Review protocol for using PET-CT scans to monitor response to treatment in people who have been or are being treated for advanced breast cancer

Field	Content
Review title	PET-CT scans for monitoring response to treatment in people who have been or are being treated for 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 monitoring response to treatment in people who have been or are being treated for advanced breast cancer?
Objective	To evaluate the clinical and cost effectiveness of FDG PET-CT compared to CT with or without bone scintigraphy for monitoring response to treatment in people who have been or are being treated for 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 (for systematic reviews only) 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 following standard NICE filters will be used to limit results by study type: cost effectiveness studies / randomised controlled trials. 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	Advanced breast cancer. Advanced is defined as with distant metastases (M1 using the TNM staging system).
Population	Inclusion: Adults (18 and over) who are being or have been treated for confirmed invasive adenocarcinoma of the breast with distant metastases (M1). Exclusion: • Adults who have not received treatment for invasive adenocarcinoma of the breast with distant metastases (M1) • Adults (18 and over) with metastases to the breast from other primary tumours. • Adults (18 and over) with non-epithelial breast tumours (for example, angiosarcoma, lymphoma).
Intervention	Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET-CT) for monitoring (i.e. detecting treatment response and progression). Other tracers that may be used with PET-CT will be excluded. Imaging analysed using artificial intelligence (AI) will be excluded.

Comparator	Contrast-enhanced CT with or without bone scintigraphy for monitoring (i.e. detecting treatment response and progression). Imaging analysed using artificial intelligence (AI) will be excluded. Imaging covering less than chest (or neck or thorax), abdomen and pelvis will be excluded.
Types of study to be included	• Systematic reviews of RCTs • RCTs.
Other exclusion criteria	• Abstracts, conference presentations, theses and narrative reviews • Non-human studies • Non-English language studies • Studies where more than 20% of the participants do not have metastatic disease and where subgroup data is not available.
Context	New evidence that could affect recommendations was identified through the NICE surveillance process. As a result of discussions with clinicians during the scoping process, it was proposed that additional areas were going to be included in this update. One of these areas was on the use of PET-CT scans for monitoring response to treatment.
Primary outcomes	• Overall survival (OS) (time to event data) • Cancer-specific survival (time to event data) - equivalent to breast cancer mortality ○ Some studies may report cancer-specific survival as breast cancer mortality (dichotomous data). This will be extracted as a proxy outcome where cancer-specific survival data is not reported in the study. **MIDs:** any statistically significant difference. **Timepoints:** • longest reported timepoint from each study will be combined for time to event outcomes. • longest reported timepoint up to and including 5 years, and longest reported timepoint at over 5 years will be reported separately for dichotomous outcomes.
Secondary outcomes	• Change to management or treatment (event data), for example: ○ People whose treatments were stopped as they were no longer working

	○ People who moved to a further line of treatment. • Quality of life (all validated measures including EQ-5D). **MIDs:** • 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 ○ WHOQOL-100: 1 point Any statistically significant difference will be used for the rest of the important outcomes. **Timepoints:** • change to management or treatment: any • Quality of life: longest reported timepoint from each study will be combined
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 interventions if relevant, 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. Studies included in an included systematic review will not have a full data extraction form conducted, but study details will be checked and high-level details reported in the review.
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. 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: • CT with / without bone scintigraphy • 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 Where evidence is 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">May 2025</td></tr>
<tr><td>Anticipated completion date</td><td colspan="3">Autumn / Winter 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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• James Hawkins, Health economics adviser
• Tzujung Lai, Health economist
• Andrea Heath, Information specialist</td></tr>
</table>

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	Not applicable
Reference/URL for published protocol	Not applicable
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; PET-CT; CE-CT; bone scintigraphy

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	