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A core outcome set for locoregional treatment reporting in neoadjuvant systemic breast cancer treatment trials



Shelley Potter^{1,2,305}✉, Kerry Avery^{1,3,4}, Rosina Ahmed⁵, Jana de Boniface^{6,7}, Sanjoy Chatterjee⁵, David Dodwell⁸, Peter Dubsy^{9,10}, Jingjing Federmann¹¹, Sandra Finestone¹², Michael Gnant^{11,13}, Dominik Hlauschek¹¹, Hiroji Iwata¹⁴, Michael Y. Jiang¹, Orit Kaidar-Person¹⁵, Han-Byoel Lee¹⁶, Mairead MacKenzie¹⁷, Anne Meyn¹², Philip Poortmans¹⁸, Fiorita Poulakaki^{19,20}, Andrea L. Richardson²¹, Karla A. Sepulveda²², Andrew J. Spillane²³, Alastair M. Thompson²², Gustavo Werutsky²⁴, Philipp Wittmann¹¹, Jean L. Wright²⁵, Nicholas Zdenkowski²⁶, Katherine Cowan²⁷ & Stuart A. McIntosh^{28,305}
On behalf of the PRECEDENT Study Group*

Accurate information about locoregional breast cancer treatments following neoadjuvant systemic therapy (NST) is essential for meaningful interpretation of oncological outcomes but reporting is currently poor. We developed a core outcome set (COS) to improve the quality and consistency of locoregional outcome reporting in breast cancer NST trials. The COS was developed in three phases according to COS-STAD guidance, with the generation of a list of relevant outcome domains, prioritisation of outcomes through two rounds of an international online multi-stakeholder Delphi survey and a consensus meeting. 159 unique locoregional outcomes were classified into 101 outcome domains for inclusion in the Delphi survey, which was completed by 470 international professionals. The final 15-item COS, which included the pre-NST surgical plan, details of surgery performed following completion of treatment and details of radiation therapy, was agreed at an in-person consensus meeting. Widespread COS implementation will improve the quality and value of future NST trials.

Neoadjuvant (or primary) systemic therapy (NST) is increasingly used in the treatment of early breast cancer as it confers multiple potential benefits for patients¹. These include permitting downstaging of locoregional treatments such as surgery^{2,3} and radiation therapy

(RT)⁴ in those who have a good treatment response and allowing response-adapted tailoring of adjuvant systemic therapies^{5,6} with escalation or de-escalation of treatments to optimise both oncological outcomes and quality of life. As treatment response is also highly

¹Bristol Surgical and Perioperative Care Complex Intervention Collaboration; Bristol Medical School, Bristol, UK. ²Bristol Breast Care Centre, North Bristol NHS Trust, Bristol, UK. ³Centre for Surgical Research, Bristol Medical School, Bristol, UK. ⁴NIHR Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and University of Bristol, Bristol, UK. ⁵Tata Medical Centre, Kolkata, India. ⁶Breast Unit, Capio St. Göran's Hospital, Stockholm, Sweden. ⁷Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. ⁸University of Oxford, Oxford, UK. ⁹Hirsländan Klinik St Anna, Lucerne, Switzerland. ¹⁰University of Lucerne, Lucerne, Switzerland. ¹¹Austrian Breast & Colorectal Cancer Study Group, Vienna, Austria. ¹²Patient advocate, California, United States of America. ¹³Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria. ¹⁴Aichi Cancer Centre, Nagoya, Japan. ¹⁵Breast Radiation Unit, Sheba Medical Centre, Ramat Gan, Israel; School of Medicine, Faculty of Medical & Health Sciences, Tel-Aviv University, Tel-Aviv, Israel; GROW- Research Institute for Oncology and Reproduction, Maastricht University, Maastricht, Netherlands. ¹⁶Dept. of Surgery, Seoul National University College of Medicine; Cancer Research Institute, Seoul National University; Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea. ¹⁷Independent Cancer Patients' Voice, London, UK. ¹⁸Department of Radiation Oncology, Iridium Network, Wilrijk-Antwerp, Belgium; University of Antwerp, Faculty of Medicine and Health Sciences, Wilrijk-Antwerp, Belgium. ¹⁹Europa Donna - The European Breast Cancer Coalition, Milan, Italy. ²⁰Breast Surgery Department, Athens Medical Centre, Maroussi, Greece. ²¹John's Hopkins Medicine, Baltimore, USA. ²²Baylor College of Medicine, Houston, TX, USA. ²³University of Sydney, Sydney, Australia. ²⁴Latin American Cooperative Oncology Group, Porto Alegre, Brazil. ²⁵Department of Radiation Oncology at the University of North Carolina School of Medicine, Chapel Hill, NC, USA. ²⁶University of Newcastle, Newcastle, Australia. ²⁷Katherine Cowan Consulting, Thame, UK. ²⁸Patrick G Johnson Centre for Cancer Research, Queen's University Belfast, Belfast, UK. ³⁰⁵These authors contributed equally: Shelley Potter, Stuart A. McIntosh. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: shelley.potter@bristol.ac.uk



prognostic on an individual level^{7,8}, NST has become the standard of care for specific disease subtypes^{9–11}.

Locoregional therapies, however, remain an integral component of the effective management of early breast cancer and accurate information about the surgery and RT performed following completion of NST is essential for the meaningful interpretation of trial results. The quality and consistency of locoregional treatment reporting in NST trials, however, is poor and needs to be improved^{12,13}. This was first highlighted in 2018 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of the outcomes of neoadjuvant and adjuvant chemotherapy, which included ten trials involving 5,250 women and suggested a higher rate of locoregional recurrence (LRR) in patients receiving NST¹². This difference in LRR did not translate into significant differences in either distant recurrence or overall survival between the groups and the authors commented that the poor quality of locoregional treatment reporting in the included trials precluded meaningful interpretation of the results¹². While it could be argued that the trials included in the EBCTCG meta-analysis were largely historic and reporting will have improved over time, a recent systematic review of contemporary NST studies suggests that locoregional treatment reporting remains heterogenous and inconsistent¹³. This review which included 137 NST trials involving 575,531 women published between 2018 and 2023 showed that most studies continued to report minimal, if any information regarding the surgery and RT performed¹³. Not only does this hamper accurate interpretation of key oncological outcomes such as LRR, it may also explain the consistent failure to translate breast cancer downstaging into a reduction in the extent of surgery in both trials and real-world cohorts, where significant proportions of patients continue to undergo mastectomy despite achieving a complete pathological response (pCR)^{2,3,14}.

One solution to addressing poor and inconsistent outcome reporting in NST trials may be to develop and implement a core outcome set (COS), *'an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials'*¹⁵. For this approach to be successful, however, it is vital that the international breast cancer research community is engaged in the development of a COS and committed to future implementation. The aim of the PRECEDENT (imProving REporting of loCoregional therapies in nEoaDjuvant brEast caNcer Trials) project was therefore to work with key international stakeholders to develop a COS for locoregional treatment measurement and reporting in NST trials.

Results

Phase 1: Generation of a list of outcome domains

A total of 747 locoregional outcomes (510 surgical and 237 RT related) identified from the systematic review¹³ were categorised into 68 surgical and 28 RT outcome domains. Focused discussion with key stakeholders identified one additional surgical and four additional RT outcome domains for inclusion. Following discussion and iterative refinement by the steering group, a total of 101 outcome domains (69 surgical and 32 RT related) were carried forward for survey prioritisation.

Phase 2: Outcome domain prioritisation

The 101 outcome domains grouped thematically into nine surgery and four RT sections and formatted into 101 questionnaire items for inclusion in the international Delphi survey.

A total of 470 healthcare professionals prioritised at least one COS item in Round 1 and there was good multidisciplinary representation from the surgical ($n = 206$, 43.8%), medical ($n = 144$, 30.6%) and radiation ($n = 98$, 20.8%) oncology communities (Table 1). Respondents were predominantly from Europe ($n = 274$, 58.3%) but there was broad geographical representation reflecting good international engagement with the survey. Most participants were research active ($n = 437$, 93.0%), experienced clinicians (>10 years at consultant/attending level $n = 307$, 65.3%) working in Academic/University/Teaching hospital settings ($n = 338$, 71.9%) and over half ($n = 248$, 55.8%) identified as female.

Table 1 | Demographics of Delphi participants

	Round 1 (N = 470)	Round 2 (N = 336)
Role^a		
Surgeon ^a	206 (43.8)	153 (45.5)
Medical Oncologist	144 (30.6)	90 (26.8)
Radiation Oncologist ^c	98 (20.8)	77 (22.9)
Other ^d	22 (4.7)	16 (4.8)
Age		
<30	5 (1.1)	4 (1.2)
30–39	96 (20.4)	69 (20.5)
40–49	158 (33.6)	118 (35.1)
50–59	146 (31.1)	99 (29.5)
60 or over	56 (11.9)	39 (11.6)
Prefer not to say/not reported	9 (1.9)	7 (2.1)
Geographical location of practice		
Europe	274 (58.3)	209 (62.2)
Asia	60 (12.8)	45 (13.4)
North America	46 (9.8)	30 (8.9)
South America	38 (8.1)	19 (5.7)
Australia/New Zealand	32 (6.8)	20 (6.0)
Middle East	14 (3.0)	9 (2.7)
Africa	6 (1.3)	4 (1.2)
Gender		
Female	248 (55.8)	173 (51.5)
Male	213 (45.2)	155 (46.1)
Prefer not to say/not reported	9 (1.9)	8 (2.4)
Years of experience at Consultant/Attending level		
< 5 years	64 (13.6)	47 (14.0)
5–10 years	94 (20.0)	69 (20.5)
>10 years	307 (65.3)	216 (64.3)
Prefer not to say/ not reported	5 (1.1)	4 (1.2)
Main type of practice		
Academic/University/Teaching	338 (71.9)	246 (73.2)
Hospital	58 (12.3)	38 (11.3)
Public Hospital	56 (11.9)	40 (11.9)
Private Hospital	18 (3.8)	12 (3.6)
Other		
Research active^e		
	437 (93.0)	316 (94.1)

^aIf more than one role stated, respondents were classified according to involvement in locoregional breast cancer treatments.

^b13 surgeons also prescribed chemotherapy.

^cIncludes 1 Consultant Therapeutic Radiographer (RTT) and 18 respondents who prescribed chemotherapy and gave radiation therapy.

^dRadiologist $n = 4$; pathologist $n = 2$; non-clinical role $n = 6$, not stated = 3.

^eDefined broadly as designing, leading or recruiting to clinical trials or other research studies.

A total of 336 (71.5%) Round 1 participants (153/206 (74.3%) surgeons, 90/144 (62.5%) medical oncologists and 77/98 (78.6%) radiation oncologists) prioritised at least one COS item in Round 2. Respondent demographics were similar between rounds (Table 1).

Scores for each outcome domain following Round 2 are summarised by stakeholder group in Supplementary Table 1. Applying the revised definitions of consensus (Table 2), 31 outcome domains were scored 'consensus in' (scored 'very important' by $\geq 70\%$ surgeons and/or radiation oncologists and/or other professionals). These were reviewed and, where thematically relevant, combined into 15 summary outcome domains that were carried forward for review and ratification at the consensus meeting (Supplementary Table 2). Ten outcome domains were scored as 'no consensus' (scored very important by 60–70% of surgeons and/or radiation oncologists) so were carried forward for discussion and voting at the meeting. The remaining 60 outcome domains were scored 'consensus out' (scored 'very important' (7–9) by <60% surgeons and/or radiation oncologists) and were carried forward to the consensus meeting to ratify their exclusion (Supplementary Table 1).

Table 2 | Definitions of consensus

Category	Original (Rounds 1 and 2)		Revised (Round 2 only)		Consensus Meeting	
	Definition	Action	Definition	Action	Definition	Outcome
'Consensus in'	Scored as very important (7–9) by $\geq 70\%$ and not important (1–3) by $< 15\%$ of any stakeholder group (surgeons and/or radiation oncologists and/or others)	Domain retained for next survey round/consensus meeting	Scored as very important (7–9) by $\geq 70\%$ of any stakeholder group (surgeons and/or radiation oncologists and/or others)	Domain reviewed and thematically similar outcomes merged into broader summary outcomes for review/ratification at consensus meeting	Scored as 'very important' by $\geq 70\%$ meeting participants ^a	Summary domain included in final COS following ratification*
'Consensus out'	Scored as not important (1–3) by $\geq 70\%$ and very important (7–9) by $< 15\%$ any stakeholder group (surgeons and/or radiation oncologists and/or others)	Domain discarded after Round 2 (to be ratified at consensus meeting)	Scored as very important by $< 60\%$ of locoregional therapists (surgeons and/or radiation oncologists)	Same as original	Scored as 'very important' by $< 70\%$ of meeting participants	Domain not included in final COS, following ratification
'No consensus'	None of the criteria above are met	Domain retained for next survey round/consensus meeting	Neither of the above criteria are met	Same as original	Same as Round 2	Included in final COS if voted 'very important' by $\geq 70\%$ meeting participants ^{**} Not included in final COS if voted 'very important' by $< 70\%$ meeting participants, following ratification

*either as originally worded for revised/merged with another domain(s), **may be included as separate outcome domain or merged with another summary domain.

^aFor ratification agreement was required from $\geq 70\%$ meeting participants.

Phase 3: Consensus meeting. Twenty-three experienced professionals including seven surgeons, 13 radiation oncologists, two medical oncologists, a radiologist and five patient advocates with broad international representation (Europe $n = 18$, North America $n = 4$; Middle East 2, Asia $n = 3$; Australia $n = 1$) attended the in-person consensus meeting. Following discussion, participants agreed to include the 15 'consensus in' summary outcome domains in the final COS but proposed that the 'side effects of RT' domain was amended to reflect the morbidity associated with locoregional treatments (surgery and RT) more broadly. Minor revisions of outcome domain wording were discussed and ratified. Following discussions and voting, none of the 10 'no consensus' items met the threshold for inclusion ($\geq 70\%$ meeting participants scoring outcome 'very important') in the COS so these and the 60 'consensus out' items were excluded. The final revised 15-item COS for locoregional outcome reporting in NST studies was agreed and ratified (Table 3).

Discussion

This robust international consensus process has developed a core outcome set for locoregional outcome reporting in breast cancer neoadjuvant systemic therapy trials. It includes 15 outcomes that all key stakeholders think are essential to measure and report as a minimum in all future NST studies. Surgical outcomes include the type of breast and axillary surgery performed; how response to NST is assessed; the adequacy of surgery performed, the proportion of patients who had their breast or axillary surgery downstaged and how many avoided surgery due to an exceptional treatment response. Radiation therapy outcomes included receipt of RT and details of target volumes, dose and fractionation. Short and long-term locoregional treatment morbidity (as defined in the protocol) was also a key outcome. Reporting this essential information regarding locoregional therapy in NST trials will improve their quality and value, ensure that results can be translated into practice and important oncological outcomes such as locoregional recurrence can be interpreted with confidence.

Previous attempts have been made to standardise outcome reporting^{16,17}, but these have not been widely implemented into practice. One reason for this may be that these recommendations were developed based on expert opinion without engagement of the wider breast cancer community. The PRECEDENT COS has specifically been developed in collaboration with key professional stakeholders and experienced patient advocates involved in breast cancer trials worldwide using established methods for consensus to promote engagement and future implementation of the COS from the start¹⁸. The COS developed using this collaborative, inclusive and methodologically robust approach, therefore includes outcomes that are meaningful to the international breast cancer community, who should then feel empowered to promote the uptake and implementation of the COS in future NST studies.

Complexity may also represent a barrier to implementation. Several international groups have robustly developed detailed recommendations for locoregional therapy reporting¹⁹, but collecting significant amounts of additional data is time consuming and expensive. This is a specific concern in the NST setting where many trials are designed and funded by the pharmaceutical industry to meet regulatory requirements, often without the involvement of surgeons or radiation oncologists to emphasise the importance and relevance of reporting locoregional treatments. A COS is, by definition, an essential set of outcomes that are important to all key stakeholders that should be reported as a *minimum* in all future NST trials. This minimalistic approach to locoregional outcome selection may represent a more acceptable strategy to improving outcome reporting in NST trials but engagement with funders, trialists and regulators including the US Food and Drug Administration and the UK Medicines and Healthcare products Regulatory Agency will be essential to ensure robust locoregional outcome reporting in all future studies of drugs used in the neoadjuvant setting.

It is also important to consider how the purpose of this COS differs from other breast cancer metrics, such as quality indicators (QIs)²⁰. Core outcome sets aim to improve the quality and consistency of outcome reporting in trials, facilitate data synthesis and reduce research waste²¹. They

Table 3 | Final core outcome set for locoregional treatment outcome reporting in breast cancer neoadjuvant systemic therapy trials

No	Core outcome set domain
1	The type of breast and axillary surgery planned before starting NST
2	<i>The proportion of patients who did not have surgery after NST due to disease progression, treatment toxicities or other comorbidities</i>
3	The number/proportion of patients with a complete response to NST not having surgery to the breast and/or axilla, and how response was assessed
4	How response to NST in the breast and axilla was assessed
5	Type of initial breast and axillary surgery performed after NST
6	<i>Proportion of patients with involved margins after initial and final surgery, and number of procedures required (and recorded definition of clear margins at trial level^a)</i>
7	Total number of excised and involved axillary lymph nodes, with extent of involvement
8	Further axillary treatment in patients with ypN+ disease after sentinel node biopsy/targeted axillary dissection (SLNB/TAD)
9	Proportion of patients in whom breast and/or axillary surgery was downstaged
10	The proportion of patients having radiation therapy
11	Indications for radiation therapy at trial level ^a (recorded in protocol and reported)
12	Details of breast/chest wall and nodal targets
13	Details of dose and fractionation to breast/chest wall and nodal areas
14	Receipt of boost; indications for boost (at trial level ^a)
15	<i>Morbidity of locoregional treatments (short and long term as defined in protocol)</i>

Denotes revised wording agreed and ratified at consensus meeting; NST neoadjuvant systemic therapy; ^ashould be described/recorded a priori in the trial protocol.

represent a *minimum* reporting standard in clinical trials; they do not restrict the number of outcomes that can be measured or imply that other outcomes are not important. Quality indicators (QIs), by contrast, are used to monitor the quality of clinical care in routine practice. Unlike core outcome sets, which are limited to a small number of essential outcomes that must be reported¹⁸, there is no restriction on the number of QIs that may be proposed, as these should, by definition, cover all aspects of the treatment pathway. This difference in function explains why the COS and published QIs differ. Outcomes such as ‘time from completion of NST to surgery’ for example are not considered essential to include in the COS for locoregional outcome reporting in NST trials, but are a key quality indicator²⁰ as delays in surgery adversely impact oncological outcomes²². By contrast, the proportion of patients with an exceptional response post NST who are able to omit or avoid surgery is a core outcome that should be reported in all NST trials but is not currently considered a quality indicator used to measure the quality of the care received.

This work has limitations that should be considered. Firstly, given the complexity of the topic, the consensus process was undertaken in English. This may have limited the participation to individuals with high levels of English proficiency. However, the key stakeholders for this COS were experienced breast cancer trialists. English is the primary language for scientific communication so restricting the process to English would be unlikely to significantly impact the results.

A robust international engagement strategy was embedded in the project a priori to optimise future implementation. Central to this strategy was a partnership with the BIG-NCTN network and the recruitment of multidisciplinary representatives of the major international breast cancer research groups to the steering group to provide access to global speciality networks. This strategy was partially successful, with excellent engagement with professionals from Europe and good international participation overall. There were, however, notably fewer Delphi participants from North

America (<10%) with less than two thirds of these individuals participating in both survey rounds. Reasons for this are unclear but there was excellent international representation at the consensus meeting to ensure the final COS was acceptable in different healthcare settings. Similarly, despite strong steering group representation from the radiation oncology community, proportionally fewer radiation oncologists participated in the Delphi. This group, however, were the most likely to complete both survey rounds and were well represented at the consensus meeting, providing confidence that the RT outcomes included in the COS were the most important to radiation oncologists more broadly.

Finally, although patients did not participate in the Delphi, every effort was made to ensure that both the project and the final COS were patient-focused. This was achieved from the start, with experienced patient advocate members of the steering group actively participating in discussions about the project and helping to shape the Delphi survey. Strong international patient representation at the consensus meeting ensured the patient perspective was central to discussions. The final COS, therefore, included outcomes that were equally important to patients as well as professionals.

For the newly developed COS to improve the quality and consistency of locoregional outcome reporting in breast cancer NST trials, however, it will need to be accepted and effectively implemented into practice. To facilitate this process, the PRECEDENT group have worked with experienced trialists and data managers from the Austrian Breast and Colorectal Cancer Study Group to operationalise the 15-item COS into an easy-to-use, practical case report form (CRF) that can be embedded in all future NST trials (Supplementary Materials 3). The CRF is available in several electronic formats that can be uploaded into trial databases, minimising the effort required to include the COS in a trial dataset. The CRF includes clear, well-defined outcomes that will allow all trialists to consistently collect the same, minimum locoregional treatment dataset across all future NST studies; promote standardised implementation of the COS in future trials and facilitate data pooling and future meta-analysis. It may also enable streamlined data collection using artificial intelligence-driven real-world datasets as research methods continue to evolve^{23,24}. Work is now needed to engage funders, study sponsors and regulatory agencies worldwide in the need to mandate inclusion of the locoregional reporting COS in all future NST studies, improving their quality and value to patients, trialists and the international breast cancer community as part of our ongoing efforts to improve care.

Methods

The COS was developed using international consensus methods in accordance with Core Outcome Measures in Effectiveness Trials (COMET)¹⁸ and Core Outcome Set-STAndards for Development (COS-STAD) guidelines²⁵. The full protocol including key definitions of ‘locoregional therapy’ and ‘NST’ has been published previously²⁶ and the study prospectively registered on the COMET website (<https://www.comet-initiative.org/Studies/Details/2854>).

The PRECEDENT project comprised three phases: 1) Generation of a list of outcomes from the literature and interviews with key stakeholders; 2) Outcome prioritisation in an international Delphi survey; 3) A consensus meeting to agree the final COS (Fig. 1).

Stakeholder, patient and public engagement

This project was developed and delivered in conjunction with the Breast International Group (BIG) and the North American National Cancer Institute National Clinical Trials Network (NCI-NCTN) (BIG-NCTN collaborative group). A collaborative approach was chosen to promote engagement with the international breast cancer research community, to ensure the future COS would be broadly applicable across all healthcare settings and to optimise future adoption and implementation. An expert steering group, including representatives from the major breast cancer research networks across the world and patient advocates, was convened to provide overall oversight of the project. The steering group comprised 23 key stakeholders with expertise in breast cancer NST trials including patients, surgeons, medical and radiation oncologists, radiologists,

Fig. 1 | PRECEDENT COS development process.



pathologists, trialists and methodologists. Patient advocates advised on all aspects of the project and attended the consensus meeting to ensure the final COS included outcomes that were relevant and meaningful to patients.

Phase I: Generation of a list of outcomes

A systematic review of primary NST studies published between 2018 and 2023 was used to identify locoregional outcome domains for inclusion in the Delphi survey¹³. Outcomes were defined broadly and included traditional outcomes such as complications following surgery, as well as additional factors which would influence the interpretation of locoregional recurrence, such as the adequacy of surgical resection or target volumes irradiated. All outcomes were extracted verbatim by two reviewers, with discrepancies resolved by discussion. The long list was then categorised into outcome domains by the study team (MJ/SP/SAMcI) and discussed with a purposively selected group of expert stakeholders (surgeons and radiation oncologists) to review the comprehensiveness of the list and identify additionally relevant domains in a series of brief focused interviews. The final long list of outcome domains was reviewed and refined by the steering group prior to outcome prioritisation.

Phase II: Outcome domain prioritisation

Sequential rounds of an international multistakeholder Delphi survey were used to prioritise the outcome domains for inclusion in the COS.

Outcome domains were operationalized into survey questionnaire items for inclusion in the Delphi survey. Questions were written in English and reviewed by the international steering group to ensure the terminology used was appropriate and comprehensible to participants from different geographical regions. The survey was piloted with a small group of surgeons and radiation oncologists who were not involved in the project to ensure face validity prior to launch.

Respondents were asked how important it would be to include each outcome domain in a COS on a nine point Likert scale ranging from 1 (not important) to 9 (extremely important) based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale for including items in the final COS²⁷.

Key stakeholders were professionals involved in breast cancer NST trials worldwide. This included surgeons, radiation and medical oncologists, radiologists and methodologists. Steering group members circulated the Round 1 survey widely through their professional networks, breast cancer groups and social media to promote participation and international engagement.

Following extensive discussion with the steering group, including patient advocates, it was agreed that patients would not be recruited to participate in the Delphi survey. This was due to the highly technical nature of the surgery and radiation oncology outcome domains. An alternative patient involvement strategy was devised. This included active patient

advocate involvement in survey development including review of the long list to ensure its comprehensiveness and patient participation in the consensus meeting to ensure the final COS maintained a patient focus. To enable their full participation in the consensus meeting, preparatory briefing meetings were held with attending patient advocates to answer questions and explain the processes/methods that would be involved.

Participants completed two sequential survey rounds. Round 1 was open between 03/28/24 and 06/13/2024 and Round 2 between 06/26/24 and 08/02/2024. The survey was administered online using REDCap²⁸ data capture software to facilitate international engagement and collaboration. Respondents were categorised into three key stakeholder groups: (i) surgeons, (ii) radiation oncologists and (iii) other professionals as the views of locoregional therapists were considered particularly relevant to consensus development. All Round 1 participants were invited to participate in Round 2. In Round 2, each survey item was accompanied by anonymised feedback about how that item was scored in Round 1, with the aim of promoting consensus across groups whose views may differ^{18,29,30}. The feedback included (i) the participant's own Round 1 score, (ii) a table summarising the median scores for each key stakeholder group and (iii) a histogram showing the distribution of scores by the stakeholder group. All items were retained between survey rounds, allowing participants to review their score and re-score each item, considering the feedback received. It was agreed a priori that a third survey round may be required if sufficient consensus was not achieved following Round 2.

Simple summary statistics were used to describe the participants' characteristics in each survey round.

Following Round 2, the proportion of participants in each key stakeholder group scoring each item as 'not important' (score 1–3); 'equivocal' (score 4–6) and 'very important' (score 7–9) was calculated and each item categorised as 'consensus in', 'consensus out' or 'no consensus'.

Consensus was defined a priori (Table 1). However, review of scoring across stakeholder groups between Round 1 and 2 demonstrated two potential issues; i) that survey respondents were reluctant to score outcomes as 'not important' (score 1–3) resulting in an unmanageable number of 'no consensus items' that would need to be discussed at the consensus meeting and ii) an impractical number of 'consensus in' items for inclusion in a future COS. Following discussion with the steering group, it was considered unlikely that a further survey round would result in any further prioritisation. It was therefore decided post hoc to revise the definition of 'consensus out' (Table 1). The definition of 'consensus in' was retained, but thematically similar items were merged to create a smaller number of broader 'summary' outcome domains for inclusion in the final COS. Both the original and proposed summary outcome domains were reviewed and revised by the steering group prior to the consensus meeting, where the outcomes were presented for review and ratification.

All data were analysed in STATA V18 (www.stata.com).

Participant attrition between rounds was monitored. Weekly automatic reminder e-mails were sent to Round 1 participants who had either not completed or only partially completed the Round 2 survey to optimise participation.

Phase III: Consensus meeting

The in-person consensus meeting was held in Barcelona, Spain on 14th September 2024. Professional participants were purposively selected from those individuals who had completed both survey rounds and expressed an interest in attending the meeting. Sampling was based on stakeholder group, gender and geographical location to ensure a broad representation of views. An international group of experienced patient advocates were also invited to attend to ensure the discussions were patient focused. The meeting was facilitated by an independent chair (KC) who encouraged all participants to openly express their views. All participants were sent a meeting pack prior to the event which included a summary of the process and details of the consensus meeting format together with lists of the i) summary ‘consensus in’ and ii) ‘consensus out’ items for review, and iii) ‘no consensus’ items for discussion and voting at the meeting.

At the consensus meeting, a summary of the Delphi survey results was presented together with the patient and professional perspectives on the importance of a COS for context. ‘Consensus in’ and ‘consensus out’ items were then presented and participants given the opportunity for brief discussion to consider any objections to these items being included or excluded. Participants were then asked to vote to ratify the inclusion of outcome domains classified as ‘consensus in’ and exclusion of items classified as ‘consensus out’. Next, the ‘no consensus’ outcome domains were discussed in smaller multidisciplinary breakout groups. Each group was asked to identify up to three ‘no consensus’ items for inclusion in the COS and to provide a supporting justification. Each breakout group reported back verbally to the main group and all participants then voted on whether each ‘no consensus’ outcome domain was ‘very important’, ‘equivocal’ or ‘not important’ to include in the final COS. Domains voted as ‘very important’ by ≥70% of participants were included, either as separate outcomes or, if considered more appropriate, combined with existing ‘consensus in’ domains. All other items were discarded. Voting was conducted anonymously using MentiMeter software (www.mentimeter.com). The consensus meeting concluded with review and ratification of the final COS by meeting participants.

Sample size

There is no standard sample size for consensus processes¹⁸ so the aim was to ensure good representation from key stakeholder groups across all geographical regions. A target sample size of 250–300 professionals for the survey and 20–25 participants for the consensus meeting was therefore agreed upon based on similar research^{31,32}.

Ethics

Ethical approval was obtained from the Queen’s University Belfast Faculty of Medicine, Health and Life Sciences Ethics committee (reference MHLS 23_167). Formal written consent was not obtained, as participation and attendance were taken as implied consent.

Data availability

All the data generated by this work has been included in the manuscript, tables and supplementary materials. No additional data are available.

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Author contributions

S.P. and S.A.M.c.I. conceived and initiated the study and secured funding. M.J., S.P. and S.A.M.c.I. led the systematic review; S.P., K.A., R.A., J.d.e.B., S.C., D.D., P.D., S.F., H.I., M.Y.J., O.K.P., H.B.L., M.M., P.P., F.P., A.L.R., K.A.S., A.J.S., A.M.T., G.W., J.L.W., N.Z., K.C. and S.A.M.c.I. were steering group members and contributed to study design and conduct. M.G., P.W., J.F. and D.H. developed the case report forms. S.P. undertook the data analysis and wrote the first draft of the manuscript. All authors critically revised the manuscript and have read and approved the manuscript prior to submission.

Competing interests

S.P. reports speaker honoraria from Astra Zeneca and BD.SMCI reports speaker honoraria from MSD, Roche, BD, Astra Zeneca, Veracyte and Exact Sciences; advisory boards for Lilly, Novartis, MSD, Roche and Astra Zeneca; conference travel and support from Roche, Lilly and MSD, and institutional research funding from Novartis. J.D.B. reports speaker honoraria from Astra Zeneca, Lily Oncology and Novartis.HI reports consulting fees from Daiichi Sankyo, Chugai, Astra Zeneca, Lilly, MSD, Pfizer and Gilead; honoraria from Daiichi Sankyo, Chugai, Astra Zeneca, Lilly, MSD, Pfizer, Taiho and Kyowa Kirin, and institutional research funding from Chugai, Daiichi Sankyo and Astra Zeneca. P.D. reports institutional research funding from Cepheid and Roche; consulting fees from Roche, and honoraria from Astra Zeneca and Oncoview, and conference and travel support from Roche.M. Gnant reports personal fees/travel support from Amgen, AstraZeneca, Bayer, DaiichiSankyo, EliLilly, EPG Health (IQVIA), Menarini-Stemline, MSD, Novartis, PierreFabre, Veracyte. H.-B.L. reports research funding from Devicor Medical Product Inc.; speaker honoraria and/or consulting fees from Alvogen, Boryung, Hologic, Intuitive, Lilly, Need, Novartis, Roche, Takeda, Celltrion Pharm, and Shin Poong Pharm; and being a co-founder and member of the DCGen Co., Ltd board of directors, AR reports consulting fees from Astra Zeneca and royalties from Myriad Genetics.GW reports consulting fees from Astra Zeneca, MSD, Novartis, Daiichi Sankyo and Roche; honoraria from Astra Zeneca, MSD, Novartis, Roche, Pfizer and Daiichi-Sankyo, and institutional research funding from Astra Zeneca/ Medimmune, Roche/Genentech, GlaxoSmithKline, Novartis, Pfizer, Roche, MSD, Merck, Bayer, Janssen, Astellas Pharma, Libbs and Takeda.NZ reports consulting fees from Lilly, Eisai, Astra Zeneca, MSD, Novartis and Gilead; honoraria from Roche, Pfizer, Eisai, Amgen, Gilead, Novartis, Lilly and Astra Zeneca, and conference travel and support from Novartis, Astra Zeneca and Lilly. AS reports speaker honoraria from Lilly and Limbic. The remaining authors have no conflicts of interest to declare.

Additional information

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Correspondence and requests for materials should be addressed to Shelley Potter.

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On behalf of the PRECEDENT Study Group

Nick Abbott²⁹, Roxolyana Abdah-Bortnyak³⁰, Khaled Abdelwahab³¹, Puteri Abdul Haris³², Stefan Aebi³³, Gaurav Agarwal³⁴, Cinta Albacar³⁵, Manuel Algara³⁶, Emmanouil Aligizakis²⁰, Raphael Garcia³⁷, Nikolay Amirov³⁸, Saika Amreen³⁹, Maria Belén Anca⁴⁰, Sofía Aragón⁴¹, Akif Enes Arian⁴², Cynthia Aristei⁴³, Farah Asif⁴⁴, Marianne Aznar⁴⁵, Selvamani Backianathan⁴⁶, Hiroko Bando⁴⁷, Maggie Banyas-Paluchowski⁴⁸, Vincent Barrette⁴⁹, Peter Barry⁵⁰, Carlotta Becherini⁵¹, Rossana Berardi⁵², Rinat Bernstein-Molho⁵³, Aniwat Berpan⁵⁴, Björn Beurer⁵⁵, Indrani Bhattacharya⁵⁶, Vesna Bjelic-Radic⁵⁷, Liesbeth Boersma⁵⁸, Eduard-Alexandru Bonci⁵⁹, Andrea Bonetti⁶⁰, Elaine Borg⁶¹, Tony Branson⁶², Ursa Brown-Glaberman⁶³, Eraldo Oreste Bucci⁶⁴, Coralía Bueno⁶⁵, Güney Cem Bülbüloğlu⁶⁶, Brian Burnette⁶⁷, Henry Cain⁶⁸, Beth Campbell⁶⁹, Alicia Cano-Jimenez⁷⁰, Alp Ömer-Cantürk⁷¹, Ana Car Peterko⁷², Amtl Carmichael⁷³, Cecilia Castillo⁷⁴, Nancy Chan⁷⁵, Samantha Chen⁷⁶, Matthew Kin Liang Chiu⁷⁷, Amit Choraria⁷⁸, Juncal Claros⁷⁹, John Collins⁸⁰, Veronica Conde-Herrero^{81,82}, Anastasia Constantinidou⁸³, Suzanne Coopey⁸⁴, Ellen Copson⁸⁵, Stefanie Corradini⁸⁶, Fabio Corsi⁸⁷, Paulo Cortes⁸⁸, Kyle Crawford⁸⁹, Elisabetta Cretella⁹⁰, Josefina Cruz⁹¹, Ramsey Cutress⁸⁵, Massimiliano Daiuto⁹², Iskra Daskalova⁹³, Mark Davies⁹⁴, Alex De Caluwé⁹⁵, Carolina De La Pinta⁹⁶, Sonia Del Barca Berron⁹⁷, Geoff P. Delaney⁹⁸, Sarah Deschuymer⁹⁹, Rosa Di Micco¹⁰⁰, Ana Aurora Diaz-Gavela¹⁰¹, Dobromir Dimitrov¹⁰², Lutfi Dogan¹⁰³, Véréne Dougoud-Chauvin¹⁰⁴, Stergios Douvetzemis¹⁰⁵, Dimitrios Dragoumis¹⁰⁶, Frances Duane^{107,108}, Florian Ebner¹⁰⁹, Jenny Edge¹¹⁰, Inês Eiriz¹¹¹, Elisabeth Elder¹¹², Constanze Elfgen¹¹³, Beatrix Elsberger¹¹⁴, Arantxa Eraso¹¹⁵, Serap Erel¹¹⁶, Tamar Esakia¹¹⁷, Martin Espinosa-Bravo¹¹⁸, Maria Del Pilar Estevez-Diz¹¹⁹, Veronica Yamila Fabiano⁴⁰, Waleed Fahmy¹²⁰, Alessandro Fancellu¹²¹, Isaura Fernandez¹²², Luis Fernández-Morales¹²³, Josefa Ferreira¹²⁴, Francesco Fiorica¹²⁵, José Fougo¹²⁶, Gianluca Franceschini¹²⁷, Hugo Fuentes¹²⁸, Niharika Garach¹²⁹, Maria Luisa Gasparri¹³⁰, Daniele Generali¹³¹, Matteo Ghilli¹³², Miguel Gil-Gil¹¹⁵, Henry Leonidas Gomez¹³³, Gustavo Gössling²⁴, Stephen Grobmyer¹³⁴, Christoph Großmann¹³⁵, Semra Gunay¹³⁶, Tal Hadar¹³⁷, Nawale Hajjaji¹³⁸, Nisha Hariharan¹³⁹, Grant Harris¹⁴⁰, Gemma Hegarty¹⁴¹, Martin Heidinger¹⁴², Tarek Hijal¹⁴³, Cary Hsu²², Thomas Hubbard¹⁴⁴, Farhanul Huda¹⁴⁵, Alessandra Huscher¹⁴⁶, Rabia Ikram¹⁴⁷, Jose Juan Illarramendi¹⁴⁸, Gareth Irwin⁸⁹, Reshma Jaggi¹⁴⁹, Melissa James¹⁵⁰, Guy Jerusalem¹⁵¹, Katarzyna Jerzak¹⁵², Carol Johnson¹⁵³, Nathalie Johnson¹⁵⁴, Kylie Jung¹⁵⁵, Ji-Jung Jung¹⁶, Vishvak Chanthar¹⁵⁶, Geeta Kadayaprath¹⁵⁷, Ayfer Kamali Polat¹⁵⁸, Taewoo Kang¹⁵⁹, Lohita Krishna Kanyadhara¹⁶⁰, Gülideniz Karadeniz Çakmak¹⁶¹, Andreas Karakatsanis¹⁶², Martin Karamanliev¹⁰², Mah Muneer Khan¹⁶³, Alba Kihn-Alarcón¹⁶⁴, Emma Kipps⁵⁰, Cliona Kirwan⁴⁵, Evelyn Klein¹⁶⁵, Hyun Soo Ko¹⁶⁶, Assia Konsoulova¹⁶⁷, Apostolos Konstantis¹⁶⁸, Michalis Kontos¹⁶⁹, Antigoni Kretsi¹⁷⁰, David Krug¹⁷¹, Ian Kunkler¹⁷², Siobhan Laws¹⁷³, Sara Leal¹⁷⁴, Jeeyeon Lee¹⁷⁵, Rhea Liang¹⁷⁶, Elisenda Llabres Valenti¹⁷⁷, Michelle Ludwig²², Diana Lüftner¹⁷⁸, Manjola Luzi¹⁷⁹, Melanie Machiels¹⁸⁰, Emma Macinnes¹⁸¹, Iain Macpherson¹⁸², Pedro Madeira¹⁸³, John Maduro¹⁸⁴, George Marios Makris²⁰, Pablo Mando¹⁸⁵, James Mansell¹⁸⁶, Willam Mantilla¹⁸⁷, Maja Maraldo¹⁸⁸, Yiola Marcou¹⁸⁹, Julie Margenthaler¹⁹⁰, Gustavo Marta¹⁹¹, Karyne Martel¹⁹², Covadonga Martí¹⁹³, Ana Isabel Martin-Quesada¹⁹⁴, Tamara Martos³⁶, Yazan Masannat¹⁹⁵, Valeria Masiello¹²⁷, Norikazu Masuda¹⁹⁶, Christine I. Mau¹⁹⁷, Shaurav Maulik⁵, Icro Meattini¹⁹⁸, Bruno Meduri¹⁹⁹, Tuomo Meretoja²⁰⁰, Sarkis Meterissian²⁰¹, Alessandro Marco Minisini²⁰², Shagun Misra³⁴, Angel Montero²⁰³, Jenna Morgan²⁰⁴, Teresa Muñoz Migueláñez⁹⁶, Elisabetta Munzone²⁰⁵, Dawid Murawa²⁰⁶, Karez Namiq²⁰⁷, María Alejandra Naranjo Sánchez²⁰⁸, Kazutaka Narui²⁰⁹, Toan Nguyen²¹⁰, Dejan Nikolic²¹¹, Angeliki Nikopoulou²¹², Conor O'Neill²¹³, Seamus O'Reilly¹⁰⁸, Ira Oikonomou²¹⁴, Roger Olofsson Bagge²¹⁵, Amparo Oltra Ferrando²¹⁶, Lazaros Papadopoulos²¹⁷, Javier Pascual²¹⁸, David Pasquier¹³⁸, Alice Pellegrini²¹⁹, Tamar Peretz-Yablonski¹³⁷, Cristina Pérez Segura²²⁰, Antonio Piñero-Madrona²²¹, Katarzyna Pogoda²²², Razvan Popescu²²³, Matthew Poppe²²⁴, Mauro Porpiglia²²⁵, Daniel Portik²²⁶, Jose Fernando Prado Moura²²⁷, Elena Provenzano⁵⁶, Marina Puchinskaya²²⁸, Paul Martin Putora²²⁹, Venkatraman Radhakrishnan²³⁰, Ishtiaq Ur Rahim²³¹, Duvern Ramiah¹¹⁰, Smitha Rao²³², Ivica Ratosa²³³, Evangelia Razis²³⁴, Rebecca Read²³⁵, Lia Rebaza¹³³, Andrew Redfern²³⁶, Tomas Reinert²³⁷, Javier Retamales²³⁸, Margit Riis²³⁹, Neill Roberts¹⁸¹, Nicola Rocco²⁴⁰, Beatriz Rojas²⁴¹, Chandeena Roshanlal²⁴², Laurent Rosset²⁴³, Francesca Rovera²⁴⁴, Isabel T. Rubio²⁴⁵, Nicola Russell²⁴⁶, Natacha Ruysers²⁴⁷, Jai Min Ryu²⁴⁸, Helena Sackey²⁴⁹, Sunita Saha²⁵⁰, Jorge Emilio Salinas²⁵¹, Jose I. Sánchez-Méndez¹⁹³, Constantinos Savva⁸⁵, Lorenzo Scardina¹²⁷, Margherita Serra²¹⁹, Jiraporn Setakornnukul²⁵², Mukesh Shanthilal²⁵³, Iman Sharawy²⁵⁴, Shelly Sharma²², Shashank Shenoy⁵, Preethi S. Shetty²⁵⁵, Mery Shoshkova²⁵⁶, Mark Sibbering²⁵⁷, Zacharoula Sidiropoulou²⁵⁸, Aumilto Silva²⁵⁹, Richard Simcock²⁶⁰, Bhawana Sirohi²⁶¹, Fiona Smith²⁵⁷, Kylie Snook²⁶², Enrique Soto Perez De Celis²⁶³, Philip Spanheimer²⁶⁴, Heidi Stranzl²⁶⁵, Kirsty Stuart¹¹², Yisihak Suga²⁶⁶, Tommaso Susini¹⁹⁸, Michael Swinden²⁶⁷, Megha Tandon²⁶⁸, Maria Saveria Tavoletta²⁶⁹, Donatienne Taylor²⁷⁰, Vitor Teixeira Liutti²⁷¹, Evrim Tezcanli²⁷², Wajana Thaweerat²⁵², Jacqui Thomson²⁷³, Mangesh Thorat²⁷⁴, Marinos Tsiatas²⁷⁵, Pelagia Tsoutsou²⁷⁶, Tove Tvedskov²⁷⁷, Takayuki Ueno²⁷⁸, Jayant Vaidya²⁷⁹, Antonis Valachis²⁸⁰, Franchette Van Den Berkmoortel²⁸¹, Jos Van Der Hage²⁸², Frederieke Van Duijnhoven²⁴⁶, Marissa C. Van Maaren^{283,284}, Ad Vandermeulen²⁸⁵, Beatriz Vázquez-Barreiro²⁸⁶, Umesh Velu²⁸⁷, Ramachandran Venkitaraman²⁸⁸, Sergi Vidal-Sicart²⁸⁹, Lubna Vohra²⁹⁰, Ioannis Voutsadakis²⁹¹, Tabassum Wadasadawala²⁹², Melanie Walker²⁹³, Irene Wapnir²⁹⁴, Fredrik Warnberg²⁹⁵, Ericka Wiebe²⁹⁶, Stephanie Wong¹⁴³, Lynda Wyld²⁰⁴, Sanjay Kumar²⁹⁷,

Janice Yeh¹⁶⁶, Anneza Yiallourou²⁹⁸, Hyun Jo Youn²⁹⁹, Jan Žatecký³⁰⁰, Gastón Zatta Cobos³⁰¹, Amanda Zeko³⁰², Marija Zivkovic³⁰³ & Anagha Zope³⁰⁴

²⁹NHS Highland, Inverness, UK. ³⁰Rambam Health Care Campus, Haifa, Israel. ³¹Mansoura University, Mansoura, Egypt. ³²Oxford University Hospitals NHS Trust, Oxford, UK. ³³Lucerne Cantonal Hospital and University of Bern, Bern, Switzerland. ³⁴Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India. ³⁵Miró Hospital Universitario Sant Joan De Reus, Reus, Spain. ³⁶Hospital Del Mar, Barcelona, Spain. ³⁷Alves Hospital Universitaria Evangelico Mackenzie, Curitiba, Brazil. ³⁸National Medical Research Center of Oncology named after N.N.Petrov, St Petersburg, Russia. ³⁹Mid And South Essex NHS Foundation Trust, Essex, UK. ⁴⁰Instituto Alexander Fleming, Buenos Aires, Argentina. ⁴¹University Hospital 12 De Octubre, Madrid, Spain. ⁴²Acibadem University, Istanbul, Turkey. ⁴³University Of Perugia and Perugia General Hospital, Perugia, Italy. ⁴⁴Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. ⁴⁵University of Manchester, Manchester, UK. ⁴⁶Christian Medical College, Vellore, India. ⁴⁷University of Tsukuba, Tsukuba, Japan. ⁴⁸University Hospital Schleswig-Holstein Campus, Lübeck, Germany. ⁴⁹CISSS De Chaudière-Appalaches, Ste Marie, Canada. ⁵⁰Royal Marsden NHS Foundation Trust, London, UK. ⁵¹Careggi University Hospital, Florence, Italy. ⁵²Università Politecnica Delle Marche and AOU Delle Marche, Ancona, Italy. ⁵³Sheba Tel Hashomer Medical Center, Raman Gat, Israel. ⁵⁴Vajira Hospital, Bangkok, Thailand. ⁵⁵Klinikum Ernst Von Bergmann, Potsdam, Germany. ⁵⁶Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. ⁵⁷Helios University Hospital Wuppertal - University Witten/Herdecke, Wuppertal, Germany. ⁵⁸Maastricht University Medical Centre, Maastricht, The Netherlands. ⁵⁹Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania. ⁶⁰Pederzoli Hospital Peschiera Del Garda, Peschiera Del Garda, Italy. ⁶¹Mater Dei Hospital, Msida, Malta. ⁶²Northern Centre for Cancer Care, Newcastle-upon-Tyne, UK. ⁶³University of New Mexico, Albuquerque, NM, USA. ⁶⁴Ospedale Multimedita Castellanza, Castellanza, Italy. ⁶⁵Hospital Infanta Cristina, Madrid, Spain. ⁶⁶Adana Kozan State Hospital, Kozan, Turkey. ⁶⁷SHS St Vincent Hospital/Crown, Green Bay, WI, USA. ⁶⁸Newcastle Upon Tyne NHS Hospitals, Newcastle, USA. ⁶⁹Uniting Health, Brisbane, Australia. ⁷⁰Hospital Universitario De Jaen, Jaen, Spain. ⁷¹Sakarya University Training and Research Hospital, Sakarya, Turkey. ⁷²Peterko Clinical Hospital Centre Rijeka, Rijeka, Croatia. ⁷³United Hospitals of Derby and Burton, Derby, UK. ⁷⁴Hospital de Clinicas Dr Manuel Quintela, Montevideo, Uruguay. ⁷⁵NYU Langone Perlmutter Cancer Center, New York, USA. ⁷⁶Prince Of Wales Hospital and the Royal Hospital for Women, Sydney, Australia. ⁷⁷University of Hong Kong/Queen Mary Hospital, Hong Kong, Hong Kong. ⁷⁸Apollo Multispecialty Hospital, Kolkata, India. ⁷⁹Ampuero Hospital Universitario Severo Ochoa, Leganés, Spain. ⁸⁰Melbourne University Department of Surgery, Melbourne, Australia. ⁸¹Medical Oncology Unit, H.U Virgen De Las Nieves, Granada, Spain. ⁸²Instituto De Investigacion Biosanitaria Ibs. Granada, Granada, Spain. ⁸³University Of Cyprus Medical School and Bank of Cyprus Oncology Centre, Nicosia, Cyprus. ⁸⁴Allegheny Health Network, Pittsburgh, PA, USA. ⁸⁵University Of Southampton, Southampton, UK. ⁸⁶Ludwig-Maximilians-University Hospital, Munich, Germany. ⁸⁷ICS Maugeri, Pavia, Italy. ⁸⁸Hospital Lusíadas Lisboa Oncology Center, Lisbon, Portugal. ⁸⁹Belfast Health and Social Care Trust, Belfast, UK. ⁹⁰Ospedale Di Bolzano Azienda Sanitari Alto Adige, Bolzano, Italy. ⁹¹Hospital Universitario Canarias, Santa Cruz de Tenerife, Tenerife, Spain. ⁹²ASL Napoli 3 Sud, Naples, Italy. ⁹³European Medical Center, Moscow, Russia. ⁹⁴Swansea Bay University Health Board, Swansea, UK. ⁹⁵Université Libre De Bruxelles, Hôpital Universitaire De Bruxelles, Institut Jules Bordet, Brussels, Belgium. ⁹⁶Hospital Universitario Ramón Y Cajal, Madrid, Spain. ⁹⁷Instituto Catalan Oncologia, Girona, Spain. ⁹⁸University Of New South Wales School Of Clinical Medicine, Kensington, Australia. ⁹⁹Ghent University Hospital, Ghent, Belgium. ¹⁰⁰IRCCS San Raffaele Scientific Institute, Milan, Italy. ¹⁰¹Quironsalud Madrid University Hospital, Madrid, Spain. ¹⁰²Medical University-Pleven, Pleven, Bulgaria. ¹⁰³Ankara Etilik City Hospital, Ankara, Turkey. ¹⁰⁴HFR Fribourg Hospital, Fribourg, Switzerland. ¹⁰⁵Metropolitan General Hospital of Athens, Athens, Greece. ¹⁰⁶St Luke's Hospital, Thessaloniki, Greece. ¹⁰⁷Trinity St James's Cancer Institute, Dublin, Ireland. ¹⁰⁸Cancer Trials Ireland, Dublin, Ireland. ¹⁰⁹Frauenklinik Ebingen, Ebingen, Germany. ¹¹⁰University Witwatersrand, Johannesburg, South Africa. ¹¹¹Hospital Prof. Doutor Fernando Fonseca- ULS Amadora/Sintra, Amadora, Portugal. ¹¹²Westmead Hospital, Westmead, Australia. ¹¹³Breast-Center Zurich, Zurich, Switzerland. ¹¹⁴Aberdeen Royal Infirmary, Aberdeen, UK. ¹¹⁵Institut Català D'Oncologia, Barcelona, Spain. ¹¹⁶Ankara Training and Research Hospital, Ankara, Turkey. ¹¹⁷Todua Clinic, Tbilisi, Georgia. ¹¹⁸Hospital Universitari Vall D'Hebron, Barcelona, Spain. ¹¹⁹Instituto Do Cancer Do Estado De Sao Paulo - Faculdade De Medicina Da Universidade De Sao Paulo, Sao Paulo, Brazil. ¹²⁰Kettering General Hospital, Kettering, UK. ¹²¹AOU Sassari, Sassari, Italy. ¹²²Alvaro Cunqueiro Hospital, Vigo, Spain. ¹²³Parc Tauli University Hospital, Sabadell, Spain. ¹²⁴Osakidetza, Bilbao, Spain. ¹²⁵AULSS 9 Scaligera, Verona, Italy. ¹²⁶São João University Hospital, Porto, Portugal. ¹²⁷Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy. ¹²⁸Instituto Nacional De Enfermedades Neoplasicas, Surquillo, Peru. ¹²⁹Specialty Surgical Oncology, Mumbai, India. ¹³⁰Università Della Svizzera Italiana, Lugano, Italy. ¹³¹ASST Of Cremona/ University of Trieste, Cremona, Italy. ¹³²University Hospital of Pisa, Pisa, Italy. ¹³³Oncosalud Auna, Lima, Peru. ¹³⁴Cleveland Clinic Abu Dhabi, Adu Dhabi, United Arab Emirates. ¹³⁵Gynäkologische Praxisklinik Hamburg Harburg, Hamburg, Germany. ¹³⁶Prof. Dr. Cemil Taşcıoğlu Hospital, Istanbul, Turkey. ¹³⁷Hadassah Hebrew University Medical Center, Jerusalem, Israel. ¹³⁸Centre Oscar Lambret, Lille, France. ¹³⁹Basavatakrakam Indo American Cancer Hospital and Research Institute, Hyderabad, India. ¹⁴⁰Northumbria Healthcare NHS Foundation Trust, Newcastle Upon Tyne, UK. ¹⁴¹Maidstone And Tunbridge Wells NHS Trust, Maidstone, UK. ¹⁴²University Hospital Basel, Basel, Switzerland. ¹⁴³McGill University, Montreal, Canada. ¹⁴⁴University Of Exeter, Exeter, UK. ¹⁴⁵All India Institute of Medical Sciences, Rishikesh, India. ¹⁴⁶Fondazione Poliambulanza, Brescia, Italy. ¹⁴⁷Shaikh Zayed Hospital Lahore and Rashid Latif Medical Complex, Lahore, Pakistan. ¹⁴⁸Hospital Universitario De Navarra, Pamplona, Spain. ¹⁴⁹Emory University School of Medicine, Atlanta, GA, USA. ¹⁵⁰Health New Zealand, Canterbury, New Zealand. ¹⁵¹Centre Hospitalier Universitaire de Liège, Liège, Belgium. ¹⁵²University Of Toronto, Toronto, Canada. ¹⁵³Wellington Hospital, Wellington, New Zealand. ¹⁵⁴Legacy Health Cancer Institute, Portland, Oregon, USA. ¹⁵⁵The Canberra Hospital, Canberra, Australia. ¹⁵⁶K M M Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India. ¹⁵⁷Apollo Hospitals, Delhi, India. ¹⁵⁸Ondokuz Mayıs University General Surgery Department, Samsun, Turkey. ¹⁵⁹Pusan National University Hospital, Busan, South Korea. ¹⁶⁰Sri Shankara Cancer Hospital and Research Centre, Bengaluru, India. ¹⁶¹Zonguldak Bulent Ecevit University, Zonguldak, Turkey. ¹⁶²Uppsala University, Uppsala, Sweden. ¹⁶³Khyber Medical College and Khyber Teaching Hospital, Peshawar, Pakistan. ¹⁶⁴Liga Nacional Contra El Cáncer and Instituto De Cancerología, Guatemala City, Guatemala. ¹⁶⁵Klinikum Rechts Der Isar, Tu Munich, Germany. ¹⁶⁶Peter MacCallum Cancer Centre, Melbourne, Australia. ¹⁶⁷Ushato Prof. Ivan Chernozevski, Sofia, Bulgaria. ¹⁶⁸Princess Alexandra Hospital, Harlow, UK. ¹⁶⁹National and Kapodistrian University of Athens, Athens, Greece. ¹⁷⁰Europa Donna Hellas, Athens, Greece. ¹⁷¹Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany. ¹⁷²University Of Edinburgh, Edinburgh, UK. ¹⁷³Hampshire Hospitals, Winchester, UK. ¹⁷⁴Hospital Universitario De Badajoz, Badajoz, Spain. ¹⁷⁵Kyungpook National University Chilgok Hospital, Daegu, South Korea. ¹⁷⁶Gold Coast HHS, Southport, Australia. ¹⁷⁷Hospital Universitario Insular De Gran Canaria, Las Palmas de Gran Canaria, Spain. ¹⁷⁸Immanuel Klinik Märkische Schweiz, Buckow, Germany. ¹⁷⁹Catholic Hospital "Our Lady of Good Counsel", Tirana, Albania. ¹⁸⁰University of Antwerp, Antwerp, Belgium. ¹⁸¹Leeds Teaching Hospitals, Leeds, UK. ¹⁸²University of Glasgow, Glasgow, UK. ¹⁸³Instituto Português De Oncologia De Coimbra Francisco Gentil, E.P.E., Coimbra, Portugal. ¹⁸⁴University Medical Centre Groningen, Groningen, Netherlands. ¹⁸⁵Centro De Educación Médica E Investigaciones Clínicas, Buenos Aires, Argentina. ¹⁸⁶Gartnaveel General Hospital, Glasgow, UK. ¹⁸⁷Center for Treatment and Cancer Research, Bogota, Colombia. ¹⁸⁸Rigshospitalet, Copenhagen, Denmark. ¹⁸⁹Bank Of Cyprus Oncology Centre, Strovolos, Cyprus. ¹⁹⁰Washington University School of Medicine, Washington DC, USA. ¹⁹¹Hospital Sirio-Libanês, Sao Paulo, Brazil. ¹⁹²McGill University Jewish General Hospital, Montreal, Canada. ¹⁹³Hospital Universitario La Paz, Madrid, Spain. ¹⁹⁴Lausanne University Hospital, Lausanne, Switzerland. ¹⁹⁵Broomfield Hospital, Mid and South Essex NHS Trust, Chelmsford, Essex, England, UK. ¹⁹⁶Kyoto University, Kyoto, Japan. ¹⁹⁷Helios Klinikum Berlin Buch Breast Center, Berlin, Germany. ¹⁹⁸University of Florence, AOU Careggi, Florence, Italy. ¹⁹⁹University Hospital of Modena, Modena, Italy. ²⁰⁰Helsinki University Hospital, Helsinki, Finland. ²⁰¹McGill University Health

Center, Montreal, Canada. ²⁰²Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy. ²⁰³HM Hospitales, Madrid, Spain. ²⁰⁴University of Sheffield, Sheffield, UK. ²⁰⁵European Institute of Oncology, IRCCS, Milan, Italy. ²⁰⁶University Hospital Zielona Gora Poland Clinic of General Surgery and Surgical Oncology, Zielona Gora, Poland. ²⁰⁷Hawler Medical University, Erbil, Iraq. ²⁰⁸Hospital Universitario Lucus Augusti, Lugo, Spain. ²⁰⁹Yokohama City University Medical Center, Yokohama, Japan. ²¹⁰Westchester Medical Center, Valhalla, New York, USA. ²¹¹UMC Bezanijaska Kosa, Belgrade, Serbia. ²¹²Athens Medical Group, Athens, Greece. ²¹³North West Cancer Centre, Altnagelvin Hospital, Londonderry, UK. ²¹⁴Södersjukhuset, Stockholm, Sweden. ²¹⁵Sahlgrenska University Hospital, Gothenburg, Sweden. ²¹⁶Hospital Virgen De Los Lirios, Alcoy, Spain. ²¹⁷IASO Maternity Hospital, Marusi, Greece. ²¹⁸Regional And Virgen De La Victoria University Hospitals, Malaga, Spain. ²¹⁹IRCCS Azienda Ospedaliero Universitaria Di Bologna, Bologna, Italy. ²²⁰Xarxa Santa Tecla Sanitària, Tarragona, Spain. ²²¹Hospital Clínico Universitario Virgen De La Arrixaca, Murcia, Spain. ²²²Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland. ²²³Tumor Zentrum Aarau, Aarau, Switzerland. ²²⁴Huntsman Cancer Institute, Salt Lake City, UT, USA. ²²⁵Breast Unit, Sant'Anna Hospital, Turin, Italy. ²²⁶European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium. ²²⁷Real Hospital Beneficência Portuguesa Pernambuco, Recife, Brazil. ²²⁸Minsk City Clinical Oncology Centre, Minsk, Belarus. ²²⁹Kantonsspital St. Gallen, St. Gallen, Switzerland. ²³⁰Cancer Institute (W.I.A), Adyar, Chennai, India. ²³¹Square Hospitals Ltd, Dhaka, Bangladesh. ²³²K S Hegde Medical Academy, Nitte University, Mangalore, India. ²³³University of Ljubljana, Ljubljana, Slovenia. ²³⁴Hygeia Hospital, Athens, Greece. ²³⁵ACT Health, Australian National University, Canberra, Australia. ²³⁶Fiona Stanley Hospital, Murdoch, Australia. ²³⁷Santa Casa De Porto Alegre, Porto Alegre, Brazil. ²³⁸Grupo Oncologico Cooperativo Chileno De Investigacion, Santiago, Chile. ²³⁹Oslo University Hospital, Oslo, Norway. ²⁴⁰University of Naples Federico II, Naples, Italy. ²⁴¹Centro Integral Oncológico Clara Campal, Madrid, Spain. ²⁴²East Cheshire NHS Trust, Macclesfield, UK. ²⁴³Centre Du Sein, Fribourg, Switzerland. ²⁴⁴ASST Sette Laghi Di Varese, Varese, Italy. ²⁴⁵Clinica Universidad De Navarra, Madrid, Spain. ²⁴⁶The Netherlands Cancer Institute, Amsterdam, Netherlands. ²⁴⁷AZ Turnhout, Turnhout, Belgium. ²⁴⁸Samsung Medical Center, Seoul, South Korea. ²⁴⁹Karolinska Institutet Stockholm, Stockholm, Sweden. ²⁵⁰Colchester Hospital, Colchester, UK. ²⁵¹Centro Medico Privado "Cemaic"/Hospital Oncologico De Cordoba, Cordoba, Argentina. ²⁵²Siriraj Hospital - Mahidol University, Bangkok, Thailand. ²⁵³Mysore Medical College and Research Institute, Mysore, India. ²⁵⁴Ain Shams University, Cairo, Egypt. ²⁵⁵Kasturba Medical College and Hospital, Manipal, India. ²⁵⁶Dr G. Strask University Hospital, Pleven, Bulgaria. ²⁵⁷University Hospitals of Derby and Burton, Derby, UK. ²⁵⁸West Lisbon Local Health Unit, Lisbon, Portugal. ²⁵⁹Hospital Santa Catarina Paulista, São Paulo, Brazil. ²⁶⁰University Hospitals Sussex NHS Foundation Trust, Brighton, UK. ²⁶¹Vedanat Medical Research Foundation, Balco Medical Centre, Naya Raipur, India. ²⁶²Mater Hospital, Sydney, Australia. ²⁶³University of Colorado Anschutz Medical Center, Aurora, CO, USA. ²⁶⁴University of North Carolina, Chapel Hill, NC, USA. ²⁶⁵Lawatsch Med Universität Graz Strahlentherapie, Graz, Austria. ²⁶⁶Saint Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia. ²⁶⁷Health New Zealand, Wellington, New Zealand. ²⁶⁸Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India. ²⁶⁹U.O.C.Senologia Chirurgica ASL2 Abruzzo, Abruzzo, Italy. ²⁷⁰CHU UCL Namur Sainte Elisabeth, Namur, Belgium. ²⁷¹Hospital Do Câncer De Londrina, Londrina, Brazil. ²⁷²Acibadem Altunizade Hospital, Istanbul, Turkey. ²⁷³Peninsula Health, Frankston, Australia. ²⁷⁴Queen Mary University of London, London, UK. ²⁷⁵Athens Medical Centre, Athens, Greece. ²⁷⁶Geneva University Hospital, Geneva, Switzerland. ²⁷⁷Gentofte Hospital, Hellerup, Denmark. ²⁷⁸Cancer Institute Hospital of JFCR, Tokyo, Japan. ²⁷⁹University College London, London, UK. ²⁸⁰Örebro University, Örebro, Sweden. ²⁸¹Zuyderland MC, Heerlen, Netherlands. ²⁸²Leiden University Medical Center, Leiden, Netherlands. ²⁸³Technical Medical Centre, University of Twente, Enschede, The Netherlands. ²⁸⁴Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands. ²⁸⁵Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium. ²⁸⁶Hospital Meixoeiro, Vigo, Spain. ²⁸⁷Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India. ²⁸⁸Ipswich Hospital, Ipswich, UK. ²⁸⁹Hospital Clinic de Barcelona, Barcelona, Spain. ²⁹⁰Aga Khan University Hospital, Karachi, Pakistan. ²⁹¹Sault Area Hospital, Sault Ste Marie, Canada. ²⁹²Tata Memorial Centre, Mumbai, India. ²⁹³Alfred Health, Melbourne, Australia. ²⁹⁴Stanford University, Stanford, CA, USA. ²⁹⁵Gothenburg University, Gothenburg, Sweden. ²⁹⁶Cross Cancer Institute, Edmonton, Canada. ²⁹⁷Yadav NSCB Medical College, Jabalpur, India. ²⁹⁸University of Cyprus, Nicosia, Cyprus. ²⁹⁹Jeonbuk National University Medical School, Jeonju, South Korea. ³⁰⁰Silesian University, Opava, Czech Republic. ³⁰¹Hospital General De Granollers, Granollers, Spain. ³⁰²University Hospital "Mother Teresa", Tirana, Albania. ³⁰³Radojevic University of Kragujevac, Kragujevac, Serbia. ³⁰⁴Mar-engo Cims Hospital, Ahmedabad, India.