Review protocol for the detection and subsequent management of distant metastases in people with suspected advanced breast cancer using PET-CT and CT

Field	Content
Review title	The effectiveness and cost effectiveness of PET-CT compared to CT with or without bone scintigraphy for detection, and for informing subsequent management, of distant metastases in people who have suspected advanced breast cancer.
Review question	What is the clinical and cost effectiveness of FDG PET-CT compared to CT (with or without bone scintigraphy) for diagnosing distant metastases and determining subsequent management in people with suspected advanced breast cancer?
Objective	To evaluate and compare the clinical effectiveness and cost effectiveness of FDG PET-CT and CT with or without bone scintigraphy for diagnosing distant metastases and informing the subsequent management in adults with suspected advanced breast cancer.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be limited to exclude: • papers published before 2005 • Papers not published in the English language • Animal studies • Conference abstracts and posters

	• Editorials, letters, news items and commentaries • Theses and dissertations • Clinical trial registry records For the economics review the following databases will be searched: • Embase • MEDLINE ALL • INAHTA International HTA Database The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.
Condition or domain being studied	Suspected advanced breast cancer Advanced is defined as people with a distant metastasis (M1 using the TNM staging system).
Population	Inclusion: Adults (18 and over) with invasive adenocarcinoma of the breast who have suspected distant metastases (M1).
Intervention	• Fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) [FDG PET-CT] followed by management of the metastases based on the results of the test Exclusion • PET-CT used for screening • Imaging analysed using artificial intelligence (AI)

	• Imaging covering less than chest (or neck or thorax), abdomen and pelvis.
Comparator	• Contrast-enhanced Computed Tomography (CECT) scan • Contrast-enhanced Computed Tomography (CECT) scan, with bone scintigraphy Both comparators will be followed by management of the metastases based on the results of the test. Exclusion • CECT used for screening • Imaging analysed using artificial intelligence (AI) • Imaging covering less than chest (or neck or thorax), abdomen and pelvis.
Types of study to be included	• Test and treat RCTs • Systematic reviews of test and treat RCTs
Other exclusion criteria	• Abstracts, conference presentations, theses and narrative reviews • Non-human studies • Non-English language studies • RCTs that are not Test and Treat studies
Context	This guideline will update the NICE guideline on advanced breast cancer: diagnosis and treatment (CG81). New evidence that could affect recommendations was identified through the surveillance process. The surveillance review appendix noted increasing use of PET-CT scans in practice, and stakeholders identified this area for update. A timely and accurate diagnosis of metastatic breast cancer is important for guiding treatment and improving patient outcomes. PET-CT will be assessed alongside contrast-enhanced CT with or without bone scintigraphy, which is current practice for diagnosing metastatic breast cancer, to determine accuracy.
Primary outcomes	Critical outcomes: • Overall survival (time to event data)

(critical outcomes)	• Breast cancer-specific survival (time to event data or event data if time to event not available) – breast cancer mortality will be accepted if breast cancer-specific survival is not reported Any statistically significant difference will be taken as clinically meaningful for the critical outcomes. **Timepoints:** The longest follow-up periods will be prioritised for all outcomes if multiple time points are reported.

Secondary outcomes (important outcomes)	• Quality of life (all validated measures including EQ-5D)
	• Changes to management or treatment (event data), for example:
	  ○ People who avoided treatments aimed at non-metastatic disease
	  ○ People who started treatment for metastatic disease
	
	Minimal important differences
	• Quality of life MID values from the literature:
	  ○ FACT-G total: 3-7 points
	  ○ FACT-B total: 7-8 points
	  ○ TOI (trial outcome index) of FACT-B: 5-6 points
	  ○ BCS of FACT-B: 2-3 points
	  ○ EORTC QLQ-C30: improvement 11 points and deterioration minus 8 points
	  ○ WHOQOL-100: 1 point
	
	Any statistically significant difference will be used to assess whether an effect is clinically meaningful for the rest of the important outcomes.
	
	Timepoints:
	The longest follow-up periods will be prioritised for all outcomes if multiple time points are reported.

Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the index and reference standard tests, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. This review may make use of the priority screening functionality within the EPPI-reviewer software. If priority screening is used, the following rules will be adopted to determine when to stop screening: • at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened • After this point, screening is only terminated if a threshold of 750 is met for a number of abstracts being screened without a single new include being identified. • if sifting is terminated before the full database has been looked at additional checks will be carried out to ensure that relevant studies have not been missed.

Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as hazard ratios or risk ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 40% and 60% will be considered as serious and very serious heterogeneity, respectively. Where I^2 >40% in a fixed effects model, a random effects model will be fitted if it reduces the heterogeneity. Where I^2 is 80% or above, consideration will be given to whether the data should be pooled. Heterogeneity will be explored as appropriate using pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias

Analysis of sub-groups	Evidence will be subgrouped only for critical outcomes by the following: • Location of metastases (bone vs visceral) • Receptor types (HER2-positive, triple negative, ER+/HER2-) • Invasive lobular carcinoma vs all other types. • Inflammatory breast cancer vs all other types • Size of tumour (T1 to T2 vs T3+) • Nodal status (N0 vs N1 to N3) Where evidence is stratified or subgrouped, the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
Language	English

<table>
<tr><td>Country</td><td colspan="3">England</td></tr>
<tr><td>Anticipated or actual start date</td><td colspan="3">June 2025</td></tr>
<tr><td>Anticipated completion date</td><td colspan="3">December 2025</td></tr>
<tr><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>X</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>X</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
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<tr><td>Review team members</td><td colspan="3">From the Guideline Development Team

• Marie Harrisingh, Topic lead</td></tr>
</table>

	• Olivia Crane, Senior technical analyst • Adefisayo Abba-Abba, Technical analyst • Yolanda Martinez, Technical analyst • James Hawkins, Health economist adviser • Tzujung Lai, Health economist analyst • Andrea Heath, Information specialist
Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Advanced breast cancer: diagnosis and treatment.
Other registration details	None
Reference/URL for published protocol	None

Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Advanced breast cancer, FDG PET-CT, distant metastasis, Stage 4 breast cancer
Details of existing review of same topic by same authors	None
Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
Additional information	None

Details of final publication	www.nice.org.uk