Review protocol for effectiveness of risk-reducing mastectomy in people at increased risk of heritable breast cancer: People with a personal history of breast cancer

ID	Field	Content
1.	Review title	Effectiveness of risk-reducing mastectomy in people at increased risk of heritable breast cancer.
2.	Review question	How effective is risk-reducing mastectomy (RRM) compared to other risk-reducing interventions: chemoprevention and surveillance (alone or in combination) or no risk-reducing strategies at improving survival in: • women, trans-men and non-binary people born with female reproductive organs, and • trans-women and non-binary people who have been on gender-affirming hormone therapy for 5 years or more who have a personal history of breast cancer suspected or confirmed to be heritable (considering risk thresholds, specific pathogenic variants, and age)?
3.	Objective	To identify the populations that will benefit the most and least from risk-reducing mastectomy by considering participant characteristics such as baseline risk of developing future breast cancer, previous breast cancer history, known pathogenic variants or likely variants, and age, alongside outcomes such as breast cancer incidence, mortality, satisfaction, and quality of life measures.
4.	Searches	The following bibliographic databases will be searched: • Medline ALL (Ovid platform) • Embase (Ovid platform) • Cochrane Database of Systematic Reviews (Wiley platform) • Epistemonikos (for systematic reviews-only)

		Searching for systematic reviews will be limited to Epistemonikos and the Cochrane Database of Systematic Reviews-only. References to studies included in the previous NICE guideline (NG241, 2024) will also be included in the present review, along with any other relevant studies NICE has already identified during the guidance surveillance and prioritisation process. Reference lists for any relevant systematic reviews identified will be checked for additional primary studies. The guideline committee or other stakeholders will be asked for details of any additional, relevant studies they may be aware of. The full search strategies for all databases will be published as an appendix to the final evidence review. Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Preprints
5.	Condition or domain being studied	Heritable breast cancer
6.	Population	Inclusion: People with a personal history of breast cancer (women, trans men and non-binary people born with female reproductive organs, and trans women and non-binary people who have been on female gender-affirming hormone therapy for 5 years or more) who have one or more of the following:

		• A pathogenic variant/likely pathogenic variant in a gene (such as *BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51D, RAD51C*, TP53 and *BARD1)* that is associated with an increased risk of developing breast cancer • Strong family history of breast or breast and ovarian cancer • Breast cancer diagnosed at a young age as defined in the study (likely to be under 40 as it's more likely to be a genetic cause when diagnosed under 40)
7.	Intervention	• Bilateral risk-reducing mastectomy (BRRM) • Contralateral risk reducing mastectomy (CRRM) Types of risk-reducing mastectomy eligible: simple (total) mastectomy and skin-sparing with or without nipple-sparing mastectomy.
8.	Comparator	Ideally studies will report whether people in the comparator group received surveillance or chemoprevention. In this case the following comparators will be used: • Surveillance without risk reducing surgery • Chemoprevention without risk reducing surgery • Chemoprevention and surveillance without risk reducing surgery • No risk-reducing strategies (No risk reducing surgery, surveillance or chemoprevention) Where studies do not report whether participants in the comparator group received surveillance or chemoprevention: • No risk reducing surgery
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs

		• Quasi-randomised controlled trials
		
		It is unlikely that RCT and quasi-randomised controlled trial evidence will be identified as these studies would not be ethical, and uptake of the intervention is dependent upon participant preferences.
		
		• Non-randomised comparative studies and systematic reviews of these studies:
		  ○ Non-randomised controlled trials/Prospective cohort studies
		  ○ Retrospective cohort studies
		  ○ Historically controlled studies
		
		Non-randomised studies will only be included if they adjust for the following covariates in their analysis when there are differences between groups at baseline:
		• Strength of family history of breast or ovarian cancer
		• Presence of pathogenic variants in breast cancer predisposition genes
		• Age

10.	Other exclusion criteria	• Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Preprints
11.	Context	People with a heritable predisposition to breast cancer may choose to have risk-reducing mastectomy to reduce the chance that they will develop breast cancer in the future. This may apply to people who either have a known pathogenic variant in breast cancer predisposition genes or a strong family history of breast cancer. The

		type of risk-reducing surgery may also differ depending on whether the person has previously had breast cancer, with bilateral risk-reducing mastectomy relevant to people who do not have a personal history of breast cancer, or where a person with a previous history of breast cancer has received breast-conserving treatment, and contralateral risk reducing mastectomy relevant to people who have a personal history of breast cancer (who have had a mastectomy as part of their treatment) to reduce the risk that they will develop breast cancer in the contralateral breast. NICE's guideline on familial breast cancer [CG164] does not currently specify which populations should be offered risk-reducing mastectomy, and the aim of this review is to identify evidence that will help the committee to make recommendations around who should have risk-reducing mastectomy.
12.	Primary outcomes	Survival outcomes (at 10 years or latest follow-up time): ○ Overall survival/all-cause mortality ○ Breast cancer mortality ○ Disease-free survival We will prioritise data reported as hazard ratios (HRs) for these outcomes.
13.	Secondary outcomes	• New breast cancer incidence (at 10 years or latest follow-up time) • Quality of life and satisfaction (at 10 years or latest follow-up time): ○ Quality of life including the following scales: Breast-Q, EQ-5D-3L and EQ-5D-5L, SF-36 ○ Satisfaction with decision to have RRM • Adverse events according to The Common Terminology Criteria for Adverse Events, specifically grade 3 and 4
14.	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; 90% agreement is required. 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 (age, sex and gender, ethnicity, previous history of breast cancer, breast cancer risk threshold and presence of pathogenic variants), inclusion and exclusion criteria, details of the interventions (type of surgical procedure and type of reconstruction and comparator, 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.
15.	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 and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.

16.	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 risk ratios or odds 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, the following criteria will be used to assess heterogeneity: no serious I^2 = <40%; serious I^2 = 40-60%; very serious I^2 = >60%. Where I^2 is 80% or above, the data will not be pooled. Heterogeneity will be explored as appropriate using sensitivity analyses and 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. Publication bias will be investigated using a funnel plot when there are 10 or more studies in an analysis. 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/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). MIDs for each outcome are detailed in the methods supplement for this guideline. Where there are no published MIDs such as for survival outcomes, the committee will use the line of no effect in combination with optimal information size to assess imprecision.

17.	Analysis of sub-groups	Depending on how risk is reported in the literature. evidence will be stratified by:
		• Risk thresholds (moderate risk, high risk and very high risk or equivalent thresholds based on either 10-year, or lifetime risk or remaining risk of developing breast cancer) or
		• Presence of specific pathogenic variants:
		  ○ Risk group 1: BRCA1, BRCA2, PALB2, ATM (biallelic), CHEK 2 (biallelic) and TP53
		  ○ Risk group 2: CHEK2, ATM, RAD51C,D and BARD1
		
		Evidence will be subgrouped by:
		• Age at the time of risk-reducing mastectomy (less than 30 years, 30 to 39 years, 40 and over)
		
		Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
		• Type of surgical procedure [simple (total) mastectomy and skin-sparing with or without nipple-sparing mastectomy].
		• Type of reconstruction (for example, autologous reconstruction, and non-autologous reconstruction with possible revision to maintain cosmesis) for quality of life and satisfaction outcome only
		• Ethnicity
		• Gender (women, trans men, nonbinary people born with female reproductive organs)
		
		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.		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	5th January 2026		
22.	Anticipated completion date	22nd April 2027		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE **5b Named contact e-mail** familialbreastcancer@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
25.	Review team members	• Sarah Boyce [NICE Senior technical analyst] • Lina Ford [NICE Technical Analyst] • Yolanda Martinez [NICE Technical Analyst] • Sarah Matthews [NICE Technical Analyst • Eric Slade [NICE Health economics adviser] • Tzujung Lai [NICE Health economist] • Daniel Tuvey [NICE Senior information specialist] • Marie Harrisingh [NICE Topic Lead]		

26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
27.	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.
28.	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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10438.
29.	Other registration details	None
30.	Reference/URL for published protocol	
31.	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.
32.	Keywords	Breast cancer, high risk, risk-reducing mastectomy

33.	Details of existing review of same topic by same authors	Not applicable
34.	Current review status	☐ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk