 20 mins before SLNB, followed by 5 mins massage. Sentimag probe used for detection. To avoid interference, polymer retractors and forceps were used.
	10b	Reference standard, in sufficient detail to allow replication	Materials and Methods, Intraoperative Proceedings. Radioisotope following 1or 2 day protocol. Tc-99m injected periareolary or peritumorally and lymphoscintigraphy performed pre-operatively. Explicitly states: "No additional injection of blue dye was performed." Gamma probe used for detection.
	11	Rationale for choosing the reference standard (if alternatives exist)	Introduction states gold standard as radiotracer alone or in combination with blue dye.
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	Materials and Methods, Intraoperative Proceedings. "All LNs marked with either tracer were excised." "A LN with less than 10% of the maximum SLN count number was defined as a non-SLN for both techniques. Therefore, SLNB was stopped when the residual activity in the axilla was less than 10%. SLNs and non-SLNs were submitted separately for histopathological examination."
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Materials and Methods, Intraoperative Proceedings; as above.
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	Materials and Methods, Intraoperative Proceedings; reference standard performed by the surgeon identifying lymph nodes for retrieval (not blinded). SLNs marked with either tracer excised, probe counts were performed prior to incision and procedures performed in parallel.
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	Materials and Methods, Intraoperative Proceedings; index test also performed by the surgeon identifying lymph nodes for retrieval (not blinded). SLNs marked with either tracer excised, probe counts were performed prior to incision and procedures performed in parallel.
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	Materials and Methods, Study Objectives and Statistical Analyses; "Concordance was defined as the number of simultaneously radioisotope- and

			SPIO-positive patients or nodes, divided by the number of patients or nodes marked by radioisotope. Reverse concordance was defined as the number of simultaneously radioisotope and SPIO positive patients or nodes, divided by the number of patients or nodes marked by the SPIO tracer."
	15	How indeterminate index test or reference standard results were handled	Detection rate reported as binary value (detected/not detected) so indeterminate results not applicable.
	16	How missing data on the index test and reference standard were handled	Not explicitly reported, Fig 2 includes SLNs not detected by either method but not explicit how these were identified for excision. All SLNs identified by either method retrieved.
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Materials and Methods, Study Objectives and Statistical Analyses: "Detection rate was additionally tested in a right-sided binominal test with the alternative hypothesis that the proportion of successful SLNBs was greater than 0.92 for each tracer."
	18	Intended sample size and how it was determined	Power calculation based on 97% detection rate of standard care, defined limit for equivalence of -5%, statistical threshold for detection rate was prospectively set at 92% to accept non-inferiority of the magnetic method.
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Fig 1, study workflow. Number of patients withdrawn or invited not reported.
	20	Baseline demographic and clinical characteristics of participants	Tab 1; tabulated overview of patient characteristics.
	21a	Distribution of severity of disease in those with the target condition	Tab 1 reports the diagnostic status of the participants (carcinoma type, tumour size, lymph node status (unclear why given inclusion criteria), grading, estrogen, progesterone receptor and HER2 status), not referenced to expected population statistics. Disease status integral to inclusion criteria.
	21b	Distribution of alternative diagnoses in those without the target condition	Detection rates for positive nodes and patients (malignancy) reported in Results, Fig 2E-H, but not referenced to expected population statistics. Disease status integral to inclusion criteria.
	22	Time interval and any clinical interventions between index test and reference standard	Materials and Methods, Intraoperative Proceedings; order of test analysis assumed to be index test and reference standard; paper states performed in parallel.
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Narrative provided in Results; results also reported in Fig 2.
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Narrative provided in Results section; concordance with CI values reported.

	25	Any adverse events from performing the index test or the reference standard	Results; "No complications in terms of allergic reactions, or irritations at the injection-site were observed". Assume refers to both index and reference standard.
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	Limitations not reported. Generalisability: "Moreover, all patients with malignant LN involvement would have been identified after sampling the two lymph nodes with the highest magnetic or radioisotope count even if more LNs were retrieved using either method, suggesting a low false negative rate if Sienna+ is to be introduced into clinical routine as standard method."
	27	Implications for practice, including the intended use and clinical role of the index test	Discussion; non-inferiority concluded. Conclusion; index test can be rapidly implemented into daily routine care. States "If further and consistent results prove its efficacy, this technique has the potential to become standard of care."
OTHER INFORMATION			
	28	Registration number and name of registry	Not reported.
	29	Where the full study protocol can be accessed	Full protocol not provided.
	30	Sources of funding and other support; role of funders	Acknowledgements; study sponsored by index test manufacturer and role of funder reported (Company had no involvement in the collection and interpretation of data, writing of the manuscript and the decision for publication). Scientific support in data analysis was provided by two named personnel from the Company.

Appendix B3: Observational studies, assessment using the NIH National Heart, Ling and Blood Institute Cohort tool.

Bazire *et al.* 2019 (n=288)

First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			Single institutional analysis of acceptability and experience of radiation therapy following magnetic tracer use in SLNB.
2. Was the study population clearly specified and defined?	✓			Single-centre experience, consecutive patients with early stage breast cancer receiving neoadjuvant treatment following SLNB with Sienna+ between specified recruitment period (Oct 2013-Dec 2016). Specific to breast cancer patients undergoing SLNB and tumour localisation with magnetic markers
3. Was the participation rate of eligible persons at least 50%?	✓			520 patients in database, 364 with early breast cancer without any neoadjuvant treatment, 288 (79.1%) had adjuvant radiotherapy.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Prospective database review. Specific data collection methods not specified.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		Reasons for this sampling not specified, however large sample size from all patients screened for inclusion reported.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Prospective study. No trial registration.

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			✓	Skin pigmentation reported up to 6-9 months after surgery, however mean follow-up and loss to follow-up not explicitly reported.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?	✓			2ml Sienna+, injected peri-areolar area.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		"For first 30 patients double detection was implemented with the isotope method. Then, only the magnetic procedure was performed."
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		Number of SLNs detected and excised, patient characteristics including ranges where appropriate, adverse events captured from review of medical note review; checking and quality assurance processes not specified.
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?			✓	Mean follow-up not reported.
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between		✓		No multivariate analysis applied, no statistical tests. Narrative description of results.

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
exposure(s) and outcome(s)?				
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	No anaphylactic reaction reported. Authors acknowledge the study as the largest series published regarding tolerance of radiotherapy after use of magnetic tracer for sentinel lymph node detection in breast cancer. However acknowledge lack of published data for comparison, lack of follow-up MRI studies. Report that patients with genetic features requiring MRI in the follow-up period should not receive the magnetic tracer. Author contributions not reported, funding source not reported, authors declare no conflict of interests.			
Quality Rating	Poor			

Chapman *et al.* 2020 (n=16)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			"The aim of this study is to investigate the early impact of SPIO-related artifact on the interpretation of postoperative breast MRI at our institution."
2. Was the study population clearly specified and defined?	✓			Single-centre experience with explorative retrospective study design, patients with MRI reports following SLNB with Sienna+/Magtrace between specified recruitment period (1st January 2015 and 1st May 2020).
3. Was the participation rate of eligible persons at least 50%?			✓	No patient flow diagram, no narrative of participants.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Retrospective database review with MRI reports, images, and relevant oncologic and surgical history collected. Method of data collection and reviewers not explicitly reported.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		Reasons for this sampling not specified, assumed to be convenience sampling from existing database.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			MRI reports, images, and relevant oncologic and surgical history were collected from institution's online radiology database. No trial registration.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			Mean time from injection of SPIO particles to baseline postoperative MRI was 10.8 months (3-18 months).

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?		✓		2-5ml subareolar injection of SPIO after anaesthesia.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		All but 1 patient had axillary lymph nodes removed intraoperatively – axillary magnetic signal not detected due to technical reasons, SLNB deferred.
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		Pathology results, skin discolouration, MRI outcomes including artefact).
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?	✓			Intrinsic to study selection (patients MRI with previous SPIO injection).
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		✓		No multivariate analysis applied, no statistical tests. Narrative description of results.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	Authors highlight that convenience of non-radioactive SPIO which do not require nuclear medicine facilities must be weighed against the need for post-operative diagnostic and surveillance MRI. Authors acknowledge that study is small, does			

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
	not include statistical analysis and does not assess if artefact lessens with time. Author contributions not reported. Funding: none declared. Conflict of interest: none declared.			
Quality Rating	Poor			

Gutesa *et al*. 2016 (n=128)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			Analysis of initial experience with SentiMag and Magtrace.
2. Was the study population clearly specified and defined?	✓			Preliminary study, prospectively recruited patients from single centre. Inclusion and exclusion criteria listed.
3. Was the participation rate of eligible persons at least 50%?	✓			Only 3/128 excluded (DCIS from final pathology).
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			✓	Prospective study. Time period undefined. Inclusion and exclusion criteria listed.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		No sample size calculations provided.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Methods of data collection, categories of data and missing data not explicitly reported. Number of adverse events and signal detection issues recorded. No trial registration.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			Intraoperative results only. [Discussion] Inconsistent probe readings in patients with high BMI, vascular diseases, smokers, diabetics, and elderly patients.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as	✓			2ml Sienna+ applied subcutaneously under nipple areola complex.

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?				
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Sentimag applied transcutaneously to hint location, then skin incision and lymph node tracked with probe signals.
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		Not prospectively defined (adverse events incidental finding).
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?			✓	No follow-up, intraoperatively only.
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		✓		No multivariate analysis applied, no statistical tests. Narrative description of results.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	Author contributions not reported, funding source and conflict of interests not reported. Authors do not list any limitations of study.			
Quality Rating	Poor			

Hersi *et al.* 2021 (n=534)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			"The aim of this study was to compare the SLN detection rate using Magtrace® at lower doses, with different timeframes and injection-sites, and to investigate whether they were noninferior to the previous SPIO solution of Sienna+®."
2. Was the study population clearly specified and defined?	✓			Inclusion and exclusion criteria lists. Dataset of Nordic SentiMag trial used for comparison.
3. Was the participation rate of eligible persons at least 50%?			✓	Patient flow diagram not included, no narrative description of patient participation.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?		✓		Consecutive patients were recruited. Recruitment period August 2017 and August 2018 (1.5ml) and May 2018 and September 2019 (1.0ml). Protocol violation resulted in 2 patients being excluded from the 1.5ml cohort.
5. Was a sample size justification, power description, or variance and effect estimates provided?	✓			Sample size calculations provided; non-inferiority design. Non-inferiority margin 4%. 150 patients, 10% drop-out, requiring 165 patients per cohort.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Multi-centre (N=6), prospective study. Trial registration: ISRTCN11156955
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			Skin staining reported up to 6 months postoperatively. "Long-term follow-up will be reported elsewhere."

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?	✓			Study is looking at difference in volumes of injection (2ml, 1.5ml, 1.0ml).
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			All SLNs detected intraoperatively with the Sentimag®, gamma probe or stained brown or blue were excised.
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Number of SLNs detected and excised, localisation time, excision time and calculated resection ratio calculated. Number of adverse events and skin staining recorded.
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?	✓			Mean follow-up not reported. Results from 6 months reported in 129/163 (1.5ml cohort) and 141/165 (1.0ml cohort), 82.5%
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	✓			Statistical comparisons for different methods were analysed. One stage individual patient data meta-analysis. Correction for multiple comparisons performed. Multi-variable regression reported.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	Exclude cohort where 1.5ml Magtrace used (against IFU). Authors acknowledge lack of randomisation, however study design was pragmatic. Author contributions reported. Company (Endomagnetics)			

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
	provided the Sentimag device and Magtrace for the trials, institutional funding provided by university and cancer foundation. Sponsors had no role in study design, collection, analysis or interpretation of the study. No conflict of interests declared.			
Quality Rating	Good			

Jazrawi *et al*. 2021 (n=79)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			Study aim was to determine whether the combination of Superparamagnetic iron oxide nanoparticles (SPIO) MRI-lymphography (MRI-LG) and a Magnetic-guided Axillary UltraSound (MagUS) with biopsy can allow for minimally invasive, axillary evaluation to de-escalate surgery.
2. Was the study population clearly specified and defined?	✓			Adult patients with clinically and ultrasound node-negative early breast cancer planned for SLNB. Exclusion criteria listed.
3. Was the participation rate of eligible persons at least 50%?			✓	Patient flow diagram not included, no narrative description of patient participation.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?		✓		Prospective data collection. Radiology imaging reviewed by multiple clinicians. Single centre, single-arm prospective trial design. Patients consenting during recruitment period of September 2017 to December 2017, single-centre experience perspective. Of 79 included patients, 48 had early breast cancer and underwent upfront surgery, 12 underwent neoadjuvant therapy, and 19 had recurrent breast cancer after previous breast and axillary surgery.
5. Was a sample size justification, power description, or variance and effect estimates provided?	✓			Power calculation described, 75 required between a maximum futility proportion of 95% (corresponding to the proportion of successful detection above which the method can

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
				be further considered) and a minimum efficacy of proportion of 85% (corresponding to the proportion of successful detection under which, the method should not warrant further investigation).
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Prospective study. No trial registration.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			MRI-LG 1-14 days after injection.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?	✓			2ml Magtrace,
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			The core needle biopsy was evaluated for the presence of brown staining and magnetic uptake with the SentiMag probe (ex vivo).
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Detection, malignancy.
12. Were the outcome assessors blinded to the		✓		Cannot blind (different injection, different probe).

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
exposure status of participants?				
13. Was loss to follow-up after baseline 20% or less?			✓	Not reported.
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		✓		Types and categories of data reported in Trial Design and Study Endpoints section with statistical analysis where appropriate.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	Authors acknowledge need for randomised trial. Author contributions reported. Institutional funding from university and breast cancer association; confirmed sponsors and funding bodies had no role in the study design, data collection, analysis or interpretation. No conflict of interests declared. Data available from corresponding author.			
Quality Rating	Fair			

Kurylcio *et al.* 2021 (n=78)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			Acceptability and experience of an existing SLNB technique in patients receiving neoadjuvant chemotherapy.
2. Was the study population clearly specified and defined?		✓		Inclusion and exclusion criteria not explicitly defined. Results state female patients only.
3. Was the participation rate of eligible persons at least 50%?			✓	Patient flow diagram not included, no narrative description of patient participation.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Patients operated on between February 2013 and December 2020. Database review, single centre.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		Feasibility study therefore no sample size calculations performed.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Sampled from a single-centre prospectively maintained database
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			Intraoperative outcomes only.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*,		✓		Sienna (2ml) and Magtrace (1ml; used from June 2019); no analysis between subgroups.

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
categories of exposure, or exposure measured as continuous variable)?				
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		SLN identification based on Sentimag and/or brown staining. All identified SN removed until background signal was less than 10% of highest value during SLNB.
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		Lymphadenectomy performed in 13 patients. Surgical margin, median time of lymph node retrieval, median number of resected SNs, serious adverse events.
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?	✓			Intraoperative outcomes only.
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	✓			Statistical management tool reported (MedCalc), use of median, IQR and ranges used for continuous variables; frequency and percentages were used for categorical variables.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	No limitations acknowledged by authors. Lack of comparative data. Author contributions; multiple authors and roles in methodology, data collection and validation. Confirms research received no external funding. No conflicts of interest declared. No data available.			
Quality Rating	Poor			

Lorek *et al.* 2019 (n=303)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			"The objective of this paper was to assess complications, including paresthesias, restricted upper limb mobility, lymphedema, and skin discolorations, following the sentinel lymph node biopsy (SLNB) in breast cancer patients using the SentiMag® method after 3.5 years from application."
2. Was the study population clearly specified and defined?	✓			Primary operative breast cancer, who received SLNB with wide local excision or simple mastectomy, or had autonomous SLNB prior to induction treatment based on SentiMag.
3. Was the participation rate of eligible persons at least 50%?	✓			303/368 attended follow-up outpatient clinic.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Database review (single centre) for patients who has undergone a SLNB procedure with SPIO between January 2014 and September 2017 with sufficient follow-up data retrievable.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		No sample size calculation.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Database review (single centre).
7. Was the timeframe sufficient so that one could reasonably expect to see an	✓			"The longest observation period was 42 months while the shortest was 5 months, yielding

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
association between exposure and outcome if it existed?				25.5 months of follow-up on average." Different follow-up for different cohorts (wide lesion excision, simple mastectomy, autonomous SLNB).
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?	✓			2ml Sienna+ administered under the areola.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Time between administration of tracer to dissection ranges between 1-12 hours (mean 3.8 hours).
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			"following medical history and clinical examinations: 1) sensory disturbances in the form of paresthesias (including hyperesthesia on the skin of the arm); 2) restricted range of motion (ROM) in the upper limb; 3) presence of lymphedema; and 4) discolorations on the skin of the breast."
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?	✓			Intrinsic to study selection.
14. Were key potential confounding variables measured and adjusted statistically for their impact	✓			Statistical data collected in database in Excel 2013, comparison of complications between WLE+SLNB and simple

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
on the relationship between exposure(s) and outcome(s)?				mastectomy+SLNB. No. of patients with discolouration over time also reported.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	No early or delayed hypersensitivity reactions identified [Discussion]. Author contributions reported with key next to author names. Funding source reported as departmental sources. Conflicts of interest not reported.			
Quality Rating	Fair			

Man *et al.* 2019 (n=328)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			"In this study, we aim to evaluate this new magnetic technique as the only agent used for sentinel lymph node mapping."
2. Was the study population clearly specified and defined?	✓			Inclusion and exclusion criteria listed. Male patients excluded.
3. Was the participation rate of eligible persons at least 50%?			✓	Patient flow diagram not included, no narrative description of patient participation.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Retrospective analysis of a prospectively maintained database (ClinicSolution 7.0) with participants recruited August 2016 and December 2017.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		Sampling strategy with justification not provided.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Prospectively maintained database. No trial registration.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			Intraoperative outcomes only.
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*,	✓			2ml Sienna XP, subareolar injection. All SLNs detected intraoperatively by handheld magnetometer or

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
categories of exposure, or exposure measured as continuous variable)?				nodes that were stained black were excised for frozen section.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		✓		Radioisotope was also injected in a similar way at the subareolar region in the first 22 patients, and blue dye was omitted in all patients in this cohort.
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Detection of sentinel node, number of sentinel nodes, median number of sentinel nodes removed, adverse events
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?			✓	No follow-up (intraop outcomes only)
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		✓		No statistical analysis reported.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	No comparative data, include for reporting of adverse events only. No allergies reported. Author contributions not reported, conflicts of interests not reported, funding not reported. Accepted for poster presentation.			
Quality Rating	Poor			

Pohlodek *et al.* 2018 (n=10)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			"The aim of our study was to acquire initial experience in simultaneous use of the magnetic method in tumor localization and SLNs detection in breast cancer patients."
2. Was the study population clearly specified and defined?	✓			Inclusion and exclusion criteria reported.
3. Was the participation rate of eligible persons at least 50%?			✓	Pilot, 10 patients included.
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Recruitment April and May 2018, single centre.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		Pilot study so no sample size calculations performed.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Pilot study, prospectively recruited patients from single centre. No trial registration.
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓			Intra-op outcomes reported only.
8. For exposures that can vary in amount or level, did the study examine different	✓			2ml Sienna, subareolarly interstitial tissue at least 20 minutes before SLNB.

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?				
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			All SLNs detected intraoperatively with the Sentimag probe (2nd generation).
10. Was the exposure(s) assessed more than once over time?	✓			Magnetic counts reported in situ, and ex-vivo.
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Not explicitly reported. Number of lymph nodes retrieved, detection rates and pathological assessment reported.
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?			✓	No follow-up reported (intra-operative outcomes only)
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			✓	No statistical analysis performed.
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	Small (n=10). Study funded by Sysmex; authors received no financial support for the research, authorship, and/or publication of article. Authors have no other relevant affiliations or financial involvement with any other organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the			

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
	manuscript apart from those disclosed. Author contributions reported. Author contributions reported.			
Quality Rating	Poor			

Vural and Yilmaz 2020 (n=104)
First reviewer: RP Second reviewer: KK

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
1. Was the research question or objective in this paper clearly stated?	✓			"our aim was to evaluate the feasibility and safety of the sentimag technique (Sentimag®/Sienna + ®) in Turkish early breast cancer patients."
2. Was the study population clearly specified and defined?	✓			Inclusion and exclusion criteria listed (excluded male patients). 143 with early breast cancer.
3. Was the participation rate of eligible persons at least 50%?	✓			Analysis conducted in 104/143 patients (26 excluded due to neoadjuvant therapy, 13 had a T3 tumour).
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓			Feasibility study, prospectively recruited patients from single centre between 2013 and 2017.
5. Was a sample size justification, power description, or variance and effect estimates provided?		✓		Feasibility study so no sample size calculations performed.
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓			Reporting outcomes following Magtrace injection. No trial registration.
7. Was the timeframe sufficient so that one could reasonably expect to see an association		✓		Study does not report the proportion of patients injected with Magtrace on the day of surgery, or the distribution of

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
between exposure and outcome if it existed?				time between injection and surgery
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (*e.g.*, categories of exposure, or exposure measured as continuous variable)?		✓		2ml Sienna+ at least 20 minutes before surgery in retro-areolar area. In last part of study SPIO was injected into the peritumoral area for non-palpable tumours. No subgroup analysis.
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Intraop SLN identification with Sentimag probe. After axillary incision, all nodes identified with the probe and nodes coloured brown were removed.
10. Was the exposure(s) assessed more than once over time?		✓		Sentinel lymph node identification only (no repeat injection or repeat localisation described).
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓			Number of adverse events recorded, surgeon noted pigmentation outcomes at follow up.
12. Were the outcome assessors blinded to the exposure status of participants?		✓		Cannot blind (different injection, different probe).
13. Was loss to follow-up after baseline 20% or less?			✓	No follow-up (intra-op outcomes only).
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		✓		No statistical analysis performed.

Criteria	Yes	No	Other (CD, NR, NA*)	EAC Justification
*CD, cannot determine; NA, not applicable; NR, not reported				
Comment	Author contributions not reported, no conflict of interests declared.			
Quality Rating	Poor			

Appendix C: Ongoing studies

Appendix C1: Completed studies with no publication

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
MAGnetic marker TO detect primary lesion and sentinel node in breast cancer. The randomised MAGTOtal trial [ISRCTN11914537] Sweden (N=2)	Study design: RCT (localisation of breast tumour using guide wire or magnetic clip) Status: completed no longer recruiting (last updated 05/11/2019) Estimated completion: February 2022 (recruitment end date October 2021, intention to publish Jan 2023) SiennaXP and Magseed provided by Endomagnetics Ltd	Target enrolment: 200 Inclusion criteria: patients aged 18 years or older, with DCIS or invasive breast cancer requiring localisation planned for primary surgery including sentinel node biopsy. Exclusion criteria: intolerance or hypersensitivity to iron or dextran compounds or Sienna XP, iron overload disease, pacemaker or other implantable device in chest wall or prosthesis in the shoulder, deprived of liberty or under guardianship, pregnant or lactating, inability to provide informed consent.	Radical excision, defined as free surgical margins of the specimen of the primary tumour according to preoperative diagnosis.	Width of margins per study arm in mm from the tumour to the resection margin both on specimen radiology and on final pathology. Operative time from the beginning of the breast operation until the excision of the specimen in minutes. Intraoperative and postoperative complications on 30 days, described by the Clavien Dindo classification and the Comprehensive Complication Index. Cost/benefit analysis based on the expenses of inpatient and outpatient care regarding the operation and 30 days of the postoperative period.
Sienna+MR Long-term Uptake. [NCT03243435] Switzerland (N=1)	Study design: single arm Status: completed (last updated 09/08/2017)	Target enrolment: 34 Inclusion criteria: female patients, participation in previous study, informed consent Exclusion criteria: contraindication to MRI	Analysis if the supraparamagnetic trace is still detectable [Timeframe April 2017]	Analysis to which degree of impairment of imaging is detected [Timeframe: April 2017]
Abbreviations: RCT, randomised controlled trial; MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ				

Appendix C2: Ongoing studies

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Postoperative breast MRI in patients undergoing sentinel node biopsy using super paramagnetic iron oxide nanoparticles (POSTMAG MRI) [ISRCTN85167182] Sweden (N=2) *Listed in NICE MIB263*	Study design: longitudinal cohort (up to 5 years follow-up) Status: No longer recruiting, ongoing Expected completion: February 2023 Funded by Endomagnetics Ltd	Target enrollment: n=93 (minimum) Inclusion criteria: Adult female participants with DCIS or T1 to T3 invasive breast cancer planned for BCS and SLNB study. Exclusion criteria: Intolerance or hypersensitivity to iron or dextran compounds or Sienna XP, patients with an iron overload disease, patients with pacemakers or other implantable devices in the chest-wall, or prosthesis in the shoulder, pregnant or lactating patients, intraoperative or postoperative conversion to mastectomy, inability to provide informed consent	Magnetic signal in the breast and discoloration are registered intraoperatively 1 and 3 months after surgery. If SPIO artefacts are seen on postoperative baseline MRI conducted 3 months after the operation, the patient will be followed up 6 months postoperatively and thereafter annually with controls as stated above up to 5 years postoperatively.	Impact of different SPIO volumes on the prevalence of skin staining and MRI artefacts
Magnetic Tracer in the Sentinel Node Procedure in Breast Cancer: the Non-radioactive Alternative for Radio-isotopes (MagTrace) [NCT05122585] Netherlands: single site *Included in Company submission*	Study design: Single arm (interventional) Status: recruiting Expected completion: February 2022	Target enrollment: n=40 Inclusion criteria: Female patient of 18 years or older, patient with breast cancer and indication for sentinel node procedure Exclusion criteria: Patients with a previous history of the sentinel node procedure or axillary lymph node dissection in the unilateral breast, unable to comprehend implications and extent of study and sign for informed consent, known allergy or hypersensitivity to iron oxide or dextran.	Number of sentinel lymph nodes detected using Magtrace and Technetium-99m and their concordance [Time point: during surgery]	Operation time of sentinel node procedure [Time point: during surgery]

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
Magseed and Magtrace Localization for Breast Cancer [NCT05161507] Czech Republic (N=1) *Included in Company submission*	Study design: cohort Status: recruiting Expected completion: December 2023 3 publications listed on trial registration	Estimated enrollment (observational): n=70 Inclusion criteria: Patients aged 18 years or older with cT0-4 breast cancer, with or without axillary lymph node metastasis with pathologic confirmation by needle biopsy, with or without received neoadjuvant chemotherapy prior to surgical resection Exclusion Criteria: Distant metastases, pregnant, pacemaker of another implantable device in the chest wall, allergy to dextran or other iron-containing particles.	Accuracy of Magseed placement, surgeon-rated ease of lymph node localisation and removal, number of nodes retrieved, surgeon-rated ease of detected labelled lesion localisation and removal, transcutaneous detection rate [Time frame: during surgical procedure]. Adverse events [Time frame: up to 6 weeks post-procedure].	None reported.
Delayed Sentinel Lymph Node Biopsy in Ductal Cancer in Situ: SENTINOT-2 [NCT04722692] Multi-centre (N=9): Sweden (N=7), Hong Kong (N=1), USA (N=1) *Included in Company submission*	Study design: RCT (Intervention: SLND SPIO-guided and isotope activity controlled as background; Control: SLND isotope-guided and SPIO activity controlled as background) Status: Recruiting	Target enrolment: n=500 Inclusion criteria: Female, aged 18 years and older, preoperative diagnosis of DCIS (any grade, any size) planned mastectomy, or planned risk-reducing mastectomy with SLND, or patients with a preoperative diagnosis of pre-invasive or unclear lesion with SLND. Exclusion Criteria: Intolerance or hypersensitivity to iron, dextran compounds or SPIO, an iron overload disease, patient deprived of liberty or under guardianship, pregnant or lactating.	Detection rate with each technique (Magtrace and Sentimag; Tc-99m) in delayed and late SLND procedure both independent and combined, nodal concordance [Time frame: at operation]	Number of SLND procedures avoided, per patient concordance, malignancy rate, nodal malignancy rate [Time frame: at operation] Adverse events, cost effectiveness, QALY, HR-QoL, EORTC-QLQ-B23 (breast specific HR-QoL), BreastQ

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
	Estimated completion: December 2027 No device or manufacturer name explicitly stated, however refers to SENTINOT trial that used Magtrace and Sentimag.			(PROMs) [Time frame: 1, 6 and 12 months post-operatively] Disease free interval [Time frame: 10 years].
Sienna and Sentimag in Sentinel Lymph Node Biopsy (Sienna) [NCT03036475] Hong Kong (N=1)	Study type: diagnostic study (Sienna and radioisotope) Status: Unknown (last update February 2017) Estimated completion: December 2018	Target enrollment: n=52 Inclusion criteria: Female patients aged 18 years and older with early-stage breast cancer or DCIS, clinically and radiologically node-negative undergoing SLNB and SNOLL with the use of radioisotope. Exclusion criteria: T3 or T4 breast cancer, contraindication to SLNB, pacemaker or other implantable device in chest wall.	Proportion of successful procedures for sentinel lymph node detection (per patient) by each procedure.	None reported.
Use of magnetic tracer for sentinel lymph node biopsy in breast cancer is non inferior to the standard dual tracers technique: A multi-centre non-inferior randomised trial	Study type: cluster randomisation (magnetic tracer vs. dual tracer) using computer-generated 1:1 randomisation	Target enrolment: 150 Inclusion criteria: male, patient with breast cancer scheduled for SLNB who are clinically and radiologically node negative. [The trial registration states “male” gender, however the Company have stated that this study is not restricted to male patients].	Identification rate of SLN, SPIO related AEs.	Not reported

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
[ChiCTR2000038120; 61246-Chinese] Hong Kong (N=2) *EAC assumes included in Company submission (details not explicitly provided)*	Status: pending (date of first enrolment Nov 2020) Estimated completion: not reported Study sponsored by Endomagnetic Ltd.	Exclusion criteria: Patient treated with neoadjuvant chemotherapy, history of axillary radiation, history of ipsilateral axillary surgery; non palpable breast cancer requiring simultaneous localization; patient with known intolerance or hypersensitivity to iron or dextran compounds, magnetic tracers or SPIO; with an iron-overload disease; with pacemakers or other implantable devices on the chest wall; with known hypersensitivity to blue dye; who could not or did not receive radioisotope.		
Evaluation of clinical efficacy and safety of sentinel lymph node biopsy using magnetic nanoparticle and magnetic probe [JPRN-UMIN000031240]	Study type: single arm (1 ml SPIO – no device or manufacturer name explicitly stated - on day of surgery) Status: recruiting Estimated completion: not reported [The Company have noted that Magtrace and Sentimag are not licenced for use or	Target recruitment: 180 Inclusion criteria: female patients aged 20 years or older, primary breast cancer with clinically no lymph node metastasis Exclusion criteria: breast cancer recurrence, history or operation of axilla, post-operative status of augmentation mammoplasty, male breast cancer.	SLN identification rate	Safety, adverse events

Study title, reference	Status, estimated completion	Population (n)	Primary outcome measure(s)	Secondary outcome measure(s)
	distributed in Japan and so this study relates to another SPIO device.]			
Abbreviations: EORTC-QLQ-B23; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires breast version 23; HR-QoL, Health Related Quality of Life; SLND, sentinel lymph node dissection; SNOLL (sentinel node and occult lesion localisation); SPIO, superparamagnetic iron oxide; QALY, quality adjusted life years; AEs, adverse events; SLN, sentinel lymph nodes; PROMs, patient reported outcome measures; DCIS, ductal carcinoma in situ				

Appendix D: Critical appraisal of economic evidence

Appendix D1: Critique of Company *de novo* model (Drummond checklist 1996)

First assessment: KK, QA: RP

	Judgement				
Item	**Yes**	**No**	**Not clear**	**Not appropriate**	**EAC comment**
Study design					
1*. The research question is stated.	X	¨	¨		"A cost-minimisation analysis compares the cost to the NHS of using Magtrace and Sentimag compared with technetium 99m (Tc-99m) and blue dye for localisation of the sentinel nodes during SLNB surgery"
2*. The economic importance of the research question is stated.	X	¨	¨		NHS resource impact lists benefits as: enhanced NHS capacity, reduces uncertainty and improved theatre scheduling, reduce burden on nuclear medicine, reduces risk of cancelled surgeries.
3*. The viewpoint(s) of the analysis are clearly stated and justified.	X	¨	¨		Perspective list as NHS and PSS (in line with scope).
4*. The rationale for choosing alternative programmes or interventions compared is stated.	X	¨	¨		Tc-99m and blue dye represents standard of care.
5*. The alternatives being compared are clearly described.	X	¨	¨		Tc-99m and blue dye, compared with Magtrace and Sentimag (described in section 3.1 of Company Economic Submission).
6*. The form of economic evaluation used is stated.	X	¨	¨		Cost-minimisation analysis.
7*. The choice of form of economic evaluation is justified in relation to the questions addressed.	X	¨	¨		Majority of evidence within Clinical Submission demonstrates non-inferiority in terms of SLN detection (see section 3.4 of Company Economic Submission), therefore model choice justified.
Data collection					
8*. The source(s) of effectiveness estimates used are stated.	X	¨	¨		Only costs associated with acquiring the different tracers, delivery of the tracer, and opportunity cost of operating time which is lost (due to disruption to the supply of radioisotope or shortage of nuclear medicine staff).
9. Details of the design and results of effectiveness study are	¨	¨	¨	X	Cost-minimisation analysis. Effectiveness not included (assumed non-inferior in terms of detection)

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
given (if based on a single study).					
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	¨	¨	¨	X	No synthesised data from Company Clinical Submission included in the economic analysis.
11*. The primary outcome measure(s) for the economic evaluation are clearly stated.	X	¨	¨		Costs split into tracer acquisition costs, staff time to administer the tracer costs and opportunity costs associate with lost theatre time.
12. Methods to value benefits are stated.	¨	¨	¨	X	N/A – Cost-minimisation analysis
13. Details of the subjects from whom valuations were obtained were given.	X	¨	¨		3 NHS hospitals listed in the Economic Submission and also within the Excel economic analysis (the majority of variables are from 2 NHS hospitals). None of the consulted hospitals have an integrated Nuclear Medicine department (EAC checked on hospital websites).
14. Productivity changes (if included) are reported separately.	¨	¨	¨	X	N/A, however opportunity costs associated with lost theatre time in the comparator arm are reported separately.
15. The relevance of productivity changes to the study question is discussed.	¨	¨	¨	X	N/A (not included)
16*. Quantities of resource use are reported separately from their unit costs.	X	¨	¨		Yes. Staff time (minutes), number of staff, reported separately from costs. Number of vials, number of procedures per vial of tracer reported separately from costs (for Magtrace and radioisotope; not blue dye).
17*. Methods for the estimation of quantities and unit costs are described.	X	¨	¨		Sources reported. EAC has checked all sources and noted minor disprepancies. EAC refers to NHS Reference costs (latest available 2019/20), however Company has reported tariff costs. Company states HRG code changed from 1st April 2020, which is irrelevant to 2019/20 costs. EAC has queried HRG code with clinical coding department.
18*. Currency and price data are recorded.	X	¨	¨		All costs in submission and model reported in GBP.
19*. Details of currency of price adjustments for inflation or currency conversion are given.	X	¨	-		Latest sources used (2021/22 NHS tariff, 2021 PSSRU), all reported in £; therefore no need for inflation or conversion.

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
20. Details of any model used are given.	X	¨	¨	¨	Cost-minimisation analysis used
21. The choice of model used and the key parameters on which it is based are justified.	¨	X	¨	¨	Choice of model and parameters supporting it are justified in the Economic Submission. However some assumptions not listed (e.g. Sentimag costs not included, no adverse events included for blue dye, no long-term results)
Analysis and interpretation of results					
22*. Time horizon of costs and benefits is stated.	¨	¨	X		Time horizon stated in the Economic Submission is the period from the preparation and administration of the tracer to the end of surgery. However, the cost of the SLNB procedure itself not included (only included as opportunity cost for lost theatre time in comparator arm).
23. The discount rate(s) is stated.	¨	¨	¨	X	Short time (operation only). Discounting not required.
24. The choice of discount rate(s) is justified.	¨	¨	¨	X	N/A
25. An explanation is given if costs and benefits are not discounted.	X	¨	¨	¨	“NA: Because of the short (<1 year) time horizon of the analysis” in Table 4 of the Company Economic Submission.
26. Details of statistical tests and confidence intervals are given for stochastic data.	¨	¨	¨	X	Only difference between arms reported. No statistical tests applied.
27. The approach to sensitivity analysis is given.	X	¨	¨	¨	Univariate analysis reported in section 3.7 of the Economic Submission. “Individual parameters varied within a realistic range”.
28. The choice of variables for sensitivity analysis is justified.	X	¨	¨	¨	Model parameters varied: radioisotope acquisition cost (not delivery cost, blue dye cost), staff time for radioisotope and Magtrace (but not blue dye), opportunity cost for theatre time lost in comparator arm.
29. The ranges over which the variables are varied are justified.	¨	X	¨	¨	Acquisition cost of radioisotope varied +/- 50%, nuclear medicine time varied +/- 20 minutes, Magtrace injection varied +/-10 minutes, proportion of lost time realised varied by 30% and 60%, earlier start time realised varied in 30%. No justification of these parameters provided, range does not appear to align with responses gained from 3 NHS hospitals (provided in the Excel spreadsheet).

Item	Judgement				EAC comment
	Yes	No	Not clear	Not appropriate	
30. Relevant alternatives are compared.	X	¨	¨	¨	Tc-99m and blue represents standard of care and is in line with final scope (NICE, 2021).
31. Incremental analysis is reported.	¨	X	¨	¨	Univariate analysis reported (not combination of changes).
32*. Major outcomes are presented in a disaggregated as well as aggregated form.	X	¨	¨		Table 5 of total costs per procedure broken down by acquisition costs, staff time to administer the tracer, theatre time lost due to staff shortage, and theatre time lost due to injection on same day included.
33*. The answer to the study question is given.	X	¨	¨		"Magtrace is expected to save £105 per procedure. Magtrace is a dominant option."
34*. Conclusions follow from the data reported.	X	¨	¨		"In the base-case the saving is £105 per procedure. More importantly it improves NHS efficiency by releasing resources in nuclear medicine and theatre time lost to delays or cancellation."
35*. Conclusions are accompanied by the appropriate caveats.	¨	X	¨		No limitations reported.

* *"Not appropriate"* is not considered an available option

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

External Assessment Centre report

Produced by: Newcastle External Assessment Centre

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Date completed: 21/04/2022

Contains confidential information: No

EAC Identification of on-site facilities

The EAC note that there is large uncertainty in the proportion of NHS Trusts able to realise opportunity costs due to the accessibility of radiopharmacy and nuclear medicine facilities at the same site of the SLNB procedure. The EAC note that NHS Trusts providing SLNB with on-site radiopharmacy and nuclear medicine facilities may be less likely to realise opportunity costs due to the delays by the lack of availability of radioisotope.

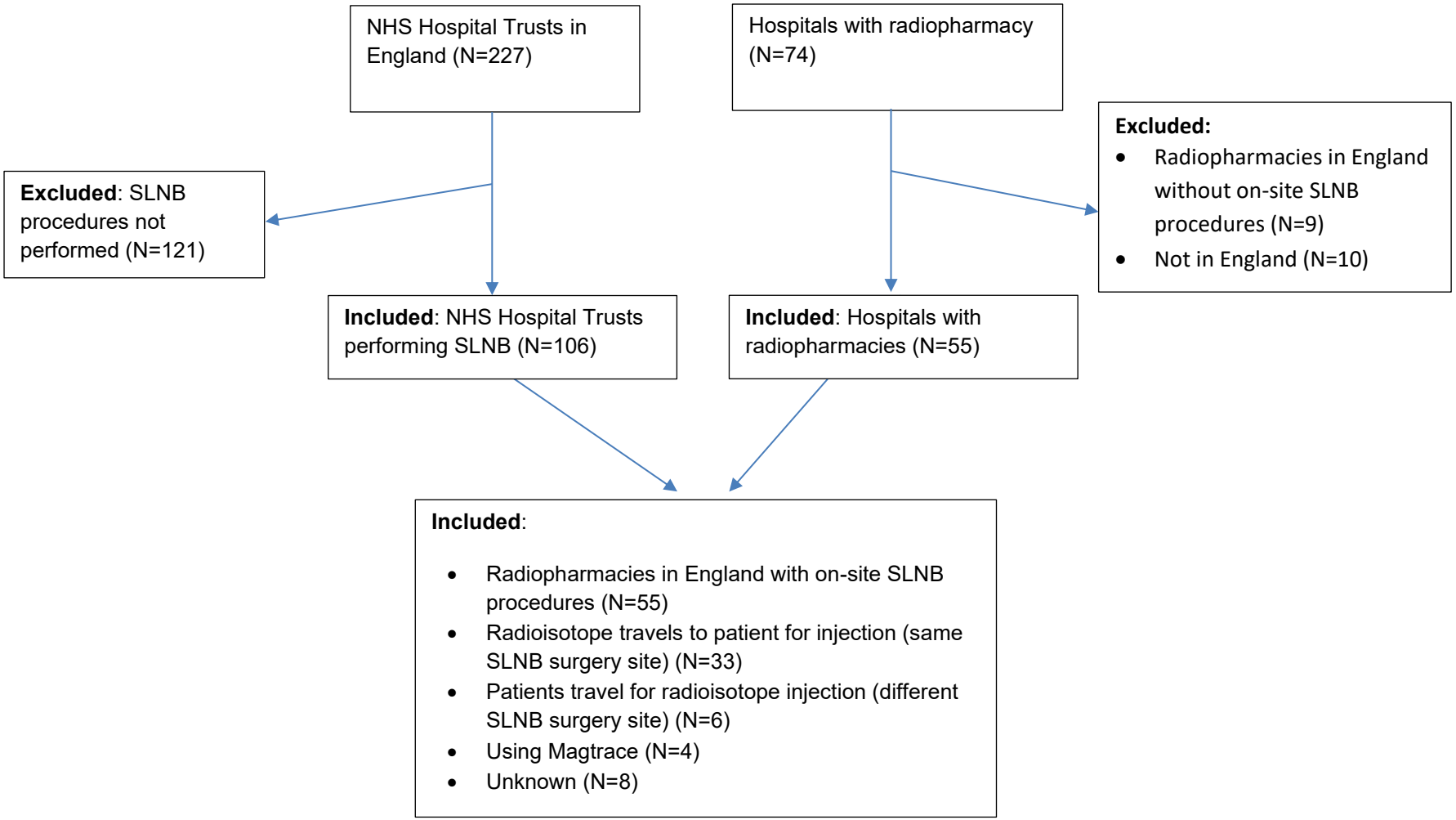
The EAC were asked to try to quantify the proportion of NHS Trusts with the potential to realise opportunity costs by the following three defined scenarios:

- radiopharmacy on the same site as the theatre where the SLNB procedure is performed;
- patients travel to a site with radiopharmacy to receive radioisotope injection; and then attends a different site with theatre where the SLNB is performed.
- radioisotope is transported to a site with the theatre where SLNB takes place for local nuclear medicine staff to administer.

The EAC contacted the British Nuclear Medicine Society (BNMS) on 13/04/2022 requesting assistance in the identification of the number of radiopharmacies in the UK. The BNMS replied via e-mail on 13/04/2022 with an Excel spreadsheet with a total 74 named UK *hospitals* with on-site radiopharmacies. The EAC noted the locations of radiopharmacies across the home nations with 64 in England, 5 in Scotland, 2 in Wales, 2 in Northern Ireland, and 1 in the Isle of Man.

The EAC identified 227 NHS Trusts through a search of https://www.nhs.uk/ on 13/04/2022, importing to Excel. The EAC identified the location of the radiopharmacies associated with each NHS Trust in England via the same website or relevant service website and manually aligned these. The EAC considered that only NHS Trusts providing SLNB procedures for breast cancer were relevant to the decision problem and identified this through the same search methods, Figure 1.

Figure 1: Flow of facilities identification



The EAC identified 106 of 227 (46.7%) English NHS Trusts where SLNB procedures were performed, of which:

- 55 (51.2%) NHS Trusts had on-site radiopharmacies and nuclear medicine support;
- 33 (31.1%) NHS Trusts where radioisotope is delivered from a radiopharmacy and administered by on-site nuclear medicine staff at the same site as the SLNB procedure;
- 6 (5.7%) NHS Trusts where patients travel to another site for radioisotope injection;
- 8 (7.5%) unknown or unconfirmed patient pathway;
- 3 (3.8%) NHS Trusts using Magtrace rather than dual technique;
- 1 (0.9%) NHS Trusts using Magtrace with or without radioisotope with unconfirmed patient pathway for radioisotope injection.

The EAC consider that 55.9% of NHS Trusts would therefore be less likely to realise opportunity costs based on the availability and accessibility of radiopharmacy and nuclear medicine facilities (due to on-site access), or through existing use of Magtrace and Sentimag. Opportunity costs may be realised in the remaining 44.1% of NHS Trusts; which is close to the value applied in the EAC base case economic analysis (50%).

The Clinical experts noted that SLNB procedures are rarely conducted in isolation and would likely be included with breast surgery (EAC Correspondence Log, 2022), which may also influence the ability to realise opportunity costs associated with ability to perform additional SLNB procedures. Realisation of opportunity costs may also be mitigated by theatre scheduling.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Decision problem from the scope

1 The technology

The Magtrace and Sentimag system (Endomag) comprises of a magnetic liquid tracer (Magtrace) and a handheld magnetic sensing probe (Sentimag). It is used to locate sentinel lymph nodes in people with cancer during sentinel lymph node biopsy (SLNB) procedures.

Magtrace is a non-radioactive dark brown liquid containing superparamagnetic iron oxide with a carboxydextran coating that acts as a magnetic marker and a visual dye, because of the dark colour of the particles. Magtrace is injected into the tissue beneath the areola or interstitial tissue around a tumour, then the particles are absorbed into lymphatics and become trapped in sentinel lymph nodes. It can be injected in the operating theatre 20 minutes before the procedure or up to 30 days before surgery at an outpatient clinic. During surgery, the Sentimag probe detects the tracer trapped in the lymph nodes and guides the surgeon to remove them for biopsy. Sentimag uses a visual reading and sounds of different pitches to indicate how close the surgeon is to the tracer.

The key innovative feature of the Magtrace and Sentimag system is its magnetic mechanism of action. This means that unlike the dual technique the system can be used without the need for nuclear medicine safety procedures and facilities. Magtrace can also be injected up to 30 days before surgery, whereas the tracers used in current practice can be given no more than a day before.

2 Proposed use of the technology

2.1 Disease or condition

Breast cancer is the most common cancer in the UK with approximately 54,000 new cases of invasive disease annually. The vast majority of breast cancers occur in women, but over 300 men in the UK are also diagnosed with invasive breast cancer each year. SLNBs help to diagnose cancer that has spread to the lymph nodes.

2.2 Patient group

Magtrace and Sentimag is intended for use in people with invasive breast cancer or people with ductal carcinoma in-situ who are having a SLNB. Invasive breast cancer means that the cancer cells have broken through the walls of the duct and growth has spread into the surrounding breast tissue. Ductal carcinoma in-situ is the presence of abnormal cells inside a milk duct of the breast. It is non-invasive, which means that the cancer cells have not spread out of the milk duct into other parts of the breast.

NICE guideline on early and locally advanced breast cancer states that SLNB is the preferred technique to stage the axilla for people with invasive breast cancer and no evidence of lymph involvement on ultrasound or a negative ultrasound-guided needle biopsy.

2.3 Current management

The current treatment option for locating sentinel lymph nodes during SLNB is a combination of a tracer containing a radioactive isotope, technetium-99m and blue dye. Where technetium-99m is not available, blue dye may be used on its own, but this can reduce the detection rate of sentinel lymph nodes. When using Technetium-99m for locating sentinel lymph nodes during SLNB, it will be injected following preparation by nuclear medicine specialists. In some hospitals, the isotope is prepared off-site and then transported to the healthcare setting. On some occasions this can lead to the procedure being delayed. There can also be uncertainty around availability of Technetium-99m. Cancellations and later starting times for procedures can waste resources and cause issues for surgical scheduling so planning and logistical oversight is required.

NICE has published guidance on the use of SLNB for early and locally advanced breast cancer. The guideline recommends that the dual technique with isotope and blue dye should be used when performing SLNB. Specifically, SLNB is recommended for people with invasive breast cancer who had no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. The guideline also recommends that SLNB

should be offered to people who are having a mastectomy for ductal carcinoma in-situ (DCIS) breast cancer and people with a pre-operative diagnosis of DCIS who are considered to be at high risk of invasive disease.

2.4 Proposed management with new technology

The Magtrace and Sentimag system is intended for locating sentinel lymph nodes during SLNB procedures for breast cancer. It is an alternative to current treatment for locating sentinel lymph nodes during SLNB. Magtrace is injected by a healthcare professional before the procedure, then the Sentimag probe detects the tracer trapped in lymph nodes which helps the surgeon to remove sentinel lymph nodes for biopsy. The use of Magtrace does not require the involvement of a nuclear medicine team.

When Magtrace is adopted in a healthcare setting, the company offer training to clinicians on how to use the technology. Clinical experts highlighted that there is a learning period associated with the technology with peer support. The company suggest a minimum of five cases to ensure competency with the technology. Three of the surgical clinical experts reported the use of blue dye with Magtrace to assist with SLN detection during the learning period.

3 Company claimed benefits and the decision problem

Table 1 describes the decision problem in the scope and company input.

Table 1: The Decision Problem

Decision problem	Scope	Company input
Population	People with high-grade ductal carcinoma in-situ or invasive breast cancer having a sentinel lymph node biopsy	No variation
Comparator	Technetium-99m in combination with blue dye	No variation
Outcomes	The outcome measures to consider include: - Sentinel lymph node detection rate	No variation, company clarified: - Sentinel lymph node detection rate: per-patient proportion of SLNB operations in

	- Mean number of sentinel lymph nodes retrieved per procedure - Time taken for SLNB procedure - Patient-reported outcome measures - Device-related adverse events	which one or more sentinel lymph nodes were successfully identified and resected. - Mean number of sentinel lymph nodes retrieved per procedure: per-patient mean number of sentinel lymph nodes identified and resected. - Time taken for SLNB procedure: per-patient mean time taken to complete the SLNB procedure.
Subgroups	None to be considered.	No variation.
Special considerations	• Technetium-99m is not always available. Where there is a shortage of Technetium-99m, blue dye is used alone. The dual technique has been shown to improve the rate of identification of SLNs. • People who may experience anaphylaxis as an adverse reaction to blue dye would currently be given Technetium-99m only or a four-node axillary sample. • Known contraindications for Magtrace include: people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or chest.	

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 31 papers in total; 22 studies and 9 conference abstracts which were considered relevant and within the scope of the decision problem. The EAC excluded ten of these (Table 2 in the Assessment Report). The EAC undertook its own literature search (see section 4.1 of the EAC's assessment report) and identified an additional 15 papers that were relevant to the scope.

Of the 36 included studies, 18 are non-randomised controlled trials, 16 are cohort studies (7 retrospective, 6 prospective, 1 feasibility study, 1 pilot study and 1 propensity-matched study), 1 is a prospective paired comparison and 1

is a validation study. The 36 studies include a total of 4,202 patients where Magtrace and Sentimag were used.

Comparators included the dual technique (radioisotope in combination with blue dye) and radioisotope alone. Five studies compared the dual technique with Magtrace and Sentimag (Alvarado *et al.* 2019; Karakatsanis *et al.* 2017; Karakatsanis *et al.* 2018; Pouw *et al.* 2015; Sreedhar *et al.* 2021) and are considered most relevant to the decision problem (Table 3a in the Assessment Report). 11 studies compared Magtrace and Sentimag with radioisotope alone and 6 studies included both the dual technique and radioisotope only and did not report outcomes exclusively. The remaining 14 non-comparative studies were included for patient reported outcomes and adverse events.

Table 2: Studies included and excluded from the assessment

Studies included in the assessment	
Publication and study design	21 studies included by the company and EAC: • 13 RCTs (Alvarado et al. 2019; Karakatsanis et al. 2017; Ghili et al. 2017; Gimenez-Climent et al. 2021; Rubio et al. 2015; Rubio et al. 2020; Shams et al. 2021; Thill et al. 2014; Douek et al. 2014; Houpeau et al. 2014; Karakatsanis et al. 2016; Pinero-Madrona et al. 2015; Hersi et al. 2021) • 4 retrospective cohort studies (Munawwar et al. 2021; Lorek et al. 2019; Man et al. 2019; Paepke et al. 2020) • 2 prospective feasibility studies (Pouw et al. 2015; Kurylcio et al. 2021) • 1 prospective cohort study (Vural and Yilmaz 2020) • 1 pilot cohort study (Pohlodek et al. 2018) 15 additional studies included by the EAC: • 5 RCTs (Sreedhar et al. 2021; Castillo-Berrio et al. 2015; Granados et al. 2015; Douek et al. 2013; Sukumar et al. 2020) • 4 retrospective cohort studies (Bazire et al. 2019; Chapman et al. 2020; Gutesa et al. 2016; Hannebicque et al. 2017) • 3 prospective cohort studies (Jazrawi et al. 2021; Szynglarewicz et al. 2019; Wamberg et al. 2019) • 1 prospective feasibility study (Karakatsanis et al. 2018) • 1 propensity-matched cohort study (Pelc et al. 2022) • 1 validation study (Ahmed et al. 2014)
Studies excluded from the assessment	
Publication and study design	10 studies included by the company and excluded by the EAC:

	• Ahmed et al. 2015 – Non-randomised controlled trial This study was excluded because the dosage administered was not in line with the IFU • Hersi et al. 2019 – Prospective feasibility study This study was excluded as it was single-arm and patient-reported outcome measures and adverse events were not reported. • Karakatsanis et al. 2019 – Prospective cohort study This study was excluded as patients without signal detection were excluded from the study. Patients were also administered Magtrace outside the therapeutic window indicated in the IFU. • Karakatsanis et al. 2020 (abstract) – Non-randomised controlled trial) This study was excluded as the results were later published in a full paper (Hersi et al. 2021) • Mullapudi et al. 2020 (abstract) – Prospective paired comparison This study was excluded as it does not explicitly state use in breast cancer patients only. Also overlaps with Sukumar et al. (2020) abstract which was included. • Qureshi et al. 2021 (abstract) – Prospective cohort study This study was excluded as it was single-arm and patient-reported outcome measures and adverse events were not reported. • Raus and Faridova 2020 (abstract) – Retrospective cohort study This study was excluded as it is a comparison with a historical SPIO intervention. Adverse events and patient-reported outcome measures were not reported. • Rubio et al. 2016 (abstract) – Non-randomised controlled trial This study was excluded as the intervention is out of scope. • Scally et al. 2020 (abstract) – Retrospective cohort study This study was excluded as it does not explicitly state use in breast cancer patients only. The comparator is also out of scope. • Syahkal et al. 2019 (abstract) – Retrospective service evaluation This study was excluded as the intervention and comparator are out of scope.

One study was conducted exclusively in a UK NHS setting (Sukumar *et al*. 2020). The SentiMAG study was based in the UK and the Netherlands, and four associated papers were included in the EAC review (Ahmed *et al.* 2014b; Douek *et al.* 2013; Douek *et al.* 2014; Pouw *et al.* 2015). Four studies were set outside of Europe; Alvarado *et al.* (2019) and Chapman *et al.* (2020) in USA; Man *et al*. (2019) in Hong Kong; Sreedhar *et al.* (2021) in New Zealand. The remaining 27 studies were set in European locations.

Overall, there is good quality evidence that supports the non-inferiority of Magtrace and Sentimag to the dual technique for detection of SLNs, including those that are malignant. 12 studies were statistically powered to evaluate non-inferiority of detection rates. The EAC did not identify significant evidence to suggest that the number of nodes excised differs between methods. Of the four studies that statistically compared detection between techniques, no study reported a significant difference in per patient detection rates between techniques. Per patient concordance between Magtrace and Tc-99m with and without blue dye ranged from 89.7% to 100.0%, with seven studies reporting 100.0% concordance.

There are no significant concerns relating to the safety of the technology. The main adverse event relating to Magtrace is the incidence of skin staining. Although the literature and clinical expert opinion suggest that deeper injections reduce this occurrence. There is no comparative evidence reporting the difference in skin staining associated with Magtrace compared to blue dye.

6 studies noted future imaging with MRI and mammography being impacted by artefacts up to 5 years after Magtrace administration. But there is currently no long-term evidence to determine the impact of this on future diagnoses or treatment. Alternative tests are available for diagnostic assessment where MRI or mammography interpretation is not feasible, however these may not be readily available across all services and may have higher associated costs. Consensus from clinical experts is that Magtrace would not be advised for patients who are anticipated to require MRI within three months of SLNB procedure.

There is a lack of robust comparative evidence to determine the impact of the use of Magtrace on the SLNB procedure time. From the available published literature, there is no evidence to support earlier Magtrace administration affecting detection rate. Of the 36 included studies, 18 administered Magtrace intraoperatively or on the day of surgery; 6 did not report injection timing and 5 included patients injected prior to 3 days before surgery. Clinical experts advised that Magtrace injected during a prior routine clinic visit provides better sentinel lymph node detection compared to intraoperative injection.

4.2 Summary of economic evidence

The company included 3 studies in their economic submission. The EAC considered two relevant to the decision problem (Karakatsanis *et al.* 2017; Shams *et al.* 2021). The other study (Man *et al.* 2019) only reported a single sentence regarding costs and was excluded by the EAC. The EAC identified an additional study which was relevant to the decision problem (Sreedhar *et al.* 2021). A summary of the three studies reporting on costs associated with Magtrace and Sentimag can be found in Table 11 of the Assessment Report.

None of the three included studies were from the perspective of the UK NHS. Karakatsanis *et al.* (2017), conducted in Sweden, reported use of Magtrace to be cost saving by €27 per person and reported larger savings of €352 per person if Magtrace was injected in a prior clinic (saving 20 minutes of theatre time). Shams *et al.* (2021), conducted in Germany, reported that reimbursement costs to hospitals was unaffected by choice of localisation method. It is unclear if the cost of Magtrace solution and probe were included in the diagnosis-related group tariffs. Sreedhar *et al.* (2021), conducted in New Zealand, reported Magtrace to be cost saving by $860.30 per procedure when including speculative costs of patient car travel and hotel expenses. The Company did not use any parameters from the included economic studies to inform their de novo model.

De novo analysis

The Company developed a cost-minimisation analysis from an NHS and PSS perspective. The population was defined as people with breast cancer

undergoing sentinel lymph node biopsy, in line with the scope. Magtrace and Sentimag was compared with the dual technique (radioisotope Tc-99m and blue dye) for the localisation of the sentinel lymph nodes during SLNB surgery. The time horizon of the model is from the time the patient attends the hospital for SLNB to the end of the procedure. Due to the short-term nature of the study, no discounting was applied.

The company's base case analysis assumes:

- Magtrace is appropriate in 100% of patients. The EAC stated that Magtrace is contraindicated in patients with hypersensitivity to iron oxide or dextran compounds, patients with iron overload disease and patients with a metal implant close to the expected sentinel lymph node location. Clinical experts advised that routine screening would not be carried out in patients undergoing Magtrace injection and estimated that the total proportion of patients with any contraindication would be rare; less than 1%. The EAC recommended that the provision of the dual technique in patients with a contraindication to Magtrace is considered in the scenario analysis.

- Each hospital carries out 250 SLNB procedures annually, approximately 5 procedures weekly for 50 weeks. The EAC consulted clinical experts, who stated that the number of SLNB procedures carried out in a year range from 200 to 600.

- The hospital receives one delivery weekly of two vials of Technetium-99m. The EAC assumed that the cost for isotope delivery would be included within the costing for radioisotope injection.

- Magtrace and blue dye do not require any special delivery or storage arrangements and one vial of each is required per SLNB procedure. The EAC highlighted that storage and disposal costs were not applied to either arm.

- Opportunity cost of theatre time lost due to delays in surgery is measured by the number of SLNB procedures foregone. Only 50% of potential additional procedures could be realised. The EAC considered that delay to surgery may not occur across all hospitals. Also, intraoperative injections of Magtrace would add 20 minutes to total theatre time.

Clinical parameters

No clinical outcomes were included in the company cost-minimisation analysis.

Costs and resource use

The main costs used in the modelling were the cost of the technology and comparators. An additional weekly cost of delivery was added for the radioactive isotope. The cost of hospital staff for the injection of Magtrace or the radioactive isotope and blue dye was also included.

Resource use data was based on responses three NHS Trusts in England. The company's model included the cost of a vial for each of the three tracer injections. Magtrace costs £1350 (excluding VAT) per vial. Weekly delivery costs were included for the radioisotope only. The cost of the Sentimag probe for detection of Magtrace or gamma probe for use with the dual technique were not included in the model. The Company advised that NHS Trusts that enter a consumable commitment of 100 to 120 consumable units per annum receive the Sentimag system free of charge. Outside of this contract, the Sentimag probe is £24,900 to purchase with a minimum expected device lifetime of 5 years. As gamma probes are used for a range of procedures in a hospital, the per-procedure use may be regarded as negligible.

Staff time for injection was calculated separately for each arm, based on the level of staff required and expected time to administer the injection. The timing and hospital setting of each tracer injection was not explicitly stated. Exclusion of the timing of the Magtrace injection was considered to be a key limitation by the EAC and was therefore included in their model. The company model does

not include costs for local anaesthesia in either arm, which may be needed if the tracer is injected at an appointment prior to the SLNB procedure.

For the dual technique arm, theatre time lost due to supply chain disruptions or a lack of nuclear medicine staff was accounted for as an opportunity cost. The company stated that SLNB procedures using the dual technique cannot practically be scheduled to start before 10.30am due to the time needed to prepare and administer an isotope injection, and for the tracer to migrate from the breast to the lymph nodes. The reason for the inclusion of these opportunity costs is that the cumulative total theatre time lost would provide sufficient time to perform additional SLNB procedures annually. The company assumed that only 50% of this lost theatre time could be usefully redeployed and was valued using the HRG tariff for a SLNB procedure.

The EAC considered that opportunity costs associated with additional procedures may not be realised by all NHS hospitals conducting breast surgery and that the values for these opportunity costs came from one NHS hospital that does not have an embedded Nuclear Medicine department. Clinical experts from Nuclear Medicine advised that supply chain issues are rare and do not result in delay of SLNB procedures. Also, 20-50% of patients would have isotope injection the day before the procedure and would therefore not incur a delay. The EAC recommended removing the opportunity cost associated with supply chain disruptions and shortage of nuclear medicine staff. The EAC stated that additional surgical procedures could be performed on a morning with Magtrace and that that this opportunity cost is could be considered in the sensitivity analysis.

The use of blue dye is associated with a risk of anaphylaxis. Severe anaphylaxis usually results in a critical care admission according to the clinical experts. The cost of treating anaphylaxis was not included in the comparator arm of the company's economic analysis. The potential of long-term MRI implications, which would require alternate modes of imaging, were not included in the company's base case analysis.

A summary of the cost parameters used in the company model and suggested EAC changes can be found in Table 13 of the Assessment Report.

Company base case results

In the company's base case, the cost of using Magtrace and Sentimag was £240 per procedure, compared with £345 per procedure using the dual technique (radioisotope and blue dye). This resulted in a cost-saving per procedure of £105. Cost savings were driven by the opportunity costs, particularly those associated with the ability to carry out additional SLNBs in the Magtrace arm.

Table 5: Summary of company base case results

	Company base-case analysis, per procedure		
	Magtrace and Sentimag	**Dual technique (Tc-9m and blue dye)**	**Incremental cost (Magtrace and Sentimag minus dual technique)**
Tracer acquisition costs	£226	£70	£156
Tracer administration costs	£14	£73	-£59
Theatre time lost due to supply or staff shortage	£0	£81	-£81
Theatre time lost due to Tc-99m injection on day of surgery	£0	£121	-£121
Total (per patient)	**£240**	**£345**	**-£105**
Negative values (shaded green) indicate a cost saving.			

Sensitivity analyses

The company's univariate deterministic sensitivity analysis varied the following parameters:

- Number of radioisotope vials required per week
- The cost per radioisotope vial
- Number of nuclear medicine staff required for isotope injection
- Nuclear medicine staff time per radioisotope injection
- Nurse time per Magtrace injection

- Value of theatre time
- Lost theatre time realised
- Earlier start time realised

Magtrace and Sentimag was shown to be cost-saving when each parameter was varied. The EAC considered the ranges used to be acceptable. The results of the company's univariate deterministic sensitivity analysis are provided in Table 15 in the Assessment Report.

Additional analysis

The EAC was able to replicate the Company's base case. The EAC conducted a number of univariate changes to the Company economic analysis to determine the impact on procedure costs.

Two primary changes were made to the company base-case:

- Opportunity costs associated with lost theatre time was removed (due to supply or staff shortage and due to radioisotope injection being administered on the day of surgery)
- 20 minutes of theatre time was added for intraoperative Magtrace injection

Table 7: EAC univariate changes to the Company base-case analysis

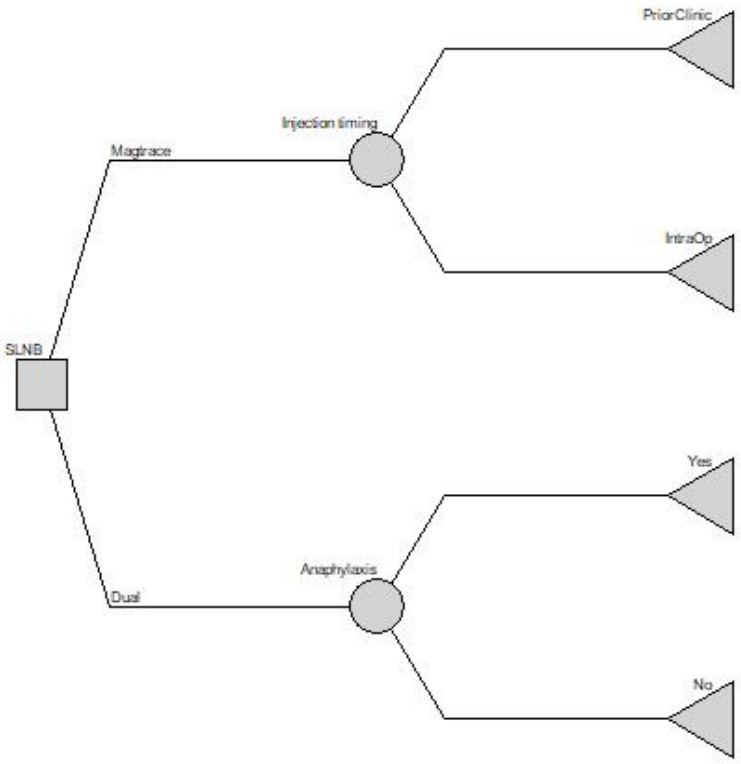
			Cost per procedure		
Parameter	**Base case**	**Value used in sensitivity analysis**	**Magtrace and Sentimag**	**Dual technique (Tc-9m and blue dye)**	**Incremental cost (Magtrace and Sentimag minus dual technique)**
Base case	**-**	**-**	£240	£345	**-£105**
Removing opportunity cost associated with theatre time lost due to supply or staff shortage	£80.53	£0.00	£240	£264	**-£24.47**
Removing opportunity cost associated with theatre time lost due to Tc-99m injection on day of surgery	£120.80	£0.00	£240	£224	**+£16**

Adding 20 minutes theatre time for Magtrace intraoperative injection (based on direct theatre cost per hour £1,072, which would include staff time)	£0.00	£357.33	£597	£345	**+£252**
Negative values (shaded green) indicate a cost saving.					

EAC base case

Although the EAC accepted the company's base case analysis, the EAC reformulated the company's base case into a decision tree to improve the clarity of the clinical pathway and parameters. The decision tree embodies the decision problem in a conventional form and incorporates the company's base case for a particular set of values of the model variables. The decision tree structure also enables probabilistic sensitivity analysis.

Figure 1: EAC base-case represented by a decision tree



To represent the current care pathway across the NHS, the EAC included three arms to represent the different timing and setting of the tracer injections:

- Magtrace injected intraoperatively (20 minutes before SLNB following administration of anaesthesia)
- Magtrace injected at a separate clinic (up to 30 days before SLNB)
- Radioisotope injected at separate clinic (up to 1 day before SLNB, or 1 hour before)

All patients in the comparator arm (dual technique) incur costs for a separate Nuclear Medicine clinic appointment for the radioisotope injection. The timing of the injection does not vary cost based on the unbundled HRG code RN19Z. All patients in the Magtrace arm incur additional costs associated with staff time depending on whether the injection is administered intraoperatively or at a prior appointment. The EAC assumes that intraoperative injection of blue dye requires five minutes of breast massage to promote drainage to the axilla prior to SLNB procedure. The model also assumes that anaphylaxis only occurs in the comparator arm because of blue dye. The proportion of patients experiencing severe anaphylaxis was derived from meta-analysis (Perenyei et al. 2021.

All patients across all arms incur costs associated with the SLNB procedure, presented by a HRG code which includes blue dye injection, gamma probe detection and anaphylaxis associated costs. The cost of blue dye injection and costs of anaphylaxis care were removed from the appropriate branches of the decision tree. Costs associated with gamma probe detection of the isotope are assumed to be negligible. The EAC did not include opportunity costs associated with a lack of availability of radioisotope, but opportunity costs for one additional SLNB procedure each week was included in the base-case. In line with the assumption made by the company, the EAC assumes that opportunity costs are achieved in 50% of hospitals. Although patient costs (travel and wait times) are likely to be different between hospitals with and without on-site Nuclear Medicine facilities, these are not incorporated into the

economic model. The EAC base case model parameters are described in Table 17 of the Assessment Report.

EAC base case results

The cost of Magtrace and Sentmag was calculated as £2,488.83 per procedure and the dual technique cost £2,567.73 per procedure. This results in Magtrace and Sentimag having a cost-saving of £78.90 per patient.

Table 9: Summary of EAC base case results

	Magtrace & Sentimag	Comparator (dual technique)	Cost difference (Intervention-Comparator)
Cost of tracer (including staff time for injection)	£411.50	£239.00	+£172.50
Cost associated with SLNB	£2077.33	£2191.66	-£114.33
Opportunity cost (one additional SLNB procedure per week)	£0	£137.06	-£137.06
Total	**£2488.83**	**£2567.73**	**-£78.90**

EAC sensitivity analyses

Due to a lack of national audit data, the EAC conducted various univariate sensitivity analyses across parameters and a scenario analysis, informed by the feedback of clinical experts.

The following parameters were evaluated in univariate analysis:

- **Proportion of Magtrace injections conducted at prior appointment (range 0% to 100%)**
  The higher the proportion conducted at a prior appointment the larger the cost-saving associated with Magtrace; the threshold at which Magtrace becomes cost-saving is 0.27 (base case was 0.50).

- **Additional theatre time in the Magtrace arm due to delay associated with intraoperative subareolar injection of Magtrace (range 0 mins to 30 mins)**
  A reduction in additional theatre time results in an increased cost

saving for Magtrace. From threshold analysis, the additional theatre time waiting for drainage to axilla using Magtrace would need to exceed 29 minutes before it was considered cost-incurring.

- **Opportunity cost – Number of additional SLNB procedures conducted each week (range 0 to 2 procedures)**
  The threshold at which Magtrace became cost-incurring was 0.42 additional procedures per week. The EAC notes that if a hospital was unable to realise any additional procedures in a week, Magtrace would be cost-incurring by £58.17 per procedure.

- **Proportion of centres realising the opportunity costs associated with conducting one additional SLNB procedure each week (range 0% to 100%)**
  In the base case (50% of hospitals achieving 1 additional SLNB procedure), Magtrace was cost-saving by £78.90 per procedure. The threshold at which Magtrace become cost-incurring is if 21% of hospitals can conduct 1 additional SLNB additional procedure. If no centre was able to realise additional SLNB procedures, Magtrace would become cost-incurring by £58.17 per procedure.

- **Hospital volume of SLNB procedures conducted annually (range 200 to 600 annual procedures)**
  Whilst the base case included the mid-point estimate from the Clinical experts (400 SLNB annually), lower volume centres may achieve larger cost-savings with Magtrace (200 SLNB per year: cost saving £215.96 per patient), whereas higher volume centres may achieve smaller cost-savings with Magtrace (600 SLNB per year: cost-saving £33.21 per patient), assuming 1 session per week is wasted in each case.

The EAC illustrated the multiple univariate sensitivity analysis of three parameters (probability of centres realising opportunity costs associated with gaining one additional SLNB per week, proportion of SLNB procedures where Magtrace was injected at a prior clinic, and probability of anaphylaxis due to blue dye) in a tornado diagram. Each parameter was varied over their

corresponding 95% confidence interval, with the rest of the variables set to their point estimates due to a lack of robust published data. When varying these three parameters, the mean cost difference from probabilistic sensitivity analysis between Magtrace and dual technique was -£79.41 (95% CI -£117.88 to -£43.89) per patient, with 100% of simulations being cost-saving. This analysis is demonstrated in Figure 16 of the Assessment Report.

Table 10: Summary of scenario analysis conducted on EAC base case

Scenario	Magtrace & Sentimag	Radioisotope & Blue dye	Cost difference (%)
Base case	£2488.83	£2567.73	-£78.90 (3.1%)
Magtrace not injected in theatre, injected at additional outpatient appointment	£2385.66	£2567.73	-£182.07 (7.1%)
0.5% patients contraindicated to Magtrace and require dual technique	£2489.22	£2567.73	-£78.50 (3.1%)
1.0% patients contraindicated to Magtrace and require dual technique	£2489.62	£2567.73	-£78.11 (3.0%)
Assume 1% of patients in both arms require future MRI, and that 5% of those in Magtrace arm are uninterpretable and require contrast enhanced MRI	£2490.34	£2569.16	-£78.82 (3.1%)

Due to the sensitivity of the model to additional minutes of theatre time, the EAC modelled a scenario where Magtrace was instead injected at a prior non-routine outpatient clinical oncology appointment without occurring 20 minute delay in theatre. In this scenario, cost savings associated with Magtrace increased to £182.07 per procedure. Additional scenarios were modelled to account for patients contraindicated to Magtrace that would require standard of care (dual technique). When assuming 0.5% contraindicated, Magtrace remains cost-saving by £78.50 per procedure. The EAC notes that if the proportion of patients contraindicated to Magtrace increased (from 0.5% to 1.0%) then Magtrace remains cost-saving at £78.11 per procedure.

Published clinical evidence suggests that patients injected with Magtrace can present with artefacts in future MRI. The Clinical experts advise that a small proportion of breast cancer patients require MRI after breast surgery as part of their routine surveillance conducted alongside mammography. The EAC developed an additional scenario analysis, which assumed a proportion of all

patients require additional diagnostic imaging during routine follow-up. In the standard of care arm, it is assumed that this proportion of patients all undergo standard MRI. In the intervention arm the same proportion of patients undergo standard MRI, but a small proportion would be uninterpretable and thus require an additional Gadolinium enhanced MRI. With the inclusion of this scenario, Magtrace remains cost-saving at £78.82 per procedure.

5 Ongoing research

There are 10 ongoing studies, 3 of which are RCTs, 3 are single arm observational studies, 2 are longitudinal studies, 1 is a cohort study and 1 is a diagnostic study. See Appendix C of the EAC's assessment report.

6 Issues for consideration by the Committee

Clinical evidence

- The clinical evidence supports the non-inferiority of Magtrace and Sentimag compared with the dual technique (radioactive isotope and blue dye) for detection rates in SLNB for breast cancer. The evidence shows that Magtrace can cause MRI artefacts for a significant period of time after an SLNB procedure. The committee may wish to consider the impact this could have on future imaging and treatment for patients.

- There are no significant concerns relating to the safety of Magtrace and Sentimag. The main adverse event relating to Magtrace is the incidence of skin staining. The committee may wish to consider whether this is a significant issue for the use of Magtrace.

- Magtrace is contraindicated for people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or chest).

Cost evidence

- The EAC reformulated the company's base case into a decision tree to improve the clarity of the clinical pathway and parameters. The

committee may wish to consider whether the EAC model and updated parameters are more accurate than the company model to estimate the costs of Magtrace and Sentimag compared with the dual technique.

- In the UK, SLNB procedures using the dual technique are carried out at hospitals with on-site nuclear medicine facilities and hospitals that do not have these facilities. The committee may wish to consider whether the costs and resource use impact should be considered separately for these two settings.

- Clinical experts advised that they now inject Magtrace at a prior appointment for an easier procedure and it can also improve the trace. The committee may wish to consider whether this a reasonable assumption for all patients and whether there are any implications for different timings of the Magtrace injection.

- Lack of availability of isotopes or nuclear medicine staff are mentioned as a possible issue for using the dual technique. The committee may wish to consider if an opportunity cost should be included in the model.

- Both the company and EAC assume that hospitals will be able to conduct additional SLNB procedures if Magtrace is adopted. The committee may wish to consider whether centres will be able to realise these additional SLNB procedures.

7 Authors

Farhaan Jamadar, Health Technology Assessment Analyst, NICE Medical Technologies Evaluation Programme

Lizzy Latimer, Health Technology Assessment Adviser, NICE Medical Technologies Evaluation Programme

April 2022

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Keltie K, Parker R, et al. Magtrace and Sentimag for locating sentinel lymph nodes

B Submissions from the following sponsor:

- Endomag Ltd

C Related NICE guidance

- Guidance on early and locally advanced breast cancer: diagnosis and management. NICE guideline NG101 (2018).
  Available from: https://www.nice.org.uk/guidance/ng101

D References

Please see EAC assessment report for full list of references.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Tomasz Graja

Consultant Breast Oncoplastic and General Surgeon,

Dorset County Hospital NHS Foundation Trust

Ms Elizabeth Jefferson

Head of Nuclear Medicine,

Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Dermot Murphy

Consultant Breast Surgeon,

NHS Lanarkshire and NHS Dumfries and Galloway

Dr Caroline Osborne

Consultant General Surgeon specialising in Breast Surgery,

Yeovil District Hospital NHS Foundation Trust

Ms Hayley Richardson

Clinical Coding Trainer,

Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr James Scuffham

Head of Nuclear Medicine Physics,

Royal Surrey NHS Foundation Trust

Dr Nagabhushan Seshadri

Consultant in Nuclear Medicine,

Liverpool University Hospitals NHS Foundation Trust

Ms Sunita Shrotria
Consultant General Surgeon,
Ashford and St. Peter's Hospitals NHS Foundation Trust

Dr Kate Williams
Consultant Oncoplastic Breast and Chest Wall Surgeon,
Manchester University NHS Foundation Trust

Dr Ming Young Simon Wan
Consultant Radiologist,
University College London Hospitals NHS Foundation Trust

Appendix C: Claimed benefits and decision problem from scope

The benefits to patients claimed by the company are:

- Reduced risk of anaphylactic reaction during SLNB procedures that use blue dye
- Reduced waiting times for patients because hospitals currently rely on a supply of technetium-99m to perform an SLNB
- Increased convenience of being able to have the Magtrace injection up to 30 days before the procedure. Currently people will usually have the technetium-99m injection and wait in the healthcare setting before the procedure. Blue dye is injected once the patient is anaesthetised in the operating theatre

The benefits to the healthcare system claimed by the company are:

- Improved patient management and co-ordination of care
- Improved efficiency in the use of facilities and staff resource
- Does not require involvement of nuclear medicine scientists or radiologists

Population	• People with high grade ductal carcinoma in-situ or invasive breast cancer having a sentinel lymph node biopsy
Intervention	Magtrace and Sentimag
Comparator(s)	• Technetium-99m in combination with blue dye
Outcomes	The outcome measures to consider include: • sentinel lymph node detection rate • mean number of sentinel lymph nodes retrieved per procedure • time taken for SLNB procedure • patient-reported outcome measures • device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.
Subgroups to be considered	Not applicable.
Special considerations, including those related to equality	People with cancer are protected under the Equalities Act 2010. People who may experience anaphylaxis as an adverse reaction to blue dye would currently be given Technetium-99m only or a four-node axillary sample. Magtrace and Sentimag could offer an alternative treatment option for this group. Known contraindications include people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or in the chest. This may be recognised as an equality issue as some people may be excluded from treatment with the technology. Magtrace and Sentimag may improve access to healthcare services as it could be used in smaller sites where there is not access to nuclear medicine. Currently, healthcare settings must have systems in place to handle, store and dispose of radioactive substances. The broader timing for the injection of Magtrace, between 1 and 30 days before surgery, may improve management of healthcare resources related to the procedure. Outcomes relevant to service delivery, efficiency gains and resource use could also be considered as part of the economic model. Technetium-99m is not always available and is usually prepared and used on the same day as the procedure. Where there is a shortage of Technetium-99m, blue dye is used alone. The dual technique has been shown to improve the rate of identification of SLNs.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	No specific equality issues have been identified relating to using the device.	
Any other special considerations	When injected directly into the bloodstream, the presence of Magtrace may cause image artefacts to present during Magnetic Resonance Imaging (MRI) of the injection and drainage site.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Magtrace and Sentimag for locating sentinel lymph nodes for breast cancer

1 Technology

1.1 Description of the technology

The Magtrace and Sentimag system (Endomag) comprises of a magnetic liquid tracer (Magtrace) and a handheld magnetic sensing probe (Sentimag). Magtrace is intended for use only with the Sentimag system. Magtrace is a non-radioactive dark brown liquid containing superparamagnetic iron oxide with a carboxydextran coating. It is both a magnetic marker and a visual dye (because of the dark colour of the particles). Magtrace is injected into the tissue beneath the areola or interstitial tissue around a tumour, then the particles are absorbed into lymphatics and become trapped in sentinel lymph nodes that can then be detected by the magnetic sensing probe to assist with biopsy. It can be injected by healthcare professionals such as surgeons or nurses before a sentinel lymph node biopsy (SLNB). This can be done in the operating theatre 20 minutes before the procedure or up to 30 days before surgery at an outpatient clinic.

During surgery, the Sentimag probe detects the tracer trapped in the lymph nodes and guides the surgeon to remove them for biopsy. Sentimag uses a visual reading and sounds of different pitches to indicate how close the surgeon is to the tracer. The nodes often appear dark brown or black in colour, which also helps identification.

The key innovative feature of the Magtrace and Sentimag system is its magnetic mechanism of action. This means that unlike other interventions used in current practice, the system can be used without the need for nuclear

medicine safety procedures and facilities. Magtrace can also be injected up to 30 days before surgery, whereas the tracers used in current practice can be given no more than a day before.

1.2 Relevant diseases and conditions

The Magtrace and Sentimag system, in people with breast cancer, is intended for locating sentinel lymph nodes during SLNB procedures for breast cancer staging.

NICE guideline on early and locally advanced breast cancer says that SLNB is the preferred technique to stage the axilla for people with invasive breast cancer and no evidence of lymph involvement on ultrasound or a negative ultrasound-guided needle biopsy.

Breast cancer is the most common cancer in the UK with approximately 54,000 new cases of invasive disease annually. The vast majority of breast cancers occur in women, but just over 300 men in the UK are also diagnosed with invasive breast cancer each year.

The company notes that Magtrace has been used in SLNB for breast cancer and other cancers such as melanoma, endometrial, cervical, prostate and oral cancer.

1.3 Current management

SLNBs help to diagnose cancer that has spread to the lymph nodes. The current treatment option for locating sentinel lymph nodes during SLNB is a combination of a tracer containing a radioactive isotope, technetium-99m and blue dye. Where technetium-99m is not available, blue dye may be used on its own, but this can reduce the detection rate of sentinel lymph nodes.

When using Technetium-99m for locating sentinel lymph nodes during SLNB it will be injected on the morning of the procedure following its preparation by nuclear medicine specialists. In some hospitals, the isotope is prepared off-site and then transported to the healthcare setting. On some occasions this can lead to the procedure being delayed. There can also be uncertainty

around availability of Technetium-99m. Cancellations and later starting times for procedures can waste resources and cause issues for surgical scheduling so significant planning and logistical oversight is required.

NICE has published guidance on the use of SLNB for early and locally advanced breast cancer. The guideline recommends that the dual technique with isotope and blue dye should be used when performing SLNB. Specifically, SLNB is recommended by NICE for people with invasive breast cancer who had no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy.

The guideline also recommends that SLNB should be offered to people who are having a mastectomy for ductal carcinoma in-situ (DCIS) breast cancer and people with a pre-operative diagnosis of DCIS who are considered to be at high risk of invasive disease.

1.4 Regulatory status

Magtrace received a CE mark in November 2012 and Sentimag received a CE mark in December 2010, both as class IIa devices for locating sentinel lymph nodes under the Medical Device Directive.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Reduced risk of anaphylactic reaction during SLNB procedures that use blue dye
- Reduced waiting times for patients because hospitals currently rely on a supply of technetium-99m to perform an SLNB
- Increased convenience of being able to have the Magtrace injection up to 30 days before the procedure. Currently people will usually have the technetium-99m injection and wait in the healthcare setting before the procedure. Blue dye is injected once the patient is anaesthetised in the operating theatre

The benefits to the healthcare system claimed by the company are:

- Improved patient management and co-ordination of care
- Improved efficiency in the use of facilities and staff resource
- Does not require involvement of nuclear medicine scientists or radiologists

2 Decision problem

Population	• People with high grade ductal carcinoma in-situ or invasive breast cancer having a sentinel lymph node biopsy
Intervention	Magtrace and Sentimag
Comparator(s)	• Technetium-99m in combination with blue dye
Outcomes	The outcome measures to consider include: • sentinel lymph node detection rate • mean number of sentinel lymph nodes retrieved per procedure • time taken for SLNB procedure • patient-reported outcome measures • device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.
Subgroups to be considered	Not applicable.
Special considerations, including those related to equality	People with cancer are protected under the Equalities Act 2010. People who may experience anaphylaxis as an adverse reaction to blue dye would currently be given Technetium-99m only or a four-node axillary sample. Magtrace and Sentimag could offer an alternative treatment option for this group. Known contraindications include people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or in the chest. This may be recognised as an equality issue as some people may be excluded from treatment with the technology. Magtrace and Sentimag may improve access to healthcare services as it could be used in smaller sites where there is not access to nuclear medicine. Currently, healthcare settings must have systems in place to handle, store and dispose of radioactive substances. The broader timing for the injection of Magtrace, between 1 and 30 days before surgery, may improve management of healthcare resources related to the procedure. Outcomes relevant to service delivery, efficiency gains and resource use could also be considered as part of the economic model.

	Technetium-99m is not always available and is usually prepared and used on the same day as the procedure. Where there is a shortage of Technetium-99m, blue dye is used alone. The dual technique has been shown to improve the rate of identification of SLNs.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
	No specific equality issues have been identified relating to using the device.	
Any other special considerations	When injected directly into the bloodstream, the presence of Magtrace may cause image artefacts to present during Magnetic Resonance Imaging (MRI) of the injection and drainage site.	

3 Related NICE guidance

Published

- Early and locally advanced breast cancer: diagnosis and management (2018) NICE guideline NG101
- Intraoperative tests for detecting sentinel lymph node metastases in breast cancer NICE diagnostics guidance DG8

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Breast Cancer Research Foundation
- British Nuclear Medicine Society
- Cancer Research UK
- European Society of Breast Cancer Specialists
- Health and Care Professions Council

- MacMillan
- National Breast Cancer Foundation
- Royal College of Radiologists

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Breast Cancer Now
- Breast Cancer Research Trust
- Breast Cancer UK
- CoppaFeel!
- National Hereditary Breast Cancer Helpline
- Pink Ribbon Foundation
- Prevent Breast Cancer
- The Inflammatory Breast Cancer Network UK
- Walk the Walk

NICE National Institute for Health and Care Excellence

Adoption report

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Summary

Adoption levers identified by contributors

- Streamlining the patient pathway and flexibility in scheduling.
- Increased nuclear medicine capacity.
- Reduction in the disposal of radioactive contaminated waste.
- May reduce pain
- Reduced incidence of anaphylaxis associated with use of blue dye.
- No exposure to radioactive isotopes and no need for ARSAC licensing of staff or unit.

Adoption barriers identified by contributors

- May not be suitable for patients:
    - with a very high BMI
    - who need an MRI soon after surgery
    - with haemochromatosis
    - with a pacemaker fitted
- Impact on MRI if needed post-surgery
- Loss of contract with isotope providers if numbers fall below financially viable parameters
- Deskilling of service if isotope use infrequent

1. Introduction

The adoption team has collated information from healthcare professionals working within NHS organisations. This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice

and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technology. It does not represent the opinion of NICE or MTAC.

The device has been available in the UK since 2012 and is used in 30 NHS organisations in England.

2. Contributors

The adoption team spoke to 5 NHS clinicians: 4 consultant oncoplastic breast surgeons (2 users of the technology) and a consultant clinical scientist in nuclear medicine (previously used the technology in urology).

3. Use of Magtrace and Sentimag in practice

The Magtrace (lymphatic tracer) and Sentimag localisation system (magnetic sensing) is intended to be used in people with cancer, during a sentinel lymph biopsy (SLNB) procedure. The company reports that Magtrace has been used in SLNB for breast cancer as well as melanoma, endometrial, cervical, prostate and oral cancer. This report focuses on the use of Magtrace in SLNB specifically for breast cancer.

The lymphatic tracer can be injected by healthcare professionals such as surgeons, radiologists, radiographers, or nurses before an SLNB procedure.

One user administers the injection in theatre at the time of the operation and the other user administers at the pre-operative assessment approximately 2 weeks earlier.

The surgeon then uses Sentimag to identify the lymph nodes that are mapped by the tracer.

4. Insights from the NHS

Care pathway

The potential impact the use of the technology could have on care pathways and theatre scheduling was identified as a significant benefit by some contributors. The 2 current users stated that it had revolutionised their theatre lists. Magtrace can be injected up to 30 days before surgery and this allows flexibility in scheduling as there

is no longer a requirement for the nuclear medicine team to administer radioactive isotopes on the day or afternoon before surgery due to short half-life. Theatre scheduling was not an issue for one oncoplastic surgeon as isotope injections are given the day before within their service and does not impact on day of procedure timetabling. Availability and capacity within nuclear medicine can impact on scheduling SNLB procedures, particularly where this facility is not on site. All contributors agreed the advantages of using Magtrace, which does not require storage, administration, regulation and monitoring by nuclear medicine with no requirement for ARSAC (Administration of Radioactive Substances Advisory Committee) licensing for staff or the unit. Users also highlighted the benefits of not having to consider the disposal of radioactive contaminated waste with no concerns about staff exposure.

Patient selection

Contributors reported that as Magtrace leaves artifacts in the breast it would not be suitable if it was known that the patient needed an MRI soon after surgery, though all stated that this was highly unlikely as all imaging should be done prior to surgery. Contributors also stated this could be an issue if artifacts were present at the 12-month MRI surveillance for younger patients, those with difficult to interpret breasts, or gene mutations.

All contributors reported potential difficulties in detecting Magtrace in people with a very high BMI due to high amounts of subcutaneous fat. However, this was also the case with radioactive isotopes.

One contributor suggested Magtrace is not suitable for use on patients with haemochromatosis (iron overload).

All contributors stated that if the tumour was in the upper outer quadrant of the breast and close to the sentinel lymph nodes in the axilla, they would need to be able to differentiate between the Magtrace and Magseed (designed to mark the site of a tumour and help with its removal in surgery). Different approaches were described including:

- first resecting the tumour after localising with Magseed and then proceeding to a Magtrace sentinel node biopsy.
- injecting Magtrace subareolar and at least 2cm from Magseed into deep subcutaneous tissues (but not parenchyma).
- using radioactive isotope tracer and Magtrace, rather than blue dye, to reduce the risk of anaphylaxis in a high risk patient.

One current user identified that this technology should not be used for people with a pacemaker where the probe would need to be in close proximity to the pacemaker.

All contributors agreed that whilst the technology has some advantages over the current care pathway there will always be patients for whom it is not suitable and who would require the use of radioactive isotopes. Non-users expressed concerns about the potential impact on availability and competency of nuclear medicine staff if the use of radioactive isotopes significantly decreases.

Clinician confidence/acceptance

One contributor said the technology was most useful for breast SLNB or other cancers where drainage to the sentinel lymph nodes is relatively predictable.

Another contributor stated that the level of uptake of radioactive tracers within the nodes can vary significantly between patients and as there is no clear reason for this questioned whether the same would be true for Magtrace. A current user reported stronger results with Magtrace if they administered it at the pre-operative appointment.

One current user reported the technology to be less intuitive and slower to use in theatre compared with technetium and blue dye because the Sentimag probe is bigger and more difficult to use and manipulate when inside the axilla compared with the gamma probe used for radioactive isotope tracers, and is very specific, picking up a signal when close to the node.

This user said they experienced better results if they injected deeper into the breast than they would normally do with technetium and blue dye.

Both users said that whilst there is some additional time on the table if injected at the time of surgery, because the surgeon is required to massage the breast for 5 to 10 minutes longer than when using a radioactive tracer to ensure the lymphatic tracer reaches the nodes, this is not significant and the gain in scheduling benefits outweighs this.

The other user considered the technology to be as intuitive and easy to use as other tracers.

Procurement and resource impact

Procurement of Magtrace was not reported to be an issue by users of the technology and contributors considered the cost to be similar to using isotopes.

All non-users reported that positive NICE guidance on the use of the technology would be useful for developing successful business cases. One non-user commented that the Magtrace probes are expensive and quite fragile so a more robust cost comparison is required with servicing, rental costs and insurance included.

Training

The two current users reported the technique to be similar to injecting technetium and blue dye.

It was reported that surgeons would need to become accustomed to listening for a change of sound on the Sentimag as well as reading the display.

Patient experience

Both current users reported a better patient experience using Magtrace in comparison the radioactive isotope tracers and blue dye as it appears to be generally less painful, with less staining to the skin (particularly if injected more deeply), with a more natural colour.

One non-user stated that no concerns have been expressed by patients regarding pain in association with isotope injections.

Patient/clinician safety

All contributors highlighted the risk of patients experiencing anaphylaxis when using blue dye (estimated to be 1:500) with several contributors stating that they had experience of this with a small number (1 or 2) patients. All contributors said when this happens patients normally require immediate treatment in ICU. This can be a significant safety risk if they do not have access to an ICU bed. This has been a particular issue during the COVID-19 pandemic and one contributor no longer uses blue dye for this reason.

Reducing the incidence of anaphylaxis associated with the use of blue dye was considered to be a significant benefit and non-users were keen to see evidence of this.

Whilst all contributors acknowledged the potential risks, to both clinicians and patients, associated with using a radioactive isotope, they considered these to be minimal. No patients were reported to have refused treatment using radioactive isotopes.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Endomag Ltd
Submission date	14 January 2022
Regulatory documents attached	• Sienna+ IFU (SIE-006 Instructions For Use Issue 15.0) • SiennaXP IFU (SIE-006a SiennaXP Instructions For Use Issue 6.0) • Magtrace IFU (MTR-006EN Instructions For Use v.3.0) • Sentimag Gen1 IFU (775L12 Iss 19 - SentiMag IFU) • Sentimag Gen2 IFU (775L12EU Iss 30.0 - SentiMag IFU) • CE Sentimag and Magtrace (CE 563405)
Contains confidential information	Yes

Contents

1 Decision problem

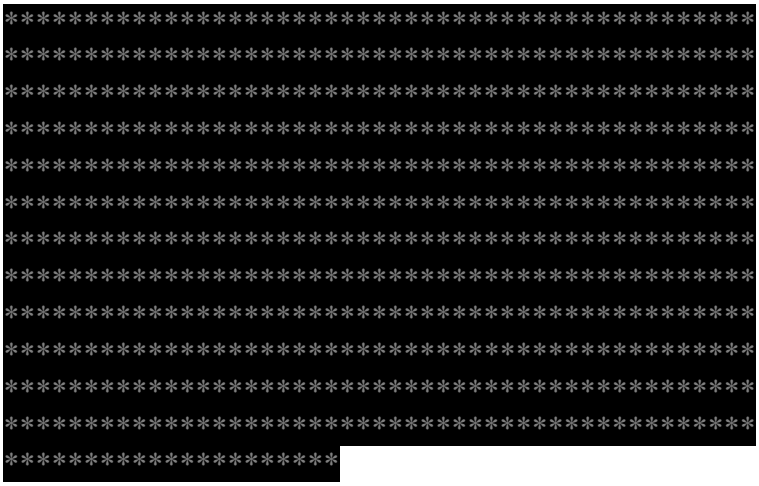
	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with high grade ductal carcinoma in-situ or invasive breast cancer having a sentinel lymph node biopsy	Enter text.	Enter text.
Intervention	Magtrace and Sentimag	Enter text.	Enter text.
Comparator(s)	Technetium-99m in combination with blue dye	Enter text.	Enter text.
Outcomes	• sentinel lymph node detection rate • mean number of sentinel lymph nodes retrieved per procedure • time taken for SLNB procedure • patient-reported outcome measures • device-related adverse events	The metrics used have not varied from the scope but have been defined in more detail in P415J003 section 3	Enter text.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.	Enter text.	Enter text.
Subgroups to be considered	Not applicable.	Enter text.	Enter text.
Special considerations, including issues related to equality	People with cancer are protected under the Equalities Act 2010. People who may experience anaphylaxis as an adverse reaction to blue dye would currently be given Technetium-99m only or a four-node axillary sample. Magtrace and Sentimag could offer an alternative treatment option for this group.	Enter text.	Enter text.

	Known contraindications include people with known hypersensitivity to iron oxide or dextran compounds, people with iron overload disease and people with a metal implant in the axilla or in the chest. This may be recognised as an equality issue as some people may be excluded from treatment with the technology. Magtrace and Sentimag may improve access to healthcare services as it could be used in smaller sites where there is not access to nuclear medicine. Currently, healthcare settings must have systems in place to handle, store and dispose of radioactive substances. The broader timing for the injection of Magtrace, between 1 and 30 days before surgery, may improve management of healthcare resources related to the procedure. Outcomes relevant to service delivery, efficiency gains and resource use could also be considered as part of the economic model. Technetium-99m is not always available and is usually prepared and used on the same day as the procedure. Where there is a shortage of Technetium-99m, blue dye is used alone. The dual technique has been shown to improve the rate of identification of SLNs.		

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	Magtrace® & Sentimag®
Approved name	Magtrace® & Sentimag®
UKCA/ CE mark class and date of authorisation	Magtrace received a CE mark in November 2012 and Sentimag received a CE mark in December 2010, both as class IIa devices for locating sentinel lymph nodes under the Medical Device Directive.

Version(s)	Launched	Features
Sentimag Generation 1	2011	Larger probe diameter, lighter footswitch, no probe holder, probe was less sensitive, probe cable shorter in length, External casework was made from PEEK1000 which was initially replaced by PEEK CLASSIX polymer in Gen 2 in September 2012 and ultimately by HC1204F PC/ABS resin blend in March 2013. 
SiennaXP	2013	The difference between SiennaXP and Magtrace is a name change only.
Sienna+	2011	 

		[redacted]
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Reduced risk of anaphylactic reaction during SLNB procedures that use blue dye	P415J003 _NICE literature review	Blue Dye is associated with a risk of anaphylaxis, Magtrace is not.
Reduced waiting times for patients because hospitals currently rely on a supply of technetium-99m to perform an SLNB	Magtrace IFU + Shams 2021	Magtrace can be administered up to 30 days before the procedure or 20 minutes prior to the procedure, which allows flexibility of administration
Increased convenience of being able to have the Magtrace injection up to 30 days before the procedure. Currently people will usually have the technetium-99m injection and wait in the healthcare setting before the procedure. Blue dye is injected once the patient is anaesthetised in the operating theatre	Magtrace IFU + Karakatsanis 2018, 2020	Technitium99 has a half-life that's limits the window of administration, BD is typically injected once the patient is anaesthetised. Magtrace can be administered upto 30 days before the procedure
System benefits		
Improved patient management and co-ordination of care	Magtrace IFU + Shams 2021+ Karakatsanis 2018, 2020	Magtrace can be administered up to 30 days before the procedure or 20 minutes prior to the procedure, which allows flexibility of administration, this can be done by theatre staff if required cutting dependence on Tc99 availability and nuclear

		medicine personnel resource
Improved efficiency in the use of facilities and staff resource	Magtrace IFU	Magtrace can be administered up to 30 days before the procedure or 20 minutes prior to the procedure, which allows flexibility of administration, this can be done by theatre staff if required cutting dependence on Tc99 availability and nuclear medicine personnel resource
Does not require involvement of nuclear medicine scientists or radiologists	Enter text.	Magtrace is not radioactive
Cost benefits		
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Sustainability benefits		
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

Magtrace® is a unique Super Paramagnetic Iron Oxide particle solution designed to mark and locate lymph nodes in cancer patients.

These lymph nodes can then be accurately located using the Sentimag® system, which is a highly sensitive magnetic sensor. The handheld Sentimag probe induces the paramagnetic properties of the Magtrace® and by visual and audible feedback, guides the surgeon to the marked lymph node location. The natural dark brown colour of the Magtrace® also provides the surgeon with a visual aid during dissection.

The marked lymph nodes can then be removed as part of a Sentinel Lymph Node Biopsy (SLNB) at the surgeon's discretion. The natural dark brown colour of the Magtrace® also provides the surgeon with a visual aid during dissection to find the marked node.

Specifically, Magtrace® consists of an iron oxide core, enveloped in a carboxydextran coating. This allows for a tightly controlled particle size of 60nm which enables rapid lymphatic uptake, but is mechanically filtered by the first draining lymphatic nodes.

Because Magtrace® does not rely on radioisotopes it relives the regulatory oversight associated with radioactive material, enabling significant streamlining of the patient pathways.

In addition, Magtrace® has a long injection window of 30 days, compared to less than 24 hours for radioisotopes. This means that if the patient pathway necessitates Magtrace® injection at an appointment prior to surgery, this can be done easily in a clinic setting. This is not possible with traditional radioisotopes.

Blue dye is known to cause anaphylaxis in a small but significant number of patients. There have been no reports of anaphylaxis associated with Magtrace®

As per the literature review above, Magtrace® has been shown to be non-inferior to the dual technique of radioisotopes and blue dye for SLNB in breast cancer patients.

To summarise, Magtrace® removes radioactivity from node marking procedures as well as removing the potential for anaphylaxis with blue dyes. These properties, and its long injection window mean significant efficiencies in the patient pathways can often be realised, without compromising quality of care.

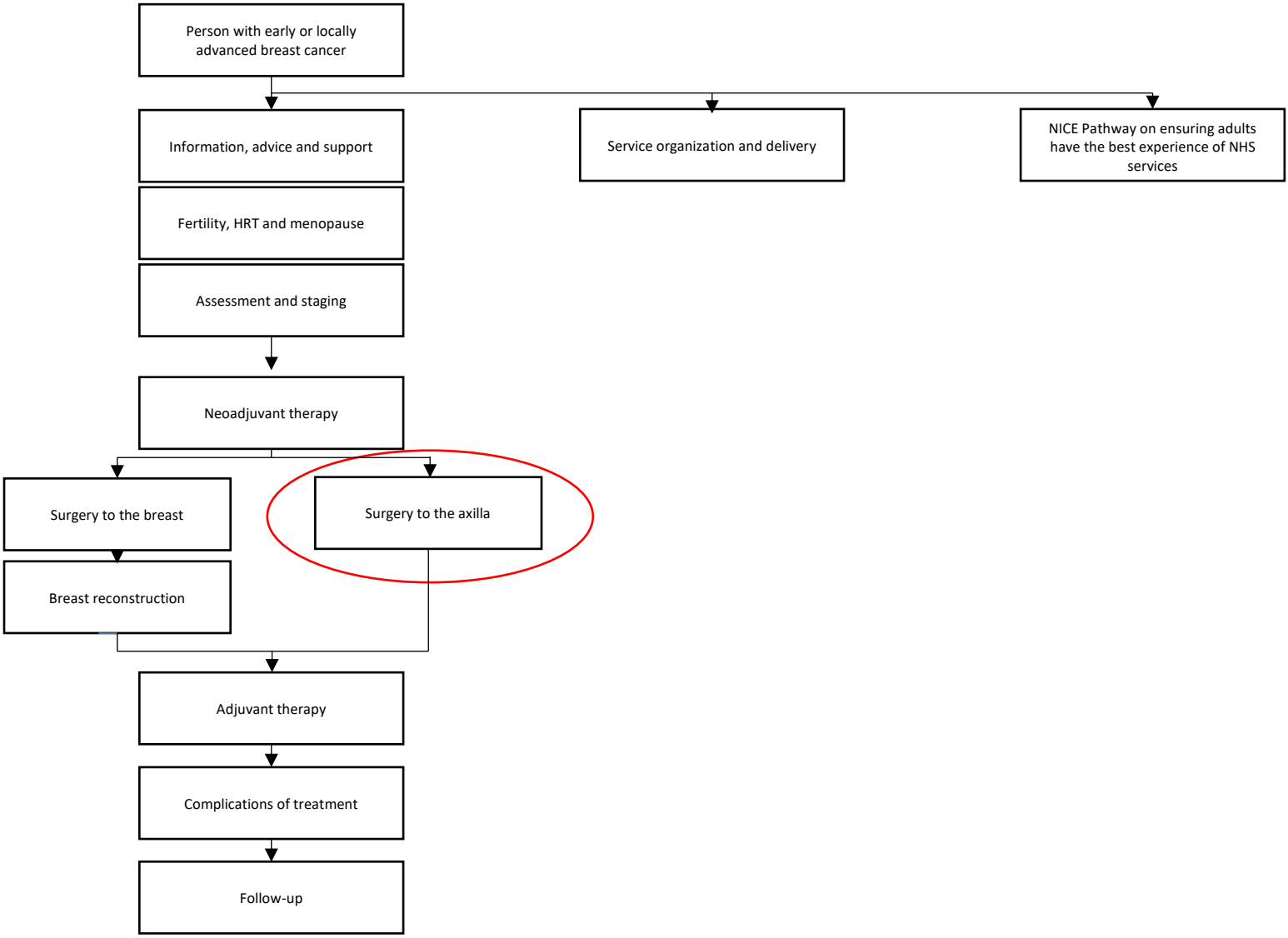
Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Magtrace is non-radioactive and therefore no radioactive isotopes are involved and no radioactive waste is produced during its production. As a result it has a lower environmental impact than the manufacturing of Tc99.

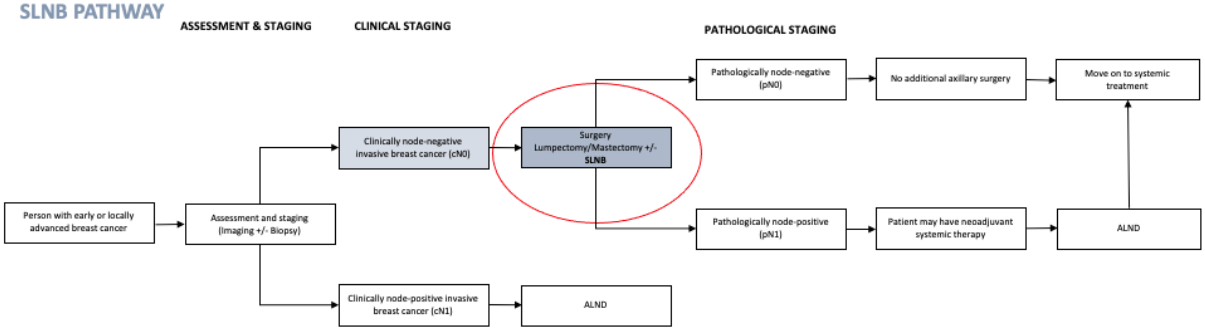
3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

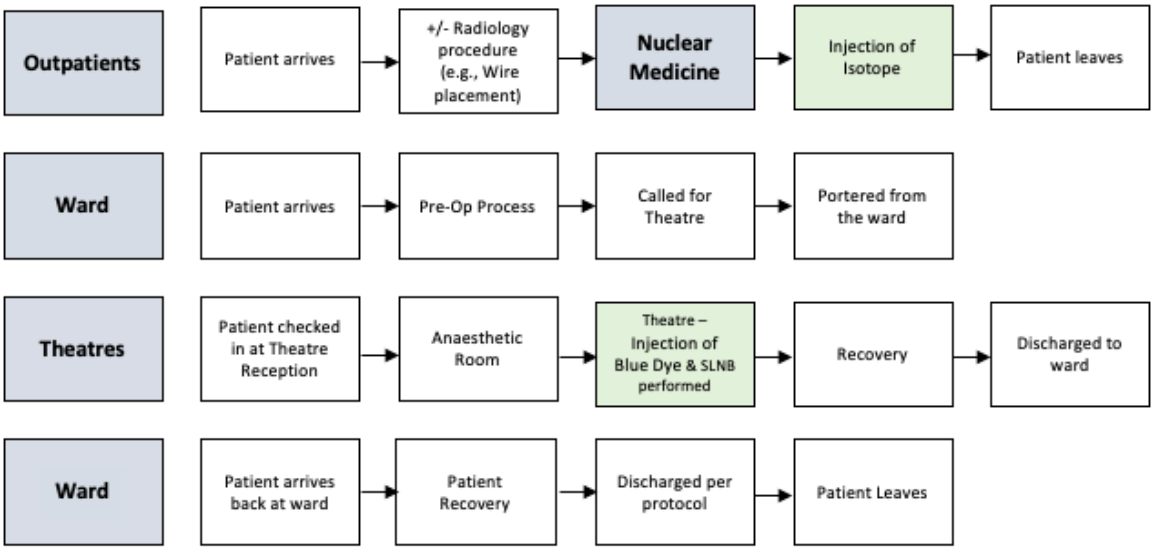
EARLY AND LOCALLY ADVANCED BREAST CANCER OVERVIEW, NICE PATHWAYS, NICE 2022
https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer



SLNB PATHWAY

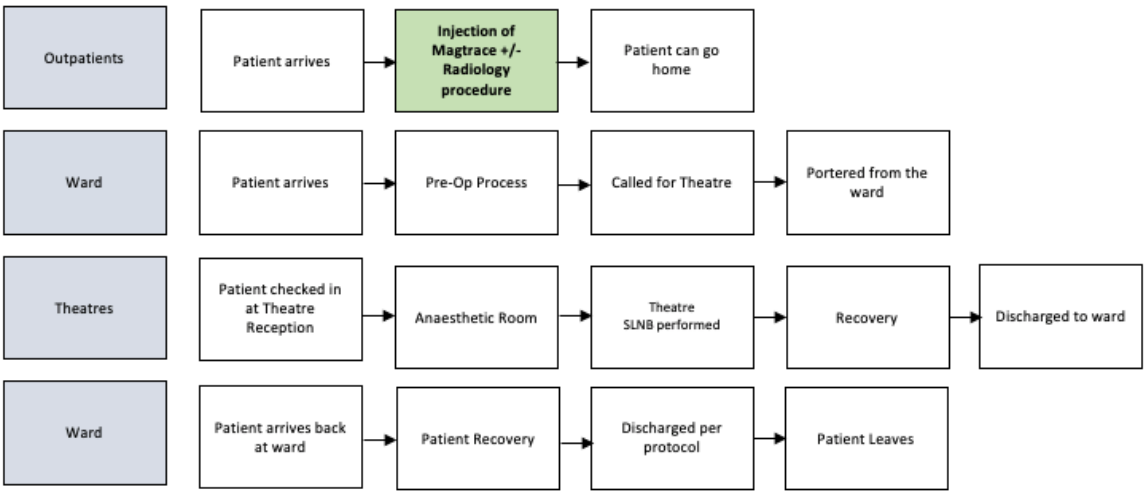


INJECTION OF A TRACER: CURRENT GOLD STANDARD (TC99 + BLUE DYE) PATIENT FLOW DIAGRAM



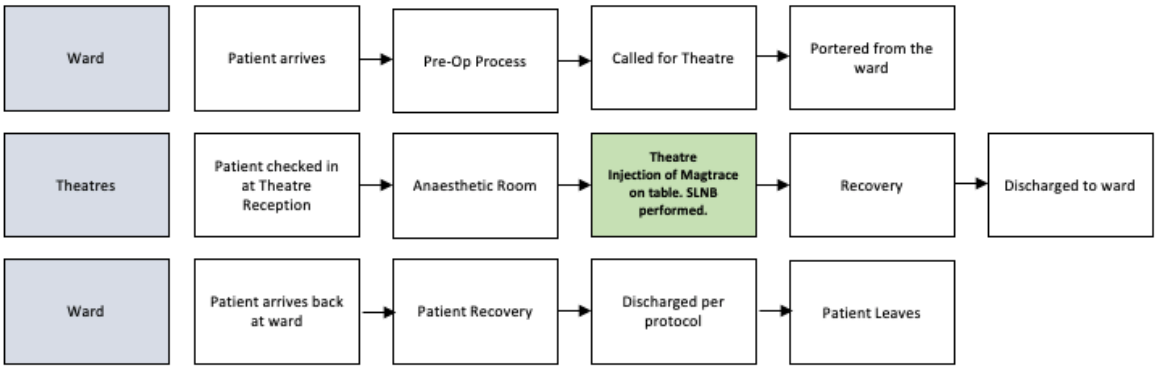
INJECTION OF A TRACER (SLNB) - MAGTRACE : PATIENT FLOW DIAGRAM (PRE-OP WITHIN 30 DAYS OF SLNB)

Magtrace administration can be between 20 minutes immediately prior to the procedure or up to 30 days before the procedure



INJECTION OF A TRACER (SLNB) - MAGTRACE : PATIENT FLOW DIAGRAM (PERI-OPERATIVE INJECTION)

Magtrace administration can be between 20 minutes immediately prior to the procedure or up to 30 days before the procedure which means that patient flow can be simplified as Nuclear Medicine can be avoided.



Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

Magtrace and Sentimag utilise a surgical technique that surgeons are familiar with when using Tc / blue dye and the gamma probe used for sentinel lymph node detection; in consequence surgical technique is not modified.

Training on the device itself is provided for health care providers. This is facilitated by Endomag by technical and clinical experts in the use of the technology.

There is a standard procedure that those trainers follow on request for training or with a centre / new operator trialling Magtrace.

New and existing users have access to online media which features their peers discussing and demonstrating the relevant techniques. This has been developed and made in conjunction with Endomag. It is made available to them by Endomag.

In addition, those materials are incorporated into an on-site delivered 'in-service' style training facilitated by Endomag technical and clinical experts in the use of the technology, which is offered to the health care providers by role prior to the first cases.

In-person support of procedures is provided by the same, Endomag, technical and clinical experts. This is maintained for as long as Endomag and / or the health care providers feel is necessary to ensure procedures can be carried out safely and effectively and support is further provided on request or periodically on a need assessed basis to ensure best practice is maintained.

Endomag technical and clinical experts also work to a set of standardized criteria to ensure that training standards are uniformly maintained across sites and end users.

Training of site staff is documented, and records maintained.

No formal education of patients is required due to the introduction of Magtrace and Sentimag. It is understood from the literature that patients may benefit from simple advice that skin discolouration likely to fade over time can be associated with the use of Magtrace and the opportunity to discuss this with their surgeon. Training on injection site options and dosing associated with the amelioration of skin discolouration associated with the use of Magtrace is provided to health care providers as part of the mechanisms outlined above.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		36
Number of studies identified as being relevant to the decision problem.		22
9Of the relevant studies identified:*	Number of published studies (included in table 1).	22
	Number of abstracts (included in table 2).	9
	Number of ongoing studies (included in table 3).	4

- Note: A distinction is made here between the peer-reviewed published sources listed in Table1 that were both relevant to the decision problem and suitable for use in quantitative meta-analysis as reported in Section 7, and the abstracts and ongoing studies listed in Tables 2 and 3 that were worthy of note but were not used in the quantitative analysis.

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies *(Note: See abbreviation meanings at foot of table)*

Data source[a]	Author, year and location	Study design	Patient population, setting, withdrawals/lost to follow up[b]	Intervention[c]	Comparator(s)[d]	Main outcomes[e]
PMed/WoS	Ahmed, 2015, UK	Feasibility	32 PIBC; 3 NCH; 0 WL	SLND + LL	Mag vs Tc/Blue	IR, NN
PMed/WoS	Alvarado, 2019, USA	Non-inferiority	160 Early stage PIBC or DCIS; 6 NCH; 14 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR, NCR
PMed/WoS	Douek, 2014, UK & the Netherlands	Non-inferiority	161 PIBC; 6 NCH; 1 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR, NCR
PMed/WoS	Ghilli, 2017, Italy	Non-inferiority	199 PIBC or DCIS; 3 NCH; 6 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR, NCR
PMed/WoS	Gimenez-Climent, 2021, Spain	Non-inferiority	89 post-NAC PIBC; 5 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR, NCR
PMed/WoS	Hersi, 2019, Sweden	Feasibility	32 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR
PMed/WoS	Hersi, 2021, Sweden	Non-inferiority	534 PIBC; 6 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN
PMed/WoS	Houpeau, 2016, France	Feasibility	115 T0-T2 stage PIBC; 4 NCH, 7 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR, NCR
PMed/WoS	Karakatsanis, 2016, Sweden & Norway	Non-inferiority	206 PIBC or DCIS; 7 NCH; 0 WL	SLND	Mag vs Tc/Blue	NRR, NCR
PMed/WoS	Karakatsanis, 2017, Sweden	Non-inferiority	183 PIBC; 1 NCH; 0 WL	SLND	Mag only	IR, NN
PMed/WoS	Karakatsanis, 2019, Sweden	Feasibility	40 DCIS; 5 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, CR
PMed/WoS	Kurylcio, 2021, Poland	Feasibility	74 post-NAC PIBC or DCIS; 1 NCH, 0 WL	SLND	Mag only	IR, CR
PMed/WoS	Lorek, 2019, Poland	Assess complications	303 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN, CR
PMed/WoS	Man, 2019, Hong Kong	Feasibility	333 PIBC; 1 NCH; 0WL	SLND	Mag only	IR, NN
PMed/WoS	Pinero-Madrona, 2015, Spain	Non-inferiority	181 PIBC; 9 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR, NCR
PMed/WoS	Pohlodek, 2018, Slovakia	Feasibility	10 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN, CR

.

Data source[a]	Author, year and location	Study design	Patient population, setting, withdrawals/lost to follow up[b]	Intervention[c]	Comparator(s)[d]	Main outcomes[e]
PMed/WoS	Pouw, 2015, UK & the Netherlands	Feasibility	11 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN
PMed/WoS	Rubio, 2015, Spain	Non-inferiority	120 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN, NRR
PMed/WoS	Rubio, 2020, Spain	Non-inferiority at reduced doses	135 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN
PMed/WoS	Shams, 2021, Germany	Care pathway	30 PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR
PMed/WoS	Thill, 2014, Germany, Poland & Switzerland	Non-inferiority	150 PIBC; 4 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN, CR, NRR, NCR
PMed/WoS	Vural, 2020, Turkey	Feasibility	104 early-stage PIBC; 1 NCH; 0 WL	SLND	Mag vs Tc/Blue	IR, NN

[a] **Data Sources**: PubMed ("PMed") and Web of Science ("WoS") databases.

[b] **Patients, Setting etc**: Primary invasive breast cancer patients ("PIBC"); Ductal carcinoma in situ patients ("DCIS"); Neo-adjuvant chemotherapy ("NAC"); National/City hospitals or cancer centres ("NCH"); Withdrawals or Lost to follow-up ("WL").

[c] **Interventions**: Sentinel lymph node detection ("SLND"); Lesion localisation ("LL").

[d] **Comparators**: Magtrace tracer with Sentimag proximity detector ("Mag"); Radioactive Tracer ± Blue Dye with Gamma Probe proximity detector ("Tc/Blue").

[e] **Main Outcomes**: Identification Rate ("IR"); Number of Nodes ("NN"); Complications Rate ("CR"); Sentimag-versus-Gamma Nodal Retrieval Rate ("NRR"); Sentimag-to-Gamma Nodal Concordance Rate ("NCR").

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
European Journal of Cancer 138, Suppl. 1 (2020) S18–S124	Karakatsanis, A. 2020. Sweden	Non-inferiority to gold standard and non-inferiority at reduced doses	330 PIBC, 0 WL	SLND	Mag vs Tc/blue dye	IR, NN, Skin Discolouration
https://www.ejso.com/article/S0748-7983(20)30160-8/fulltext	Mullapudi, N.A. 2020, UK	Non-inferiority	113 patients, PIBC, 4 WL	SLND	Mag vs Tc99 +/- Blue dye	IR, NRR, NCR, Malignancy rate, Malignancy concordance rate
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0041-1730181	Munawwar, B. 2021. Germany	Non-inferiority	Text55 patients, PIBC, NAC. 0 WL	SLND	Mag vs Tc	IR, NN,
European Journal of Cancer 138, Suppl. 1 (2020) S18–S124	Paepke, S. 2020, Germany	feasibility	50 PIBC, 0 WL	SLND	none	IR, Median operation time, Skin staining
European Journal of Surgical Oncology 47 (2021) e296ee347	Qureshi, M. 202, UK.	Feasibility, Non-inferiority at different injection windows	214 PIBC 0 WL	SLND	No technique comparator.	IR, NN, Malignancy

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European Journal of Cancer 138, Suppl. 1 (2020) S18–S124	Raus, K. 2020, Czech Republic	Feasibility	137 PIBC or DCIS, 29 NAT, 18 ALND, 119 SLNB. 0 WL	SLND	Magtrace vs Sienna+	IR, NN,
https://cancerres.aacrjournals.org/content/76/4_Supplement/P3-01-04	Rubio, I. 2015, Spain	Non-inferiority	PIBC 188 Tc99, 92 SPIO/Tc99, NAC, 0 WL	SLND	Mag vs Tc99	IR, FNR (false negative rate)
European Journal of Surgical Oncology 46 (2020) e11ee53	Scally, N. 2020. UK	Feasibility	PIBC, 45 patients, 0 WL	SLND	None	IR, NN
Abstracts / European Journal of Surgical Oncology 45 (2019) 886e926	Syahkal, B. 2019, UK	Feasibility	134 PIBC, 0 WL	SLND	Blue dye assisted Four node sampling (ANS)	NN

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Clinicaltrials.gov (NCT05122585)	Yvonne Vissers, expected completion Feb 2022, Zuyderland Medisch Centrum, Netherlands)	A prospective cohort of forty patients with breast cancer and an indication for a sentinel node procedure will be injected with both Technetium (radioisotope) and Magtrace (magnetic). All patients in this study will receive both tracers.	Patients of 18 years or older with breast cancer and an indication for a sentinel node procedure will be included. These patients will be recruited by their breast surgeon in the outpatient department of the Breast Care Centre in Zuyderland Medical Centre.	Sentinel node procedure using a magnetic tracer next to Technetium.	Technetium	The concordance in detection of sentinel nodes by Magtrace and the Technetium tracer
Clinicaltrials.gov (NCT05161507)	Petr Vávra, Ass.Prof.,MD,PhD Expected completion December 31, 2023. University Hospital Ostrava, Czechia	Prospective single site comparison of Magtrace vs Technetium	Patients with breast carcinoma at the University Hospital Ostrava, Czechia	Sentinel node procedure using a magnetic tracer next to Technetium.	Technetium	Surgeon-rated ease of detected lymph node localization and removal.
Clinicaltrials.gov (NCT04722692)	Andreas Karakatsanis PhD, Expected completion December 30,	All patients will have been injected with SPIO during the breast procedure. Those who have invasive breast	DCIS, Breast Cancer, Breast Neoplasms	SLND performed after surgery for DCIS or other pre-invasive lesions, where final	Technetium +/- Blue Dye	d-SLND detection rate, Nodal concordance

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	2027. Uppsala University	cancer on final pathology will receive radioisotope and undergo SLND. Patients will be randomly allocated to one of two arms: Experimental arm (SLND will be SPIO-guided and the isotope activity will be controlled as background) and control arm (SLND will be isotope-guided and SPIO activity will be controlled as background).		pathology showed invasive breast cancer. Patients have received SPIO in the breast at the first operation, prior to dissection and resection and the SLN has already been marked with SPIO. These SLNs are to be removed.		
Endomag supported Investigator initiated Study	Dr R Hung, Expected completions December 2022. North District Hospital Hong Kong	RCT Magtrace Vs Tc99+BD	Breast cancer patients requiring SLNB at North district and Princess Margaret Hospitals	Participants will be randomised to either Magtrace or Tc99+BD	Technetium +/- Blue Dye	identification rate of sentinel lymph node

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Ahmed 2015	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Alvarado 2019	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Douek 2014	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Ghilli 2017	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Gimenez-Climent 2021	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Hersi 2019	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Hersi 2021	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Houpeau 2016	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Karakatsanis 2016	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Karakatsanis 2017	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Karakatsanis 2019	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Karakatsanis 2020	Non-peer reviewed indication of clinician experience	Comments noted
Kurylcio 2021	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Lorek 2019	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Man 2019	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Mullapudi 2020	Non-peer reviewed indication of clinician experience	Comments noted
Munawwar 2021	Non-peer reviewed indication of clinician experience	Comments noted
Paepke 2020	Non-peer reviewed indication of clinician experience	Comments noted
Pinero-Madrona 2015	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Pohlodek 2018	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Pouw 2015	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Qureshi 2021	Non-peer reviewed indication of clinician experience	Comments noted
Raus 2020	Non-peer reviewed indication of clinician experience	Comments noted
Rubio 2015	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Rubio 2015	Non-peer reviewed indication of clinician experience	Comments noted

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Rubio 2020	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Scally 2020	Non-peer reviewed indication of clinician experience	Comments noted
Shams 2021	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Syahkal 2019	Non-peer reviewed indication of clinician experience	Comments noted
Thill 2014	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.
Vural 2020	Provides data re clinical effectiveness metrics.	Data used in quantitative meta-analyses.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Peer Reviewed papers from Table 1

Ahmed 2015	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Low sample numbers (N = 32).
How was the study funded?	Investigator-sourced funding. Endomag provided magnetic tracer and equipment support

Alvarado 2019	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 160).
How was the study funded?	Endomag funded and sponsored study

Douek 2014	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 161).
How was the study funded?	Unrestricted Education Grant from Endomagnetics Ltd., UK. UK National Institute of Health Research (NIHR) adopted trial.

Ghilli 2017

How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 199).
How was the study funded?	Investigator-sourced funding. The study was supported by Sysmex Europe, which provided for free the equipment of SentiMag" devices and the tracer Sienna" for the period of the study. Sysmex is the EU distributor for Endomag

Gimenez-Climent 2021	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 89).
How was the study funded?	Investigator-sourced funding. Sysmex Spain funded this work without participating in its design, analysis of data, or preparation of the manuscript. Sysmex is the EU distributor for Endomag

Hersi 2019	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR metric.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Low sample numbers (N = 32); single site.
How was the study funded?	Investigator-sourced funding. EndoMagnetics Ltd (Cambridge, UK) provided the Magseed® and the SPIO (Mag- traceTM) for the study.

Hersi 2021

How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None identified (N = 534).
How was the study funded?	Sysmex Europe GmbH and Endomagnetics, Cambridge, UK, provided the SentiMag® device and Magtrace® vials for the trial. Institutional grants were provided by Uppsala University and Västmanland Cancer Foundation

Houpeau 2016	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 115).
How was the study funded?	Sysmex provided grant sponsorship, Sysmex and Endomag provided magnetic tracer and Sentimag units for the study. Sysmex is the EU distributor for Endomag

Karakatsanis 2016	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 206).
How was the study funded?	Investigator-sourced funding. The SentiMag detection system and Sienna+ vials were provided by Sysmex Europe during the study. Sysmex is the EU distributor for Endomag

Karakatsanis 2017

How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 183); single site.
How was the study funded?	The study was funded by Uppsala University

Karakatsanis 2019	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & CR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Low sample numbers (N = 40).
How was the study funded?	The study was funded by Uppsala University and by a fund from the Swedish Breast Cancer Association (Bröstcancerförbundet; https://www.bro.org.se).

Kurylcio 2021	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & CR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 74); single site.
How was the study funded?	Investigator-sourced funding, no external funding.

Lorek 2019	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN & CR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Single site (N = 303).
How was the study funded?	Investigator-sourced funding.

Man 2019	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Single site (N = 333).
How was the study funded?	Investigator-sourced funding.

Pinero-Madrona 2015	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	None identified (N = 333).
How was the study funded?	Investigator-sourced funding.

Pohlodek 2018	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN & CR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Low sample numbers (N = 10); single site.
How was the study funded?	The study was funded by Sysmex Europe. Sysmex is a distributor for Endomag

Pouw 2015	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Low sample numbers (N = 11); single site.
How was the study funded?	This research was supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organisation for Scientific Research

	(NWO), and which is partly funded by the Ministry of Economic Affairs. This research was supported by an unrestricted Educational Grant from Endomagnetics Ltd, UK. This research is part of an UK National Institute for Health Research (NIHR) adopted trial.

Rubio 2015	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN & NRR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 120); single site.
How was the study funded?	Investigator-sourced funding. Sysmex Espana S.L provided the device and SPIO tracer. Sysmex is a distributor for Endomag

Rubio 2020	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 135); single site.
How was the study funded?	Investigator-sourced funding. Sysmex Espana S.L provided the device and SPIO tracer. Sysmex is a distributor for Endomag

Shams 2021	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.

Does this evidence support any of the claimed benefits for the technology? If so, which?	IR metric.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Low sample numbers (N = 30); single site.
How was the study funded?	Investigator-sourced funding. Open Access funding enabled and organized by Projekt DEAL

Thill 2014	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, CR, NRR & NCR metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 150).
How was the study funded?	The study was sponsored by Sysmex Europe. Sysmex is a distributor for Endomag

Vural 2020	
How are the findings relevant to the decision problem?	Provides data re clinical effectiveness metrics.
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR & NN metrics.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Moderate sample numbers (N = 104); single site.
How was the study funded?	Investigator-sourced funding.

Abstracts from Table 2

Karakatsanis 2020

How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Sysmex funded. Sysmex is the distributor for Endomag

Mullapudi 2020	
How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NRR, NCR, Malignancy rate, Malignancy concordance rate
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Sysmex funded. Sysmex is the distributor for Endomag

Munawwar 2020

How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding

Paepke 2020	
How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, Median Operation Time
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding

Qureshi 2021

How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN, Malignancy rate
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding

Raus 2020	
How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding

Rubio 2015

How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, FNR
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding. Sysmex Espana S.L provided the device and SPIO tracer. Sysmex is a distributor for Endomag

Scally 2020	
How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	IR, NN
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding

Syahkal 2019

How are the findings relevant to the decision problem?	Non-peer reviewed indication of clinician experience
Does this evidence support any of the claimed benefits for the technology? If so, which?	NN
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Non-peer reviewed
How was the study funded?	Investigator-sourced funding

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

There were no adverse events associated with Magtrace or Sentimag.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

The company has identified evidence in the clinical literature of two further types of adverse events associated with the Magtrace/Sentimag modality for sentinel lymph node marking.

The first type of reported adverse event that the company has noted is the **Complications Rate (CR)**, meaning the per-patient proportion of surgical SLNB operations performed following which a significant clinical complication – such as infection, lymphoedema, haematoma/seroma, and urticaria – requiring adapted or additional medical treatment occurs, excluding anaphylaxis. Less severe, or more transient, or purely neurological clinical complications, including paraesthesia, restricted upper limb mobility, and pain, are also excluded.

Quantitative data on Complications Rates have been identified and subjected to meta-analysis as detailed in **Section 7** of this report.

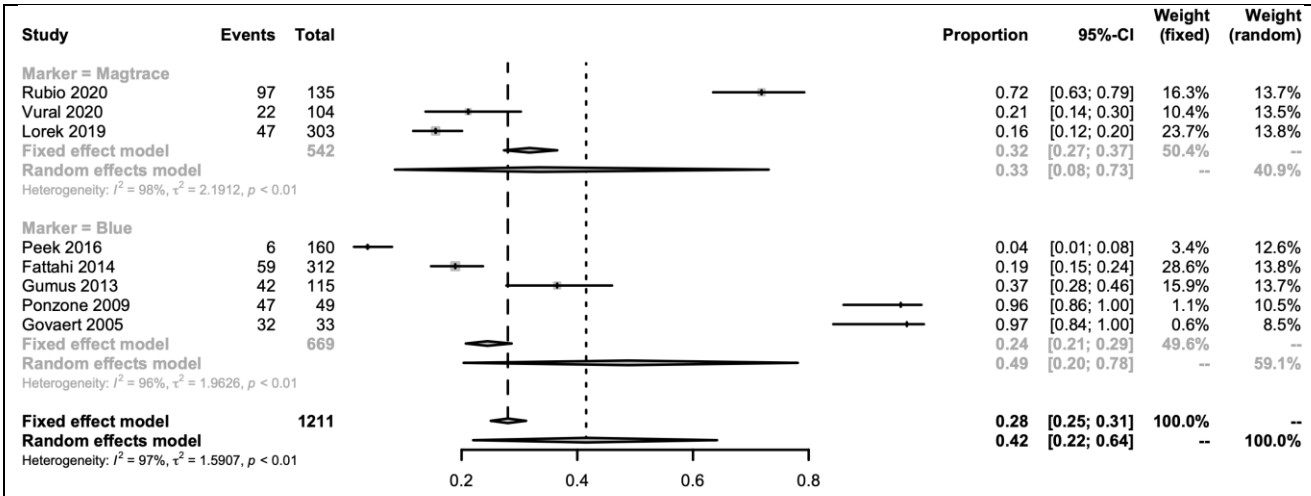
The second type of reported adverse event that the company has noted is the **Staining Complications Rate (SCR)**, meaning the probability that a patient will present with post-operative dermatological staining following the SLNB procedure. This metric is associated specifically with the use of Magtrace and of the Blue dye; the latter being routinely used as an optical marker in conjunction with radioactive markers in the Tc/Blue method of sentinel lymph node marking.

Given that dermatological staining is a matter of cosmesis rather than clinical effectiveness, it was considered appropriate to exclude it from explicit assessment in this report. However, it has been documented and reported in detail elsewhere, *viz.* in the document **P415J003** that the company has submitted to NICE as part of its overall submission.

For completeness, a summary of the quantitative data sourced and evaluated in P415J003 is presented below, along with comparator data for dermatological staining associated with Blue dye. The meta-analysis methods used were the same as those reported in Section 7 of this report.

Staining Complications Rates (SCR)

Staining Complications Rates for Blue dye and/or for Magtrace were reported in **8** studies, as shown in the Forest plot below.



Pooled heterogeneity was calculated as I^2 = 97%, indicating considerable heterogeneity.

Metric	No. studies	No. patients	Pooled Proportion	95% CI
Staining Complication Rate - Magtrace	5	542	33%	8 to 73%
Staining Complication Rate – Blue Dye	5	689	49%	20 to 64%

Conclusions drawn:

- The **Staining Complications Rate** metric is occasionally reported in the literature, and patient numbers are moderate. There is therefore a reasonably strong indication that the Magnetic modality is preferred (i.e., has a lower Staining Complications Rate) over the Blue dye modality.

It was also noted, as discussed in P415J003, and based on published Patient-Reported Outcomes, that the dermatological staining occasionally associated with the Magnetic modality is not a significant concern for a substantial majority of patients.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Methods Applied

Statistical analysis was performed using the “meta” package in “R”, version 3.5.3. Pooling was via the inverse variance method. Proportions, incidence rates, and risk differences were evaluated using the “metaprop”, “metarate”, and “metabin” commands respectively. Confidence levels were assigned using the Random Effects Model.

Heterogeneity among different studies was assessed using the I^2 metric, and following the Cochrane Handbook guidance for interpretation, as follows:

- I^2 in the range 0% to 40%: heterogeneity might not be important;
- I^2 in the range 30% to 60%: may represent moderate heterogeneity;

- I^2 in the range 50% to 90%: may represent substantial heterogeneity;
- I^2 in the range 75% to 100%: considerable heterogeneity.

Inclusion Criteria

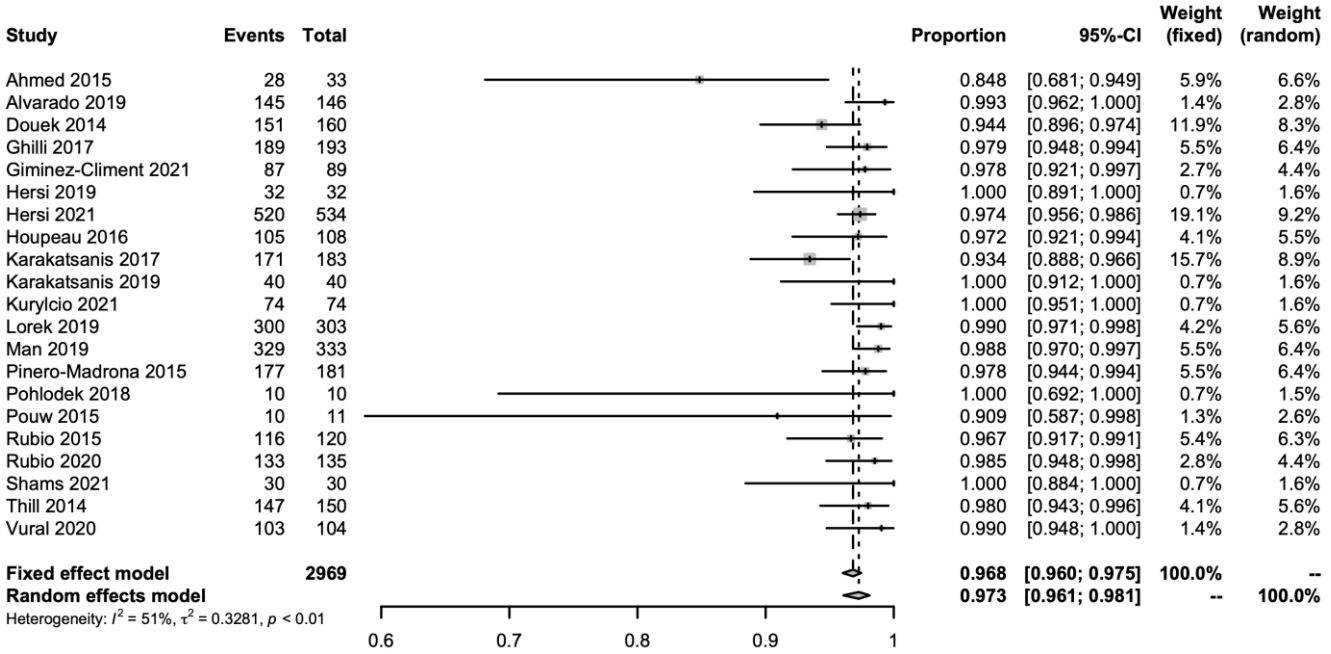
Included sources were those peer-reviewed, published sources, that, on manual full-text inspection, were found to contain evidentiary material of relevance to the decision problem, in relation to one or more of the following clinical effectiveness metrics:

- The **Identification Rate (IR)**, meaning the per-patient proportion of surgical SLNB operations performed in which one or more sentinel lymph nodes are successfully identified and resected.
- The **Number of Nodes (NN)**, meaning the per-patient mean number of sentinel nodes identified and resected during the SLNB surgical procedure. The denominator includes all patients in a study, even those from whom no nodes were retrieved.
- The **Complications Rate (CR)**, meaning the per-patient proportion of surgical SLNB operations performed following which a significant clinical complication – such as infection, lymphoedema, haematoma/seroma, and urticaria – requiring adapted or additional medical treatment occurs, excluding anaphylaxis. Less severe, or more transient, or purely neurological clinical complications, including paraesthesia, restricted upper limb mobility, and pain, are also excluded.
- The **Sentimag-versus-Gamma Nodal Retrieval Rate (NRR)**, meaning the per-node proportion of surgically retrieved nodes that are successfully identified by Sentimag / Magtrace compared to the corresponding (i.e., same study) per-node proportion of surgically retrieved nodes that are successfully identified by Gamma / radiotracer.
- The **Sentimag-to-Gamma Nodal Concordance Rate (NCR)**, meaning the per-node proportion of Gamma Probe / radiotracer detected nodes that are also detected (i.e., in the same study) by Sentimag / Magtrace.

Report all relevant results, including diagrams if appropriate.

Results re Identification Rate (IR)

Identification Rates for Magtrace were reported in **21** studies, as shown in the Forest plot below.

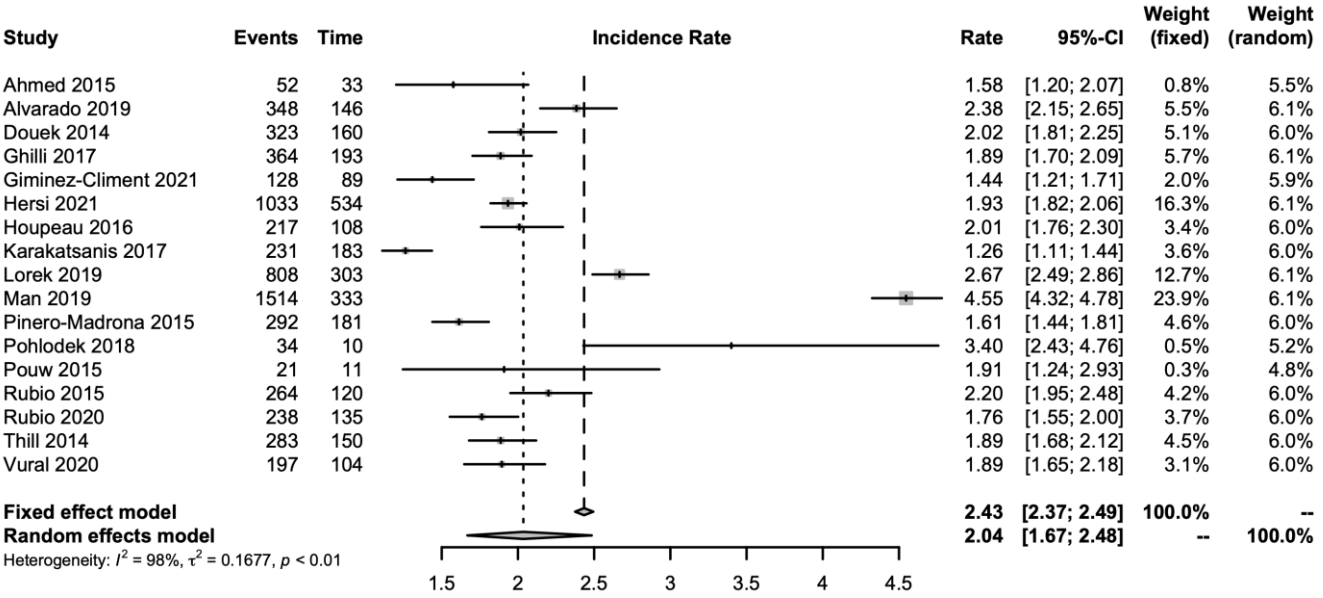


Pooled heterogeneity I^2 = 51%, indicating moderate or substantial heterogeneity.

Metric	No. studies	No. patients	Pooled Proportion	95% CI
Identification Rate	21	2969	97.3%	96.1 to 98.1%

Results re Number of Nodes (NN)

Numbers of Nodes for Magtrace were reported in **17** studies, as shown in the Forest plot below.

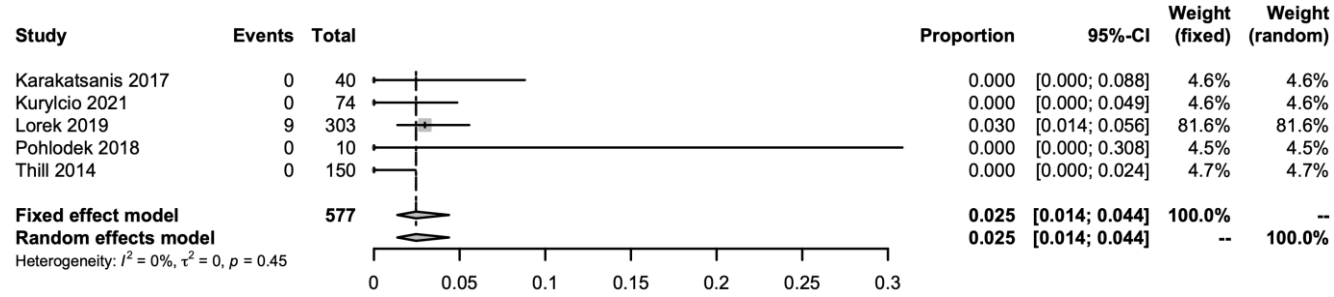


Pooled heterogeneity I^2 = 98%, indicating considerable heterogeneity.

Metric	No. studies	No. patients	Pooled Incidence Rate	95% CI
Number of Nodes	17	2793	2.04	1.67 to 2.48

Results re Complications Rate (CR)

Complications Rates for Magtrace were reported in **5** studies, as shown in the Forest plot below.

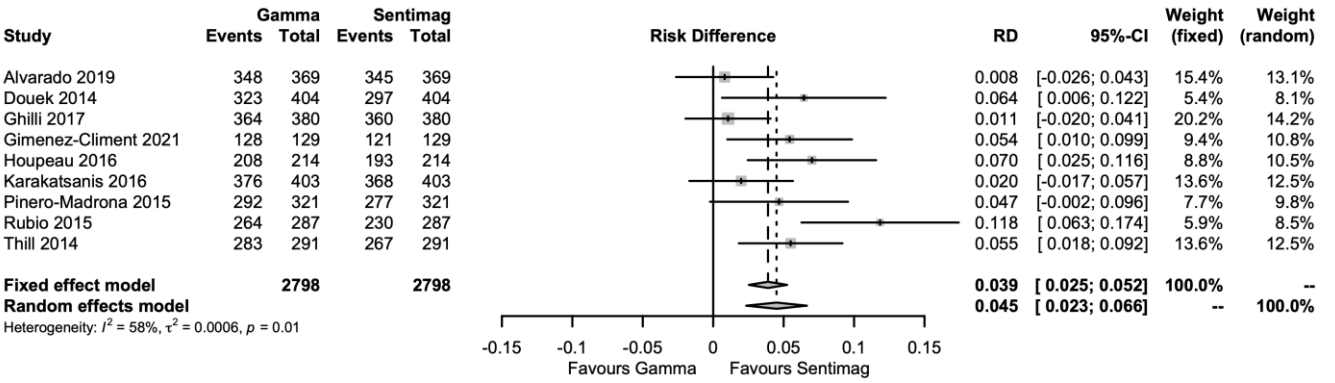


Pooled heterogeneity I^2 = 0%, indicating that heterogeneity might not be important.

Metric	No. studies	No. patients	Pooled Proportion	95% CI
Complications Rate	5	577	2.5%	1.4 to 4.4%

Results re Sentimag-versus-Gamma Nodal Retrieval Rate (NRR)

Sentimag-versus-Gamma Nodal Retrieval Rates for Tc/Gamma and Magtrace/Sentimag were reported in **9** studies. The risk differences calculated for each study are shown in the Forest plot below.

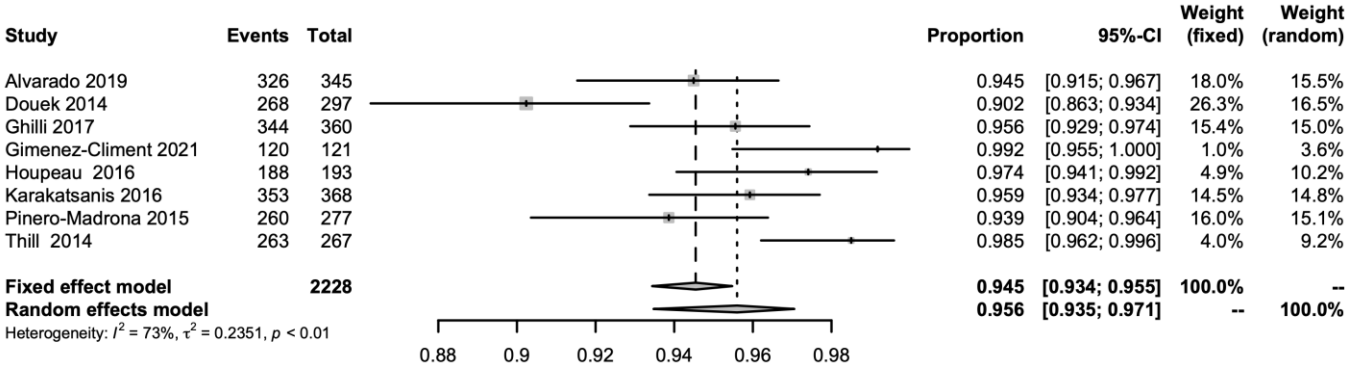


Pooled heterogeneity I^2 = 58%, indicating moderate or substantial heterogeneity.

Metric	No. studies	No. events	Pooled Risk Difference	95% CI
Nodal Retrieval Rate	9	2798	+4.5%	+2.3 to +6.6%

Results re Sentimag-to-Gamma Nodal Concordance Rate (NCR)

Sentimag-to-Gamma Nodal Concordance Rates for Tc/Gamma and Magtrace/Sentimag were reported in **8** studies, as shown in the Forest plot below.



Pooled heterogeneity I^2 = 73%, indicating substantial heterogeneity.

Metric	No. studies	No. events	Pooled Proportion	95% CI
Nodal Concordance Rate	8	2228	95.6%	93.5 to 97.14%

Explain the main findings and conclusions drawn from the evidence synthesis.

Per-patient metrics:

Results for the per-patient clinical-effectiveness metrics for the Magtrace tracer with Sentimag proximity detector ("Mag") are summarised in the table below, along with comparator metrics for the Radioactive Tracer ± Blue Dye with Gamma Probe proximity detector ("Tc/Blue"). The Tc/Blue metrics were provided by Endomag on the basis of a literature review of peer-reviewed sources.

Metric	Mag		Tc/Blue		Implication
	No. patients	Value	No. patients	Value	
Identification Rate	2969	97.3%	24186	96.4%	Non-inferiority
Number of Nodes	2683	2.0	15373	1.8	Favours Mag
Complications Rate	577	2.5%	1152	12%	Favours Mag

Conclusions drawn:

- The **Identification Rate** metric is frequently and consistently reported in the literature. Substantial patient numbers indicate high confidence in the conclusion that the Magnetic and the Radiotracer modalities are equally effective in the intended purpose of identifying sentinel lymph nodes for breast cancer SLND.
- The **Number of Nodes** metric is frequently and reasonably consistently reported in the literature. Substantial patient/node numbers indicate high confidence in the conclusion that the Magnetic modality is preferred (i.e., results in the excision of significantly more nodes per patient) over the Radiotracer modality.
- The **Complications Rate** metric is occasionally reported in the literature, and patient numbers are moderate. There is therefore a reasonably strong indication that the Magnetic modality is preferred (i.e., has a lower Complications Rate) over the Radiotracer modality.

Per-node metrics:

Results for the per-node clinical-effectiveness metrics are summarised in the table below.

Metric	Commentary	Implication
Nodal Retrieval Rate	Pooled risk difference from N=2798 nodes = +4.5% in favour of Sentimag in relation to Gamma	Favours Mag
Number of Nodes	Pooled proportion from N=2228 nodes = 95% concordance	Favours Concordance

Conclusions drawn:

- The **Sentimag-versus-Gamma Nodal Retrieval Rate** metric is frequently and consistently reported in the literature. Substantial patient/node numbers indicate high confidence in the conclusion that the Sentimag modality is preferred (i.e., has a higher Nodal Retrieval Rate) over the Gamma modality.
- The **Sentimag-to-Gamma Nodal Concordance Rate** metric is frequently and consistently reported in the literature. Substantial patient/node numbers indicate high confidence in the conclusion that the Sentimag and Gamma modalities are substantially concordant.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

A focused Scientific and Clinical Literature Review has been undertaken to provide evidential material relating to the clinical effectiveness of the use of the Magtrace magnetic tracer with the Sentimag proximity detector – both products manufactured by Endomag Ltd – for the purpose of locating sentinel lymph nodes as part of the treatment of breast cancer.

As a result of this review, **22** peer-reviewed published sources have been identified and subjected to detailed full-text evaluation. Data from those sources has been pooled and analysed with respect to the following **5** clinical outcome measures:

- the per-patient **Identification Rate (IR)** metric;
- the per-patient **Number of Nodes (NN)** metric;
- the per-patient **Complications Rate (CR)** metric;
- the per-node **Sentimag-versus-Gamma Nodal Retrieval Rate (NNR)** metric; and
- the per-node **Sentimag-to-Gamma Nodal Concordance Rate (NCR)** metric;

After due consideration, it is concluded that the clinical evidence supports the following conclusions:

- That there is high confidence based on substantial patient/node numbers:
  - that the Magnetic and the Radiotracer modalities are equally effective in identifying at least one sentinel lymph node per patient for breast cancer SLND (the IR metric);

- that the Magnetic modality is preferred over the Radiotracer modality in terms of the detection of significantly more sentinel nodes per patient during the SLND procedure (the NN metric);
- that on a node-by-node basis, there is substantial concordance between the Magnetic and Radiotracer modalities (the NCR metric); and
- that on a node-by-node basis, the Magnetic modality consistently identifies more of a given patient's sentinel nodes than does the Radiotracer modality (the NRR metric).

- That there is a reasonably strong indication based on moderate patient numbers:
  - that the Magnetic modality is preferred over the Radiotracer modality in that it results in a lower rate of significant post-operative clinical complications requiring medical intervention, such as infection, lymphoedema, haematoma/seroma, and urticaria (the CR metric).

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The evidence base is very well aligned to the scope of the technology review, on the basis that the clinical effectiveness metrics reviewed were frequently and consistently reported in the literature, and that in addition they are metrics that are routinely used and understood by clinicians in the field.

The only caveat to this is that the Complications Rate metric is less consistently reported than the other metrics, and is sometimes ill-defined, and somewhat subjective with regard to severity.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The geographical range of the evidence base is as follows (applying the UN Geoscheme definitions for the regions of the world):

Country	No. studies	No. patients	Region	No. studies	No. patients
UK	1	32	Northern Europe	6	1027
Sweden	4	789			
Sweden & Norway	1	206			
UK & the Netherlands	2	172	Northern & Western Europe	2	172
France	1	115	Western Europe	2	145
Germany	1	30			
Hong Kong	1	333	Eastern Asia	1	333
Italy	1	199	Southern Europe	5	724
Spain	4	525			
Poland	2	377	Eastern Europe	3	387
Slovakia	1	10			
Poland & Switzerland	1	150	Eastern & Western Europe	1	150
Turkey	1	104	Western Asia	1	104
USA	1	160	Northern America	1	160

From this it is apparent that ca. 42% (1344/3202) of the clinical evidence cases pertain to patients attending hospitals or clinics in Northern or Western Europe, with a further ca. 23% (724/3202) being for patients attending hospitals or clinics in Southern Europe.

As such it is considered that approximately two thirds of the material upon which the clinical evidence is based will not be substantially different from that which would apply to patients undergoing routine breast cancer care in the UK NHS.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

No a priori differentiation is considered necessary for the selection of patients for whom it would be appropriate the use of the Magtrace and Sentimag devices, for the purpose of locating sentinel lymph nodes as part of the treatment of breast cancer.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

Key limitations:

- low sample numbers (less than 50 patients) in 6/22 studies;
- moderate sample numbers (from 50 to 250 patients) in 12/22 studies; and
- single site reportage in 11/22 studies.

Key strengths:

- high quality peer-reviewed data, mostly published in high-impact-factor journals;
- similarity of study protocols;
- comparability of outcome metrics; and
- overall substantial sample size – in total 3202 patients.

9 References

Please include all references below using NICE's standard referencing style.

Ahmed M, Anninga B, Goyal S, et al. (2015) Magnetic sentinel node and occult lesion localization in breast cancer (MagSNOLL Trial). Br J Surg, 102: 646-52

Alvarado MD, Mittendorf EA, Teshome M, et al. (2019) SentimagIC: A Non-inferiority Trial Comparing Superparamagnetic Iron Oxide Versus Technetium-99m and Blue Dye in the Detection of Axillary Sentinel Nodes in Patients with Early-Stage Breast Cancer. Ann Surg Oncol, 26: 3510-3516

Douek M, Klaase J, Monypenny I, et al. (2014) Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG Multicentre Trial. Ann Surg Oncol, 21: 1237-45

Ghilli M, Carretta E, Di Filippo F, et al. (2017) The superparamagnetic iron oxide tracer: a valid alternative in sentinel node biopsy for breast cancer treatment. Eur J Cancer Care (Engl), 26:

Gimenez-Climent J, Marin-Hernandez C, Fuster-Diana CA, et al. (2021) Sentinel lymph node biopsy in breast cancer after neoadjuvant therapy using a magnetic tracer versus standard technique: A multicentre comparative non-inferiority study (IMAGINE-II). International Journal of Surgery Open, 35:

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Houpeau J-L, Chauvet M-P, Guillemin F, et al. (2016) Sentinel Lymph Node Identification Using Superparamagnetic Iron Oxide Particles Versus Radioisotope: The French Sentimag Feasibility Trial. Journal of Surgical Oncology, 113: 501-507

Johnson L, Pinder SE, Douek M (2013) Deposition of superparamagnetic iron-oxide nanoparticles in axillary sentinel lymph nodes following subcutaneous injection. Histopathology, 62: 481-486

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Karakatsanis A, Hersi AF, Pistiolis L, et al. (2019) Effect of preoperative injection of superparamagnetic iron oxide particles on rates of sentinel lymph node dissection in women undergoing surgery for ductal carcinoma in situ (SentiNot study). British Journal of Surgery, 106: 720-+

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Karakatsanis, A. (2020) SentiDose Trial: Optimising dose and injection timing in magnetic sentinel node detection for early breast cancer. European Journal of Cancer 138, Suppl. 1 (2020) S18-S124

Kurylcio A, Pelc Z, Skorzewska M, et al. (2021) Superparamagnetic Iron Oxide for Identifying Sentinel Lymph Node in Breast Cancer after Neoadjuvant Chemotherapy: Feasibility Study. Journal of Clinical Medicine, 10:

Lorek A, Stojčev Z, Zarębski W, et al. (2019) Analysis of Postoperative Complications After 303 Sentinel Lymph Node Identification Procedures Using the SentiMag® Method in Breast Cancer Patients. Med Sci Monit, 25: 3154-3160

Man V, Wong TT, Co M, et al. (2019) Sentinel Lymph Node Biopsy in Early Breast Cancer: Magnetic Tracer as the Only Localizing Agent. World J Surg, 43: 1991-1996

Mullapudi, N.A. (2020) Sentinel lymph node identification using super paramagnetic iron oxide versus radioisotope: The UK Sentimag Trial (SMART study). European Journal of Surgical Oncology. Abstract Volume 46, Issue 6, E2-E3, June 01, 2020

Munawwar, B. (2021) Comparison of Techmetium (Tc) and SPIO-guided Sentinel Lymph Node Biopsy (SLNB) in Patients with Neoadjuvant Chemotherapy (PST) in Early Breast Cancer – first retrospective data. Senologie - Zeitschrift für Mammadiagnostik und -therapie 2021; 18(02): e19

Paepke, S. (2020). SPIO-Guided Sentinel Lymph Node Biopsy (SLNB) in early Breast Cancer – first monoinstitutional data and perspectives. European Journal of Cancer 138, Suppl. 1 (2020) S18-S124

Pinero-Madrona A, Torro-Richart JA, De Leon-Carrillo JM, et al. (2015) Superparamagnetic iron oxide as a tracer for sentinel node biopsy in breast cancer: A comparative non-inferiority study. Ejso, 41**:** 991-997

Pohlodek K, Foltín M, Mečiarová I, et al. (2018) Simultaneous use of magnetic method in localization of impalpable breast cancer and sentinel lymph nodes detection: initial experience. Nanomedicine (Lond), 13**:** 3075-3081

Pouw JJ, Grootendorst MR, Bezooijen R, et al. (2015) Pre-operative sentinel lymph node localization in breast cancer with superparamagnetic iron oxide MRI: the SentiMAG Multicentre Trial imaging subprotocol. Br J Radiol, 88**:** 20150634

Qureshi, M. (2021). Use of Magtrace outside of its licensing period to safeguard breast cancer patients during the covid pandemic does not reduce efficacy. European Journal of Surgical Oncology 47 (2021) e-296-e347

Raus, K. (2020) Innovative Magnetic Tracers for sentinel node detection in primary breast cancer surgery and after neoadjuvant therapy. European Journal of Cancer 138, Suppl. 1 (2020) S18-S124

Rubio, I. (2015) Abstarct P3-01-04: Improved sentinel lymph node detection with the use of superparamagnetic iron oxide tracer after neoadjuvant treatment in breast cancer patients. aacrjournals.org/content/76/4_Supplement/P3-01-04

Rubio IT, Diaz-Botero S, Esgueva A, et al. (2015) The superparamagnetic iron oxide is equivalent to the Tc99 radiotracer method for identifying the sentinel lymph node in breast cancer. Eur J Surg Oncol, 41**:** 46-51

Rubio IT, Rodriguez-Revuelto R, Espinosa-Bravo M, et al. (2020) A randomized study comparing different doses of superparamagnetic iron oxide tracer for sentinel lymph node biopsy in breast cancer: The SUNRISE study. Eur J Surg Oncol, 46**:** 2195-2201

Scally, N. (2020) A pilot study to compare magnetic tracer and patent blue dye as an alternative technique to assess the axillary sentinel lymph node. European Journal of Surgical Oncology 46 (2020) e11 – e53

Shams S, Lippold K, Blohmer JU, et al. (2021) A Pilot Study Evaluating the Effects of Magtrace® for Sentinel Node Biopsy in Breast Cancer Patients Regarding Care Process Optimization, Reimbursement, Surgical Time, and Patient Comfort Compared With Standard Technetium(99). Ann Surg Oncol, 28**:** 3232-324

Syahkal, B. (2019) Comparison of axillary node sampling and sentinel lymph node biopsy before and after the introduction of Sentimag magnetic tracer technology. European Journal of Surgical Oncology 45 (2019) 886-926

Teshome M, Wei C, Hunt KK, et al. (2016) Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage Breast Cancer Patients: A Meta-analysis. Annals of Surgical Oncology, 23**:** 1508-1514

Thill M, Kurylcio A, Welter R, et al. (2014) The Central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope. Breast, 23**:** 175-9

Vural V, Yılmaz OC (2020) The Turkish SentiMAG feasibility trial: preliminary results. Breast Cancer, 27**:** 261-265

Warnberg F, Stigberg E, Obondo C, et al. (2019) Long-Term Outcome After Retro-Areolar Versus Peri-Tumoral Injection of Superparamagnetic Iron Oxide Nanoparticles (SPIO) for Sentinel Lymph Node Detection in Breast Cancer Surgery. Annals of Surgical Oncology, 26**:** 1247-1253

Zada A, Peek MCL, Ahmed M, et al. (2016) Meta-analysis of sentinel lymph node biopsy in breast cancer using the magnetic technique. British Journal of Surgery, 103**:** 1409-1419

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	11 January 2022
Date span of search:	No limits imposed
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Databases searched: PubMed and Web of Science (Extended). Searched under the "TS" field tag (title, abstract, author & database keywords). Compound search using Boolean operators AND and OR. Search term: TS = ((breast AND sentinel AND lymph AND node) AND (Magtrace OR Sienna OR Endomag OR Sentimag OR "magnetic tracer" OR "superparamagnetic iron oxide" OR SPIO)) Rationale for search term: #1 AND (#2 OR #3), where #1 = terms for sentinel lymph node detection in breast cancer; #2 = terms for Endomag products; and #3 = terms for more generic descriptions of magnetic tracers.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
No additional searches were undertaken.	
Inclusion and exclusion criteria:	
Exclusion criteria before screening: duplicate sources; sources that were not peer-reviewed (including conference abstracts); sources that were not in the English language. Exclusion criteria at screening Stage 1: sources that did not pertain to breast cancer; sources that reported solely on preclinical or benchtop studies; sources that pertained solely to imaging methods or modalities; overarching reviews including pedagogical reviews and opinion pieces; sources reporting on other magnetic devices, i.e., not Magtrace/Sentimag. Exclusion criteria at screening Stage 2: sources that did not contain evidentiary material of relevance to the decision problem; sources that presented data that had already been captured in other sources; sources that were published in journals that fell in the lowest quartile category as recorded by the Clarivate Analytics InCites Journal Citation Reports 2019.	

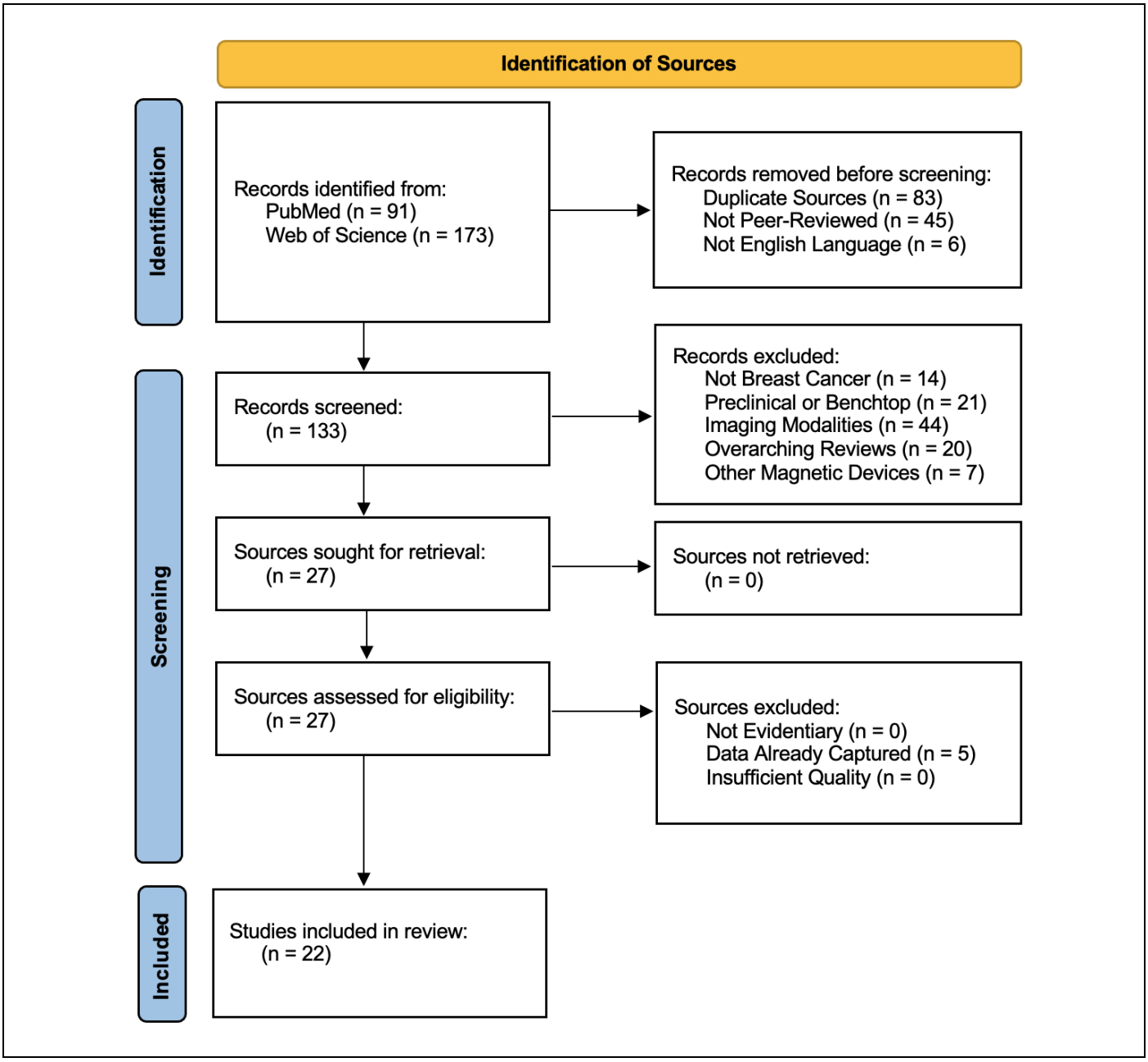
Inclusion criteria: sources that contained evidentiary material of relevance to the decision problem, in relation to one or more of the following clinical-effectiveness metrics: the Identification Rate (IR) metric; the Number of Nodes (NN) metric; the Complications Rate (CR) metric; the Sentimag-versus-Gamma Nodal Retrieval Rate (NRR) metric; and/or the Sentimag-to-Gamma Nodal Concordance Rate (NCR) metric.
Data abstraction strategy:
Before screening: manual appraisal of the titles and abstracts of the sources. At screening: manual appraisal of full-text download copies of the sources.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Johnson (2012)	Prospective, feasibility; Mag & Tc/Blue	Data captured in other sources	Data incorporated in the set reported in Douek (2014)
Teshome (2016)	Meta-analysis	Data captured in other sources	Data captured in Douek (2014), Thill (2014), Ghilli (2015), Pinero-Madrona (2015), and Rubio (2015)
Zada (2016)	Meta-analysis	Data captured in other sources	Data captured in Douek (2014), Thill (2014), Ghilli (2015), Pinero-Madrona (2015), Rubio (2015), Houpeau (2016) and Karakatsanis (2016)
Karakatsanis (2018)	Prospective feasibility; Mag & Tc/Blue	Data captured in other sources	Data incorporated in the set reported in Karakatsanis (2019)
Warnberg (2019)	Patient-reported cosmesis; Mag & Tc/Blue	Data not relevant to decision problem	Evidentiary data from same patients reported in Karakatsanis (2016), Karakatsanis (2017), and Karakatsanis (2019)

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Appendix B: Search strategy for adverse events

Date search conducted:	13 January 2022
Date span of search:	1 Jan 1993 to 13 Jan 2022

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

This search query was conducted with MedBoard (https://www.medboard.com). MedBoard covers more than 200k various regulatory authority sources. All information made available by these authorities is compiled into this database and is further classified through their software in an organized and efficient way. The data compiled is then monitored continuously via a Data Research team or by specific request from regulatory professionals.

Searches cover FSCAs, Recalls and Safety Alerts from the following regulatory bodies:
*Note: Adverse Events were only searched from FDA MAUDE, MHRA and Health Canada Registry databases.

TGA (Australia)
AFMPS (Belgium)
ANVISA (Brazil)
HC (Canada)
NMPA (China)
INVIMA (Columbia)
HALMED (Croatia)
SUKL (Czech Republic)
DMA (Denmark)
ANSM (France)
BfArM (Germany)
MDD (Hong Kong)
IMED (Iran)
HPRA (Ireland)
Italian Ministry of Health
Infarmed (Portugal)
MoPH (Lebanon)
IGJ (Netherlands)
Medsafe (New Zealand)
URLP (Poland)
SFDA (Saudi Arabia)
HSA (Singapore)
PMDAS (Japan)
MFDS (South Korea)
AEMPS (Spain)
Lakemedelsverket (Sweden)
Swissmedic (Switzerland)
TFDA (Taiwan)
MoPH (Thailand)
TMMDA (Turkey)
MHRA (United Kingdom)
FDA (USA)

Sources and websites of interest are analysed individually by the data scientist team. In terms of regulatory and vigilance repositories, this data is gathered through either the regulatory authority repositories themselves or, if no databases are provided, data is extracted through a regulatory body's website.

MedBoard structures all the information by specific fields and categorizes the types of data though a powerful search engine. This is highly beneficial as most websites used by regulatory authorities either do not support complex/systematic searches or do not have adequate search functionality. In addition, metadata is included to complement the information, further widening search capabilities.

In terms of specific search methods, there is no allocated weight of keywords during searches. All matches matching the complex query or keywords used are returned to the user in a chronological fashion. The user can also do sub-searches and additional filtering in the databases, as this provides the experienced professional an outstanding control over the review process and results.

Below is a table of related Boolean search terms used to conduct a review of Adverse Events related to Magtrace, Sentimag and related competitor products:

Search terms	Rationale
Magtrace Sienna+ SiennaXP magnetic tracer magnetic fluid	Terms associated with Magtrace and former iterations of the Magtrace product
Sentimag	Terms associated with the Sentimag base unit

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

As noted in **Section 6**, the company has identified two further types of adverse events mentioned in the clinical literature in relation to the Magtrace/Sentimag modality for sentinel lymph node marking.

The first is the **Complications Rate** metric, which has been reported and discussed in **Section 7** of this report. The second is the **Staining Complications Rate** metric, which has been reported and discussed briefly in **Section 6** of this report, and in more detail in the document **P415J003** that the company has submitted to NICE as part of its overall submission.

Inclusion and exclusion criteria:

Any event related to Sentimag or Magtrace or any former iterations of Magtrace were included

Data abstraction strategy:

MedBoard:

Not applicable, as no events were identified.

Complications Rate & Staining Complications Rate:

Before screening: manual appraisal of the titles and abstracts of the sources.
At screening: manual appraisal of full-text download copies of the sources.

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

MedBoard:
Not applicable, as no events were identified.

Complications Rate:
Please see flow chart in **Appendix A** of this document.

Staining Complications Rate:
Please see details in the document **P415J003** that the company has submitted to NICE as part of its overall submission.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
5&6	☒ Commercial in confidence ☐ Academic in confidence	Contains information as to the formulation of Magtrace and confidential interactions with the companies Notified Body	Indefinate
Details	Enter text.		
P415J003 pages 3,8, 10, 11,12,13, 27,	☒ Commercial in confidence ☐ Academic in confidence	These highlighted sections contain information, methods and knowhow that developed by the company are commercially sensitive.	Indefinate
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	14JAN2022
Print:	Eric Mayes	**Role / organisation:**	CEO
Contact email:	emayes@endomag.com		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Company evidence submission

Part 2: Economic evidence

Company name	Endomag Limited
Submission date	14 February 2022
Contains confidential information	Yes – commercial in confidence (this version is redacted)

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

A single search was carried out in January 2022 to identify clinical and economic evidence. Details of the search strategy and sources are in Part 1 of this submission, Appendix A. Five costing studies were identified, three of which reported a comparison of procedure costs between sentinel lymph node biopsy (SLNB) and axillary lymph node biopsy (ALNB). None of these studies involved use of a superparamagnetic iron oxide (SPIO) tracer such as Magtrace, and none reported a separate costing of the use of technetium (Tc-99m) plus blue dye. Two studies identified in the original search appeared to be relevant to the decision problem (Shams, 2021; Karakatsanis, 2017).[1,2] One further study (Man, 2019)[3] was identified through a hand search of bibliographic records. No studies relate to the UK.

Number of costing studies identified in a systematic search.		6
Number of costing studies identified as being relevant to the decision problem.		3
Of the relevant costing studies identified:	Number of published studies.	3
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

The aim of the MONOS study was to evaluate the use of SPIO as a sole tracer compared with standard use of Tc-99m plus blue dye (Karakatsanis, 2017).[2] All patients scheduled for SLNB between September 2014 and June 2015 at two trial sites in Sweden were recruited. Patients at Uppsala University Hospital (n=184) were enrolled to the SPIO arm and patients at Vastmanlands County Hospital (n=159) were treated using Tc-99m and blue dye. Tc-99m was injected in the department of nuclear medicine. SPIO was injected either at the preoperative outpatient visit (1-4 weeks before surgery) or on the morning of surgery. The study analysed the cost per patient between the two arms, including the cost of the tracer and injection expenses. Logistics were simplified in the SPIO arm because the need for nuclear medicine involvement was removed. The costs per procedure were €225 (SPIO)

and €252 (Tc-99m). Compared with perioperative administration of SPIO, preoperative administration saved an additional 20 minutes per case in the operating theatre, valued at the mean cost per hour of OR time (€17.6/minute) equal to €352 per procedure.

Man (2019)[3] reports results of a non-comparative retrospective cohort study including all patients with sentinel lymph node localisation using SPIO carried out between August 2016 and December 2017 at the University of Hong Kong. The primary aim of the study was to report on outcomes, but the authors also report that the use of SPIO led to savings of US$22,300 per year. For example: costs of nuclear medicine involvement, avoidance of day admission to administer radioisotope injections, avoidance of the costs of specialised transportation for frozen specimens, and costs associated with on-site contamination monitoring.

A German study (Shams, 2021)[1] compared patients undergoing SLNB treated with Tc-99m (n=29) or SPIO (n=30) according to the preference of the surgeon. The primary aims of the study were to measure time spent on the preoperative pathway and operating time. Secondary outcomes were pain levels and hospital reimbursement. Patients in the Tc-99m group received an injection in the department of nuclear medicine followed by lymphoscintigraphy. Preoperative time included time for the patient to get to nuclear medicine and back, waiting time pre- and post-injection, time for Tc-99m preparation and administration, and time for lymphoscintigraphy. SPIO was administered at the routine preoperative outpatient visit between 3 and 5 days before, or in two patients the injection was administered intraoperatively. Preoperative time was measured from the time the patient was undressing to the time they finished redressing. The mean time spent on the preoperative pathway was significantly shorter in the SPIO group: (5.4 ±1.3 min vs. 82 ± 20 min) ($p<0.0001$). There was no significant difference in operative time or patient pain levels.

Table 1 Summary of relevant studies

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Outcomes	Results
Karakatsanis 2017[2]	Sweden	Prospective cohort study comparing SLNB performed using either Tc-99m plus blue dye or SPIO (Magtrace).	All consecutive patients undergoing SLNB between September 2014 and June 2015 at two hospitals: Uppsala University Hospital and Vastmanlands County Hospital (n=338). Patients at Uppsala were assigned to SPIO (n=183); patients at Vastmanlands to Tc-99m and blue dye (n=155).	Cost of the tracer and administration of the injection. Costs were measured in Swedish crowns, converted to Euro at December 2016 exchange rate.	Cost of SPIO vs. Tc-99m plus blue dye	Mean cost per procedure: €225 (SPIO) €252 (Tc-99m plus blue dye). 2016 prices. Preoperative administration of SPIO saved a minimum of 20 minutes in the operating theatre. Valued at €17.6 per minute = €352 per procedure.
Man 2019[3]	Hong Kong	Retrospective database analysis	All patients undergoing SLNB with SPIO localisation (Magtrace) between August 2016 and December 2017 (n=328)	Annual cost of SLNB using SPIO compared with historic costs of standard tracer (Tc-99m plus blue dye).	SPIO resource use	Use of SPIO alone resulted in savings of $22,300 per year. No need for nuclear medicine involvement on day admission for Tc-99m administration. No costs for specialised transportation of frozen specimens and on-site contamination protocols
Shams 2021[1]	Germany	Non-randomised prospective study comparing SLNB performed using either SPIO (Magtrace) or Tc-99m.	Patients undergoing SLNB between May 2019 and January 2020 were equally allocated to the two arms. The method of allocation was surgeon's choice.	No costs	Time on the preoperative patient pathway, operating theatre time, patient-reported pain, hospital reimbursement	Mean preoperative time per patient: SPIO 5.4 ± 1.3 min; Tc-99m 82 ± 20 min. $p<0.0001$. No significant difference in operative time, pain or reimbursement.

2 Details of relevant studies

Table 2 Details of relevant studies

Karakatsanis, 2017.[2] Superparamagnetic iron oxide nanoparticles as the sole method for sentinel node biopsy detection in patients with breast cancer.	
What are main differences in resource use and clinical outcomes between the technologies?	-Costs per procedure €225 (Magtrace) vs. €252 (Tc-99m) -Detection rates for SPIO and Tc-99m were 95·6% and 96·9% (P = 0·537). Fewer nodes were retrieved with SPIO (mean 1·35 versus 1·89), regardless of whether blue dye was used (P < 0·001). -Preoperative SPIO injection (58·7 per cent of procedures), a median of 16 (range 2–27) days before the procedure, was associated with a better tracer-specific detection rate (95·3 versus 86 per cent; P = 0·031) and retrieval of more nodes (mean 1·43 versus 1·03; P < 0·001) than perioperative administration. -The use of SPIO alone is a safe alternative, with results comparable to those of the standard dual technique using Tc-99m and blue dye. The efficacy of injection in the preoperative setting simplifies logistics and improves performance. -Logistics were simplified in the SPIO arm, as the preoperative visit to the department of nuclear medicine could be omitted. -Compared with perioperative administration, preoperative injection of SPIO saved an additional minimum of 20 min in the operating theatre, which is the time needed for SPIO to migrate to the axilla.
How are the findings relevant to the decision problem?	The study is relevant to a comparison of acquisition and administration costs for Tc-99m and Magtrace
Does this evidence support any of the claimed benefits for the technology? If so, which?	Shortening the preoperative patient pathway, improving theatre planning, and saving on the costs of nuclear medicine
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	The analysis measured the cost of the tracer and administration of the injection per procedure and provides a comparison between Tc-99m and Magtrace
What are the limitations of this evidence?	-Non-randomised study in which the two comparators were employed in standard SLNB procedures carried out in different hospitals. -No details are presented of the costings and no statistical significance testing
How was the study funded?	Study was funded by Uppsala University

Man, 2019.[3] Sentinel lymph node biopsy in early breast cancer: magnetic tracer as the only localizing agent.	
What are main differences in resource use and clinical outcomes between the technologies?	-A total of 329 successful SLNB were undertaken with 1514 sentinel lymph nodes identified. 153 (10.1%) of the sentinel nodes were positive for malignancy. The success rate of SPIO in sentinel lymph node localisation was 98.8% -SLN localisation using SPIO saved US$22,300 per year compared with conventional dual tracers
How are the findings relevant to the decision problem?	The study notes sources of savings for SPIO compared with Tc-99m: No need for nuclear medicine involvement on the day of the surgery; saving on specialised transport for radioactive specimens; saving in on-site contamination tests and monitoring.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: it supports improvement in surgery planning and overall reduction in resource use and costs
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	No details of the cost analysis are reported.
What are the limitations of this evidence?	Non-comparative study. Estimate of potential cost and resource savings are not derived from data reported in the study.
How was the study funded?	No funding source is stated

Shams, 2021.[1] Pilot study evaluating the effects of Magtrace® for sentinel node biopsy in beast cancer patients regarding care process optimization, reimbursement, surgical time, and patient comfort compared with standard technetium	
What are main differences in resource use and clinical outcomes between the technologies?	-Mean time on preoperative patient pathway shorter with Magtrace: (5.4 ± 1.3 minutes) vs. (82 ± 20 minutes) with Tc-99m ($p<0.0001$) -No significant difference in operative time, patient reported pain, and hospital length of stay
How are the findings relevant to the decision problem?	The study is relevant to a comparison of the length of the preoperative pathway between Magtrace and Tc-99m
Does this evidence support any of the claimed benefits for the technology? If so, which?	Shortening the preoperative patient pathway, improving theatre planning
Will any information from this study be used in the economic model?	No
What cost analysis was done in the study? Please explain the results.	No cost analysis
What are the limitations of this evidence?	Non-randomised study. No costing analysis reported.
How was the study funded?	Materials and equipment were provided free of charge by Sysmex. No other study funding was received

3 Economic model

In the absence of published studies which directly address the scope, a *de novo* cost analysis was developed by drawing on the experience of three NHS Trusts in England gained through interviews and a locally produced business case. Resource use and costs will vary between hospitals, but the pathway is likely to be similar and the estimates here are designed to be conservative. The main assumptions are tested in one-way sensitivity analysis.

A cost-minimisation analysis compares the cost to the NHS of using Magtrace and Sentimag compared with technetium 99m (Tc-99m) and blue dye for localisation of the sentinel nodes during SLNB surgery. The timescale of the analysis is the period from preparation and administration of the tracer to the end of surgery. Costs include acquisition costs and costs of administering the tracer to the patient. The analysis also includes the opportunity cost of operating theatre time which is lost because of disruption to the supply of technetium or shortages of nuclear medicine staff.

3.1 Technology and comparator

Magtrace is a superparamagnetic non-radioactive lymphatic tracer which is detected in the lymphatic system by a Sentimag probe during sentinel node biopsy (SLNB) in patients with breast cancer. It can be injected by a healthcare professional such as a surgeon or nurse at a routine appointment from 30 days to 20 minutes before surgery. Magtrace is intended to be used in place of the current standard of care which involves injecting a radioactive tracer (technetium-99m) and blue dye before SLNB surgery to help the surgeon localise and visualise sentinel nodes.

Technetium-99m (Tc-99m) is a radioactive tracer which emits gamma radiation that can be detected by a gamma camera. Combined with blue dye, Tc-99m is currently recommended to identify prominent lymph nodes draining cancer cells in the breast.[4] Tc-99m is produced as a by-product of nuclear fission. This process produces Molybdenum (Mo-99) which decays to Tc-99m over time. Tc-99m is delivered to the hospital in the form of a Mo-99 generator. The half-life of Mo-99 is 66 hours (2.75 days) which makes long-term on-site storage impossible. A hospital using Tc-99m relies on regular deliveries.

Handling radioactive material requires support from pharmacy and nuclear medicine.[5] The half-life of Tc-99m for gamma emission is 6 hours (94% decay within 24 hours), and for this

reason the injection needs to be given on the day of the planned procedure. On the day of surgery, Tc-99m is chemically extracted from the Mo-99 generator and prepared for injection. The injection must be prepared and administered by nuclear medicine. Unused product is stored in a lead container for 24-48 hours until the Tc-99m is fully decayed.

The short half-life of Mo-99 precludes stockpiling and demands a regular and secure source of supply. Production of a Mo-99 generator depends on three separate processes: irradiation of enriched uranium in a nuclear research reactor; extraction of Mo99 from target material; and manufacture of Mo-99 generators which are delivered to end-users. The majority of irradiation is carried out in one of four research reactors located in Belgium, South Africa, the Netherlands, and France.

Each of these reactors is more than 50 years old and all are subject to regular shutdowns for maintenance or breakdown. Significant disruptions to supply have occurred regularly since 2005. A major interruption in the supply of Mo-99 to the NHS in 2009-2010 led to a review commissioned by the Department of Health into the impact of shortages and recommendations to avoid disruption in the future.[6] When shortages occur hospitals either cancel surgery or proceed with blue dye only which is not consistent with best-practice clinical guidelines.

Three companies supply Mo-99 generators to the UK, one is based in the UK and the others are in the Netherlands and France. The primary sources of Mo-99 for the UK market are reactors in South Africa, the Netherlands and France, all of which were commissioned in the 1960's. None of the suppliers of Mo-99 generators in the UK work at the weekend which makes Monday surgical lists problematic.

3.2 Potential benefits of the technology

The main benefits of Magtrace follow from the fact that it does not require involvement of nuclear medicine, and it does not have to be administered on the day of surgery

NHS Resource impact

Removing the need for nuclear medicine involvement

- Enhances NHS capacity to perform breast cancer surgery because procedures can now be provided in hospitals without access to nuclear medicine.
- Reduces uncertainty and improves theatre scheduling

- Reduces the burden on nuclear medicine staff and releases resources that can be used elsewhere.

Removing the requirement for the injection to be administered on the day of surgery

- Enhances NHS theatre capacity and makes more efficient use of staff and facilities by making it possible for surgery to start earlier in the morning and eliminating the time the patient has to wait for an injection on the day of the procedure
- Reduces the risk that surgery is cancelled or delayed at short notice, either because of disruption to the supply of Tc-99m or because of a shortage of nuclear medicine staff. Reducing theatre time lost because of cancellation or delays enhances capacity and improves theatre scheduling

Impact on patients

- Avoiding the need for patients to go to the nuclear medicine department to have the injection and shortening the time waiting for the tracer to migrate to the lymph nodes reduces the length of time a patient spends in hospital on the day of the procedure
- Reducing the risk of cancellation and/or delays to surgery, or the possibility the procedure goes ahead using blue dye alone
- Reduces exposure to radioactivity and eliminates the risk of a serious anaphylactic reaction to blue dye in some patients

3.3 Assumptions

Table 3: Assumptions

Assumption	Justification
The costing relates to a hospital carrying out 250 SLNB procedures annually: approximately 5 procedures in a single surgery list weekly for 50 weeks.	Estimating annual costs requires an assumption about volumes. The relative cost-effectiveness of a tracer does not depend on the annual volume of procedures
The hospital receives one delivery weekly of two vials of Tc-99m.	The radioactive isotope requires specialist delivery with associated costs. The number of weekly deliveries depends on the number of planned procedures. One vial of Tc-99m is typically used for 2-3 procedures, hence 2 vials is assumed for 5 procedures. Unused material cannot be stored.
Magtrace and blue dye can be ordered in bulk and stored until required. The shelf-life of Magtrace is approximately 2 years. No	

special delivery or storage arrangements are necessary. One vial of each is required per SLNB procedure.	
The opportunity cost of theatre time lost through delays to surgery is measured by the number of SLNB procedures forgone, valued at the HRG tariff	An alternative approach would be to value theatre time at a cost per hour (£1200).[7] This approach is less likely to represent the true opportunity cost.
OPCS code T87.3 relates to SLNB performed as a surgical procedure. T87.3 maps to HRG JA43 "unilateral intermediate breast procedures"	See note on coding below
A SLNB procedure takes 30-45 minutes.[8] The opportunity cost of forgone procedures assumes only 50% of potential additional procedures could be realised	There will be constraints other than theatre time on the potential number of procedures which can be performed

A note on coding. OPCS code T91.1 "biopsy of sentinel lymph node" relates to a radiological procedure which maps to HRG code YJ04. Since 2020, the coding has been refined to differentiate a surgical sentinel lymph node biopsy, which is coded as T87.3 "excision or biopsy of axillary lymph node". T87.3 maps to HRG JA43 "unilateral intermediate breast procedures".

Details are in a 2020 update from the ABS Clinical Practice & Standards Committee.

https://associationofbreastsurgery.org.uk/media/299806/abs_update-on-coding-and-hrgs_kc-and-jh_june-2020_v2.pdf

3.4 Clinical parameters

The clinical evidence supports the hypothesis of non-inferiority of Magtrace compared with Tc-99m and blue dye (Part 1 of the submission). The cost analysis assumes that patient outcomes are the same irrespective of the tracer used in the SLNB procedure.

3.5 Other parameters in the model

Data sources

Information on NHS resource use is not available from published sources. Base-case estimates are derived from information provided by three NHS Trusts in England [redacted] Most of the information relates to 2020 or 2021. Unit costs for Tc-99m and blue dye are those provided by the Trusts and may not be current. Information was provided in interviews or a business case produced by [redacted][8] Parameter values are varied in a univariate sensitivity analysis.

Hourly costs for hospital nursing staff and scientific and professional staff are from Unit Costs of Health and Social care, 2021.[9] Rates per hour include salary plus on-costs, overheads and an adjustment for working hours. The NHS tariff for HRG JA43B is for combined day case and ordinary elective spell from NHS National Tariff Payment System, 2021-22 .[10]

Table 4 Other parameters in the model

Parameter	Description	Justification	Source
Time horizon	From the time the patient attends the hospital for SLNB to the end of the procedure	Choice of tracer has no long-term implications for patient outcomes or costs	Clinical evidence
Discount rate	NA	Because of the short (<1 year) time horizon of the analysis	
Perspective	NHS/PSS	In line with the scope	
Tc-99m cost	£100 per vial including delivery and pharmacy time to elute the Tc-99 generator and dispense patient injections. Delivery cost is an additional £25 per delivery by secure transportation		NHS Trust experience
Nuclear medicine (NM) time to prepare and administer Tc99m injection	Two Band 6 staff 40 minutes each to prepare and administer injection to a patient, perform imaging procedures using a gamma camera, complete documentation and handle radioactive waste		NHS Trust experience
Nurse time to administer Magtrace injection	1 Band 5 nurse in a 20-minute routine appointment		NHS Trust experience
Blue dye	£25 per vial		Trust experience
Magtrace	£226 per vial		
Band 6 hospital scientific and technical staff	£55/hour		PSRU 2021[9]
Band 5 hospital nurse	£41/hour		PSSRU 2021[9]
Operating theatre time per SLNB procedure	45 minutes		NHS Trust experience
SLNB HRG Tariff	£1208	HRG code JA43B, combined day-case and ordinary elective spell	NHS National Tariff Payment System 2021-22.[10]
Theatre time lost to supply disruption and/or shortage of NM staff	20% of procedures delayed by an average of 30 minutes		NHS Trust experience

Implementation costs

The technology represents a direct replacement of a radioactive tracer plus blue dye with Sentimag and a single non-radioactive tracer. No additional resources are required to implement the technology in the NHS and training requirements would be minimal. The change which is anticipated would permit a simplification of the treatment pathway by eliminating the need for nuclear medicine involvement.

Adverse event costs

No adverse events are included

Miscellaneous costs

There are no additional costs. The training required to implement the technology is minimal and what information is required about the product will be provided at no extra cost by the company.

3.6 Results

Acquisition costs

Mo-99 generators are delivered to the hospital weekly or twice-weekly along with other medical isotopes. One vial of Tc-99m can be used for more than one procedure and the cost model assumes two vials per week to cover an average of 5 procedures. A representative cost is £100 per vial including cold kit and radioactive tracer, pharmacy staff time, overheads, and consumables. Delivery costs account for an additional £25 per delivery. The cost per procedure is £45.

Blue dye is used in conjunction with Tc-99m as a marker to make it easier for the surgeon to visualise the sentinel nodes. A representative cost is £25 per vial. One vial is required per procedure.

The cost of Magtrace is £226 per vial. One vial is required per procedure. No cost is included for the Sentimag probe. Hospitals who have adopted Magseed will already have the probe, and for most other hospitals the probe will be provided as part of an annual contract at no extra cost.

Costs of preparation and administration

UK hospitals typically receive delivery of Mo-99 generators on a weekly or twice weekly basis. Each morning pharmacy staff elute the generator and dispense individual patient injections. A single batch can be prepared to supply procedures scheduled for the day. Production of radiopharmaceuticals must be performed in an aseptic environment, generally in a laminar airflow hood located within a cleanroom. No estimate is available separately for the amount of pharmacy time required per procedure, and the cost of pharmacy time is included in the Tc-99m acquisition cost.

Senior nuclear medicine staff are required to administer injections and carry out imaging procedures using a gamma camera. Staff may also carry out image processing and provide the results of data analysis to a clinician for interpretation. Administering an injection is usually scheduled for a 30-minute session in the nuclear medicine department and requires two Band 6 scientific or technical staff grades at £55/hr. The cost per procedure is £55. Some additional time is required for documentation and handling radioactive waste. This is assumed to require two Band 6 staff for 10 minutes each (total of £18.33 per procedure).

Magtrace can be administered by a surgeon or nurse in a routine 20-minute appointment up to 30 days before surgery. The cost of nurse time to administer an injection is £14.

Opportunity cost of theatre time

The international Tc-99m supply chain is fragile and supply shortages can lead to cancellation of surgery lists at short notice. Theatre time is also lost because of staff shortages in nuclear medicine leading to delays in getting the Tc-99m to the patient at the appropriate time. The [redacted] USS Guided Wire Excision & Sentinel Node Biopsy Patient Pathway Review suggests that an average of 30 minutes was lost in 20% of 1200 procedures annually.[8] Assuming 250 procedures, this equates to a total of 25 hours of theatre time annually, sufficient to perform 33 additional SLNB procedures. Not all of this time could be usefully redeployed. Valued at the HRG tariff for a SLNB procedure, and assuming only 50% of time could be utilised, the opportunity cost of theatre time lost to delays would be £20,133 annually, £80.53 per procedure.

Because nuclear medicine staff time is required on the morning of surgery to prepare and administer an injection, and further time is required for the tracer to migrate from the breast to the lymph nodes, SLNB procedures cannot practically be scheduled to start before around 10.30 in the morning, and later on a Monday. Compared with a 9.00am start this involves a loss of at least 1-1.5 hours of operating time per list. The opportunity cost to the NHS of this time is the value of at least one additional SLNB procedure per list: 50

procedures annually. Assuming only 50% of this potential could be realised, the opportunity cost would be £30,200 annually, £120.80 per procedure.

Total costs

Table 5 summarises the costs of standard practice with Tc-99m and blue dye. The total cost is £86,168 annually for a facility undertaking 250 procedures: £345 per procedure (29% of the Tariff rate). The cost of Magtrace would be £60,000 annually: £240 per procedure. A switch to Magtrace is expected to save £105 per procedure. Magtrace is a dominant option.

Table 5: Total costs per procedure

	Tc-99m + blue dye		**Magtrace + Sentimag**		**Incremental cost**	
	Per procedure	Annually	Per procedure	Annually	Per procedure	Annually
Tc-99m acquisition cost	£45	£11,250				
Blue dye acquisition cost	£25	£6,250				
Magtrace acquisition cost			£226	£56,500		
Nuclear medicine (NM) staff time to administer Tc-99m injection	£73	£18,333				
Nurse time to administer Magtrace injection			£14	£3,500		
Theatre time lost through supply disruption or shortage of NM staff	£81	£20,133				
Theatre time lost because of time required for Tc-99m injection on the day of surgery	£121	£30,200				
Total	£345	£86,168	£240	£60,000	-£105	-£26,168

3.7 Sensitivity analysis

Table 6 reports the result of univariate sensitivity analysis (SA). Individual parameters are varied within a realistic range. In the base-case, Magtrace is expected to result in a saving

of £105 per procedure. Each of the sensitivity analyses results in an expected saving with Magtrace, ranging from £56.68 to £141.67. Results are most sensitive to assumptions about the use of nuclear medicine (NM) resource and the opportunity cost of theatre time. Assuming only one Band 6 NM staff member is required to prepare and administer injections, or reducing the time required from 40 minutes to 20 minutes reduces the estimated saving to £68.33 per procedure. Increasing the time required from 40 to 60 minutes increases the estimated saving to £141.67. Assuming only 30% of additional procedures could be realised by starting the theatre schedule earlier in the morning reduces the estimated saving to £56.68, and assuming only 30% of theatre time saved by reducing delays can be utilised reduces the saving to £72.79.

Table 6: Sensitivity analysis

	Standard practice cost per procedure	Incremental cost of Magtrace
Base case	£344.67	-£105.00
Acquisition cost of Tc-99m		
SA1: One vial per theatre list	£324.67	-£85.00
SA2: Unit costs - 50%	£322.17	-£82.50
SA3: Unit costs + 50%	£367.17	-£127.50
Nuclear medicine (NM) time		
SA4: One Band 6 per injection	£308.00	-£68.33
SA5: NM time +20 minutes	£381.33	-£141.67
SA6: NM time -20 minutes	£308.00	-£68.33
Magtrace injection		
SA7: Nurse time +10 minutes	£344.67	-£98.17
SA8: Nurse time - 10 minutes	£344.67	-£111.83
Opportunity cost of lost theatre time		
SA9: Value theatre time at £1200/hr	£324.13	-£84.47
SA10: Proportion of lost time realised 30%	£312.45	-£72.79
Sa11: Proportion of lost time realised 60%	£360.77	-£121.11
SA12: Earlier start time realised 30%	£296,35	-£56.68

4 Summary and interpretation of economic evidence

The economic case for Magtrace is based on its long-term sustainability and environmental impact, efficiency gains for the NHS and benefits for patients. Not all benefits can be quantified but the cost analysis supports the view that in most plausible scenarios Magtrace will be cost saving. In the base-case the saving is £105 per procedure. More importantly it improves NHS efficiency by releasing resources in nuclear medicine and theatre time lost to delays or cancellation.

The raw material for Tc-99m is produced in a small number of ageing nuclear reactors outside the UK. The supply chain is notably fragile, with frequent disruption caused by routine maintenance or breakdown. Disruption to the supply chain leads to delay or cancellation of surgical lists and makes theatre scheduling difficult. Since at least 2009 major users of technetium including the UK have sought alternatives which are better able to secure a reliable supply of medical tracers.[6,11,12]

Irradiation of enriched uranium to produce technetium generates hazardous radioactive waste which requires long-term storage in a secure facility. Similarly, because of its short half-life, technetium is transported primarily by air. The technetium used by the suppliers of Mo-99 generators to the UK is obtained from South Africa, the Netherlands, and France. Long supply lines have an important environmental impact and run counter to the stated aims of the NHS. In October 2020 the NHS produced a report outlining plans to achieve net zero by 2045 with an ambition to reach 80% reduction in carbon footprint by 2036-2039.[13] One of the stated objectives was “to work with suppliers to ensure that the supply chain achieves net zero emissions by the end of the decade”. Magtrace is manufactured in the UK.

Handling radioactive material requires specialist facilities. Magtrace enhances the capacity of the NHS to carry out breast procedures because it can be used in hospitals without access to nuclear medicine. It also reduces pressure on nuclear medicine resources where these are available.

Tc-99m is prepared and administered on the morning of surgery. Allowing time for the injection and for the tracer to migrate to the sentinel nodes limits the time at which the first procedure can be scheduled. Similarly, delays in getting the Tc-99m to the patient, either because of supply disruption or a shortage of nuclear medicine staff, impacts the utilisation

of theatre resources. In 2020 the NHS launched the *Productive Operating Theatre* programme designed "to improve the quality of patient experience, the safety and outcomes of surgical services, and the effective use of theatre time and staff experience."[7] Magtrace contributes to improving theatre efficiency by eliminating time and uncertainty from the treatment pathway.

The main benefit for patients is reducing preoperative waiting time and reducing the possibility of delays or cancellation of surgery at short notice. The exact amount of time which can be saved depends on a number of local factors, including the layout of the hospital, but reduced patient waiting time of between 1 and 1.5 hours has been demonstrated.[1] Blue dye carries a small risk of anaphylactic shock, but the consequences for the patient can be severe and demand immediate access to intensive care.[14] The pressure on intensive care beds is unremitting, particularly at the present time. Magtrace replaces the need for blue dye.

Magtrace is a highly innovative technology which represents a paradigm shift in the way breast cancer is treated in the NHS. The potential of the Sentimag system is not limited to SLNB. The same technology is used already in a range of procedures, such as in conjunction with Magseed for breast cancer lesion localisation.[15] The technology provides an opportunity for the NHS to realise cost savings without compromising patient outcomes.

5 References

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Appendices

Appendix A: Search strategy for economic evidence

Details of the search are in Part 1 of this submission (Appendix A)

Appendix B: Model structure

Not applicable

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☒ Commercial in confidence ☐ Academic in confidence	Information provided by NHS Trusts in confidence	UFN
Details	Names of NHS Trusts on page 13 (section 3.5),16 (section 3.6) and Reference 8 on page 21.		
#		Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	Click or tap here to enter text.
Print:	Click or tap here to enter text.	**Role / organisation:**	Click or tap here to enter text.
Contact email:	Click or tap here to enter text.		

Document Number P415J003-NICE

Scientific and Clinical Literature Review – Magtrace – December 2021

Focused Review – Breast Cancer – Response to NICE Invitation for Comment re Medical Technology Draft Scope – GID-MT568 – "Magtrace and Sentimag for Locating Sentinel Nodes for Breast Cancer"

Author	Position	Signed	Date
Quentin Pankhurst	Director of the UCL Healthcare Biomagnetics Laboratory and Professor of Physics, University College London	*Q. A. Pankhurst*	05-Jan-2022

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1. Scope

This focused Scientific and Clinical Literature Review has been undertaken to provide evidential material towards Endomag's response to the Medical Technology Draft Scope document "MT568 – Magtrace and Sentimag for Locating Sentinel Nodes for Breast Cancer" that was published in December 2021 by the UK National Institute for Health and Care Excellence (NICE).

In particular, the authors' intentions are to collate and report on both the qualitative and quantitative published data currently available in peer-reviewed scientific and clinical literature with regard to the items listed in the **outcomes** and **cost analysis** sections of the "Decision Problem" table in the NICE document:

Comparator(s)	• Technetium-99m in combination with blue dye
Outcomes	The outcome measures to consider include: • sentinel lymph node detection rate • mean number of sentinel lymph nodes retrieved per procedure • time taken for SLNB procedure • patient-reported outcome measures • device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters.

This literature search builds on a series of proprietary searches conducted by Endomag in relation to the safety, performance, design characteristics, and intended purpose of the Magtrace and Sentimag medical devices, and of equivalent or similar devices. The results of these searches are included and identified in this report as "tertiary sources".

In addition to this, new literature searches have been designed and implemented to (a) identify and collate new sources relevant to the NICE specification that have been published since May/June 2021 (the date of the last proprietary search); and (b) to search specifically for sources that report on patient-reported outcomes and cost analyses. The results of these searches are included and identified in this report as "primary sources".

This literature search is intended to complement and extend the separate and self-contained literature search that is reported in the "MT Company Evidence Submission – Part 1 Clinical" document. In particular, the purpose here is to evaluate a series of clinical outcome metrics reported in the literature for the Magtrace and Sentimag devices alongside those same metrics as reported for comparable, state-of-the-art, CE-marked devices as currently used for sentinel lymph node detection. In this way it is somewhat more far-reaching and holistic that the literature search reported in the "Part 1 Clinical" submission.

2. Definition of Outcome Metrics

The outcome measures as described in the NICE scope document are useful indicators of the performance and costs associated with different approaches to sentinel lymph node detection. However, unless they are precisely defined, they may be open to ambiguous interpretation.

In the interest of clarity, therefore, the NICE descriptions and the corresponding Endomag outcome metric definitions are listed in the table below.

NICE	Endomag Metric
Sentinel lymph node (SLN) detection rate	Quantitative metric: the **Identification Rate (IR)**, meaning the per-patient proportion of surgical SLNB operations performed in which one or more sentinel lymph nodes are successfully identified and resected. This is a widely reported metric, and one that is almost always on a per-patient basis. *Metric collated and used in comparative meta-analysis.*
Mean number of SLNs retrieved per procedure	Quantitative metric: the **Number of Nodes (NN)**, meaning the per-patient mean number of sentinel nodes identified and resected during the SLNB surgical procedure. This is a widely reported metric, albeit one that is the subject of variability in definition: (1) it is usually reported per-patient, but it is sometimes reported per-procedure when patients have bilateral operations; and (2) it is usually reported for all SLNB patients in a given cohort, but it is sometimes reported only for those patients that have 1 or more nodes retrieved. Re (1), the Endomag approach is to use the more common per-patient definition of the metric, to keep it consistent with the per-patient definition of the Identification Rate. Re (2), the Endomag approach is to use the more common definition, where the denominator includes all patients in a given study, even those from whom no nodes were retrieved. *Metric collated and used in comparative meta-analysis.*
Time taken for SLNB procedure	Quantitative metric: the **Procedure Time (PT)**, meaning the per-patient mean time taken to complete the SNLB procedure. This metric is rarely reported, and even when it is, there are variations in the definitions applied. As used by Endomag, the metric refers to the time taken, in the operation room, for the SLNB procedure to be completed. This means the time from the first and definite usage of the proximity detection probe (Gamma probe or Sentimag) to the removal of the last of the identified sentinel nodes. *Metric collated and used in comparative meta-analysis.*
Patient-reported outcome measures	Semi-quantitative metrics and discursive reports: relatively uncommon, reported methods & metrics not standardized. Measures reported include patient-reported experiences regarding lymphoedema, upper limb mobility, pain, and cosmesis. *Reports collated and reviewed.*
Device-related adverse events	"Device-related" adverse events are clearly different from "procedure-related" adverse events, but there is considerable ambiguity in the literature regarding this point, as well as regarding the meaning of the term “adverse event”. For this reason, Endomag uses three different metrics associated with adverse events – the Complications Rate (CR); the Anaphylaxis Complications Rate (ACR); and the Staining Complications Rate (SCR) – see below.
	Quantitative metric: the **Complications Rate (CR)**, meaning the per-patient proportion of surgical SLNB operations performed following which a significant clinical complication requiring adapted or additional medical treatment occurs, excluding anaphylaxis. This is an infrequently reported metric, and it is often not well defined. As used by Endomag, the metric refers to “significant” clinical complications such as infection, lymphoedema, haematoma/seroma, and urticaria. Less severe, or more transient, or purely neurological clinical complications, including paraesthesia, restricted upper limb mobility, and pain, are excluded. Anaphylaxis is also excluded, on the basis of its specificity to Blue dye, and its very low (0.15%) incidence rate compared to that of infection, lymphoedema, haematoma/seroma, and urticaria. *Metric collated and used in comparative meta-analysis.*

NICE	Endomag Metric
	Quantitative metric: the **Anaphylaxis Complications Rate (ACR)**, meaning the per-patient proportion of surgical SLNB operations performed following which anaphylaxis occurs requiring adapted or additional medical treatment. This metric is associated specifically with the use of Blue dye. *Metric collated and used in comparative meta-analysis.*
	Quantitative metric: the **Staining Complications Rate (SCR)**, meaning the probability that a patient will present with post-operative dermatological staining following the SLNB procedure. This metric is associated specifically with the use of Magtrace and of Blue dye. It is a quantitative but subjective metric that depends intrinsically on the assessment of the observer as to what constitutes "significant" dermatological discolouration, and what does not. It is also time-dependent, in that the discolouration fades with time. Both the subjectivity and time-dependence need to be considered when assessing this metric. *Metric collated and used in comparative meta-analysis.*
Cost analysis	Semi-quantitative metrics and discursive reports: relatively uncommon, reported methods & metrics not standardized. *Reports collated and reviewed.*

In addition to the outcome measures listed in the NICE scope document, two additional metrics defined by Endomag are considered to be relevant to the current review, both of which relate to direct comparisons between the Magtrace/Sentimag SLND modality and the Technetium and Blue Dye / Gamma Probe SLND modality.

NICE	Endomag Metric
Comparator: Technetium-99m in conjunction with blue dye	Quantitative metric: the Sentimag-versus-Gamma **Nodal Retrieval Rate** (NRR), meaning the per-node proportion of surgically retrieved nodes that are successfully identified by Sentimag / magnetic tracer compared to the corresponding (i.e., from the same study) per-node proportion of surgically retrieved nodes that are successfully identified by Gamma Probe / radiotracer. *Metric collated and used in comparative meta-analysis.*
	Quantitative metric: the Sentimag-to-Gamma **Nodal Concordance Rate** (NCR), meaning the per-node proportion of Gamma Probe / radiotracer detected nodes that are also detected i.e., in the same study) by Sentimag / magnetic tracer. *Metric collated and used in comparative meta-analysis.*

3. Responsibilities

The **Lead Evaluator** for this literature review is:

- Professor Quentin Pankhurst, Director of the UCL Healthcare Biomagnetics Laboratory and Professor of Physics, University College London.

The **Reviewer** for this literature review is:

- Dr Matt Womack, Clinical Development Director Endomagnetics.

4. Definitions

The following terms, abbreviations and acronyms are used in this report:

ALND – axillary lymph node dissection; a surgical procedure in breast cancer wherein all of the lymph nodes in the axilla are removed as a way to limit or prevent metastatic spread.

Assessed Sources – the complete set of primary, secondary, and tertiary sources gathered and assessed as part of the literature review.

BCT – breast-conserving surgery.

Carboxydextran – a sugar with molecular formula $C_6H_{11}O_6$-$(C_6H_{10}O_5)_n$-$C_6H_{11}O_5$.

CKST – compound keyword search term; a combination of keywords and Boolean operators (AND, OR, NOT, and/or NEAR) used to construct a logical search of either the PubMed or Web of Science (Extended) bibliographic databases.

CONSORT-Style Diagram – a flow diagram based on the methodology of the Consolidated Standards of Reporting Trials Group (http://www.consort-statement.org). The CONSORT terminology is used informally, to refer to a flow diagram outlining the management of primary, secondary, and tertiary sources during the identification, appraisal, and evaluation phases.

DCIS – ductal carcinoma in situ, a non-invasive form of breast cancer that has not spread beyond the milk duct into any normal surrounding tissue.

Evaluation Sources – the subset of assessed sources determined (a) to not fall within any of the mechanistic exclusion criteria and (b) to be of sufficient relevance and quality to be taken forward to the evaluation phase.

Hydrogel Method – a soft-tissue marking method based on the implantation of a hygroscopic solid-state tag that swells and becomes visible under ultrasound imaging. (Sometimes referred to as the “HydroMark method”.)

Mechanistic Exclusion Criteria – exclusion criteria based on mechanistic properties of the assessed sources that render them unsuitable for evaluation, *viz.* sources that are patents, more than 25 years old, duplicates, fragments, and/or garbled.

NP or MNP – nanoparticle; or magnetic nanoparticle.

PCR or PCOR – patient-centred research, or patient-centred outcomes research.

Primary Sources – peer-reviewed and published papers, book chapters, books, monographs, and similar literary records as listed in either the PubMed or the Web of Science (Extended) bibliographic databases.

RFID Method – a soft-tissue marking method based on the implantation of a miniature implanted radiofrequency identification (RFID) tag. (Sometimes referred to as the “Localizer RFID method”.)

ROC Curve – a receiver operating characteristic curve, or ROC curve, is a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied.

ROLL – radioactive occult lesion localisation; a soft-tissue marking method based on the injection of a liquid radioisotope fluid rather than a solid-state seed.

ROS – reactive oxygen species.

RSL - radioactive seed localisation; a soft-tissue marking method based on the implantation of a solid-state seed, often containing iodine-125, and detected using a gamma-detector.

SAVI Scout Method – a soft-tissue marking method based on the implantation of radar-based markers, which function via the detection of reflected electromagnetic signals. (Sometimes referred to as the “SAVI method”.)

Secondary Sources – sources that are published after, and cite, one or more Watch List sources.

SLND and SLNB – sentinel lymph node detection and sentinel lymph node biopsy; a surgical procedure wherein the lymph node/s that is/are the first recipient/s of any material originating from a given cancerous lesion are identified and selectively excised from the body. The procedure enables histopathological analysis to determine whether the primary cancer has spread to the node and established a metastatic site, which may then be used by appropriately trained and experienced healthcare professionals to determine the staging of on-going patient care.

Source – an accessible written source of data, information, or opinion, such as an indexed paper in a bibliographic library.

SPIO or SPION – superparamagnetic iron oxide; or superparamagnetic iron oxide nanoparticle.

SPION Tracer – a magnetic tracer based on superparamagnetic iron oxide nanoparticles.

Superparamagnetism – a form of magnetism which appears in small ferromagnetic or ferrimagnetic nanoparticles where their magnetisation can randomly flip, under the influence of temperature, at such a rate such that their net magnetisation averages to zero. In this superparamagnetic state an external magnetic field can magnetise the nanoparticles, as in a paramagnet, but with a much larger magnetic susceptibility than that of paramagnets.

Targeted Axillary Dissection (TAD) – a surgical approach for patients with one or more biopsy-identified positive lymph nodes who (a) have an implanted marker placed at the node biopsy site; and (b) subsequently receive neoadjuvant systemic therapy such as chemotherapy. On the day of surgery, the TAD refers to the selective removal of the marked node for postoperative testing.

Tertiary Sources – sources obtained from a variety of other information repositories including clinical trials databases, manufacturer’s data, and internet website sources.

Watch List Sources – sources that, as the result of an earlier scientific and clinical literature search, are identified as being of particular relevance and/or significance for the given Endomag product, such that it is of interest to monitor subsequent sources that cite that Watch List source.

WGL – wire guided localisation; a soft-tissue marking method based on the use of an implanted wire extending through the skin, placed on the day of operation.

5. Bibliographic Software Package Used

The following software package was used in compiling and analysing this literature review:

Clarivate Analytics EndNote X9.3.3.

6. Identification Phase

6.1. Primary Sources

6.1.1. Methodology

Primary Sources are peer-reviewed and published papers, book chapters, books, monographs, and similar literary records as listed in the PubMed and/or Web of Science (Extended) bibliographic databases. The identification of the Primary Sources is driven by the selection of a

set of Compound Keyword Search Terms (CKST) for logical searches, often using one or more of the Boolean operators AND, OR, NOT, and NEAR to control the scope of those searches.

For this review, a new search was designed and implemented to:

(a) identify and collate new sources relevant to the NICE specification that have been published since May/June 2021 (the date of the last proprietary literature search) – this being the "UPDATE" review; and

(b) search more specifically for sources that report on the NICE specification topics patient-reported outcomes and cost analyses – these being the "PRO" and "COST" reviews respectively.

To this end, the following CKSTs were defined:

#UPDATE =

(TOPIC = (breast AND sentinel AND lymph AND node) **) AND (YEAR =** (2021 OR 2022) **)**

for the UPDATE review, where the search is limited to sources with publication dates listed as 2021 or 2022; and

#PRO =

(TOPIC = (breast AND sentinel AND lymph AND node) AND (patient AND (centered OR centred OR reported) AND (outcome OR research)) **)**

for the PRO (patient-reported outcomes) review; and:

#COST =

(TOPIC = (breast AND sentinel AND lymph AND node) AND ((cost AND analy*) OR (health AND technology AND assessment) OR (HTA)) **)**

for the COST review, where the search terms include "cost analysis" and variants, and also "health technology assessment" and variants.

6.1.2. Results

A bibliographic search of the PubMed and Web of Science (Extended) databases was conducted by the Lead Evaluator on 29th December 2021, as follows:

Search CKST	PubMed	WoS
#UPDATE	571	756
#PRO	604	630
#COST	170	215
TOTAL = #UPDATE OR **#PRO** OR **#COST**	1,647	

These sources were imported into the "Primary Sources" Group Set of the "P415J003-NICE Assessed Sources" EndNote Library. To avoid duplication with sources already identified in the

earlier proprietary searches relating to Magtrace and to Sentimag, the library was pre-loaded with those sources. In this way, using the "Discard Duplicates" filter in the Endnote programme, a total of **1,647** new primary sources were imported into the library.

6.2. Secondary Sources

6.2.1. Methodology

Secondary sources are sources that are published after, and cite, a source that, as the result of an earlier scientific and clinical literature search, has been added to a 'Watch List', denoting their particular relevance and/or significance for the product.

6.2.2. Results

Following a review by the Lead Evaluator of existing proprietary Magtrace and Sentimag Watch Lists, it was determined that none were of relevance to the subject matter of the current review, as none of them related to either patient-reported outcomes or cost analyses. It was further considered that the #UPDATE primary sources search term was sufficiently general to capture all other relevant sources. As such, **no** secondary sources were identified for this review.

6.3. Tertiary Sources

6.3.1. Methodology

Tertiary sources are sources obtained from a variety of other information repositories, including clinical trials databases, manufacturer's data, and internet website sources.

6.3.2. Results

A set of **45** tertiary sources – all of which had been the subject of full-text evaluation in earlier proprietary Magtrace and Sentimag reviews – were imported into the "Tertiary Sources" Group Set of the "P415J003-NICE Assessed Sources" EndNote Library.

7. Mechanistic Review Phase

7.1. Methodology

The mechanistic review phase was undertaken by the Lead Evaluator, and involved identifying any sources that should be discarded based on one or more of the following criteria:

- Duplicate sources;
- Sources published 25 or more years ago;
- Sources that were not peer-reviewed (including patents and conference abstracts);
- Sources written in a language other than English; and
- Fragmented, incomplete, garbled, spliced, or otherwise incomprehensible sources.

7.2. Results

Primary Sources:

On inspection, it was determined that of the **1,647** primary sources in the Endnote Library:

- **7** were patents;
- **185** were duplicates;
- **34** were not published in the English language; and

- **154** were fragments or incomplete.

These **380** sources were moved to the “Discarded Sources” Group Set of the Endnote Library, leaving a remainder of **1,267** sources in the “Primary Sources” Group Set.

Secondary Sources:

There were **0** sources in the “Secondary Sources” Group Set.

Tertiary Sources:

All **45** were retained in the “Tertiary Sources” Group Set.

8. Appraisal Phase

It is understood that data from papers and other sources should form part of the literature review report only if they have sufficient suitability and/or provide a significant contribution. This is intended to ensure that relevant and good quality scientific and clinical data are available for analysis as part of the process of clinical evaluation.

8.1. Appraisal for Suitability

8.1.1. Methodology

Appraisal for suitability was undertaken by the Lead Evaluator. This process involved reading and forming a mental assessment of the suitability of each source, on the basis of its title and abstract (or equivalent), in relation to the following criteria:

- clinical indication, c.f. breast cancer;
- intended use, c.f. sentinel lymph node detection; and
- target tissue, c.f. sentinel lymph nodes.

8.1.2. Results

Primary Sources:

Given the large number (**1,267**) of primary sources to review, an initial inspection was undertaken to gauge the characteristics of the dataset.

It was noted that for the most part the sources looked to be relevant, good quality publications, albeit relating to a wide range of aspects of sentinel lymph node detection.

A decision was therefore taken to identify and set aside these more general sources. In total, **1,228** primary sources were identified and placed in this category. The remaining **39** primary sources were considered to be suitable for continued assessment.

Secondary Sources:

There were **0** sources in the “Secondary Sources” Group Set.

Tertiary Sources:

All **45** sources in the “Tertiary Sources” Group Set were considered to be suitable for continued assessment.

8.2. Appraisal for Quality

8.2.1. Methodology

Appraisal for quality and reliability appraisal was undertaken by the Lead Evaluator. This process involved a second assessment of the titles and abstracts (or equivalent) of each source.

Where possible, data obtained from the Clarivate Analytics InCites Journal Citation Reports (JCR) database was used to validate the peer-based reputation of the source publication.

8.2.2. Results

Primary Sources:

On inspection, it was determined that the abstracts of all **39** of the primary sources were comprehensible and meaningful. However, with reference to the Clarivate Analytics JCR database, **6** sources were found to have been published in journals with a JIF Quartile ranking of Q4, placing them in the lowest 25% of all journals in the same category. These were therefore discarded, leaving **33** primary sources to pass forward for further assessment.

It was noted at this point that of these **33** primary sources:

- **11** had been identified in the #UPDATE search; [1-11]
- **10** had been identified in the #PRO search; [12-21] and
- **12** had been identified in the #COST search. [22-33]

Secondary Sources:

There were **0** sources in the "Secondary Sources" Group Set.

Tertiary Sources:

All **45** of the tertiary sources were comprehensible and meaningful, and published in journals with a JIF Quartile ranking of Q1, Q2, or Q3. It was therefore determined that all **45** tertiary sources should be carried forward to the evaluation phase.

It was noted at this point that of these **45** tertiary sources:

- **33** had been identified in Magtrace June 2021 search; [34-66]
- **10** had been identified in the Magtrace (Focus on Breast Cancer) June 2021 search; [44,46,57,61,67-72] and
- **10** had been identified in the Sentimag May 2021 search. [47,56,59,68,73-78]

In several cases, the same source was identified in more than one of the Magtrace or Sentimag searches.

9. Evaluation Phase

9.1. Methodology

In the evaluation phase, each of the evaluation sources was manually reviewed by the Lead Evaluator, wherever possible through scrutiny of a full-text download of the source, but otherwise through scrutiny of as much information related to the source as was reasonably and reliably obtainable.

For each of the evaluation sources, a brief commentary report was written, containing the following information:

- Reference number of the source as listed in the report's appendices;
- First author's family name & year of publication;
- A commentary on the source, ranging from brief notes for sources considered to be of relatively little import, through to narrative reports (including, where appropriate, selected data/text from the source to illustrate a point) for the most significant or notable sources.
- The Lead Evaluator's conclusion as to the significance of the source, and recommendations for further action with regard to the source, such as placing it on the Watch List for inclusion in future secondary-source literature searches.

As described below, the evaluation was undertaken in two parts. In the first part, the **33** primary sources were reviewed to identify those which warranted full text evaluation. In the second part, full text reviews were performed on the sub-set of **14** primary sources thus selected, alongside the previously-identified **45** tertiary sources.

9.2. First Evaluation

A first manual evaluation was undertaken to select a suitable and representative sub-set of the evaluation sources for full-text review.

Ref.	Author/Year	First Evaluation Commentary[1]	Action
1	Gimenez-Climent, 2021	Magtrace vs Tc concordance study.	Full-text review.
2	Hermansyah, 2021	Blue-only clinical study. Outside scope.	No further action.
3	Inagaki, 2021	Benchtop study of magnetic particle imaging for SLND. Too technical.	No further action.
4	Jazrawi, 2021	New SLND modality of magnetic tracer + pre-op MRI and intra-op US.	Full-text review.
5	Kim, 2021	Correlation of no. nodes resected & lymphedema. Too clinical.	No further action.
6	Kurochkin, 2021	SLND review re non-radioactive tracers.	Full-text review.
7	Papasavva, 2021	New Tc tracer – benchtop study. Too technical.	No further action.
8	Peristeri, 2021	Review & meta-analysis of SLND vs ALND recurrence rates. Too clinical.	No further action.
9	Pla Farnos, 2021	Review of SLND state-of-the-art.	Full-text review.
10	Wang, 2021	Blue-only clinical study. Outside scope.	No further action.
11	Zhang, 2021	Clinical review of SLND outcomes in DCIS patients. Too clinical.	No further action.
12	Poulsen, 2021	Patient-reported lymphoedema after SLND.	Full-text review.
13	Tarkowska, 2021	Quality of life of patients post-BCT vs post-mastectomy. Outside scope.	No further action.
14	Chandarana, 2020	Patient-reported upper limb mobility after SLND.	Full-text review.
15	Young-Afat, 2019	Quality of life effect of oedema following BCT & radiotherapy. Outside scope.	No further action.
16	Sackey, 2015	Quality of life re self-perceived vs objective post-surgery lymphoedema.	Full-text review.
17	Cooney, 2013	Systematic review of reported pain after breast cancer treatment.	Full-text review.
18	Radowsky, 2012	Patient pain ratings re Tc injections.	Full-text review.

Ref.	Author/Year	First Evaluation Commentary[1]	Action
19	Land, 2010	Patient-reported outcomes post SLND or ALND.	Full-text review.
20	Reimer, 2010	Quality of life considerations for breast cancer treatment of the elderly. Outside scope.	No further action.
21	Smith, 2010	Audit of patient-centred quality measures for SLND.	Full-text review.
22	Bredbeck, 2021	Cost analysis for SLND & radiotherapy in over-70 year olds. Outside scope.	No further action.
23	Mattar, 2021	Cost comparisons between SLND & ALND, following US Z0011 study.	Full-text review.
24	Castelo, 2020	Cost analysis of different management strategies for positive SNs. Outside scope.	No further action.
25	McEvoy, 2020	Cost comparisons between SLND & observation for post-menopausal women. Outside scope.	No further action.
26	Dreyer, 2018	Socioeconomic study of breast cancer survival rates. Outside scope.	No further action.
27	Coromilas, 2015	Factors influencing ALND in DCIS patients. Outside scope.	No further action.
28	Zurrida, 2015	Opinion piece on breast cancer treatment. Outside scope.	No further action.
29	Gorey, 2013	Socioeconomic factors influening breast cancer treatment options. Outside scope.	No further action.
30	Classe, 2012	Cost comparisons between SLND & ALND, using Tc/Blue.	Full-text review.
31	Verry, 2012	Cost comparisons between SLND & ALND, using Tc/Blue.	Full-text review.
32	Meng, 2011	Cost effectiveness of MRI & PET for evaluation of metastases. Outside scope.	No further action.
33	Landercasper, 2010	Quality & cost metrics for breast cancer treatment. Too broad.	No further action.

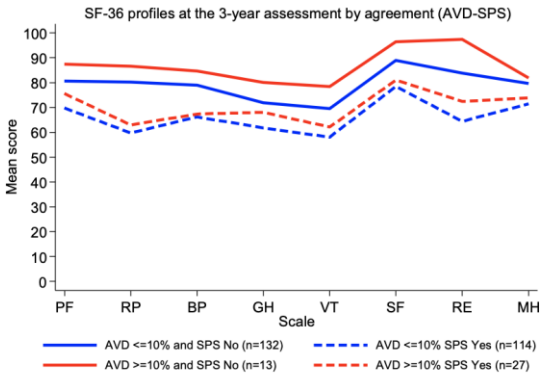
[1] *Abbreviations are used to denote marker fluid types: Tc = technetium-99m radiocolloid; Blue = blue dye; Mag = Magtrace; and ICG = indocyanine green dye.*

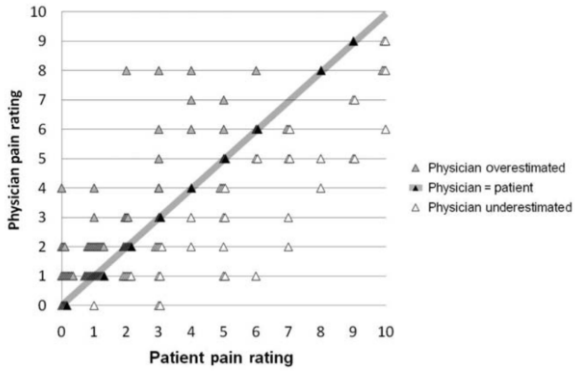
The sub-set of **14** primary sources thus identified were then added to the previously-identified **45** tertiary sources and were taken forward for full-text review.

9.3. Second Evaluation

The results of the second, full-text evaluations are reported in the table below.

Ref.	Author/Year	Second Evaluation Commentary	Action
Primary Sources: Update of SLND Clinical Studies			
1	Gimenez-Climent, 2021	Magtrace vs Tc multi-centre concordance study of 89 post-NAC patients. Mag: IR = 87/89; NN = 128/89; NRR = 128/129. Tc: IR = 87/89; NN = 121/89; NRR = 121/129. NCR = 120/121.	Meta-analysis: IR, NN, NRR, NCR.

Ref.	Author/Year	Second Evaluation Commentary	Action
4	Jazrawi, 2021	New SLND modality of magnetic tracer + pre-op MRI and intra-op US. Focused on the screening/diagnostic aspects of the use of MRI, rather than on the SLND itself.	No further action.
6	Kurochkin, 2021	SLND review re non-radioactive tracers. Discursive review, intended for a non-clinical readership.	No further action.
9	Pla Farnos, 2021	Review of SLND state-of-the-art in breast cancer, for a gynaecological oncology journal. High level, focused on clinical aspects.	No further action.
Primary Sources: Patient-Reported Outcomes			
12	Poulsen, 2021	Patient-reported upper limb lymphedema after SLND or ALND. N=3044 patients (92% ALND, 8% SLND), post-op online REDCap survey. Authors conclude: "*There is no difference in women with upper extremity lymphedema after SLND or ALND on the LYMPH-Q UE module scales measuring arm symptoms, function, distress, and appearance*."	Review: PRO.
14	Chandarana, 2020	Patient-reported upper limb mobility after SLND. N=99 patients, using the quickDASH questionnaire pre-op & then 2 weeks & 3 months post-op. Mean scores 8.5, 16.1 & 13.4 at the three timepoints, where lower scores mean higher mobility. Authors conclude that: "*there is a significant post- procedure deterioration in upper limb function following SLNB. The function improves significantly at 3 months but does not reach baseline levels*."	Review: PRO.
16	Sackey, 2015	Quality of life re self-perceived vs objective post-surgery lymphoedema. Study of N=140 SLND and N=280 ALND patients, with N=420 respondents to the Swedish SF-36 survey, used to assess health-related quality of life (HRQoL). Objective arm-volume measurements made pre-op and 1 & 3 years post-op, with 10% increase indicating lymphoedema .  Figure 4. SF-36 profiles at 3 years by agreement. Arm volume difference (AVD), self-perceived lymphoedema (SPS). Authors report that: "*there was no statistically significant agreement between self-perceived arm lymphoedema and objectively measured arm lymphoedema one and three years after surgery*", and that "*Women reporting self-perceived arm lymphoedema .. scored lower on all eight SF-36 domains than those who did not report self-perceived arm lymphoedema*."	Review: PRO.
17	Cooney, 2013	Systematic review of 26 prospective studies including reported pain after breast cancer treatment. Prevalence, when reported, ranged from 13% to 51%, albeit different studies focused on different anatomical regions or specific types of pain, such as phantom pain. "*In all but one study, axillary dissection (ANLD) resulted in considerably higher pain prevalence than sentinel node biopsy (SLNB)*." Re intensity, "*the mean intensity of the pain reported seems to be reasonably low on the visual analog scale (VAS), with most figures falling into what is generally classified as the mild pain category*".	Review: PRO.

<table>
<tr><th>Ref.</th><th>Author/Year</th><th>Second Evaluation Commentary</th><th>Action</th></tr>
<tr><td>18</td><td>Radowsky, 2012</td><td>Patient pain ratings re Tc injections. Prospective study with N=140 patients, sub-areolar injections, randomly assigned into 4 groups, 1 standard Tc, & 3 other Tc-and-lidocaine-containing non-standard formulations. (Lidocaine chosen as a potential way to lessen pain.) Patients & physicians both then rated the experienced/perceived injection pain on 0-10 scale. Considerable variations observed:
 

There was no observed difference between the 4 groups.</td><td>Review: PRO.</td></tr>
<tr><td>19</td><td>Land, 2010</td><td>Patient-reported outcomes post SLND or ALND – arm mobility & QoL – via questionnaires pre-op & at 6 month intervals up to 3 years post-op.
Authors report that arm symptoms were “significantly more bothersome” for ALND vs SLND patients at 6 and 12 months; but that “from 12 to 36 months, fewer than 15%” of either set “reported moderate or greater severity of any given symptom or activity limitation”.
Authors conclude that “Arm morbidity was greater with SNAD than with SNR. Despite considerable fears about complications from AD for breast cancer, this study demonstrates that initial problems with either surgery resolve over time”.</td><td>Review: PRO.</td></tr>
<tr><td>21</td><td>Smith, 2010</td><td>Audit of patient-centred quality measures for SLND. Focus on accountability & transparency for the healthcare provider.</td><td>No further action.</td></tr>
<tr><td colspan="4">Primary Sources: Cost Analyses</td></tr>
<tr><td>23</td><td>Mattar, 2021</td><td>Cost comparisons between SLND & ALND, following the adoption of the outcomes of the US Z0011 study (which recommended SLND over ALND) in the authors institution (IEO, Milan, Italy) in 2016.
Main outcomes as follows: Table 4 gives the prospective standard costs per procedure; & Table 5 the retrospective actual costs per patient.
Table 4
Standard costs (Euros) per patients according to intervention type.
<table>
<tr><th></th><th>SLN Only
Pre-Z0011</th><th>SLN Only
Post-Z0011</th><th>SLN + ALND</th><th>ALND</th></tr>
<tr><td>Materials</td><td>102€</td><td>102€</td><td>102€</td><td>102€</td></tr>
<tr><td>Pre-Surgery</td><td>281€</td><td>281€</td><td>281€</td><td>170€</td></tr>
<tr><td>APA</td><td></td><td></td><td></td><td>206€</td></tr>
<tr><td>No Frozen Section</td><td></td><td>176€</td><td></td><td>–</td></tr>
<tr><td>Frozen Section</td><td>247€</td><td></td><td>316€</td><td>–</td></tr>
<tr><td>Drugs</td><td>20€</td><td>20€</td><td>26€</td><td>23€</td></tr>
<tr><td>Disposable</td><td>61€</td><td>61€</td><td>82€</td><td>124€</td></tr>
<tr><td>Operation Room Costs</td><td>218€</td><td>218€</td><td>386€</td><td>303€</td></tr>
<tr><td>Personnel</td><td>133€</td><td>133€</td><td>420€</td><td>274€</td></tr>
<tr><td>Hospital Stay</td><td>250€</td><td>250€</td><td>1000€</td><td>1000€</td></tr>
<tr><td>Total</td><td>1312€</td><td>1241€</td><td>2613€</td><td>2202€</td></tr>
</table>
Table 5
Total costs and Length of Hospital Stay Costs (Euros) per patients according to Study Group.
<table>
<tr><th></th><th>Pre Z0011 (N = 1882)</th><th>Post Z0011 (N = 2030)</th></tr>
<tr><td>Calendar Years of Surgery</td><td>2013–2015</td><td>2016–2018</td></tr>
<tr><td>Hospital Stay, Mean (IQR)</td><td>€651 (250–1000)</td><td>€487 (250–500)</td></tr>
<tr><td>Total Cost, Mean (IQR)</td><td>€1807 (1312–2062)</td><td>€1498 (1241–1491)</td></tr>
</table></td><td>Review: Cost.</td></tr>
</table>

Ref.	Author/Year	Second Evaluation Commentary	Action
		"*The mean total cost in the pre-Z0011 cohort was €1807 per patient, while in the post-Z0011 cohort it was €1498. The application of Z0011 resulted in an overall mean cost savings of €309 for each patient*."	
30	Classe, 2012	Cost comparisons between SLND & ALND, using Tc/Blue, in France. Costings based on "*the micro-costing method from the diagnosis until 1 month after the last surgery*", data from 839 SLND & 146 ALND patients. Authors conclude that: "*The cost generated for a patient with an SLND, with one preoperative scintigraphy, a combined method for sentinel node detection, an intraoperative pathological analysis without lymphadenectomy, was lower than the cost generated for a patient with lymphadenectomy [€2947 (σ = 580) versus €3331 (σ = 902)].*"	Review: Cost.
31	Verry, 2012	Cost comparisons between SLND & ALND, using Tc/Blue, from Australian healthcare system perspective, and "*included the direct health care costs associated with the 20-year natural history of breast cancer*". Authors conclude that: "*The SLNB was more effective and less costly than the ALND over 20 years, with 8 QALYs gained and $883 000 saved per 1000 patients*."	Review: Cost.
Tertiary Sources: SLND Clinical Studies			
34	Frountzas, 2021	Provides 2 case reports of anaphylactic reactions following Blue dye injection in breast SLND, and comments on 21 previous reports of a total of 57 similar cases from 2001 to 2008. Authors comment that the complications rate is 0.7%, inferring a complications rate of 59 in 8430. Breast: ACR= 59/8430.	Meta-analysis: ACR.
35	Hersi, 2021	Magtrace vs Tc/Blue, breast SLND. A complex study with N=534 patients summed over 3 separate studies – the Nordic Trial (reported also in Karakatsanis 2016) & 2 Sentidose Trials – varying Magtrace doses, timeframes and injection sites. All patients also received Tc/Blue tracers. *"The SPIO injections were well-tolerated and no adverse effects were reported in the groups."* Mag: IR = 520/534; NN = 1033/534. Tc/Blue: IR not reported; NN = 985/534.	Meta-analysis: IR, NN.
36	Karsten, 2021	Opinion piece by Shams 2021 authors, highlighting the results of that study, and promoting the use of Magtrace. "*A more flexible schedule and thus an increase in patient comfort might be achieved by using superparamagnetic iron oxide (SPIO). Proven equivalent to Tc99 for primary SNB by multiple meta-analyses, SPIO can be administered up to 7 days before surgery*."	No further action.
37	Kedrzycki, 2020	ICG vs Tc/Blue for breast SLNB. Meta-analysis of 10 studies, of which 2 are new to this review. Evaluator-pooled data below. No mention of complications. **Pts / ICG - IR / Blue - IR / ICG - NN / Blue - NN** He 2016: 99 / 99 / 99 / 276 / 202 **99 / 99 / 99 / 276 / 202** **Pts / ICG - IR / Tc/Blue - IR / ICG - NN / Tc/Blue - NN** Somashekhar 2020: 100 / 100 / 100 / 280 / 246 **100 / 100 / 100 / 280 / 246**	Meta-analysis: IR, NN.
38	Malhotra, 2021	Periareolar vs peritumoural injection site for Tc/Blue SLNB, breast cancer. N=110 patients; 108 successful node identifications. Tc/Blue: IR= 108/110; NN not reported.	Meta-analysis: IR.
39	Perenyei, 2021	In a meta-analysis of 109 studies notes 94/61951 = 0.15% cases of anaphylaxis in Blue dye SLNB, across all cancer types. For breast cancer alone, the rate was 61/40268, for all Blue dyes. Breast: ACR= 61/40268.	Meta-analysis: ACR.

<table>
<tr><th>Ref.</th><th>Author/Year</th><th>Second Evaluation Commentary</th><th>Action</th></tr>
<tr><td>40</td><td>Shams, 2021</td><td>Magtrace vs Tc SLNB breast cancer, N=30 & 29 patients respectively. Focus on “Care Process Optimization, Reimbursement, Surgical Time, and Patient Comfort”.

Pre-op time for the tracer injection (on day before surgery) was measured: 5.4 ± 1.3 min for Magtrace; 82 ± 20 min for Tc.

Intra-op SLNB Procedure Time measured. Medians: 9 min Magtrace; 10 min Tc. Inter-quartile ranges (IQRs): 4-15 min Magtrace; 7-15 min Tc.

Evaluator-interpreted data: assuming Gaussian distribution, take mean PT to be the centre of the IQR.

PT = 285/30 Magtrace; 319/29 Tc.

Re patient-reported outcomes, patients filled out a QUIPS pain questionnaire before & after injection. No relevant difference was seen between Magtrace & Tc. “The median pain level after the tracer injection in the Tc99 arm was 0 (IQR, 0–1), and all the patients in the Magtrace group reported no pain at all.”

Re cost, the authors conclude: “Reimbursement was similar in the two groups, but we found that using Magtrace had a cost-saving effect compared with the use of Tc99 at our institution. In 2019, the costs for Tc99-based lymph node localization at the Charite Department of Nuclear Medicine were €360 per case for medical staff, material, infrastructure, and clinic overhead. This stands in contrast to the costs associated with the time required for Magtrace injection by a senior breast surgeon, which were calculated at €7.50.”</td><td>Meta-analysis: PT.

Review: PRO, Cost.</td></tr>
<tr><td>41</td><td>Yin, 2021</td><td>ICG vs Tc/Blue in breast SLNB. Meta-analysis of 21 studies. Evaluator-pooled data below – converted to IR & NN values for each type of marker fluid. No mention of complications rates in the review.

<table>
<tr><th></th><th>Pts</th><th>ICG - IR</th><th>Blue - IR</th><th>ICG - NN</th><th>Blue - NN</th></tr>
<tr><td>Hirano 2012</td><td>108</td><td>107</td><td>100</td><td>-</td><td>-</td></tr>
<tr><td>Wishart 2012</td><td>104</td><td>104</td><td>101</td><td>201</td><td>191</td></tr>
<tr><td>van der Vorst 2012</td><td>12</td><td>12</td><td>12</td><td>19</td><td>16</td></tr>
<tr><td>Jung 2014</td><td>43</td><td>43</td><td>39</td><td>-</td><td>-</td></tr>
<tr><td>Hojo 2010</td><td>113</td><td>113</td><td>105</td><td>-</td><td>-</td></tr>
<tr><td>Sugie 2013</td><td>99</td><td>98</td><td>77</td><td>281</td><td>121</td></tr>
<tr><td>Pitsinis 2015</td><td>50</td><td>50</td><td>48</td><td>87</td><td>84</td></tr>
<tr><td>Guo 2014</td><td>86</td><td>80</td><td>70</td><td>281</td><td>255</td></tr>
<tr><td>Schaafsma 2013</td><td>32</td><td>-</td><td>-</td><td>48</td><td>42</td></tr>
<tr><td>Liu 2017</td><td>60</td><td>60</td><td>53</td><td>177</td><td>106</td></tr>
<tr><td>Tong 2014</td><td>96</td><td>93</td><td>83</td><td>-</td><td>-</td></tr>
<tr><td>Ji 2017</td><td>65</td><td>-</td><td>-</td><td>232</td><td>198</td></tr>
<tr><td>Hutteman 2011</td><td>10</td><td>-</td><td>-</td><td>14</td><td>10</td></tr>
<tr><td>Verbeek 2014</td><td>27</td><td>-</td><td>-</td><td>40</td><td>31</td></tr>
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</table>

<table>
<tr><th></th><th>Pts</th><th>ICG - IR</th><th>Tc - IR</th><th>ICG - NN</th><th>Tc - NN</th></tr>
<tr><td>Ballardini 2013</td><td>134</td><td>134</td><td>133</td><td>245</td><td>231</td></tr>
<tr><td>Samorani 2015</td><td>301</td><td>297</td><td>287</td><td>583</td><td>452</td></tr>
<tr><td>Wishart 2012</td><td>104</td><td>104</td><td>93</td><td>201</td><td>156</td></tr>
<tr><td>van der Vorst 2012</td><td>24</td><td>23</td><td>23</td><td>37</td><td>35</td></tr>
<tr><td>Polom 2012</td><td>28</td><td>28</td><td>27</td><td>68</td><td>58</td></tr>
<tr><td>Jung 2014</td><td>43</td><td>43</td><td>43</td><td>-</td><td>-</td></tr>
<tr><td>Hojo 2010</td><td>29</td><td>29</td><td>27</td><td>-</td><td>-</td></tr>
<tr><td>Sugie 2016</td><td>821</td><td>798</td><td>796</td><td>-</td><td>-</td></tr>
<tr><td>Schaafsma 2013</td><td>32</td><td>32</td><td>32</td><td>48</td><td>48</td></tr>
<tr><td>Murawa 2009</td><td>20</td><td>20</td><td>17</td><td>-</td><td>-</td></tr>
<tr><td>Stoffels 2015</td><td>80</td><td>78</td><td>80</td><td>147</td><td>141</td></tr>
<tr><td>Grischke 2015</td><td>105</td><td>93</td><td>103</td><td>138</td><td>157</td></tr>
<tr><td>Hutteman 2011</td><td>10</td><td>10</td><td>10</td><td>14</td><td>14</td></tr>
<tr><td>Verbeek 2014</td><td>177</td><td>-</td><td>-</td><td>177</td><td>155</td></tr>
<tr><td></td><td>1908</td><td>1689</td><td>1671</td><td>1658</td><td>1447</td></tr>
</table>
</td><td>Meta-analysis: IR, NN.</td></tr>
</table>

Ref.	Author/Year	Second Evaluation Commentary	Action
		<table><tr><th></th><th>Pts</th><th>ICG - IR</th><th>Tc/Blue - IR</th><th>ICG - NN</th><th>Tc/Blue - NN</th></tr><tr><td>Wishart 2012</td><td>104</td><td>104</td><td>102</td><td>-</td><td>-</td></tr><tr><td>van der Vorst 2012</td><td>12</td><td>12</td><td>12</td><td>19</td><td>19</td></tr><tr><td>Jung 2014</td><td>43</td><td>43</td><td>43</td><td>-</td><td>-</td></tr><tr><td>Hutteman 2011</td><td>10</td><td>10</td><td>10</td><td>14</td><td>14</td></tr><tr><td></td><td>169</td><td>169</td><td>167</td><td>33</td><td>33</td></tr></table>	
42	Agrawal, 2020	ICG/Blue vs Tc/Blue for breast SLNB. Methylene blue; N=207 patients (total). No mention of complications. ICG/Blue: IR = 100/103; NN = 282/103. Tc/Blue: IR = 99/104; NN = 330/104.	Meta-analysis: IR, NN.
43	Goonawardena, 2020	ICG vs Tc/Blue in breast SLNB. Meta-analysis of 19 studies, of which 6 are new to this review. Rates reported as percentages. Evaluator-pooled data below, converted to IR & NN rates. No mention of complications. <table><tr><th></th><th>Pts</th><th>ICG - IR</th><th>Tc - IR</th><th>ICG - NN</th><th>Tc - NN</th></tr><tr><td>Mazouni 2018</td><td>122</td><td>100</td><td>118</td><td>244</td><td>244</td></tr><tr><td>Papathemelis 2018</td><td>99</td><td>97</td><td>97</td><td>218</td><td>168</td></tr><tr><td>Sorrentino 2018</td><td>71</td><td>66</td><td>68</td><td>78</td><td>71</td></tr><tr><td>Valente 2019</td><td>92</td><td>91</td><td>90</td><td>224</td><td>202</td></tr><tr><td></td><td>384</td><td>354</td><td>373</td><td>764</td><td>686</td></tr></table> <table><tr><th></th><th>Pts</th><th>ICG - IR</th><th>Tc/Blue - IR</th><th>ICG - NN</th><th>Tc/Blue - NN</th></tr><tr><td>Mieog 2011</td><td>24</td><td>24</td><td>24</td><td>-</td><td>-</td></tr><tr><td>Rauch 2017</td><td>98</td><td>93</td><td>97</td><td>225</td><td>225</td></tr><tr><td></td><td>122</td><td>117</td><td>121</td><td>225</td><td>225</td></tr></table>	Meta-analysis: IR, NN.
44	Rubio, 2020	Magtrace vs Tc for SLNB in breast cancer – the “SUNRISE” dosing study. Subareolar Magtrace in N=135 patients, 3 groups each of 45 patients receiving undiluted (a) 1.0 mL, (b) 1.5 mL, and (c) 2.0 mL respectively. Some discussion of staining, but no clinical complications mentioned. Mag: IR = 133/135; NN = 238/135. Tc: IR = 132/135; NN = 232/135.	Meta-analysis: IR, NN.
45	Thongvitokomarn, 2020	ICG vs Tc/Blue for breast SLNB. Meta-analysis of 30 studies, of which 7 are new to this review. Evaluator-pooled data below. No mention of complications. <table><tr><th></th><th>Pts</th><th>ICG - IR</th><th>Blue - IR</th><th>ICG - NN</th><th>Blue - NN</th></tr><tr><td>Qin 2019</td><td>60</td><td>60</td><td>58</td><td>199</td><td>102</td></tr><tr><td>Hokimoto 2017</td><td>91</td><td>91</td><td>87</td><td>-</td><td>-</td></tr><tr><td>Guo 2017</td><td>198</td><td>194</td><td>178</td><td>-</td><td>-</td></tr><tr><td>Abe 2011</td><td>128</td><td>128</td><td>84</td><td>397</td><td>84</td></tr><tr><td>Tagaya 2008</td><td>25</td><td>25</td><td>23</td><td>135</td><td>53</td></tr><tr><td></td><td>502</td><td>498</td><td>430</td><td>731</td><td>239</td></tr></table> <table><tr><th></th><th>Pts</th><th>ICG - IR</th><th>Tc - IR</th><th>ICG - NN</th><th>Tc - NN</th></tr><tr><td>Jung 2019</td><td>58</td><td>54</td><td>-</td><td>127</td><td>-</td></tr><tr><td>Jung 2019</td><td>122</td><td>-</td><td>113</td><td>-</td><td>232</td></tr><tr><td>Hokimoto 2017</td><td>91</td><td>-</td><td>89</td><td>-</td><td>-</td></tr><tr><td>Motomura 2003</td><td>116</td><td>80</td><td>112</td><td>-</td><td>-</td></tr><tr><td></td><td>387</td><td>134</td><td>314</td><td>127</td><td>232</td></tr></table>	Meta-analysis: IR, NN.
46	Vural, 2020	Magtrace SLNB breast – clinical study. The “Turkish Sentimag trial”. Skin staining in some cases, but no clinical complications. Mag: IR = 103/104; NN = 197/104.	Meta-analysis: IR, NN.
47	Alvarado, 2019	Magtrace vs Tc/Blue for breast SLNB. No complications mentioned. Mag: IR = 145/146; NN = 348/146. Tc/Blue: IR = 144/146; NN = 345/146.	Meta-analysis: IR, NN.
48	Hersi, 2019	Magtrace SLND & Magseed lesion marking, breast. Pilot study; no complications mentioned. Mag: IR = 32/32; NN not reported.	Meta-analysis: IR.

Ref.	Author/Year	Second Evaluation Commentary	Action
49	Karakatsanis, 2019	SPIO (Magtrace) SLND for DCIS breast cancer. *"No adverse effects were noted."* Patients with invasive breast cancer. Mag/Blue: IR = 40/40; NN not reported; CR = 0/40. Tc/Blue: IR = 26/40; NN, CR not reported.	Meta-analysis: IR, CR.
50	Man, 2019	SPIO SLND breast, N=333 patients. Mag: IR = 329/333; NN = 1514/333.	Meta-analysis: IR, NN.
51	Taruno, 2019	Breast SLNB with magnetic tracer (Resovist, not Magtrace) vs Tc, & a bespoke magnetic probe (not Sentimag). N=210 multicentre study. No mention of complications. Resovist: IR = 199/210; NN not reported. Tc: IR = 206/210; NN not reported.	Meta-analysis: IR.
52	Vermersch, 2019	ICG/Tc vs Tc alone for breast SLNB. Clinical complications reported: 11 seroma, 5 haematoma & 2 pain in N=50 ICG/Tc cases; and 6 seroma, 7 haematoma & 2 pain in N=49 Tc cases. No allergic reactions in either group. ICG/Tc: IR = 50/50; NN = 108/50; CR = 16/49. Tc: IR = 49 /49; NN = 87/49; CR = 13/49.	Meta-analysis: IR, NN, CR.
53	Pohlodek, 2018	Magtrace & magnetic seed in breast treatment. N=10 patients. *"No complications or adverse events recorded"*. Mag: IR = 10/10; NN = 34/10; CR = 0/10.	Meta-analysis: IR, NN, CR.
54	Yuan, 2018	Tc/Blue vs ICG/Blue for breast SLNB. No mention of complications. ICG/Blue: IR = 198/200; NN = 744/200. Tc/Blue: IR = 270/271; NN = 1060/271.	Meta-analysis: IR, NN.
55	Berrocal, 2017	Tc breast SLNB. Single centre retrospective study. Tc: IR = 2333/2338; NN = 5448/2338.	Meta-analysis: IR, NN.
56	Ghilli, 2017	Magtrace vs Tc/Blue for breast SLNB. No mention of complications. Mag: IR = 189/193; NN = 364/193. Tc/Blue: IR = 191/193; NN = 360/193.	Meta-analysis: IR, NN.
57	Karakatsanis, 2017	Magtrace vs Tc/Blue for breast SLNB. Rather complex study design with Tc ± Blue and Magtrace ± Blue rates reported; and variations in both Magtrace injection site (periareolar versus peritumoural) & Magtrace injection timing (2-27 days preoperative versus perioperative). Mag: IR = 171/183; NN = 231/183. Mag/Blue: IR = 175/183; NN = 247/183. Tc: IR = 152/155; NN = 271/155. Tc/Blue: IR = 154/155; NN = 300/155. Comparative cost analysis (Sweden) performed: "*The primary cost per patient when SPIO was used compared with radioisotope and blue dye in the same healthcare setting was analysed. This included the cost of tracer and the cost of the preoperative visit to the department of nuclear medicine. Costs were initially calculated in Swedish crowns and then converted to euros (exchange rate 20 December 2016).*" Results as reported: "*Logistics were simplified in the SPIO arm, as the preoperative visit to the department of nuclear medicine could be omitted. As far as the tracer and injection expenses per procedure were concerned, the mean was €225 for the SPIO arm versus €252 for the 99m Tc arm, with SPIO being slightly cheaper by approximately €27.*"	Meta-analysis: IR, NN. Review: Cost.

<table>
<tr><th>Ref.</th><th>Author/Year</th><th>Second Evaluation Commentary</th><th>Action</th></tr>
<tr><td>58</td><td>Peek, 2017</td><td>Optimum Blue dye for breast SLNB – meta-analysis of 21 studies, of which 15 are new to this review. Evaluator-pooled data below. Complication rates not reported.
<table>
<tr><th></th><th>Pts</th><th>Tc/Blue - IR</th><th>Blue - IR</th><th>Tc/Blue - NN</th><th>Blue - NN</th></tr>
<tr><td>Bostick 1997</td><td>117</td><td>112</td><td>107</td><td>163</td><td>163</td></tr>
<tr><td>Canavese 2000</td><td>103</td><td>94</td><td>66</td><td>133</td><td>113</td></tr>
<tr><td>Cserni 2002</td><td>199</td><td>199</td><td>173</td><td>258</td><td>278</td></tr>
<tr><td>Degnim 2005</td><td>475</td><td>475</td><td>465</td><td>-</td><td>-</td></tr>
<tr><td>Elmadahm 2015</td><td>1088</td><td>1044</td><td>935</td><td>-</td><td>-</td></tr>
<tr><td>Gipponi 2004</td><td>165</td><td>165</td><td>148</td><td>313</td><td>231</td></tr>
<tr><td>Hung 2005</td><td>118</td><td>118</td><td>101</td><td>247</td><td>212</td></tr>
<tr><td>Ikeda 2000</td><td>81</td><td>66</td><td>72</td><td>162</td><td>170</td></tr>
<tr><td>Mamounas 2005</td><td>428</td><td>376</td><td>333</td><td>-</td><td>-</td></tr>
<tr><td>Meyer-Rochaw 2003</td><td>104</td><td>101</td><td>93</td><td>-</td><td>-</td></tr>
<tr><td>Morrow 1999</td><td>139</td><td>119</td><td>101</td><td>264</td><td>250</td></tr>
<tr><td>Nathanson 2007</td><td>1187</td><td>1139</td><td>1056</td><td>-</td><td>-</td></tr>
<tr><td>Noguchi 1999</td><td>72</td><td>69</td><td>58</td><td>-</td><td>-</td></tr>
<tr><td>Radovanovic 2004</td><td>150</td><td>124</td><td>102</td><td>240</td><td>255</td></tr>
<tr><td>Syme 2005</td><td>362</td><td>322</td><td>347</td><td>651</td><td>470</td></tr>
<tr><td></td><td>4788</td><td>4523</td><td>4157</td><td>2431</td><td>2142</td></tr>
</table></td><td>Meta-analysis: IR, NN.</td></tr>
<tr><td>59</td><td>Houpeau, 2016</td><td>Magtrace vs Tc/Blue breast SLNB – “the French Sentimag study”. N=108. No complications reported, other than “brown dermopigmentation among 22 patients”, which were “in line with the expected complications from the procedure”.
Mag: IR = 105/108; NN = 217/108.
Tc/Blue: IR = 103/108; NN = 210/108.</td><td>Meta-analysis: IR, NN.</td></tr>
<tr><td>60</td><td>Niebling 2016</td><td>Large review & meta-analysis of SLNB in breast cancer & melanoma. Includes IR & NN data from 76 breast cancer studies published from 1997 to 2011, most of which are new to this review. Tabulated data for Blue, Tc, and Tc/Blue marker fluids. “No adverse reactions were reported in any of the conducted studies.”
<u>Note</u>: In light of the high number of more recent studies already identified & evaluated as part of this review, a decision was taken by the Evaluator to limit the selection of data (from Niebling 2016, for use in this review) to studies with 500+ patients in at least one of the study arms.
Evaluator-pooled data:
<table>
<tr><th></th><th>Pts</th><th>Tc - IR</th><th>Tc - NN</th></tr>
<tr><td>Cox 2000</td><td>1147</td><td>1016</td><td>2408</td></tr>
<tr><td>Derossis 2001</td><td>2000</td><td>1802</td><td>-</td></tr>
<tr><td>King 2004</td><td>1719</td><td>1672</td><td>-</td></tr>
<tr><td>Lo 2006</td><td>175</td><td>165</td><td>192</td></tr>
<tr><td>Hayashida 2010</td><td>640</td><td>606</td><td>1536</td></tr>
<tr><td>Kang 2010</td><td>1353</td><td>1331</td><td>3923</td></tr>
<tr><td>Straver 2010</td><td>1953</td><td>1870</td><td>-</td></tr>
<tr><td></td><td>8987</td><td>8462</td><td>8059</td></tr>
</table>
<table>
<tr><th></th><th>Pts</th><th>Blue - IR</th><th>Blue - NN</th></tr>
<tr><td>Cox 2000</td><td>1147</td><td>921</td><td>2408</td></tr>
<tr><td>Derossis 2001</td><td>2000</td><td>1658</td><td>1390</td></tr>
<tr><td>King 2004</td><td>1719</td><td>1449</td><td>-</td></tr>
<tr><td>Hayashida 2010</td><td>640</td><td>510</td><td>1536</td></tr>
<tr><td>Straver 2010</td><td>1953</td><td>1724</td><td>-</td></tr>
<tr><td></td><td>7459</td><td>6262</td><td>5334</td></tr>
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<table>
<tr><th></th><th>Pts</th><th>Tc/Blue - IR</th><th>Tc/Blue - NN</th></tr>
<tr><td>Cox 2000</td><td>1147</td><td>1101</td><td>2408</td></tr>
<tr><td>Derossis 2001</td><td>2000</td><td>1940</td><td>-</td></tr>
<tr><td>Tafra 2001</td><td>535</td><td>465</td><td>856</td></tr>
<tr><td>Gray 2004</td><td>546</td><td>540</td><td>709</td></tr>
<tr><td>King 2004</td><td>1719</td><td>1701</td><td>-</td></tr>
<tr><td>Lo 2006</td><td>758</td><td>674</td><td>1516</td></tr>
<tr><td>Krag 2007</td><td>5536</td><td>5369</td><td>7196</td></tr>
<tr><td>Hayashida 2010</td><td>640</td><td>627</td><td>1536</td></tr>
<tr><td>Kang 2010</td><td>2049</td><td>2008</td><td>5532</td></tr>
<tr><td>Straver 2010</td><td>1953</td><td>1894</td><td>-</td></tr>
<tr><td></td><td>16883</td><td>16319</td><td>19753</td></tr>
</table></td><td>Meta-analysis: IR, NN.</td></tr>
</table>

<table>
<tr><th>Ref.</th><th>Author/Year</th><th>Second Evaluation Commentary</th><th>Action</th></tr>
<tr><td>61</td><td>Peek, 2016</td><td>Tc-alone vs Blue-alone vs Tc/Blue for breast SLNB. N=160 patients. “No anaphylactic reactions were reported and blue skin staining was reported in six (3.8%) patients.”
Tc: IR = 156/160; NN = 316/160.
Blue: IR = 148/160; NN = 271/160.
Tc/Blue: IR = 158/160; NN = 324/160.</td><td>Meta-analysis: IR, NN.</td></tr>
<tr><td>62</td><td>Teshome, 2016</td><td>Magtrace vs Tc/Blue breast SLNB – meta-analysis of 5 studies, all of which are new to this review. No mention of complications. Evaluator-pooled data:
<table>
<tr><th></th><th>Pts</th><th>Mag - IR</th><th>Tc/Blue - IR</th><th>Mag - NN</th><th>Tc/Blue - NN</th></tr>
<tr><td>Douek 2014</td><td>160</td><td>151</td><td>152</td><td>323</td><td>297</td></tr>
<tr><td>Thill 2014</td><td>150</td><td>147</td><td>146</td><td>283</td><td>267</td></tr>
<tr><td>Rubio 2015</td><td>120</td><td>116</td><td>113</td><td>264</td><td>230</td></tr>
<tr><td>Pinero-Madrona 2015</td><td>181</td><td>177</td><td>178</td><td>292</td><td>277</td></tr>
<tr><td>Ghilli 2015</td><td>193</td><td>189</td><td>191</td><td>364</td><td>360</td></tr>
<tr><td></td><td>804</td><td>780</td><td>780</td><td>1526</td><td>1431</td></tr>
</table></td><td>Meta-analysis: IR, NN.</td></tr>
<tr><td>63</td><td>Ahmed, 2015</td><td>Magtrace vs Tc/Blue breast SLNB. N=32 patients, N=33 procedures. No complications mentioned.
Mag: IR = 28/33; NN = 52/33.
Mag/Blue: IR = 32/33; NN = 60/33.
Tc/Blue: IR = 32/33; NN = 62/33.</td><td>Meta-analysis: IR, NN.</td></tr>
<tr><td>64</td><td>Pouw, 2015</td><td>Magtrace breast SLNB. N=11 patients. No mention of complications.
Mag: IR = 10/11; NN = 21/11.</td><td>Meta-analysis: IR, NN.</td></tr>
<tr><td>65</td><td>Jung, 2014</td><td>ICG+Tc+Blue vs Tc-alone SLNB breast cancer, N=43 patients respectively.
Intra-op SLNB Procedure Time measured, and reported as mean ± one standard deviation: 17.6 ± 7.1 min for ICG/Tc/Blue; 15.0 ± 7.6 min for Tc.
PT = 757/43 ICG/Tc/Blue; 645/43 Tc.</td><td>Meta-analysis: PT.</td></tr>
<tr><td>66</td><td>Cigna, 2012</td><td>Although focused on Tc/Blue SLND for melanoma, the authors refer to reported complications (infection, lymphadaema, & haematoma/seroma) in both melanoma & breast cancer, as follows:
<table>
<tr><th>Breast Cancer</th><th>Pts</th><th>Tc/Blue - CR</th></tr>
<tr><td>Schrenk 2000</td><td>35</td><td>0</td></tr>
<tr><td>Swenson 2002</td><td>169</td><td>17</td></tr>
<tr><td>Haid 2002</td><td>66</td><td>7</td></tr>
<tr><td>Blanchard 2003</td><td>683</td><td>109</td></tr>
<tr><td></td><td>953</td><td>133</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><th>Melanoma</th><th>Pts</th><th>Tc/Blue - CR</th></tr>
<tr><td>Wrightson 2003</td><td>2120</td><td>19</td></tr>
<tr><td>Wasserberg 2004</td><td>250</td><td>25</td></tr>
<tr><td></td><td>2370</td><td>44</td></tr>
</table></td><td>Meta-analysis: CR.</td></tr>
</table>

Ref.	Author/Year	Second Evaluation Commentary	Action
Tertiary Sources: Dermatological Staining			
44	Rubio, 2020	Subareolar Magtrace in N=135 patients, 3 groups each of 45 patients receiving undiluted (a) 1.0 mL, (b) 1.5 mL, and (c) 2.0 mL respectively. (Note that the Magtrace IFU advises that 2 mL of the tracer should be diluted with 3 mL saline before use.) Staining complication rate (SCR: the probability that a patient will present with post-operative dermatological staining) determined both by patient self-reporting & surgeon review, the latter at 6 months follow-up. Surgeon-determined SCR at 6 months: (a) = 25/45; (b) = 37/45; (c) = 35/45. Overall SCR = 97/135. Patient questionnaire at postoperative & 6 months timepoints: in response to the question whether skin staining was a problem for them, 4/114 = 3.5% of respondents reported that it was "an important problem"; the remainder reporting either that it was either "not a problem" (81/114 = 71.1%), or "a problem but I do not worry (21/114 = 18.4%), or "a problem but not important" (8/114 = 7.0%).	Meta-analysis: SCR. Review: PRO.
46	Vural, 2020	Periareolar Magtrace, 2 mL diluted with 3 mL saline, N=104 patients. Surgeon reported SCR = 22/104 at postoperative consultation.	Meta-analysis: SCR.
67	Lorek, 2019	Subareolar Magtrace, 2 mL diluted with 3 mL saline, N=303 patients. SCR determined by surgeons at 3-monthly follow-up meetings up to 2 years post-op. SCR = 47/303 at 3 months, falling quasi-linearly to 11/303 at 24 months. *"Lymphedema of minimal severity was observed in 9 patients (7.5%), which include 2 patients (1%) after WLE with SLNB and 7 patients (6.5%) after mastectomy with SLNB." As such,* CR = 9/303.	Meta-analysis: SCR, CR.
61	Peek, 2016	Periareolar Patent Blue dye, N=160 patients. Surgeon reported SCR = 6/160 at postoperative consultation.	Meta-analysis: SCR.
69	Fattahi, 2014	Study with (a) N=147 Tc & Methylene Blue, and (b) N=145 Tc & Patent Blue. Postoperative SCR: (a) 22/156; and (b) 37/156. Overall SCR = 59/312.	Meta-analysis: SCR.
70	Gumus, 2013	Periareolar Patent Blue dye, N=236 patients. SCR determined by surgeons at (a) 1 year, (b) 2 years, and (3) > 3 years post-op. Most patients attended one review session only; 41 attended twice. Surgeon reported SCR: (a) = 42/115; (b) = 25/106; (c) = 5/58.	Meta-analysis: SCR.
71	Ponzone, 2009	Subdermal Patent Blue dye, injected "*in the cranial third of the inner aspect of the arm*", N=49 patients. Authors note that: "*After a few occurrences, the subdermis was chosen as site of injection, because it is associated with less persistent skin tattooing than the dermis but allows good tracer migration*". Surgeon reported "moderate" SCR = 47/49 at postoperative consultation; falling to 19/49 at 1 month; 16/49 at 4 months; and 10/49 at >6 months.	Meta-analysis: SCR.
72	Govaert, 2005	Patent Blue dye, "*injected intradermally into the peri-areolar region of the tumour quadrant*", in N=33 patients. Study designed to investigate the duration of post-operative dermatological staining with 3-monthly telephone interviews. SCR = 32/33 postoperative; falling to 23/33 at 3 months; 21/33 at 6 months; 14/32 at 9 months; and 13/32 at 12 months.	Meta-analysis: SCR.

Ref.	Author/Year	Second Evaluation Commentary	Action
57	Karakatsanis, 2017	Rather complex study design with (a) N=155 Tc & Blue, (b) N=102 Magtrace (2 mL diluted with 3 mL saline) only, and (c) N=105 Magtrace (2 mL diluted with 3 mL saline) & Blue; and variations in both Magtrace injection site (periareolar versus peritumoural) & Magtrace injection timing (2-27 days preoperative versus perioperative). SCR recorded by surgeon follow-up for N=183 of the Magtrace-injected patients, albeit with no distinction made between those that received Magtrace & Blue versus Magtrace only. (SCR was not recorded for the Tc/Blue study arm.) SCR = 73/183 at 3 months; 66/183 at 15 months. Authors note that: "*All 66 patients with discoloration remaining after more than 10 months responded to the questionnaire at both time points [10-11 months & 12-14 months post-surgery]. Only two patients in this subgroup (3%) complained that they were affected by the stain. Views regarding skin staining and cosmesis were mixed. The majority of patients considered staining a minor problem, if an issue at all (60% at the first assessment and 61% at the second). No substantial change in views was noted between the two time points.*". Re cost: "*Logistics were simplified in the SPIO arm, as the preoperative visit to the department of nuclear medicine could be omitted. As far as the tracer and injection expenses per procedure were concerned, the mean was €225 for the SPIO arm versus €252 for the 99m Tc arm, with SPIO being slightly cheaper by approximately €27.* *Compared with perioperative administration, preoperative injection of SPIO saved an additional minimum of 20 min in the operating theatre, which is the time needed for SPIO to migrate to the axilla. With a mean cost of €17·6 per min for the operating theatre in the Uppsala Örebro Region, €352·7 was saved per procedure*.".	Meta-analysis: SCR. Review: PRO, Cost.
68	Karakatsanis, 2016	Study with N=206 patients, all receiving subareaolar Magtrace (2 mL diluted with 3 mL saline) and Periareolar Tc & Blue dye. SCR = 73/206 at 0-3 months; 43/206 at 12 months; and 18/206 at 15 months.	Meta-analysis: SCR.
Tertiary Sources: Sentimag versus Gamma Detection			
73	Pinero-Madrona, 2020	Melanoma SLND, N=60 patients, radiotracer (Europrobe 3) vs Sentimag concordance study. The authors note concordance: "*126 nodes were detected with the gamma probe, with an average of 2.2 ± 1.4 nodes/basin, and 124 were detected with Sentimag, with an average of 2.2 ± 1.4 nodes/basin*". Total N=133 nodes retrieved. Node Retrieval Rate (NRR) = 124/133 Sentimag; 126/133 Gamma. Nodal Concordance Rate (NCR) = 118/126 Gamma-detected nodes also detected by Sentimag.	Meta-analysis: NRR, NCR.

Ref.	Author/Year	Second Evaluation Commentary	Action
47	Alvarado, 2019	Breast cancer SLND, N=146 patients, N=369 nodes retrieved; radiotracer vs Sentimag concordance study. The study design was as follows: "*Once the incision was made, SLNs were first identified using the Sentimag, either by the magnetic signal detected by the probe or via visual confirmation of the black/brown color of the tracer in the node. Non-metallic retractors were utilized in the axilla while the probe was in use. Magnetic counts were taken for each sentinel node prior to excision (in vivo) and again following removal of the node (ex vivo). A radioisotope count was also taken using the gamma probe both in vivo and ex vivo. All nodes identified by the Sentimag, the gamma probe, or by visual confirmation of blue dye or black staining were excised, and ex vivo counts were recorded for both detection systems. The SLNB was considered complete when the residual count in the axilla was < 10% of the highest ex vivo reading for both the radioisotope and magnetic tracer.*" The per-node concordance was reported as: "*Of the 146 patients with analyzable nodes, the dual tracer identified 144 (98.6%, 95% CI 96.7–100.0%), and the magnetic tracer identified 145 (99.3%, 95% CI 98.0–100.0%). At least one node was detected by both methods in 144 patients (98.6%).*" (Dual method here means radiotracer plus blue dye.) The authors conclude that: "*In this study, we show the Magtrace tracer to be non-inferior to radioisotope combined with blue dye for sentinel node detection in early-stage breast cancer in a combination of academic and community centers. The magnetic technique identified all patients in whom a malignant node was found when using the standard technique, and identified all the malignant nodes that the standard technique identified.*" NRR = 348/369 Sentimag; 345/369 Gamma. NCR = 326/345.	Meta-analysis: NRR, NCR.
56	Ghilli, 2017	Breast cancer SLND, N=193 patients, N=380 nodes retrieved; radiotracer vs Sentimag concordance study. Authors report on detection rates both per patient & per node. NRR = 364/380 Sentimag; 360/380 Gamma. NCR = 344/360.	Meta-analysis: NRR, NCR.
74	Anninga, 2016	Melanoma SLND, N=129 patients, N=166 procedures performed, N=257 nodes retrieved; radiotracer (Europrobe or GammaFinder) vs Sentimag concordance study. Similar study design to Alvarado 2019. Report concordance rates of 94.6% between dual method & Sentimag; and of 92.2% between radiotracer-only & Sentimag. NRR = 241/257 Sentimag; 230/257 Gamma. Per-node NCR not reported.	Meta-analysis: NRR, NCR.
59	Houpeau, 2016	Breast cancer SLND, N=108 patients, N=214 nodes retrieved; radiotracer vs Sentimag concordance study. Similar study design to Alvarado 2019. Report concordance rates between dual method & Sentimag of 99.0% (CI: 94.7% to 100%) per patient and 974% (CI: 94.1% to 99.2%) per node. NRR = 208/214 Sentimag; 193/214 Gamma. NCR = 188/193.	Meta-analysis: NRR, NCR.

Ref.	Author/Year	Second Evaluation Commentary	Action
68	Karakatsanis, 2016	Breast cancer SLND, N=206 patients, N=403 nodes retrieved; radiotracer vs Sentimag concordance study. Also a literature-based meta-analysis of earlier study results. The authors note: "*The distortion of the ferromagnetic signal by metallic instruments has also been addressed by the removal of metallic instruments when the probe is to be used, or by the use of plastic instrument*." Concordance rate reported as 98%, with 95% CI from 94.6% to 99.4%. NRR = 376/403 Sentimag; 368/403 Gamma. NCR = 353/368.	Meta-analysis: NRR, NCR.
75	Pinero-Madrona, 2015	Breast cancer SLND, N=181 patients, N=321 nodes retrieved; radiotracer vs Sentimag concordance study. Similar study design to Alvarado 2019. Report concordance rates between dual method & Sentimag of > 97% for both transcutaneous & intraoperative detection rates, and 99.4% for ex vivo detection rates. NRR = 292/321 Sentimag; 277/321 Gamma. NCR = 260/277.	Meta-analysis: NRR, NCR.
76	Rubio, 2015	Breast cancer SLND, N=118 patients, N=287 nodes retrieved; radiotracer (Europrobe) vs Sentimag concordance study. Concordance rate 98.2% NRR = 264/287 Sentimag; 230/287 Gamma. NCR not reported.	Meta-analysis: NRR, NCR.
77	Douek, 2014	Breast cancer SLND, N=160 patients, N=404 nodes retrieved; radiotracer vs Sentimag concordance study. Discordance rate 6.9%. NRR = 323/404 Sentimag; 297/404 Gamma. NCR = 268/297.	Meta-analysis: NRR, NCR.
78	Thill, 2014	Breast cancer SLND, N=150 patients, N=291 nodes retrieved; radiotracer vs Sentimag concordance study. Concordance rate 97.3% (146/150) per patient. NRR = 283/291 Sentimag; 267/291 Gamma. NCR = 263/267. Authors report that *"No complications in terms of allergic reactions, or irritations at the injection site were observed"*. CR = 0/150 for both Magtrace & Tc/Blue.	Meta-analysis: NRR, NCR, CR.

10. Statistical Meta-Analysis of Relevant Study Outcomes

10.1. Methods Applied

Statistical analysis was performed using the "meta" package in "R", version 3.5.3. Pooling was via the inverse variance method. Proportions, incidence rates, and risk differences were evaluated using the "metaprop", "metarate", and "metabin" commands respectively. Confidence levels were assigned using the Random Effects Model.

Heterogeneity among different studies was assessed using the I^2 metric, and following the Cochrane Handbook guidance for interpretation, as follows:

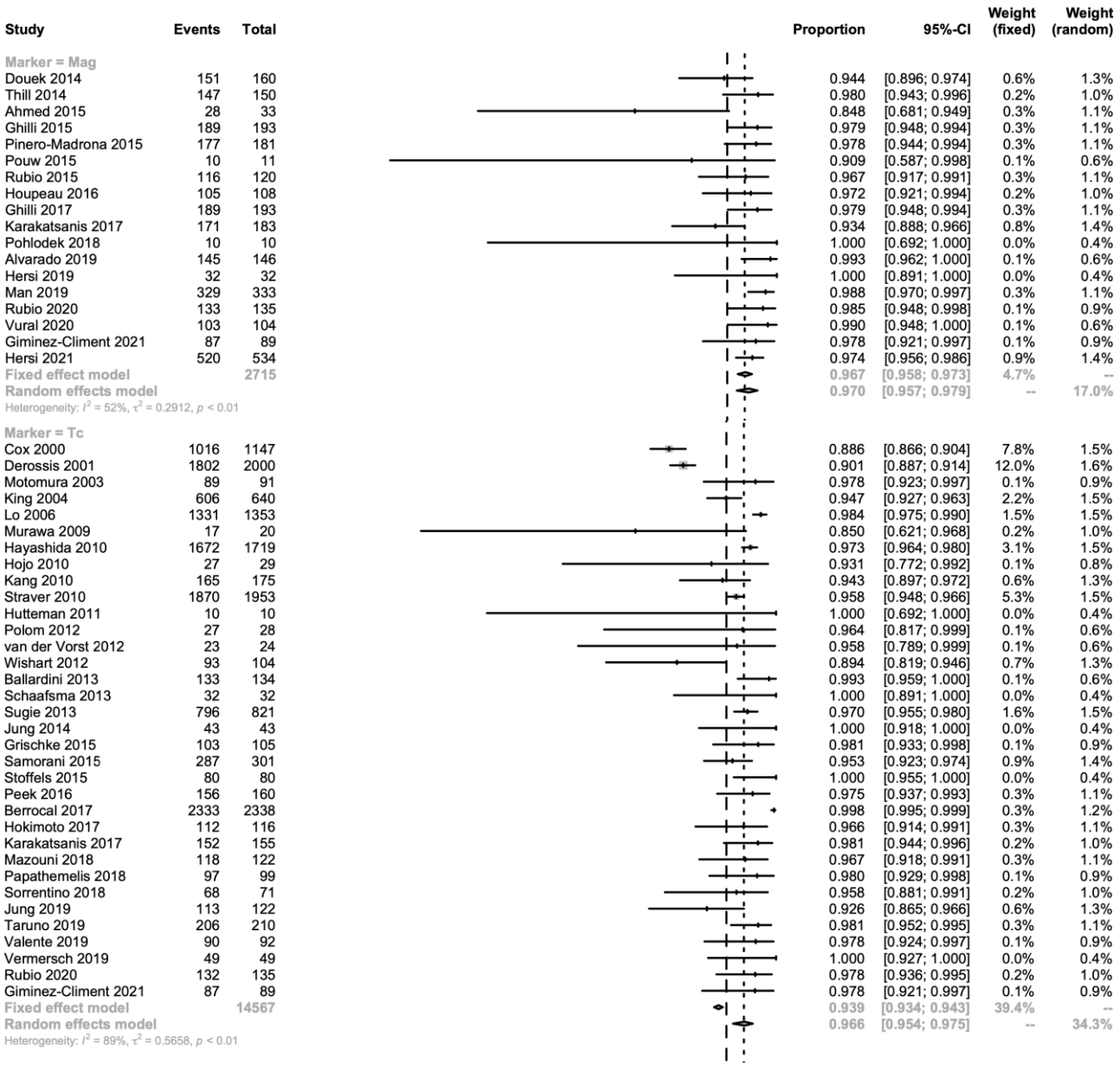
- I^2 in the range 0% to 40%: heterogeneity might not be important;
- I^2 in the range 30% to 60%: may represent moderate heterogeneity;

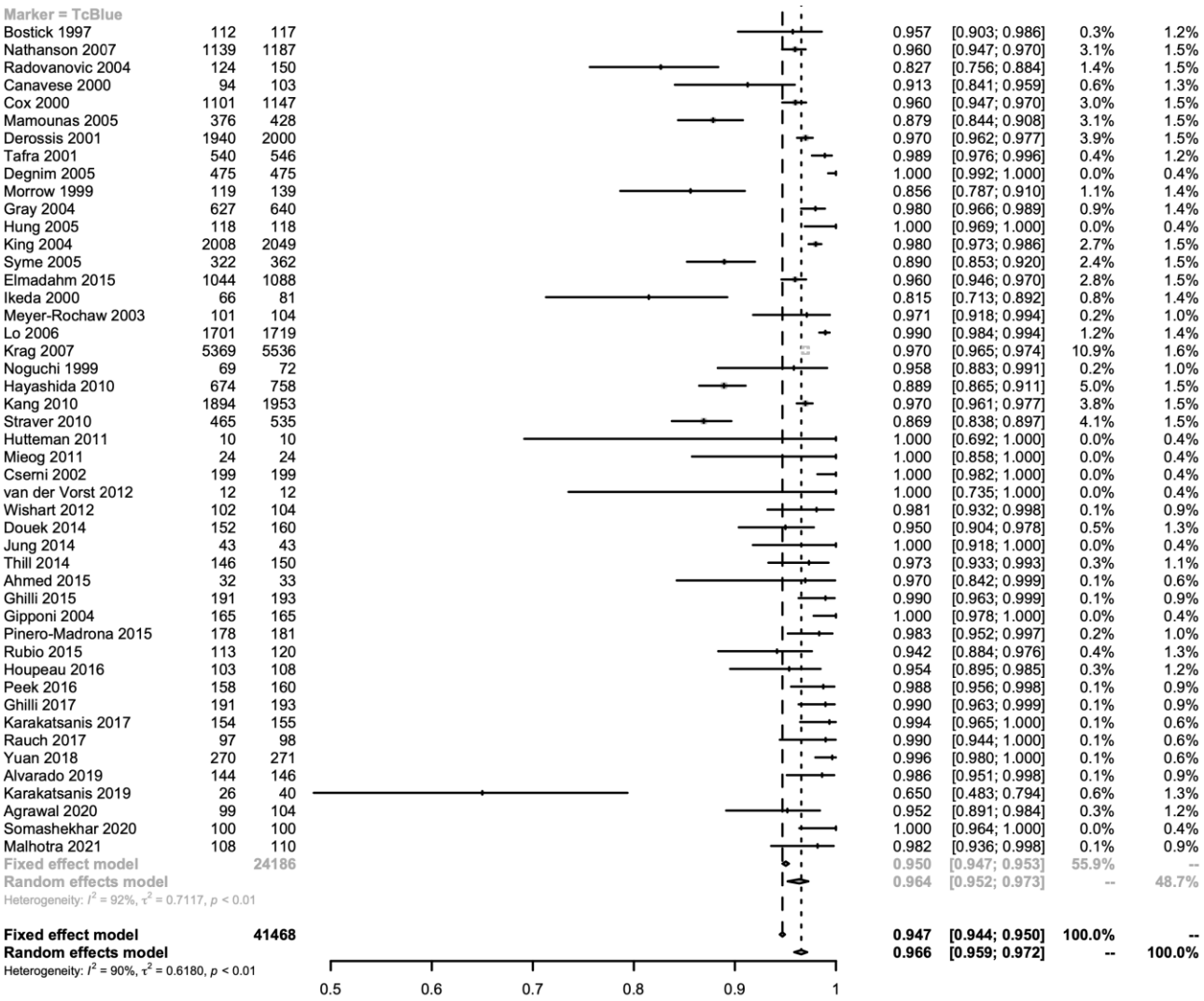
- I^2 in the range 50% to 90%: may represent substantial heterogeneity;
- I^2 in the range 75% to 100%: considerable heterogeneity.

10.2. Results

10.2.1. Identification Rate (IR)

Identification Rates for Tc ± Blue and/or for Magtrace were reported in **74** studies, as shown in the Forest plot below.



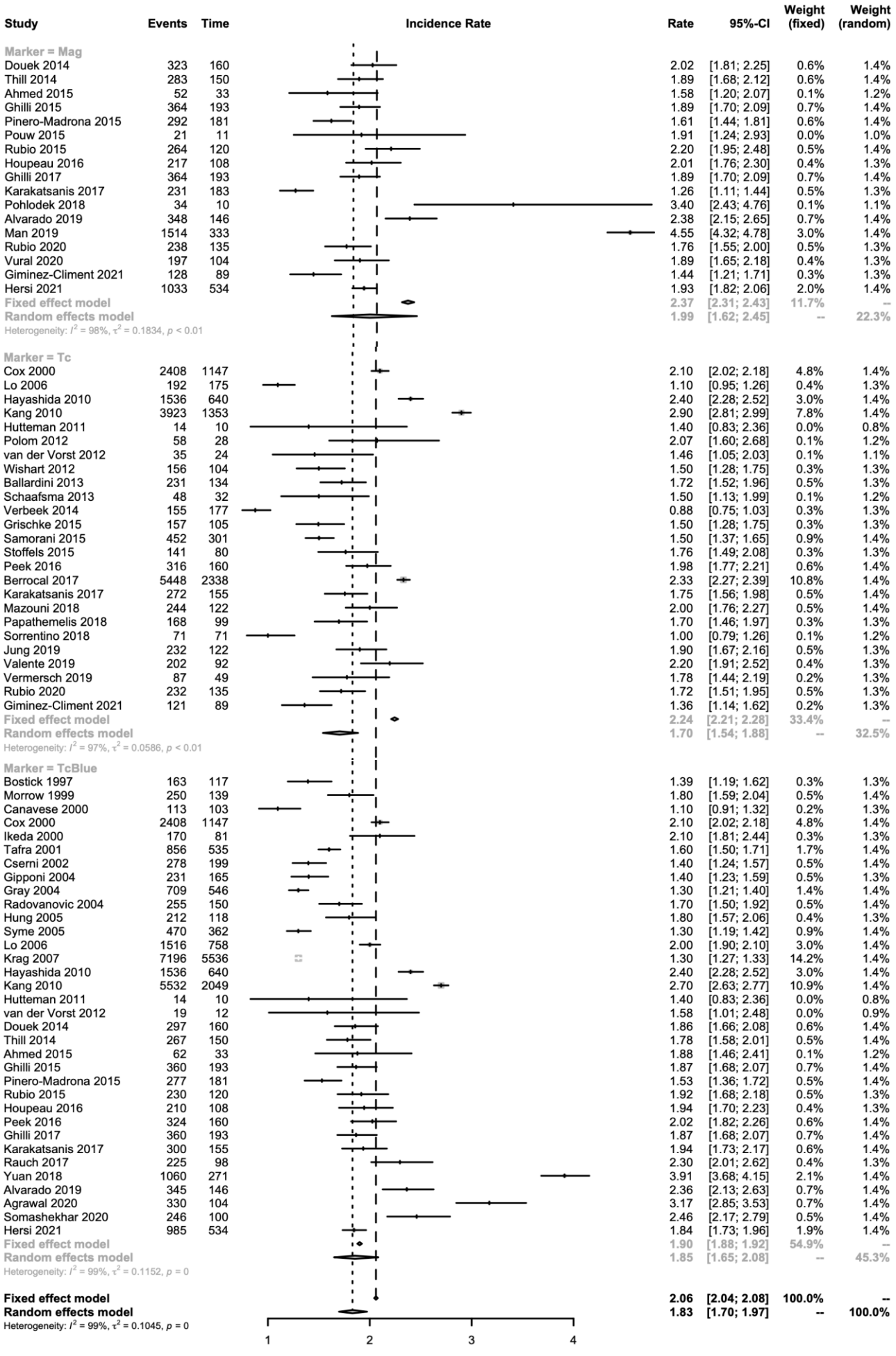


Pooled heterogeneity was calculated as I^2 = 90%, indicating substantial or considerable heterogeneity. The pooled proportions for the reported **Identification Rate** metrics were:

Device	Number of studies	Number of patients	Pooled proportion	95% Confidence Interval
Magtrace	18	2715	97.0%	95.7 to 97.9%
Tc	34	14567	96.6%	95.4 to 97.5%
Tc/Blue	47	24186	96.4%	95.2 to 97.3%

10.2.2. Number of Nodes (NN)

Number of Nodes for Tc ± Blue and/or for Magtrace were reported in **55** studies, as shown in the Forest plot below.

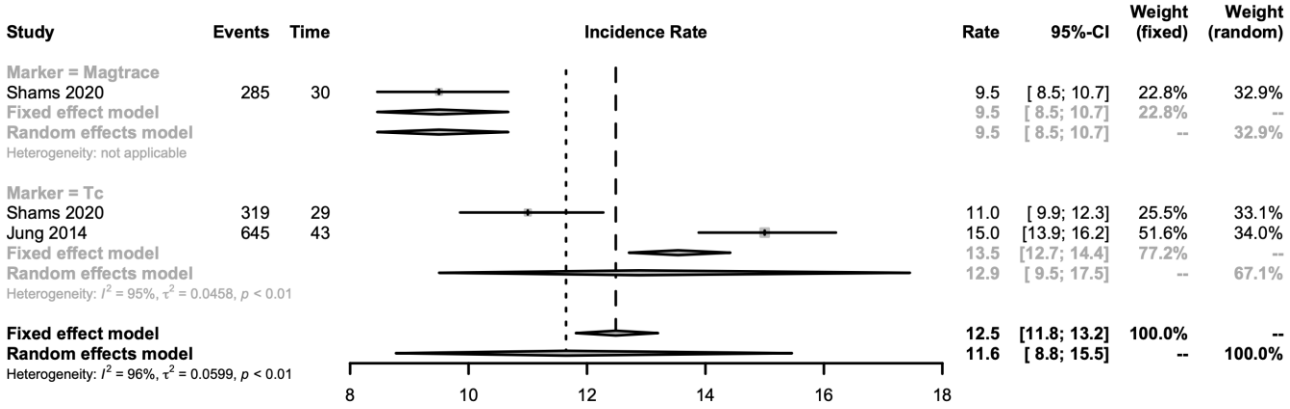

Study
Events
Time
Incidence Rate
Rate
95%-CI
Weight (fixed)
Weight (random)
Marker = Mag
Douek 2014 323 160 2.02 [1.81; 2.25] 0.6% 1.4%
Thill 2014 283 150 1.89 [1.68; 2.12] 0.6% 1.4%
Ahmed 2015 52 33 1.58 [1.20; 2.07] 0.1% 1.2%
Ghilli 2015 364 193 1.89 [1.70; 2.09] 0.7% 1.4%
Pinero-Madrona 2015 292 181 1.61 [1.44; 1.81] 0.6% 1.4%
Pouw 2015 21 11 1.91 [1.24; 2.93] 0.0% 1.0%
Rubio 2015 264 120 2.20 [1.95; 2.48] 0.5% 1.4%
Houpeau 2016 217 108 2.01 [1.76; 2.30] 0.4% 1.3%
Ghilli 2017 364 193 1.89 [1.70; 2.09] 0.7% 1.4%
Karakatsanis 2017 231 183 1.26 [1.11; 1.44] 0.5% 1.3%
Pohlodek 2018 34 10 3.40 [2.43; 4.76] 0.1% 1.1%
Alvarado 2019 348 146 2.38 [2.15; 2.65] 0.7% 1.4%
Man 2019 1514 333 4.55 [4.32; 4.78] 3.0% 1.4%
Rubio 2020 238 135 1.76 [1.55; 2.00] 0.5% 1.3%
Vural 2020 197 104 1.89 [1.65; 2.18] 0.4% 1.3%
Giminez-Climent 2021 128 89 1.44 [1.21; 1.71] 0.3% 1.3%
Hersi 2021 1033 534 1.93 [1.82; 2.06] 2.0% 1.4%
Fixed effect model 2.37 [2.31; 2.43] 11.7% --
Random effects model 1.99 [1.62; 2.45] -- 22.3%
Heterogeneity: I^2 = 98%, τ^2 = 0.1834, p < 0.01
Marker = Tc
Cox 2000 2408 1147 2.10 [2.02; 2.18] 4.8% 1.4%
Lo 2006 192 175 1.10 [0.95; 1.26] 0.4% 1.3%
Hayashida 2010 1536 640 2.40 [2.28; 2.52] 3.0% 1.4%
Kang 2010 3923 1353 2.90 [2.81; 2.99] 7.8% 1.4%
Hutteman 2011 14 10 1.40 [0.83; 2.36] 0.0% 0.8%
Polom 2012 58 28 2.07 [1.60; 2.68] 0.1% 1.2%
van der Vorst 2012 35 24 1.46 [1.05; 2.03] 0.1% 1.1%
Wishart 2012 156 104 1.50 [1.28; 1.75] 0.3% 1.3%
Ballardini 2013 231 134 1.72 [1.52; 1.96] 0.5% 1.3%
Schaafsma 2013 48 32 1.50 [1.13; 1.99] 0.1% 1.2%
Verbeek 2014 155 177 0.88 [0.75; 1.03] 0.3% 1.3%
Grischke 2015 157 105 1.50 [1.28; 1.75] 0.3% 1.3%
Samorani 2015 452 301 1.50 [1.37; 1.65] 0.9% 1.4%
Stoffels 2015 141 80 1.76 [1.49; 2.08] 0.3% 1.3%
Peek 2016 316 160 1.98 [1.77; 2.21] 0.6% 1.4%
Berrocal 2017 5448 2338 2.33 [2.27; 2.39] 10.8% 1.4%
Karakatsanis 2017 272 155 1.75 [1.56; 1.98] 0.5% 1.4%
Mazouni 2018 244 122 2.00 [1.76; 2.27] 0.5% 1.4%
Papathemelis 2018 168 99 1.70 [1.46; 1.97] 0.3% 1.3%
Sorrentino 2018 71 71 1.00 [0.79; 1.26] 0.1% 1.2%
Jung 2019 232 122 1.90 [1.67; 2.16] 0.5% 1.3%
Valente 2019 202 92 2.20 [1.91; 2.52] 0.4% 1.3%
Vermersch 2019 87 49 1.78 [1.44; 2.19] 0.2% 1.3%
Rubio 2020 232 135 1.72 [1.51; 1.95] 0.5% 1.3%
Giminez-Climent 2021 121 89 1.36 [1.14; 1.62] 0.2% 1.3%
Fixed effect model 2.24 [2.21; 2.28] 33.4% --
Random effects model 1.70 [1.54; 1.88] -- 32.5%
Heterogeneity: I^2 = 97%, τ^2 = 0.0586, p < 0.01
Marker = TcBlue
Bostick 1997 163 117 1.39 [1.19; 1.62] 0.3% 1.3%
Morrow 1999 250 139 1.80 [1.59; 2.04] 0.5% 1.4%
Canavese 2000 113 103 1.10 [0.91; 1.32] 0.2% 1.3%
Cox 2000 2408 1147 2.10 [2.02; 2.18] 4.8% 1.4%
Ikeda 2000 170 81 2.10 [1.81; 2.44] 0.3% 1.3%
Tafra 2001 856 535 1.60 [1.50; 1.71] 1.7% 1.4%
Cserni 2002 278 199 1.40 [1.24; 1.57] 0.5% 1.4%
Gipponi 2004 231 165 1.40 [1.23; 1.59] 0.5% 1.3%
Gray 2004 709 546 1.30 [1.21; 1.40] 1.4% 1.4%
Radovanovic 2004 255 150 1.70 [1.50; 1.92] 0.5% 1.4%
Hung 2005 212 118 1.80 [1.57; 2.06] 0.4% 1.3%
Syme 2005 470 362 1.30 [1.19; 1.42] 0.9% 1.4%
Lo 2006 1516 758 2.00 [1.90; 2.10] 3.0% 1.4%
Krag 2007 7196 5536 1.30 [1.27; 1.33] 14.2% 1.4%
Hayashida 2010 1536 640 2.40 [2.28; 2.52] 3.0% 1.4%
Kang 2010 5532 2049 2.70 [2.63; 2.77] 10.9% 1.4%
Hutteman 2011 14 10 1.40 [0.83; 2.36] 0.0% 0.8%
van der Vorst 2012 19 12 1.58 [1.01; 2.48] 0.0% 0.9%
Douek 2014 297 160 1.86 [1.66; 2.08] 0.6% 1.4%
Thill 2014 267 150 1.78 [1.58; 2.01] 0.5% 1.4%
Ahmed 2015 62 33 1.88 [1.46; 2.41] 0.1% 1.2%
Ghilli 2015 360 193 1.87 [1.68; 2.07] 0.7% 1.4%
Pinero-Madrona 2015 277 181 1.53 [1.36; 1.72] 0.5% 1.4%
Rubio 2015 230 120 1.92 [1.68; 2.18] 0.5% 1.3%
Houpeau 2016 210 108 1.94 [1.70; 2.23] 0.4% 1.3%
Peek 2016 324 160 2.02 [1.82; 2.26] 0.6% 1.4%
Ghilli 2017 360 193 1.87 [1.68; 2.07] 0.7% 1.4%
Karakatsanis 2017 300 155 1.94 [1.73; 2.17] 0.6% 1.4%
Rauch 2017 225 98 2.30 [2.01; 2.62] 0.4% 1.3%
Yuan 2018 1060 271 3.91 [3.68; 4.15] 2.1% 1.4%
Alvarado 2019 345 146 2.36 [2.13; 2.63] 0.7% 1.4%
Agrawal 2020 330 104 3.17 [2.85; 3.53] 0.7% 1.4%
Somashekhar 2020 246 100 2.46 [2.17; 2.79] 0.5% 1.4%
Hersi 2021 985 534 1.84 [1.73; 1.96] 1.9% 1.4%
Fixed effect model 1.90 [1.88; 1.92] 54.9% --
Random effects model 1.85 [1.65; 2.08] -- 45.3%
Heterogeneity: I^2 = 99%, τ^2 = 0.1152, p = 0
Fixed effect model 2.06 [2.04; 2.08] 100.0% --
Random effects model 1.83 [1.70; 1.97] -- 100.0%
Heterogeneity: I^2 = 99%, τ^2 = 0.1045, p = 0
1
2
3
4

Pooled heterogeneity was calculated as I^2 = 99%, indicating considerable heterogeneity. The pooled incidence rates for the reported **Number of Nodes** metrics were:

Device	Number of studies	Number of patients	Pooled incidence rate	95% Confidence Interval
Magtrace	17	2683	1.99	1.62 to 2.45
Tc	25	7742	1.70	1.54 to 1.88
Tc/Blue	34	15373	1.85	1.65 to 2.08

10.2.3. Procedure Time (PT)

SLND Procedure Times for Tc and/or for Magtrace were reported in **2** studies, as shown in the Forest plot below.

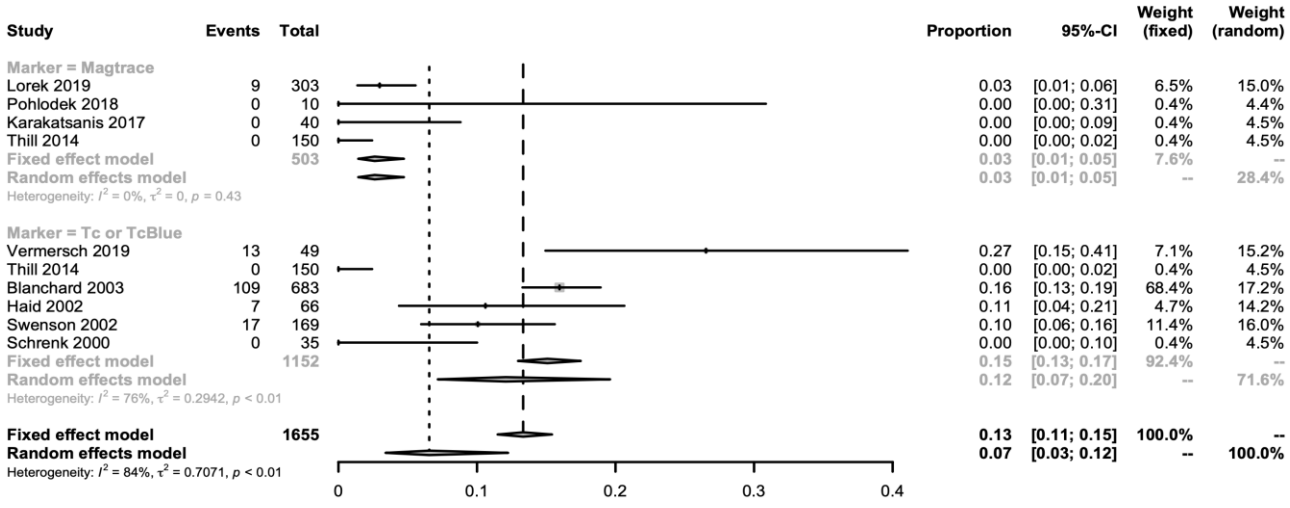


Pooled heterogeneity was calculated as I^2 = 96%, indicating considerable heterogeneity. The pooled incidence rates for the reported **Procedure Time** metrics were:

Device	Number of studies	Number of patients	Pooled incidence rate	95% Confidence Interval
Magtrace	1	30	9.5 minutes	8.5 to 10.7 minutes
Tc	2	72	12.9 minutes	9.5 to 17.5 minutes

10.2.4. Complications Rate (CR)

Complications Rates for Tc ± Blue and/or for Magtrace were reported in **10** studies, as shown in the Forest plot below.

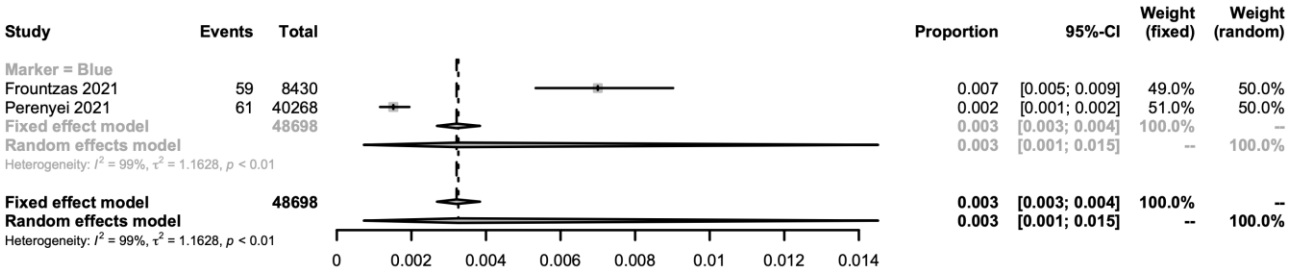


Pooled heterogeneity was calculated as I^2 = 84%, indicating substantial or considerable heterogeneity. The pooled proportions for the reported **Complications Rate** metrics were:

Device	Number of studies	Number of patients	Pooled proportion	95% Confidence Interval
Magtrace	4	503	3%	1% to 5%
Tc/Blue	6	1152	12%	7% to 20%

10.2.5. Anaphylaxis Complications Rate (ACR)

Anaphylaxis Complications Rates for Blue dye were reported in **2** meta-studies, pooling data from ca. **90** reports/studies, as shown in the Forest plot below.

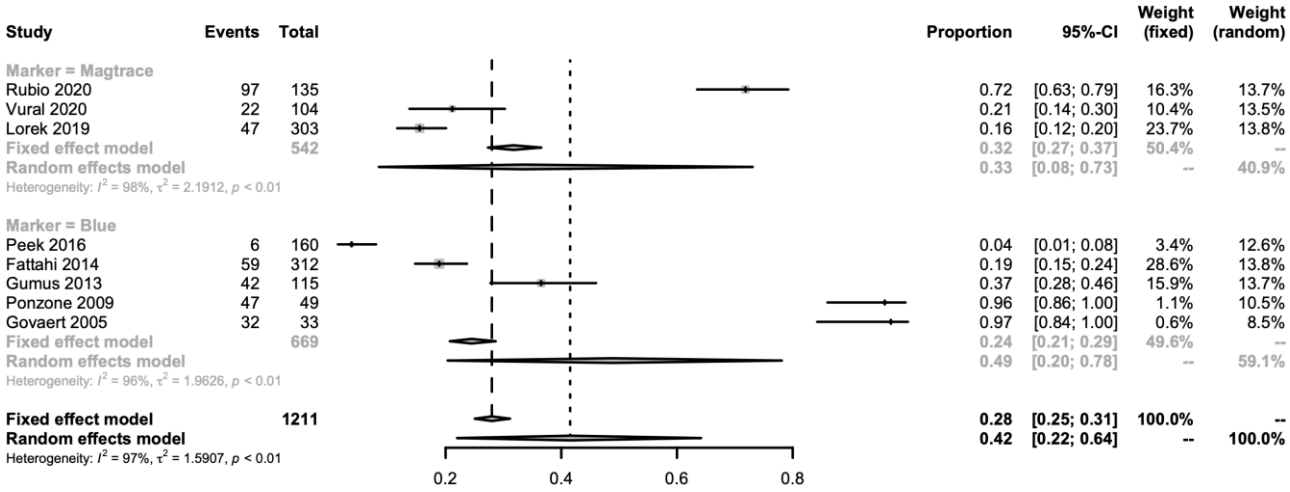


Pooled heterogeneity was calculated as I^2 = 99%, indicating considerable heterogeneity. The pooled proportions for the reported **Anaphylaxis Complications Rate** metrics were:

Device	Number of studies	Number of patients	Pooled proportion	95% Confidence Interval
Blue	90 (est.)	48698	0.3%	0.1% to 1.5%

10.2.6. Staining Complications Rates (SCR)

Staining Complications Rates for Blue dye and/or for Magtrace were reported in **8** studies, as shown in the Forest plot below.

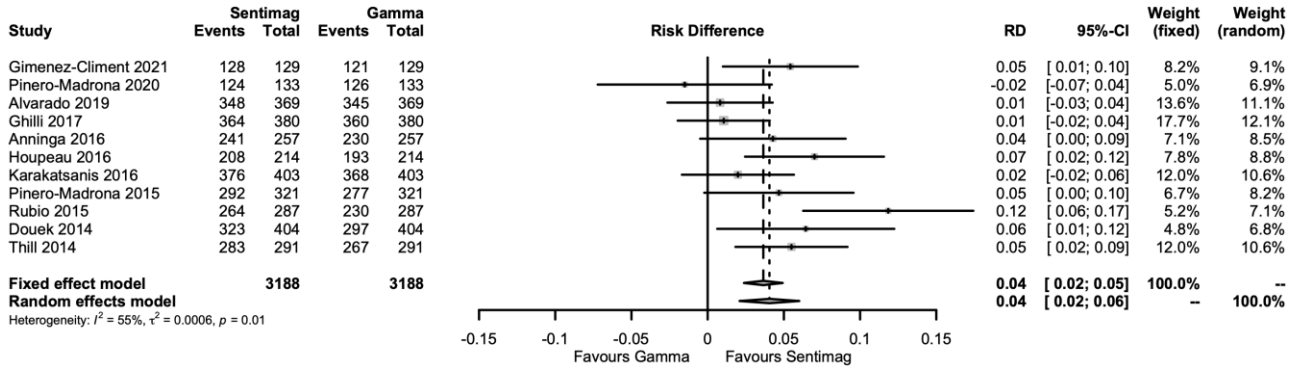


Pooled heterogeneity was calculated as I^2 = 97%, indicating considerable heterogeneity. The pooled proportions for the reported **Staining Complications Rate** metrics were:

Device	Number of studies	Number of patients	Pooled proportion	95% Confidence Interval
Magtrace	3	542	33%	8 to 73%
Blue	5	669	49%	20 to 64%

10.2.7. Sentimag-versus-Gamma Nodal Retrieval Rate (NRR)

Sentimag-versus-Gamma Nodal Retrieval Rates for Tc/Gamma and Magtrace/Sentimag were reported in **11** studies. The risk differences calculated for each study are shown in the Forest plot below.

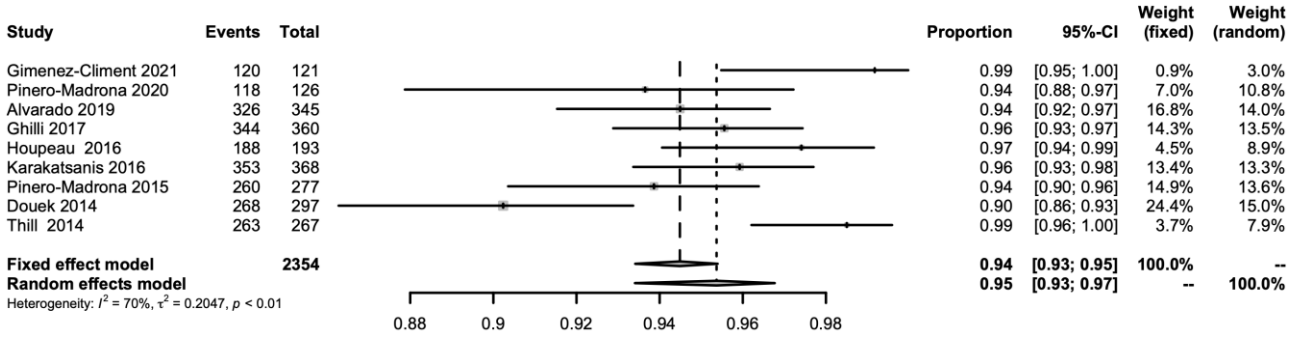


Pooled heterogeneity was calculated as I^2 = 55%, indicating moderate or substantial heterogeneity. The pooled risk difference for the reported **Sentimag-versus-Gamma Nodal Retrieval Rate** metrics were:

Device	Number of studies	Number of events	Pooled risk difference	95% Confidence Interval
Favours Sentimag	11	3188	+4%	+2 to +6%

10.2.8. Sentimag-to-Gamma Nodal Concordance Rate (NCR)

Sentimag-to-Gamma Nodal Concordance Rates for Tc/Gamma and Magtrace/Sentimag were reported in **9** studies, as shown in the Forest plot below.



Pooled heterogeneity was calculated as I^2 = 70%, indicating substantial heterogeneity. The pooled proportions for the reported **Sentimag-to-Gamma Nodal Concordance Rate** metrics were:

Device	Number of studies	Number of events	Pooled proportion	95% Confidence Interval
Sentimag-to-Gamma	9	2354	95%	93 to 97%

11. Qualitative Analysis of Relevant Study Outcomes

11.1. Methods Applied

Two of the study outcomes of interest in the current review – patient-reported outcome measures, and costs analyses – were not suitable for statistical meta-analysis, as they were found to not be presented with respect to standardised methods, nor to be related to standardised metrics, in the literature. As an alternative, therefore, a qualitative analysis of these two outcomes was performed, as reported below.

11.2. Results

11.2.1. Patient-Reported Outcomes

Patient-Reported Outcomes were reported in **8** studies.

On inspection, it was found that **4** of these reports compared patient-reported outcomes (PROs) between the surgical procedures of sentinel lymph node detection (SLND) and axillary lymph node dissection (ALND), as summarised below:

Study	PRO	Comment
Poulsen, 2021[12]	Lymphoedema	No difference in reported levels of post-op lymphoedema for SLND or for ALND.
Sackey, 2015[16]	Lymphoedema	Patient-perceived lymphoedema is not correlated to objective measures, but nevertheless affects the patient's quality of life.
Cooney, 2013[17]	Pain	Mild post-op pain reported with prevalence ranging from 13% to 51%. More common in ALND than in SLND.
Land, 2010[19]	Upper limb mobility	Symptoms significantly worse for ALND than for SLND, but, for both, the morbidity resolves by 12 months post-op.

The Sackey 2015 report is particularly interesting here, indicating as it does that a patient's perception of a clinical outcome may well be at odds with an objective assessment of that outcome (in this case lymphoedema), and that furthermore that may affect the patients quality of life.

The remaining **4** studies reported on SLND alone; with **2** on Tc -based SLND:

Study	PRO	Comment
Chandarana, 2020[14]	Upper limb mobility	Significant post-op deterioration in upper limb function that improves but has not fully recovered at 3 months post-op.
Radowsky, 2012[18]	Injection pain	Patient-rated pain on sub-areolar injection varies considerably, from 0 to 10 on a 10-point scale.

and **2** on Magtrace-based SLND:

Study	PRO	Comment
Rubio, 2020[44]	Cosmesis	At 6 months post-op, dermatological staining a concern for 4/135 = 3% of patients.
Karakatsanis, 2017[57]	Cosmesis	At 12 months post-op, dermatological staining a concern for 2/183 = 1% of patients.

Here, the Radowsky 2012 report is interesting, as a reminder of the degree to which pain is a variable, patient-specific clinical outcome, such that the same procedure (in this case sub-areolar injection) has elicit the full spectrum of responses from "nothing at all" to "excruciating".

Re upper limb mobility, the Chandarana 2020 and Land 2010 reports look to be consistent, in that the former reports at an earlier time post-op, when morbidity is still present, whereas the latter reports at 12 months post-op, by which time the morbidity is resolved.

However, of most relevance to the current review, the Rubio 2020 and Karaktsanis 2017 reports on patient-reported perceptions of dermatological staining after Magtrace-based SLND are notable, if only for the very low numbers of patients who are concerned about it, and for the trend towards full resolution by 12 months post-op. This is a direct and clear indication that the known complication of dermatological staining is both transient, and of no concern to most patients.

11.2.2. Cost Analyses

Cost Analyses were reported in **5** studies.

On inspection, it was found that **3** of these reports related to comparisons between the costs of sentinel lymph node detection (SLND) and of the more invasive surgical procedure of axillary lymph node dissection (ALND). All reported a cost reduction for SLND relative to ALND:

Study	Country	ALND	SLND	Comment
Mattar, 2021[23]	Italy	€1807	€1498	SLND saves 21% per patient.
Classe, 2012[30]	Sweden	€3331	€2947	SLND saves 12% per patient.
Verry, 2012[31]	Australia	$58380	$57490	SLND saves 2% per patient.

The costs reported in the Australian study were for a full 20-year course of treatment for a breast cancer patient, which may explain why the cost differential they report is relatively small compared to the Italian and Swedish reports, which were for the primary treatment only.

However, for the current review, the more pertinent question is the cost comparison between SLND undertaken with Tc/Blue and Gamma probes compared to SLND undertaken with Magtrace and Sentimag. In this respect, **2** reports were identified, both of which indicated cost reductions associated with the magnetic modality, as summarised below:

Study	Country	Tc-SLND	Mag-SLND	Comment*
Shams, 2021[40]	Germany	€360	€7.50 staff €260 materials	Mag-SLND saves 26% per injection.
Karakatsanis, 2017[57]	Sweden	€252	€225	Mag-SLND saves 11% per injection.

*These cost reductions relate to the tracer injection step only, and not to the complete treatment. To estimate the cost reduction over the entire SLND procedure, we might assume a cost per patient of order €1500, as reported by Mattar 2021, to arrive at a per-patient Mag-SLND cost saving relative to Tc-SLND of ca. 6% in Germany, and ca. 2% in Sweden.

12. Discussion

12.1. Commentary on the Review Process

As part of this focused review, a set of **1627** new primary sources were identified and reviewed, leading to the selection of **33** primary sources for full-text review.

In addition, a set of **45** tertiary sources, all of which had been the subject of full-text evaluation in the proprietary Magtrace and Sentimag reviews undertaken in May/June 2021, was included.

In total, therefore, **78** sources were used in the full-text evaluation phase of this review.

12.2. Definition of Clinical Outcome Measures

The focus of the review was to identify and compare literature reports on a series of clinical outcome measures listed in the NICE scope document “MT568 – Magtrace and Sentimag for Locating Sentinel Nodes for Breast Cancer” that was published in December 2021.

After due consideration by the Lead Evaluator, this set of NICE-defined outcome measures was related to a corresponding set of Endomag outcome metrics, as described in detail in Section 2, and summarised in the table below:

NICE	Endomag Metric
Sentinel lymph node (SLN) detection rate	The **Identification Rate (IR)**, meaning the per-patient proportion of surgical SLNB operations performed in which one or more sentinel lymph nodes are successfully identified and resected.
Mean number of SLNs retrieved per procedure	The **Number of Nodes (NN)**, meaning the per-patient mean number of sentinel nodes identified and resected during the SLNB surgical procedure. The denominator includes all patients in a study, even those from whom no nodes were retrieved.
Time taken for SLNB procedure	The **Procedure Time (PT)**, meaning the per-patient mean time taken to complete the SNLB procedure, i.e., from the first definite usage of the proximity detection probe (Gamma or Sentimag) to the removal of the last of the identified sentinel nodes.
Patient-reported outcome measures	**Patient-Reported Outcomes**, including survey or questionnaire based patient’s experiences regarding lymphoedema, upper limb mobility, pain, and cosmesis.
Device-related adverse events	The **Complications Rate (CR)**, meaning the per-patient proportion of surgical SLNB operations performed following which a significant clinical complication – such as infection, lymphoedema, haematoma/seroma, and urticaria – requiring adapted or additional medical treatment occurs, excluding anaphylaxis. Less severe, or more transient, or purely neurological clinical complications, including paraesthesia, restricted upper limb mobility, and pain, are also excluded.
	The **Anaphylaxis Complications Rate (ACR)**, meaning the per-patient proportion of surgical SLNB operations performed following which anaphylaxis occurs requiring medical treatment. This metric is associated specifically with the use of Blue dye.
	The **Staining Complications Rate (SCR)**, meaning the probability that a patient will present with post-operative dermatological staining following the SLNB procedure. This metric is associated specifically with the use of Magtrace and of Blue dye.
Cost analysis	**Cost Analyses**, including cost comparisons between different surgical procedures or elements thereof, or of entire breast cancer treatment pathways.
Comparator: Technetium-99m in conjunction with blue dye	The **Sentimag-versus-Gamma Nodal Retrieval Rate (NRR)**, meaning the per-node proportion of surgically retrieved nodes that are successfully identified by Sentimag / Magtrace compared to the corresponding (i.e., same study) per-node proportion of surgically retrieved nodes that are successfully identified by Gamma / radiotracer.
	The **Sentimag-to-Gamma Nodal Concordance Rate (NCR)**, meaning the per-node proportion of Gamma Probe / radiotracer detected nodes that are also detected (i.e., in the same study) by Sentimag / Magtrace.

12.3. Comparison of Clinical Outcome Measures

Wherever possible, statistical meta-analyses were performed using data gathered from the literature sources.

12.3.1. Per-Patient Metrics

Results for the per-patient metrics are described in detail in Section 10.2, and are summarised in the table below.

Per-Patient Metric	Magtrace/Sentimag		Tc ± Blue/Gamma			Implication
	Pts.	Value	Tracer	Pts.	Value	
Identification Rate	2715	97.0%	Tc TcBlue	14567 24186	96.6% 96.4%	Neutral
Number of Nodes	2683	2.0	Tc TcBlue	7742 15373	1.7 1.8	Favours Mag
Procedure Time (minutes)	30	9.5	Tc	72	12.9	Slightly Favours Mag
Complications Rate	503	3%	TcBlue	1152	12%	Favours Mag
Anaphylaxis Complications Rate	NA	Zero	Blue	48698	0.3%	Favours Mag
Staining Complications Rate	542	33%	Blue	669	49%	Favours Mag

Discussion points:

- The **Identification Rate** metric is frequently and consistently reported in the literature. Substantial patient numbers indicate high confidence in the conclusion that the Magnetic and the Radiotracer modalities are equally effective in the intended purpose of identifying sentinel lymph nodes for breast cancer SLND.
- The **Number of Nodes** metric is frequently and reasonably consistently reported in the literature. Substantial patient/node numbers indicate high confidence in the conclusion that the Magnetic modality is preferred (i.e., results in the excision of significantly more nodes per patient) over the Radiotracer modality.
- The **Procedure Time** metric is seldom reported in the literature, and patient numbers are very low. There is however a tentative indication that the Magnetic modality is slightly preferred (i.e., has a shorter SLND Procedure Time) over the Radiotracer modality.
- The **Complications Rate** metric is occasionally reported in the literature, and patient numbers are moderate. There is therefore a reasonably strong indication that the Magnetic modality is preferred (i.e., has a lower Complications Rate) over the Radiotracer modality.
- The **Anaphylaxis Complications Rate** metric is seldom reported in the literature, but the patient numbers are considerable. There is therefore a very strong indication that the Magnetic modality is preferred (i.e., has a lower Anaphylaxis Complications Rate) over the Blue dye modality.
- The **Staining Complications Rate** metric is occasionally reported in the literature, and patient numbers are moderate. There is therefore a reasonably strong indication that the Magnetic modality is preferred (i.e., has a lower Staining Complications Rate) over the Blue dye modality.

12.3.2. Per-Node Metrics

Results for the per-node metrics are described in detail in Section 10.2, and are summarised in the table below.

Per-Node Metric	Commentary	Implication
Nodal Retrieval Rate	Pooled risk difference from N=3188 nodes = +4% in favour of Sentimag in relation to Gamma.	Favours Mag
Nodal Concordance Rate	Pooled proportion from N=2354 nodes = 95% concordance.	Favours Concordance

Discussion points:

- The **Sentimag-versus-Gamma Nodal Retrieval Rate** metric is frequently and consistently reported in the literature. Substantial patient/node numbers indicate high confidence in the conclusion that the Sentimag modality is preferred (i.e., has a higher Nodal Retrieval Rate) over the Gamma modality.

- The **Sentimag-to-Gamma Nodal Concordance Rate** metric is frequently and consistently reported in the literature. Substantial patient/node numbers indicate high confidence in the conclusion that the Sentimag and Gamma modalities are substantially concordant.

12.3.3. Qualitative Metrics

Results for the more qualitative metrics are described in detail in Section11.2, and are summarised in the table below.

Metric	Commentary	Implication
Patient-Reported Outcomes	Re cosmesis, dermatological staining due to Magtrace is of concern to 1% of patients at 12 months post-op.	Neutral
Cost Analyses	Direct comparisons of per-injection costs – Mag 26% cheaper than Tc in Germany; 11% cheaper in Sweden.	Slightly Favours Mag

Discussion points:

- Several **Patient-Reported Outcomes** were identified in the literature, but most were for comparisons between the SLND and ALND surgical procedures. The most relevant patient-reported outcome for the current review related to perceptions of the importance of residual dermatological staining in the breast. Patient numbers for this outcome measure were moderate (N=318). There is therefore a reasonably strong indication that dermatological staining is not a significant concern for a substantial majority of patients.

- Several **Cost Analyses** were identified in the literature, but most were for comparisons between the SLND and ALND surgical procedures. The most relevant analyses for the current review related to tracer injection costs in Germany and Sweden. Given the paucity of information it is not possible to generalise, however there is a tentative indication that the Magnetic modality is slightly preferred (i.e., has a lower cumulative cost per injection) over the Radiotracer modality.

13. Conclusions

This focused Scientific and Clinical Literature Review has been undertaken to provide evidential material towards Endomag's response to the Medical Technology Draft Scope document "MT568 – Magtrace and Sentimag for Locating Sentinel Nodes for Breast Cancer" that was published in December 2021 by the UK National Institute for Health and Care Excellence (NICE).

During the course of the review, **59** peer-reviewed published sources have been identified and subjected to detailed full-text evaluation. Data from those sources has been pooled and analysed with respect to **10** different clinical outcome measures:

- the per-patient **Identification Rate (IR)** metric;
- the per-patient **Number of Nodes (NN)** metric;
- the per-patient **Procedure Time (PT)** metric;
- the per-patient **Complications Rate (CR)** metric;
- the per-patient **Anaphylaxis Complications Rate (ACR)** metric;
- the per-patient **Staining Complications Rate (SCR)** metric;
- the per-node **Sentimag-versus-Gamma Nodal Retrieval Rate (NNR)** metric;
- the per-node **Sentimag-to-Gamma Nodal Concordance Rate (NCR)** metric;
- qualitative **Patient-Reported Outcomes** metrics; and
- qualitative **Cost Analysis** metrics.

After due consideration, it was determined that the literature data supported the following conclusions:

- That there is high confidence based on substantial patient/node numbers:
  - that the Magnetic and the Radiotracer modalities are equally effective in identifying at least one sentinel lymph node per patient for breast cancer SLND (the IR metric);
  - that the Magnetic modality is preferred over the Radiotracer modality in terms of the detection of significantly more sentinel nodes per patient during the SLND procedure (the NN metric);
  - that on a node-by-node basis, there is substantial concordance between the Magnetic and Radiotracer modalities (the NCR metric); and
  - that on a node-by-node basis, the Magnetic modality consistently identifies more of a given patient's sentinel nodes than does the Radiotracer modality (the NRR metric).

- That there is a very strong indication based on considerable patient numbers:
  - that the Magnetic modality is preferred over the Radiotracer modality in that it does not involve the use of Blue dye, and therefore removes the risk of anaphylaxis complications (the ACR metric).

- That there is a reasonably strong indication based on moderate patient numbers:
  - that the Magnetic modality is preferred over the Radiotracer modality in that it results in a lower rate of significant post-operative clinical complications requiring medical intervention, such as infection, lymphoedema, haematoma/seroma, and urticaria (the CR metric);
  - that the Magnetic modality is preferred over the Radiotracer modality in that it results in a lower rate of post-operative dermatological staining complications (the SCR metric); and
  - that the dermatological staining occasionally associated with the Magnetic modality is not a significant concern for a substantial majority of patients (based on Patient-Reported Outcomes).

- That there is a tentative indication based on low patient numbers or local studies:
  - that the Magnetic modality is slightly preferred over the Radiotracer modality in terms of requiring a shorter intra-operative SLND procedure time (the PT metric); and
  - that the Magnetic modality is slightly preferred over the Radiotracer modality in terms of the cumulative cost per injection (based on Cost Analyses).

Appendix 1 – Evaluation Sources

[1] J. Gimenez-Climent, C. Marin-Hernandez, C. A. Fuster-Diana, J. A. Torro-Richart, J. Navarro-Cecilia, and E. Grp Estudios Senologicos Soc, **Sentinel lymph node biopsy in breast cancer after neoadjuvant therapy using a magnetic tracer versus standard technique: A multicentre comparative non-inferiority study (IMAGINE-II)**, Introduction: Previous studies have shown that a magnetic tracer technique using superparamagnetic iron oxide (SPIO) and a manual magnetometer (Sentimag, SM) is as effective as the standard technique using a radioisotope injection and a gamma probe (GP) for the detection of sentinel lymph nodes (SLNs) in breast cancer (BC) patients. This study was designed to investigate the performance of SM for post-neoadjuvant (NAT) SLN biopsy in BC patients. Materials and methods: Post-NAT BC patients were recruited from five centres. Readings of SLNs were recorded in transcutaneous, intraoperative and ex vivo scenarios by both GP and SM techniques. SLNs were assessed by OSNA (One-Step Nucleic Acid Amplification). Results: A total of 89 patients were included. At the patient level, the transcutaneous and intraoperative SLN detection rate was 97.8% by both techniques. At the node level, the GP detection rate intraoperatively was lower than that of SM (93.8% vs. 99.2%), with a concordance rate of 93% (90% CI 1.25; 9.44). The ex vivo detection rate was lower for GP compared to SM both per patient 96.6% vs. 97.8%, and per node 90.6% vs. 98.4% (90% CI-2.03; 4.22 and 1.82; 13.68, respectively). Furthermore, the detection rate of pathologically positive SLNs per patient and per node was lower for GP than SM both intraoperatively and ex vivo. These results showed the non-inferiority of SM intraoperatively per node (90% CI-4.89; 20.89) and ex vivo per patient (90% CI-2.38; 29.66). Conclusion: Our study showed the non-inferiority of SM compared to GP for detecting SLNs in post-NAT BC patients. (C) 2021 The Author(s). Published by Elsevier Ltd on behalf of Surgical Associates Ltd., International Journal of Surgery Open **35**, (2021). *[3.xxx CC1]*

[2] D. Hermansyah, Y. Rahayu, A. Azrah, G. Pricilia, D. Paramita, E. S. Siregar, S. Sufida, and A. Simarmata, **Accuracy of Methylene Blue Test as Single Technique for Sentinel Lymph Node Biopsy in Early Stages Breast Cancer**, AIM: Sentinel Lymph Node Biopsy (SLNB) establishes as a gold standard for diagnostic lymph node involvement in early breast cancer. Most of the developed country does not have radiotracer and nuclear medicine facilities. Unless in Indonesia there is Methylene Blue as an alternative agent for SLNB. This study measure accuracy of sentinel lymph node biopsy as a single technique using the Methylene Blue test. METHODS: This cross-sectional study enrolled 60 female patients with breast cancer stage I-II. We performed SNB using 2-5 cc of 1% Methylene-blue dye (MBD) injected to periareolar tissue and proceeded with axillary lymph nodes dissection (ALND). The histopathology results of sentinel nodes (SNs) and axillary lymph nodes (ALNs) analyze for diagnostic value assessments. RESULTS: The identification rate of SN was 97.62 %, and the median number of identified SNs was 4 (2-7). Sentinel node metastasis was found in (19/60) % cases and % of them were macrometastases. The sensitivity and specificity of MBD were 91.67% and 96.67% respectively. The negative predictive value (NPV) of SNs to predict axillary metastasis was 96.67% (95% CI, 81-99%). CONCLUSION: Injection of 1% MBD as a single technique in breast cancer SNB has a favorable identification rate and predictive value., Asian Pac J Cancer Prev **22**, 2765, (2021). *[3.xxx CC1]*

[3] A. Inagaki, T. Suzuki, Y. Mima, and K. Kimura, **Development of Magnetic Particle Distribution Imaging Using Magnetic Field Reconstruction for Biopsy of the Sentinel Lymph Node**, The sentinel lymph node is the first lymph-node-draining cancer metastasis. The identification of the sentinel lymph node using magnetic particles and a magnetic sensor has attracted attention in recent years, as this method is less invasive than the conventional method of radiotracer injection. However, the development of a two-dimensional measurement method for sentinel lymph nodes using magnetic nanoparticles remains an issue. In the present study, a method and apparatus for the two-dimensional imaging of magnetic particle distribution were developed to detect a lymph node with magnetic particles concentrated within lymphoid tissues. The method comprises the reconstruction of the magnetic field measured with a high-sensitivity magnetic sensor and with a magnetic detection ability of 2 nT/root Hz at 100 Hz (5 nT/root Hz at 1 Hz). The proposed system measures the two-dimensional magnetic field distribution in an area of up to 25 x 25 mm(2) using a coil generating a 0.77 mT external magnetic field applied to the measurement target. The improved spatial resolution of the images makes it possible to use two-dimensional imaging for diagnostics of breast cancer metastases., Magnetochemistry **7**, (2021). *[3.xxx CC1]*

[4] A. Jazrawi, E. Pantiora, S. Abdsaleh, D. V. Bacovia, S. Eriksson, H. Leonhardt, F. Wärnberg, and A. Karakatsanis, **Magnetic-Guided Axillary UltraSound (MagUS) Sentinel Lymph Node Biopsy and Mapping in Patients with Early Breast Cancer. A Phase 2, Single-Arm Prospective Clinical Trial**, Lymph Node Dissection (SLND) is standard of care for diagnosing sentinel lymph node (SLN) status in

patients with early breast cancer. Study aim was to determine whether the combination of Superparamagnetic iron oxide nanoparticles (SPIO) MRI-lymphography (MRI-LG) and a Magnetic-guided Axillary UltraSound (MagUS) with biopsy can allow for minimally invasive, axillary evaluation to de-escalate surgery. Patients were injected with 2 mL of SPIO and underwent MRI-LG for SN mapping. Thereafter MagUS and core needle biopsy (CNB) were performed. Patients planned for neoadjuvant treatment, the SLN was clipped and SLND was performed after neoadjuvant with the addition of isotope. During surgery, SLNs were controlled for signs of previous biopsy or clip. The primary endpoint was MagUS SLN detection rate, defined as successful SLN detection of at least one SLN of those retrieved in SLND. In 79 patients, 48 underwent upfront surgery, 12 received neoadjuvant and 19 had recurrent cancer. MagUS traced the SLN in all upfront and neoadjuvant cases, detecting all patients with macrometastases (n = 10). MagUS missed only one micrometastasis, outperforming baseline axillary ultrasound AUS (AUC: 0.950 vs. 0.508, p < 0.001) and showing no discordance to SLND (p = 1.000). MagUS provides the niche for minimally invasive axillary mapping that can reduce diagnostic surgery., Cancers (Basel) **13**, (2021). *[3.xxx CC1]*

5 H.-K. Kim *et al.*, **Association between Number of Retrieved Sentinel Lymph Nodes and Breast Cancer-related Lymphedema**, Purpose: Sentinel lymph node biopsy (SLNB) has become a standard axillary staging surgery for early breast cancer, and the proportion of patients requiring axillary lymph node dissection (ALND) is decreasing. We aimed to evaluate the association between the number of sentinel lymph nodes (SLNs) retrieved and the risk of lymphedema of the ipsilateral arm. Methods: Prospectively collected medical records of 910 patients were reviewed. Lymphedema was defined as a difference in circumference > 2 cm compared to the contralateral arm and/or having clinical records of lymphedema treatment in the rehabilitation clinic. Results: Together with an objective and subjective assessment of lymphedema, 36 patients (6.1%) had lymphedema in the SLNB group and 85 patients (27.0%) had lymphedema in the ALND group (p < 0.001). In a multivariate analysis of the whole cohort, risk factors significantly associated risk with the development of lymphedema were body mass index, mastectomy (vs. breast-conserving surgery), ALND, and radiation therapy. In logistic regression models in the SLNB group only, there was no correlation between the number of retrieved SLNs and the incidence of lymphedema. In addition, in the Pearson correlation analysis, no correlation was observed between the number of retrieved SLNs and the difference in circumference between the ipsilateral and contralateral upper extremities (correlation coefficients = 0.067, p= 0.111). Conclusion: The risk of lymphedema in breast cancer surgery and adjuvant treatments is multifactorial. The number of retrieved lymph nodes during sentinel biopsy was not associated with the incidence of lymphedema., Journal of Breast Cancer **24**, 63, (2021). *[3.xxx CC1]*

6 M. A. Kurochkin, S. V. German, A. Abalymov, D. A. Vorontsov, D. A. Gorin, and M. V. Novoselova, **Sentinel lymph node detection by combining nonradioactive techniques with contrast agents: State of the art and prospects**, The status of sentinel lymph nodes (SLNs) has a substantial prognostic value because these nodes are the first place where cancer cells accumulate along their spreading route. Routine SLN biopsy ("gold standard") involves peritumoral injections of radiopharmaceuticals, such as technetium-99m, which has obvious disadvantages. This review examines the methods used as "gold standard" analogs to diagnose SLNs. Nonradioactive preoperative and intraoperative methods of SLN detection are analyzed. Promising photonic tools for SLNs detection are reviewed, including NIR-I/NIR-II fluorescence imaging, photoswitching dyes for SLN detection, in vivo photoacoustic detection, imaging and biopsy of SLNs. Also are discussed methods of SLN detection by magnetic resonance imaging, ultrasonic imaging systems including as combined with photoacoustic imaging, and methods based on the magnetometer-aided detection of superparamagnetic nanoparticles. The advantages and disadvantages of nonradioactive SLN-detection methods are shown. The review concludes with prospects for the use of conservative diagnostic methods in combination with photonic tools., Journal of Biophotonics, (2021). *[3.xxx CC1]*

7 A. Papasavva *et al.*, **Comparative Study of a Series of Tc-99m(CO)(3) Mannosylated Dextran Derivatives for Sentinel Lymph Node Detection**, Sentinel lymph node detection (SLND) is rapidly entering common practice in the management of patients with tumors. The introduction of mannose molecules to Tc-99m-labeled dextrans, so far, showed that the sentinel node could trap these agents due to their recognition by the mannose receptors of lymph node macrophages. The current study aimed to synthesize, characterize, and biologically evaluate a series of mannosylated dextran derivatives labeled with Tc-99m for potential use in SLND. The compounds were designed to have a dextran with a molecular weight of 10-500 kDa as a backbone, S-derivatized cysteines, efficient SNO chelators, and mannose moieties for binding to mannose receptors. They were successfully synthesized, thoroughly characterized using NMR techniques, and labeled with the fac-[Tc-99m(CO)(3)](+) synthon. Labeling with high yields and radiochemical purities was achieved with all derivatives. In vivo biodistribution and imaging studies demonstrated high uptake in the first lymph node and low uptakes in the following node

and confirmed the ability to visualize the SLN. Among the compounds studied, Tc-99m-D75CM demonstrated the most attractive biological features, and in combination with the high radiochemical yield and stability of the compound, its further evaluation as a new radiopharmaceutical for sentinel lymph node detection was justified., Molecules **26**, (2021). *[3.xxx CC1]*

[8] D. V. Peristeri and H. V. Harissis, **Axillary lymph node dissection vs sentinel biopsy only among women with early-stage breast cancer and sentinel node metastasis: A systematic review and meta-analysis**, Axillary lymph node dissection (ALND) in early-stage breast cancer with limited sentinel node metastasis may not be superior to sentinel lymph node dissection (SLND). We performed a meta-analysis comparing SLND/Radiotherapy (RT) with ALND. All data were analyzed using Review Manager Software 5.3. Five randomized controlled trials (RCTs) were included. Overall survival, death, and disease-free survival were estimated higher in the SLND group compared to the ALND group. Statistically significant differences in axillary recurrence were observed in favor of ALND. Omission of ALND in patients with <3 positive SLNs is indicated., Breast J **27**, 158, (2021). *[3.xxx CC1]*

[9] M. J. Pla Farnos *et al.*, **Role of sentinel node biopsy in breast cancer: a review**, Axillary lymph node involvement is still an important predictor of recurrence and survival in breast cancer. Axillary staging was classically done by axillary lymph node dissection (ALND), but the introduction of sentinel lymph node biopsy (SLNB) has led to a progressive and continuing de-escalation in its use. Therefore, SLNB can now be considered the standard procedure for axillary staging in clinically No patients. Different studies have also begun to report that a positive sentinel node does not always require ALND, reducing the morbidity derived from this technique. Fears that this sentinel node approach might not be accurate for neoadjuyant chemotherapy have been allayed by several studies showing that post-neoadjuyant SLNB in clinical No patients reduces the rate of ALN D. This approach benefits from axillary pathological complete response with an acceptable false-negative rate. By contrast, however, cN1 disease still requires that we optimise the technique to reduce the rate of false negatives. Currently, SLNB is the best method for axillary staging in breast cancer, allowing patients to be treated according to risk of recurrence, and with good evidence that morbidity is lower than with other more radical techniques., European Journal of Gynaecological Oncology **42**, 982, (2021). *[3.xxx CC1]*

[10] X. Wang, L. Tang, W. Huang, Z. Cui, D. Hu, Z. Zhong, and X. Wu, **The combination of contrast-enhanced ultrasonography with blue dye for sentinel lymph node detection in clinically negative node breast cancer**, PURPOSE: The aim of this prospective study was to evaluate the value of the combination of contrast-enhanced ultrasonography (CEUS) and blue dye (BD) for SLN detection in patients with clinically negative node breast cancer. METHODS: Patients with clinically negative node breast cancer were randomized into two cohorts for SLN biopsy (SLNB): the combination method cohort using CEUS and BD together, and the single BD method cohort. Standard axillary lymph node dissection was performed if any of the SLNs confirmed positive by pathology. The identification rate, the number of SLNs removed and recurrence-free survival (RFS) rates were evaluated between two cohorts. In addition, we assessed the sensitivity, specificity, accuracy, false-negative rate of CEUS for diagnosis of SLNs based on patterns of CEUS enhancement. RESULTS: 144 consecutive patients with clinically negative node breast cancer were randomized into two cohorts. Each cohort consisted of 72 cases. In the combination method cohort, contrast-enhanced lymphatic vessels were clearly visualized and SLNs were accurately localized in 72 cases. The identification rate and the mean number of SLNs detected by the combination method were 100% (72/72) and 3.26 (1-9), respectively. In contrast, in the single BD method cohort, SLNs in 69 cases were successfully identified. The identification rate and the mean number of SLNs using BD alone were 95.8% (69/72) and 2.21 (1-4), respectively. According to patterns of CEUS enhancement, the sensitivity, specificity, accuracy, and the FNR of CEUS for SLN diagnosis were 69.2%, 96.6%, 91.7%, and 30.8%, respectively. After a median follow-up of 50 months for the combination method cohort and 51 months for the blue dye alone cohort, five patients in the combination method cohort and nine in the blue dye alone cohort had recurrence. RFS rates showed no significant difference (P = 0.26) between two cohorts. CONCLUSION: The combination of CEUS and BD is more effective than BD alone for SLNB in clinically negative node patients with an identification rate as high as 100%. Use of BD and CEUS in combination may provide the possibility of a non-radioactive alternative method for SLNB in centers without access to radioisotope., Arch Gynecol Obstet **304**, 1551, (2021). *[3.xxx CC1]*

[11] J. Zhang, Y. Ling, T. Wang, C. Yan, M. Huang, Z. Fan, and R. Ling, **Analysis of sentinel lymph node biopsy and non-sentinel lymph node metastasis in invasive ductal and invasive lobular breast cancer: a nationwide cross-sectional study (CSBrS-001)**, BACKGROUND: Information regarding the implementation of sentinel lymph node biopsy (SLNB) in invasive lobular carcinoma (ILC) is scarce, and whether ILC patients with 1-2 positive sentinel lymph nodes (SLNs) can be omitted from axillary lymph node dissection (ALND) remains controversial. This study aimed to compare involvement of SLNs and

non-SLNs between patients with invasive ductal carcinoma (IDC) and ILC. METHODS: We retrospectively collected the clinical and pathological data of invasive breast cancer patients from 37 medical centers in China from January 2018 to December 2018. The number of resected SLNs, positive rate of SLNs, and non-SLNs metastasis were compared between patients with IDC and ILC. RESULTS: A total of 6,922 patients were included, comprising 6,650 with IDC (96.1%) and 272 with ILC (3.9%). No difference was observed in the number of resected SLNs between patients with IDC and ILC (IDC: 4.0±1.9 vs. ILC: 3.9±1.6, P=0.352). The positive rate of SLNs was significantly higher in patients with IDC than that in patients with ILC (19.3% in IDC vs. 12.9% in ILC, P=0.008). The difference in positive rate of SLNs between IDC and ILC was mainly attributed to macro-metastasis. For patients with positive SLNs who received ALND, and those with 1-2 positive SLNs, the metastatic rate of non-SLNs in the ILC group was higher than that in the IDC group (for patients with positive SLNs: 50.0% in ILC vs. 39.9% in IDC, P=0.317; for patients with 1-2 positive SLNs: 45.4% in ILC vs. 34.8% in IDC, P=0.366), but the differences were not statistically significant. CONCLUSIONS: Patients with ILC had similar number of resected SLNs and lower positive rate of SLNs compared to those with IDC. In participants with 1-2 positive SLNs, the ILC group had an increased tendency for non-SLNs metastasis compared with the IDC group. Surgeons may need to be more cautious about omitting ALND for ILC patients with 1-2 positive SLNs., Ann Transl Med **9**, 1588, (2021). *[3.xxx CC1]*

[12] L. Poulsen, M. Kaur, A. L. Jacobsen, M. P. Bjarnesen, A. P. Bjarnesen, A. F. Klassen, A. L. Pusic, C. E. E. de Vries, and J. A. Sørensen, **Comparison of upper extremity lymphedema after sentinel lymph node biopsy and axillary lymph node dissection: patient-reported outcomes in 3044 patients**, PURPOSE: A limited number of studies have examined the impact of type of axillary lymph node surgery on breast cancer-related lymphedema (BCRL) from the patient's perspective. The objective of this study was to assess the impact of sentinel lymph node dissection (SLND) and axillary lymph node dissection (ALND) on the health-related quality of life (HRQOL) in women diagnosed with BCRL using a condition specific patient-reported outcome measure (PROM), the LYMPH-Q upper extremity (UE) module. METHODS: Adult women diagnosed with BCRL were identified from the Danish National Health Data Authority database for the period 2008 to 2020 and were sent an online REDCap survey with the LYMPH-Q UE module. Information pertaining to axillary surgery was obtained from an online pathology repository. Multivariable linear regression was used to examine differences in the SLND and ALND groups on the LYMPH-Q UE scale scores. RESULTS: Three thousand and fourty four women with BCRL were included in the analysis. The mean follow-up duration was 8.6 ± 5.15 years (range, 0-36 years). The majority of participants underwent ALND (n = 2805, 92.1%) and only 7.9% (n = 239) received SLND. The mean number of lymph nodes removed in the SLND group was 2.2 ± 1.4. No statistically significant difference was found in the two groups on the LYMPH-Q UE scale scores. CONCLUSION: There is no difference in women with upper extremity lymphedema after SLND or ALND on the LYMPH-Q UE module scales measuring arm symptoms, function, distress, and appearance., Breast Cancer Res Treat, (2021). *[3.xxx RR1]*

[13] M. Tarkowska, I. Głowacka-Mrotek, T. Nowikiewicz, A. Goch, and W. Zegarski, **Quality of Life in Women Subjected to Surgical Treatment of Breast Cancer Depending on the Procedure Performed within the Breast and Axillary Fossa-A Single-Center, One Year Prospective Analysis**, The aim of this study was to evaluate the quality of life of patients undergoing surgical treatment of breast cancer depending on the type of procedure involving the breast (mastectomy vs. breast conserving treatment) and axillary fossa (sentinel lymph node biopsy vs. axillary lymph node dissection). The prospective study was carried out in a group of 338 females undergoing breast cancer treatment. Study variables were assessed by means of a diagnostic survey using standardized QLQ C30 and BR23 questionnaires as well as the Acceptance of Illness Scale and Mini-MAC scales. The quality of life was assessed at threetime points: on the day before the surgical procedure (I assessment) as well as three and 12 months after surgery (II and III assessment). Statistically significant differences between study groups were observed in the overall quality of life subscale (I, II, III-p < 0.0001), physical functioning (I-p < 0.0001; II-p = 0.0413; III-p < 0.0001), role functioning (I-p = 0.0002; III-p < 0.0001), emotional functioning (III-p = 0.0082), cognitive functioning (I-p = 0.0112; III-p < 0.0001), social functioning (III-p < 0.0001), body image (I, II, III-p < 0.0001), and sexual functioning (I-p = 0.0233; III-p = 0.0011). In most symptomatic scales, significant (p < 0.05) differences were also noted. Mastectomy and limfadenectomy patients were significantly (p < 0.0001) more prone to present with destructive coping strategies one year after surgery. Breast conserving therapy is associated with better quality of life outcomes as compared to mastectomy. Sentinel lymph node biopsy is associated with a lower intensity of adverse changes in multiple dimensions of patients' functioning., J Clin Med **10**, (2021). *[3.xxx RR1]*

[14] M. Chandarana, Y. Y. Tan, R. Kirby, S. Jafferbhoy, S. Marla, S. Narayanan, and S. Soumian, **Patient-reported Upper Limb Function After Sentinel Lymph Node Biopsy for Breast Cancer: A Prospective Observational Study**, INTRODUCTION: Sentinel lymph node biopsy (SLNB) is the

standard procedure for axillary staging in breast cancer. There is a lack of consistency in studies reporting on upper limb morbidity after SLNB. We present a prospective study evaluating upper limb function after SLNB using the validated quickDASH questionnaire. MATERIALS AND METHODS: Consecutive patients who underwent wide local excision and SLNB were included in the study. Arm function was assessed using the quickDASH questionnaire at 3 time points - prior to surgery and 2 weeks and 3 months after SLNB. The scores obtained were labeled as A, B, and C respectively. The mean and median scores were compared using the paired t test and Wilcoxon signed rank test. RESULTS: Ninety-nine patients met all inclusion criteria and were included in the final analysis. The mean A, B, and C scores were 8.46, 16.05, and 13.36. The median A, B, and C scores were 2.27, 7.5, and 4.54. There was a statistically significant difference between mean and median A and B scores, B and C scores, and A and C scores. A similar trend was observed in patients with better preoperative upper limb function. Patients with a higher body mass index had significantly worse B and C scores. CONCLUSION: There is a significant deterioration in upper limb function following SLNB. This improves at 3 months but does not reach baseline levels. Larger studies with long-term follow-up are required to establish the extent of upper limb functional morbidity and natural course of functional recovery after SLNB., Clin Breast Cancer **20**, e584, (2020). *[3.xxx RR1]*

[15] D. A. Young-Afat *et al.*, **Breast Edema Following Breast-Conserving Surgery and Radiotherapy: Patient-Reported Prevalence, Determinants, and Effect on Health-Related Quality of Life**, Background: The association between lymphedema of the arm and impaired health-related QoL (HR-QoL) has led to changes in clinical practice. However, data on lymphedema of the breast (ie, breast edema) are lacking. We prospectively evaluated patient-reported prevalence and determinants of breast edema and its effect on patient-reported HR-QoL and breast pain. Methods: We prospectively included 836 patients undergoing breast-conserving surgery followed by radiotherapy between October 2013 and October 2016 (UMBRELLA cohort). Patient-reported breast edema, HR-QoL, and breast pain were assessed by means of European Organisation for Research and Treatment of Cancer- C30/BR23 before starting radiotherapy and at 3, 6, 12, and 18 months thereafter. We assessed which patient, tumor, and treatment characteristics were associated with breast edema. With mixed-effects models, we assessed the impact of breast edema on patient- reported HR-QoL domains and breast pain over time, adjusting for confounders. Results: Within a median follow-up of 28 months (interquartile range [IQR] = 15), 207 (24.8%) patients reported breast edema at some point in time. Prevalence of breast edema was highest at 6 months (12.4%, 95% confidence interval [CI] = 10.0 to 14.7). Larger tumor size, oncoplastic surgery, axillary lymph node dissection, locoregional radiotherapy, radiotherapy boost on the tumor bed, and adjuvant chemotherapy were associated with breast edema. Breast edema was independently associated with more breast pain and with poorer QoL, physical functioning, and body image. Conclusions: Breast edema occurs frequently within the first year after breast-conserving surgery and radiotherapy and is independently associated with impaired HR-QoL and more breast pain. This information is important for use in clinical practice and should be discussed with patients during shared decision making., Jnci Cancer Spectrum **3**, (2019). *[3.xxx RR1]*

[16] H. Sackey, H. Johansson, K. Sandelin, G. Liljegren, G. MacLean, J. Frisell, and Y. Brandberg, **Self-perceived, but not objective lymphoedema is associated with decreased long-term health-related quality of life after breast cancer surgery**, BACKGROUND: The primary aim was to compare long-term health-related quality of life (HRQoL) in patients undergoing sentinel lymph node biopsy (SLNB) alone versus axillary lymph node dissection (ALND), with or without axillary metastases. Secondary aims were to a) investigate agreement between objectively measured and self-reported lymphoedema and b) compare, with respect to HRQoL, women with objective arm lymphoedema without subjective ratings and those with no objective but subjective ratings of arm lymphoedema. METHODS: The three study groups were defined by axillary surgery: 1) SLNB alone (N = 140), 2) ALND in patients without axillary metastases (N = 125) and 3) ALND in patients with axillary metastases (N = 155). Preoperatively, one and three years postoperatively arm volume was measured and questionnaires regarding self-perceived symptoms of arm lymphoedema and HRQoL were completed (The Swedish Short Form-36 Health Survey, SF-36). RESULTS: Out of the original 516 who had axillary surgery, 420 (81%) completed the study. There were no statistically significant differences in HRQoL between the three study groups. No statistically significant agreement was found between self-perceived and objectively measured arm lymphoedema. Women without self-perceived arm lymphoedema, regardless of objective arm lymphoedema or not, scored higher on all eight SF-36 domains than those who reported self-perceived arm lymphoedema. CONCLUSION: Women reporting self-perceived arm lymphoedema, regardless of objective lymphoedema or not, have a decreased long-term health-related quality of life. This indicates that more attention should be given to the subjective reports of symptom in order to better help these women., Eur J Surg Oncol **41**, 577, (2015). *[3.xxx RR1]*

[17] M. A. Cooney, E. Culleton-Quinn, and E. Stokes, **Current Knowledge of Pain After Breast Cancer Treatment: A Systematic Review**, Pain and functional compromise are reported as effects that can be expected after breast cancer treatment. The reported prevalence of pain after breast cancer treatment varies widely, ranging from 13% (n = 74) to 93% (n = 590). To date, pain after breast cancer treatment has not been the focus of a systematic review. The aim of this study was to present what is known about the prevalence, location, intensity, nature, and temporal factors of the pain experienced by patients after breast cancer treatment. Searches of the Pubmed, Embase, Scopus, Amed, and Cinhal databases identified 69 articles on the topic. Studies were methodologically assessed by two independent reviewers using a checklist of 18 criteria. Twenty-six of the articles were identified as meeting inclusion criteria. Findings related to research conducted on 15 patient cohorts. Pain is confirmed as a prevalent treatment-related symptom experienced by 13%-51% of women in several different anatomic locations. The onset is variable, ranging from immediate to 24 months, highlighting the need to assess for pain at every evaluation interval. Little is known about the nature of the pain, but descriptors used (tenderness, soreness) suggest that the type of pain may not be confined to neuropathic pain. Reported average numeric intensity is low, but no study measured the impact of pain on function. Incidence of posttreatment pain has yet to be established. Further exploration of the nature, temporal factors, and impact that the pain experienced after treatment has on function, activity, and participation is needed to guide intervention and test its efficacy. (c) 2013 by the American Society for Pain Management Nursing, Pain Management Nursing **14**, 110, (2013). *[3.xxx RR1]*

[18] J. S. Radowsky, L. Baines, R. S. Howard, C. D. Shriver, C. C. Buckenmaier, 3rd, and A. Stojadinovic, **Pain ratings by patients and their providers of radionucleotide injection for breast cancer lymphatic mapping**, BACKGROUND: Disparity between patient report and physician perception of pain from radiotracer injection for sentinel node biopsy is thought to center on the severity of the intervention, ethnic composition of population queried, and socioeconomic factors. OBJECTIVE: The objectives of this study were, first, to explore agreement between physicians' and their breast cancer patients' pain assessment during subareolar radionucleotide injection; and second, to evaluate potential ethnic differences in ratings. METHODS: A trial was conducted, from January 2006 to April 2009, where 140 breast cancer patients were randomly assigned to standard topical lidocaine-4% cream and 99mTc-sulfur colloid injection, or to one of three other groups: placebo cream and 99mTc-sulfur colloid injection containing NaHCO3, 1% lidocaine, or NaHCO3 + 1% lidocaine. Providers and patients completed numeric pain scales (0-10) immediately after injection. RESULTS: Patients and providers rated pain similarly over the entire cohort (median, 3 vs 2, P = 0.15). Patients rated pain statistically significantly higher than physicians in the standard (6 vs 5, P = 0.045) and placebo + NaHCO3 (5 vs 4, P = 0.032) groups. No significant difference in scores existed between all African Americans and their physicians (3 vs 4, P = 0.27). CONCLUSION: Patient-physician pain assessment congruence over the less painful injections and their statistically similar scores with the more painful methods suggests the importance of utilizing the least painful method possible. Providers tended to underestimate patients with the highest pain ratings-those in the greatest analgesic need. Lack of statistical difference between African American and physician scores may reflect the equal-access-to-care over the entire patient cohort, supporting the conclusion that socioeconomic factors may lie at the heart of previously reported discrepancies., Pain Med **13**, 670, (2012). *[3.xxx RR1]*

[19] S. R. Land *et al.*, **Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32**, PURPOSE: Sentinel lymph node resection (SNR) may reduce morbidity while providing the same clinical utility as conventional axillary dissection (AD). National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 is a randomized phase III trial comparing SNR immediately followed by AD (SNAD) to SNR and subsequent AD if SN is positive. We report the definitive patient-reported outcomes (PRO) comparisons. PATIENTS AND METHODS: Eligible patients had clinically node-negative, operable invasive breast cancer. The PRO substudy included all SN-negative participants enrolled May 2001 to February 2004 at community institutions in the United States (n = 749; 78% age > or = 50; 87% clinical tumor size < or = 2.0 cm; 84% lumpectomy; 87% white). They completed questionnaires presurgery, 1 and 2 to 3 weeks postoperatively, and every 6 months through year 3. Arm symptoms, arm use avoidance, activity limitations, and quality of life (QOL) were compared with intent-to-treat two-sample t-tests and repeated measures analyses. RESULTS: Arm symptoms were significantly more bothersome for SNAD compared with SNR patients at 6 months (mean, 4.8 v 3.0; P < .001) and at 12 months (3.6 v 2.5; P = .006). Longitudinally, SNAD patients were more likely to experience ipsilateral arm and breast symptoms, restricted work and social activity, and impaired QOL (P < or = .002 all items). From 12 to 36 months, fewer than 15% of either SNAD or SNR patients reported moderate or greater severity of any given symptom or activity limitation. CONCLUSION: Arm morbidity was greater with SNAD than with SNR. Despite considerable fears about complications from AD for

breast cancer, this study demonstrates that initial problems with either surgery resolve over time., J Clin Oncol **28**, 3929, (2010). *[3.xxx RR1]*

[20] T. Reimer and B. Gerber, **Quality-of-life considerations in the treatment of early-stage breast cancer in the elderly**, Breast cancer is a common tumour in the elderly population and management of early disease in particular is a major challenge for oncologists and geriatricians alike. An important aspect is a differentiated knowledge about the short-term effects and long-term perspectives regarding levels of functioning and subjective well-being associated with different treatment strategies. The article focuses on available quality-of-life (QOL) measurement instruments in elderly patients with early breast cancer and the impact of various local or systemic treatments on QOL scores. A selective literature search was carried out in the PubMed database from January 2000 to May 2010 using the terms 'early breast cancer', 'elderly' and 'quality of life'. Contributions to international congresses on breast cancer in 2009 were also included. Of the 80 articles retrieved, 46 publications were excluded from further consideration due to failure to fulfil inclusion criteria (e.g. not restricted to the elderly, inclusion of patients with metastatic disease, no adjuvant treatment). Sixteen papers focusing on complementary treatment were also rejected. The remaining 18 articles were extensively reviewed. The selection of described QOL measurements was very heterogeneous in these 18 studies. Commonly used QOL instruments were the European Organization for Research and Treatment of Cancer QOL questionnaires (EORTC QLQ-C30, EORTC QLQ-BR23) and the Functional Assessment of Cancer Therapy questionnaires (FACT-G, FACT-B) and its subscales. Additionally, the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36), the Hospital Anxiety and Depression Scale (HADS) and the International Breast Cancer Study Group (IBCSG) approach were used by various study groups. The general limitations of QOL assessment in the elderly population are discussed in the review. Surgery, when considered from a technical point of view, does not differ significantly with patient age. Furthermore, age in itself should not be a contraindication to breast-conserving surgery (BCS) because QOL appears somewhat better after conservative surgical treatment. Avoiding axillary surgery and undergoing sentinel lymph node dissection in elderly patients are both associated with better short-term QOL. However, conventional axillary surgery has little effect on long-term QOL in older women. The advent of innovative radiotherapy techniques has resulted in marked improvements in short-term tolerability together with reductions in the incidence and severity of late normal tissue damage. A potential alternative to conventional postoperative radiotherapy after BCS in the future is the intraoperative radiotherapy technique. Chemotherapy has considerable effects on QOL in breast cancer patients. Most studies found that overall QOL was maintained or improved in patients receiving either aromatase inhibitors or tamoxifen but patients reported different adverse effects. For the majority of older breast cancer survivors, cancer-specific well-being and general emotional health do not change substantially after a breast cancer diagnosis. In summary, issues related to baseline co-morbidities in frail elderly, the adverse effects of novel chemotherapeutic agents (e.g. nanoparticle albumin-bound paclitaxel) or target drugs (biologicals) and compliance in the elderly population should receive more attention in evaluations of QOL in elderly breast cancer patients. Future studies that include QOL measurements should also provide details on the data collection and quality control methodologies used., Drugs Aging **27**, 791, (2010). *[3.xxx RR1]*

[21] T. J. Smith, J. Landercasper, J. D. Gundrum, B. M. De Maiffe, J. J. Andersen, J. M. Johnson, and P. J. Haller, **Perioperative quality metrics for one step breast cancer surgery: a patient-centered approach**, BACKGROUND AND OBJECTIVES: Patient-centered care is recommended by the Institute of Medicine to build a better healthcare system. The aim of this study was to audit patient-centered quality measures (QM) to create a breast center report card that could be provided to patients for education and informed consent. METHODS: An IRB approved retrospective review of 695 patients undergoing sentinel lymph node biopsy for breast cancer was conducted to audit the components of one step surgery and other QM. RESULTS: The intraoperative sensitivity to detect node positive patients was 25% (2/8), 27% (9/34), and 87% (68/78) for pN0(i+), pN1mi, pN1 patients, respectively. The re-excision lumpectomy rate was 15% (72/471) and the one step surgery success rate, which included lumpectomy and mastectomy patients, was 86% (598/695). Patient self-assessment of "very good to excellent" cosmesis and pain control were 77% (103/134) and 83% (60/72). Local recurrence rate was 2% (12/695) at a mean 3.1-year follow-up. CONCLUSIONS: The components of care that contribute to a patient-centered assessment of breast cancer surgery are measurable. "Bundling" of QM creates a perioperative report card that aids patients' informed consent and provides a framework for future comparative effectiveness studies., J Surg Oncol **102**, 34, (2010). *[3.xxx RR1]*

[22] B. C. Bredbeck *et al.*, **Incremental Spending Associated with Low-Value Treatments in Older Women with Breast Cancer**, BACKGROUND: In most women ≥ 70 years old with hormone-receptor-positive breast cancer, axillary staging and adjuvant radiotherapy provide no survival advantage over surgery and hormone therapy alone. Despite recommendations for their omission, sentinel lymph node biopsy (SLNB) and adjuvant radiotherapy rates remain high. While treatment side effects are well

documented, less is known about the incremental spending associated with SLNB and adjuvant radiotherapy. METHODS: Using a statewide multipayer claims registry, we examined spending associated with breast cancer treatment in a retrospective cohort of women ≥ 70 years old undergoing surgery. RESULTS: 9074 women ≥70 years old underwent breast cancer resection between 2012 and 2019, with 78% (n = 7122) receiving SLNB and/or adjuvant radiotherapy within 90 days of surgery. Women undergoing SLNB were more likely to receive radiation (51% vs. 28%; $p < 0.001$ and OR = 2.68). Average 90-day spending varied substantially based upon treatment received, ranging from US$10,367 (breast-conserving surgery alone) to US$27,370 (mastectomy with SLNB and adjuvant radiotherapy). The relative increases in 90-day treatment spending in the breast-conserving surgery cohort was 65% for SLNB, 82% for adjuvant radiotherapy, and 120% for both treatments. CONCLUSIONS: SLNB and adjuvant radiotherapy have significant spending implications in older women with breast cancer, even though they are unlikely to improve survival., Ann Surg Oncol, (2021). *[3.xxx RR1]*

[23] D. Mattar *et al.*, **Economic implications of ACOSOG Z0011 trial application into clinical practice at the European Institute of Oncology**, BACKGROUND AND OBJECTIVES: The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that in clinically node-negative women undergoing breast-conserving therapy (BCT) and found to have metastases to 1 or 2 sentinel nodes, sentinel lymph node biopsy (SLNB) alone resulted in rates of local control, disease-free survival, and overall survival equivalent to those seen after axillary lymph node dissection (ALND), but with significantly lower morbidity. Application of the Z0011 guidelines resulted in fewer ALNDs without affecting locoregional recurrence or survival. Changes in practice inevitably affect health care costs. The current study investigated the actual impact of applying the Z0011 guidelines to eligible patients and determined the costs of care at a single institution. PATIENTS AND METHODS: We compared axillary nodal management and cost data in breast cancer patients who met the Z0011 criteria and were treated with BCT and SLNB. Patients were allocated into two mutually exclusive cohorts based on the date of surgery: pre-Z0011 (June 2013 to December 2015) and post-Z0011 (June 2016 to December 2018). RESULTS: Of 3912 patients, 433 (23%) and 357 (17.6%) patients in the pre- and post-Z0011 era had positive lymph nodes. ALND decreased from 15.3% to 1.57% in the post-Z0011 era. The mean overall cost of SLNB in the pre-Z0011 cohort was €1312 per patient, while that for SLNB with completion ALND was €2613. Intraoperative frozen section (FS) use decreased from 100% to 12%. Omitting the FS decreased mean costs from €247 to €176. The mean total cost in the pre-Z0011 cohort was €1807 per patient, while in the post-Z0011 cohort it was €1498. The application of Z0011 resulted in an overall mean cost savings of €309 for each patient. CONCLUSIONS: Application of the Z0011 criteria to patients undergoing BCT at our institution results in more than half a million Euro cost savings., Eur J Surg Oncol **47**, 2499, (2021). *[3.xxx RR1]*

[24] M. Castelo, S. Y. Hu, F. Dossa, S. A. Acuna, and A. S. Scheer, **Comparing Observation, Axillary Radiotherapy, and Completion Axillary Lymph Node Dissection for Management of Axilla in Breast Cancer in Patients with Positive Sentinel Nodes: A Systematic Review**, PURPOSE: Several randomized controlled trials (RCTs) have investigated observation or axillary radiotherapy (ART) in place of completion axillary lymph node dissection (cALND) for management of positive sentinel nodes (SNs) in clinically node-negative women with breast cancer. The optimal treatment strategy for this population is not known. METHODS: MEDLINE, Embase, and EBM Reviews-NHS Economic Evaluation Database were searched from inception until July 2019. A systematic review and narrative summary was performed of RCTs comparing observation or ART versus cALND in clinically node-negative female breast cancer patients with positive SNs. The Cochrane risk of bias tool for RCTs was used to assess risk of bias. Outcomes of interest included overall survival (OS), disease-free survival (DFS), axillary recurrence, and axillary surgery-related morbidity. RESULTS: Three trials compared observation with cALND, and two trials compared ART with cALND. No studies blinded participants or personnel, and there was heterogeneity in inclusion criteria, study design, and follow-up. Neither observation nor ART resulted in statistically inferior 5- or 8-year OS or DFS compared with cALND. There was also no statistically significant increase in axillary recurrences associated with either approach. Four trials reported morbidity outcomes, and all showed cALND was associated with significantly more lymphedema, paresthesia, and shoulder dysfunction compared with observation or ART. CONCLUSIONS: Women with clinically node-negative breast cancer and positive SNs can safely be managed without cALND., Ann Surg Oncol **27**, 2664, (2020). *[3.xxx RR1]*

[25] A. M. McEvoy *et al.*, **Cost-effectiveness analyses demonstrate that observation is superior to sentinel lymph node biopsy for postmenopausal women with HR + breast cancer and negative axillary ultrasound**, PURPOSE: To evaluate the cost-effectiveness of axillary observation versus sentinel lymph node biopsy (SLNB) after negative axillary ultrasound (AUS). In patients with clinical T1-T2 N0 breast cancer and negative AUS, SLNB is the current standard of care for axillary staging. However, SLNB is costly, invasive, decreasing in importance for medical decision-making, and is not

considered therapeutic. Observation alone is currently being evaluated in randomized clinical trials, and is thought to be non-inferior to SLNB for patients with negative AUS. METHODS: We performed cost-effectiveness analyses of observation versus SLNB after negative AUS in postmenopausal women with clinical T1-T2 N0, HR(+)/HER2(-) breast cancer. Costs at the 2016 price level were evaluated from a third-party commercial payer perspective using the MarketScan® Database. We compared cost, quality-adjusted life years (QALYs), and net monetary benefit (NMB). Multiple sensitivity analyses varying baseline probabilities, costs, utilities, and willingness-to-pay thresholds were performed. RESULTS: Observation was superior to SLNB for patients with N0 and N1 disease, and for the entire patient population (NMB in US$: $655,659 for observation versus $641,778 for SLNB for the entire patient population). In the N0 and N1 groups, observation incurred lower cost and was associated with greater QALYs. SLNB was superior for patients with > 3 positive lymph nodes, representing approximately 5% of the population. Sensitivity analyses consistently demonstrated that observation is the optimal strategy for AUS-negative patients. CONCLUSION: Considering both cost and effectiveness, observation is superior to SLNB in postmenopausal women with cT1-T2 N0, HR(+)/HER2(-) breast cancer and negative AUS., Breast Cancer Res Treat **183**, 251, (2020). *[3.xxx RR1]*

[26] M. S. Dreyer, A. B. Nattinger, E. L. McGinley, and L. E. Pezzin, **Socioeconomic status and breast cancer treatment**, PURPOSE: Evidence suggests substantial disparities in breast cancer survival by socioeconomic status (SES). We examine the extent to which receipt of newer, less invasive, or more effective treatments-a plausible source of disparities in survival-varies by SES among elderly women with early-stage breast cancer. METHODS: Multivariate regression analyses applied to 11,368 women (age 66-90 years) identified from SEER-Medicare as having invasive breast cancer diagnosed in 2006-2009. Socioeconomic status was defined based on Medicaid enrollment and level of poverty of the census tract of residence. All analyses controlled for demographic, clinical health status, spatial, and healthcare system characteristics. RESULTS: Poor and near-poor women were less likely than high SES women to receive sentinel lymph node biopsy and radiation after breast-conserving surgery (BCS). Poor women were also less likely than near-poor or high SES women to receive any axillary surgery and adjuvant chemotherapy. There were no significant differences in use of aromatase inhibitors (AI) between poor and high SES women. However, near-poor women who initiated hormonal therapy were more likely to rely exclusively on tamoxifen, and less likely to use the more expensive but more effective AI when compared to both poor and high SES women. CONCLUSIONS: Our results indicate that SES disparities in the receipt of treatments for incident breast cancer are both pervasive and substantial. These disparities remained despite women's geographic area of residence and extent of disease, suggesting important gaps in access to effective breast cancer care., Breast Cancer Res Treat **167**, 1, (2018). *[3.xxx RR1]*

[27] E. J. Coromilas, J. D. Wright, Y. Huang, S. Feldman, A. I. Neugut, L. Chen, and D. L. Hershman, **The Influence of Hospital and Surgeon Factors on the Prevalence of Axillary Lymph Node Evaluation in Ductal Carcinoma In Situ**, IMPORTANCE: Although axillary lymph node evaluation is standard of care in the surgical management of invasive breast cancer, a benefit has not been demonstrated in ductal carcinoma in situ (DCIS). Despite uncertainty regarding the efficacy, axillary evaluation is often performed in women with DCIS. OBJECTIVE: To determine the incidence of axillary evaluation in women with DCIS and identify clinical, hospital, and surgeon-related factors associated with axillary evaluation. DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional analysis conducted from January 2006 through December 2012 of medical records contained in the Perspective database for women with DCIS who underwent breast-conserving surgery (BCS) or mastectomy. A total of 35,591 women aged 18 to 90 years were included in the analysis. MAIN OUTCOMES AND MEASURES: Receipt or nonreceipt of surgical axillary evaluation, categorized as sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND), or none. Analyses were stratified by surgery type, and multivariable regression analysis was used to identify factors associated with axillary evaluation. RESULTS: Of women identified with DCIS, 26,580 (74.7%) underwent BCS while 9011 (25.3%) underwent mastectomy; 17.7% undergoing BCS and 63.0% undergoing mastectomy had an axillary evaluation. Rates of axillary evaluation increased over time with mastectomy (2006, 56.6%; 2012, 67.4%) and were relatively stable with BCS (2006, 18.5%; 2012, 16.2%). Rates of ALND decreased in women undergoing mastectomy (2006, 20.0%; 2012, 10.7%) and BCS (2006, 1.2%; 2012, 0.3%), with increasing use of SLNB. In a multivariable analysis, hospital factors including nonteaching hospital (risk ratio [RR], 1.17; 95% CI, 1.05-1.30) and urban location (RR, 1.15; 95% CI, 1.03-1.29) influenced axillary evaluation with mastectomy. Surgeon volume was the most significant predictor of axillary evaluation among women undergoing BCS (mid vs low volume: RR, 0.87; 95% CI, 0.70-0.94; high vs low volume: RR, 0.54; 95% CI, 0.44-0.65). CONCLUSIONS AND RELEVANCE: Despite guidelines recommending against axillary lymph node evaluation in women with DCIS undergoing BCS and uncertainty regarding its use with mastectomy, SLNB or ALND is performed frequently. Given the additional morbidity and cost of these procedures,

alternative surgical approaches or prospective evaluation of the clinical benefit of axillary evaluation in women with DCIS is needed., JAMA Oncol **1**, 323, (2015). *[3.xxx RR1]*

[28] S. Zurrida and U. Veronesi, **Milestones in Breast Cancer Treatment**, Modern treatment started in the 1880s with Halsted's mastectomy. The next milestonea century laterwas breast-conserving surgery, with equivalent survival but better esthetic outcomes than mastectomy. Sentinel node biopsy, introduced in the 1990s, was a milestone that permitted avoidance of axillary dissection if the sentinel node was disease-free. Chemotherapy was established for early breast cancer in the 1980s and its efficacy continues to improve; however side effects remain a concern, particularly since chemotherapy does not benefit most patients. External whole breast irradiation was introduced with conservative surgery, as it reduces recurrences. By the 2000s, 3-week regimens had been shown equivalent to standard 6-week regimenseasing pressure on patients and radiation centers. Intraoperative partial breast irradiation is potentially more beneficial as it permits complete local treatment in a single session; however, trials show that patients must be very carefully selected. From the 1990s irradiation technology was combined with imaging and computer technologies to produce equipment that directs radiation to more precisely defined target volumes, allowing increased dose to the target and markedly reduced dose to nearby tissues. Irradiation systems are evolving rapidly but are being implemented without data on long-term morbidity or efficacy, while costs rise steeply. The first targeted treatment was tamoxifen, a selective estrogen receptor inhibitor. Since its widespread use starting in the 1980s, tamoxifen has saved the lives or prolonged the survival of millions with estrogen-positive disease; it is cheap and has limited (but not negligible) side effects. The same cannot be said of newer targeted treatments like trastuzumab and pertuzumab, which, although effective against human epidermal growth factor receptor 2-positive cancer, come with important side effects and huge costs. Breast cancer mortality is declining in rich countries, but treatments have become more demanding and more expensive, so the outlook for the increasing numbers of women worldwide who develop the disease is uncertain., Breast Journal **21**, 3, (2015). *[3.xxx RR1]*

[29] K. M. Gorey, I. N. Luginaah, E. J. Holowaty, G. Zou, C. Hamm, and M. K. Balagurusamy, **Mediation of the effects of living in extremely poor neighborhoods by health insurance: breast cancer care and survival in California, 1996 to 2011**, Background: We examined the mediating effect of health insurance on poverty-breast cancer care and survival relationships and the moderating effect of poverty on health insurance-breast cancer care and survival relationships in California. Methods: Registry data for 6,300 women with breast cancer diagnosed between 1996 and 2000 and followed until 2011 on stage at diagnosis, surgeries, adjuvant treatments and survival were analyzed. Socioeconomic data were obtained for residences from the 2000 census to categorize neighborhoods: high poverty (30% or more poor), middle poverty (5%-29% poor) and low poverty (less than 5% poor). Primary payers or health insurers were Medicaid, Medicare, private or uninsured. Results: Evidence of survival mediation was observed for women with node negative breast cancer. The apparent effect of poverty disappeared in the presence of Medicare or private health insurance. Women who were so insured were advantaged on 8-year survival compared to the uninsured or those insured by Medicaid (OR = 1.89). Evidence of payer moderation by poverty was also observed for women with node negative breast cancer. The survival advantaging effect of Medicare or private insurance was stronger in low poverty (OR = 1.81) than it was in middle poverty (OR = 1.57) or in high poverty neighborhoods (OR = 1.16). This same pattern of mediated and moderated effects was also observed for early stage at diagnosis, shorter waits for adjuvant radiation therapy and for the receipt of sentinel lymph node biopsies. These findings are consistent with the theory that more facilitative social and economic capital is available in low poverty neighborhoods, where women with breast cancer may be better able to absorb the indirect and direct, but uncovered, costs of care. As for treatments, main protective effects as well as moderator effects indicative of protection, particularly in high poverty neighborhoods were observed for women with private health insurance. Conclusions: America's multi-tiered health insurance system mediates the quality of breast cancer care. The system is inequitable and unjust as it advantages the well insured and the well to do. Recent health care reforms ought to be enacted in ways that are consistent with their federal legislative intent, that high quality health care be truly available to all., International Journal for Equity in Health **12**, (2013). *[3.xxx RR1]*

[30] J. M. Classe *et al.*, **Cost comparison of axillary sentinel lymph node detection and axillary lymphadenectomy in early breast cancer. A national study based on a prospective multi-institutional series of 985 patients 'on behalf of the Group of Surgeons from the French Unicancer Federation'**, Our objective was to assess the global cost of the sentinel lymph node detection [axillary sentinel lymph node detection (ASLND)] compared with standard axillary lymphadenectomy [axillary lymph node dissection (ALND)] for early breast cancer patients. We conducted a prospective, multi-institutional, observational, cost comparative analysis. Cost calculations were realized with the micro-costing method from the diagnosis until 1 month after the last surgery. Eight hundred and thirty nine

patients were included in the ASLND group and 146 in the ALND group. The cost generated for a patient with an ASLND, with one preoperative scintigraphy, a combined method for sentinel node detection, an intraoperative pathological analysis without lymphadenectomy, was lower than the cost generated for a patient with lymphadenectomy [euro2947 (Sigma = 580) versus euro3331 (Sigma = 902); P = 0.0001]. ASLND, involving expensive techniques, was finally less expensive than ALND. The length of hospital stay was the cost driver of these procedures. The current observational study points the heterogeneous practices for this validated and largely diffused technique. Several technical choices have an impact on the cost of ASLND, as intraoperative analysis allowing to reduce rehospitalization rate for secondary lymphadenectomy or preoperative scintigraphy, suggesting possible savings on hospital resources., Annals of Oncology **23**, 1170, (2012). *[3.xxx RR1]*

31 H. Verry, S. J. Lord, A. Martin, G. Gill, C. K. Lee, K. Howard, N. Wetzig, and J. Simes, **Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis**, BACKGROUND: Sentinel lymph node biopsy (SLNB) is less invasive than axillary lymph node dissection (ALND) for staging early breast cancer, and has a lower risk of arm lymphoedema and similar rates of locoregional recurrence up to 8 years. This study estimates the longer-term effectiveness and cost-effectiveness of SLNB. METHODS: A Markov decision model was developed to estimate the incremental quality-adjusted life years (QALYs) and costs of an SLNB-based staging and management strategy compared with ALND over 20 years' follow-up. The probability and quality-of-life weighting (utility) of outcomes were estimated from published data and population statistics. Costs were estimated from the perspective of the Australian health care system. The model was used to identify key factors affecting treatment decisions. RESULTS: The SLNB was more effective and less costly than the ALND over 20 years, with 8 QALYs gained and $883,000 saved per 1000 patients. The SLNB was less effective when: SLNB false negative (FN) rate >13%; 5-year incidence of axillary recurrence after an SLNB FN>19%; risk of an SLNB-positive result >48%; lymphoedema prevalence after ALND <14%; or lymphoedema utility decrement <0.012. CONCLUSION: The long-term advantage of SLNB over ALND was modest and sensitive to variations in key assumptions, indicating a need for reliable information on lymphoedema incidence and disutility following SLNB. In addition to awaiting longer-term trial data, risk models to better identify patients at high risk of axillary metastasis will be valuable to inform decision-making., Br J Cancer **106**, 1045, (2012). *[3.xxx RR1]*

32 Y. Meng, S. Ward, K. Cooper, S. Harnan, and L. Wyld, **Cost-effectiveness of MRI and PET imaging for the evaluation of axillary lymph node metastases in early stage breast cancer**, BACKGROUND: UK guidelines for breast cancer recommend axillary nodal assessment via surgical methods such as sentinel lymph node biopsy (SLNB). However, these procedures are associated with adverse effects such as lymphoedema. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are non-invasive imaging techniques. The aim of this study is to evaluate the cost-effectiveness of MRI and PET compared with SLNB for assessment of axillary lymph node metastases in newly-diagnosed early stage breast cancer patients in the UK. METHODS: An individual patient discrete-event simulation model was developed in SIMUL8(®) to estimate the lifetime costs and benefits of replacing SLNB with MRI or PET, or adding MRI or PET before SLNB. Effectiveness outcomes were derived from a recent systematic review; patient utilities and resource use data were sourced from the literature. RESULTS: Based on our analysis the baseline SLNB strategy is dominated by the strategies of replacing SLNB with either MRI or PET. The strategy of replacing SLNB with MRI has the highest total quality-adjusted life years (QALYs) and lowest total costs. However, clinical evidence for MRI is based on a limited number of small studies and replacing SLNB with MRI or PET leads to more false-positive and false-negative cases. The strategy of adding MRI before SLNB is cost-effective, but subject to greater uncertainty. CONCLUSIONS: Based on this analysis the most cost-effective strategy is to replace SLNB with MRI. However, further large studies using up-to-date techniques are required to obtain more accurate data on the sensitivity and specificity of MRI., Eur J Surg Oncol **37**, 40, (2011). *[3.xxx RR1]*

33 J. Landercasper and L. Tafra, **The relationship between quality and cost during the perioperative breast cancer episode of care**, The relationship between quality and cost of care for breast cancer surgery was investigated by literature review. The guidelines, policy statements, quality measures (QM) and target goals for performance described by professional organizations were also reviewed. After review, the relationship between quality and cost of care for the components of perioperative care were assigned an inverse, direct or uncertain relationship. Identification of processes of care with an inverse relationship between quality and cost, such as performing a needle biopsy to diagnose cancer compared to an open surgical biopsy, provide opportunity to concurrently lower cost and improve quality. Other components of care, such as post-mastectomy reconstruction, demonstrate a direct relationship between quality and cost. Recognition of the variability of performance of QM's with an inverse quality and cost relationship has the potential to lower breast cancer population healthcare expenditures, if average

performance for those QM can be improved. (c) 2010 Elsevier Ltd. All rights reserved., Breast **19**, 289, (2010). *[3.xxx RR1]*

[34] M. Frountzas, C. Theodoropoulos, P. Karathanasis, C. Nikolaou, C. G. Zografos, A. Larentzakis, G. C. Zografos, and N. V. Michalopoulos, **Severe anaphylactic reaction after blue dye injection for sentinel lymph node biopsy in breast surgery: Report of two cases and literature review**, Anaphylactic reactions, and especially the severe ones (types III and IV), should be kept in mind as considerable adverse effects while using blue dyes for SLNB., Clinical Case Reports, (2021). *[6.222 BB1]*

[35] A.-F. Hersi *et al.*, **Optimizing Dose and Timing in Magnetic Tracer Techniques for Sentinel Lymph Node Detection in Early Breast Cancers: The Prospective Multicenter SentiDose Trial**, Simple Summary Superparamagnetic iron oxide (SPIO) nanoparticles have comparable performance to the combination of radioisotope and blue dye (RI + BD) for sentinel lymph node (SLN) biopsy in breast cancer. In this multicenter prospective study, lower SPIO doses (undiluted 1.5 vs. 1.0 mL) in different timeframes (perioperative vs. 1-7 days preoperative) and injection sites (subareolar vs. peritumoral) were compared to the previous standard (diluted 2.0 mL perioperatively) from the earlier Nordic trial. RI + BD were co-administered as background. In total, 534 patients were analyzed. SPIO SLN detection rates were similar (97.5% vs. 100% vs. 97.6%, p = 0.11) and respectively non-inferior to the dual technique. Significantly more SLNs were retrieved in the preoperative 1.0 mL cohort compared with 1.5 mL and the Nordic cohorts (2.18 vs. 1.85 vs. 1.83, p = 0.003). Thus, SPIO at 1.5 and 1.0 mL was non-inferior to both Sienna+(R) and the dual technique for SLN detection. Superparamagnetic iron oxide nanoparticles (SPIO) are non-inferior to radioisotope and blue dye (RI + BD) for sentinel lymph node (SLN) detection. Previously, 2 mL SPIO (Sienna+(R)) in 3 mL NaCl was used. In this dose-optimizing study, lower doses of a new refined SPIO solution (Magtrace(R)) (1.5 vs. 1.0 mL) were tested in different timeframes (0-24 h perioperative vs. 1-7 days preoperative) and injections sites (subareolar vs. peritumoral). Two consecutive breast cancer cohorts (n = 328) scheduled for SLN-biopsy were included from 2017 to 2019. All patients received isotope +/- blue dye as back-up. SLNs were identified primarily with the SentiMag(R) probe and thereafter a gamma-probe. The primary endpoint was SLN detection rate with SPIO. Analyses were performed as a one-step individual patient-level meta-analysis using patient-level data from the previously published Nordic Trial (n = 206) as a third, reference cohort. In 534 patients, the SPIO SLN detection rates were similar (97.5% vs. 100% vs. 97.6%, p = 0.11) and non-inferior to the dual technique. Significantly more SLNs were retrieved in the preoperative 1.0 mL cohort compared with 1.5 and the 2.0 mL cohorts (2.18 vs. 1.85 vs. 1.83, p = 0.003). Lower SPIO volumes injected up to 7 days before the operation have comparable efficacy to standard SPIO dose and RI + BD for SLN detection., Cancers **13**, (2021). *[6.222 CC1]*

[36] M. M. Karsten, S. Shams, and F. Kuhn, **ASO Author Reflections: Non-radioactive Sentinel Node Localization with Superparamagnetic Iron Oxide in Clinically Node-Negative Breast Cancer Patients: A Possibility for Improvement of the Care Pathway**, Ann Surg Oncol **28**, 3241, (2021). *[6.222 CC1]*

[37] M. S. Kedrzycki, M. Leiloglou, H. Ashrafian, N. Jiwa, P. T. R. Thiruchelvam, D. S. Elson, and D. R. Leff, **Meta-analysis Comparing Fluorescence Imaging with Radioisotope and Blue Dye-Guided Sentinel Node Identification for Breast Cancer Surgery**, Introduction Conventional methods for axillary sentinel lymph node biopsy (SLNB) are fraught with complications such as allergic reactions, skin tattooing, radiation, and limitations on infrastructure. A novel technique has been developed for lymphatic mapping utilizing fluorescence imaging. This meta-analysis aims to compare the gold standard blue dye and radioisotope (BD-RI) technique with fluorescence-guided SLNB using indocyanine green (ICG). Methods This study was registered with PROSPERO (CRD42019129224). The MEDLINE, EMBASE, Scopus, and Web of Science databases were searched using the Medical Subject Heading (MESH) terms 'Surgery' AND 'Lymph node' AND 'Near infrared fluorescence' AND 'Indocyanine green'. Studies containing raw data on the sentinel node identification rate in breast cancer surgery were included. A heterogeneity test (using Cochran's Q) determined the use of fixed- or random-effects models for pooled odds ratios (OR). Results Overall, 1748 studies were screened, of which 10 met the inclusion criteria for meta-analysis. ICG was equivalent to radioisotope (RI) at sentinel node identification (OR 2.58, 95% confidence interval [CI] 0.35-19.08, p 0.05) but superior to blue dye (BD) (OR 9.07, 95% CI 6.73-12.23, p 0.05). Furthermore, ICG was superior to the gold standard BD-RI technique (OR 4.22, 95% CI 2.17-8.20, p 0.001). Conclusion Fluorescence imaging for axillary sentinel node identification with ICG is equivalent to the single technique using RI, and superior to the dual technique (RI-BD) and single technique with BD. Hospitals using RI and/or BD could consider changing their practice to ICG given the comparable efficacy and improved safety profile, as well as the lesser burden on hospital infrastructure., Annals of Surgical Oncology **28**, 3738, (2021). *[6.222 RR1]*

[38] C. Malhotra, R. Pawar, S. Patni, Sucheta, M. Kaushik, and N. Sharma, **Efficacy of Periareolar Versus Peritumoral Injection of TC99-Labelled Sulphur Colloid and Methylene Blue Dye for Detection of Sentinel Lymph Node in Patients with Early Breast Cancer: a Comparative Study**, Sentinel lymph node biopsy using dual methods of blue dye and radioactive isotope is what is practised as the standard of care at most of the centres. The combined use of radioactive colloid and blue dye injection is considered the gold standard for axillary sentinel lymph node biopsy in breast cancer with a 97% accuracy rate. The aim of this study is to determine the optimal injection site for methylene blue dye and Tc99-labelled sulphur colloid for sentinel lymph node biopsy in early breast cancer. In both periareolar and peritumoral groups of patients, overall rate of identifying sentinel lymph node (hot, blue and hot and blue nodes) with dual dye was comparable (100% and 96.36%) with p value = 0.475. Also in both groups of patients, overall rate of getting pathological positive sentinel lymph node on final histopathological report was comparable (52.73% and 45.28%) with p value = 0.561. Periareolar versus peritumoral injection of dual dye shows comparable success rates for axillary sentinel lymph node identification and can be considered rapid and reliable method. However, the periareolar route is technically simple and especially privileged in nonpalpable (T0) and upper outer quadrant lesions mainly for the prevention of the shine through phenomenon., Indian J Surg Oncol **12**, 119, (2021). *[5.212 CC1]*

[39] M. Perenyei, Z. E. Barber, J. Gibson, S. Hemington-Gorse, and T. D. Dobbs, **Anaphylactic Reaction Rates to Blue Dyes Used for Sentinel Lymph Node Mapping: Systematic Review and Meta-analysis**, OBJECTIVE: The primary objective of this study was to quantify the risk of anaphylaxis to blue dyes used in SLNB for cancer. Secondary outcomes included the identification of factors that may influence this risk. SUMMARY OF BACKGROUND DATA: Blue dyes are widely used to help identify sentinel lymph nodes in oncological surgery. The rate of severe allergic reactions to blue dyes remains a controversial topic, with the true incidence and influencing factors uncertain. METHODS: A systematic review and meta-analysis was performed to identify all studies which report on the incidence of severe adverse reactions and anaphylaxis to blue dyes (patent blue, isosulfan blue, methylene blue, and indigo carmine), when used for SLNB. Collected data included cancer and dye type, volume, and method of injection. Incidence was estimated using the arcsine method of statistical analysis. RESULTS: One hundred nine studies documenting 94 episodes of anaphylaxis in a total of 61,951 SLNB procedures, resulting in a weighed anaphylaxis rate of 0.061%. SLNB for breast cancer carries an anaphylaxis risk of 0.083%, with the risk markedly lower in melanoma surgery (0.0043%). Low dye volume (<2mL) and intradermal injection are both associated with lower rates of anaphylaxis (0.031% and 0.0068%). Isosulfan blue seems to be the most anaphylactogenic amongst blue dyes with a rate of 0.16%. There were no reported cases of death in this cohort. CONCLUSION: Anaphylaxis to blue dyes in SLNB is rare. Methylene blue, patent blue, lower dye volumes, and intradermal administration are all associated with a lower incidence of anaphylaxis., Ann Surg **273**, 1087, (2021). *[6.222 RR1]*

[40] S. Shams, K. Lippold, J. U. Blohmer, R. Röhle, F. Kühn, and M. M. Karsten, **A Pilot Study Evaluating the Effects of Magtrace® for Sentinel Node Biopsy in Breast Cancer Patients Regarding Care Process Optimization, Reimbursement, Surgical Time, and Patient Comfort Compared With Standard Technetium(99)**, BACKGROUND: Sentinel lymph node biopsy after technetium-99 (Tc(99)) localization is a mainstay of oncologic breast surgery. The timing of Tc(99) injection can complicate operating room schedules, which can cause increasing overall costs of care and patient discomfort. METHODS: This study compared 59 patients who underwent breast cancer surgery including sentinel lymph node biopsy. Based on the surgeon's choice, 29 patients were treated with Tc(99), and 30 patients received the iron-based tracer, Magtrace. The primary outcomes were time spent on the care pathway and operating time from commissioning of the probe to removal of the sentinel node. The secondary outcomes were patient pain levels and reimbursement. RESULTS: The mean time spent on the preoperative breast cancer care pathway was significantly shorter for the Magtrace group (5.4 ± 1.3 min) than for the Tc(99) group (82 ± 20 min) ($p < 0.0001$). The median time from probe usage to sentinel node extirpation was slightly but not significantly shorter in the Magtrace group (5 min; interquartile range [IQR], 3-15 min vs 10 min; IQR, 7-15 min; $p = 0.151$). Reimbursement and pain levels remained unchanged, and the hospital length of stay was similar in the two groups (Magtrace: 5.1 ± 2.3 days vs Tc(99): 4.5 ± 3.2 days). CONCLUSIONS: Magtrace localization shortened the preoperative care pathway and did not affect surgical time or reimbursement. Once established, it could allow for cost reduction and improve patient comfort., Ann Surg Oncol **28**, 3232, (2021). *[6.222 CC1]*

[41] R. Yin, L.-Y. Ding, Q.-Z. Wei, Y. Zhou, G.-Y. Tang, and X. Zhu, **Comparisons of ICG-fluorescence with conventional tracers in sentinel lymph node biopsy for patients with early-stage breast cancer: A meta-analysis**, Radioisotopes (RI) and blue dye (BD) are routinely used markers for staining during sentinel lymph node biopsy (SLNB) in breast cancer. Compared with traditional tracers, tracer performance of indocyanine green (ICG) has been controversial. A total of 21 studies were selected from the PubMed, EMBASE and Cochrane Library databases. Detection ability was judged based on four

endpoints: i) The identification rate (IR) of the patients; ii) the IR of the sentinel lymph nodes (SLNs); iii) the IR of the positive SLNs; and iv) the false negative rate (FNR). Compared with BD, ICG was superior in terms of the IR of the patients [odds ratio (OR)=7.17; 95% CI, 3.98-12.94), the IR of the SLNs (OR=8.84; 95% CI, 6.71-11.66) and FNR (OR=0.20; 95% CI, 0.08-0.48) using a fixed-effects model. There was a significant difference in both the IR of the positive SLNs (OR=21.32; 95% CI, 2.84-160.14) and FNR (OR=0.46; 95% CI, 0.23-0.91) in the ICG vs. RI group. Furthermore, when using ICG at the recommended dose, a significant difference was found in the IR of the patients (OR=1.77; 95% CI, 1.09-2.85) and the IR of the SLNs (OR=21.62; 95% CI, 5.23-89.43) using a fixed-effects model. In the ICG vs. BD combined with RI group, there were no differences in either the IR of the patients (OR=5.10; 95% CI, 0.24-107.48) or the IR of SLNs (OR=5.10; 95% CI, 0.60-256.66). In conclusion, ICG was a better tracer compared with BD or RI alone and was not a worse tracer compared with BD combined with RI. The use of the recommended dose of ICG had an improved tracer effect. ICG is expected to be widely used in SLNB in view of its clinical advantages., Oncology Letters **21**, (2021). *[6.222 CC1]*

42 S. K. Agrawal, I. Hashlamoun, B. Karki, A. Sharma, I. Arun, and R. Ahmed, **Diagnostic Performance of Indocyanine Green Plus Methylene Blue Versus Radioisotope Plus Methylene Blue Dye Method for Sentinel Lymph Node Biopsy in Node-Negative Early Breast Cancer**, PURPOSE: Sentinel lymph node biopsy (SLNB) by dual-dye method (radioisotope plus blue) is the gold standard for axillary staging in patients with breast cancer, but in developing countries, logistic issues and financial constraint play a vital role. Recently, indocyanine green (ICG) has emerged as an alternative to radioisotope (technetium-99 [Tc-99]) for SLNB in breast cancer. This study compared the diagnostic performance of Tc-99 plus methylene blue (MB) dye versus ICG + MB dye SLNB. METHODS: Two hundred seven patients with early breast cancer (T1-3N0) were included in the study from 2017 to 2019. SLNB was done either with Tc-99 + MB or with ICG + MB as per availability of radioisotope. SLN identification rate (IR), SLN positivity rate, and metastatic SLN counts were compared between the 2 groups. RESULTS: IR was 199 (96%) of 207. IR was 95% in Tc-99 + MB compared with 97% with ICG + MB. The mean number of SLNs identified were 3.17 (standard deviation [SD], 1.84), with > 1 SLN identified in 87% patients by Tc-99 + MB. SLN was positive in 31.3% of patients with a metastatic SLN count of 0.37 (SD, 0.76). With ICG + MB, the number of SLNs was 2.73 (SD, 1.55), with > 1 SLN identified in 79% of patients. Twenty-eight percent of patients had positive SLNs, with a metastatic SLN count of 0.41 (SD, 0.77). A sharp decline in the availability of Tc-99 was observed, with 58% of patients in 2014 and only 12% of patients in 2018. CONCLUSION: ICG is equivalent to Tc-99 for SLNB in early breast cancer and has a good potential to be adopted by surgeons in resource-constrained setups., JCO Glob Oncol **6**, 1225, (2020). *[6.222 CC1]*

43 J. Goonawardena, C. Yong, and M. Law, **Use of indocyanine green fluorescence compared to radioisotope for sentinel lymph node biopsy in early-stage breast cancer: systematic review and meta-analysis**, BACKGROUND: In early-stage breast cancer, indocyanine green (ICG)-fluorescence based sentinel lymph node (SLN) detection is being considered. This is a meta-analysis of SLN detection rates and sensitivity of ICG-fluorescence compared to radioisotope (RI), to evaluate its clinical applicability. DATA SOURCES: Systematic review of full-text articles from PubMed and Scopus, of women with early breast cancer who underwent SLN mapping using ICG and RI concurrently was performed. The meta-analysis was performed using the Mantel-Haenszel method. RESULTS: 2301 patients from 19 studies were included. No significant difference was observed between ICG and RI for SLN detection (OR0.90,95%CI0.66-1.24) or sensitivity (OR1.23,95%CI0.73-2.05) with heterogeneity between studies (I(2) = 58%,P = 0.003). Sensitivity of dual mapping (ICG + RI) was significantly better compared to single mapping with RI (OR3.69,95%CI1.79-7.62) or ICG (OR3.32,95%CI1.52-7.24) alone with no heterogeneity between studies (I(2) = 0%,P = 0.004). CONCLUSION: ICG-fluorescence could complement RI method or provide alternative in centers with poor accessibility to RI lymphoscintigraphy., Am J Surg **220**, 665, (2020). *[5.212 RR1]*

44 I. T. Rubio, R. Rodriguez-Revuelto, M. Espinosa-Bravo, C. Siso, J. Rivero, and A. Esgueva, **A randomized study comparing different doses of superparamagnetic iron oxide tracer for sentinel lymph node biopsy in breast cancer: The SUNRISE study**, INTRODUCTION: The non-radioactive method that uses the magnetic tracer (SPIO/Sienna) has shown to be a feasible technique for the SLN detection in breast cancer patients. The aim of this study is to assess the efficacy of different doses of a new magnetic tracer Sienna XP (Magtrace) compared to Tc-99 m and to evaluate its non-inferiority. METHODS: Patients diagnosed with early-stage breast cancer cT1-3 N0, from October 2016 to August 2018 were eligible and consecutively randomized to three different doses of new SPIO used: group 1 (1 mL), group 2 (1.5 mL) and group 3 (2 mL). RESULTS: A total of 135 patients were included in the study, 45 in each group. Detection of SLNs with the three doses of Sienna XP (1 mL, 1.5 mL and 2 mL) showed non-inferior rates compared to the conventional technique with radiotracer (p = 0.654). Concordance by patients with SLN positive was 100% for all groups. 83 (70.3%) patients reported skin staining at one month postoperatively, significantly lower in group 1 (p = 0.042). At 6 months follow up,

group 1 remains with significantly lower skin discoloration (p = 0,01). In multivariate analysis, dose of 2 mL showed statistically significant for the skin staining. The majority of patients (70%) felt that skin discoloration does not represent a problem. CONCLUSION: The use of the Sienna XP magnetic tracer at 1 mL is not inferior to higher doses of magnetic tracer neither is inferior to radiotracer. 1 mL of magnetic tracer resulted in significantly less skin discoloration compared to higher doses., Eur J Surg Oncol **46**, 2195, (2020). *[6.222 CC1]*

[45] S. Thongvitokomarn and N. Polchai, **Indocyanine Green Fluorescence Versus Blue Dye or Radioisotope Regarding Detection Rate of Sentinel Lymph Node Biopsy and Nodes Removed in Breast Cancer: A Systematic Review and Meta-Analysis**, BACKGROUND: Either blue dye (BD) or radioisotope (RI) is mainly used for sentinel lymph node biopsy (SLNB) in breast cancer patients. Unlike the BD, RI has lower false-negative rate of SLNB. However, its lymphoscintigraphy, difficulty in preoperative injection, and undetected sentinel lymph nodes in some cases cause surgeons to rely only on BD. Currently, indocyanine green (ICG) fluorescence method (ICG-SLNB) is increasingly used as an alternative to the conventional mapping methods in many centers. This systematic review compared ICG with the conventional method of BD or RI in terms of detection rate of SLNB and the number of sentinel lymph nodes (SLNs) removed in. METHODS: We searched all relevant studies published between January 2000 and October 2019. All data on for evaluation of SLN detection rate, number of SLNs removed per patient, and tumor positive rate of SLNB were extracted. RESULTS: A total of 30 studies, including 4,216 SLN procedures were retrieved. There was a statistically significant difference between ICG and BD method in terms of SLN detection rate (OR, 6.73; 95% CI, 4.20-10.78). However, there was no significant difference between ICG and RI in this regard (OR, 0.90; 95% CI, 0.40-2.03). The number of SLNs removed per patient were 2.35 (1.46-5.4), 1.92 (1.0-3.64), and 1.72 (1.35-2.08) for ICG, BD, and RI, respectively. Only in 8 studies, the tumor positive rates in SLNB could be analyzed (ICG, 8.5-20.7%; BD, 12.7-21.4%; RI, 11.3-16%). CONCLUSION: ICG-SLNB could be an additional or an alternative method for axillary node mapping in breast cancer.
. Asian Pac J Cancer Prev **21**, 1187, (2020). *[5.212 RR1]*

[46] V. Vural and O. C. Yılmaz, **The Turkish SentiMAG feasibility trial: preliminary results**, BACKGROUND: Sentinel node biopsy (SNB) is the standard of care for staging of the clinically and radiologically negative axillary lymph nodes in breast cancer patients. Sentinel node biopsy, with using Technetium-sulphur colloid (99 m Tc) alone or with blue dye is standard technique for evaluating axillary lymph nodes. This technique has drawbacks such as radiation exposure. Superparamagnetic iron oxide nanoparticles (SPIO) can represent a valid option for SNB. In this study; we tried to evaluate feasibility of new magnetic technique in Turkish early breast cancer patients. MATERIAL AND METHODS: The study sample consists of 143 women affected by early breast carcinoma with clinically negative axillary lymph nodes. Sentinel node localization was performed using magnetic technique. Detection rate of magnetic technique was calculated and postoperative complications were assessed. RESULTS: Results are based on 104 patients. Sentinel node identification rate was 99% (103/104, 95% CI 0.97-1.01) for magnetic technique. A median of two SNs per patient was removed. Major adverse reaction was the permanent skin coloration (7.1%). CONCLUSIONS: The magnetic technique is a feasible method for detecting SN in breast cancer patients with minimal adverse effects. Magnetic technique may be alternative to standard technique especially in breast units, where nuclear medicine unit is not available., Breast Cancer **27**, 261, (2020). *[6.222 CC1]*

[47] M. D. Alvarado *et al.*, **SentimagIC: A Non-inferiority Trial Comparing Superparamagnetic Iron Oxide Versus Technetium-99m and Blue Dye in the Detection of Axillary Sentinel Nodes in Patients with Early-Stage Breast Cancer**, BACKGROUND: Sentinel lymph node biopsy (SLNB) is a highly accurate method for staging the axilla in early breast cancer. Superparamagnetic iron oxide mapping agents have been explored to overcome the disadvantages of the standard SLNB technique, which uses a radioisotope tracer with or without blue dye. One such agent, Sienna+, was shown to be non-inferior to the standard technique for SLNB in a number of studies. The SentimagIC trial was designed to establish the non-inferiority of a new formulation of this magnetic tracer, Magtrace (formerly SiennaXP). METHODS: Patients with clinically node-negative early-stage breast cancer were recruited from six centers in the US. Patients received radioisotope and isosulfan blue dye injections, followed by an intraoperative injection of magnetic tracer, prior to SLNB. The sentinel node identification rate was compared between the magnetic and standard techniques to evaluate non-inferiority and concordance. RESULTS: Data were collected for 146 procedures in 146 patients. The per patient detection rate was 99.3% (145/146) when using the magnetic tracer and 98.6% (144/146) when using the standard technique, while the nodal detection rate was 94.3% (348/369 nodes) when using the magnetic tracer and 93.5% (345/369) when using the standard technique (difference 0.8%, 95% binomial confidence interval lower bound - 2.1%). Of the 22 patients with positive sentinel lymph nodes (SLNs), 21 (95.4%) were detected by both the magnetic tracer and the standard technique. All malignant nodes detected by

standard technique were also identified by the magnetic technique. CONCLUSION: The magnetic technique is non-inferior to the standard technique of radioisotope and blue dye for axillary SLN detection in early-stage breast cancer. The magnetic technique is therefore a viable alternative., Ann Surg Oncol **26**, 3510, (2019). *[6.222 CC1]*

48 A.-F. Hersi, S. Eriksson, J. Ramos, S. Abdsaleh, F. Warnberg, and A. Karakatsanis, **A combined, totally magnetic technique with a magnetic marker for non-palpable tumour localization and superparamagnetic iron oxide nanoparticles for sentinel lymph node detection in breast cancer surgery**, Background: Surgery for non-palpable breast cancer may often be a challenging procedure. Recently, a magnetic seed (Magseed (R)) used for tumour localization has been developed. Superparamagnetic iron oxide nanoparticles (SPIO) for sentinel lymph node (SN) detection is a novel tracer that may be injected up to four weeks preoperatively. This study is the first combining the magnetic seed and SPIO. Material and methods: Patients planned for breast conserving surgery and SN-biopsy (SNB) were recruited from two units in Sweden. Patients underwent lesion localization with Magseed (R) and SPIO injection (MagtracerM) by the breast radiologist in the preoperative period. Feasibility of successful lesion localization and excision together with a successful SNB detection was evaluated. Seed migration, number of SNs, specimen volume and calculated resection ratio (CRR) were reported.A survey of the physicians' experience was conducted. Results: Localization was performed at a median of three days before surgery (range 0-25). All 32 patients underwent microscopically radical resection with a CRR of 1.49. No seed migration was noticed. SNB was successful in all patients. A median of two SNs was retrieved. Radiologists and surgeons reported the procedure easy to learn and outperformed guidewire localization in terms of localization and excision time. They thought the technique facilitated planning localization and surgery. Conclusions: The combined magnetic technique provided accuracy in tumour localization and SN detection without excess tissue excision and with promising results for flexibility in delivery of care. Larger studies are needed to confirm these findings. (C) 2018 Elsevier Ltd, BASO similar to The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved., Ejso **45**, 544, (2019). *[6.222 CC1]*

49 A. Karakatsanis *et al.*, **Effect of preoperative injection of superparamagnetic iron oxide particles on rates of sentinel lymph node dissection in women undergoing surgery for ductal carcinoma in situ (SentiNot study)**, Background: One-fifth of patients with a preoperative diagnosis of ductal carcinoma in situ (DCIS) have invasive breast cancer (IBC) on definitive histology. Sentinel lymph node dissection (SLND) is performed in almost half of women having surgery for DCIS in Sweden. The aim of the present study was to try to minimize unnecessary SLND by injecting superparamagnetic iron oxide (SPIO) nanoparticles at the time of primary breast surgery, enabling SLND to be performed later, if IBC is found in the primary specimen. Methods: Women with DCIS at high risk for the presence of invasion undergoing breast conservation, and patients with DCIS undergoing mastectomy were included. The primary outcome was whether this technique could reduce SLND. Secondary outcomes were number of SLNDs avoided, detection rate and procedure-related costs. Results: This was a preplanned interim analysis of 189 procedures. IBC was found in 47 and a secondary SLND was performed in 41 women. Thus, 78.3 per cent of patients avoided SLND (P<0.001). At reoperation, SPIO plus blue dye outperformed isotope and blue dye in detection of the sentinel node (40 of 40 versus 26 of 40 women; P<0.001). Costs were reduced by a mean of 24.5 per cent in women without IBC (3990 versus 5286; P<0.001). Conclusion: Marking the sentinel node with SPIO in women having surgery for DCIS was effective at avoiding unnecessary SLND in this study. Registration number: ISRCTN18430240 (http://www.isrctn.com). British Journal of Surgery **106**, 720, (2019). *[6.222 CC1]*

50 V. Man, T. T. Wong, M. Co, D. Suen, and A. Kwong, **Sentinel Lymph Node Biopsy in Early Breast Cancer: Magnetic Tracer as the Only Localizing Agent**, BACKGROUND: The combined use of radioisotope and blue dye is the gold standard in sentinel lymph node (SLN) localization in early breast cancer. Superparamagnetic iron oxide (SPIO) has recently emerged as a non-inferior new tracer in sentinel lymph node mapping with fewer disadvantages. This study represents the first and the largest cohort of superparamagnetic iron oxide application in Asian population. METHODS: Retrospective analysis of a prospectively maintained database was performed from August 2016 to December 2017. All patients with SLN localization by SPIO were included in this study. RESULTS: A total of 328 breast cancer patients with 333 SLNB procedures were included in this study. Median age was 54 years (range 32-86). Median tumor size was 1.9 cm (range 0.1-12 cm).There were 138 breast-conserving surgeries and 195 mastectomies. All patients received injection of SPIO 1 day prior to operation. A total of 329 successful sentinel lymph node biopsy (SLNB) procedures were undertaken with 1514 sentinel lymph nodes (SLNs) identified. One hundred and fifty-three (10.1%) of the SLNs were positive for malignancy. There were 54 patients with macrometastases, 26 with micrometastases and 24 with isolated tumor cells. Sixty-seven patients underwent subsequent axillary dissection. Four patients failed sentinel lymph node identification with SPIO. The success rate of SPIO in sentinel lymph node localization was 98.8%.

CONCLUSION: SPIO represents a feasible alternative in sentinel lymph node mapping with comparably high nodal detection rate., World J Surg **43**, 1991, (2019). *[6.222 CC1]*

51 K. Taruno *et al.*, **Multicenter clinical trial on sentinel lymph node biopsy using superparamagnetic iron oxide nanoparticles and a novel handheld magnetic probe**, BACKGROUND: Sentinel lymph node biopsy is a standard staging procedure for early axillary lymph node-negative breast cancer. As an alternative to the currently used radioactive tracers for sentinel lymph node (SLN) detection during the surgical procedure, a number of studies have shown promising results using superparamagnetic iron oxide (SPIO) nanoparticles. Here, we developed a new handheld, cordless, and lightweight magnetic probe for SPIO detection. METHODS: Resovist (SPIO nanoparticles) were detected by the newly developed handheld probe, and the SLN detection rate was compared to that of the standard radioisotope (RI) method using radioactive colloids ((99m) Tc) and a blue dye (indigo carmine). This was a multicenter prospective clinical trial that included 220 patients with breast cancer scheduled for sentinel node biopsy after a clinical diagnosis of negative axillary lymph node from three facilities in Japan. RESULTS: Of the 210 patients analyzed, SLN was detected in 94.8% (199/210 cases, 90% confidence interval [CI]) with our magnetic method and in 98.1% (206/210 cases, 90% CI) with the RI method. The magnetic method exceeded the threshold identification rate of 90%. CONCLUSION: This was the first clinical study to use a novel handheld magnetometer to detect SLN, which we demonstrate to be not inferior to the RI method., J Surg Oncol **120**, 1391, (2019). *[6.222 CC1]*

52 C. Vermersch, T. Raia-Barjat, C. Chapelle, S. Lima, and C. Chauleur, **Randomized comparison between indocyanine green fluorescence plus (99m)technetium and (99m)technetium alone methods for sentinel lymph node biopsy in breast cancer**, Use of both patent blue and a radioisotope to locate, and reduce the risk of sentinel lymph node (SLN) detection failure in breast cancer is recommended, but drawbacks commonly lead to using only a radioisotope. An alternative method would therefore be valuable. This randomized, controlled study in 99 patients compared SLN detection using (99m)technetium (Tc) alone versus Tc combined with indocyanine green (ICG). The primary endpoint was the SLN identification rate. The primary outcome measure was the number of patients with <2 SLN detected. One SLN was detected in 44.0% of patients in the dual detection group and 40.8% in the (99m)Tc alone group (RR = 1.08 (95% CI 0.68; 1.72), p = 0.84). A mean (±SD) of 2.14 ± 1.23 SLN were identified in the dual detection group vs. 1.77 ± 0.85 using Tc alone (p = 0.09). Eight-five (78.7%) SLN were both ICG+ and TC+, 15 (13.9%) ICG+ and Tc-, and 7 (6.5%) ICG- and Tc+. SLN detected were ICG-positive in 92.6% of patients and (99m)Tc-positive in 85.2% with. No adverse event related to ICG injection was recorded. Dual detection of SLN using ICG and radioisotope is reliable and sensitive but was not superior to isotope alone in successfully locating SLN in our pilot randomized trial., Sci Rep **9**, 6943, (2019). *[5.212 CC1]*

53 K. Pohlodek, M. Foltín, I. Mečiarová, and F. Ondriaš, **Simultaneous use of magnetic method in localization of impalpable breast cancer and sentinel lymph nodes detection: initial experience**, AIM: In this study we used a new technology for localization of non-palpable breast tumors using a small steel marker in conjunction of sentinel nodes (SLNs) detection through injection of SPIO nanoparticles; both detected through a magnetic probe. Materials & methods: Ten patients with biopsy-proven nonpalpable invasive breast carcinoma or premalignant lesions eligible for SLNs biopsy were enrolled in this study. RESULTS: All tumors were removed with safe surgical margins. The mean nodal detection rate was 3.4 nodes per patient. No interferences in magnetic probe measurements due to the presence of both markers in the same breast were observed. CONCLUSION: Simultaneous use of the magnetic method in localization of impalpable breast tumors and SNs detection makes breast surgery convenient., Nanomedicine (Lond) **13**, 3075, (2018). *[5.212 CC1]*

54 L. Yuan *et al.*, **Comparison of sentinel lymph node detection performances using blue dye in conjunction with indocyanine green or radioisotope in breast cancer patients: a prospective single-center randomized study**, OBJECTIVE: This randomized study aimed to compare the clinical efficacy between the novel dual tracer composed of indocyanine green (ICG) and blue dye (BD) and the conventional dual tracer composed of radioisotope and BD for sentinel lymph node (SLN) mapping in patients with breast cancer. METHODS: This study enrolled 471 clinically lymph node-negative patients with primary breast cancer. All patients underwent mastectomy, and those undergoing sentinel lymph node biopsy (SLNB) were randomized to receive blue dye plus radioisotope (RB group) or BD plus ICG (IB group). The detection performances on SLN identification rate, positive SLN counts, detection sensitivity, and false-negative rate were compared between the two groups. RESULTS: In the IB group, 97% (194/200) of the patients who underwent the ICG and BD dual tracer injection showed fluorescent-positive lymphatic vessels within 2-5 min. The identification rate of SLNs was comparable between the IB group (99.0%, 198/200) and the RB group (99.6%, 270/271) (P = 0.79). No significant differences were observed in the identification rate of metastatic SLNs (22.5% vs. 22.9%, P > 0.05, RB group vs. IB group,

the same below), positive SLN counts (3.72 ± 2.28 vs. 3.91 ± 2.13, P > 0.05), positive metastatic SLN counts (0.38 ± 0.84 vs. 0.34 ± 0.78, P > 0.05), SLNB detection sensitivity (94.4% vs. 92.5%, P > 0.05), or false-negative rate (5.6% vs. 7.5%, P > 0.05) between the two groups. CONCLUSIONS: ICG can be used as a promising alternative tracer for radioisotope in SLN mapping, and when it is combined with BD in lymphangiography, it offers comparable detection sensitivity compared to the conventional lymphatic mapping strategies that are widely used in clinical practice., Cancer Biol Med **15**, 452, (2018). *[5.212 BB1]*

[55] J. Berrocal, L. Saperstein, B. Grube, N. R. Horowitz, A. B. Chagpar, B. K. Killelea, and D. R. Lannin, **Intraoperative Injection of Technetium-99m Sulfur Colloid for Sentinel Lymph Node Biopsy in Breast Cancer Patients: A Single Institution Experience**, Background. Most institutions require a patient undergoing sentinel lymph node biopsy to go through nuclear medicine prior to surgery to be injected with radioisotope. This study describes the long-term results using intraoperative injection of radioisotope. Methods. Since late 2002, all patients undergoing a sentinel lymph node biopsy at the Yale-New Haven Breast Center underwent intraoperative injection of technetium-99m sulfur colloid. Endpoints included number of sentinel and nonsentinel lymph nodes obtained and number of positive sentinel and nonsentinel lymph nodes. Results. At least one sentinel lymph node was obtained in 2,333 out of 2,338 cases of sentinel node biopsy for an identification rate of 99.8%. The median number of sentinel nodes found was 2 and the mean was 2.33 (range: 1-15). There were 512 cases (21.9%) in which a sentinel node was positive for metastatic carcinoma. Of the patients with a positive sentinel lymph node who underwent axillary dissection, there were 242 cases (54.2%) with no additional positive nonsentinel lymph nodes. Advantages of intraoperative injection included increased comfort for the patient and simplification of scheduling. There were no radiation related complications. Conclusion. Intraoperative injection of technetium-99m sulfur colloid is convenient, effective, safe, and comfortable for the patient., Surg Res Pract **2017**, 5924802, (2017). *[6.222 CC1]*

[56] M. Ghilli *et al.*, **The superparamagnetic iron oxide tracer: a valid alternative in sentinel node biopsy for breast cancer treatment**, The European Union has determined that from 2016 breast cancer patients should be treated in Specialist Breast Units that achieve the minimum standards for the mandatory quality indicators as defined by Eusoma. The existing standard for axillary lymph node staging in breast cancer is sentinel node biopsy (SNB), performed using Technetium-sulphur colloid ((99m) Tc) alone or with blue dye. The major limits of radioisotope consist in the problems linked to radioactivity, in the shortage of tracer and nuclear medicine units. Among existing alternative tracers, SentiMag(®) , which uses superparamagnetic iron oxide particles, can represent a valid option for SNB. We conducted a paired, prospective, multicentre study to evaluate the non-inferiority of SentiMag(®) vs. (99m) Tc. The primary end point was the detection rate (DR) per patient. The study sample consists of 193 women affected by breast carcinoma with negative axillary assessment. The concordance rate per patients between (99m) Tc and SentiMag(®) was 97.9%. The DR per patient was 99.0% for (99m) Tc and 97.9% for SentiMag(®) . SentiMag(®) appears to be non-inferior to the radiotracer and safe. While (99m) Tc remains the standard, SentiMag(®) DR appears adequate after a minimum learning curve. In health care settings where nuclear medicine units are not available, SentiMag/Sienna+(®) allows effective treatment of breast cancer patients., Eur J Cancer Care (Engl) **26**, (2017). *[6.222 CC1]*

[57] A. Karakatsanis, K. Daskalakis, P. Stålberg, H. Olofsson, Y. Andersson, S. Eriksson, L. Bergkvist, and F. Wärnberg, **Superparamagnetic iron oxide nanoparticles as the sole method for sentinel node biopsy detection in patients with breast cancer**, BACKGROUND: Sentinel node biopsy (SNB) using superparamagnetic iron oxide (SPIO) nanoparticles is a novel method in breast cancer. Several studies have verified the non-inferiority of SPIO compared with the standard use of radioisotope (99m) Tc with or without blue dye. The aim of the MONOS study presented here was to evaluate the use of SPIO as a sole tracer and the efficacy of tracer injection in the preoperative setting. METHODS: This prospective cohort study was carried out in two hospitals, one using (99m) Tc and the other SPIO. (99m) Tc was injected in the morning of the day of surgery or the day before. SPIO was either injected before surgery in the outpatient clinic or 1 h before the operation. RESULTS: A total of 338 consecutive patients with breast cancer underwent 343 procedures; SPIO nanoparticles were used in 184 procedures and (99m) Tc-labelled tracer in 159. Detection rates for SPIO and (99m) Tc were 95·6 and 96·9 per cent respectively (P = 0·537). All nodes with SPIO uptake were coloured brown. Fewer nodes were retrieved with SPIO (mean 1·35 versus 1·89), regardless of whether blue dye was used (P < 0·001). Preoperative SPIO injection (58·7 per cent of procedures), a median of 16 (range 2-27) days before the procedure, was associated with a better tracer-specific detection rate (95·3 versus 86 per cent; P = 0·031) and retrieval of more nodes (mean 1·43 versus 1·03; P < 0·001) than perioperative administration. Skin staining was present in 39·9 per cent of patients, and was related to breast-conserving surgery and periareolar injection. CONCLUSION: The use of SPIO alone is a safe alternative, with results comparable to those of the standard dual technique using (99m) Tc and blue dye. The efficacy of

injection in the preoperative setting simplifies logistics and improves performance. Skin staining can be prevented by a deeper peritumoral injection., Br J Surg **104**, 1675, (2017). *[6.222 CC1]*

58 M. C. Peek, P. Charalampoudis, B. Anninga, R. Baker, and M. Douek, **Blue dye for identification of sentinel nodes in breast cancer and malignant melanoma: a systematic review and meta-analysis**, The combined technique (radioisotope and blue dye) is the gold standard for sentinel lymph node biopsy (SLNB) and there is wide variation in techniques and blue dyes used. We performed a systematic review and meta-analysis to assess the need for radioisotope and the optimal blue dye for SLNB. A total of 21 studies were included. The SLNB identification rates are high with all the commonly used blue dyes. Furthermore, methylene blue is superior to iso-sulfan blue and Patent Blue V with respect to false-negative rates. The combined technique remains the most accurate and effective technique for SLNB. In order to standardize the SLNB technique, comparative trials to determine the most effective blue dye and national guidelines are required., Future Oncol **13**, 455, (2017). *[5.212 RR1]*

59 J.-L. Houpeau, M.-P. Chauvet, F. Guillemin, C. Bendavid-Athias, H. Charitansky, A. Kramar, and S. Giard, **Sentinel Lymph Node Identification Using Superparamagnetic Iron Oxide Particles Versus Radioisotope: The French Sentimag Feasibility Trial**, Background and Objectives: The French Sentimag feasibility trial evaluated a new method for the localization of breast cancer sentinel lymph node (SLN) using Sienna+(R), superparamagnetic iron oxide particles, and Sentimag (R) detection in comparison to the standard technique (isotopes +/- blue dye). Methods: We conducted a prospective multicentric paired comparison trial on 115 patients. SLN localization was performed using both the magnetic technique and the standard method. Detection rate and concordance between magnetic and standard tracers were calculated. Postoperative complications were assessed after 30 days. Results: Results are based on 108 patients. SLN identification rate was 98.1% [93.5-99.8] for both methods, 97.2% [92.1-99.4] for Sienna+(R) and 95.4% [89.5-98.5] for standard technique. A mean of 2.1 SLNs per patient was removed. The concordance rate was 99.0% [94.7-100.0%] per patient and 97.4% [94.1-99.2] per node. Forty-six patients (43.4%) had nodal involvement. Among involved SLNs, concordance rate was 97.7% [88.0-99.9] per patient and 98.1% [90.1-100.0] per node. Conclusions: This new magnetic tracer is a feasible method and a promising alternative to the isotope. It could offer benefits for ambulatory surgery or sites without nuclear medicine departments. (C) 2016 Wiley Periodicals, Inc., Journal of Surgical Oncology **113**, 501, (2016). *[6.222 CC1]*

60 M. G. Niebling, R. G. Pleijhuis, E. Bastiaannet, A. H. Brouwers, G. M. van Dam, and H. J. Hoekstra, **A systematic review and meta-analyses of sentinel lymph node identification in breast cancer and melanoma, a plea for tracer mapping**, PURPOSE: Sentinel lymph node biopsy (SLNB) has become a widely accepted staging procedure for both breast carcinoma and melanoma. The aim of our study was to systematically review different SLNB techniques and perform a meta-analysis for corresponding identification and false-negative rates. METHODS: A systematic review of the literature on SLNB in patients with early stage breast carcinoma and melanoma was performed. Only original study groups were included. The SLN identification rate and false negative rate were pooled for patients with breast carcinoma or melanoma according to radiocolloid tracer, blue dye, indocyanine green (ICG), or a combination of a radiocolloid tracer with blue dye or ICG. RESULTS: Between 1992 and 2012, a total of 154 studies (88 breast carcinoma and 66 melanoma) were reported that met our eligibility criteria. These studies included a total of 44,172 patients. The pooled SLN identification rate in breast carcinoma and melanoma patients using solely blue dye was 85% (range: 65-100%) and 84% (range: 59-100%), while for radiocolloid alone it was 94% (range: 67-100%) and 99% (range: 83-100%), respectively. Using a combination of radiocolloid and blue, identification rates were 95% (range 94-95%) and 98% (range: 98-98%). CONCLUSIONS: The current meta-analysis provides data that favors the use of radiocolloid or radiocolloid combined with a blue dye for SLN identification. Performing SLNB with radiocolloid alone is the technique of choice for experienced surgeons, since blue dye has multiple disadvantages. SLNB using ICG as a fluorescent dye seems a promising technique for the near future., Eur J Surg Oncol **42**, 466, (2016). *[6.222 RR1]*

61 M. C. Peek, T. Kovacs, R. Baker, H. Hamed, A. Kothari, and M. Douek, **Is blue dye still required during sentinel lymph node biopsy for breast cancer?**, BACKGROUND: In early breast cancer, the optimal technique for sentinel lymph node biopsy (SLNB) is the combined technique (radioisotope and Patent Blue V) which achieves high identification rates. Despite this, many centres have decided to stop using blue dye due to blue-dye-related complications (tattoo, anaphylaxis). We evaluated the SLNB identification rate using the combined technique with and without Patent Blue V and the blue-dye-related complication rates. METHODS: Clinical and histological data were analysed on patients undergoing SLNB between March 2014 and April 2015. SLNB was performed following standard hospital protocols using the combined technique. RESULTS: A total of 208 patients underwent SLNB and 160 patients (342 nodes) with complete operation notes were available for final analysis. The identification rate with the

combined technique was 98.8% (n = 158/160), with blue dye alone 92.5% (n = 148/160) and with radioisotope alone 97.5% (n = 156/160). A total of 76.9% (263/342) of nodes were radioactive and blue, 15.5% (53/342) only radioactive and 2.3% (8/342) only blue, 5.3% (18/342) were neither radioactive nor blue. No anaphylactic reactions were reported and blue skin staining was reported in six (3.8%) patients. CONCLUSION: The combined technique should continue be the preferred technique for SLNB and should be standardised. Radioisotope alone (but not blue dye alone) has comparable sentinel node identification rates in experienced hands. National guidelines are required to optimise operative documentation., Ecancermedicalscience **10**, 674, (2016). *[6.222 RR1]*

62 M. Teshome, C. Wei, K. K. Hunt, A. Thompson, K. Rodriguez, and E. A. Mittendorf, **Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage Breast Cancer Patients: A Meta-analysis**, BACKGROUND: Sentinel lymph node (SLN) dissection involves lymphatic mapping and selective removal of clinically negative lymph nodes at highest risk for harboring metastases. Lymphatic mapping is most often performed using radioisotope with or without blue dye (standard tracers). Sienna+(®), a superparamagnetic iron oxide that can be detected using the Sentimag(®) magnetometer, is an alternative mapping agent to identify SLNs that has been investigated in five clinical trials. This meta-analysis was performed to determine if Sienna+(®) is non-inferior for SLN detection when compared to standard tracers. METHODS: Five clinical trials comparing Sienna+(®) to a standard technique were identified, and data from these studies were used to determine the agreement by Kappa statistic between Sienna+(®) and standard tracers in identifying SLNs and malignant SLNs. The trials included 1683 SLNs identified in 804 patients. Data from the studies were imbalanced, therefore additional agreement indices were utilized to compare techniques. The estimated difference between the techniques was analyzed and a margin of ≤5 % was used to determine non-inferiority. RESULTS: Agreement between the Sienna+(®) and standard tracers was strong for SLN detection by patient [prevalence-adjusted bias-adjusted kappa (PABAK) 0.94, 95 % confidence interval (CI) 0.89-0.98], moderate to substantial for SLN detection by node (PABAK 0.68, 95 % CI 0.54-0.82), and strong for the detection of malignant SLNs by patient (PABAK 0.89, 95 % CI 0.84-0.95). Sienna+(®) demonstrated non-inferiority compared with standard tracers. CONCLUSIONS: The Sienna+(®) mapping agent is non-inferior to the standard method for SLN detection in patients with clinically node-negative breast cancer., Ann Surg Oncol **23**, 1508, (2016). *[6.222 CC1]*

63 M. Ahmed, B. Anninga, S. Goyal, P. Young, Q. A. Pankhurst, M. Douek, and S. T. G. Mag, **Magnetic sentinel node and occult lesion localization in breast cancer (MagSNOLL Trial)**, BACKGROUND: Non-palpable breast cancers require localization-guided surgery and axillary staging using sentinel lymph node biopsy (SLNB). This study investigated the novel technique of magnetic-guided lesion localization and concurrent SLNB, which avoids the need for wire-guided localization and radioisotopes. METHODS: An ultrasound-guided intratumoral injection of magnetic tracer (0.5 ml) was performed in a protocol-driven predefined minimum of ten patients with palpable breast cancer to assess the ability of the magnetic tracer safely to localize the tumour at the site of injection and concurrently drain to the lymphatics. Once successful lesion localization had been confirmed (peak magnetometer count retained at the centre of the tumour), the technique was undertaken in a further 20 patients with non-palpable breast cancers awaiting wide local excision and SLNB. All patients underwent SLNB with both the magnetic and standard dual (radioisotope and Patent Blue V dye) techniques. RESULTS: Thirty-two patients were recruited, of whom 12 (1 with bilateral disease) presented with palpable and 20 with non-palpable breast cancer. Peak magnetometer counts were retained at the tumour centre in all palpable (13) and non-palpable (20) breast cancers. Re-excisions for involved margins were necessary in two patients with non-palpable breast cancers. The sentinel lymph node identification rates were 28 of 33 procedures for the magnetic technique alone, 32 of 33 for the magnetic technique combined with blue dye, and 32 of 33 for the standard dual technique. CONCLUSION: Magnetic lesion localization is feasible, with intratumoral magnetic tracer injection combined with a periareolar injection of blue dye for subsequent SNLB., Br J Surg **102**, 646, (2015). *[6.222 CC1]*

64 J. J. Pouw, M. R. Grootendorst, R. Bezooijen, C. A. Klazen, W. I. De Bruin, J. M. Klaase, M. A. Hall-Craggs, M. Douek, and B. Ten Haken, **Pre-operative sentinel lymph node localization in breast cancer with superparamagnetic iron oxide MRI: the SentiMAG Multicentre Trial imaging subprotocol**, OBJECTIVE: Sentinel lymph node biopsy (SLNB) with a superparamagnetic iron oxide (SPIO) tracer was shown to be non-inferior to the standard combined technique in the SentiMAG Multicentre Trial. The MRI subprotocol of this trial aimed to develop a magnetic alternative for pre-operative lymphoscintigraphy (LS). We evaluated the feasibility of using MRI following the administration of magnetic tracer for pre-operative localization of sentinel lymph nodes (SLNs) and its potential for non-invasive identification of lymph node (LN) metastases. METHODS: Patients with breast cancer scheduled to undergo SLNB were recruited for pre-operative LS, single photon emission CT (SPECT)-CT and SPIO MRI. T1 weighted turbo spin echo and T2 weighted gradient echo sequences were used

before and after interstitial injection of magnetic tracer into the breast. SLNs on MRI were defined as LNs with signal drop and direct lymphatic drainage from the injection site. LNs showing inhomogeneous SPIO uptake were classified as metastatic. During surgery, a handheld magnetometer was used for SLNB. Blue or radioactive nodes were also excised. The number of SLNs and MR assessment of metastatic involvement were compared with surgical and histological outcomes. RESULTS: 11 patients were recruited. SPIO MRI successfully identified SLNs in 10 of 11 patients vs 11 of 11 patients with LS/SPECT-CT. One patient had metastatic involvement of four LNs, and this was identified in one node on pre-operative MRI. CONCLUSION: SPIO MRI is a feasible technique for pre-operative localization of SLNs and, in combination with intraoperative use of a handheld magnetometer, provides an entirely radioisotope-free technique for SLNB. Further research is needed for the evaluation of MRI characterization of LN involvement using subcutaneous injection of magnetic tracer. ADVANCES IN KNOWLEDGE: This study is the first to demonstrate that an interstitially administered magnetic tracer can be used both for pre-operative imaging and intraoperative SLNB, with equal performance to imaging and localization with radioisotopes., Br J Radiol **88**, 20150634, (2015). *[6.222 CC1]*

65 S.-Y. Jung *et al.*, **Comparison of Sentinel Lymph Node Biopsy Guided by the Multimodal Method of Indocyanine Green Fluorescence, Radioisotope, and Blue Dye Versus the Radioisotope Method in Breast Cancer: A Randomized Controlled Trial**, Purpose. This study aimed to evaluate the identification rate and surgery time of sentinel lymph node biopsy (SLNB) by a multimodal method (MMM) using a mixture of indocyanine green (ICG), radioisotope (RI), and blue dye (BD) compared with the RI alone. Methods. In this phase II randomized study, 86 patients with clinically node-negative breast cancer were enrolled and received SLNB with either MMM or RI. We compared the identification rate, number of sentinel lymph nodes (SLNs), and detection time of SLNB and evaluated the safety. Results. The mean age of the MMM group and RI group was 48.2 and 51.0 years ($p = 0.12$), respectively. There were no differences in histopathologic factors, including tumor size, node positivity, and hormone receptor positivity between groups. SLNs were identified in all patients of both groups (100 % in the MMM group and 100 % in the RI group). The average number of SLNs in the MMM group was more than that in the RI group (3.4 +/- 1.37 vs. 2.3 +/- 1.04, respectively; $p < 0.001$). The time to detect the first sentinel lymph node was similar in each group (6.5 +/- 5.16 vs. 8.0 +/- 4.35 min; $p = 0.13$). In the MMM group, percutaneous lymphatic drainage was visualized by fluorescent imaging in 90.7 % (39 of 43 patients). During and after the operation, there were no complications, including allergic reactions, skin staining, or necrosis. Conclusions. This study is the first randomized trial that compared MMM using ICG, RI, and BD and the conventional RI method for SLNB. MMM is a feasible and safe method for SLNB., Annals of Surgical Oncology **21**, 1254, (2014). *[6.222 CC1]*

66 E. Cigna, A. Gradilone, D. Ribuffo, P. Gazzaniga, P. Fino, V. Sorvillo, and N. Scuderi, **Morbidity of selective lymph node biopsy for melanoma: meta-analysis of complications**, BACKGROUND AND AIM: Intraoperative lymphatic mapping and selective lymph node biopsy is accepted worldwide as the standard procedure for staging regional lymph nodes of 1-4 mm thick melanomas, as well as for other neoplasms. Although it is often stated that selective lymph node biopsy is a minimally invasive procedure associated with few complications, few data exist concerning the morbidity associated with the procedure. The present analysis was performed to evaluate the morbidity associated with selective lymph node biopsy in a long-term follow-up. MATERIALS AND METHODS: The study provides a review of 437 selective lymph node biopsies on 269 patients, operated on between the 1994 and the 2009, for the lymph node biopsy of head and neck, groin, axilla, upper and lower limbs and nodal basins. Patients' history and follow-up were reviewed for 2 weeks after surgery, every 3 months for the first 2 years, every 4 months during the third year, and every 6 months subsequently, and postoperative morbidity was evaluated. RESULTS: After sentinel node biopsy, 14 patients developed one of the following complications: hematoma, 1 case (0.30%); lymphedema, 1 case (0.30%); seroma, 2 cases (0.61%); wound infection, 6 cases (1.83%); keloid scar, 2 cases (0.61%); and postoperative pain, 2 cases (0.61%). The total complication rate was 4.26%. CONCLUSIONS: Selective lymph node biopsy for melanoma, as for other tumors, in respect to radical lymphadenectomy, is not a complications-free procedure but is usually not severe., Tumori **98**, 94, (2012).

67 A. Lorek, Z. Stojčev, W. Zarębski, M. Kowalczyk, and K. Szyluk, **Analysis of Postoperative Complications After 303 Sentinel Lymph Node Identification Procedures Using the SentiMag® Method in Breast Cancer Patients**, BACKGROUND The objective of this paper was to assess the complications following sentinel lymph node biopsy (SLNB) in breast cancer patients using the SentiMag® method. MATERIAL AND METHODS The study material consisted of 368 patients who had received the SLNB procedure in combination with wide local excision (WLE), simple mastectomy or who had an autonomous SLNB procedure in the period from January 2014 to September 2017. The final study group consisted of 303 patients who attended follow-up consultations. RESULTS Sensory disturbances in the arm occurred in 12 patients (9.9%), including 3 patients (1.5%) after WLE and 9

patients (8.4%) after simple mastectomy. Restricted mobility in the upper limb was experienced by 9 patients (7.1%), including 3 patients (1.5%) after WLE and 6 patients (5.6%) after simple mastectomy. Minimal-degree lymphedema developed in 9 patients (7.5%), including 2 patients (1%) after WLE and 7 patients (6.5%) after simple mastectomy. A significant correlation was demonstrated between the incidence of these complications and the number of lymph nodes dissected. A significantly higher incidence of paresthesia and lymphedema was revealed for simple mastectomy with SLNB when compared to WLE with SLNB. Discolorations upon tracer administration were observed in 47 patients (15.5%). CONCLUSIONS SentiMag® is a safe sentinel lymph node identification method used in breast cancer and has a low risk of complications. The rate of complications increases together with the number of dissected lymph nodes and the extent of the surgery. The possibility of temporary discolorations on the skin should be communicated to the patients explicitly prior to surgery., Med Sci Monit **25**, 3154, (2019). *[6.222 CC1]*

[68] A. Karakatsanis *et al.*, **The Nordic SentiMag trial: a comparison of super paramagnetic iron oxide (SPIO) nanoparticles versus Tc-99 and patent blue in the detection of sentinel node (SN) in patients with breast cancer and a meta-analysis of earlier studies**, The aim of the study is to compare the efficacy of SPIO as a tracer in sentinel node biopsy (SNB) in breast cancer with Tc and patent blue in a multicentre prospective study and perform a meta-analysis of all published studies. It also aims to follow skin discoloration after SPIO injection and describe when and how it resolves. Totally 206 patients with early breast cancer were recruited. Tc and patent blue were administered in standard fashion. Patients were injected with SPIO (Sienna+) preoperatively. SNB was performed and detection rates were recorded for both methods. Skin discoloration was followed and documented postoperatively. Data extraction and subsequent meta-analysis of all previous studies were also performed. SN detection rates were similar between standard technique succeeded and SPIO both per patient (97.1 vs. 97.6 %, p = 0.76) as well as per node (91.3 vs. 93.3 %, p = 0.34), something which was not affected by the presence of malignancy. Concordance rates were also consistently high (98.0 % per patient and 95.9 % per node). Discoloring was present in 35.5 % of patients postoperatively, almost exclusively in breast conservation. It fades slowly and is still detectable in 8.6 % of patients after 15 months. Meta-analysis depicted similar detection rates (p = 0.71) and concordance rates (p = 0.82) per patient. However, it seems that SPIO is characterized by higher nodal retrieval (p < 0.001). SPIO is an effective method for the detection of SN in patients with breast cancer. It is comparable to the standard technique and seems to simplify logistics. Potential skin discoloration is something of consideration in patients planned for breast conservation., Breast Cancer Research and Treatment **157**, 281, (2016). *[6.222 CC1]*

[69] A. S. Fattahi, A. Tavassoli, O. Rohbakhshfar, R. Sadeghi, A. Abdollahi, and M. N. Forghani, **Can methylene blue dye be used as an alternative to patent blue dye to find the sentinel lymph node in breast cancer surgery?**, BACKGROUND: Sentinel lymph node biopsy (SLNB) is standard care to evaluate axillary involvement in early breast cancer. It has fewer complications than complete lymph node dissection; however, using blue dye in SLNB is controversial. We have evaluated the detection rate and local complications associated with methylene blue dye (MBD) used in SLNB in early breast cancer patients and compared these results to patent blue dye (PBD). MATERIALS AND METHODS: In a cohort prospective study, 312 patients with early breast cancer without axillary lymph node involvement were divided into two groups according to dye type. All of the patients received radiotracer and one type of blue dye. We filled out a checklist for the patients that contained demographic data, size of tumor, stage, detection of sentinel lymph node, and complications and then analyzed the data. RESULTS: Demographic and histopathologic characteristics were not significantly different in both groups. Mean (standard deviation [SD]) tumor size in all patients was 2.4 (0.8) cm. Detection rate in the MBD group was 77.5% with dye alone and 94.2% with dye and radioisotope; and in the PBD group it was 80.1% and 92.9% respectively (P > 0.05). We had blue discoloration of the skin in 23.7% in the PBD and 14.1% in the MBD group (P < 0.05) local inflammation was detected in one patient in the PBD and five in the MBD group (P < 0.05). Skin necrosis and systemic complications were not observed. CONCLUSION: Methylene blue has an acceptable detection rate, which may be a good alternative in SLNB. Complication such as blue discoloration of the skin was also lower with MBD., J Res Med Sci **19**, 918, (2014). *[6.222 CC1]*

[70] M. Gumus, H. Gumus, S. E. Jones, P. A. Jones, A. R. Sever, and J. Weeks, **How long will I be blue? Prolonged skin staining following sentinel lymph node biopsy using intradermal patent blue dye**, BACKGROUND: Blue dye used for sentinel lymph node biopsy (SLNB) in breast cancer patients may cause prolonged skin discoloration at the site of injection. The aim of this study was to assess the duration of such skin discoloration. PATIENTS AND METHODS: 236 consecutive patients who had undergone breast conserving surgery and SLNB for breast cancer were reviewed prospectively from January 2007 to December 2009. RESULTS: Of the 236 patients, 2 had undergone bilateral surgery, and 41 had been examined in consecutive yearly reviews. Blue discoloration remained visible at the injection

site after 12, 24, and > 36 months in 36.5, 23.6, and 8.6% of the patients, respectively. CONCLUSION: The use of patent blue for identification of the sentinel lymph node in patients undergoing breast cancer surgery may result in prolonged discoloration of the skin at the injection site., Breast Care (Basel) **8**, 199, (2013). *[6.222 CC1]*

71 R. Ponzone, N. T. Cont, F. Maggiorotto, E. Cassina, P. Mininanni, N. Biglia, and P. Sismondi, **Extensive nodal disease may impair axillary reverse mapping in patients with breast cancer**, PURPOSE: The aim of axillary reverse mapping (ARM) is to preserve arm lymphatics in patients with breast cancer who underwent surgical axillary staging. PATIENTS AND METHODS: From June 2007 to December 2008, 49 patients who required axillary dissection (AD) underwent ARM. One milliliter of patent blue dye was injected in the ipsilateral arm, and all blue nodes identified during AD were sent separately for pathologic examination. Main variables associated with the detection rates of blue lymphatics, the pathologic status of blue and nonblue nodes, and the complications of the procedure were analyzed. Results Identification rates of blue lymphatics and blue nodes were 73.5% and 55.1%, respectively. Blue node identification was influenced by the time elapsed between injection of blue dye and surgery (P = .002) but not by the learning curve of the procedure. Although the blue node was clear of metastases in 24 of 27 patients, three patients with extensive nodal metastatic involvement (ie, pN2a and pN3a) showed breast cancer metastatic cells in the blue nodes as well. The only adverse effect of the procedure was skin tattooing at the injection site, which disappeared within 4 months in almost 80% of the procedures. CONCLUSION: In patients with clinically negative axillary nodes, additional study is warranted to assess whether ARM may be used to spare the lymphatics from the arm. In the presence of extensive nodal disease, this technique may identify metastatic blue nodes, which demonstrates that there is not reliable separation of arm and breast lymphatic pathways., J Clin Oncol **27**, 5547, (2009). *[6.222 CC1]*

72 G. A. Govaert, R. J. Oostenbroek, and P. W. Plaisier, **Prolonged skin staining after intradermal use of patent blue in sentinel lymph node biopsy for breast cancer**, AIMS: To investigate the duration of staining of the skin after intradermal injection of patent blue during sentinel lymph node biopsy (SLNB) for breast cancer. METHODS: The clinical data of 33 consecutive patients who underwent a SLNB in combination with breast conserving therapy (BCT) in our hospital were retrospectively reviewed. Also, patients were interviewed at intervals of 3 months until the blue staining of their skin had disappeared. RESULTS: At mean follow-up of 18 months (range: 12-28) patent blue was visible at the site of injection after 3, 6, 9 and 12 months in 70, 64, 44 and 41% of the patients, respectively. CONCLUSIONS: Use of the intradermal injection technique of patent blue during sentinel lymph node biopsy in BCT may result in remarkably long discolouring of the skin at the site of injection., Eur J Surg Oncol **31**, 373, (2005). *[6.222 CC1]*

73 A. Pinero-Madrona *et al.*, **Correlation between ferromagnetic and isotopic tracers for sentinel lymph node detection in cutaneous melanoma: IMINEM study**, Background The usefulness of sentinel lymph node biopsy (SLNB) in staging cutaneous melanoma has been proven. Therefore, different tracers have been used to identify the sentinel lymph nodes (SLNs). The use of isotopic tracers together with radioactivity detectors allowed a much more precise and direct approach to the SLNs. However, not all centres have access to a Nuclear Medicine department hindering sentinel lymph node detection (SLND) and consequently, other markers such as ferromagnetic tracers have been evaluated looking for the same advantages and effectiveness as isotopic tracers. Ferromagnetic tracers have proven their usefulness in other cancer entities such as breast, prostate and thyroid cancer. The objective was to assess the detection and concordance rates between isotopic and ferromagnetic techniques for SLNB in cutaneous melanoma. Method Isotopic SLNB technique and ferromagnetic tracer were compared for cutaneous melanoma in a non-inferiority multicentre prospective study carried out in six Spanish hospitals. Results A total of 60 patients were recruited and 133 lymph nodes removed. The detection rate was slightly higher with ferromagnetic tracer in head-neck and trunk melanomas, and with isotopic tracer in limbs. The patients' and nodes' concordance rates between both techniques for ex vivo samples were 95% and 86% for head-neck and trunk tumours and 97% and 93% for limbs tumours, respectively. The concordance rates for involved nodes were 100% and 88.2% for patients and nodes, respectively. Conclusion The intraoperative detection and biopsy of SLN in cutaneous melanoma using a ferromagnetic was a reliable alternative method to the isotopic technique in cutaneous melanomas., Journal of Surgical Oncology, (2020). *[6.222 CC1]*

74 B. Anninga *et al.*, **Magnetic Technique for Sentinel Lymph Node Biopsy in Melanoma: The MELAMAG Trial**, Sentinel lymph node biopsy (SLNB) in melanoma is currently performed using the standard dual technique (radioisotope and blue dye). The magnetic technique is non-radioactive and provides a brown color change in the sentinel lymph node (SLN) through an intradermal injection of a magnetic tracer, and utilizes a handheld magnetometer. The MELAMAG Trial compared the magnetic technique with the standard technique for SLNB in melanoma. Clinically node-negative patients with

primary cutaneous melanoma were recruited from four centers. SLNB was undertaken after intradermal administration of both the standard (blue dye and radioisotope) and magnetic tracers. The SLN identification rate per patient, with the two techniques, was compared. A total of 133 patients were recruited, 129 of which were available for final analysis. The sentinel node identification rate was 97.7 % (126/129) with the standard technique and 95.3 % (123/129) with the magnetic technique [2.3 % difference; 95 % upper confidence limit (CL) 6.4; 5.4 % discordance]. With radioisotope alone, the SLN identification rate was 95.3 % (123/129), as with the magnetic technique (0 % difference; 95 % upper CL 4.5; 7.8 % discordance). The lymph node retrieval rate was 1.99 nodes per patient overall, 1.78 with the standard technique and 1.87 with the magnetic technique. The magnetic technique is feasible for SLNB in melanoma with a high SLN identification rate, but is associated with skin staining. When compared with the standard dual technique, it did not reach our predefined non-inferiority margin., Annals of Surgical Oncology **23**, 2070, (2016). *[6.222 CC1]*

75 A. Pinero-Madrona *et al.*, **Superparamagnetic iron oxide as a tracer for sentinel node biopsy in breast cancer: A comparative non-inferiority study**, Aims: The gold standard for detection of Sentinel Lymph Nodes (SLN) is a combined radioisotope and blue dye breast injection, using a gamma probe (GP). A new, non-radioactive method was developed, using a tracer (Sienna+(R)) of superparamagnetic iron oxide (SPIO) nanoparticles and a manual magnetometer (SentiMag (R)) (SM). The IMAGINE study was designed to show the non-inferiority of SM compared to GP, for the detection of SLN in breast cancer patients with SLN biopsy indication. Methods: From November 2013 to June 2014, 181 patients were recruited, and 321 nodes were excised and assessed ex-vivo. Readings from both SM and GP devices were recorded during transcutaneous, intraoperative, and ex-vivo detection attempts. Results: At the patient level, ex-vivo detection rates (primary variable) with SM and GP were 97.8% and 98.3% (concordance rate 99.4%). Transcutaneous and intraoperative detection rates were 95.5% vs 97.2%, and 97.2% vs 97.8% for SM and GP respectively (concordance rates > 97%). At the node level, intraoperative and ex-vivo detection rates were 92.5% vs 89.3% and 91.0% vs 86.3% for SM and GP respectively. In all cases the non-inferiority of SM compared to SM was shown by ruling out a predefined non-inferiority margin of 5%. Conclusions: Our study showed the non-inferiority of SM as compared to GP. Moreover, the ex-vivo and intraoperative detection rates at the node level were slightly higher with SM. (C) 2015 Elsevier Ltd. All rights reserved., Ejso **41**, 991, (2015). *[6.222 CC1]*

76 I. T. Rubio, S. Diaz-Botero, A. Esgueva, R. Rodriguez, T. Cortadellas, O. Cordoba, and M. Espinosa-Bravo, **The superparamagnetic iron oxide is equivalent to the Tc99 radiotracer method for identifying the sentinel lymph node in breast cancer**, BACKGROUND: Preoperative injection of Tc99 is standardly performed before sentinel lymph node biopsy (SLN) for breast cancer. Multiple questions have arisen concerning appropriate technique for SLNBs including site of injection, timing and injection material. The aim of this study was to assess the concordance between a new method, superparamagnetic iron oxide (SPIO) and the Tc99 radiotracer to identify the SLN in early breast cancer. MATERIAL AND METHODS: Between July 2013 and March 2014, 120 patients with clinically node negative early breast cancer were included in the study. Patients were injected the day before the radiotracer for lymphoscintigraphy and injected the SPIO subareolar intraoperatively. SLN was excised if it was radioactive, magnetic or palpable. Patients signed an inform consent. RESULTS: There was no drainage by either technique in 2 patients, so this leaves 118 patients for further analysis. Detection rate by Tc 99 was successful in 113 (95.7%%) patients and by SPIO in 116 (98.3%). Concordance rates per patient between techniques was 98.2%. The SLN was positive in 36 (30%) patients. Of this, SLN positivity was detected by both techniques in 32 patients. Mean number of SLNs by 99Tc and SPIO were 1.9 and 2.21 respectively (p = 0.001). DISCUSSION: Detection of SLNs with SPIO allows for easy identification of axillary nodes, at a frequency not inferior to the radiotracer. It is an oncologically safe procedure, facilitates patients and operative room management and can be used to reliably identify SLNs in breast cancer., Eur J Surg Oncol **41**, 46, (2015). *[6.222 CC1]*

77 M. Douek *et al.*, **Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG Multicentre Trial**, BACKGROUND: The SentiMAG Multicentre Trial evaluated a new magnetic technique for sentinel lymph node biopsy (SLNB) against the standard (radioisotope and blue dye or radioisotope alone). The magnetic technique does not use radiation and provides both a color change (brown dye) and a handheld probe for node localization. The primary end point of this trial was defined as the proportion of sentinel nodes detected with each technique (identification rate). METHODS: A total of 160 women with breast cancer scheduled for SLNB, who were clinically and radiologically node negative, were recruited from seven centers in the United Kingdom and The Netherlands. SLNB was undertaken after administration of both the magnetic and standard tracers (radioisotope with or without blue dye). RESULTS: A total of 170 SLNB procedures were undertaken on 161 patients, and 1 patient was excluded, leaving 160 patients for further analysis. The identification rate was 95.0 % (152 of 160) with the standard technique and 94.4 % (151 of 160) with the magnetic technique (0.6 % difference; 95

% upper confidence limit 4.4 %; 6.9 % discordance). Of the 22 % (35 of 160) of patients with lymph node involvement, 16 % (25 of 160) had at least 1 macrometastasis, and 6 % (10 of 160) had at least a micrometastasis. Another 2.5 % (4 of 160) had isolated tumor cells. Of 404 lymph nodes removed, 297 (74 %) were true sentinel nodes. The lymph node retrieval rate was 2.5 nodes per patient overall, 1.9 nodes per patient with the standard technique, and 2.0 nodes per patient with the magnetic technique. CONCLUSIONS: The magnetic technique is a feasible technique for SLNB, with an identification rate that is not inferior to the standard technique., Ann Surg Oncol **21**, 1237, (2014). *[6.222 CC1]*

78 M. Thill, A. Kurylcio, R. Welter, V. van Haasteren, B. Grosse, G. Berclaz, W. Polkowski, and N. Hauser, **The Central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope**, Sentinel lymph node biopsy (SLNB) is the standard surgical procedure for the axilla in early node-negative breast cancer. To date, the "gold standard" to localize the sentinel lymph node (SLN) is the radiotracer (99m)Tc with or without blue dye. The aim of this study was to evaluate potential equivalency of the new SentiMag((R)) technique in comparison to the "gold standard". Within this prospective, multicentric and multinational non-inferiority study including 150 patients (99m)Tc was compared with the magnetic technique, using superparamagnetic iron oxide particles (SPIOs, Sienna+((R))) for localization of SLNs. The results showed a detection rate per patient of 97.3% (146/150) for (99m)Tc vs. 98.0% (147/150) for Sienna+((R)) with a similar average number of removed SLNs per patient and a higher per patient malignancy detection rate for the SPIO tracer. We obtained convincing results that magnetic SLNB can be performed easily, safely and equivalently well in comparison to the radiotracer method., Breast **23**, 175, (2014). *[6.222 CC1]*

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Collated comments table

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Expert #7	Mr Dermot Murphy, Consultant breast surgeon, NHS Lanarkshire & NHS Dumfries & Galloway
	Nominated by: Company
	DOI: None
Expert #8	Ming Young Simon WAN, Consultant Radiologist, University College London Hospitals NHS Foundation Trust
	Nominated by: NICE
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Expert #9	Elizabeth Jefferson, Head of Nuclear Medicine, Newcastle upon Tyne Hospitals
	Nominated by: External Assessment Centre
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1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own?	Expert #1: I am familiar with Magtrace and Sentimag for 4-5 years. I am every day user for approx. 2.5 year while working at Dorset County Hospital NHS. In this time I did about 150 operations using Magtrace. I know about at least a few places using this technology in the UK eg. Breast Unit in Yeovil. I don't know about any usage of Magtrace/Sentimag outside of breast surgery although I can imagine other applications of this technique (eg. Melanoma) This is a standard and default procedure at DCH therefore we do not select patients for this procedure.

	− If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	
		Expert #2 Yes I do have experience of this technique. I have used this product while conducting a feasibility study for magseed and sienna now magtrace. An initial study of the product in 3 patients along with magseed insertion in the same patient was carried out. The methodology was in parallel with the standard technique so that identified node identified with sienna was then rechecked with the isotope probe and or blue dye intraoperatively. Not widely used in the NHS. Only in use in a few units in the UK. Once approved it is likely to have a good uptake. No
		Expert #3 I use Magtrace and the Sentimag system for all my SLNBs. I have been using the technology for 3 years and have performed over 200 SLNBs using Sentimag I use the technology in the two hospital trusts in which I work, having introduced it to the trusts. I know several other hospital using the technology and a couple of colleagues who have contacted me to discuss the technology. I know the technique has been used in patients with oral cancer although I don't know of any other specialties that use the technique.
		Expert4# Sentinel lymph node biopsy (SLNB) has been standard practice in the treatment and staging of breast cancer patients since the 1990's. The standard technique involves a combination of a

		radioactive isotope (technetium-99) and patent blue dye to locate the first draining lymph node(s) within the axilla; if the breast cancer has metastasised from the breast this is the first location at which breast cancer cells will be found and so this procedure is used to stage the disease and guide the need for adjuvant treatment. SLNB is also utilised in the treatment of melanoma and in some early-stage oral carcinoma as a standard part of practice. I have been performing sentinel lymph node biopsies since the start of my surgical training in 2004 using the standard dual technique up until April 2020 when this innovative Sentimag/magtrace technology was introduced to my breast unit in April 2020. During an initial trial period I and my surgical colleagues used magtrace alongside the long-established patent blue dye marker to ensure confidence, accuracy and safety in our patients, but after a short learning curve and prospective audit we have moved to utilising the magtrace/sentimag system alone. I have now personally performed over 60 procedures utilising this technology; it is now my standard technique for all sentinel lymph node procedures in breast cancer treatment. My four other consultant colleagues within my unit have also converted to this technique as their standard sentinel lymph node procedure. Since COVID19, NHS breast cancer surgical services have had to flex and adapt to the challenges of working and operating in unfamiliar hospitals, often without the facilities, training and licensing necessary to be able to use the standard dual technique for sentinel lymph node biopsy using both radioactive isotope technetium 99 and patent blue dye. This has meant that many NHS breast surgeons have been researching alternative ways of safely performing sentinel lymph node biopsies. The uptake for the sentimag/magtrace technology has therefore quickly increased over the past 12 months throughout the UK. This is due to numerous advantages the new technology provides. For example, the sentimag/magtrace system eliminates the need to expose patient and staff to radioactivity in theatre and makes the logistics of theatre scheduling during the COVID pandemic simpler; the production of the alternative standard technetium isotope as well as its administration requires specialist licensing and training that is specific to a hospital site/department. The Sentimag/Magtrace system is in contrast fully mobile and accessible to any theatre complex as long as the surgeon has adequate experience and expertise. Over the past 6-12 months I have been contacted by numerous colleagues from around the UK asking for advice and guidance on the introduction of this system and technology within other

		breast cancer units. I anticipate its uptake will only increase in breast cancer treatment and I can see no reason why the staging and treatment of melanoma will not follow.
		Expert #5: - I am a registered Medical Physics Expert (MPE) that supports a number of sites that use the current standard-of-care radionuclide technique for SLNB. I have a detailed knowledge of the radiopharmaceuticals and gamma probe technology used for the radionuclide technique, as well as the regulatory requirements and practicalities of providing a radionuclide SLNB service. I have helped set up and supported sites both with and without dedicated Nuclear Medicine facilities to perform these procedures. - As an MPE I provide advice and support on: quality control of gamma probe equipment, optimisation of the radiation dose to patients, safe working practices with radioactivity, and appropriate policies and procedures relating to regulatory compliance. - I am familiar with the MagTrace/SentiMag product as this has been trialled in combination with the radionuclide technique by one of the sites that our Trust provides MPE support to. - I have not used the MagTrace/SentiMag product directly myself, as this is done by surgeons and theatre staff. I am not involved directly in the selection or referral patients for this procedure as this would be done by oncologists or surgeons as appropriate as part of the multi-disciplinary management of the patient. I have an awareness of current SLNB caseload in my own Trust and those that we provide MPE support to, hence I have an understanding of the demand for this procedure within the NHS. Having supported sites to establish similar technology I am able to judge the likely speed of uptake of new technology in this area.
		Expert #6 I have been regularly involved in the use of radioactive tracers for sentinel node mapping. But with regards to Magtrace and Sentimag for locating sentinel node, my experience is only theoretical - having reviewed the literature, and have no practical experience of using it. Magtrace and Sentimag currently is used in about 50 NHS Trusts as per the last MIB published in June 2021 (www.nice.org.uk/guidance/mib263). Given that this technology offers flexibility in terms of timing of injection and free from complex legislation and radiation

		protection issues, it can be easily adopted, with a bit of staff training, without any significant changes to existing facilities. This procedure/technology (Magtrace abd Sentimag) is normally used by the operating surgeons (breast, head & Neck, oncoplastic), and Nuclear Medicine physicians as such have no role to play. Nuclear Medicine has limited or no role in patient selection or referral to other speciality for this procedure. My experience in sentinel node mapping is in the use of radioactive tracers; including injection, imaging, ARSAC cover, advise on radiation protection issues and representation in the relevant multidisciplinary meetings.
		Expert #7 Yes, we have been using sentimag with Magseed for 4 years and magtrace for 1 year Yes as above Magseed is now in general use but magtrace is in its infancy NHS Dumfries is the first unit in Scotland to trial it, with excellent results. It is about to be used in several other units in the West of Scotland as several of my regional colleagues have come to observe the procedure Not at present N/A
		Expert #8 I have no hands on clinical or research experience in relation to the use of this technology (Magtrace & Sentimag).

		I routinely support the clinical and research service for an alternative modality (nuclear medicine/ radionuclide imaging) used in sentinel node biopsy (SNB). To my awareness, use of radionuclide technique for SNB is the current clinical standard. Use of radionuclide tracer technique is a common and widely used modality for this type of surgery in the NHS, with common indications to include skin cancer/melanoma, breast cancer and oral cavity cancer.
		Expert #9 I was initially trained in SLNB procedures in 2007-8 with the New Start programme for Breast cancer, including injection, image acquisition, image processing and reporting. Started using SLNB for melanoma in 2012 and trained in 2014 using SLNB in penile cancer. Currently use Tc-99m SLNB at Newcastle Hospitals for breast cancer, melanoma, head and neck melanoma and soon will be starting SLNB for Oral cavity carcinoma. SLNB using Tc-99m was adopted very widely in the UK after the New Start programme following the early termination of the research trial clearly demonstrating the effectiveness of SLNB The Tc-99m radiopharmaceutical is manufactured on our site and our nuclear medicine team inject patients prior to surgery. This is done for Newcastle patients and also for Northumbria patients as they do not have a nuclear medicine service within the county. No experience in patient selection, only in the delivery of the technetium SLNB injections including imaging where necessary.
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have done bibliographic research on this procedure. I have had no involvement in research on this procedure.

		Expert #2 I have done bibliographic research on this procedure. I have done clinical research on this procedure involving patients or healthy volunteers.
		Expert #3 I have reviewed my clinical practice and experience with the procedure and submitted for publication. I plan a future study with my colleague assessing injection volumes and techniques
		Expert#4 Prior to introducing this technique into our breast unit, I performed a literature search and critically analysed the peer reviewed evidence for its efficacy and non-inferiority compared to the standard dual technique. I presented this evidence to my surgical colleagues and the “new medicines and innovations” committee within my Trust prior to its trial and cautious introduction. I am prospectively auditing the outcomes for all sentinel lymph node biopsies performed in our unit to ensure safety and efficacy.
		Expert #5: I have done bibliographic research on this procedure.
		Expert #6 I have done bibliographic research on this procedure. I have no practical experience on Magtrace and Sentimag for locating sentinel node nor have I undertaken any laboratory or clinical research on this technology/procedure.

		Expert #7 I have done bibliographic research on this procedure. We are auditing our results using magtrace alongside radio-isotope
		Expert #8 I have no research experience with Sentimag and Magtracer. On the other hand, I have published on the use of radionuclide tracer technique for SNB and in its combination with other tracers (fluorescent tracers). I am a co-investigator with a NIHR EME grant to study the use of a novel radionuclide tracer in oropharyngeal tumours.
		Expert #9 None I have had no involvement in research on this procedure.

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: The paradigm of axillary lymph node staging through identifying the sentinel lymph node in the axilla remains unchanged as for the Blue Dye technology or Tc99. What make the technology attractive is avoiding significant disadvantages of the Blue Dye (allergic reactions) or complex logistics with radioactive Tc99. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #2

		A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #3 Established practice and no longer new, but this now established technique utilises new tracer technology that is safer than previous tracers. Its performance is non-inferior to previous tracers.
		Expert#4 **<u>A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.</u>** The technique and safety of sentinel lymph node biopsy in the treatment and staging of breast cancer and melanoma is well-established and undisputed when performed using the standard dual technique with technetium 99 and patent blue dye. Magtrace is an innovative tracer injection but the physical surgical technique of utilising a probe within the operating theatre to locate the sentinel lymph node is well established. Of note, the Sentimag probe system is also utilised by a number of different breast units to locate impalpable breast tumours using magseed technology; many surgeons have therefore gained invaluable experience in handling the sentimag probe. The learning curve is thus not that steep from current standard surgical practice.
		Expert #5: The procedure represents a new technological innovation that can be applied to a well-established surgical procedure. As such it should be considered a minor variation. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #6

		Magtrace and Sentimag technology is a minor variation to the current standard in sentinel node mapping and uses magnetic liquid tracer instead of the established radioactive tracers and/or blue dye. It is unlikely to alter the procedure's safety. Efficacy is yet to be fully established by randomised studies and in cancers other than breast cancer.
		Expert #7 This technique is equivalent to radio-isotope injection but avoids the dependence upon nuclear medicine which is a major limiting factor in many DGHs. In addition as virtually every unit already had the sentimag probes in place for Magseed localisations there are limited additional costs involved. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #8 To my understanding, this is a variation to current standard of care, if we consider SNB as a whole. My view is that it is a minor variation on an existing procedure, which is unlikely to alter the procedure's (SNB) overall safety and efficacy.
		Expert #9 Not experienced in alternative technologies. Radiopharmaceutical use in standard of care is a "trace" amount of injected substance very unlikely to cause a reaction.

		N/a.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: The strength of this technology is safety and easy logistics.
		Expert #2 Replace ultimately existing technique – although during testing other existing modalities can be used alongside during early trials
		Expert #3 This technology could replace duel sentinel node detection with radioisotope and blue dye
		Expert#4 Yes – this technology can replace the standard of care.
		Expert #5: This procedure could replace the current standard of care.
		Expert #6 Given the non-radioactive nature of Magtrace and flexibility of its use (timing of injection, improved logistics by avoiding the need to travel to hospitals with nuclear medicine facility, free from complex legislation and radiation protection issues), it has the potential to be used as an alternative to current standard of care procedure if efficacy and cost effectiveness are fully established.

		Expert #7 Replace radio-isotope technique and blue dye which has a not insignificant risk of allergic reaction
		Expert #8 My view is that this procedure (Magtrace/Sentimag) has the potential as an alternative to the current standard of care, which is the use of radioactive tracers for SNB.
		Expert #9 Don't know

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: All patients with invasive breast cancer undergo assessment of the axillary lymph nodes with the ultrasound and than if no metastatic disease detected with sentinel lymph node biopsy. In order to find which lymph node is the first (sentinel) we attempt to replicate the natural flow of the lymph from the affected breast to axillary nodes injecting the tracer into the breast which travels through lymphatics into the sentinel node. The most popular currently are Blue Dye and radioactive Tc99 used separately or together (with intention to increase node detection).
		Expert #2 Sentinel nodes are currently identified by a dual technique of isotope and blue dye injected in the subareolar plexus
		Expert #3 Sentinel node detection with radioisotope and blue dye is current standard of care for SLNB detection
		Expert#4

		Sentinel lymph node biopsy (SLNB) has been standard practice in the treatment and staging of breast cancer patients since the 1990's. The standard technique involves a combination of a radioactive isotope (technetium-99) and patent blue dye to locate the first draining lymph node(s) within the axilla; if the breast cancer has metastasised from the breast this is the first location at which breast cancer cells will be found and so this procedure is used to stage the disease and guide the need for adjuvant treatment. Technetium 99 is a radioactive isotope that can only be produced by a small number of centres throughout the UK with specialist licensing, to then be transported and distributed to other hospital sites and administered by medical personnel with specialist training and licensing. It is a finite, scarce resource and supply has been unreliable recently, a problem only worsened by COVID19 restrictions. Technetium 99 has a short half-life (6 hours) and so the timing of its administration compared to the time of surgery is crucial (usually within 1-4 hours, given on the day of surgery). This makes surgical theatre scheduling a challenge. Technetium 99 is used alongside patent blue dye, but is injected into the breast once the patient is anaesthetised and on the operating table. Patent blue dye has an associated risk of anaphylaxis of approximately 15/100 000 administrations (the fourth most common cause of perioperative anaphylaxis in the UK). Surgeons use a Geiger counter in the operating theatre to guide axillary dissection and locate the lymph nodes that have uptake of technetium 99 within them; these are the sentinel or first draining lymph nodes of the breast. Surgeons also look for and follow blue lymphatics to guide them to any blue coloured sentinel lymph nodes (or a combination of the two).
		Expert #5: Current standard-of-care includes the injection of a radiocolloid in combination with Blue Dye, followed by localisation of the SLN(s) in theatre using a gamma probe to detect the radioactivity in combination with the visual signal from the blue dye. Administration of the radiocolloid in advance of surgery allows images of the node locations to be generated. For breast SLNB, the relatively straightforward lymph node anatomy means that imaging is not always performed and is often not felt to be useful by the surgeons performing this procedure. However, for more complex lymph node anatomy, such as for melanoma, vulva, head and neck and other indications, hybrid imaging with SPECT/CT is common and widely regarding as essential for surgical planning.
		Expert #6

		The current standard of care used in the NHS is sentinel node mapping by using radioactive tracers along with blue dye.
		Expert #7 Current sentinel node localisation is carried out using radio-isotope localisation with or without patent blue dye. This technique is aimed at removing the reliance on nuclear medicine
		Expert #8 In patients with early cancers (e.g. breast, oral cavity and melanoma) and no overt spread to lymph nodes yet on conventional clinical and imaging assessment, SNB retrieves nodes believed to have the highest chance of harboring any occult spread of tumor for detailed analysis. This information enhances accuracy for nodal staging and guides any further need for more treatment. Identification of the sentinel nodes (SN) are currently through the use of small amount of radioactive tracer injected into patients as current standard of care; the radioactive signal can help the surgeons to retrieve these nodes (i) by generating pictures prior to surgery in the scanner (gamma camera) to help pre-surgical planning, and (ii) during the operation by radiation probes to locate and confirm resection of these SN.
		Expert #9 Technetium labelled nanocolloid injection along side a blue dye injection. Sentinel lymph nodes tend to be blue and hot, but may be blue or hot.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: There are some attempts to use indocyanine green ICG for fluorescence-guided sentinel node biopsy. As far as I am aware there are a few projects going on but none in common use outside of the research. Fluorescence is developing and promising technology but not ready yet. My understanding is that fluorescence is much more expensive at this stage than standard technologies including Magtrace.
		Expert #2

		The above are in use currently. The product is different. The surgical technique with the magtrace/ sienna itself is not different.
		Expert #3 Indocyanine green is popular in the US but not widely used in UK, Same injection technique with a different tracer
		Expert#4 **Fluorescence Techniques** **1. Indocyanine Green** 1-5ml of ICG can be injected into the breast after anaesthesia. Fluorescence is not visible directly, but the theatre lights are dimmed and a specialist photodynamic eye system is used to see black and white images of fluorescent lymphatics and sentinel nodes on a monitor. ICG cannot be used in patients with iodine allergy. There are no randomised trials comparing it with standard tracer techniques. The technique is completely novel. It again eliminates exposure to ionising radiation. **2. Fluorescein** 10% fluorescein widely available and low cost and widely used in ophthalmology. A blue light source is needed to excite fluorescence, but it is directly visible so no imaging system is needed. Only evidence is from conference proceedings – research and safety data is scarce. **Non-Operative Axillary Staging** **1. Computed Tomography Lymphography** 3 D computed tomography lymphography is performed the day before surgery. 4ml of iopamidol is injected into the breast and then a CT scan is performed and 3D CT images are reconstructed to identify the lymphatics and sentinel nodes. Nodes that are poorly stained suggest the presence of metastases. These nodes are then marked on the skin using a laser navigator and then SLNB is performed with patent blue dye.

		Accurate but exposes the patient to radiation and puts added pressure onto a stretched radiology service. **2. Contrast-Enhanced Ultrasound Scan** Dynamic contrast-enhanced ultrasound scan images can be obtained to identify and biopsy the sentinel lymph nodes non-operatively. US contrast agents consist of microbubbles containing various gases within a shell. The agent is injected into the breast. The lymphatic channels are visualised on contrast pulse sequencing and followed into the axilla to the draining sentinel lymph node that accumulates the contrast agent. This is then percutaneously biopsied. The technique has a reported high false negative rate and is limited to very few centres. Further work is needed to improve sensitivity.
		Expert #5: Oncovision market a product that produces real-time images of radionuclide distribution that can be used to localise SLNs in theatre (https://oncovision.com/sentinella/). This technology has been evaluated in the UK in a small number of patients (eg, https://pubmed.ncbi.nlm.nih.gov/28033510/). This technology still requires the use of radiocolloid injection but replaces the use of gamma probes to localise the SLNs. Lightpoint medical market a laparoscopic gamma probe which is intended for the detection of lymph node metastases peri-operatively. Recent studies have demonstrated its use in prostate cancer surgery with radiocolloids (Abstract EP-074, https://link.springer.com/content/pdf/10.1007/s00259-021-05547-1.pdf). Although similar, this technology is not intended for superficial SLN removal.
		Expert #6 Sentinel node mapping by using radioactive tracer along with blue dye, which is well established as the current standard of care is the alternative technology already available to the NHS. In comparison to the current standard of care techniques, the technology described in the briefing, is non-radioactive, well tolerated with fewer side effects and improves logistics of undertaking SLNB by eliminating the dependency on Nuclear medicine units and potentially offering flexibility of use in smaller centres. The data on the use of Magtrace in sentinel node detection however is not robust, due to the lack of randomised studies, in evaluating its efficacy and cost-effectiveness when compared to the current standard of care techniques.
		Expert #7

		Radio-isotope localisation
		Expert #8 Competing alternative technology: - Radionuclide tracer as described above. Established technique and widely adopted. Allows for (i) scanning to get pictures to help plan surgery, and (ii) using probe to detect SN during the operation, as well as (iii) confirming the appropriate nodes are retrieved by applying the probe on the excised tissues and at the surgical bed after. Need infrastructures to support the use of the (minute amount of) radioactive tracer, e.g. getting ARSAC licences, basic radiation training, time from relevant staff (e.g. radiation protection personnel), maintanence of gamma camera and probes. Magtrace/Sentimag has similar functions in feasibility to enable these 3 elements. - Blue dye. Established and widely available. Provides visually perceptible 'signal' to identify lymph nodes in the drainage path. If used on its own, no pre-operative scans can be done to help plan surgical approach. It is only visible after surgery has started and incisions made. Feedback from surgical colleagues I work with is that it stains much of the surgical field - lymphatic tracks and nodes may be difficult to see in surgery. Fluorescent tracers (e.g. indocyanine green). Generally available (used also for fluorescent angiography in retinal angiography; assessment of bowel perfusion in bowel surgery). Limited penetrance with existing tracers: if used on its own, the signal cannot be detected pre-surgically (therefore no possible to plan incisions); the signal can only be 'visible' with specialised sensors/cameras. Feedback from surgical colleagues I work with is however that it shows the lymph nodes very well visually in the patient/on screen intraoperatively. This precision in the 'short range' complements with the 'longer range' offered by radionuclide tracers when used in combination.
		Expert #9 Technetium labelled nanocoll which is also fluorescent can be used to avoid the use of blue dye. This would be a very low risk option, with a low probability of patient reaction. The surgeon can identify the sentinel node visually under fluorescent lighting and because the node is radioactive.
7		Expert #1:

	What do you consider to be the potential benefits to patients from using this procedure/technology?	Safe, straightforward in use. Potentially cheaper.
		Expert #2 Patients will not need to travel to another centre (nuclear medicine department) the day before surgery for a radioactive injection. The blue dye used has been known to cause severe anaphylaxis resulting in ITU admission
		Expert #3 Magtrace and Sentimag technique is a much safer alternative to radioisotope and blue dye. There is a high rate of allergic and anaphylactoid reaction to blue dye and on occasion this led to reactions severe enough to lengthen hospital stays and require specialist care on ICU. Magtrace can be injected by the surgeon, with no specialist storage requirements and up to 7 days prior to surgery allowing for better theatre utilisation arrangements
		Expert#4 1. Reduces exposure to ionising radiation 2. Reduces the risk of intraoperative anaphylaxis 3. Reduces patient anxiety and distress on the day of surgery by eliminating the need for the patient to attend nuclear medicine for administration of technetium on the day of surgery (sometimes on a different hospital site to the surgery due to strict licensing laws) 4. Breast Cancer treatment/staging no longer dependant on a finite resource (technetium) with unreliable supply chain. 5. Allows more flexible theatre scheduling with more efficient utilisation of theatre capacity 6. Magtrace can be used to avoid sentinel lymph node biopsy all together in patients with pre invasive breast cancer who require mastectomy, which avoids the risk of surgical morbidity such as lymphoedema in a small number of patients.
		Expert #5:

		Lower radiation dose to patients, potentially increased accessibility of procedure due to simpler set-up compared to radionuclide procedure and therefore higher likelihood of adoption in DGH settings.
		Expert #6 Well tolerated, apart from skin discoloration as a side effect mentioned in the literature. It is non-radioactive. Improves logistics by avoiding patient travel and increases flexibility of scheduling sentinel node mapping procedures.
		Expert #7 By removing the nuclear medicine part of the pathway it means that for many DGHs who don't have a nuclear medicine unit patients can receive their localisation injection at the time of surgery. Currently many patients have to travel to different sites before surgery to attend a local nuclear medicine unit.
		Expert #8 In areas/institutions where access to radionuclide tracers and relevant infrastructure may be limited.
		Expert #9 Lack of ionising radiation.

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: This technology is particularly attractive for hospitals without Nuclear Medicine Departments on site. Currently many small and medium size hospitals lost their Nuclear Medicine facilities and for the radioisotopes became dependent of bigger hospitals (often distant) and bringing radioisotopes for each patient directly (cost!).
		Expert #2 All breast cancer patients with invasive disease will benefit from this. Logistically this is going to be useful but also will avoid radioactive material being injected which require precautions. After surgery there is delay in sending the specimen to the lab as the radioactivity needs to wear off before it can be safely handled by the pathologist. Hence the histopathology report takes longer to come through potentially delaying further surgery or adjuvant treatment
		Expert #3 I would say all patients having SLNB procedures and particularly those with history of allergy or atopy
		Expert#4 Patients who have a diagnosis of DCIS / pleomorphic LCIS of the breast who require a mastectomy would normally, using the standard techniques, require a SLNB at the time of their mastectomy. This is done in case there is hidden/undiagnosed invasion/micro invasion within the breast subsequent which would then require staging of the axilla. This could not be achieved with the standard dual technique as there is no longer a breast to inject the technetium/patent blue dye into. The tracer could not pre-emptively be injected at the time of mastectomy to come back to at a later date as the patent blue and the isotope would be cleared from the lymphatics and therefore would not be accurate. Magtrace can be injected at the time of mastectomy for DCIS/pleomorphic LCIS to allow the tracer to travel to and mark the sentinel lymph node. Mastectomy alone can then be performed and if incidental invasive disease is found histologically the patient can return to theatre within 30

		days to undergo a standalone SLNB as the Magtrace tracer will still be detectable within the sentinel lymph nodes. This avoids the surgical morbidity of performing an unnecessary SLNB in this specific patient group.
		Expert #5: Assuming higher likelihood of adoption of SentiMag/Magtrace, patients whose local hospitals do not have capability to use radionuclide SLNB localisation will benefit particularly, as they will not have to travel to a centre that does have this capability.
		Expert #6 Would be particularly useful in patients who are potentially allergic to blue dye and young women in whom exposure to radiation could be avoided.
		Expert #7 All node negative patients at diagnosis are eligible
		Expert #8 To my knowledge, this could act as an alternative to radionuclide technique. There are non-inferior studies comparing Magtrace/Sentimag but to my knowledge, there is no clear superiority demonstrated and no robust data on clearly better outcome.
		Expert #9 Don't know
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: I do think that it has already changed practice in many places, as discussed above, for better. It seems to be safer than Blue Dye as Magtrace is generally well tolerated. Avoiding costs of transport from the other hospital seems to benefit economical aspects.
		Expert #2 Yes as above

		Expert #3 Yes - the tracer is not radioactive so no special precautions needed in its use. The isotopes were prepared in centralised isotope labs by nuclear physics departments, needing specialist transport and handling and only could be injected on the day of surgery by an appropriately qualified nuclear physics professional – all logistically challenging. The new technology avoids all this as it does not need special storage and handling and can be injected by the surgeon up to 1 week before operating. No risk of allergy identified so safer and avoids those admissions for patients who had an allergy SLNB detection rates are not inferior to the previous technique and the surgical procedure is not any more difficult
		Expert#4 This technology avoids the need for a patient to attend nuclear medicine either on the morning of or the day before surgery. This nuclear medicine department can sometimes be located at a different hospital site to the breast operating theatres.
		Expert #5: The MIB covers SLNB generally and not relating to a specific cancer. However, I think there are different considerations relating to different tumour sites. In particular, for cancers other than breast, it is common for pre-surgical imaging and mapping of SLN locations to be carried out using the radiotracer, which cannot be achieved using the MagTrace product. For breast cancer, assuming no pre-surgical imaging is performed (which is commonly the case), the clinical pathway will not change as a result of this technology and there isn't any evidence it will improve clinical outcomes. There is potential for fewer hospital visits in some patients as no separate appointment for radiocolloid injection will be required, although some patients already have radiocolloid injected by theatre staff on the day of surgery anyway. For other SLNB indications, the lack of imaging capability may mean that adoption of the new technology may adversely affect patient outcomes. The vast majority of studies in which the technology has been investigated have been on patients with breast cancer. I am not aware of any studies that have compared outcomes in other cancers where pre-surgical imaging is

		performed with radiocolloid versus SentiMag alone. I would therefore recommend that any guidance issued focussed specifically on breast cancer until such studies have been published.
		Expert #6 The procedure could potentially improve logistics by avoiding patient travel to the nuclear medicine department and allows to undertake sentinel node mapping in smaller centres and increases flexibility in patient scheduling. There is some suggestion in literature of improved efficiency of operation theatre time, but yet to be fully established.
		Expert #7 Yes by elimination of the nuclear medicine visit Magtrace is injected by the surgical team at the time of surgery
		Expert #8 There is potential to improve on logistical challenge in coordinating various resources needed in the pathway, compared to using radionuclide technique. Radioactive tracers are relatively short-lived. The supply, injection, any scans required, and the surgery needs to be tightly coordinated before the radiation signal decays away (e.g. all done in one day; or injection & scan on afternoon of day 1, followed by surgery morning of day 2). This is usually not a problem if the Institutions have established pathways. (if the chain of event is broken, e.g. delays in theatre, then there may be need to repeat/re-inject). Signal from Magtrace/Sentimag seems longer lasting and these steps above could in theory be more loosely coupled, with less challenge to coordination.
		Expert #9 Don’t know
10	Considering the care pathway as a whole, including initial capital and possible future	Expert #1:

	costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	I think that this technique has potential to became more popular and cheaper in the future than standard Tc99 in view of avoiding costs related to the Nuclear Medicine staff, complex legislation, radiation protection, ARSAC licence etc.
		Expert #2 Likely to result in cost saving
		Expert #3 Similar to the previous standard of care. Isotope handling is expensive
		Expert#4 About the same/Less. Initial start-up costs and cost per procedure seem more than the current standard dual technique but if the decreased use of radiopharmaceuticals centres and specialist staff, transport of the technetium from the production centre, specialist nuclear medicine personnel time administering the injection and increased theatre efficiency gained from switching to the Sentimag/Magtrace system overall expenditure is either the same or reduced.
		Expert #5: The current and proposed technologies both require similar initial capital purchases of probes for the detection of the signal from the SLNs (gamma probes typically cost around £15-25k; the stated cost of the SentiMag system is £25k). The per-patient cost then mainly relates to the tracer – the stated costs are £226 for MagTrace and £195 for radiocolloid. I don't think there is sufficiently detailed analysis of the relative costs of the technologies in the MIB. In particular, I would be interested to see further detail of how the cost of the radiocolloid has been calculated (my Trust currently pays £60 per dose but this excludes transport costs). For Trusts that do not have dedicated Nuclear Medicine facilities, for the current standard-of-care radiocolloid technique, there are additional costs of set-up including consultations and appointment of RPA, RWA and MPE as appropriate. Maintenance and quality control of gamma probe systems requires access to a long-lived sealed source of radioactivity such as a Co-57 spot source which typically costs ~£3k and need replacing every 2-3 years. Gamma probe systems can be quite fragile and the chances of a probe needing repair in its lifetime is quite high. I am not sure if this

		is similar for SentiMag or if repair is as straightforward. In terms of staffing costs, it is possible to have theatre staff Taking these factors into account, on balance I expect the costs of the new technology will be similar to the current standard-of-care.
		Expert #6 The technology in evaluation is based on the same principle as the current standard of care technique in use and may potentially improve the pre-operative care pathway, but overall the impact in terms of staff and equipment may not be significant. Initial capital expenditure would involve purchase of Sentimag detection system and training. Possible financial savings on costs related to dependency on nuclear medicine facility.
		Expert #7 Less as we will no longer require nuclear medicine input. The injection is carried out by the surgeon in theatre and means that surgery is not dependent upon nuclear medicine availability.
		Expert #8 This is difficult for me without detailed data and calculations relevant to the NHS setting. My gut feeling is that it would be more, when considering need to purchasing new equipment, training and maintenance for the equipment, need for MRI time if pre-surgical localisation is desired.
		Expert #9 Don't know
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: As above
		Expert #2 Likely to be more cost effective

		Expert #3 Cost of new technique quoted as higher than standard of care but in my experience we have similar costs as before because we avoid the expense o transporting isotopes that are produced in another hospital. When I introduced the new technique to my trust we went through a very thorough business planning exercise and found that for us the costs were similar. Also no admission for allergic reactions as with blue dye which would escalate the costs of the episode
		Expert#4 As above
		Expert #5: See above.
		Expert #6 Adopting this technology is likely to cost more or less the same in terms of equipment and staff costs as the current standard of care, but a robust cost effectiveness study is yet to be undertaken.
		Expert #7 Equivalent or less than at present
		Expert #8 This is difficult for me without detailed data and calculations relevant to the NHS setting. My gut feeling is that it would be more, considering likely cost of the agent. In addition, available literature seems to suggest higher number of sentinel nodes harvested during SNB with Magtrace/Sentimag compared to radionuclide technique. This would translate to increase costs/resource needed for adequately analysing these nodes by pathology laboratory which are often already stretched. This is a fine balance, there is data to suggest harvesting more nodes with the radionuclide technique would improve false negative rates in breast cancer SNB, but it

		is unclear if this can be translated/generalised to this context. There is to my awareness lack of clear data on superior detection of pathologically confirmed metastatic nodes within harvested nodes, or outcome data, when comparing Magtrace/Sentimag with radiotracers.
		Expert #9 Don't know
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: No changes required as the technology doesn't need any capital cost except the initial purchase of Sentimag and than only Magtrace for injections.
		Expert #2 None
		Expert #3 Purchase of the Sentimag detection device is needed. Magtrace tracer must also be purchased.
		Expert#4 None. Can be safely administered in theatre once the patient is anaesthetised by the treating surgeon.
		Expert #5: Existing theatre facilities will be suitable for the new technology.
		Expert #6 No major changes are necessary to adopt this technology, apart from initial capital expenditure to purchase the Sentimag detection system and initial training. Also, metallic surgical retractors,

		which may potentially affect signal detection on the Sentimag system, may have to be replaced with plastic alternatives.
		Expert #7 None as the equipment is already in place. However by removing the radio-isotope injection any potential radiation risk is eliminated
		Expert #8 Purchasing of magnetometers/probes and the associated machines. Need for replacing standard surgical retractors with plastic ones. MRI scan time. Staff training. Decommissioning of gamma probes. Diversion of gamma camera & relevant staff times for other clinical priorities.
		Expert #9 Don't know

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: No, any breast surgeon who is familiar with Tc99 and Blue Dye Sentinel Node Biopsy will be able to adapt quickly to the magnetic tracer usage.
		Expert #2 Yes
		Expert #3

		I would recommend in person demonstration and supervised training for first 5 cases It may also be useful to undertake the first solo 25 procedures using radioisotope/blue dye in conjunction with Magtrace.
		Expert#4 The company can provide on-site training. Would usually recommend starting to use the technology in combination with patent blue dye until surgeon feels confident in their ability to locate the sentinel lymph node using the Sentimag/magtrace system alone. Staged approach for the more cautious (e.g. mastectomy patients first as better surgical access to the axilla / less technically challenging).
		Expert #5: Appropriate training for theatre staff is provided by the manufacturer
		Expert #6 Initial training on the use of Sentimag detection system will be required.
		Expert #7 The technique builds on surgical skills already in place with Magseed localisation and radio-isotope guided sentinel node biopsy
		Expert #8 I should think surgeons, radiographers, radiologists would need extra-training to: - Draw up new protocol for titrating the right dose of the agent to balance between imaging artefact and probe sensitivity; - Interpretation of images, if required; - Use of the magnetometers/probes intraoperatively.
		Expert #9 Don’t know

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: Injection of Magtrace into the breast is sometimes uncomfortable for a minute or so. The tracer leaves breast discoloration (like a brownish bruise) which takes weeks to months to resolve completely. Having said that the Blue Dye cause similar although blue discoloration. I have not experienced any other adverse reactions to Magtrace.
		Expert #2 May interfere with MRI interpretation during follow-up as the product is made of iron. Preoperative MRI may be required for patients who have lobular cancer It may take several months or longer for the product to wash out Not suitable for patients with iron metabolic disorders May mask recurrence during MRI follow-up due to the presence of artefacts
		Expert #3 Very safe – I have had no safety concerns. I have had only 2 technical failures in the 200 procedures I have done Skin staining with the Siena dye colour is common and patients need to be warned of this (own experience) Size of detector probe is large and affects resolution. Important to use visual cues – colour change in nodes is obvious Causes artefact change if patient requires a post op MRI – this can last up to 1 year

		Expert#4 Skin staining – discolouration of the breast skin is common after breast conservation (35% in the immediate post op setting) but this falls to 8.6% after 15 months. Reported patent blue dye discolouration in patients can be present in up to 23% of patients at 24 months. Interference with Magnetic Resonance Imaging of the breast in the future if breast conserving surgery performed – manipulation of the scan parameters may be required to compensate for the artefact. Skin reaction at injection site (<1%) and anaphylaxis (<0.1%)
		Expert #5: The most common adverse effect is skin discolouration which is well described in the evidence cited in the MIB. I am not aware of any other significant harm or adverse events arising from the technology, either in literature or in my experience.
		Expert #6 The technology appears to be safe and well tolerated. The main adverse event reported in the literature is skin discoloration. Skin discoloration after a 2.0 mL subareolar injection was reported in 15.6% of patients in the SentiMagIC(1)study. SUNRISE study by Rubio et al.(2) showed that by using subareolar injections in patients who underwent breast conservation surgery resulted in cutaneous staining varying from 59% in patients who received 1.0 mL to 83.3% in patients who received 2.0 mL. The long-lasting staining may pose a restriction on the use of MRI in patients who need follow-up assessment due to artefact from retained Magtrace particles. 1. Alvarado, M.D.; Mittendorf, E.A.; Teshome, M.; Thompson, A.M.; Bold, R.J.; Gittleman, M.A.; Beitsch, P.D.; Blair, S.L.; Kivilaid, K.; Harmer, Q.J.; et al. SentimagIC: A Non-inferiority Trial Comparing Superparamagnetic Iron Oxide Versus Technetium-99m and Blue Dye in the Detection of Axillary Sentinel Nodes in Patients with Early-Stage Breast Cancer. *Ann. Surg. Oncol.* **2019**, *26*, 3510–3516. 2. Rubio, I.T.; Rodriguez-Revuelto, R.; Espinosa-Bravo, M.; Siso, C.; Rivero, J.; Esgueva, A. A randomized study comparing different doses of superparamagnetic iron oxide tracer for sentinel lymph node biopsy in breast cancer: The SUNRISE study. *Eur. J. Surg. Oncol.* **2020**, *46*, 2195–2201

		Expert #7 Magtrace involves the use of heavy metals but the dose is very small and carries little risk to the patient I have not had any issues with adverse events and am not aware of any issues with significant reactions or adverse events
		Expert #8 *British Journal of Surgery*, Volume 103, Issue 11, October 2016, Pages 1409–1419, https://doi.org/10.1002/bjs.10283 1) This referenced articles describing skin pigmentation & discolouration in up to over 50% of patients, which may be long lasting. 2) Larger incisions needed to accommodate for the larger calibre magnetic probes.
		Expert #9 Don't know
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Safe, easy to use, non-inferior to TC99 and Blue Dye
		Expert #2 Identification of sentinel nodes
		Expert #3

		SLNB detection rate is high, false negative rate is low, ease of use – training and experience important, and safety profile is excellent as allergy is not reported
		Expert#4 Efficacy of detecting the SLNB False negative rates Axillary recurrence rates in the long term (over 5-10 years)
		Expert #5: There does not seem to be any clear evidence of improved efficacy compared to the current standard-of-care.
		Expert #6 Use of Magtrace is non-inferior for SLN detection in patients with breast cancer, compared to the current standard of care techniques using radiotracer and blue dye. It provides flexible administration to operating times (20 minutes to 30 days) and can be undertaken in centers without a nuclear medicine department.
		Expert #7 Easier access to theatre for patients requiring sentinel node biopsy
		Expert #8 False negative rates for the overall SNB; cost effectiveness
		Expert #9 Don’t know
16		Expert #1:

	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	None to report
		Expert #2 May not produce a suitable signal like the current technique. Injection of the patent blue dye may be necessary if this happens
		Expert #3 Adequate training to understand injection technique and use of Sentimag probe All published studies sponsored by manufacturers and small numbers although meta –analysis does present reasonable numbers
		Expert#4 None – shown to be non-inferior to standard dual technique.
		Expert #5: Standardised manufacturer-independent guidance on the quality control of gamma probes have been established for many years and there are well-documented procedures for commissioning them for clinical use, in the context of the legislation governing the use of ionising radiation for medical exposures. However, I am not aware of any similar guidance for acceptance testing and routine quality assurance for the SentiMag system. The manufacturer provides a means for testing the sensitivity of the probe but only recommend this is done annually, whereas it is recommended that gamma probes are tested prior to each use. This implies that SentiMag systems are likely to be subject to considerably less quality control than gamma probes, especially given the lack of legislative "pull" to ensure this is done. It is not clear if this is likely to have a significant impact on patient safety – the risk is that the probe is malfunctioning and not noticed due to lack of testing and that this results in SLNs not being identified in theatre. I also think there is uncertainty in the efficacy and safety of this technology for SLNB in cancers other than breast cancer for the reasons outlined above.
		Expert #6

		Lack of randomised trials comparing Magtrace with the current standard of care techniques, to judge the validity of results available in literature on the detection rate of SLN. Absence of cost effectiveness data for the use of Magtrace versus current standard of care techniques. Most of the available evidence of its use is in breast cancer. The utility of this technique in other cancer types is not fully established yet.
		Expert #7 I have no current concerns based on experience thus far
		Expert #8 None.
		Expert #9 Don't know
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: Not aware of
		Expert #2 The controversy mainly revolves around the interpretation of MRI and wash out of the injected iron
		Expert #3 Costs may be higher for some trusts that have isotopes on site but I consider the safety implications of blue dye should not be tolerated.
		Expert#4 None known

		Expert #5: As described above, the lack of imaging capability may adversely affect efficacy in SLNBs where this is essential for the pathway, but this is uncertain and further clinical studies are needed. Another outstanding question is whether a proportion of patients for whom MagTrace is contraindicated (eg, pacemakers, metal implants) will still need to undergo radiocolloid procedures and so there will still need to be some provision for this in the NHS. This could be in more centralised hubs where Nuclear Medicine expertise exists but this would involve these patients potentially travelling further for the intervention.
		Expert #6 Absence of randomised controlled trials makes it difficult to judge and also reduces the confidence of available results. Lack of long-term clinical outcome data. Absence of preoperative imaging in successful localisation of SLN using this technique is a potential disadvantage.
		Expert #7 No
		Expert #8 Ideally, more robust outcome data would be necessary to show that the technique adds value or is clearly superior to existing technology with radionuclide technique.
		Expert #9 Don’t know
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals. Cannot predict at present.

		Expert #2 Most or all district general hospitals.
		Expert #3 Most or all district general hospitals.
		Expert#4 **Most or all district general hospitals.** – I work within a busy symptomatic breast unit within a district general hospital and we utilise the technology within our department.
		Expert #5: Most or all district general hospitals.
		Expert #6 Most or all district general hospitals.
		Expert #7 Most or all district general hospitals.
		Expert #8 Cannot predict at present.
		Expert #9 Don't know
19	Please list any abstracts or conference proceedings that you are aware of that have	Expert #1:

	been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Thank you for provided research review. I have not come across on any other relevant research.
		Expert #2 This study has shown that during follow-up MRI is infrequently required and does not appear to be significant in carrying this out when needed. Assessing the Requirement for MRI During Follow Up After Breast Cancer Surgery: A Prelude to Using Sienna for Sentinel Node Biopsy. February 2020 European Journal of Surgical Oncology 46(2):e68-e69 DOI: 10.1016/j.ejso.2019.11.151  Sunita Shrotria Jack Stuart
		Expert #3 "Sentimag® technique for sentinel lymph node biopsy in breast cancer patients: evaluation of effectiveness, feasibility and challenges.", submitted to the Singapore Medical Journal.
		Expert#4 N/A
		Expert #5: I am not aware of any additional abstracts or publications relating to this technology.
		Expert #6

		Expert #7
		Expert #8 This could be achieved with usual comprehensive literature search.
		Expert #9 Don’t know
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Not aware of
		Expert #2 Not sure
		Expert #3 Not that I know of
		Expert#4 N/A
		Expert #5: Not that I am aware of
		Expert #6
		Expert #7

		Expert #8 I am not aware of any beyond what is visible on publically available resources such as clinicaltrials.gov;
		Expert #9 Don’t know
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: At DCH which diagnose approx. 280 new breast cancer per year around 150 sentinel node biopsies is performed annually. Sentimag/Magtrace has been used for all of them.
		Expert #2 All women diagnosed with invasive breast cancer require sentinel node biopsy.
		Expert #3 100% of patients with breast cancer having SLNB – approx. 20 000 in the UK
		Expert#4 Approximately 56000 new breast cancer diagnoses per annum within the UK and approximately half of these will undergo a SLNB as part of treatment/staging.
		Expert #5: This is not my area of expertise, but if adopted for Breast SLNB only, the number of people eligible for the intervention could be estimated from the cancer incidence rates and clinical input into the proportion of patients that require SLNB.
		Expert #6
		Expert #7

		All node negative cancer patients in the UK
		Expert #8 Potentially any SNB cases in the UK can be considered eligible for the technique depending on availability and surgical preference. The more prevalent indications would be SNB for early breast cancers and melanomas.
		Expert #9 Approximately 850 SNLB procedures performed at Newcastle Trust in 2019-20
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 The main negative aspect of the technology is that as magnetic field measurement any metal around alters the signal. The way to avoid this issue is to use plastic instruments (forceps, retractors) for this part of the operation. As much as this is not a big problem it requires plastic, single-used instruments and surgeon need to get used to this.
		Expert#2 No
		Expert#3 Training is the key stepping stone to usability. A better/smaller detection probe would help
		Expert#4 The Sentimag probe has a larger diameter than the probe used to detect technetium 99 meaning that axillary incisions may be slightly longer. Standard surgical retractors cannot be used – need to use plastic alternatives that are available on the market (single use and limited reusable instruments)
		Expert #5: The system is very similar to use compared to current standard-of-care and it is therefore unlikely that there will be any practical or usability issues.
		Expert #6

		Initial training in the usage of Sentimag system
		Expert #7 Potential issues with magtrace detection in patients who have had previous breast cancer surgery
		Expert #8 None addition to already discussed.
		Expert #9 Don't know
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 Some surgeons may have reservation regarding using plastic instruments. Hospitals with well staffed Nuclear Medicine on site may have no incentives to change from Tc99 to Magtrace.
		Expert#2 Lack of studies and concern about missing recurrence of breast cancer if there are artefacts on MRI. Currently however most follow-up care relies on mammograms only
		Expert#3 Concerns about cost, Reluctance to adopt new technology as the standard of care is so well established
		Expert#4 No
		Expert #5: None
		Expert #6

		The utility of this technique in cancer types other than breast cancer needs to be established. Cost-effectiveness data needed to justify initial acquisition costs of Sentimag system and recurring costs of Magtrace
		Expert #7 No
		Expert #8 None addition to already discussed.
		Expert #9 Already have a working solution in place.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 Not aware of
		Expert#2 Comparative trials
		Expert#3 Optimisation of injection timing and technique
		Expert#4 No
		Expert #5: Further research is needed comparing this technology to the current standard of care in cancers other than breast. In particular, studies are needed into the safety and efficacy of proceeding with SLN with magnetic tracer alone compared to radiocolloid with pre-surgical SPECT/CT imaging and gamma probe localisation.
		Expert #6

		Lack of randomised trials comparing Magtrace with the current standard of care techniques, to judge the validity of results available in literature on the detection rate of SLN.
		Expert #7
		Expert #8 Clear data on superiority but I acknowledge this may not be feasible given number needed to test to show this.
		Expert #9 Don't know
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#1: Beneficial outcome measures: - Audit on time injection to surgery. In my hospital we tend to inject Magtrace a few days before the operation as we noticed that injections on the day of surgery, or in particular within a 1-2 hours before seem to give lower signal and therefore might be less accurate. - Audit if injecting Magtrace in different way eg.deeper may result in less long-term skin staining. Adverse outcome measures: monitoring skin staining which sometimes takes months to resolve
		Expert#2 Beneficial outcome measures: Patient selection – inclusion and exclusion criteria Timing of injection Strength of signal Grade of colour change

		Identification of sentinel nodes No of sentinel nodes harvested Length of procedure Follow up data – Number of patients requiring MRI over 3 to 5 years Reoperation rate Patient and surgeon satisfaction questionnaire Adverse outcome measures: Allergic reaction Failure to identify sentinel nodes Recurrence of cancer - 2 year /5 year follow-up MRI interpretation issues
		Expert#3 Beneficial outcome measures: Technical failure – no signal detected – by surgeon Number of SLNBs found – at surgery/histology Rate pick up of involved SLNBs- at histology Staining of skin, resolution, after how long – PROMS from patient Adverse outcome measures:

		Allergy, injection site pain and skin staining after 6 months and 1 year
		Expert#4 Blank
		Expert #5: Beneficial outcome measures: Number of malignant SLNs identified by technology (true positive rate) – can be measured by comparison with histopathology results Duration of surgical procedure (measured in standardised form with defined start- and end-points for the procedure) Locoregional recurrence compared to current standard-of-care – 10 year follow-up would be appropriate Overall survival compared to current standard-of-care – >10 year follow-up would be appropriate Adverse outcome measures: “Negative node rate” = number of patients for whom no SLNs are identified using the technology – straightforward to count these Number of malignant SLNs not identified by technology (false negative rate) – can be measured if there is a comparator, eg, nodes identified using current standard-of-care radiocolloid technique but not identified using magnetic system that are shown in histopathology to be malignant. Frequency and severity of skin hyperpigmentation – using standardised grading system immediately after procedure and re-monitored at intervals for 1 year post-procedure Patient-reported pain score during procedure – using a standardised grading system

		Expert #6 Beneficial outcome measures: Audit on duration of localisation procedure and number of SLNs detected in the short term which may potentially advice impact on resources (theatre time, costs etc). Adverse outcome measures: Audit on patient reported experience and quality of life indices such as pre-operative wait times, adverse reaction, pain levels, cosmetic appearance and post-operative symptoms. This can be undertaken by a survey using a questionnaire perhaps in the immediate post-operative period just before discharge in the short term. Audit to monitor skin staining and its long-term impact
		Expert #7 Beneficial outcome measures: Greater flexibility in timing of surgery by eliminating the dependence upon nuclear medicine Eliminates risk of anaphylaxis from blue dye Adverse outcome measures:

		I'm not aware of any significant adverse events other than failed localisation due to other factors
		Expert #8 Beneficial outcome measures: Adverse outcome measures: (? 2 years) Skin pigmentation/discolouration – duration, intensity and extent Pain Artefact on follow up MRI False negative rate ; early recurrence rates.
		Expert #9 Beneficial outcome measures: Adverse outcome measures:

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 Blank
		Expert#2 I found the product useful and can see advantage in adopting this after completing more trials.
		Expert#3 I recommend the technology – it has made me more confident with SLNB as I do not worry that I am going cause a severe allergy with blue dye. I have experienced two patients who needed ICU care following blue dye injection, one who was unwell for several days. The usability of the new technique is much better with no concerns about couriering isotope to our hospital or storage. The timing of the injection can be chosen to fit in with other hospital visits and convenient for the patient and surgeon.
		Expert#4 N/A
		Expert #5: None
		Expert #6
		Expert #7 My experience across about 100 patients so far is extremely positve
		Expert #8 None
		Expert #9

		Don’t know

NICE National Institute for Health and Care Excellence

Patient expert statement

GID-MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Carol Johns**
2. Are you (please tick all that apply):	**X**☐ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Self nominated
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**X**☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	**X**☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It can cause anxiety. You are always fearful of the cancer returning. Some treatments can leave you with permanent issues.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Excellent and timely is my experience. All health professionals were excellent.
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Assume it assists the surgeon to locate lymph nodes.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Unfortunate that the dye causes a blue reaction, however, it is temporary. I worried about having the injection as I had visions of my body being radioactive for some time and not sure how this would affect me.
Patient population	
13. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Topic-specific questions	
16. Did you have any concerns about the use of radioisotopes and/or blue dye for the biopsy?	Unfortunate that the dye causes a blue reaction, however, it is temporary. I worried about having the injection as I had visions of my body being radioactive for some time and not sure how this would affect me.

17. What information were you provided with before having the procedure?	I was not told about the injection until I was on my way to have it. The anaesthetist did explain about the blue dye and informed me that I may have a reaction to it. The nurse informed me that urine would be bright blue after the procedure and not to be alarmed.
18. Were there any delays, cancellations or changes to your appointment related to the biopsy? If so, what happened?	Some. It was Easter holidays so this caused a slight delay. The surgeon told meat my follow up appointment but assumed I had already had a letter with the results. I had not received a letter.
19. Did you have to travel further for the procedure due to the facilities available for the biopsy at local hospitals? Did this cause inconvenience to you? If yes, please state how.	My procedure was in a hospital 10 miles from my home. It is very difficult to get to on public transport but I had a friend drive me. I had also had wires inserted in my breast the day before so it was more comfortable to be driven.
20. What was your experience of having the tracer injected before the procedure? For example, with regards to pain,	I was unprepared as nobody had told me this would happen until just beforehand. I was quite nervous and scared at the thought. It was in the nuclear medicine section and the word nuclear scared me. The staff member explained everything well however. She also asked me to stretch my breast whilst she injected and I hardly felt it.

preparation for the procedure and convenience.	
21. Did you experience skin staining after the procedure? If yes, how much of a concern was this?	Slightly stained after on the ward but others were more blue. My urine was very blue but the nurse had warned me and so I was prepared. It is quite alarming to see though but it was temporary.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your statement:

- Information and communication important
- Plain language important
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

GID-MT568 Magtrace and Sentimag

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	19/01/2022	Collated EAQs requested		Collated EAQs - Appendix 2
2.	25/01/2022	Company initiation call		Notes from Company call – Appendix 3

3.	28/01/2022	Additional questions sent to the Company	1) One paper has identified Magtrace licence period as within 7 days of surgery, please can you confirm that Magtrace is licenced for use up to 30 days prior to surgery? 2) Not all studies identified specify the use of Sentimag probe, can Magtrace be detected or used with a probe other than Sentimag? 3) As part of your clinical training, do you recommend procedure supervision (either by a Company clinical trainer or peer clinician) and if so is there a minimum requirement suggested?	1) Endomag: Yes, we can confirm that Magtrace is licenced for up to 30 days prior to surgery. 2) Endomag: There are no other devices on the market with a CE mark to be used with Magtrace. We believe that all of the studies identified for Magtrace used the Sentimag for detection. 3) Endomag: We would recommend initial cases to have procedure supervision by a company clinical trainer for each new user or for a peer clinician to provide procedure supervision to their colleagues subsequently providing they have completed cases first under company clinical trainer themselves and gone through the learning curve. the duration would be agreed with the health care provider and would be based on attainment of competency more than minimum duration, however we would expect to be present for 5 cases with a new user as a-minimum. we would remain as long as we and / or the hcp considered support was required following review of cases and mutual agreement
4.	02/02/2022	Expert Engagement Meeting		Notes from Expert Engagement Meeting – Appendix 4

5.	08/02/2022	Expert Engagement Meeting questions for discussion	Experts attending the Expert Engagement Meeting were asked to provide written responses to the discussion questions. These questions were also circulated to the Experts who were unable to attend the meeting for their comments	Collated responses to EEM discussion questions - Appendix 5
6.	18/02/2022	Additional questions for Company		Questions and responses - Appendix 6
7.	18/02/2022	Additional questions for Experts		Collated responses - Appendix 7
8.	25/02/2022	Additional questions for Experts	Thank you to those who have answered our large list of questions regarding Magtrace, Tc-99m and blue dye. I appreciate these questions have been extremely detailed and lengthy, however gaining insight (even to some or part of the questions) from multiple organisations across the NHS is extremely helpful when attempting to build a generalisable economic model which reflects current NHS care. I wondered if you were able to additionally comment on any supply issues regarding Tc-99m from the perspective of your organisation please? The reason I ask this is because the Company has emphasised lack of Tc-99m supply in Nuclear Medicine departments as a major concern in their submission and model.	Collated responses - Appendix 8

			For organisations with on-site Nuclear Medicine departments: • Can you confirm whether there are or have been supply issues regarding Tc-99m please? • Are you aware of any published local or national audit data monitoring Tc-99m procedures or supply over time? For all organisations with or without on-site Nuclear Medicine departments: • Can you confirm whether SLNB procedures have been cancelled due to lack of Tc-99m supply? If so can you estimate a proportion of SLNB that are cancelled due to this reason please? • Can you confirm whether scheduled SLNB procedures have been delayed due to lack of availability of Tc-99m? If so can you estimate the proportion of procedures delayed, and the average duration of the delay please? Again deepest apologies for these very detailed questions, however any broad or detailed feedback on your experience to determine whether Tc-99m supply is a major clinical concern would be hugely appreciated.	
9.	28/02/2022	Query to Administration of Radioactive Substances Advisory Committee (ARSAC) regarding number of Trusts with on-site nuclear medicine facilities	I hope that you are well? I am a Clinical Scientist working within a NICE External Assessment Centre and we are currently evaluating a new technology. As part of this assessment, it would be beneficial for the team to have an understanding of the availability of Nuclear Medicine departments across England. One of our Clinical experts has advised that you may be able to assist with this. I would be very grateful if you could advise on the	ARSAC Response 03/03/2022: Thank you for your query. We can give the number of NHS sites in England where there are current employer licenses. However, this number would include both Nuclear medicine (imaging and non-imaging) and Brachytherapy services to availability of Nuclear Medicine departments across England. Please confirm that this is suitable for your needs?

			number of NHS Trusts in England that have on-site Nuclear Medicine facilities? If you are unable to assist I would be thankful for any advice or signposting that you may be able to offer.	EAC Response 03/03/2022: Many thanks for your e-mail and information. Please can you clarify what you mean by 'Brachytherapy services to availability of Nuclear Medicine departments'? This will ensure we are able to interpret the information appropriately. Apologies for my confusion. ARSAC Response 08/03/2022: Apologies, it looks like there was a missing statement in the email sent out. We can give the number of NHS sites in England where there are current employer licenses for you to assess the availability of Nuclear Medicine departments across England. The number we provide would include both Nuclear medicine (imaging and non-imaging) and Brachytherapy services as it is not possible for us to easily separate these services out on our database. There are likely very low number of brachytherapy only services. EAC Response 08/03/2022: Many thanks for your prompt response and for clarifying things, it is very much appreciated. The number of sites would still be suitable for our needs, if you are able to provide this we would be very grateful. ARSAC Response 14/03/2022: According to our records there are 163 licenced NHS sites in England. This will include both Nuclear Medicine and Brachytherapy services that

				currently hold a valid Employer licence under IR(ME)R. It does not include sites who may still be operating in accordance with authorisations under the previous MARS regulations.
10.	01/03/2022	Company Engagement Meeting		Notes from Company Engagement Meeting - Appendix 9
11.	02/03/2022	Additional question to clinical expert (to clarify their response to Q7 of the questions sent 18/02/2022)	Thanks again for your responses, please can I just check with you, in response to question 7. The EAC has identified published literature which states that Magtrace can appear as artefacts in future MRI (up to 3 years after initial SLNB injection). Can you estimate the proportion of breast cancer patients, who have SLNB who then require future MRI as part of ongoing surveillance that this may impact?, you say that 3/350 patients were affected. Question 1): Just so we are totally clear, do you mean that 3/350 patients in total required a future MRI? Or do you mean that 3/350 patients required MRI and the imaging had artefects because they had previously had Magtrace? Question 2): Would standard practice be to conduct routine surveillance via mammography for all patients, then add MRI (to those aged <40, lobular carcinoma where the tumour is mammographically occult) and if there were artefacts on those MRIs, would you then proceed to additional contrast-enhanced MRI?	*No response received (as of 14/03/2022)*

12.	07/03/2022	Question to Company	Can I ask for a clarification regarding the difference between Sienna XP and Sienna+ please? You previously stated that both were considered equivalent. However one paper (Rubio et al. 2020) states that the particle diameter in Sienna XP is smaller than that of Sienna+, which permits faster migration to the sentinel lymph nodes, allowing for a lower dose. Can you please confirm if this is the case please?	Thanks for the question, there is no difference in the iron nanoparticles used in any of the previous iterations of Magtrace.
13.	07/03/2022	Question to one of the clinical experts (co-author of paper of interest)	We have identified a conference abstract 'Assessing the requirement for MRI during follow up after breast cancer surgery: a prelude to using Sienna for sentinel node biopsy'. Within the study it is stated that "of the 14 only 3 would have been affected by the use of Sienna on the ipsilateral side (1%)." Please can this be clarified; were the MRI studies impacted by artefacts or is this hypothesised? If the latter, please can you clarify how this conclusion was drawn?	*No response received (as of 14/03/2022)*
14.	08/03/2022	Question to clinical expert to clarify their response to Q8	For the economic case, can you help quantify the delay please? For example: • on average how many minutes was the delay? (e.g. 30mins, 2 hours etc) • how frequently did the delay occur? (e.g. once every day, twice a week etc) I appreciate any response to the above questions are approximations, however I want to ensure that the economic model is including data within reasonable/plausible ranges which reflect NHS.	I understand that numbers would be helpful here but this is really difficult to deliver them. I would say delay to deliver Tc99 from [redacted] was happening 1 per 10 theatre lists. The delay with the theatre time was mitigated changing the order of the list etc. I would guess on average 1 hour delay per "delayed session". For us the main point was that logistics with Magtrace turned out to be much easier, cost cheaper and first of all non-inferior clinical results.

Appendix 1

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question [redacted]:

Insert

File attachments/additional information from question [redacted]:

Insert

File attachments/additional information from question [redacted]:

Insert

Appendix 2

Collated comments table

Expert contact details and declarations of interest:

Expert #1	Mr Tomasz Graja, Consultant Breast Oncoplastic and General Surgeon, Dorset County Hospital NHS Trust, [redacted]
	Nominated by: NICE
	DOI: I have nothing to disclose.
Expert #2	Ms Sunita Shrotria, Consultant General Surgeon, Ashford & St Peters Hospital NHS Trust, [redacted]
	Nominated by: Company
	DOI: None
Expert #3	Dr Caroline Osborne, Consultant general surgeon specialising in breast surgery, Yeovil District Hospital NHS Foundation Trust, [redacted]
	Nominated by: Company
	DOI: No conflicts of interest
Expert #4	Ms Kate Williams, Consultant Oncoplastic Breast and Chest Wall Surgeon, North Manchester Hospital, [redacted]
	Nominated by: Company
	DOI: None
Expert #5	James Scuffham, Clinical Scientist, Royal Surrey County Hospital, [redacted]
	Nominated by: NICE
	DOI: None
Expert #6	Nagabhushan Seshadri, Consultant, Nuclear Medicine, Liverpool University Hospitals NHS Trust [redacted]
	Nominated by: British Nuclear Medicine Society (BNMS)
	DOI: None

Expert #7	Dermot S Murphy, Consultant breast surgeon, NHS Lanarkshire & NHS Dumfries & Galloway, [redacted] or [redacted]
	Nominated by: not stated
	DOI: None
Expert #8	Ming Young Simon WAN, Consultant Radiologist, University College London Hospitals NHS Foundation Trust, [redacted]
	Nominated by: Caroline Oxley, British Nuclear Medicine Society
	DOI: Co-investigator for a NIHR EME grant award (LOOC study, award ID 17/39/05), assessing a novel radionuclide tracer in oropharyngeal tumours, which can be perceived as a competing modality
Expert #9	Elizabeth Jefferson, Head of Nuclear Medicine, The Newcastle upon Tyne Hospitals NHS Foundation Trust, [redacted]
	Nominated by: EAC
	DOI: None

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	Expert #1: I am familiar with Magtrace and Sentimag for 4-5 years. I am every day user for approx. 2.5 year while working at Dorset County Hospital NHS. In this time I did about 150 operations using Magtrace. I know about at least a few places using this technology in the UK eg. Breast Unit in Yeovil.

	Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	I don't know about any usage of Magtrace/Sentimag outside of breast surgery although I can imagine other applications of this technique (eg. Melanoma) This is a standard and default procedure at DCH therefore we do not select patients for this procedure.
		Expert #2 Yes I do have experience of this technique. I have used this product while conducting a feasibility study for magseed and sienna now magtrace. An initial study of the product in 3 patients along with magseed insertion in the same patient was carried out. The methodology was in parallel with the standard technique so that identified node identified with sienna was then rechecked with the isotope probe and or blue dye intraoperatively. Not widely used in the NHS. Only in use in a few units in the UK. Once approved it is likely to have a good uptake. No
		Expert #3 I use Magtrace and the Sentimag system for all my SLNBs. I have been using the technology for 3 years and have performed over 200 SLNBs using Sentimag I use the technology in the two hospital trusts in which I work, having introduced it to the trusts. I know several other hospital using the technology and a couple of colleagues who have contacted me to discuss the technology. I know the technique has been used in patients with oral cancer although I don't know of any other specialties that use the technique.

		Expert4# Sentinel lymph node biopsy (SLNB) has been standard practice in the treatment and staging of breast cancer patients since the 1990's. The standard technique involves a combination of a radioactive isotope (technetium-99) and patent blue dye to locate the first draining lymph node(s) within the axilla; if the breast cancer has metastasised from the breast this is the first location at which breast cancer cells will be found and so this procedure is used to stage the disease and guide the need for adjuvant treatment. SLNB is also utilised in the treatment of melanoma and in some early-stage oral carcinoma as a standard part of practice. I have been performing sentinel lymph node biopsies since the start of my surgical training in 2004 using the standard dual technique up until April 2020 when this innovative Sentimag/magtrace technology was introduced to my breast unit in April 2020. During an initial trial period I and my surgical colleagues used magtrace alongside the long-established patent blue dye marker to ensure confidence, accuracy and safety in our patients, but after a short learning curve and prospective audit we have moved to utilising the magtrace/sentimag system alone. I have now personally performed over 60 procedures utilising this technology; it is now my standard technique for all sentinel lymph node procedures in breast cancer treatment. My four other consultant colleagues within my unit have also converted to this technique as their standard sentinel lymph node procedure. Since COVID19, NHS breast cancer surgical services have had to flex and adapt to the challenges of working and operating in unfamiliar hospitals, often without the facilities, training and licensing necessary to be able to use the standard dual technique for sentinel lymph node biopsy using both radioactive isotope technetium 99 and patent blue dye. This has meant that many NHS breast surgeons have been researching alternative ways of safely performing sentinel lymph node biopsies. The uptake for the sentimag/magtrace technology has therefore quickly increased over the past 12 months throughout the UK. This is due to numerous advantages the new technology provides. For example, the sentimag/magtrace system eliminates the need to expose patient and staff to

		radioactivity in theatre and makes the logistics of theatre scheduling during the COVID pandemic simpler; the production of the alternative standard technetium isotope as well as its administration requires specialist licensing and training that is specific to a hospital site/department. The Sentimag/Magtrace system is in contrast fully mobile and accessible to any theatre complex as long as the surgeon has adequate experience and expertise. Over the past 6-12 months I have been contacted by numerous colleagues from around the UK asking for advice and guidance on the introduction of this system and technology within other breast cancer units. I anticipate its uptake will only increase in breast cancer treatment and I can see no reason why the staging and treatment of melanoma will not follow.
		Expert #5: - I am a registered Medical Physics Expert (MPE) that supports a number of sites that use the current standard-of-care radionuclide technique for SLNB. I have a detailed knowledge of the radiopharmaceuticals and gamma probe technology used for the radionuclide technique, as well as the regulatory requirements and practicalities of providing a radionuclide SLNB service. I have helped set up and supported sites both with and without dedicated Nuclear Medicine facilities to perform these procedures. - As an MPE I provide advice and support on: quality control of gamma probe equipment, optimisation of the radiation dose to patients, safe working practices with radioactivity, and appropriate policies and procedures relating to regulatory compliance. - I am familiar with the MagTrace/SentiMag product as this has been trialled in combination with the radionuclide technique by one of the sites that our Trust provides MPE support to. - I have not used the MagTrace/SentiMag product directly myself, as this is done by surgeons and theatre staff. I am not involved directly in the selection or referral patients for this procedure as this would be done by oncologists or surgeons as appropriate as part of the multi-disciplinary management of the patient. I have an awareness of current SLNB caseload in my own Trust and those that we provide MPE support to, hence I have an understanding of the demand for this procedure within the NHS. Having supported sites to establish similar technology I am able to judge the likely speed of uptake of new technology in this area.

		Expert #6: I have been regularly involved in the use of radioactive tracers for sentinel node mapping. But with regards to Magtrace and Sentimag for locating sentinel node, my experience is only theoretical - having reviewed the literature, and have no practical experience of using it. Magtrace and Sentimag currently is used in about 50 NHS Trusts as per the last MIB published in June 2021 (www.nice.org.uk/guidance/mib263). Given that this technology offers flexibility in terms of timing of injection and free from complex legislation and radiation protection issues, it can be easily adopted, with a bit of staff training, without any significant changes to existing facilities. This procedure/technology (Magtrace abd Sentimag) is normally used by the operating surgeons (breast, head & Neck, oncoplastic), and Nuclear Medicine physicians as such have no role to play. Nuclear Medicine has limited or no role in patient selection or referral to other speciality for this procedure. My experience in sentinel node mapping is in the use of radioactive tracers; including injection, imaging, ARSAC cover, advise on radiation protection issues and representation in the relevant multidisciplinary meetings.
		Expert #7: Yes, we have been using sentimag with Magseed for 4 years and magtrace for 1 year Yes as above Magseed is now in general use but magtrace is in its infancy NHS Dumfries is the first unit in Scotland to trial it, with excellent results. It is about to be used in several other units in the West of Scotland as several of my regional colleagues have come to observe the procedure Not at present

		N/A
		Expert #8: I have no hands on clinical or research experience in relation to the use of this technology (Magtrace & Sentimag). I routinely support the clinical and research service for an alternative modality (nuclear medicine/ radionuclide imaging) used in sentinel node biopsy (SNB). To my awareness, use of radionuclide technique for SNB is the current clinical standard. Use of radionuclide tracer technique is a common and widely used modality for this type of surgery in the NHS, with common indications to include skin cancer/melanoma, breast cancer and oral cavity cancer.
		Expert #9: I was initially trained in SLNB procedures in 2007-8 with the New Start programme for Breast cancer, including injection, image acquisition, image processing and reporting. Started using SLNB for melanoma in 2012 and trained in 2014 using SLNB in penile cancer. Currently use Tc-99m SLNB at Newcastle Hospitals for breast cancer, melanoma, head and neck melanoma and soon will be starting SLNB for Oral cavity carcinoma. SLNB using Tc-99m was adopted very widely in the UK after the New Start programme following the early termination of the research trial clearly demonstrating the effectiveness of SLNB The Tc-99m radiopharmaceutical is manufactured on our site and our nuclear medicine team inject patients prior to surgery. This is done for Newcastle patients and also for Northumbria patients as they do not have a nuclear medicine service within the county. No experience in patient selection, only in the delivery of the technetium SLNB injections including imaging where necessary.

2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have done bibliographic research on this procedure. I have had no involvement in research on this procedure.
		Expert #2 I have done bibliographic research on this procedure. I have done clinical research on this procedure involving patients or healthy volunteers.
		Expert #3 I have reviewed my clinical practice and experience with the procedure and submitted for publication. I plan a future study with my colleague assessing injection volumes and techniques
		Expert#4 Prior to introducing this technique into our breast unit, I performed a literature search and critically analysed the peer reviewed evidence for its efficacy and non-inferiority compared to the standard dual technique. I presented this evidence to my surgical colleagues and the “new medicines and innovations” committee within my Trust prior to its trial and cautious introduction. I am prospectively auditing the outcomes for all sentinel lymph node biopsies performed in our unit to ensure safety and efficacy.
		Expert #5: I have done bibliographic research on this procedure.
		Expert #6: I have done bibliographic research on this procedure. I have no practical experience on Magtrace and Sentimag for locating sentinel node nor have I undertaken any laboratory or clinical research on this technology/procedure

		Expert #7: I have done bibliographic research on this procedure. We are auditing our results using magtrace alongside radio-isotope
		Expert #8: I have no research experience with Sentimag and Magtracer. On the other hand, I have published on the use of radionuclide tracer technique for SNB and in its combination with other tracers (fluorescent tracers). I am a co-investigator with a NIHR EME grant to study the use of a novel radionuclide tracer in oropharyngeal tumours.
		Expert # 9: None I have had no involvement in research on this procedure.

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: The paradigm of axillary lymph node staging through identifying the sentinel lymph node in the axilla remains unchanged as for the Blue Dye technology or Tc99. What make the technology attractive is avoiding significant disadvantages of the Blue Dye (allergic reactions) or complex logistics with radioactive Tc99. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #2

		A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #3 Established practice and no longer new, but this now established technique utilises new tracer technology that is safer than previous tracers. Its performance is non-inferior to previous tracers.
		Expert#4 **A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.** The technique and safety of sentinel lymph node biopsy in the treatment and staging of breast cancer and melanoma is well-established and undisputed when performed using the standard dual technique with technetium 99 and patent blue dye. Magtrace is an innovative tracer injection but the physical surgical technique of utilising a probe within the operating theatre to locate the sentinel lymph node is well established. Of note, the Sentimag probe system is also utilised by a number of different breast units to locate impalpable breast tumours using magseed technology; many surgeons have therefore gained invaluable experience in handling the sentimag probe. The learning curve is thus not that steep from current standard surgical practice.
		Expert #5: The procedure represents a new technological innovation that can be applied to a well-established surgical procedure. As such it should be considered a minor variation. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #6: Magtrace and Sentimag technology is a minor variation to the current standard in sentinel node mapping and uses magnetic liquid tracer instead of the established radioactive tracers and/or blue

		dye. It is unlikely to alter the procedure's safety. Efficacy is yet to be fully established by randomised studies and in cancers other than breast cancer.
		Expert #7: This technique is equivalent to radio-isotope injection but avoids the dependence upon nuclear medicine which is a major limiting factor in many DGHs. In addition as virtually every unit already had the sentimag probes in place for Magseed localisations there are limited additional costs involved. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.
		Expert #8: To my understanding, this is a variation to current standard of care, if we consider SNB as a whole. My view is that it is a minor variation on an existing procedure, which is unlikely to alter the procedure's (SNB) overall safety and efficacy.
		Expert #9: Not experienced in alternative technologies. Radiopharmaceutical use in standard of care is a "trace" amount of injected substance very unlikely to cause a reaction. N/a.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: The strength of this technology is safety and easy logistics.
		Expert #2 Replace ultimately existing technique – although during testing other existing modalities can be used alongside during early trials

		Expert #3 This technology could replace duel sentinel node detection with radioisotope and blue dye
		Expert#4 Yes – this technology can replace the standard of care.
		Expert #5: This procedure could replace the current standard of care.
		Expert #6: Given the non-radioactive nature of Magtrace and flexibility of its use (timing of injection, improved logistics by avoiding the need to travel to hospitals with nuclear medicine facility, free from complex legislation and radiation protection issues), it has the potential to be used as an alternative to current standard of care procedure if efficacy and cost effectiveness are fully established.
		Expert #7: Replace radio-isotope technique and blue dye which has a not insignificant risk of allergic reaction
		Expert #8: My view is that this procedure (Magtrace/Sentimag) has the potential as an alternative to the current standard of care, which is the use of radioactive tracers for SNB.
		Expert #9: Don't know

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: All patients with invasive breast cancer undergo assessment of the axillary lymph nodes with the ultrasound and than if no metastatic disease detected with sentinel lymph node biopsy. In order to find

		which lymph node is the first (sentinel) we attempt to replicate the natural flow of the lymph from the affected breast to axillary nodes injecting the tracer into the breast which travels through lymphatics into the sentinel node. The most popular currently are Blue Dye and radioactive Tc99 used separately or together (with intention to increase node detection).
		Expert #2 Sentinel nodes are currently identified by a dual technique of isotope and blue dye injected in the subareolar plexus
		Expert #3 Sentinel node detection with radioisotope and blue dye is current standard of care for SLNB detection
		Expert#4 Sentinel lymph node biopsy (SLNB) has been standard practice in the treatment and staging of breast cancer patients since the 1990's. The standard technique involves a combination of a radioactive isotope (technetium-99) and patent blue dye to locate the first draining lymph node(s) within the axilla; if the breast cancer has metastasised from the breast this is the first location at which breast cancer cells will be found and so this procedure is used to stage the disease and guide the need for adjuvant treatment. Technetium 99 is a radioactive isotope that can only be produced by a small number of centres throughout the UK with specialist licensing, to then be transported and distributed to other hospital sites and administered by medical personnel with specialist training and licensing. It is a finite, scarce resource and supply has been unreliable recently, a problem only worsened by COVID19 restrictions. Technetium 99 has a short half-life (6 hours) and so the timing of its administration compared to the time of surgery is crucial (usually within 1-4 hours, given on the day of surgery). This makes surgical theatre scheduling a challenge. Technetium 99 is used alongside patent blue dye, but is injected into the breast once the patient is anaesthetised and on the operating table. Patent blue dye has an associated risk of anaphylaxis of approximately 15/100 000 administrations (the fourth most common cause of perioperative anaphylaxis in the UK).

		Surgeons use a Geiger counter in the operating theatre to guide axillary dissection and locate the lymph nodes that have uptake of technetium 99 within them; these are the sentinel or first draining lymph nodes of the breast. Surgeons also look for and follow blue lymphatics to guide them to any blue coloured sentinel lymph nodes (or a combination of the two).
		Expert #5: Current standard-of-care includes the injection of a radiocolloid in combination with Blue Dye, followed by localisation of the SLN(s) in theatre using a gamma probe to detect the radioactivity in combination with the visual signal from the blue dye. Administration of the radiocolloid in advance of surgery allows images of the node locations to be generated. For breast SLNB, the relatively straightforward lymph node anatomy means that imaging is not always performed and is often not felt to be useful by the surgeons performing this procedure. However, for more complex lymph node anatomy, such as for melanoma, vulva, head and neck and other indications, hybrid imaging with SPECT/CT is common and widely regarding as essential for surgical planning.
		Expert #6: The current standard of care used in the NHS is sentinel node mapping by using radioactive tracers along with blue dye
		Expert #7: Current sentinel node localisation is carried out using radio-isotope localisation with or without patent blue dye. This technique is aimed at removing the reliance on nuclear medicine
		Expert #8: In patients with early cancers (e.g. breast, oral cavity and melanoma) and no overt spread to lymph nodes yet on conventional clinical and imaging assessment, SNB retrieves nodes believed to have the highest chance of harboring any occult spread of tumor for detailed analysis. This information enhances accuracy for nodal staging and guides any further need for more treatment.

		Identification of the sentinel nodes (SN) are currently through the use of small amount of radioactive tracer injected into patients as current standard of care; the radioactive signal can help the surgeons to retrieve these nodes (i) by generating pictures prior to surgery in the scanner (gamma camera) to help pre-surgical planning, and (ii) during the operation by radiation probes to locate and confirm resection of these SN.
		Expert #9: Technetium labelled nanocolloid injection along side a blue dye injection. Sentinel lymph nodes tend to be blue and hot, but may be blue or hot.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: There are some attempts to use indocyanine green ICG for fluorescence-guided sentinel node biopsy. As far as I am aware there are a few projects going on but none in common use outside of the research. Fluorescence is developing and promising technology but not ready yet. My understanding is that fluorescence is much more expensive at this stage than standard technologies including Magtrace.
		Expert #2 The above are in use currently. The product is different. The surgical technique with the magtrace/ sienna itself is not different.
		Expert #3 Indocyanine green is popular in the US but not widely used in UK, Same injection technique with a different tracer
		Expert#4 **Fluorescence Techniques** **1. Indocyanine Green** 1-5ml of ICG can be injected into the breast after anaesthesia. Fluorescence is not visible directly, but the theatre lights are dimmed and a specialist photodynamic eye system is used to see black and white images of fluorescent lymphatics and sentinel nodes on a monitor.

		ICG cannot be used in patients with iodine allergy. There are no randomised trials comparing it with standard tracer techniques. The technique is completely novel. It again eliminates exposure to ionising radiation. **2. Fluorescein** 10% fluorescein widely available and low cost and widely used in ophthalmology. A blue light source is needed to excite fluorescence, but it is directly visible so no imaging system is needed. Only evidence is from conference proceedings – research and safety data is scarce. **Non-Operative Axillary Staging** **1. Computed Tomography Lymphography** 3 D computed tomography lymphography is performed the day before surgery. 4ml of iopamidol is injected into the breast and then a CT scan is performed and 3D CT images are reconstructed to identify the lymphatics and sentinel nodes. Nodes that are poorly stained suggest the presence of metastases. These nodes are then marked on the skin using a laser navigator and then SLNB is performed with patent blue dye. Accurate but exposes the patient to radiation and puts added pressure onto a stretched radiology service. **2. Contrast-Enhanced Ultrasound Scan** Dynamic contrast-enhanced ultrasound scan images can be obtained to identify and biopsy the sentinel lymph nodes non-operatively. US contrast agents consist of microbubbles containing various gases within a shell. The agent is injected into the breast. The lymphatic channels are visualised on contrast pulse sequencing and followed into the axilla to the draining sentinel lymph node that accumulates the contrast agent. This is then percutaneously biopsied. The technique has a reported high false negative rate and is limited to very few centres. Further work is needed to improve sensitivity.
		Expert #5: Oncovision market a product that produces real-time images of radionuclide distribution that can be used to localise SLNs in theatre (https://oncovision.com/sentinella/). This technology has been

		evaluated in the UK in a small number of patients (eg, https://pubmed.ncbi.nlm.nih.gov/28033510/). This technology still requires the use of radiocolloid injection but replaces the use of gamma probes to localise the SLNs. Lightpoint medical market a laparoscopic gamma probe which is intended for the detection of lymph node metastases peri-operatively. Recent studies have demonstrated its use in prostate cancer surgery with radiocolloids (Abstract EP-074, https://link.springer.com/content/pdf/10.1007/s00259-021-05547-1.pdf). Although similar, this technology is not intended for superficial SLN removal.
		Expert #6: Sentinel node mapping by using radioactive tracer along with blue dye, which is well established as the current standard of care is the alternative technology already available to the NHS. In comparison to the current standard of care techniques, the technology described in the briefing, is non-radioactive, well tolerated with fewer side effects and improves logistics of undertaking SLNB by eliminating the dependency on Nuclear medicine units and potentially offering flexibility of use in smaller centres. The data on the use of Magtrace in sentinel node detection however is not robust, due to the lack of randomised studies, in evaluating its efficacy and cost-effectiveness when compared to the current standard of care techniques.
		Expert #7: Radio-isotope localisation
		Expert #8: Competing alternative technology: - Radionuclide tracer as described above. Established technique and widely adopted. Allows for (i) scanning to get pictures to help plan surgery, and (ii) using probe to detect SN during the operation, as well as (iii) confirming the appropriate nodes are retrieved by applying the probe on the excised tissues and at the surgical bed after. Need infrastructures to support the use of the (minute amount of) radioactive tracer, e.g. getting ARSAC licences, basic radiation training, time from relevant staff (e.g. radiation protection personnel), maintanence of gamma camera and probes.

		Magtrace/Sentimag has similar functions in feasibility to enable these 3 elements. - Blue dye. Established and widely available. Provides visually perceptible 'signal' to identify lymph nodes in the drainage path. If used on its own, no pre-operative scans can be done to help plan surgical approach. It is only visible after surgery has started and incisions made. Feedback from surgical colleagues I work with is that it stains much of the surgical field - lymphatic tracks and nodes may be difficult to see in surgery. - Fluorescent tracers (e.g. indocyanine green). Generally available (used also for fluorescent angiography in retinal angiography; assessment of bowel perfusion in bowel surgery). Limited penetrance with existing tracers: if used on its own, the signal cannot be detected pre-surgically (therefore no possible to plan incisions); the signal can only be 'visible' with specialised sensors/cameras. Feedback from surgical colleagues I work with is however that it shows the lymph nodes very well visually in the patient/on screen intraoperatively. This precision in the 'short range' complements with the 'longer range' offered by radionuclide tracers when used in combination.
		Expert #9: Technetium labelled nanocoll which is also fluorescent can be used to avoid the use of blue dye. This would be a very low risk option, with a low probability of patient reaction. The surgeon can identify the sentinel node visually under fluorescent lighting and because the node is radioactive
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Safe, straightforward in use. Potentially cheaper.
		Expert #2 Patients will not need to travel to another centre (nuclear medicine department) the day before surgery for a radioactive injection. The blue dye used has been known to cause severe anaphylaxis resulting in ITU admission

		Expert #3 Magtrace and Sentimag technique is a much safer alternative to radioisotope and blue dye. There is a high rate of allergic and anaphylactoid reaction to blue dye and on occasion this led to reactions severe enough to lengthen hospital stays and require specialist care on ICU. Magtrace can be injected by the surgeon, with no specialist storage requirements and up to 7 days prior to surgery allowing for better theatre utilisation arrangements
		Expert#4 1. Reduces exposure to ionising radiation 2. Reduces the risk of intraoperative anaphylaxis 3. Reduces patient anxiety and distress on the day of surgery by eliminating the need for the patient to attend nuclear medicine for administration of technetium on the day of surgery (sometimes on a different hospital site to the surgery due to strict licensing laws) 4. Breast Cancer treatment/staging no longer dependant on a finite resource (technetium) with unreliable supply chain. 5. Allows more flexible theatre scheduling with more efficient utilisation of theatre capacity 6. Magtrace can be used to avoid sentinel lymph node biopsy all together in patients with pre invasive breast cancer who require mastectomy, which avoids the risk of surgical morbidity such as lymphoedema in a small number of patients.
		Expert #5: Lower radiation dose to patients, potentially increased accessibility of procedure due to simpler set-up compared to radionuclide procedure and therefore higher likelihood of adoption in DGH settings.
		Expert #6: Well tolerated, apart from skin discoloration as a side effect mentioned in the literature. It is non-radioactive. Improves logistics by avoiding patient travel and increases flexibility of scheduling sentinel node mapping procedures.

		Expert #7: By removing the nuclear medicine part of the pathway it means that for many DGHs who don't have a nuclear medicine unit patients can receive their localisation injection at the time of surgery. Currently many patients have to travel to different sites before surgery to attend a local nuclear medicine unit.
		Expert #8: In areas/institutions where access to radionuclide tracers and relevant infrastructure may be limited.
		Expert #9: Lack of ionising radiation.

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: This technology is particularly attractive for hospitals without Nuclear Medicine Departments on site. Currently many small and medium size hospitals lost their Nuclear Medicine facilities and for the radioisotopes became dependent of bigger hospitals (often distant) and bringing radioisotopes for each patient directly (cost!).
		Expert #2 All breast cancer patients with invasive disease will benefit from this. Logistically this is going to be useful but also will avoid radioactive material being injected which require precautions. After surgery there is delay in sending the specimen to the lab as the radioactivity needs to wear off before it can be safely handled by the pathologist. Hence the histopathology report takes longer to come through potentially delaying further surgery or adjuvant treatment
		Expert #3 I would say all patients having SLNB procedures and particularly those with history of allergy or atopy
		Expert#4 Patients who have a diagnosis of DCIS / pleomorphic LCIS of the breast who require a mastectomy would normally, using the standard techniques, require a SLNB at the time of their mastectomy. This is done in case there is hidden/undiagnosed invasion/micro invasion within the breast subsequent which would then require staging of the axilla. This could not be achieved with the standard dual technique as there is no longer a breast to inject the technetium/patent blue dye into. The tracer could not pre-emptively be injected at the time of mastectomy to come back to at a later date as the patent blue and the isotope would be cleared from the lymphatics and therefore would not be accurate. Magtrace can be injected at the time of mastectomy for DCIS/pleomorphic LCIS to allow the tracer to travel to and mark the sentinel lymph node. Mastectomy alone can then be performed and if incidental invasive disease is found histologically the patient can return to theatre within 30 days to

		undergo a standalone SLNB as the Magtrace tracer will still be detectable within the sentinel lymph nodes. This avoids the surgical morbidity of performing an unnecessary SLNB in this specific patient group.
		Expert #5: Assuming higher likelihood of adoption of SentiMag/Magtrace, patients whose local hospitals do not have capability to use radionuclide SLNB localisation will benefit particularly, as they will not have to travel to a centre that does have this capability.
		Expert #6: Would be particularly useful in patients who are potentially allergic to blue dye and young women in whom exposure to radiation could be avoided.
		Expert #7: All node negative patients at diagnosis are eligible
		Expert #8: To my knowledge, this could act as an alternative to radionuclide technique. There are non-inferior studies comparing Magtrace/Sentimag but to my knowledge, there is no clear superiority demonstrated and no robust data on clearly better outcome.
		Expert #9: Don't know
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system?	Expert #1: I do think that it has already changed practice in many places, as discussed above, for better. It seems to be safer than Blue Dye as Magtrace is generally well tolerated. Avoiding costs of transport from the other hospital seems to benefit economical aspects.

	Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #2 Yes as above
		Expert #3 Yes - the tracer is not radioactive so no special precautions needed in its use. The isotopes were prepared in centralised isotope labs by nuclear physics departments, needing specialist transport and handling and only could be injected on the day of surgery by an appropriately qualified nuclear physics professional – all logistically challenging. The new technology avoids all this as it does not need special storage and handling and can be injected by the surgeon up to 1 week before operating. No risk of allergy identified so safer and avoids those admissions for patients who had an allergy SLNB detection rates are not inferior to the previous technique and the surgical procedure is not any more difficult
		Expert#4 This technology avoids the need for a patient to attend nuclear medicine either on the morning of or the day before surgery. This nuclear medicine department can sometimes be located at a different hospital site to the breast operating theatres.
		Expert #5: The MIB covers SLNB generally and not relating to a specific cancer. However, I think there are different considerations relating to different tumour sites. In particular, for cancers other than breast, it is common for pre-surgical imaging and mapping of SLN locations to be carried out using the radiotracer, which cannot be achieved using the MagTrace product. For breast cancer, assuming no pre-surgical imaging is performed (which is commonly the case), the clinical pathway will not change as a result of this technology and there isn't any evidence it will improve clinical outcomes. There is potential for fewer hospital visits in some patients as no separate appointment for radiocolloid injection will be required, although some patients already have radiocolloid injected by theatre staff on the day of surgery anyway.

		For other SLNB indications, the lack of imaging capability may mean that adoption of the new technology may adversely affect patient outcomes. The vast majority of studies in which the technology has been investigated have been on patients with breast cancer. I am not aware of any studies that have compared outcomes in other cancers where pre-surgical imaging is performed with radiocolloid versus SentiMag alone. I would therefore recommend that any guidance issued focussed specifically on breast cancer until such studies have been published.
		Expert #6: The procedure could potentially improve logistics by avoiding patient travel to the nuclear medicine department and allows to undertake sentinel node mapping in smaller centres and increases flexibility in patient scheduling. There is some suggestion in literature of improved efficiency of operation theatre time, but yet to be fully established.
		Expert #7: Yes by elimination of the nuclear medicine visit Magtrace is injected by the surgical team at the time of surgery
		Expert #8: There is potential to improve on logistical challenge in coordinating various resources needed in the pathway, compared to using radionuclide technique. Radioactive tracers are relatively short-lived. The supply, injection, any scans required, and the surgery needs to be tightly coordinated before the radiation signal decays away (e.g. all done in one day; or injection & scan on afternoon of day 1, followed by surgery morning of day 2). This is usually not a problem if the Institutions have established pathways. (if the chain of event is broken, e.g. delays in theatre, then there may be need to repeat/re-inject). Signal from Magtrace/Sentimag seems longer lasting and these steps above could in theory be more loosely coupled, with less challenge to coordination.
		Expert #9:

		Don't know
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: I think that this technique has potential to became more popular and cheaper in the future than standard Tc99 in view of avoiding costs related to the Nuclear Medicine staff, complex legislation, radiation protection, ARSAC licence etc.
		Expert #2 Likely to result in cost saving
		Expert #3 Similar to the previous standard of care. Isotope handling is expensive
		Expert#4 About the same/Less. Initial start-up costs and cost per procedure seem more than the current standard dual technique but if the decreased use of radiopharmaceuticals centres and specialist staff, transport of the technetium from the production centre, specialist nuclear medicine personnel time administering the injection and increased theatre efficiency gained from switching to the Sentimag/Magtrace system overall expenditure is either the same or reduced.
		Expert #5: The current and proposed technologies both require similar initial capital purchases of probes for the detection of the signal from the SLNs (gamma probes typically cost around £15-25k; the stated cost of the SentiMag system is £25k). The per-patient cost then mainly relates to the tracer – the stated costs are £226 for MagTrace and £195 for radiocolloid. I don't think there is sufficiently detailed analysis of the relative costs of the technologies in the MIB. In particular, I would be interested to see further detail of how the cost of the radiocolloid has been calculated (my Trust currently pays £60 per dose but this excludes transport costs). For Trusts that do not have dedicated Nuclear Medicine facilities, for the current standard-of-care radiocolloid technique, there are additional costs of set-up including consultations and appointment of RPA, RWA and MPE as appropriate.

		Maintenance and quality control of gamma probe systems requires access to a long-lived sealed source of radioactivity such as a Co-57 spot source which typically costs ~£3k and need replacing every 2-3 years. Gamma probe systems can be quite fragile and the chances of a probe needing repair in its lifetime is quite high. I am not sure if this is similar for SentiMag or if repair is as straightforward. In terms of staffing costs, it is possible to have theatre staff Taking these factors into account, on balance I expect the costs of the new technology will be similar to the current standard-of-care.
		Expert #6: The technology in evaluation is based on the same principle as the current standard of care technique in use and may potentially improve the pre-operative care pathway, but overall the impact in terms of staff and equipment may not be significant. Initial capital expenditure would involve purchase of Sentimag detection system and training. Possible financial savings on costs related to dependency on nuclear medicine facility.
		Expert #7: Less as we will no longer require nuclear medicine input. The injection is carried out by the surgeon in theatre and means that surgery is not dependent upon nuclear medicine availability.
		Expert #8: This is difficult for me without detailed data and calculations relevant to the NHS setting. My gut feeling is that it would be more, when considering need to purchasing new equipment, training and maintenance for the equipment, need for MRI time if pre-surgical localisation is desired.
		Expert #9: Don’t know
11	What do you consider to be the resource impact from adopting this	Expert #1: As above

	procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #2 Likely to be more cost effective
		Expert #3 Cost of new technique quoted as higher than standard of care but in my experience we have similar costs as before because we avoid the expense o transporting isotopes that are produced in another hospital. When I introduced the new technique to my trust we went through a very thorough business planning exercise and found that for us the costs were similar. Also no admission for allergic reactions as with blue dye which would escalate the costs of the episode
		Expert#4 As above
		Expert #5: See above.
		Expert #6: Adopting this technology is likely to cost more or less the same in terms of equipment and staff costs as the current standard of care, but a robust cost effectiveness study is yet to be undertaken.
		Expert #7: Equivalent or less than at present
		Expert #8: This is difficult for me without detailed data and calculations relevant to the NHS setting. My gut feeling is that it would be more, considering likely cost of the agent. In addition, available literature seems to suggest higher number of sentinel nodes harvested during SNB with Magtrace/Sentimag compared to radionuclide technique. This would translate to increase

		costs/resource needed for adequately analysing these nodes by pathology laboratory which are often already stretched. This is a fine balance, there is data to suggest harvesting more nodes with the radionuclide technique would improve false negative rates in breast cancer SNB, but it is unclear if this can be translated/generalised to this context. There is to my awareness lack of clear data on superior detection of pathologically confirmed metastatic nodes within harvested nodes, or outcome data, when comparing Magtrace/Sentimag with radiotracers.
		Expert #9: Don't know
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: No changes required as the technology doesn't need any capital cost except the initial purchase of Sentimag and than only Magtrace for injections.
		Expert #2 None
		Expert #3 Purchase of the Sentimag detection device is needed. Magtrace tracer must also be purchased.
		Expert#4 None. Can be safely administered in theatre once the patient is anaesthetised by the treating surgeon.
		Expert #5: Existing theatre facilities will be suitable for the new technology.
		Expert #6: No major changes are necessary to adopt this technology, apart from initial capital expenditure to purchase the Sentimag detection system and initial training. Also, metallic surgical retractors, which

		may potentially affect signal detection on the Sentimag system, may have to be replaced with plastic alternatives.
		Expert #7: None as the equipment is already in place. However by removing the radio-isotope injection any potential radiation risk is eliminated
		Expert #8: Purchasing of magnetometers/probes and the associated machines. Need for replacing standard surgical retractors with plastic ones. MRI scan time. Staff training. Decommissioning of gamma probes. Diversion of gamma camera & relevant staff times for other clinical priorities
		Expert #9: Don't know

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: No, any breast surgeon who is familiar with Tc99 and Blue Dye Sentinel Node Biopsy will be able to adapt quickly to the magnetic tracer usage.
		Expert #2 Yes
		Expert #3

		I would recommend in person demonstration and supervised training for first 5 cases It may also be useful to undertake the first solo 25 procedures using radioisotope/blue dye in conjunction with Magtrace.
		Expert#4 The company can provide on-site training. Would usually recommend starting to use the technology in combination with patent blue dye until surgeon feels confident in their ability to locate the sentinel lymph node using the Sentimag/magtrace system alone. Staged approach for the more cautious (e.g. mastectomy patients first as better surgical access to the axilla / less technically challenging).
		Expert #5: Appropriate training for theatre staff is provided by the manufacturer
		Expert #6: Initial training on the use of Sentimag detection system will be required.
		Expert #7: The technique builds on surgical skills already in place with Magseed localisation and radio-isotope guided sentinel node biopsy
		Expert #8: I should think surgeons, radiographers, radiologists would need extra-training to: - Draw up new protocol for titrating the right dose of the agent to balance between imaging artefact and probe sensitivity; - Interpretation of images, if required; - Use of the magnetometers/probes intraoperatively
		Expert #9: Don’t know

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: Injection of Magtrace into the breast is sometimes uncomfortable for a minute or so. The tracer leaves breast discoloration (like a brownish bruise) which takes weeks to months to resolve completely. Having said that the Blue Dye cause similar although blue discoloration. I have not experienced any other adverse reactions to Magtrace.
		Expert #2 May interfere with MRI interpretation during follow-up as the product is made of iron. Preoperative MRI may be required for patients who have lobular cancer It may take several months or longer for the product to wash out Not suitable for patients with iron metabolic disorders May mask recurrence during MRI follow-up due to the presence of artefacts
		Expert #3 Very safe – I have had no safety concerns. I have had only 2 technical failures in the 200 procedures I have done Skin staining with the Siena dye colour is common and patients need to be warned of this (own experience) Size of detector probe is large and affects resolution. Important to use visual cues – colour change in nodes is obvious Causes artefact change if patient requires a post op MRI – this can last up to 1 year

		Expert#4 Skin staining – discolouration of the breast skin is common after breast conservation (35% in the immediate post op setting) but this falls to 8.6% after 15 months. Reported patent blue dye discolouration in patients can be present in up to 23% of patients at 24 months. Interference with Magnetic Resonance Imaging of the breast in the future if breast conserving surgery performed – manipulation of the scan parameters may be required to compensate for the artefact. Skin reaction at injection site (<1%) and anaphylaxis (<0.1%)
		Expert #5: The most common adverse effect is skin discolouration which is well described in the evidence cited in the MIB. I am not aware of any other significant harm or adverse events arising from the technology, either in literature or in my experience.
		Expert #6: The technology appears to be safe and well tolerated. The main adverse event reported in the literature is skin discoloration. Skin discoloration after a 2.0 mL subareolar injection was reported in 15.6% of patients in the SentiMagIC(1)study. SUNRISE study by Rubio et al.(2) showed that by using subareolar injections in patients who underwent breast conservation surgery resulted in cutaneous staining varying from 59% in patients who received 1.0 mL to 83.3% in patients who received 2.0 mL. The long-lasting staining may pose a restriction on the use of MRI in patients who need follow-up assessment due to artefact from retained Magtrace particles. 1. Alvarado, M.D.; Mittendorf, E.A.; Teshome, M.; Thompson, A.M.; Bold, R.J.; Gittleman, M.A.; Beitsch, P.D.; Blair, S.L.; Kivilaid, K.; Harmer, Q.J.; et al. SentimagIC: A Non-inferiority Trial

		Comparing Superparamagnetic Iron Oxide Versus Technetium-99m and Blue Dye in the Detection of Axillary Sentinel Nodes in Patients with Early-Stage Breast Cancer. Ann. Surg. Oncol. 2019, 26, 3510–3516. 2. Rubio, I.T.; Rodriguez-Revuelto, R.; Espinosa-Bravo, M.; Siso, C.; Rivero, J.; Esgueva, A. A randomized study comparing different doses of superparamagnetic iron oxide tracer for sentinel lymph node biopsy in breast cancer: The SUNRISE study. Eur. J. Surg. Oncol. 2020, 46, 2195–2201
		Expert #7: Magtrace involves the use of heavy metals but the dose is very small and carries little risk to the patient I have not had any issues with adverse events and am not aware of any issues with significant reactions or adverse events
		Expert #8: British Journal of Surgery, Volume 103, Issue 11, October 2016, Pages 1409–1419, https://doi.org/10.1002/bjs.10283 1) This referenced articles describing skin pigmentation & discolouration in up to over 50% of patients, which may be long lasting. 2) Larger incisions needed to accommodate for the larger calibre magnetic probes.
		Expert #9: Don't know
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Safe, easy to use, non-inferior to TC99 and Blue Dye
		Expert #2

		Identification of sentinel nodes
		Expert #3 SLNB detection rate is high, false negative rate is low, ease of use – training and experience important, and safety profile is excellent as allergy is not reported
		Expert#4 Efficacy of detecting the SLNB False negative rates Axillary recurrence rates in the long term (over 5-10 years)
		Expert #5: There does not seem to be any clear evidence of improved efficacy compared to the current standard-of-care.
		Expert #6: Use of Magtrace is non-inferior for SLN detection in patients with breast cancer, compared to the current standard of care techniques using radiotracer and blue dye. It provides flexible administration to operating times (20 minutes to 30 days) and can be undertaken in centers without a nuclear medicine department.
		Expert #7: Easier access to theatre for patients requiring sentinel node biopsy
		Expert #8: False negative rates for the overall SNB; cost effectiveness.
		Expert #9:

		Don't know
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: None to report
		Expert #2 May not produce a suitable signal like the current technique. Injection of the patent blue dye may be necessary if this happens
		Expert #3 Adequate training to understand injection technique and use of Sentimag probe All published studies sponsored by manufacturers and small numbers although meta –analysis does present reasonable numbers
		Expert#4 None – shown to be non-inferior to standard dual technique.
		Expert #5: Standardised manufacturer-independent guidance on the quality control of gamma probes have been established for many years and there are well-documented procedures for commissioning them for clinical use, in the context of the legislation governing the use of ionising radiation for medical exposures. However, I am not aware of any similar guidance for acceptance testing and routine quality assurance for the SentiMag system. The manufacturer provides a means for testing the sensitivity of the probe but only recommend this is done annually, whereas it is recommended that gamma probes are tested prior to each use. This implies that SentiMag systems are likely to be subject to considerably less quality control than gamma probes, especially given the lack of legislative "pull" to ensure this is done. It is not clear if this is likely to have a significant impact on patient safety – the risk is that the probe is malfunctioning and not noticed due to lack of testing and that this results in SLNs not being identified in theatre.

		I also think there is uncertainty in the efficacy and safety of this technology for SLNB in cancers other than breast cancer for the reasons outlined above.
		Expert #6: Lack of randomised trials comparing Magtrace with the current standard of care techniques, to judge the validity of results available in literature on the detection rate of SLN. Absence of cost effectiveness data for the use of Magtrace versus current standard of care techniques. Most of the available evidence of its use is in breast cancer. The utility of this technique in other cancer types is not fully established yet.
		Expert #7: I have no current concerns based on experience thus far
		Expert #8: None.
		Expert #9: Don't know
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: Not aware of
		Expert #2 The controversy mainly revolves around the interpretation of MRI and wash out of the injected iron
		Expert #3 Costs may be higher for some trusts that have isotopes on site but I consider the safety implications of blue dye should not be tolerated.

		Expert#4 None known
		Expert #5: As described above, the lack of imaging capability may adversely affect efficacy in SLNBs where this is essential for the pathway, but this is uncertain and further clinical studies are needed. Another outstanding question is whether a proportion of patients for whom MagTrace is contraindicated (eg, pacemakers, metal implants) will still need to undergo radiocolloid procedures and so there will still need to be some provision for this in the NHS. This could be in more centralised hubs where Nuclear Medicine expertise exists but this would involve these patients potentially travelling further for the intervention.
		Expert #6: Absence of randomised controlled trials makes it difficult to judge and also reduces the confidence of available results. Lack of long-term clinical outcome data. Absence of preoperative imaging in successful localisation of SLN using this technique is a potential disadvantage.
		Expert #7: No
		Expert #8: Ideally, more robust outcome data would be necessary to show that the technique adds value or is clearly superior to existing technology with radionuclide technique.
		Expert #9: Don’t know

18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals. Cannot predict at present.
		Expert #2 Most or all district general hospitals.
		Expert #3 Most or all district general hospitals.
		Expert#4 **Most or all district general hospitals.** – I work within a busy symptomatic breast unit within a district general hospital and we utilise the technology within our department.
		Expert #5: Most or all district general hospitals.
		Expert #6: Most or all district general hospitals.
		Expert #7: Most or all district general hospitals.
		Expert #8: Cannot predict at present.
		Expert #9:

		Don't know
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1: Thank you for provided research review. I have not come across on any other relevant research.
		Expert #2 This study has shown that during follow-up MRI is infrequently required and does not appear to be significant in carrying this out when needed. Assessing the Requirement for MRI During Follow Up After Breast Cancer Surgery: A Prelude to Using Sienna for Sentinel Node Biopsy. February 2020 European Journal of Surgical Oncology 46(2):e68-e69 DOI: 10.1016/j.ejso.2019.11.151
		Expert #3 "Sentimag® technique for sentinel lymph node biopsy in breast cancer patients: evaluation of effectiveness, feasibility and challenges.", submitted to the Singapore Medical Journal.
		Expert#4 N/A
		Expert #5: I am not aware of any additional abstracts or publications relating to this technology.
		Expert #6: -

		Expert #7: -
		Expert #8: This could be achieved with usual comprehensive literature search.
		Expert #9: Don’t know
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Not aware of
		Expert #2 Not sure
		Expert #3 Not that I know of
		Expert#4 N/A
		Expert #5: Not that I am aware of
		Expert #6: -
		Expert #7:

		-
		Expert #8: I am not aware of any beyond what is visible on publically available resources such as clinicaltrials.gov;
		Expert #9: Don't know
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: At DCH which diagnose approx. 280 new breast cancer per year around 150 sentinel node biopsies is performed annually. Sentimag/Magtrace has been used for all of them.
		Expert #2 All women diagnosed with invasive breast cancer require sentinel node biopsy.
		Expert #3 100% of patients with breast cancer having SLNB – approx. 20 000 in the UK
		Expert#4 Approximately 56000 new breast cancer diagnoses per annum within the UK and approximately half of these will undergo a SLNB as part of treatment/staging.
		Expert #5: This is not my area of expertise, but if adopted for Breast SLNB only, the number of people eligible for the intervention could be estimated from the cancer incidence rates and clinical input into the proportion of patients that require SLNB.
		Expert # 6:

		-
		Expert #7: All node negative cancer patients in the UK
		Expert #8: Potentially any SNB cases in the UK can be considered eligible for the technique depending on availability and surgical preference. The more prevalent indications would be SNB for early breast cancers and melanomas.
		Expert #9: Approximately 850 SNLB procedures performed at Newcastle Trust in 2019-20
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 The main negative aspect of the technology is that as magnetic field measurement any metal around alters the signal. The way to avoid this issue is to use plastic instruments (forceps, retractors) for this part of the operation. As much as this is not a big problem it requires plastic, single-used instruments and surgeon need to get used to this.
		Expert#2 No
		Expert#3 Training is the key stepping stone to usability. A better/smaller detection probe would help
		Expert#4 The Sentimag probe has a larger diameter than the probe used to detect technetium 99 meaning that axillary incisions may be slightly longer.

		Standard surgical retractors cannot be used – need to use plastic alternatives that are available on the market (single use and limited reusable instruments)
		Expert #5: The system is very similar to use compared to current standard-of-care and it is therefore unlikely that there will be any practical or usability issues.
		Expert #6: Initial training in the usage of Sentimag system
		Expert #7: Potential issues with magtrace detection in patients who have had previous breast cancer surgery
		Expert #8: None addition to already discussed.
		Expert #9: Don't know
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 Some surgeons may have reservation regarding using plastic instruments. Hospitals with well staffed Nuclear Medicine on site may have no incentives to change from Tc99 to Magtrace.
		Expert#2 Lack of studies and concern about missing recurrence of breast cancer if there are artefacts on MRI. Currently however most follow-up care relies on mammograms only
		Expert#3

		Concerns about cost, Reluctance to adopt new technology as the standard of care is so well established
		Expert#4 No
		Expert #5: None
		Expert #6: The utility of this technique in cancer types other than breast cancer needs to be established. Cost-effectiveness data needed to justify initial acquisition costs of Sentimag system and recurring costs of Magtrace
		Expert #7: No
		Expert #8: None addition to already discussed.
		Expert #9: Already have a working solution in place.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1: Not aware of
		Expert#2: Comparative trials

		Expert#3: Optimisation of injection timing and technique
		Expert#4: No
		Expert #5: Further research is needed comparing this technology to the current standard of care in cancers other than breast. In particular, studies are needed into the safety and efficacy of proceeding with SLN with magnetic tracer alone compared to radiocolloid with pre-surgical SPECT/CT imaging and gamma probe localisation.
		Expert #6: Lack of randomised trials comparing Magtrace with the current standard of care techniques, to judge the validity of results available in literature on the detection rate of SLN.
		Expert #7: -
		Expert #8: Clear data on superiority but I acknowledge this may not be feasible given number needed to test to show this.
		Expert #9: Don’t know
25		Expert#1: Beneficial outcome measures:

	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	- Audit on time injection to surgery. In my hospital we tend to inject Magtrace a few days before the operation as we noticed that injections on the day of surgery, or in particular within a 1-2 hours before seem to give lower signal and therefore might be less accurate. - Audit if injecting Magtrace in different way eg.deeper may result in less long-term skin staining. Adverse outcome measures: monitoring skin staining which sometimes takes months to resolve
		Expert#2 Beneficial outcome measures: Patient selection – inclusion and exclusion criteria Timing of injection Strength of signal Grade of colour change Identification of sentinel nodes No of sentinel nodes harvested Length of procedure Follow up data – Number of patients requiring MRI over 3 to 5 years Reoperation rate Patient and surgeon satisfaction questionnaire Adverse outcome measures:

		Allergic reaction Failure to identify sentinel nodes Recurrence of cancer - 2 year /5 year follow-up MRI interpretation issues
		Expert#3 Beneficial outcome measures: Technical failure – no signal detected – by surgeon Number of SLNBs found – at surgery/histology Rate pick up of involved SLNBs- at histology Staining of skin, resolution, after how long – PROMS from patient Adverse outcome measures: Allergy, injection site pain and skin staining after 6 months and 1 year
		Expert#4 Blank
		Expert #5: Beneficial outcome measures: Number of malignant SLNs identified by technology (true positive rate) – can be measured by comparison with histopathology results Duration of surgical procedure (measured in standardised form with defined start- and end-points for the procedure)

		Locoregional recurrence compared to current standard-of-care – 10 year follow-up would be appropriate Overall survival compared to current standard-of-care – >10 year follow-up would be appropriate Adverse outcome measures: "Negative node rate" = number of patients for whom no SLNs are identified using the technology – straightforward to count these Number of malignant SLNs not identified by technology (false negative rate) – can be measured if there is a comparator, eg, nodes identified using current standard-of-care radiocolloid technique but not identified using magnetic system that are shown in histopathology to be malignant. Frequency and severity of skin hyperpigmentation – using standardised grading system immediately after procedure and re-monitored at intervals for 1 year post-procedure Patient-reported pain score during procedure – using a standardised grading system
		Expert #6: Beneficial outcome measures: Audit on duration of localisation procedure and number of SLNs detected in the short term which may potentially advice impact on resources (theatre time, costs etc). Adverse outcome measures: Audit on patient reported experience and quality of life indices such as pre-operative wait times, adverse reaction, pain levels, cosmetic appearance and post-operative symptoms. This can be undertaken by a survey using a questionnaire perhaps in the immediate post-operative period just before discharge in the short term. Audit to monitor skin staining and its long-term impact

		Expert #7: Beneficial outcome measures: Greater flexibility in timing of surgery by eliminating the dependence upon nuclear medicine Eliminates risk of anaphylaxis from blue dye Adverse outcome measures: I'm not aware of any significant adverse events other than failed localisation due to other factors
		Expert #8: Beneficial outcome measures: Adverse outcome measures: (? 2 years) Skin pigmentation/discolouration – duration, intensity and extent Pain Artefact on follow up MRI False negative rate ; early recurrence rates.
		Expert #9: Beneficial outcome measures: Adverse outcome measures:
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1 Blank
		Expert#2

		I found the product useful and can see advantage in adopting this after completing more trials.
		Expert#3 I recommend the technology – it has made me more confident with SLNB as I do not worry that I am going cause a severe allergy with blue dye. I have experienced two patients who needed ICU care following blue dye injection, one who was unwell for several days. The usability of the new technique is much better with no concerns about couriering isotope to our hospital or storage. The timing of the injection can be chosen to fit in with other hospital visits and convenient for the patient and surgeon.
		Expert#4 N/A
		Expert #5: None
		Expert #6: -
		Expert #7: My experience across about 100 patients so far is extremely positive
		Expert #8: None
		Expert #9: Don’t know

Appendix 3

GID-MT568 Magtrace and Sentimag

Company Introduction meeting

25 January 2022, @ 13:00

Joining Instructions

NOTES

In attendance:

Company (Endomag): Dan Sturt (DS), Matt Womack (MW), Prof Quentin Pankhurst (QP)
Newcastle EAC: Andrew Sims (AJS), Kim Keltie (KK), Rosalyn Parker (RP), Emma Belilios (EB), Joanne Davison (JD)
NICE: Lizzy Latimer (LL), Farhaan Jamadar (FJ), Victoria Fitton (VF)

1. **Welcome and introduction**
   All attendees will introduce themselves and briefly describe their role in the assessment.

   DS - Market Development Director, Endomag
   MW - Director of Clinical Development, Endomag
   QP - External consultant Endomag (author of the additional literature review)

   AJS - EAC Director
   KK - EAC Manager, Economics lead
   RP - EAC Evaluation Healthcare Scientist, Clinical lead
   EB - EAC Administrator
   JD - EAC Admin support (observing)

2. **Literature review**
   The Company shared an additional literature review document with the clinical submission. This literature review is referenced in the clinical submission, and NICE would like to share it with the Committee, as an appendix to the clinical submission, in the supporting documentation. All supporting documentation will be published during the public consultation, is the Company happy with this? MW confirmed this is acceptable, as long as the sections marked as CiC are redacted. The Company conducts the literature reviews annually, as part of their post market surveillance to compare outcomes with 'gold

standard' and to support CE Marking. LL confirmed all content highlighted as confidential will be redacted before it goes into the public domain.

QP noted that the literature review is much broader than the focussed search in the clinical submission. One is not a substitute for the other.

LL queried why methodological information has been highlighted as CiC in the literature review. MW and QP clarified that the methodology has taken years to develop to the point where they are completely happy with it. It is fully MDR compliant and meets the needs of the notified body. They would prefer not to make the strategy available to their competitors. LL suggested that if the sensitive information was classified as AiC rather than CiC, this would mean it could be discussed by the Committee in public, but would be redacted before publication. MW had not realised this was an option (assumed it related to unpublished manuscripts only).

ACTION: MW to go through literature review document, remove any superfluous redaction and change from CiC to AiC where appropriate, and resubmit to NICE

FJ asked if the Company could un-redact some of the more generic methodology. QP thought it might be possible to compose a modified version suitable for publication. If further discussion is needed, a separate meeting will be arranged, involving VF and Lee Dobson (LD). (VF left the meeting at this point).

Where guidance is informed by AiC material, there is usually an expectation that the material will be published in due course (and will then be in the public domain), which will not be the case if guidance is informed by the separate literature review. LL noted that the results of the review are not confidential, only the details of how the search was developed. QP confirmed they are happy for the EAC to approach them if they have any specific queries on sources.

LL clarified that the EAC/NIHRIO will focus on the literature search in the clinical submission in terms of their review, independent replication (following usual process).

ACTION: EAC/NIHRIO to focus on the literature search in the clinical submission

3. **EAC questions – see Appendix**
   Questions will be circulated in advance, and discussed briefly on the call. The Company will also provide full written responses via email.

Written responses from the company will also be provided as soon as possible.

4. **Company questions**
   The Company will have the chance to raise any process questions.

   QP asked if the EAC use EndNote? The Company have the bibliographic libraries if this would be useful? AJS confirmed that the EAC does use EndNote, they will contact the Company if the libraries are required.

5. **Confidentiality and the Correspondence Log**
   NB: Further to this meeting, the EAC will communicate directly with the Company (and vice versa), copying NICE in. All correspondence should be via email. ***All correspondence that informs the assessment will be published in the correspondence log on NICE's website as supporting information when the final guidance is published****. It is the Company's responsibility to highlight for redaction any information that is commercially sensitive ([redacted]) or academic in confidence ([redacted]).*

6. **Next steps**
   Company engagement meeting will allow any questions to be raised later, however company and EAC can communicate via email (as above).

7. **AOB**

   There was no other business.

Appendix - EAC Questions for Company

The technology

- *Can you confirm that the device names or versions of the technology include (and that no other variations are missing): Sienna+, Sienna XP, MagTrace, SentiMag?*

  Yes, that is the full list of names. Don't highlight/capitalise letters within the names.

- *Is there any difference in signal strength depending on the time of injection (e.g. 2 hours vs 30 days prior to procedure)? Is an optimal time recommended?*

  No, there is no optimal time recommended. Defer to Instructions for Use (IFU) for guidance. There are some data showing that the amount of signal arriving at the nodes does go up over time. Data supports use over all the timeframes. One of the attractions of Magtrace is that it gives clinicians the flexibility to streamline their own pathway. No half-life, no wash-out period. A lot of the literature shows non-inferiority based on an injection 20 minutes prior to surgery. Age, BMI, and comorbidities may influence strength, however the company confirmed that there is no separate guidance for each patient group (same standard IFU for all).

- *The maximum dose of MagTrace is 2ml, is this used in the majority of cases?*

  The Company doesn't monitor which dosage Trusts are using (2ml or 1ml). Defer to IFU. Use 1ml if using pre-operatively (day before surgery), or 2ml if using intra-operatively. When best to inject (and therefore which dose to use) depends on the pathway (hospital and clinician decision).

  RP has come across 0.5 ml increments in the literature, are there occasions when 0.5 ml increments are recommended? The Company clarified these doses are not listed in the IFU, and would only be used for research purposes.

- *In terms of environmental or cost impact, are there any alternatives to single-use plastic instruments during the procedure?*

  Many of the newer range of surgical instruments are reusable. Some clinicians will use metallic instruments and move them out of the way so they

don't cause signal interference. Titanium instruments are metallic but non-ferrous so cause less signal interference. In the US, they are looking at lightweight carbon fibre instruments, but the Company is not aware of them being used in the NHS.

- *The probe sensitivity checks and device maintenance occurs annually, are there any interim checks or ways to know whether the device is functioning appropriately prior to the procedure?*

  There is no annual service. The device comes with a probe checker which can be used to check if it is functioning correctly. Checker has a pre-recorded value, when used with the checker the system should display a value that is within a range +/- 10% of this value. Additionally, error message will show up on the device screen if there is an issue. This is in the training material and the IFUs.

  AJS asked if there are any audit data around standard operating procedures (SOPs) used in practice (how many Trusts do daily checks or per-procedure checks)? The Company encourages Centres to check the probe at the start of theatre lists, but don't have any written reports on what Centres actually do. Clinical experts (contact details provided) can advise on what happens in practice.

  ACTION: EAC to confirm practice with clinical experts.

  RP - how is it calibrated and how long for? Any cases where this has been an issue and impacted patient care (e.g. if procedure has been abandoned when anaesthetic already given)?

  The Company can share link to training materials for setting up Sentimag and checking the probe. The Sentimag unit cannot be calibrated as such, the Sentimag unit has a reset button which performs in a similar way to the tare function in that it re-zero's the device, this is not calibration. To be clear the probe checker allows the user to ensure that the Sentimag unit and probe are functioning properly.

  ACTION: Company to share training video showing device calibration.

  POST MEETING NOTE: Link to training material provided

  ACTION: Company to check if trial data on device reliability had been

published yet, and share with NICE/EAC if available.

Magtrace is passive, it will always work if you place a functioning probe over it. So if the probe breaks, user can swap over and use a new probe. Only issue is the potential for causing patient unease if they are awake during the procedure.

- *A precaution of Magtrace (listed in the IFU) is that it can alter MRI of the injection and drainage sites, and some alteration may be long-term. How long does Magtrace remain in the body and have the potential to disrupt or prevent MR imaging?*

  This can be very variable as how quickly Magtrace is broken down in the body is dependent on a number of patient characteristics. There is some data in the literature to suggest 18-24 months is a reasonable range. Mammography is not affected. The IFU highlights the potential long term effect of artefacts on MRI imaging. Contrast enhanced digital mammography or gadolium MRI are potential alternatives to standard MRI if needed. Company quoted a study where 88% of MRI images being clinically interpretable without gadolium.

  ACTION: Company to share the source of above figures with NICE/EAC.

  POST MEETING NOTE: Reference provided, Krischer B, Forte S, Niemann T, Kubik-Huch R, Leo C. Feasibility of breast MRI after sentinel procedure for breast cancer with superparamagnetic tracers. EJSO. 44 (2018) 74-79

- *Is measurement competence monitored for users of MagTrace and SentiMag?*

  No. Company will do everything they can to make sure surgeon is happy, but ultimately it is up to surgeon to operate within their scope of competence to do what's best for their patients.

- **Economic model**
  Could you give us any information regarding the economic model, in terms of:
  - *Software used (Excel, other)*
  - *Model structure (decision tree, Markov)*

Cost minimisation, short time horizon, decision tree structure, developed in Microsoft Excel.

Appendix 4

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Expert Engagement Meeting

MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Date: **02 February 2022**

Time: **11:00 – 12:30**

Documents

MIB: www.nice.org.uk/guidance/mib263

MTG Scope: www.nice.org.uk/guidance/gid-mt568/documents/final-scope

In Attendance:

NICE: Lizzy Latimer (LL), Farhaan Jamadar (FJ), Chris Chesters (CC), Helen Crosbie (HC)

Newcastle EAC: Kim Keltie (KK), Andrew Sims (AJS), Rosalyn Parker (RP), Emma Belilios (EB), Joanne Davison (JD)

Experts:

Tomasz Graja (TG), Consultant Breast Oncoplastic and General Surgeon, Dorset County Hospital NHS Trust

Caroline Osborne (CO), Consultant Oncoplastic Breast Surgeon, Yeovil District Hospital NHS Foundation Trust

James Scuffham (JS), Clinical Scientist, Royal Surrey County Hospital

Simon Wan (SW), Consultant Radiologist, University College London Hospitals NHS Foundation Trust

NOTES

Welcome and introductions

LL presented slides introducing NICE and Newcastle EAC. She clarified that the focus for this guidance is breast cancer only.

Questions for the professional experts by theme: (see below)

Patient population and understanding the current clinical pathway

One expert commented that the purpose of any tracer is to follow the same pathway through the lymphatic system as the cancer cells, to identify the sentinel lymph nodes. As the comparative technologies are performing the same function, the patient group is the same.

They have used Magtrace and Sentimag to guide sentinel lymph node biopsy (SLNB) in around 500-600 patients. The only issue they have come across is with a woman with a pacemaker and cancer in her left breast. They had concerns about the safety and efficacy of Magtrace and Sentimag in this patient due to the proximity of the tracer to the (metal) pacemaker. They could not find any published evidence on Magtrace and Sentimag in patients with pacemakers so used blue dye instead in this patient. LL noted that patients with metal implants are contraindicated for Magtrace and Sentimag in the Instructions for Use (IFUs). One expert commented that interference from the pacemaker might affect the probe, but Magtrace and SentiMag were unlikely to affect the pacemaker. One expert commented that the Company representative told them that Magtrace and Sentimag was safe to use in patients with pacemakers as long as the probe is kept at least 15 mm away from the pacemaker.

LL asked if patient preference is taken into account when selecting tracer. Do their feelings on radioisotopes affect the choice of technique? One expert commented that very few patients decline radioisotopes. Very low dose of radioactive material (much lower than

many other routine procedures). Patient leaflets set this out clearly. Dye and radioisotopes are standard care unless the hospital doesn't have access to radioisotopes, in which case Magtrace is an option.

LL asked, under what circumstances would you use blue dye only? Would it only be when radioisotopes are not available? One expert commented, the NEW START Programme introduced SLNB in 2002. The dual indicators were demonstrably better initially. Now Centres have over twenty years of experience, many are able to drop one or other tracer effectively without impacting on detection rates. Blue dye is not specifically indicated for use in SNLB, and can cause anaphylaxis. Use of blue dye for this purpose is off-label. Some Centres therefore only use radioisotopes. At their Centre, Magtrace is used as standard. Patients are not given a choice, as the Centre doesn't have the option to offer radioisotopes. They use blue dye only as an alternative.

Experience of Magtrace and Sentimag in the NHS

One expert commented their Centre started using Magtrace with radioisotopes and blue dye about three years ago as part of a trial. The radioisotopes were dropped quite quickly as the Centre lost their nuclear medicine facility locally, so were having to bring the radioisotopes in from another Centre. Using Magtrace is very similar to using radioisotopes from a technical viewpoint, so clinicians pick it up very quickly. They now use Magtrace and Sentimag only (dropped blue dye over a year ago - Magtrace is considered a dual technique, due to its brown colouration to improve visualisation, so no need for blue dye as well), and have a lot of confidence in the technology. When SLN cannot be found, it is not always a failure of the technology.

One expert commented that their Directorate (Medical Physics) supports a number of hospitals with use of radioisotopes. One is

trialling Magtrace and Sentimag. Magtrace and Sentimag are useful for hospitals that do not have a nuclear medicine facility. They are not aware of any issues with the technology.

LL asked if there are currently any supply issues with radioisotopes? One expert responded that this week a technical issue at a nuclear reactor in the Netherlands has created some short term supply issues, but overall, this is not a problem. Challenge is that the nuclear medicine support tends to be at larger hospitals. At smaller Centres where there are no on-site nuclear medicine facilities, there are two options:

i. Hospital obtains its own licences and gets approval to do procedure (huge amount of legislative background to facilitate this simple procedure, covering use, storage and disposal of radioactive product).

ii. Patient gets injection somewhere else then travels in for their procedure (usually the next day).

One expert (nuclear radiologist) commented that once a technetium generator is supplied, it lasts a couple of months, so supply of tracer at Centres with nuclear medicine facilities is not an issue. Half-life of the radioisotope is six hours, but the probes are extremely sensitive so conducting the procedure the day after the tracer is injected is fine. This does restrict when SNLB procedures can be listed as nuclear medicine departments are not often available on a weekend and SLNB procedures need to be performed on the day of injection or the day after.

One expert commented that their Centre never had a nuclear medicine department, so were reliant on a neighbouring Trust to support SLNB procedures. This caused logistical issues that led them to look for alternatives. They have subsequently adopted Magtrace

and Sentimag, which has improved the service, streamlining lists. Additionally, they have experience of frightening episodes of blue dye anaphylaxis (1-2 per year) with injection occurring on the surgery table due to this specific adverse event, so did not like taking this risk in their patients. They have been using Magtrace and Sentimag for three years now and confidence has grown. There was a learning curve (about a year) with some failures earlier on. They now do the injections in clinic at least a week before (visualisation is better if the tracer has time to reach the lymph nodes so would not recommend injection on the day of surgery). They have also moved to a deep injection technique which leads to less issues with staining (which can be permanent). Very good uptake into the lymph nodes and detection rates. Initially, the injection was given at a separate hospital visit. Now, they tend to give it during a routine clinical visit (so no separate visit required), as they know that surgery will be within 30 days.

FJ asked if patients are screened for risk of anaphylaxis (associated with blue dye). Is that risk eliminated or reduced with Magtrace and Sentimag?

One expert responded that patients would always be screened for risk of anaphylaxis (questionnaire). Blue dye would be avoided in high risk patients, but risk is not always predictable. Their Centre experienced 1-2 incidences of severe anaphylaxis each year (caused by the blue dye) before moving to Magtrace and Sentimag and impact on patient can be substantial (can require several days of ICU care). They have experienced no issues with sensitivity to Magtrace, believe it is inert. Anaesthetists don't like covering blue dye procedures as they are anxious about possible reaction. Main issue patients have with Magtrace is skin staining. This occurs with blue dye as well but tends to last longer with Magtrace. Deeper injections lessen the risk of staining.

Experts advised that anaphylaxis results in drop of blood pressure, may require steroids, in severe cases may result in ICU, intubation, extra support/monitoring for several days (increased hospital stay).

KK - contraindications for Magtrace include hypersensitivity to iron or dextran, and iron overload - how significant an issue is this? None of the experts had experienced inability to give Magtrace due to these contraindications.

One expert commented that use of tracer should be down to user preference. They did not think guidance should mandate Magtrace and Sentimag as a replacement for radioisotope, or blue dye or both.

LL - asked if there were any specific issues around use in pregnancy and breast-feeding, and use in male or transgender breast cancer patients. One expert commented that surgery would not be done on breast-feeding women; lactation would stop before surgery. There was a discussion over whether Magtrace or radioisotopes were safer in pregnant women. Radioisotopes can be used during pregnancy but would need local risk assessment and senior lead approval. Experts agreed they would not use blue dye in pregnant patients. They would probably avoid tracers altogether in pregnant patients and instead take random 4 lymph node samples in these patients. This will be effective in around 99% of cases. The experts saw no particular issues or benefits (compared with standard care) in using Magtrace and Sentimag in male or transgender breast cancer patients.

Integrating Magtrace and Sentimag into the clinical pathway

Experts agreed that with radioisotope, there are a lot of special precautions required, double bagging, double gloving, let waste sit for 48 hours which can be challenging for the theatre staff, plus concern around blue dye anaphylaxis. Magtrace and Sentimag can simplify the logistics and reduce legislation, which is more time efficient.

KK - there is a concern that Magtrace treatment can make patients unsuitable for MRIs for some time after the procedure - how big an issue is this for this patient group? One expert thought this would be more of an issue with Magseed. Patients having neoadjuvant chemotherapy treatment will need regular scanning. They thought that it would no longer be an issue by 12 month follow up (and MRI at 12 months is not standard). Magtrace could be avoided if you know the patient will need MRI follow up routinely after surgery but the experts thought this would be apply to a small patient group.

Technetium-99m and blue dye

Are any other radioisotopes used for SNLB procedures? Expert confirmed that Technetium-99m is the universal standard.

LL - asked about the efficiency gains of being able to inject patients earlier with Magtrace? Experts thought NICE should contact a clinician who currently uses the dual technique to comment. The two experts using Magtrace are both from centres with no nuclear medicine facility. One reported that before they switched to Magtrace, their surgical lists had to fit round the logistics of patients receiving injections at another Centre. They thought that there would be much less disruption at Centres with a nuclear medicine facility on site, except that involving another team will introduce some additional complexity.

KK noted that the majority of published evidence, states use of Magtrace injected on the day of the surgery. Two experts commented that it is more convenient for the patient if it's done earlier, and leads to better visualisation. When they first started using Magtrace, they wanted to do the injection on the table when the patient was anaesthetised (to avoid any pain from the injection) but visualisation wasn't good. They have learned from experience and now do the injection in advance, leading to better visualisation. Endomag

encourage this approach. Looking for magnetic signal but also the brownish colour. Injection technique has also improved and is now less painful.

By contrast the radioisotope must be injected no more than one day before the surgery (half-life of Tc-99m is 6 hours). KK asked, is it ever the case that a patient receives their injection of radioisotope the day before their surgery is planned, and the surgery then has to be postponed, would they then need a further injection? Experts commented that this would be extremely rare. Failure of the gamma probe might be an issue, but would then use blue dye to find the sentinel nodes.

One of the experts asked if injecting Magtrace earlier could lead to issues with the colouring spreading to secondary nodes. Experts confirmed this would not be the case. The sentinel nodes (which the tracer reaches first) will have the strongest magnetic signal. Use of Magtrace has not increased the number of nodes identified and removed for biopsy. Average is two, wouldn't usually take more than four.

One expert asked if imaging (lymphoscintigraphy) is done in advance of SLNB. Experts confirmed lymphoscintigraphy was dropped a while ago, they don't image the nodes before surgery. Produced a 2D image which was not particularly helpful.

FJ - asked about Magseed, which is not the focus of this assessment, but often patients receive both. What percentage have both? How are they used together? One expert responded that around 30% have both at their Centre. This will be higher at Centres with a higher proportion of screening patients. Can be difficult, but all about planning and understanding how the signals can overlap. Need to know where your Magseed is (use imaging, ultrasound, if necessary), and local practice is to make sure Magtrace is at least 3 cm away

(different quadrant). One expert commented that the identification process is the same for Magtrace and Magseed, and users can identify the separate signals if the distance is sufficient and technique adapted to identify the signals from each. They use slightly different settings on the machine.

Device needs frequent calibration during the procedure (up to ten times) conducted via foot pedal, or via button on machine with aid of theatre staff. One expert commented that users pick this up quickly.

Next steps

LL thanked the experts for their time.

The Experts agreed to provide written responses to the discussion questions below. NICE will also circulate to Experts unable to attend the meeting. There are likely to be additional questions from NICE and the EAC.

Notes from the call will be sent for review. Final notes will be published on NICE's website as supporting documentation when the guidance is published.

Questions for discussion

The format of the meeting is to allow discussion of some of the questions below that fall within the key themes in the agenda. All questions may not be covered in the meeting so we do ask, if possible, for a written response to the specific questions below. This will assist the External Assessment Centre with their assessment of the technology and the relevant evidence.

Patient population and current care pathway

	Question	Response
1	Are all breast cancer patients assessed by ultrasound and fine needle biopsy to rule out node involvement prior to Sentinel Lymph Node Biopsy (SLNB)?	
2	Can you estimate what proportion of breast cancer patients are Lymph Node Negative (LN0) and routed for SLNB?	
3	What proportion of patients with DCIS or invasive breast cancer have surgery (e.g. mastectomy, breast-conserving surgery) and SLNB at the same theatre session?	
4	Does the type of surgery conducted in Ductal Carcinoma in Situ (DCIS) and invasive breast cancer (mastectomy, breast-conserving surgery) influence the need for SLNB? Or influence the choice of tracer?	
5	What proportion of patients undergoing mastectomy surgery would later require SNLB, and would there be implications or other considerations for performing SLNB procedure in this patient group (that have previously had a mastectomy)?	
6	Magtrace is contraindicated in patients with hypersensitivity to iron oxide or dextran compounds,	

	patients with iron overload disease, or patients with a metal implant close to the expected sentinel lymph node location. Can you estimate the proportion of breast cancer patients who will have at least one of these contraindications (and would therefore be unsuitable for Magtrace) but who would be suitable for Tc-99m and blue dye.	
7	Can SLNB be performed in patients who are pregnant or breastfeeding? Are you aware of any contraindications for using radioisotopes or superparamagnetic iron oxide tracers in this group of patients?	
8	Do NHS care pathways, specifically for those being considered for SLNB, differ in pregnant patients with DCIS or breast cancer and if so please can you explain how and whether there is any NICE guidance to support this?	
9	Have you aware of cases where Magtrace has been used in men or transgender patients? Are there any specific considerations we should be aware of?	

Magtrace and Sentimag

10	Would you carry out additional screening or diagnostic tests to exclude hypersensitivity in patients before using Magtrace, or would you only know this from the patient notes?	
11	A precaution of Magtrace is that it can alter MRI of the injection and drainage sites. This alteration may be long term (i.e. these	

	patients may not be suitable for MRI of these sites for two years after they receive Magtrace). What are the consequences of this for the patient (who will presumably need to be monitored for recurrence of cancer)? Will this mean a change to standard of care for these patients?	
12	The Company proposes that contrast enhanced digital mammography and gadollium MRI are suitable alternatives to conventional MRI for patients post-Magtrace, does this seem reasonable?	
13	Metal surgical instruments can cause interference when using the Sentimag probe. If you have experience of using Sentimag, can you comment on whether you therefore switched to alternatives (e.g. single-use or reusable plastic or titanium tools)? What did you use, and were there any implications in terms of cost or acceptability within your Trust?	
14	MagTrace can be injected up to 30 days prior to surgery. How useful is this extra time in practice? Would the majority of patients continue to have the tracer injected within 24 hours of their surgery regardless? Can the length of time Magtrace is injected prior to surgery improve the detection rate? Are there circumstances when you would give 2 injections of Magtrace prior to surgery (e.g. at 2 weeks prior to surgery and then within 24 hours of surgery?)	
15	In hospitals that have access to both Magtrace and Sentimag and radioisotopes, what would be the factors that determine which tracer a patient received? Is	

	patient preference a factor in the clinical decision-making, including not using blue dye? What is communicated about the different tracer options?	
16	Is there a 'learning curve' with the technology? How many cases do you feel are required to gain sufficient competency and are there any strategies implemented to account for this (e.g. peer procedures; use of standard treatment alongside).	
17	In your experience, does tumour type, grade, size and location impact on the: a. Node detection rate b. Number of nodes retrieved c. SLNB procedure time d. SLNB Patient reported outcomes e. SLNB Complication rate	
18	In your experience, how often does Sentimag require calibrating during the procedure? Does this impact on the procedure length?	
19	Do consider there to be inefficiencies and/or unpredictability in the supply of radioisotopes that could impact management of operating lists? Could the use of Magtrace improve the planning and management of operating lists?	
20	Have you encountered any issues with calibration either before or after the procedure?	

Technetium-99m and blue dye

21	The comparator included in the scope is radioisotope (Tc-99m) **and** blue dye. Does this	

	represent standard of care in the majority of cases?	
22	Can you estimate the proportion of patients where blue dye is not used (*i.e.* Tc-99m alone is used)?	
23	Is blue dye ever used on its own without Tc-99m?	
24	Some studies report that a radioisotope is used but do not specify the type. Can we assume the isotope used in the UK NHS will always be Technetium-99m (Tc-99m)?	
25	Can you comment on whether this represents standard of care at your hospital: Injection of Tc-99m within Nuclear Medicine (within 1 hour of surgery), no imaging, blue dye administered by theatre staff immediately before surgery.	
26	What proportion of patients have imaging after injection of Tc-99m?	
27	What proportion of patients have Tc-99m injected the day before their surgery (rather than on the day of surgery)?	
28	Can you estimate the proportion of hospitals conducting breast cancer surgery who do not have their own nuclear medicine department (so the patient would have to have the Tc99m injected at a different hospital to the one where they are having their surgery)?	
29	We have identified two types of blue dye that can be used, Patent Blue V and methylene blue. Can we assume that these two (and any other blue dyes used) are equivalent in terms of performance and safety (allergy) outcomes?	
30	We understand that allergic reaction to the blue dye is rare.	

	Can you advise what proportion of patients are allergic to blue dye? Is there national data on this? Would this be something they are likely to know about in advance of SLNB? Would sensitivity testing be carried out prior to the dye being injected?	
31	Where Tc-99m is used, is the diagnostic time delayed or prolonged due to the use of the radioactive substance? If so, can you estimate how long this delay is and whether this impacts on patient care? Would you anticipate a reduction in diagnostic time if using a non-radioactive tracer?	
32	Some studies have reported the use of One Step Nucleic Acid Amplification (OSNA) intraoperatively to assess sentinel nodes. Is use of OSNA representative of standard care in the UK NHS?	
33	Are there any implications or considerations for using OSNA either with standard care or with Magtrace and Sentimag? Can it be used with both techniques?	
34	Does the timing or dose of Tc-99m (or other radioisotope) affect the procedure or results obtained? If so, please can you explain the considerations influencing dosage and administration window?	

Adverse events

35	Another precaution for MagTrace is that if inadvertently administered intravenously, anaphylactoid or cardiovascular reactions may occur. Are you	

	aware of any cases of this occurring?	
36	For balance, is inadvertent intravenous injection also a precaution for the comparator (blue dye and Tc-99m)? Are you aware if there is any data on this?	
37	Discolouration may occur with blue dye and with Magtrace. In your experience, is the proportion of patients that experience discolouration similar between blue dye and Magtrace? If not, can you estimate the proportion affected for each?	
38	Is the duration of discolouration similar for blue dye and Magtrace? If not, can you estimate the duration of discolouration for each?	

Appendix 5

Collated responses to EEM discussion questions

Experts

#1	Tomasz Graja
#2	Nagabhushan Seshadri
#3	Kate Williams
#4	Caroline Osborne
#5	James Scuffham
#6	Simon Wan

Patient population and current care pathway

	Question	Response
1	Are all breast cancer patients assessed by ultrasound and fine needle biopsy to rule out node involvement prior to Sentinel Lymph Node Biopsy (SLNB)?	Expert #1: Only patients with abnormal lymph nodes on the ultrasound have FNA or core biopsy. If the LNs look normal on US we proceed to SLNB
		Expert #2: No response
		Expert #3: All patients undergo an ultrasound scan of the relevant axilla. If the nodes look entirely normal, no FNA is performed. If there is any radiological concern, an FNA is performed.
		Expert #4: All patients with breast cancer have US of the axilla to assess the nodes; indeterminate or suspicious nodes undergo a core biopsy.
		Expert #5: Unable to comment
		Expert #6: To my knowledge yes (ultrasound certainly, biopsy if there is concern on clinical/imaging assessment).
2	Can you estimate what proportion of breast cancer patients are Lymph Node Negative (LN0) and routed for SLNB?	Expert #1: I guess about 70%
		Expert #2: No response
		Expert #3: This will vary from unit to unit, dependent on screening v symptomatic presentations but approximately 60% will be lymph

		node negative and thus will undergo SLNB.
		Expert #4: 75-80%
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate knowledge.
3	What proportion of patients with DCIS or invasive breast cancer have surgery (e.g. mastectomy, breast-conserving surgery) and SLNB at the same theatre session?	Expert #1: All patients have breast surgery and SLNB done at the same operation except a few unusual clinical situations.
		Expert #2: No response
		Expert #3: All patients with invasive disease who are deemed lymph node negative in pre-operative tests will have SLNB at the same theatre session. For patients with DCIS, traditionally only those patients undergoing mastectomy will have a SLNBx at the same theatre session. (This can be avoided for the majority with the use of a tracer such as magtrace).
		Expert #4: 100% who have invasive disease With DCIS only those having mastectomy or those with high risk of invasion will have SLNB – estimate 15%
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise, but my thoughts are majority.
4	Does the type of surgery conducted in Ductal Carcinoma in Situ (DCIS) and invasive breast cancer (mastectomy, breast-conserving surgery) influence the need for SLNB? Or influence the choice of tracer?	Expert #1: All patients with invasive cancer will need SLNB while for DCIS patients only those having mastectomy or when we suspect the invasive cancer co-exist with DCIS
		Expert #2: No response
		Expert #3: DCIS and mastectomy – traditionally these patients are subjected to a slnbx at the time of surgery, just in case there is any invasive/microinvasive disease hidden amongst the DCIS which means that the axilla should be staged to guide adjuvant treatment. This is because once the breast has been surgically removed, guided

		SLNBX is rendered impossible with traditional methods as there is nowhere to inject the radioactive isotope and blue dye. There is evidence however to say that delayed SLNBx is possible with a tracer such as magtrace – the injection is given at the time of mastectomy, but the axilla is not operated on at that time. If histological examination of the mastectomy specimen then shows there is invasive disease, then the surgeon can go back and remove the sentinel lymph node within 4 weeks of the initial surgery as the tracer remains within the first draining lymph node for this long.
		Expert #4: Only in DCIS – if surgery is mastectomy an SLNB is invariably performed, whereas very few patients with DCIS having breast conserving surgery will have an SLNB <5%. This does not influence choice of tracer.
		Expert #5: Unable to comment
		Expert #6: Yes, to my understanding routine SLNB is not clearly indicated in DCIS cases undergoing breast conserving surgery.
5	What proportion of patients undergoing mastectomy surgery would later require SNLB, and would there be implications or other considerations for performing SLNB procedure in this patient group (that have previously had a mastectomy)?	Expert #1: SLNB in this group is unlikely to work as all breast lymphatics were removed within the breast tissue during mastectomy.
		Expert #2: No response
		Expert #3: This only refers to patients who have undergone mastectomy for presumed DCIS – all patients who under mastectomy for invasive disease need an “up front” SLNB or full axillary dissection at the time of mastectomy. 20% of all breast cancers across the UK are DCIS – a percentage of these will need to undergo mastectomy.

		The majority of patients undergoing mastectomy for DCIS CAN avoid a SLNBx all together unless there is post-operative evidence of invasive or microinvasive disease. Unless a tracer such as magtrace is used (which marks the sentinel lymph node for up to 4 weeks post mastectomy) then a SLNBx has to be done at the time of mastectomy OR the patient would have to undergo an unguided axillary sample as a second procedure.
		Expert #4: If the patient has a mastectomy an SLNB would be done. I have now started doing delayed SLNB in some patients having mastectomy for DCIS – the Magtrace given to patient pre-mastectomy and SLNB delayed and only performed if invasive disease is found. A SLNB cannot be done after a mastectomy unless tracer if given preoperatively.
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise
6	Magtrace is contraindicated in patients with hypersensitivity to iron oxide or dextran compounds, patients with iron overload disease, or patients with a metal implant close to the expected sentinel lymph node location. Can you estimate the proportion of breast cancer patients who will have at least one of these contraindications (and would therefore be unsuitable for Magtrace) but who would be suitable for Tc-99m and blue dye.	Expert #1: Less than 1%
		Expert #2: No response
		Expert #3: Have used magtrace within our unit on over 300 patients and have not faced this issue yet
		Expert #4: <1%
		Expert #5: Unable to comment
		Expert #6: Iron overload disease is rare. While metal implants close to the sentinel nodal location (pacemaker, shoulder prosthesis) may be slightly more common.

		Overall proportion is still likely to be small, in the spectrum of patients referred for SLNB.
7	Can SLNB be performed in patients who are pregnant or breastfeeding? Are you aware of any contraindications for using radioisotopes or superparamagnetic iron oxide tracers in this group of patients?	Expert #1: Surgery is usually avoided in pregnant patients. If needed the decision about type of SLNB is made on case by case basis. I think in most cases the decision will be against using any of tracers and doing random node sample instead to avoid potential risks of radioactivity or Blue Dye. No hard evidence here.
		Expert #2: No response
		Expert #3: SLNBx is performed in pregnant or breast feeding mothers. Usually this is done using a radioactive isotope only (technetium 99) – patent blue dye is not given. Only very small doses of technetium 99 are absorbed systemically and these doses are safe for the growing fetus. Magtrace has not been tested on pregnant or breast feeding mothers so is not used. No known reactions – just untested.
		Expert #4: Yes with radio-isotope. I haven't used Magtrace in this group. I would tend to opt for a 4 node sample without any tracer.
		Expert #5: In principle, radionuclide SLNB can be performed in pregnancy because the amount of radioactivity used is very low. The foetal dose will be in the range 0.001 – 0.003mGy [1], corresponding to a risk of childhood cancer of less than 1 in 1000000 [2]. Carrying out such a procedure in pregnancy would need the direct justification of a practitioner holding a relevant ARSAC license. Breastfeeding patients are likely to have lactation stopped prior to surgery anyway and this will apply to both radionuclide and magnetic tracers. I am unable to comment on the contraindications for magnetic tracers. [1] – ARSAC notes for guidance

		[2] – HPA "Protection of pregnant patients…"
		Expert #6: No absolute contraindication of radio-isotope use in pregnant or breastfeeding individuals. Not sure about iron oxide tracers
8	Do NHS care pathways, specifically for those being considered for SLNB, differ in pregnant patients with DCIS or breast cancer and if so please can you explain how and whether there is any NICE guidance to support this?	Expert #1: Very few patients soMDT decision on case by case basis.
		Expert #2: No response
		Expert #3: Do not use patent blue dye in this group of patients due to the relatively high risk of allergy and unknown risk to unborn fetus. Guidance provided by the RCOG
		Expert #4: SLNB in breast cancer is an important staging procedure but should be done cautiously during pregnancy – I would tend to opt for no tracer and 4 node sampling. I am not aware of NICE support in this.
		Expert #5: See response [to Q7]
		Expert #6: Beyond my immediate expertise.
9	Have you aware of cases where Magtrace has been used in men or transgender patients? Are there any specific considerations we should be aware of?	Expert #1: Yes we do use Magtrace on male patients, can't see any problems to use Magtrace in transgender patients.
		Expert #2: No response
		Expert #3: Used in male breast cancer patients with success. Cannot think of any specific considerations relating to gender.
		Expert #4: I have used Magtrace in men – no specific differences to women. In transgender patients consideration is needed if they have had breast surgery (reduction, mastectomy) as this may lead to disruption of lymphatics.
		Expert #5: Unable to comment

		Expert #6: Beyond my immediate expertise.

Magtrace and Sentimag

10	Would you carry out additional screening or diagnostic tests to exclude hypersensitivity in patients before using Magtrace, or would you only know this from the patient notes?	Expert #1: No screening test carry on.
		Expert #2: No response
		Expert #3: No additional screening tests. Very inert when compared to patent blue dye.
		Expert #4: I would not – information from patient history.
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
11	A precaution of Magtrace is that it can alter MRI of the injection and drainage sites. This alteration may be long term (i.e. these patients may not be suitable for MRI of these sites for two years after they receive Magtrace). What are the consequences of this for the patient (who will presumably need to be monitored for recurrence of cancer)? Will this mean a change to standard of care for these patients?	Expert #1: Being aware of this downside of Magtrace I think there is very few patients who need breast MRI AFTER cancer surgery. MRI is mostly used at the time of primary diagnosis. However there is increasing number of MRI for surveillance but this is usually 1 year after surgery and always combined with mammography. Still very small group
		Expert #2: No response
		Expert #3: I work within a symptomatic unit rather than a screening unit so the number of patients this affects is much smaller. My experience in the post op setting – it does alter the appearances of the skin around the NAC on the MRI but did not render MRI interpretation impossible – Would usually combine MRI and mammographic/tomographic follow up for my patients – not MRI alone - this would not alter after magtrace but it would make interpretation of MRI follow up more technically challenging.
		Expert #4: A few patients are offered MRI follow up following cancer

		treatment – eg women under 30 or sometimes previous mammographically occult cancers. This needs to be considered before using Magtrace
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
12	The Company proposes that contrast enhanced digital mammography and gadollium MRI are suitable alternatives to conventional MRI for patients post-Magtrace, does this seem reasonable?	Expert #1: It does.
		Expert #2: No response
		Expert #3: Yes.
		Expert #4: These would be reasonable alternatives to offer in this small patient group
		Expert #5: Unable to comment
		Expert #6: Alternative modalities such as ultrasound, mammography – yes; I have no personal experience but would be anxious about reliability of MRI techniques post Magtrace even with gadolinium.
13	Metal surgical instruments can cause interference when using the Sentimag probe. If you have experience of using Sentimag, can you comment on whether you therefore switched to alternatives (e.g. single-use or reusable plastic or titanium tools)? What did you use, and were there any implications in terms of cost or acceptability within your Trust?	Expert #1: We have plastic instruments but with some experience we don't use them very often. So no negative costs implications.
		Expert #2: No response
		Expert #3: We use reusable plastic instead of metal retractors, forceps and babcocks. Cost is not prohibitive due to the efficiency savings in theatre/radiology.
		Expert #4: Initially I used non metal instruments, but now with experience I find I seldom need to use them. I simply remove the metal instruments when using the probe to localise
		Expert #5: Unable to comment

		Expert #6: Beyond my immediate expertise
14	MagTrace can be injected up to 30 days prior to surgery. How useful is this extra time in practice? Would the majority of patients continue to have the tracer injected within 24 hours of their surgery regardless? Can the length of time Magtrace is injected prior to surgery improve the detection rate? Are there circumstances when you would give 2 injections of Magtrace prior to surgery (e.g. at 2 weeks prior to surgery and then within 24 hours of surgery?)	Expert #1: Magtrace seems to work better if injected > 24 hours prior surgery. In personal experience it works well when injected between 1-30 days pre-op. I would re-inject Magtrace only if more than 30 days passed from injection to surgery.
		Expert #2: No response
		Expert #3: When we first started using magtrace we always gave the injection on the table with 5 minutes breast massage prior to starting the case. Now we are moving to giving the injection either at the same time as the magseed is put into the breast lesion in radiology or in a consenting clinic. The signal within the axilla is better when the injection is given in advance. I have never given 2 injections (and have had no need to do this). The flexibility is key here – the injection can be given at a time that is convenient to the patient and the surgeon. If given whilst the patient is conscious, it is given with local anaesthetic as it can be painful without.
		Expert #4: I find this very useful as I do the injection at the results appointment once a surgical date has been allocated. I find giving the injection at least 3 days and upto 30days helps greatly with the colour detection of the node and gives high signal in the SLNBs. I have never given 2 injections
		Expert #5: Unable to comment
		Expert #6: No practical experience but I should think this would ease the logistical challenge of coordinating tracer injection time and theatre time, as is needed for radio-isotope tracers.

15	In hospitals that have access to both Magtrace and Sentimag and radioisotopes, what would be the factors that determine which tracer a patient received? Is patient preference a factor in the clinical decision-making, including not using blue dye? What is communicated about the different tracer options?	Expert #1: I work in hospital where we provide Magtrace and on some situation BlueDye only. If I have a choice Magtrace or radioisotope I would choose Magtrace as easier to manage. We don't give patient choice of tracer.
		Expert #2: No response
		Expert #3: Both options are available in our Trust. Our standard method of choice is magtrace unless there is a technical reason why this may not be possible (eg in case of allergy (v rare)) or a surgeon is concerned about combining magtrace and a magseed that is located directly behind the NAC. The choice is a surgeon-led choice rather than patient led within our unit
		Expert #4: I only use Magtrace. If this was contra-indicated I would use blue dye only.
		Expert #5: Unable to comment
		Expert #6: At our hospital, to my knowledge, radio-isotopes are used. I should think surgeons' preference is a main factor in sites where there is/can be access to both modalities.
16	Is there a 'learning curve' with the technology? How many cases do you feel are required to gain sufficient competency and are there any strategies implemented to account for this (e.g. peer procedures; use of standard treatment alongside).	Expert #1: Definitely there is a learning curve. I think for Surgeons experience with Blue dye and radioisotopes they will need 10-30 cases to familiarize with Magtrace
		Expert #2: No response
		Expert #3: Definite learning curve. Easier if surgeon is used to using the probe for magseed detection prior to using magtrace but not necessary. Would do at least the first 10 cases in combination with patent blue dye when starting out. If possible "buddy up" with a surgeon who has more experience for tips / tricks – peer procedures. In our unit we stipulated

		that surgeons used it in combination with blue dye until confident /comfortable – some surgeons took 50 cases of dual approach whereas others only took 10 to make the switch to magtrace alone.
		Expert #4: There is a learning curve and I performed the first 10 with blue dye and Magtrace. The accuracy of detection is vastly improved by giving the injection at least 3 days in advance of the surgery.
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
17	In your experience, does tumour type, grade, size and location impact on the: a. Node detection rate b. Number of nodes retrieved c. SLNB procedure time d. SLNB Patient reported outcomes e. SLNB Complication rate	Expert #1: Not at all.
		Expert #2: No response
		Expert #3: Larger tumours that disrupt the breast parenchyma and therefore the lymphatics can make node detection rate more difficult Our data within our unit says patent blue dye did not improve on this – if magtrace failed to detect node then so did patent blue dye – the dye did not add anything. Often magtrace was more successful than patent blue dye at node detection (ie brown “hot” nodes were found rather than blue nodes where a combined approach was made). Body habitus is the most impactful thing on the difficulty of the procedure and therefore procedure time – if high BMI dissection more difficult, trace more difficult to locate (same for isotope / patent blue dye).
		Expert #4: Previously undetected LN mets of high volume or inflammatory type breast cancer can disrupt the lymphatics and therefore hamper uptake of the tracer.
		Expert #5: Unable to comment

		Expert #6: Beyond my immediate expertise. Literature would suggest higher number of retrieved nodes per case, using magnetic tracers compared to radio-isotope; I am not aware of convincing head to head data to suggest superior efficacy, or inferior post operative morbidity as a result
18	In your experience, how often does Sentimag require calibrating during the procedure? Does this impact on the procedure length?	Expert #1: Several times approx 10-15. It takes about 5 seconds to get the probe calibrated.
		Expert #2: No response
		Expert #3: Repeated calibration is needed / required after each node is located and removed / if the patient's body habitus is making detection difficult. I don't feel It impacts on procedure length – if SLNB difficult with magtrace then would have been just as difficult with isotope and patent blue dye.
		Expert #4: 5-7 times and does not cause me any problems
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
19	Do consider there to be inefficiencies and/or unpredictability in the supply of radioisotopes that could impact management of operating lists? Could the use of Magtrace improve the planning and management of operating lists?	Expert #1: In place where I work which is a district general hospital without Nuclear Medicine Department Magtrace turned out to be superior to the radioisotope in discussed aspects.
		Expert #2: No response
		Expert #3: Yes. Isotope supply has been unpredictable, especially since Brexit / Covid. Some days no isotope available and patients had to undergo blue dye guided sample instead of dual technique. When isotope is available, it doesn't arrive into our hospital until 9.30-10am so this impacts on the start of the list. We used a 2 day protocol for our morning patients when using isotope (so that patients attended the hospital the afternoon before their operation for their isotope injection

		but this was not possible for a Monday list – Monday theatre's had to be scheduled to allow for this / there were delays in theatre efficiency
		Expert #4: Radioisotopes are not easily available to my hospital and therefore I need to use an alternative tracer
		Expert #5: Radionuclide supply is generally very reliable, although in recent weeks there has been a global shortage due to a failed nuclear reactor in the Netherlands. However, SLNB is carried out with very low levels of radioactivity and are regarded as high clinical priority, and so even in times of global shortage, SLNB procedures are unlikely to be affected. Not all hospitals have nuclear medicine departments and therefore access to radionuclides is not universal and it is these hospitals who would benefit most from Magtrace.
		Expert #6: If all other factors and parameters are the same, simply from logistic and theatre list management point of view, I should think Magtrace would allow more flexibility.
20	Have you encountered any issues with calibration either before or after the procedure?	Expert #1: No
		Expert #2: No response
		Expert #3: No
		Expert #4: Sometimes there is some baseline drift of the reading and the green foot pedal can be tricky to use
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.

Technetium-99m and blue dye

21	The comparator included in the scope is radioisotope (Tc-99m) **and** blue dye. Does this represent standard of care in the majority of cases?	Expert #1: I think majority of breast units use Tc99 and Blue Dye together.
		Expert #2: Yes

		Expert #3: Yes across the UK.
		Expert #4: Yes this is the standard of care
		Expert #5: Yes, the dual-tracer technique is regarded as the gold standard. However, in hospitals where radionuclides are not available, blue dye may be the only option.
		Expert #6: There is variation in practice; radio-isotope is the conventional and established modality
22	Can you estimate the proportion of patients where blue dye is not used (*i.e.* Tc-99m alone is used)?	Expert #1: Very few, only patients with known allergy to Blue Dye or perhaps some patients with extensive history of various allergic reactions.
		Expert #2: About 5-10%
		Expert #3: Dual technique is the standard. Some surgeons in some units wanted to avoid the allergy risk of patent blue dye. Would look for a good axillary signal through the skin prior to starting the surgery – if the signal strength good then patent blue dye injection was avoided. Would occur in some units at least 50% of the time
		Expert #4: When I was using this technique I would estimate around 2% of patients.
		Expert #5: Unable to comment
		Expert #6: Beyond my expertise.
23	Is blue dye ever used on its own without Tc-99m?	Expert #1: Yes it can.
		Expert #2: Rarely, only when radiopharmaceutical supply is affected.
		Expert #3: Yes – throughout covid due to breast lists being moved to different hospital sites without access to Tc-99 and it's associated licencing – patent blue dye used alone – not as accurate – 4 node guided axillary sample aimed for rather than true SLNBx
		Expert #4: No I didn't
		Expert #5: See Q21
		Expert #6: Beyond my expertise.
24	Some studies report that a radioisotope is used but do not specify the type. Can we assume	Expert #1: I agree.

	the isotope used in the UK NHS will always be Technetium-99m (Tc-99m)?	
		Expert #2: Yes
		Expert #3: Yes
		Expert #4: Yes
		Expert #5: Yes, the use of Tc-99m colloid is a universal standard in the NHS as this is the only approved procedure by ARSAC.
		Expert #6: Yes.
25	Can you comment on whether this represents standard of care at your hospital: Injection of Tc-99m within Nuclear Medicine (within 1 hour of surgery), no imaging, blue dye administered by theatre staff immediately before surgery.	Expert #1: In our hospital we use Magtrace stand alone.
		Expert #2: At our hospital, Injection of Tc-99m within Nuclear Medicine usually happens at least 1 hour before surgery, but in a small proportion of patients it could be the day before surgery. Blue dye is administered by theatre staff immediately before surgery.
		Expert #3: Before the standard use of magtrace – yes, other than for those patients at the start of the list (so first and second patients on an all day list) – these patients would be on a 2 day Tc-99m protocol – injected a slightly larger dose of Tc-99 the day before surgery so that theatres could use their time efficiently on the day of surgery.
		Expert #4: I used this until 4 years ago.
		Expert #5: Our standard protocol is: - Injection of Tc99m in nuclear medicine on either the day before surgery, or the morning of surgery (depending on logistics – early lists tend to be injected the day before, late lists can be injected on the day). - Planar scinitgraphic imaging is acquired for all patients and the positions of the nodes identified marked with indelible ink on the patient's skin. Images are made available to the surgeon via the PACS system prior to surgery.

		- Blue dye administered by theatre staff immediately before surgery
		Expert #6: Yes.
26	What proportion of patients have imaging after injection of Tc-99m?	Expert #1: N/A In the past we dropped imaging after Tc99 as it was not really helpful and also time consuming.
		Expert #2: None
		Expert #3: None
		Expert #4: I did not used scintograms
		Expert #5: At our centre, all patients have imaging but practice is variable across the UK and many centres do not image for breast SLN localisation. Imaging would generally be regarded as mandatory for other tumour sites, such as melanoma, for which the lymphatic drainage patterns are less predictable.
		Expert #6: Very few, if any, nowdays
27	What proportion of patients have Tc-99m injected the day before their surgery (rather than on the day of surgery)?	Expert #1: I have similar experience with both. If injected on the day half of the dose is enough.
		Expert #2: About 15-20%
		Expert #3: 1/3 day before, 2/3 on day of surger.y
		Expert #4: 100% in my previous practice given on the same morning
		Expert #5: For our centre, it is probably 50/50 as it is determined by scheduling logistics.
		Expert #6: Approx. ¼ of cases reviewing last 6 months caseload (unvalidated data).
28	Can you estimate the proportion of hospitals conducting breast cancer surgery who do not have their own nuclear medicine department (so the patient would have to have the Tc99m injected at a different hospital to the one where they are having their surgery)?	Expert #1: I don't know, perhaps 30%
		Expert #2: Probably none, mainly due to radiation protection issues and licensure requirements.
		Expert #3: No idea I'm sorry.
		Expert #4: 50%
		Expert #5: I cannot provide this information, but this data could be obtained by cross-referencing a list of

		centres performing breast surgery with the records of the Administration of Radioactive Substances Advisory Committee, who issue licenses to sites to use radiopharmaceuticals.
		Expert #6: Beyond my immediate knowledge. I should think very few hospitals would adopt such pathways; I should think centres conducting breast cancer surgery without on site nuclear medicine department would have adopted blue dye or magnetic tracers only technique.
29	We have identified two types of blue dye that can be used, Patent Blue V and methylene blue. Can we assume that these two (and any other blue dyes used) are equivalent in terms of performance and safety (allergy) outcomes?	Expert #1: Definitely not! Methylene Blue is not recommended for SLNB as it may cause local soft tissue reaction. Only Patent Blue V is used for SLNB.
		Expert #2: Yes
		Expert #3: Always used patent blue dye in my practice throughout consultant career and training
		Expert #4: yes
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate knowledge.
30	We understand that allergic reaction to the blue dye is rare. Can you advise what proportion of patients are allergic to blue dye? Is there national data on this? Would this be something they are likely to know about in advance of SLNB? Would sensitivity testing be carried out prior to the dye being injected?	Expert #1: In the past we were giving patient information about 0.2% chance of severe allergic reaction. The number of severe and minor reactions will be higher.
		Expert #2: About 1-2% of patients are allergic to blue dye as per literature and trial data. NEW START (UK wide sentinel lymph node training program) data reports allergic reactions to PBV in about 0.9%. Yes, nation-wide data would be useful in advising prior to SLNB on the use of blue dye. Sensitivity testing prior to blue dye injection may not be very useful.

		Expert #3: Patent blue dye is the commonest cause for anaphylaxis in theatres across the UK. On the basis of a large clinical study (the ALMANAC trial) and follow-up program (the NEW START program) serious allergic reactions were estimated at an incidence rate of 0.1% with patent blue dye (1:1000). Patients are unlikely to know if they're allergic to patent blue dye prior to SLNBx. Surgeons show caution if a patient has a history of significant allergy to other drugs / substances but sensitivity testing isn't carried out routinely as these test take a relatively long time to organise whereas the patients are on a quick cancer treatment pathway.
		Expert #4: Severe reactions in 0.1%, but up to 1% can have a mild reaction. Patients should be counselled of this risk No sensitivity testing prior but if a reaction occurs these patients should have sensitivity testing to check cause by blue dye or other agent.
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
31	Where Tc-99m is used, is the diagnostic time delayed or prolonged due to the use of the radioactive substance? If so, can you estimate how long this delay is and whether this impacts on patient care? Would you anticipate a reduction in diagnostic time if using a non-radioactive tracer?	Expert #1: I think Tc99 works well within 1 hour from injection and the operation should be done in 24hours.
		Expert #2: Given that Tc-99m is injected atleast 1 hr prior to SLNB, and at times much earlier depending on radiopharmaceutical availability. This wait time could be potentially avoided, but not sure whether the diagnostic time (time taken for SLN detection) would be reduced
		Expert #3: No

		Expert #4: I could not perform SLNB surgery until after 1030am in the morning to allow for Tc99m transport and injection.
		Expert #5: I presume "diagnostic time" refers to pathology review of SLNB samples. There are no special radiation precautions required for pathologists examining these samples [1], and so there should not be any impact on the patient pathway. [1] – Morton et al, BJR 2003
		Expert #6: For sites already with access to radio-isotope tracer, to my awareness, tracer supply is not a rate limiting step for SLN/treatment. In terms of time per procedure, the procedure of tracer injection itself is quick.
32	Some studies have reported the use of One Step Nucleic Acid Amplification (OSNA) intraoperatively to assess sentinel nodes. Is use of OSNA representative of standard care in the UK NHS?	Expert #1: I have no experience with OSNA. I think it is less in use as guidelines on axilla management became more complex and OSNA may not give all information required
		Expert #2: No. Histopathology of the LN is the standard of care.
		Expert #3: OSNA is still available in some units but is not standard in the majority of units across the UK
		Expert #4: Not standard of care but carried in some centres
		Expert #5: OSNA is used in our centre.
		Expert #6: Not to my knowledge, but this is not my specific area of expertise.
33	Are there any implications or considerations for using OSNA either with standard care or with Magtrace and Sentimag? Can it be used with both techniques?	Expert #1: As above [Q32]
		Expert #2: No. OSNA can perhaps be used with both techniques
		Expert #3: No. Can use magtrace to detect and trace the sentinel lymph nodes and then use intraoperative OSNA to analyse the nodal status of the patient.

		Expert #4: I think so
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
34	Does the timing or dose of Tc-99m (or other radioisotope) affect the procedure or results obtained? If so, please can you explain the considerations influencing dosage and administration window?	Expert #1: Tc99 half life is about 6 hours so after 24 hours only about 6% remaining. It can be balance with a larger dose but the point is that there is window to do procedure 1-24 hours from injection.
		Expert #2: Yes, both timing and dosage affect the procedure results to some extent. Injected activity of 20MBq is generally used for surgery planned for the same day. When injection is done the afternoon prior to surgery, double the activity of 40 MBq is used. The time between injection and visualisation is variable from 1–3 hrs with slightly better detection rates with longer waits
		Expert #3: Half life of Tc-99 is only short so dose of Tc-99 needs to be times accurately with the time of surgery. Too long a time period between injection and surgery means a poor / no signal within the axilla
		Expert #4: The dose of isotope is adjusted to the timing of surgery – ie if given the day before a double dose is administered. This is due to the half life of the isotope. If surgery is delayed there is a risk of not being able to detect the signal as the isotope decays.
		Expert #5: Surgery is commonly performed between 1 and 24 hours after Tc-99m administration. Studies suggest there is no significant difference in the detection rates with either “same day” or “next day” surgery [1]. However, if surgery cannot be performed the day after injection, there will be insufficient activity for SLN localisation which would necessitate re-administration of Tc99m. [1] – van Esser et al, EJNMMI 2009
		Expert #6: Yes. Tc-99m activity (and therefore detectable signal on hand-

		held probe by the surgeon) decays predictably with a half life of approximately 6 hours. The injected activity needs to be 'calibrated' to allow for this time delay. (relatively higher activity [still low dose in absolute terms] needs to be injected if there is anticipated long time gap until surgery, e.g. next day). There is theoretical risk such that: Too low an activity at the time of surgery may result in signal (& therefore node[s]) not being found; and too high an activity may risk flooding the field and the specific node(s) are made difficult to find.

Adverse events

35	Another precaution for MagTrace is that if inadvertently administered intravenously, anaphylactoid or cardiovascular reactions may occur. Are you aware of any cases of this occurring?	Expert #1: No response
		Expert #2: No response
		Expert #3: No
		Expert #4: No
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
36	For balance, is inadvertent intravenous injection also a precaution for the comparator (blue dye and Tc-99m)? Are you aware if there is any data on this?	Expert #1: No response
		Expert #2: No response
		Expert #3: Not aware of the data
		Expert #4: Potentially - I do not know of data
		Expert #5: Intravenous injection of Tc99m nanocolloid is a hypothetical possibility and would probably only be detected if scintigraphic imaging was performed. Tc99m nanocolloid is routinely injected intravenously for other nuclear medicine studies, such as liver investigations and so there will be no very low risk of adverse

		reactions. With appropriate training in injection technique the risk of inadvertent intravenous administration is very small indeed.
		Expert #6: Inadvertent intravenous injection of radio-isotope may be detected immediately if imaging is performed at the same time. This may cause theoretical issue with less radio-isotope reaching the intended target (SLN) and therefore potential success of the procedure. A re-injection may be performed assuming dose can be made available. Inadvertent intravenous injection of radio-isotope tracer for this is in itself is not clinically significantly harmful to my knowledge.
37	Discolouration may occur with blue dye and with Magtrace. In your experience, is the proportion of patients that experience discolouration similar between blue dye and Magtrace? If not, can you estimate the proportion affected for each?	Expert #1: No response
		Expert #2: No response
		Expert #3: I think the number of patients affected by discolouration is around the same but the longer term staining is only seen in patients who have had patent blue dye – most patients who have experienced some skin staining with magtrace, their staining has improved within 12 months.
		Expert #4: Staining can last longer with Magtrace – but with Magtrace the discoloration depends on the injection technique, Subdermal injection leads to more staining that lasts longer. Subareola injection deeper into the breast tissue leads to less staining.
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.
38	Is the duration of discolouration similar for blue dye and Magtrace? If not, can you estimate the duration of discolouration for each?	Expert #1: No response

		Expert #2: No response
		Expert #3: Discolouration for magtrace – maximum 12 -18 months. Discolouration with patent blue can be for years afterwards (if not permanent in some cases).
		Expert #4: Similar if subdermal yes – but with the deeper technique staining with Magtrace id insignificant
		Expert #5: Unable to comment
		Expert #6: Beyond my immediate expertise.

Appendix 6

Company questions (18/02/2022)

1. The cost of Magtrace (vial) is included in the economic model; however no cost for the SentiMag probe has been included, can you explain why? Is there a commitment in the number of vials a hospital must order per year?

The overwhelming majority of Trusts who use a Sentimag elect to have the system placed free of charge as part of a consumable commitment. A Trust will usually require a usage volume of approximately 100 to a 120 consumable units per annum. Do note, this can be any combination of Magtrace and/or Magseed (our device for lesion localisation which works with the same Sentimag probe – see NICE MIB here). This places almost all NHS trusts who have a breast centre in a position to access a free of charge Sentimag system. Hence it has not been added to the cost per procedure.

Additionally, there are a large number of NHS Trusts who have a Sentimag in place for Magseed use, who will start using Magtrace.

Lastly, the cost of a premium gamma probe system like Neoprobe is similar to the cost of a Sentimag and we have not factored in capital costs per case for Technetium based SLNB.

2. What is the cost of the SentiMag probe?

£24,900 list price including accessories

3. What is the expected device lifetime of the SentiMag probe?

The Sentimag has a minimum life expectancy of 5 years.

1.

4. Are tools also provided with the SentiMag probe? If so what is included?

On setting up the account, the distributor provides free of charge polymer tools alongside the Sentimag system. These include retractors and grasping instruments including Debakey forceps, Allis and Babcock instruments.

5. No time has been included for the injection of blue dye in the economic model, can you explain why?

Blue dye is usually injected in the theatre once the patient is intubated, due to the risk of anaphylaxis. If you added this cost it would need to be calculated based on this scenario. Please note, if Magtrace is injected on the table in theatre, this is a similar procedure to injecting Blue dye and the cost implications with regards to time would be similar.

6. Do you have any long term evidence regarding the toxicity of Magtrace when injected into the body?

The amount of Magtraxce residue will depend on a number of factors, these include: the physiology of the patient (younger, lower BMI patients have more rapid transport to the lymph nodes than older, larger patients), the quality of post-injection massage, the time

elapsed before SLNB is commenced, the number of nodes removed, and the level of surgical trauma the patient is subjected to as part of the tumour removal.

Magtrace® consists of iron oxide nanoparticles coated in carboxydextran. Magtrace® is formulated under GMP (good manufacturing practice) conditions to provide a tight and reproducible particle size distribution and the iron oxide nanoparticle is almost completely of the ferric (Fe3+) form. This stable form of iron oxide is non-toxic and is in the same form as most iron in the body.

As it is regulated as a medical device, Magtrace® was not required to undergo pharmacological studies. However, it had to undergo rigorous safety and biocompatibility testing against the requirements for EN ISO 10993-1. Magtrace® does not lead to any of the following: cytoxicity, sensitisation, irritation or intracutaneous reactivity, systemic toxicity, subacute or subchronic toxicity or genotoxicity.

Magtrace® does not undergo any cellular interaction and is transported to the lymph nodes by a purely mechanical action. Magtrace® is injected interstitially and, because of its particle size, has no direct pathway to the blood and liver and will instead accumulate in the lymph nodes and then be broken down over time to free iron. This iron will then ultimately be collected in the iron stores. Any residual Magtrace® at the injection site will be broken down in the mononuclear phagocyte system by macrophages. This process will first break down the organic dextran coating, leaving the iron oxide particle to be further broken down and eventually distributed across iron stores in the body as below:

Haemoglobin stores in RBC	60%
Ferritin stores in the liver, spleen, and bone marrow	30%
Ferritin stores in muscle and other tissue	9%
In transit and bound to transferrin	<1%

Once broken down, the Magtrace® residue will be indistinguishable from other iron in the body. In the most conservative case (SLNB and no lumpectomy), where almost the entire injected volume is retained in the body, the amount of iron equates to approximately 5 days recommended dietary iron intake.

Magtrace has been used for more than 10 years in over 90,000 patients and there has been no evidence of toxicity observed.

7. Is there a cost associated with regular delivery of Magtrace vials to hospitals?

The delivery charge from our distributor is £10.40. This is a per delivery fee, so would be the same for a box of 10 Magtrace vials or several boxes. Of note, some account managers may negotiate to remove this for Trusts as part of the ongoing account support.

Appendix 7

Expert questions (18/02/2022)

Experts

#1	Elizabeth Jefferson
#2	Nagabhushan Seshadri
#3	James Scuffham
#4	Ming Young Simon Wan
#5	Kate Williams

1. **The company has assumed that each hospital conducts 5 SLNB procedures weekly (250 procedures annually when considering a 50 working week year). How many SLNB procedures for breast cancer does your trust conduct each year?**

#1	600
#2	Approximately 300 procedures/year
#3	Please see table below for the [redacted], which gives figures for the last four years. Excluding 2020, which is likely to have been impacted by coronavirus, on average we conduct about 500 radionuclide SLNBs per year, equating to about 10 per week. I have access to similar data for three other hospitals in the region which I could possibly share if helpful (with their consent).
#4	A brief search on the electronic health record system yielded 103 radio-isotope tracer injection procedures over last 6 months at our Trust. If this is representative, this would be just over 200 procedures per year. Note this is unvalidated data.
#5	Approximately 250-300 per annum (we are a symptomatic unit – it would be more if had screening assessment).

Calendar Year	*2018*	*2019*	*2020*	*2021*
Number of procedures	*507*	*521*	*398*	*467*

-

2. **When using dual technique (blue dye and radioisotopes), how many SLNB procedures can be performed per day? Does the use of Magtrace increase the capacity to operate on more patients per day? Also, does use of Magtrace increase the number of days that SLNB procedures can be carried out (as not dependent on availability of nuclear medicine)?**

#1	Don't know. We might inject 3 or 4 patients with radioisotope before a theatre session but that is probably related to the mix of patients rather than the limit of how many SLNB procedures can be done. Do not know about Magtrace.
#2	The number of SLNB procedures per day is dependent on surgeon and theatre availability and other concomitant breast surgery procedure undertaken along with SLNB.

	The literature reported duration of the whole SLNB procedure using dual technique and Magtrace for locating sentinel lymph nodes was similar in both groups, although the average time spent in preoperative care with Magtrace is lower. The long-time window between injection and SLNB with Magtrace perhaps affords more flexibility in scheduling the SLNB procedure, unlike with the dual technique
#3	Need a surgeon to comment on the number of procedures performed per day. Radionuclides are typically available only Mon-Fri, so weekend lists are generally not possible.
#4	I should think that the rate limiting factors are the amount/doses of radio-isotope tracer a Trust can source per day/week, and the surgical team/theatre capacity. Whether use of Magtrace can increase the capacity on a per day or per week basis depends on the relative balance between the above. To my knowledge, at our Trust, Nuclear Medicine/radio-isotope supply has not been a persistent rate limiting step.
#5	In our unit, we used to use a two-day protocol for radioisotope injection to avoid any delays on the morning of surgery, so magtrace has not increased our numbers of SLNBx per list apart from on Mondays – two-day protocol was not available on Mondays due to nuclear medicine not offering appointments at the weekend. This meant that theatre scheduling had to reflect this. With magtrace this gives us more flexibility on a Monday to do more SLNBs.

3. **Within the economic model, the company have assumed a mean operating time of 45 minutes for SLNB procedure:**
    - **Is this mean operating time representative of SLNB of breast cancer patients?**

#1	Don't know. Will need to ask a surgeon.
#2	Yes, this would be a representative estimate for SLNB
#3	Unable to comment
#4	Beyond my expertise.
#5	45 minutes for a SLNBx alone is an over-estimation of time, but SLNBx is not often performed alone, it is usually carried out with a breast procedure. Average total operating time for a wide local excision and SLNBx or simple mastectomy and SLNBx would be approximately 45-90 minutes. The SLNBx aspect of the procedure would usually take approximately 15-30 minutes.

    - **Does the mean operating time for SLNB change depending on other concomitant breast surgery procedures (e.g. mastectomy, breast conserving surgery)**

#1	Don't know. Will need to ask a surgeon.

#2	Yes, the mean operating time would differ depending on other concomitant breast surgery procedure undertaken along with SLNB.
#3	Unable to comment
#4	Beyond my expertise.
#5	

4. For patients who have Magtrace injected at a prior clinic appointment:

- **Would a separate appointment be needed for Magtrace injection, or would this be added to an existing routine appointment?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	Added to an existing routine appt (either injected in radiology or at a consent appt)

- **If Magtrace was injected during a separate appointment, would this occur in a routine outpatient consultant led clinic?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	Doesn't have to be consultant led – just has to be a trained member of staff who is able to give local anaesthetic and the magtrace.

- **If Magtrace was added to an existing routine appointment, how much extra time (in minutes) does injecting Magtrace add to this appointment?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	5 minutes

- **Is it safe to assume that if Magtrace was injected on the theatre table that an additional 20 minutes could be added to the total operating time (regardless of breast surgery procedure) because in line with the instructions for use, Magtrace needs time to drain to axilla which will delay surgery?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.

#5	No. Give at the WHO when the patient is checked into the theatre by a member of the surgical team whilst the operating surgeon scrubs. The operating surgeon then preps and drapes. The breast procedure is then performed which gives plenty of time for the tracer to reach the axilla. It does not increase the time of the procedure at all.

- **Who injects the Magtrace (consultant or nurse)?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	A member of the surgical team (either consultant or middle grade doctor).

- **How many staff are present during a breast surgery with SLNB with Magtrace (Band and number)?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	1 x operating surgeon (consultant) 1 x assistant (usually a junior doctor) 1 x anaesthetist (consultant) 1 x OPP (band 5) 1 x scrub (band 5/6/7) 2 x runners (band 4) (Minimum numbers – can be more)

- **How long is spent dealing with the Magtrace waste (in minutes)?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	Just goes in a sharps bin – no special arrangements

5. For radioisotope injection:

- **The company states that each week a hospital will require 2 vials of Tc-99m (@ £100 each) to conduct 5 SLNB procedures. Does this quantity (2 vials for 5 procedures) sound reasonable?**

#1	No. Each vial cost <£60. We can then do as many patients of the same type as needed that session. So we could do 5 patients out of a single vial if needed in the same session.
#2	Yes, this is a reasonable estimate
#3	The unit of "vials" is probably not relevant here as the number of patients that can be injected from one vial will vary depending on what is ordered and the decay of the product. It might make more sense to calculate a cost per patient injection. We currently pay £60 per patient dose of Tc-99m

	nanocolloid (from one of the larger independent radiopharmaceutical providers). This would equate to £300 for 5 SLNB procedures.
#4	Agree this sounds reasonable to my awareness and knowledge.
#5	Yes.

- **The company has incorporated a £25 delivery charge for Tc-99m. Is this applicable to all hospitals (those with and without an embedded Nuclear Medicine department)? Is this cost reasonable?**

#1	If the radioactive material needs to be carried on a public road to another hospital then The Carriage of Dangerous Goods legislation may apply. A cost of £25 is reasonable for the packaging and paperwork needed. Trusts may use their own internal courier service. In [redacted] we don't send the radioactive material, we ask that the patient comes to us the day before their surgery.
#2	The delivery charge would be applicable perhaps to those hospitals without an embedded Radiopharmacy
#3	We pay significantly more than this (£160), but our radiopharmaceutical supplier is a long way away geographically so this probably represents the top end of the spectrum in terms of costs. The figure of £25 is probably representative for hospitals without on-site radiopharmacies (but this cost would be shared with delivery of other radiopharmaceuticals for other tests and procedures). This delivery charge would not apply to centres with on-site radiopharmacies.
#4	Some hospitals (usually large units) have in-house radiopharmacy and 'Generators', as part of or in addition to Nuclear Medicine department. Delivery charge may not be applicable. Many Nuclear Medicine departments receive vials or doses from external sites, for which delivery charge may be applicable. To my awareness and knowledge, the given price sounds reasonable.
#5	Yes to both

- **What percentage split of patients have the radioisotope injected:**
  - **the day before SLNB?**

#1	Of the 600 [redacted] patients 20% are injected the day before if a) they are melanoma or other patients that require an extended imaging slot and reporting prior to surgery AND they are booked for theatre first thing in the morning.
#2	About 20%
#3	In our practice the split between day before and same day but several hours before is about 50/50 depending on scheduling logistics. Injection in theatre is likely only to occur in centres where there is no nuclear medicine department, and for these centres there would be no split - all patients would be injected in theatre.
#4	At our hospital, it would appear that ¼ of last 6months cohort had the radio-isotope injected day before SLNB, and ¾ was injected on the same day several hours before.
#5	Day before – first two cases on the list (2/5)

- **On the same day as SLNB but several hours before?**

#1	Breast cancer patients do not require imaging so are all injected the morning of surgery as they are on the day surgery ward awaiting all their other operation checks. Some melanoma patients are injected and imaged in the morning if their surgery is booked for the afternoon. 80%
#2	About 60%
#3	In our practice the split between day before and same day but several hours before is about 50/50 depending on scheduling logistics. Injection in theatre is likely only to occur in centres where there is no nuclear medicine department, and for these centres there would be no split - all patients would be injected in theatre.
#4	At our hospital, it would appear that ¼ of last 6months cohort had the radio-isotope injected day before SLNB, and ¾ was injected on the same day several hours before.
#5	Same day a few hours before (3/5)

- **On the same day as SLNB but during SLNB theatre visit?**

#1	No one is injected in surgery itself. 0%
#2	About 20%
#3	In our practice the split between day before and same day but several hours before is about 50/50 depending on scheduling logistics. Injection in theatre is likely only to occur in centres where there is no nuclear medicine department, and for these centres there would be no split - all patients would be injected in theatre.
#4	No response (given previous responses add to 100%, EAC assumes 0% injected during theatre visit)
#5	Same day during theatre visit – none. Isotope needs to be given at least 2 hours prior to surgery.

- **Where within the hospital is the TC-99m injected?**

#1	In the nuclear medicine department gamma camera room if imaging is needed. On the day surgery ward if imaging not needed
#2	In the Nuclear Medicine department
#3	If the hospital has a nuclear medicine department, the injection will be done there. If the hospital does not have a nuclear medicine department, injection will be done in theatre.
#4	Nuclear Medicine Department
#5	Within the nuclear medicine department

- **Who injects the Tc-99m (which band of staff)?**

#1	Band 6 Nuclear medicine technologists, radiographers or nurse specialists inject the radiopharmaceutal. Need training in Ionising Radiations (Medical Exposure) Regulations 2017 to administer a radiation dose to a patient.
#2	Staff Nurse (Band 6 or 7)
#3	Band 6 or 7 nuclear medicine practitioner or radiographer
#4	Nuclear Medicine Technologists/Radiographers (band 6-7)

#5	I'm sorry I have no idea

- **How long is preparation time (in minutes)?**

#1	Time taken for a radiopharmacy staff member to do quality control checks, get changed, clean items prior to manufacture, elute the generator, manufacture the kit, allow to incubate, withdraw patient dose, measure it and for a second member of staff to formally release the product, whilst completing all the records required for good manufacturing practice: 50 minutes However it is very rare that this radiopharmaceutical would be made alone and most of the time taken is the preparation and cleaning which would be similar if we were manufacturing one vial or ten. Actual time to manufacture this vial and withdraw patient doses and release: 25 minutes (10 minutes of which is the incubation time of the product).
#2	The preparation time for this injection is about 5-10 minutes (checking patient demographics, request, site, type and activity of radiopharmaceutical
#3	5 mins to prepare injection
#4	Approximately 15 minutes (dose 'calibration', checking of patient ID/pregnancy status/laterality, explanation and verbal consent).
#5	Cannot answer – dealt with in nuclear medicine

- **How long does the injection take (in minutes)?**

#1	Injection takes 10 seconds for each injection site (breast requires one, melanoma requires 4. Obviously need longer to explain to the patient what we are doing, clean the area, make sure this is the correct patient, correct injection site etc. For a breast cancer patient, the total procedure may take 5 minutes.
#2	< 2 minutes
#3	10mins (including explanation of procedure to patient – actual injection is about 30seconds)
#4	Approximately 3-5 minutes
#5	Cannot answer – dealt with in nuclear medicine

- **How long is spent dealing with the waste (in minutes)?**

#1	At time of injection the waste is the empty syringe and a small absorbent pad, which is then put into a dedicated sharps bin for decay. Waste is theatre will be bagged for decay. Some segregation required. Five minutes to collect waste.
#2	About 5 minutes
#3	This is difficult to estimate as waste will be combined with waste from many other investigations and procedures. Logging and disposing of one sharps bin would take a Band 4 assistant approximately 5 minutes to do
#4	Approximately 0-1 minute (assuming downstream monitoring and waste management is absorbed into wider daily routine of the department).
#5	Cannot answer – dealt with in nuclear medicine

- **How many staff are present during a breast surgery with SLNB with dual technique (radioisotope and blue dye) including Band and number of staff?**

#1	Need to ask surgical team. Surgeon, anaesthetist, lead nurse, other nurses??
#2	No response
#3	Need a surgeon to answer this
#4	Beyond my knowledge/expertise.
#5	• 1 x operating surgeon (consultant) • 1 x assistant (usually a junior doctor) • 1 x anaesthetist (consultant) • 1 x OPP (band 5) • 1 x scrub (band 5/6/7) • 2 x runners (band 4) (Minimum numbers quoted – can be more)

- **The EAC assumes that there a standard HRG code for Tc-99m injection (which will include all the microcosts for the above mentioned prep and injection). Do you know the standard HRG code for this radioisotope injection for SLNB?**

#1	RN19Z - However codes and tariffs for nuclear medicine procedures have always been complete nonsense and entirely unrelated to the cost of doing the procedure. Government has never engaged with the British Nuclear Medicine Society about this problem presumably as we are a small specialism. But I would be very wary of making decisions based on extremely bad data.
#2	£ 161 (2021/2022)
#3	In the 2020-2021 National Tariff workbook, the appropriate HRG is RN19Z with a tariff of £155 and reporting cost of £26.
#4	Beyond my knowledge/expertise. However, I would be very surprised if such specific HRG code exists (for Tc-99m injection only) and not as part of a wider 'procedure' (e.g. sentinel lymph node scan).
#5	No response given

-

6. For blue dye:

- **The company states that each vial of blue dye injection costs £25, does this sound reasonable?**

#1	Don't know, need to ask a surgeon, they do this part in theatre.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	Yes

- **How many SLNB procedures would this vial be used for?**

#1	Don't know, need to ask a surgeon, they do this part in theatre.

#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	One

- **Who injects the blue dye?**

#1	Don't know, need to ask a surgeon, they do this part in theatre.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	A member of the surgical team

- **How long does the blue dye injection take (in minutes)?**

#1	Don't know, need to ask a surgeon, they do this part in theatre.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	Seconds but have breast massage for 5 minutes afterwards

- **Do you need to wait a defined length of time between injecting blue dye and starting SLNB? If so how long do you wait?**

#1	Don't know, need to ask a surgeon, they do this part in theatre.
#2	No response
#3	Unable to comment
#4	Beyond my expertise.
#5	No

7. **The EAC has identified published literature which states that Magtrace can appear as artefacts in future MRI (up to 3 years after initial SLNB injection). Can you estimate the proportion of breast cancer patients, who have SLNB who then require future MRI as part of ongoing surveillance that this may impact?**

#1	Don't know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise. However, I should think that MRI is not used as routine 'on-going surveillance' post surgically per se, but rather for problem solving in cases of new symptoms/concern. I suspect the proportion of this is small.
#5	Up to now this has only affected 3 of our patients (symptomatic unit – may be more in a screening unit. This is in 350 cases followed up to date so approx. 1-2%

8. Where further imaging is required, can you confirm MRI and mammography is standard of care?

#1	Don’t know.
#2	No response
#3	Unable to comment
#4	Depends on context, ultrasound may also need to be added.
#5	Standard imaging for all patients is mammographic surviellence. MRI only used in those <40 years when diagnosed or in rare cases of lobular carcinoma where the tumour is mammographically occult

-

9. Are there specific subgroups of patients in which an MRI is likely to be required as part of ongoing surveillance?

#1	Don’t know.
#2	No response
#3	Unable to comment
#4	Beyond my expertise; however I should think if there is any group that needs ‘surveillance’, it would be those with high risk genetic predisposition for breast cancers (e.g. BRCA mutations).
#5	As above. Those diagnosed under the age of 40 years or or in rare cases of lobular carcinoma where the tumour is mammographically occult

Appendix 8

20220225 Questions to Experts - Availability of Tc-99m

I wondered if you were able to additionally comment on any supply issues regarding Tc-99m from the perspective of your organisation please? The reason I ask this is because the Company has emphasised lack of Tc-99m supply in Nuclear Medicine departments as a major concern in their submission and model.

Experts

#1	Elizabeth Jefferson
#2	James Scuffham
#3	Kate Williams
#4	Tomasz Graja

For organisations **with on-site** Nuclear Medicine departments:

- Can you confirm whether there are or have been supply issues regarding Tc-99m please?

#1	We do sometimes get supply issues of our Molybdenum/ Technetium generator. This would rarely impact on the delivery of a radiopharmaceutical for SLNB as we would still have last week's generator we can use which has less activity due to radioactive decay but the vial does not require a lot of activity to make it up. We'd be less likely to cancel these patient's procedures because it will have the knock on effect on their cancer surgery. We'd be more likely to cancel routine outpatient studies.
#2	The supply chain for Tc-99m is quite fragile as the parent radionuclide, Mo-99 is produced in only a handful of nuclear reactors across the world. In recent weeks, one of these reactors experienced technical problems which has led to a global shortage of Tc-99m and "rationing" of supply across the UK (link – need to use Google translate!). There was a similar shortage in 2008 and 2009 due to reactor failures. Probably the best background reference for the supply of Tc99m is the British Nuclear Medicine Society report on the topic published in Dec 2014 (link). When the supply chain is not interrupted by reactor problems, there is sufficient Tc99m to meet the UK's needs and so it's probably not fair to consider this a chronic problem but rather an intermittent one. At times of shortage, supply coverage is best wherever there are large radiopharmacy facilities with sufficient buying power to secure the available Tc99m generators. This means hospitals with on-site nuclear medicine and radiopharmacy facilities are less likely to be significantly affected than smaller regional centres without these facilities. However, a really important relevant factor is that Tc99m SLN procedures use relatively small quantities of Tc99m and are generally given very high clinical priority, and so it is easier to maintain these services at times of shortage. We do not have an on-site radiopharmacy at the Royal Surrey, and during the recent supply issues (and also in the previous supply interruption in ~2008), I can confirm that in our centre we did not delay or

	cancel any Tc99m SLNB patients due to radionuclide supply problems, for exactly the reasons above (low activity and high clinical priority). So in summary, there are intermittent supply chain problems with Tc99m, but SLN services are quite robust against this and the number of patients this affects should be minimal, so I do not think this is a major concern limiting patient pathways. Probably a more important factor is the "patchiness" of Tc99m supply within the UK, i.e., how many hospitals don't have access to Tc99m at all because they have no nearby Nuclear Medicine facilities. Understanding how many hospitals this affects is obviously a key factor in the modelling as these are the ones that will benefit most from Magtrace. The expert panel was possibly slightly biased in this respect as experts with the most experience of Magtrace are more likely to come from centres without Tc99m access. It might be difficult to estimate of how many hospitals this affects, as it's not as easy as counting how many hospitals with breast surgery practices also have Nuc Med departments. This is because a lot of centres will have Tc99m administered at a neighbouring hospital with Nuc Med facilities but carry out the surgery themselves. In theory, the Administration of Radioactive Substances Advisory Committee (ARSAC) should hold information about how many hospitals provide SLN injection services to neighbouring centres, and so it would be worth speaking to them about this. You asked for any data on Tc99m supply and procedures and the best I can offer is a download of the NHS Digital Diagnostic Imaging Dataset (https://iview.hscic.gov.uk/DomainInfo/DiagnosticImaging) which I have attached that shows a growing number of these procedures since 2012, with lower numbers in 2020 and 2021 probably reflective of covid. The caveat for this data is that it doesn't always specifically separate out breast SLN from other tumours, depending on the codes used by hospitals. The "single photon emission computed tomography" codes are more likely to be melanoma so I excluded these in the totals.
#3	In the 6 months prior to us introducing magtrace into our department, we did experience some supply issues with Tc-99m and had to either juggle theatre listings around to fit around when Tc-99m was available or use a blue dye axillary sample technique. We switched to magtrace in May 2020
#4	No response

- Are you aware of any published local or national audit data monitoring Tc-99m procedures or supply over time?

#1	If there is anything, it will be held by the British Nuclear Medicine Society. They inform their members of upcoming issues, and have lobbied government over isotope availability, particularly over Brexit. They are most likely to have kept records or audits of the national picture.
#2	No response
#3	No
#4	No response

For all organisations **with or without on-site** Nuclear Medicine departments:

- Can you confirm whether SLNB procedures have been *cancelled* due to lack of Tc-99m supply? If so can you estimate a proportion of SLNB that are cancelled due to this reason please?

#1	No response
#2	No response
#3	Not all cancelled – after discussion with patient re risks some chose to have a blue dye guided sample instead / patients theatre dates were rescheduled to a different day
#4	In my hospital, Dorset County Hospital at Dorchester the main driver to abandon Tc99 and start using Magtrace was the fact that our Nuclear Medicine Department closed as a few people retired and it was difficult to run it. We never run out of Tc99 supply but every single dose was coming from Southampton which is nearly 2 hours drive away. So we had access to Tc99 but logistics became complicated and the whole service was expensive (if I remember well the costs of providing Tc99 to the Trust were around £20k/annum). I recall a few situations when the transport was delayed which has knock on effect on the theatre sessions but the main issue was costs and logistics behind Tc99.

- Can you confirm whether scheduled SLNB procedures have been *delayed* due to lack of availability of Tc-99m? If so can you estimate the proportion of procedures delayed, and the average duration of the delay please?

#1	No response
#2	No response
#3	Some re-scheduled to a different / later date. Duration of delay would be max 7 days. Number – small numbers as we switched to magtrace early (May 2020) to avoid this ongoing issue.
#4	No response

Again deepest apologies for these very detailed questions, however any broad or detailed feedback on your experience to determine whether Tc-99m supply is a major clinical concern would be hugely appreciated.

Appendix 9

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Engagement Meeting

MT568 Magtrace and Sentimag for locating sentinel lymph nodes for breast cancer

Date: **1 March 2022**

Time: **13:00 – 14:30**

Documents:

MIB: **MIB263 Magtrace and Sentimag for locating sentinel lymph nodes**

MTG Scope: **www.nice.org.uk/guidance/gid-mt568/documents/final-scope**

In Attendance:

NICE: Lizzy Latimer (LL), Farhaan Jamadar (FJ)

Newcastle EAC: Kim Keltie (KK), Rosalyn Parker (RP), Emma Belilios (EB), Joanne Davison (JD)

Company: Dan Sturt (DS), Matt Womack (MW), John Posnett (Freelance Health Economic Consultant)

Apologies: Andrew Sims (AJS)

Welcome and introductions

LL presented slides introducing attendees. This is a standard meeting to address any outstanding queries before the draft assessment report is submitted.

EAC clinical evidence review

The EAC presented their summary of the clinical evidence submission.

The Company identified 31 papers; 22 studies and 9 conference abstracts. The EAC considered 10 of these out of scope (reasons for exclusion included: volume or timing of Magtrace injection was outside the recommendations of the IFU, interventions or comparators deemed out of scope, population not exclusively breast cancer patients). The EAC identified an additional 15 papers that were relevant to the scope, comprising 9 additional peer-reviewed publications and 6 conference abstracts.

The 36 studies included as the evidence base comprise 22 comparative studies and 14 single-arm studies included for patient-reported outcome measures (PROMs) and adverse events only. There is some overlap in the clinical evidence with multiple publications coming from some studies.

The EAC identified a high level of heterogeneity across the published evidence with differences in the population included (patients with invasive breast cancer and ductal carcinoma in situ, tumour and hormone receptor status, with a range of co-morbidities and different proportion of patients undergoing mastectomy or breast conserving surgery). The administration of Magtrace and radioisotope tracer also differed across studies (in terms of injection site, depth, timing, dosage and imaging protocols used). There is variation in the comparators used across the studies with 5 papers comparing Magtrace with the dual technique, 11 using radioisotope alone and 6 using dual technique and radioisotope tracer alone but not reporting outcomes exclusively. Studies comparing Magtrace to blue dye alone were considered out of scope of the assessment due to the known inferiority of blue dye as an independent tracer and the Clinical experts reporting few patients decline the use of radioisotopes.

Outcomes:

The EAC identified evidence to support the non-inferiority of Magtrace compared with the current dual technique standard of care for detection of SLNs and detection of malignant nodes.

The EAC identified a lack of robust comparative evidence to determine the impact of the use of Magtrace compared with the standard of care dual tracer on SLNB time.

Meta-analysis conducted by the EAC (which included 6 comparative studies) found no evidence to suggest that the number of nodes excised differs between Magtrace and dual technique.

The EAC identified a lack of comparative evidence for patient reported quality of life and pain outcomes. The EAC identified no published evidence that directly compares skin-staining outcomes of Magtrace with blue dye, although it was noted that the published evidence and opinion from Clinical experts does not identify skin staining as a significant problem for patients.

The EAC have not identified any immediate or short-term safety concerns relating to the use of Magtrace and Sentimag.

The Company asked if they will have access to the EAC's report and supporting documentation. They expressed concern that the EAC's literature search found relevant studies that their search missed (although these might be studies they found but excluded). LL confirmed the Company will have a chance to fact check the assessment report before it goes to the Committee. This is to identify factual inaccuracies only, i.e. the Company cannot give their opinion on the EAC's findings at this stage. Following the Committee meeting, the draft guidance will go out for Public consultation. This will give the Company access to all the supporting documentation, and provide opportunity to comment.

Further questions from the External Assessment Centre for the evidence assessment

What proportion of centres purchasing Magtrace also purchase Magseed?

The Company thought that all UK Centres using Magtrace will also use Magseed. This is because for commercial reasons Magseed was promoted

first when the Company launched in the UK. DS will check commercial data to confirm that this is the case.

ACTION: DS to check commercial data - do all UK Centres using Magtrace also use Magseed?

The EAC queried how many Centres would use both Magtrace and Magseed together in the same surgery? The Company clarified that this would depend on the type of surgery. Magseed is used to locate impalpable lesions for surgical removal, Company estimated broadly this may be 50% of cases. Magtrace could be used together with Magseed to locate sentinel lymph nodes in the same procedure. Magseed may be used alone for targeted axiliary dissection. Around 20% of breast cancer patients will have a mastectomy (so would require Magtrace only, not Magseed).

Is there any known impact for travel for patients receiving Magtrace, for example passing through body scanners at airports? Are there any precautions recommended in these circumstances?

No impact. Won't set off airport scanners. Additional iron content in the body from Magtrace post-SLNB is low (equivalent to 5 days recommended iron intake).

The cost minimisation model submitted includes an opportunity cost associated with theatre time lost because of the time required for Tc-99m injection on the day of surgery, equivalent of 1 additional procedure each week. However no source or reference was provided for this estimation. Can you advise where this data was sourced from please?

The Company clarified that they couldn't find any published information, also, practice will vary by hospital. They therefore took an estimate from talking to three NHS hospitals (two took part in telephone interviews, one submitted their business case). The hospitals agreed they would rarely be able to start

an SLNB procedure before 10:30 if using radioisotopes. The Company assumed a starting time of 09:00 and a procedure duration of 45 minutes for SLNB with Magtrace. Assuming 50% realised, and one theatre session a week, this would result in one additional procedure each week.

In confidence data in the economic submission

In the economic submission, there is data highlighted as AiC (yellow highlights) but described as CiC. NICE clarified that it is necessary to be really clear on this as AiC and CiC information is treated differently. JW clarified that the data should be treated as CiC. He gave permission for LL to change the highlight colour to blue. LL will also confirm this with them by email.

In the references section, the Company have redacted the full reference to the business case, but confirmed it is the hospital name only that needs to be redacted (title of the business case is not confidential). The business case itself is commercially sensitive and will be kept in confidence.

ACTION: LL to confirm with Company by email, then change highlight colour of confidential information in the economic submission from yellow (AiC) to blue (CiC) and resend latest versions to EAC.

POST-MEETING NOTE: LL sent email 01/03/2022. Awaiting written confirmation from Company.

Next steps

15/03/2022 - Company will receive the assessment report for fact check. They will have until 18/03/2022 to highlight any factual inaccuracies (not

opinion). EAC will then have the opportunity to respond and make any amendments. Assessment report will then go to the Committee.

24/04/2022 - First MTAC meeting. Company will be invited to register representatives to attend as observers. They will attend Part 1 (public session) only, and will not be able to speak. The Company will be invited to nominate a representative to be available to respond to any direct queries from the Committee (they will not be able to speak otherwise). Meetings are held remotely via Zoom.

16/05/2022 - Draft Guidance and supporting documentation will go out for public consultation for four weeks (closes 15/06/2022). The Company can use this opportunity to submit their comments. LL recommended that the Company should submit consultation comments even if they are in full agreement with the assessment report and the guidance recommendations as they will then be registered as a stakeholder and will receive the final guidance and supporting documentation when it goes out for resolution (final stage before publication).

22/07/2022 - Second MTAC meeting. Company can register as observers (but will not be required to respond to questions). The Committee will discuss comments received from public consultation and consider if the draft recommendations should change.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

GID- MT568 Magtrace and Sentimag for locating sentinel lymph nodes

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Newcastle upon Tyne Hospitals External Assessment Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **Friday 18th March 2022** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

15th March 2022

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
'when injected directly into the bloodstream' p13	'When injected…'	Factual accuracy, as per IFU, Magtrace is not intended for intravenous injection	Thank you for your response. Quotation taken from the NICE final scope (NICE MT568 Final Scope, 2021); the EAC is unable to amend the final scope after finalisation. The injection of Magtrace intravenously is considered an adverse event and this has been listed for the EAC to consider under 'any other special considerations' within the scope. The EAC can confirm that no occurrences of intravenous administration of Magtrace were reported in the published literature or by Clinical experts. The EAC has added this to Section 6, Adverse Events of the Assessment Report, 2022.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
'Each Magtrace vial contains 1ml of Magtrace fluid' p15	Each Magtrace Vial contains 2ml of Magtrace fluid	Factual accuracy – also please check this hasn't changed the economic considerations	Thank you for highlighting this; the value has been corrected to reflect 2 ml vial contents. No alteration to the economic considerations required as EAC included one vial per patient regardless of the administered volume.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The magnetic particles…" p15	Magtrace particles are not inherently magnetic, they are superparamagnetic	Factual accuracy	Thank you for highlighting this; the EAC has correct this to "superparamagnetic".

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
'Magtrace may leave a brown bruise-like coloration around the area of injection in some people, which may fade over time.'p16	'Magtrace may leave a brown bruise-like coloration around the area of injection in some people, which will fade over time.'	Factual accuracy – literature shows discoloration fades over time. E.g. Lorek 2019, Warnberg	Thank you for your response. The EAC recognise that in some patients skin discolouration resolves fully, however there is also published evidence to demonstrate that this is not the case for *all* patients. For the two references provided by the Company: Lorek *et al.* (2019) reported 11 patients with remaining skin discolouration at 30 months post Magtrace administration. Warnberg *et al.* (2019) reported skin staining in women undergoing breast conserving surgery with staining present at 36 months in 46.2% (out of 104 women) undergoing retro-areolar injection of Magtrace, and in 9.4% (out of 117 women) undergoing peritumoural injection of Magtrace.

			Additionally, Hersi *et al.* (2021) reported skin staining in 18.4% of patients with a mean size of 11.2 cm^2 at 6 months postoperatively. Szynglarewicz *et al.* (2019) reported 17% of patients with remaining skin staining at 12 months postoperatively. Hannebicque *et al.* (2017) reported 36.2% of patients presented with skin staining after 20.2 (14.4-25.9) months postoperatively. The EAC did not identify any published evidence that compared the skin staining of Magtrace to that of blue dye. There was disagreement amongst the Clinical experts as to the duration of skin staining with Magtrace. One Clinical expert reported that staining was greater in Magtrace while another Clinical expert reported that skin staining was more significant with blue dye. Another expert commented that staining with blue dye can last longer (sometimes permanently, compared to 12 to 18 months for Magtrace), while another commented staining associated with Magtrace lasted longer (EAC Correspondence Log, 2022). The EAC note from the Magtrace IFU Warnings and Precautions point 6: "some transient or long-term brownish skin coloration may occur", where 'long-term' remains undefined and does not support the claim that there is a

			complete resolution of skin staining in all patients. Due to the lack of longitudinal evidence to demonstrate that all patients experience a full resolution of skin staining to support this claim, the EAC considers that "which may fade (partially or completely) over time" is more appropriate.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
'SLNBs help to diagnose cancer.'p16, "	'SLNBs help to stage cancer.'	Factual accuracy	Thank you for your comment; a correction has been made for clarity.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
According to Haemochromatosis UK and the British Liver Trust the genetic iron overload condition is found in 1 in 150 to 200 people and	Remove statement. Hereditary Haemochromatosis is not the same as having active, clinically diagnosed, iron overload disease. Most people with Haemochromatosis do not progress to being diagnosed with iron overload disease. The Magtrace IFU contraindication states: 'Do not administer to any patients with iron overload disease'. Additionally, iron overload disease affects	Statement is factually inaccurate when applied to the Magtrace contraindication referenced.	Thank you for your comment. The Magtrace IFU states the contraindication "Do not administer to any patient with iron overload disease". The EAC has attempted to quantify the number of patients with iron over disease (in line with the device IFU), however has not attempted to quantify the number of patients with iron overload symptoms

prevalence is higher in those of Celtic descent.	males significantly more than females, despite equal inheritance patterns of Haemochromatosis. Magtrace use in breast cancer is predominantly in females. Therefore, this statement should not be applied to the Magtrace contraindication of iron overload disease.		(e.g. in patients with sickle cell anaemia requiring blood transfusion). Iron overload disease, or haemochromatosis (US National Institutes of Health), is an inherited condition where iron levels in the body slowly build up over many years (NHS, 2022). According to Haemochromatosis UK and the British Liver Trust the genetic haemochromatosis is iron overload condition is found in 1 in 150 people in England and Wales, and in 1 in 113 people in Scotland and Northern Ireland. The British Liver Trust reports that haemochromatosis is underdiagnosed; with only 1 in 5,000 people being diagnosed. A review by the UK National Screening Committee in 2021 identified insufficient evidence to support routine national screening for Haemochromatosis in UK adults." The EAC have also stated that the "Clinical experts agreed that they do not routinely screen for iron overload disease in patients receiving Magtrace, although have not encountered any issues with the use of Magtrace in clinical practice (EAC Correspondence Log, 2022)." The EAC has amended the Special Considerations section to clarify the sources of information.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
'number of SLNB procedures in a week ranging between 200 and 600'p111	Should this be per year? 'number of SLNB procedures in a year…'	Factual accuracy	Thank you very much for highlighting this, correction made.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC notes that the Company has not considered that intraoperative injections of Magtrace would add 20 minutes to total theatre time. P112	We have considered this and in our experience this is not the case. If administered intra-operatively, Magtrace is usually injected prior to surgical preparation. The 20 'wait' happens, in reality, whilst the surgeons scrub up and the theatre team prep the patient. Often the surgeon will delegate the 5 min massage to another team member in order to also negate this as a potential delay whilst they scrub.	Factual accuracy	Thank you very much for your comment. The EAC has changed the wording to the following: "The EAC notes that the Company has not considered within their economic model that intraoperative injections of Magtrace would add 20 minutes to total theatre time." The EAC have considered the additional theatre time within sensitivity analysis, see Figure 12 in Assessment Report, 2022. The 20 minute waiting time following injection was taken from Magtrace IFU: "For subareolar injection, surgeons should wait at least 20 minutes before attempting transcutaneous

			measurement of the axilla. Peritumoral injection may require a longer wait." The published evidence describing intraoperative injection also reported 20 minutes wait before starting surgery (Karakatsanis *et al.* 2016; Alvarado *et al.* 2019; Ghilli *et al*. 2017; Thill *et al*. 2014). The EAC would consider that the "wait" described in the comment by the Company fact check comment (which occurs whilst the surgeons scrub up and the theatre team prepare the patient), still incurs an additional 20 minutes of theatre time. Additionally, the EAC would highlight that in the EAC base case that not all patients undergo intraoperative Magtrace injection; 50% undergo injection at a prior clinic appointment and therefore do not incur additional theatre time costs.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Use of Magtrace intraoperatively may add 20 minutes (as the tracer needs time to drain to the axilla). P118	As per comment above	Factual accuracy	Thank you very much for your comment. Note use of "may" in this sentence. No change required. See response to Issue 8.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Adding 20 mins theatre time for Magtrace P123	As per comment above	Factual accuracy	Thank you very much for your comment. This is within Table 16, demonstrating the changes made to the Company model by the EAC, and therefore does not represent a factual inaccuracy. No change required.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
A minimum of 20 minutes is required following Magtrace administration to allow lymphatic drainage (in line with the Magtrace IFU), with the published evidence confirming the SLNB did not start until at least 20 minutes had elapsed following Magtrace administration when used intraoperatively (Karakatsanis *et al.* 2016; Alvarado *et al.* 2019; Ghilli	As per comments above	Factual accuracy	Thank you very much for your comment. The EAC has summarised the device IFU, published literature and an assumption made in the EAC base case – therefore this is not a factual inaccuracy. The EAC has however clarified the text regarding the Magtrace IFU: "A minimum of 20 minutes is required following Magtrace administration to allow lymphatic drainage before attempting transcutaneous measurement of the axilla (in line with the Magtrace IFU)"

et al. 2017; Thill *et al.* 2014). The EAC assumes that the 20 additional minutes will include 5 minutes of breast massage to promote drainage to the axilla. P125			

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg. 113. Row 2. Referring to opportunity costs of lost theatre time other than Monday scheduling. EAC suggests this variable should be varied in sensitivity analysis (SA). In fact, it is omitted altogether from the EAC base-case and SA (Pg. 130).	More accurate would be to say that this potential opportunity cost has been omitted from the analysis, even though the current wording acknowledges that this might be relevant to some hospitals ("The EAC considers that opportunity costs may not be realised in some hospitals").	The current statement is not accurate if it refers to opportunity costs other than Monday start time (cited on Pg. 112)	Thank you very much for your comment. It is unclear to the EAC where the factual inaccuracy is. The EAC have further defined the justification and likelihood for opportunity costs relating to additional surgeries within Table 12. The number of additional procedures each week, and the proportion of centres realising these additional procedures have both been applied in sensitivity analysis (Figures 13 and 14 respectively) to address this uncertainty.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 16, col 4, row 4. £244 should be £240?	Replace £244 with £240 Replace incremental cost £20 with £16.	The sensitivity reported in this row should not affect the cost of Magtrace/Sentimag ?	Thank you for highlighting this; this has been amended (with additional information provided so that others can replicate this change to the Company model).

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 131 (para 2), 142 (para 2), Pg 145 (para 3) Describes “marginal” cost savings. What is the cut-off value for a cost saving to be non-marginal?	Please omit the qualifier altogether.	The qualifier implies a subjective judgement about which cost savings are important. The sensitivity analysis, including PSA, shows that in fact cost saving is a robust outcome.	Thank you very much for your comment. The EAC has removed the use of “marginally” throughout the report. The EAC have also clarified that the cost-saving represents 3% of the total cost of an SLNB procedure.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg. 139 Table 19. Some of the figures appear to be wrong	Row 1: base case. Magtrce/Sentmag cost should be £2,488.33 (as in table 18) Row 4: M/S cost should be £2,496.72 to give a cost difference of -£71.01		Thank you for highlighting this. Table 19 has been reviewed and updated.

	Row 5: M/S cost should be £2,490.34 to give a cost difference of -£78.82		

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg. 142, line 18. Refers to the model being sensitive to "minor changes". In fact, based on the analysis on pages 132-139 the changes are quite substantial.	Please omit the qualifier altogether. "However, the model was sensitive to changes…"	The use of the qualifier implies a subjective judgement that results from the base-case analysis are not robust. In fact, the SA shows that in most cases the threshold values are quite a long way from the base-case values.	Thank you very much for your comment. The word "minor" has been removed.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg. 147. "However, for services with established Nuclear Medicine facilities, implementing the new technology may not be beneficial". This doesn't follow from the analysis	Please delete this sentence.	In hospitals with NM facilities, the opportunity cost of lost theatre time caused by delays in radioisotope or non-availability of NM staff may not be relevant. But, in the EAC base-case model, Magtrace/Sentimag is still cost-effective even though this opportunity cost is omitted. The potential benefits of an additional case on a Monday are still relevant to hospitals with NM facilities. Hence the statement contradicts the	Thank you very much for your comment. Where the opportunity costs are not realised (through effective theatre scheduling) Magtrace and Sentimag is shown to be cost-incurring by £58.17 per procedure (Figure 13 & 14; Assessment Report, 2022). The EAC has clarified this in the report (narrative of Figure 13, section 10.2, section 11) to make this clearer.

		results of the EAC analysis (Table 18)	

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg. 282 "Inclusion criteria: male, patient…"	Remove the word male	Factual accuracy – this study is not limited to males	Thank you very much for your comment. The information accessed through the Chinese Clinical Trial Registry and WHO International Clinical Trials Registry specifies that the gender of recruited patients is male. The EAC has added the following text: "[The trial registration states "male" gender, however the Company have stated that this study is not restricted to male patients]."

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg. 283 "[JPRN-UMIN000031240]"	Remove study	Magtrace and Sentimag are not licenced and therefore distributed in	Thank you for highlighting this. The EAC has added additional text to the table to

		Japan, other SPIO and detectors are available in this region. This study isn't Magtrace or Sentimag	clarify that the device name nor manufacturer is listed on the trial registration and also added: "The Company have noted that Magtrace and Sentimag are not licenced for use or distributed in Japan."