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Protocol for the development of a core outcome set and reporting guidelines for locoregional treatment in neoadjuvant systemic breast cancer treatment trials: the PRECEDENT project

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ABSTRACT

Introduction Neoadjuvant systemic anticancer therapy (neoSACT) is increasingly used in the treatment of early breast cancer. Response to therapy is prognostic and allows locoregional and adjuvant systemic treatments to be tailored to minimise morbidity and optimise oncological outcomes and quality of life. Accurate information about locoregional treatments following neoSACT is vital to allow the translation of downstaging benefits into practice and facilitate meaningful interpretation of oncological outcomes, particularly locoregional recurrence. Reporting of locoregional treatments in neoSACT studies, however, is currently poor. The development of a core outcome set (COS) and reporting guidelines is one strategy by which this may be improved.

Methods and analysis A COS for reporting locoregional treatment (surgery and radiotherapy) in neoSACT trials will be developed in accordance with Core Outcome Measures in Effectiveness Trials (COMET) and Core Outcome Set-Standards for Development guidelines. Reporting guidance will be developed concurrently.

The project will have three phases: (1) generation of a long list of relevant outcome domains and reporting items from a systematic review of published neoSACT studies and interviews with key stakeholders. Identified items and domains will be categorised and formatted into Delphi consensus questionnaire items. (2) At least two rounds of an international online Delphi survey in which at least 250 key stakeholders (surgeons/oncologists/radiologists/pathologists/trialists/methodologists) will score the importance of reporting each outcome. (3) A consensus meeting with key stakeholders to discuss and agree the final COS and reporting guidance.

Ethics and dissemination Ethical approval for the consensus process will be obtained from the Queen's University Belfast Faculty Ethics Committee. The COS/reporting guidelines will be presented at international meetings and published in peer-reviewed journals. Dissemination materials will be produced in collaboration with our steering group and patient advocates so the results can be shared widely.

Registration The study has been prospectively registered on the COMET website (https://www.comet-initiative.org/Studies/Details/2854).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multiple data sources and robust consensus methods will be used to develop a core outcome set (COS) and reporting guidance for locoregional treatments in neoadjuvant breast cancer trials.
⇒ COS and reporting guidance will be developed with international multidisciplinary stakeholders including surgeons, clinical and radiation oncologists, radiologists, pathologists, patients, trialists and methodologists.
⇒ Engagement of international breast cancer trial networks will promote engagement with and implementation of the final COS/guidance in future neoadjuvant breast cancer studies.
⇒ Future work will be needed to monitor the use of the guidance and COS in neoadjuvant breast cancer studies.

INTRODUCTION

Treatment for breast cancer is multimodal and involves a combination of surgery, radiotherapy and systemic anticancer therapies, including cytotoxic chemotherapies, anti-HER2 therapies, immune checkpoint inhibitors and endocrine therapy. Neoadjuvant systemic anticancer therapy (neoSACT), given prior to surgery, is increasingly used in the treatment of early breast cancer and is becoming the standard of care for specific

disease subtypes, namely, triple-negative and HER2-positive diseases.[1–3]

Neoadjuvant treatment has several advantages. Pathological response to neoSACT provides valuable prognostic information at an individual patient level, and response to treatment can be used to tailor adjuvant systemic therapies, for example, escalating treatment for patients with residual HER2+and triple-negative diseases to improve survival[4 5] and increasingly, de-escalating therapy to reduce morbidity. By downstaging disease, neoSACT can also potentially allow de-escalation of locoregional treatments to the breast and axilla, allowing patients to avoid mastectomy or axillary node clearance,[6 7] respectively. Reducing the extent of surgery can improve outcomes for patients by reducing complications and improving quality of life and psychological well-being.[8 9]

Despite these potential benefits, many patients who respond well to neoSACT are currently not offered response-adjusted surgery after neoSACT, even if they achieve a complete pathological response.[6 7 10] Reasons for this are unclear and likely to be multifactorial. However, the inconsistent and often limited reporting of locoregional therapies in neoSACT trials makes the interpretation of surgical downstaging challenging and may prevent the effective translation of downstaging benefits into practice. Furthermore, inadequate reporting of surgery and radiotherapy following neoSACT prevents meaningful interpretation of key oncological outcomes, in particular locoregional recurrence (LRR). This was highlighted in a recent Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis, which reported higher rates of LRR in patients receiving neoSACT compared with those having adjuvant SACT following surgery. The authors, however, concluded that the lack of robust consistent reporting of locoregional treatments within the included neoSACT trials hampered the interpretation of the results.[11]

There is, therefore, an urgent need to improve reporting of locoregional therapies in neoSACT trials not only to support more informed surgical decision-making following the completion of neoadjuvant treatment but also to allow meaningful interpretation of LRR in these studies. Previous attempts to standardise outcome reporting in neoSACT studies have not specifically focused on locoregional treatment.[12 13] Furthermore, as they were largely based on expert opinion, they have not to date been widely adopted. An international consensus-based approach with the engagement of the global breast cancer community is therefore needed, and the development of a core outcome set (COS), 'an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials'[14] for locoregional treatment following neoSACT using these methods is likely to be a more effective strategy.

Aim

The overall aim of the imProving REporting of loCoregional therapies in nEoaDjuvant brEast caNcer Trials (PRECEDENT) project is to develop a COS and reporting guidelines for locoregional treatments in neoSACT trials to improve the quality and value of future research in this area.

METHODS AND ANALYSIS

Overview

The COS will be developed according to the *Core Outcome Measures in Effectiveness Trials (COMET) Handbook*[15] and the Core Outcome Set-STAndards for Development guidelines,[16] with input from an international steering group of key stakeholders nominated by the Breast International Group (BIG) and the North American National Cancer Institute National Clinical Trials Network (NCI-NCTN) (BIG-NCTN). Reporting guidelines will be developed concurrently. The project has been prospectively registered on the COMET website (https://www.comet-initiative.org/Studies/Details/2854).

The PRECEDENT project will have three phases:

1. Generation of a comprehensive list of possible outcomes/reporting items.
2. Prioritisation of identified items using an international online Delphi survey of stakeholders.
3. An international stakeholder consensus meeting to agree and ratify the final COS and reporting guidelines.

Scope of the guidance and COS

The reporting guidance and COS will support standardised locoregional treatment outcome reporting in neoSACT studies. The COS will be developed specifically for use in the context of neoSACT effectiveness trials, but it will be applicable to any research and audit setting where the outcomes of neoadjuvant systematic anticancer therapy are being evaluated.

The reporting guidance will be developed using established methodologies,[17] which will include the involvement of an expert international multidisciplinary steering group comprising breast cancer surgeons, oncologists, pathologists, radiologists, trialists, methodologists and patients; Delphi consensus methods and a face-to-face meeting to agree and ratify the proposed guidelines. Guideline development will be registered on the EQUATOR network website to promote visibility and optimise implementation.

Definition of neoSACT

neoSACT will be defined as any systemic therapy given with curative intent prior to breast cancer surgery. It will include but not be limited to cytotoxic chemotherapies, targeted agents such anti-HER2 therapies, immune checkpoint inhibitors and endocrine therapy. Neoadjuvant radiotherapy will not be included as this is considered a locoregional rather than systemic treatment.

Definition of locoregional treatments and outcomes

Locoregional treatments will be defined as surgery and radiotherapy only to the breast and/or regional nodal

areas. A key aim of developing the COS and reporting guidelines is to allow standardised reporting and therefore improved interpretation of oncological outcomes, specifically LRR, in future studies. Locoregional treatment outcomes and accompanying reporting guidelines will therefore include factors that may impact the interpretation of LRR, including how locoregional treatments are selected and planned (eg, using clinical assessment and/or imaging post neoSACT, radiotherapy treatment planning and delivery methods such as 3D conformal, intensity modulated radiation therapy, volumetric modulated arc therapy or protons); specific details of the treatments themselves and their timing (eg, type of breast and axillary surgery performed, radiotherapy target volumes, dose and fractionation) and more traditional outcomes such as completeness of excision following breast-conserving surgery.

Stakeholder involvement

This is an international project delivered in conjunction with the BIG and the NCI-NCTN (BIG-NCTN collaborative group). This international collaborative approach will promote the engagement of the breast cancer research community worldwide, ensure that the COS/reporting guidelines are broadly applicable to all healthcare settings and can be widely adopted and implemented within future trials. Our stakeholder group will include representatives from all geographical areas with expertise in managing patients receiving neoSACT and conducting neoSACT trials. This will include surgeons, oncologists, radiation oncologists, radiologists, pathologists, trialists and methodologists with international patient and public involvement through the BIG-NCTN network and patient advocacy groups worldwide. A study steering group with international multidisciplinary representation will be convened to provide overall oversight of the project.

Patient and public involvement and engagement

Patient advocates with global representation will be recruited via the BIG-NCTN network and patient advocacy groups. Patient advocates will sit on the study steering group and provide the patient perspective on all aspects of the study to ensure it retains a patient focus.

As the project aims to produce a COS and reporting guidelines focusing on technical aspects of breast cancer surgery and radiotherapy, the involvement of patients in the Delphi survey would not be appropriate. However, the shortlist of outcomes generated from the Delphi to be discussed at the consensus meeting will be reviewed by a wider group of patients from the BIG-NCTN network and patient advocacy groups. The views of this wider patient advisory group will be presented at the consensus meeting which will also have patient/public representation. This will ensure the project remains patient focused and includes outcomes that patients feel are important.

Phase 1: generation of a comprehensive list of reporting items and outcomes domains

Standard methods[15] will be used to identify potential outcomes for inclusion in the long list for the COS and reporting guidelines.

Systematic review

The review was prospectively registered on the PROSPERO International Prospective Register of Systematic Reviews (CRD42023470891) on 10 October 2023.

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023470891.

Search strategy and data sources

A comprehensive literature search will be undertaken in PUBMED using a search strategy adapted from an existing meta-analysis[18] to identify all primary research studies published in full reporting the outcomes of patients with breast cancer undergoing neoSACT followed by locoregional therapy with surgery and/or radiotherapy with curative intent. The full search strategy is summarised in online supplemental appendix 1. The search will be limited to human studies, published in English between 1 January 2018 and 8 September 2023 to focus the review on current outcome reporting and reflect the date of publication of the EBCTCG meta-analysis[9] that highlighted the need for this work.

Inclusion and exclusion criteria

All randomised controlled trials and large cohort studies including >250 participants, published in full, in English, reporting at least one outcome specifically relating to locoregional therapy (surgery and/or radiotherapy) will be eligible for inclusion. Excluded will be cohorts including <250 participants as these are unlikely to impact clinical practice; non-breast cancer studies; studies including metastatic or locally advanced/unresectable breast cancer; those evaluating chemotherapy given for non-curative (palliative) intent, and those not reporting at least one locoregional outcome in patients receiving neoSACT. Also, excluded will be abstracts and conference proceedings due to difficulties interpreting incomplete information, editorials, opinion pieces, reviews and letters. Snowball searching of reference lists of reviews and relevant papers will be used to identify any additional potentially relevant publications.

Abstracts will be imported into EndNote reference management software and screened for inclusion using prespecified inclusion criteria (table 1). Where uncertainty exists, the full text will be obtained for review. Any continued uncertainties will be resolved by discussion with the wider review team.

Data extraction

Data will be extracted using a data collection proforma iteratively developed and refined in Microsoft Excel by the review team. Approximately 25% of studies will be double data extracted to ensure consistency and methodological rigour. Data extracted will include study details,

Table 1 Inclusion and exclusion criteria for the systematic review

Inclusion criteria	Exclusion criteria
► All randomised controlled trials and cohort studies with >250 participants ► Including patients with breast cancer receiving neoadjuvant systematic anticancer therapy of any regimen/modality followed by loco-regional therapy (surgery and/or radiotherapy) ► Published in English between 1 January 2018 and 8 September 2023 ► Reporting at least one locoregional outcome relating to surgery and/or radiotherapy	► Not primary research studies ► Studies published prior to 1 January 2018 ► Studies including any neoplasm other than breast cancer ► Studies including metastatic or locally advanced/unresectable breast cancer or evaluating palliative chemotherapy ► Cohort studies with <250 patients ► Studies not published in English ► Studies not reporting at least one locoregional outcome

specifically author and year of publication, study design, geographical location of study, number of participants and type of neoSACT used. Any locoregional outcomes together with any definitions of the outcome reported in each study will be extracted verbatim. Uncertainties will be discussed and resolved by discussion with the wider review team.

Analysis

Outcomes will be reviewed and categorised using a content analysis approach.[19] The final list of outcomes and definitions will be reviewed and discussed with the project Steering Group prior to undertaking the qualitative interviews. This will ensure the proposed terminology is appropriate and comprehensible to a broad group of international stakeholders and allow any additional outcomes that may not have been identified from the review to be highlighted so that these can be further explored.

Interviews with key stakeholders

Semi-structured qualitative interviews with key stakeholders (surgeons, oncologists, radiologists, pathologists, trialists and patient advocates) will be used to review the outcomes generated from the literature and any identified definitions. This will ensure the list of outcomes is comprehensive and allow stakeholders to provide feedback on the way the outcomes are described prior to the Delphi survey. Stakeholders will be identified by the Steering Group, and interviews will be conducted, either online or in person by the study team. Participants will be sent the list of outcomes from the systematic review by e-mail so they can be reviewed prior to the interview.

Targeted content analysis will be used to identify and summarise any additional outcomes and views regarding definitions and proposed terminology for the Delphi survey. No outcomes identified by the systematic review will be removed at this stage, although outcomes may be merged if appropriate following interviews. Interviews will be conducted until no new outcomes are identified and saturation has been achieved.

The findings from the systematic review and interviews will be combined to create a final long list for inclusion in the Delphi survey (Phase 2).

Phase 2: prioritisation of outcomes and reporting items using an international multi-stakeholder Delphi survey

A consensus process comprising two sequential rounds of an online international multi-stakeholder Delphi survey followed by a face-to-face consensus meeting will be used to prioritise the long list of outcomes and agree the final COS and reporting guidelines. The Delphi process will allow diverse stakeholders from a broad geographic area to participate anonymously, avoiding the impact of any dominant groups or individuals.[15]

Development of the Delphi survey questionnaire

Each outcome and reporting item from the long list described above will be operationalised and formatted into a survey item. Each item will be scored on a Likert scale ranging from 1 (not essential) to 9 (extremely important) based on the Grading of Recommendations Assessment, Development and Evaluation scale for including items in the final COS and reporting guidelines.[20] The questionnaire will be reviewed by the international steering group prior to survey launch. Surgeon and radiation/clinical oncologist steering group members will provide specialist review of the proposed terminology for the surgical and radiotherapy items. All steering group members will ensure the language used is appropriate and comprehensible to participants from broad geographical regions and clinical specialities. The draft survey will be piloted with a small number of professionals (surgeons and oncologists) from various geographical regions (eg, UK, Europe, Asia, North and South America) to ensure face validity prior to survey launch.

Participant sampling and invitations

Representatives from all broad stakeholder groups will be invited to participate. The steering group will identify relevant international professional associations (eg, surgical and oncological bodies) across all geographical regions and contacts within each of these groups. Each group will be contacted and asked to circulate the invitation to their membership. Steering group members with links to specific international professional associations will be responsible for liaising with their groups and promoting the Delphi to their professional networks. This inclusive international multidisciplinary approach

using existing professional networks in conjunction with BIG-NCTN project endorsement will optimise engagement and participation. The project will also be widely promoted to professionals through appropriate social media channels.

Delphi survey rounds

Participants will complete two sequential questionnaire rounds over a 6-month period. In both rounds, each participant will be asked to rate the importance of including each item in the COS and reporting guidelines on a 9-point Likert scale from 1 (not essential) to 9 (extremely important). All survey questionnaires will be administered using online software to optimise international participation.

All participants who complete round 1 of the survey will be sent the round two questionnaire. The round two survey will include all items from round 1 (see below) together with anonymised feedback in the form of summary scores (eg, medians or means) for the respondents overall and by professional subgroup (eg, surgeons, oncologists, radiation oncologists, etc). Respondents will then be asked to re-prioritise items in light of the feedback received. This method has been shown to improve the degree of consensus achieved.[15 21]

Items retained after the round 2 Delphi survey will be carried forward for discussion at the consensus meeting.

Attrition between rounds

Participant attrition between rounds will be monitored and differences in scores between those who do and do not complete all survey rounds explored.

Phase 3: international consensus meeting of key stakeholders to discuss and agree the final reporting guidelines and COS

A face-to-face international consensus meeting attended by key stakeholders and facilitated by an independent chair with global representation and patient advocates will be held to discuss and agree the final COS and reporting guidelines.

A purposive sample of between 20 and 25 professionals who completed at least one round of the Delphi survey will be invited to participate in the consensus meeting together with four to five experienced patient advocates from the BIG-NCTN and/or other patient advocacy groups. Sampling will be based on professional expertise and geographical representation to ensure that consensus meeting participants are broadly representative of the global breast cancer research community.

The consensus meeting will include a presentation of the survey results with input from patient advocates to ensure the patient's voice is heard. Participants will be asked to ratify the items scored 'consensus in' and 'consensus out' from the Delphi survey and to anonymously rescore items for which consensus was not reached in the Delphi survey. Facilitated rounds of discussion and re-voting will take place until consensus is achieved.

Sample size

There is no standard sample size for consensus processes so the aim will be to ensure good representation from key stakeholders across all geographical regions and all relevant professional groups. It is anticipated that 250–300 professionals will be involved in the Delphi survey and 20–25 will participate in the consensus meeting.

Data analysis

Survey analysis and provision of feedback

Data will be captured and stored using online software and downloaded into statistical software for cleaning and analysis.

Respondent demographics for each round will be summarised using descriptive statistics and tabulated. Summary statistics will be calculated for each item and the proportion of participants scoring each item as 'not important' (score 1–3), 'equivocal' (score 4–6) and 'very important' (score 7–9) calculated. All items will be retained between rounds 1 and 2 so that respondents are able to re-prioritise each item based on the feedback received. Each stakeholder group will be analysed separately and feedback between rounds 1 and 2 provided for respondents overall and by professional group.

At the end of round 2, items will be categorised as 'consensus in', 'consensus out' or 'equivocal' as described in table 2. Items will be scored overall and by each respondent group separately so that all views are considered. This will ensure that no outcomes are excluded prematurely and that the outcomes of importance to the majority of participants are included in the final COS.[15]

Consensus meeting

After the first round of voting, items will be categorised as 'consensus in' or 'consensus out' based on the criteria outlined in table 2. Items voted 'consensus in' will be

Table 2 Definitions of consensus (following survey round 2)

Category	Score	Outcome
'Consensus in'	Scored as very important (7–9) by ≥70% and not important (1–3) by <15% of any stakeholder group (surgeons and/or oncologists)	Discussed/ratified at consensus meeting
'Consensus out'	Scored as not important (1–3) by ≥70% and very important (7–9) by <15% of any stakeholder group (surgeons and/or oncologists)	Discussed/ratified at consensus meeting
'No consensus'	None of the criteria above are met	Discussed and voted on at consensus meeting

included in the final COS/reporting guidelines; those voted 'consensus out' will be discarded. Further rounds of discussion and voting will take place for the items for which consensus is not reached. These will continue until consensus is achieved. A final vote will be used to ratify the COS and reporting guidelines.

Implementation of the COS and reporting guidelines

The COS and reporting guidelines will be developed in conjunction with the BIG-NCTN group with the involvement of the breast cancer research community globally through an international multidisciplinary steering group of trialists and opinion leaders, international professional associations and patient advocates. It is anticipated that this inclusive, global approach will promote widespread professional engagement, ensure that the COS/reporting guidelines are applicable across all settings and optimise future implementation into neoSACT trials. In addition, we will engage with regulators including the US Food and Drug Administration and the UK MHRA to highlight the need to embed robust locoregional outcome reporting in all future studies of drugs used in the neoadjuvant setting. The project will be registered on the EQUATOR website and we will work with breast cancer trialists worldwide through the PRECEDENT network to promote routine inclusion of the locoregional reporting COS in all future neoSACT studies. This will ensure standardised reporting of locoregional outcomes, facilitate data pooling for evaluation of long-term oncological outcomes and optimise the value of future studies for surgical decision-making.

ETHICS AND DISSEMINATION

Ethical approval for the project has been obtained from the Queen's University Belfast Faculty of Medicine, Health and Life Sciences Ethics committee (reference MHLS 23_167). Participation in the Delphi survey by professional participants will be taken as implied consent. Written consent will be obtained prior to the consensus meeting.

The COS/reporting guidelines will be presented at international meetings and published in peer-reviewed journals. Dissemination materials will be produced in collaboration with our steering group and patient advocates so the results can be shared widely.

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