Review protocol for platinum-containing chemotherapy regimens in people with advanced breast cancer that is triple negative and/or who have BRCA germline mutations

Field	Content
Review title	What is the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced: • triple negative breast cancer? • breast cancer of any receptor sub-type with BRCA germline mutations?
Review question	What is the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced: • triple negative breast cancer • breast cancer of any receptor sub-type with BRCA germline mutations?
Objective	To assess the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced: • triple negative breast cancer • breast cancer of any receptor sub-type with BRCA germline mutations
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistimonikos • MEDLINE ALL For the economics review the following databases will be searched:

	• Embase • MEDLINE ALL • INAHTA Searches will be restricted by: • English language • Human studies • Abstracts, conference presentations, and theses will be excluded. • Systematic reviews and RCTs The following standard NICE filters will be used to limit results by study type: cost effectiveness studies /systematic reviews / 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 that is triple negative or of any receptor sub-type with BRCA germline mutations. Advanced is defined as with distant metastases (M1 using the TNM staging system).
Population	Inclusion: • Adults (18 and over) with invasive adenocarcinoma of the breast with distant metastases (M1) who have:

	○ Triple negative breast cancer ○ Breast cancer of any receptor sub-type with BRCA germline mutations Exclusion: • Adults (18 and over) who have invasive adenocarcinoma of the breast with distant metastases that is not triple negative and do not have BRCA germline mutations • Adults (18 and over) with newly diagnosed invasive adenocarcinoma of the breast of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0) • 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) • Adults (18 and over) with benign breast conditions (for example, fibroadenoma, benign phyllodes tumours)
Intervention	Any chemotherapy regimen containing a platinum agent. Platinums of interest: • Carboplatin (all doses and regimens) • Cisplatin (all doses and regimens). All of these comparisons will be included: 1. Regimen A + platinum agent vs regimen A 2. Regimen A + platinum agent vs regimen B 3. Single agent platinum vs regimen C

Comparator	Any chemotherapy regimen without a platinum agent. • We will exclude any chemotherapies which are not used in UK clinical practice.
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 meet protocol criteria (have locoregional disease / do not have BRCA germline mutations (for the BRCA analyses) / do not have TNBC (for the TNBC analysis) and where subgroup data is not available.
Context	There are currently no recommendations on the use of platinum-containing chemotherapy regimens in people with advanced breast cancer that is triple negative and/or who have BRCA germline mutations of other receptor subtypes. The 2023 surveillance review suggests there may now be some evidence to support the development of advice in this area.
Primary outcomes (critical outcomes)	• Progression-free survival (time to event data) • Overall survival (time to event data) • Objective tumour response rates (OTRR) (dichotomous data) **MIDs:** any statistically significant difference. **Timepoints:** longest reported from each study will be combined.

Secondary outcomes (important outcomes)	• 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.
	• Adverse events* (event data)
	  ○ Anaemia
	  ○ Fatigue
	  ○ Hair loss (alopecia)
	  ○ Leukopenia
	  ○ Nausea/vomiting
	  ○ Nephrotoxicity
	  ○ Neuropathy (also reported as peripheral neuropathy)
	  ○ Neutropenia
	  ○ Neutropenic sepsis (reported as febrile neutropenia)
	  ○ Ototoxicity (including tinnitus and hearing loss, with all types analysed together)
	  ○ Thrombocytopenia
	  ○ Treatment-related death
	• Adherence to / completion of treatment
	  ○ If not reported, treatment discontinuation due to adverse events will be extracted.
	• Quality of life (all validated measures including EQ-5D).
	
	*Outcomes will only be reported where severity grade is specified using the Common Terminology Criteria for Adverse Events (CTCAE). Outcomes at severity levels 1-2 will not be reported for any adverse event outcome except hair loss, fatigue and ototoxicity. Grade 3-4 severity will be reported (combined) for all outcomes.
	
	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

	○ EORTC QLQ-C30: improvement 11 points and deterioration minus 8 points ○ WHOQOL-100: 1 point Any statistically significant difference will be used 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, length of time since the assessment of receptor subtype [e.g. biopsy]), 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 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 stratified by:

	• Advanced triple negative breast cancer • Advanced BRCA germline mutations Evidence will be subgrouped only for critical outcomes by the following: • Type of comparison (1, 2 or 3) • Type of platinum agent (carboplatin, cisplatin) • First-line therapy: (a) first-line therapy for >80% of participants, (b) second- or third-line therapy for ≥20% of participants • Within advanced TNBC: with / without BRCA mutation • Within BRCA mutation: receptor subtype (triple negative, HER2+, HR+) 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

Country	England		
Anticipated or actual start date	April 2025		
Anticipated completion date	Autumn / Winter 2025		
Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
	Preliminary searches	☐	X
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐

	Data analysis	☐	☐
Named contact	**24a. Named contact** NICE **24b Named contact e-mail** breastcancerupdate@nice.org.uk **24c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
Review team members	• Marie Harrisingh, Technical adviser • Olivia Crane, Senior 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	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, triple negative breast cancer, BRCA germline mutations, platinum chemotherapy.
Details of existing review of same topic by same authors	Not applicable.
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