



Understanding the barriers to, and facilitators of, ovarian toxicity assessment in breast cancer clinical trials

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ABSTRACT

Background: Detailed toxicity data are routinely collected in breast cancer (BC) clinical trials. However, ovarian toxicity is infrequently assessed, despite the adverse impacts on fertility and long-term health from treatment-induced ovarian insufficiency.

Objectives: To determine the barriers to and facilitators of ovarian toxicity assessment in BC trials of anti-cancer drugs.

Methods: Semi-structured interviews were conducted with purposively selected stakeholders from multiple countries involved in BC clinical trials (clinicians, consumers, pharmaceutical company representatives, members of drug-regulatory agencies). Participants were asked to describe the perceived benefits and barriers to evaluating ovarian toxicity. Interviews were transcribed verbatim, coded in NVivo software and analysed using inductive thematic analysis.

Results: Saturation of the main themes was reached and the final sample size included 25 participants from 14 countries (9 clinicians, 7 consumers, 5 members of regulatory agencies, 4 pharmaceutical company representatives); half were female. The main reported barrier to ovarian toxicity assessment was that the issue was rarely considered. Reasons included that these data are less important than survival data and are not required for regulatory approval. Overall, most participants believed evaluating the impact of BC treatments on ovarian function is valuable. Suggested strategies to increase ovarian toxicity assessment were to include it in clinical trial design guidelines and stakeholder advocacy.

Conclusion: Lack of consideration about measuring ovarian toxicity in BC clinical trials that include premenopausal women suggest that guidelines and stronger advocacy from stakeholders, including regulators, would facilitate its more frequent inclusion in future trials, allowing women to make better informed treatment decisions.

1. Introduction

Ovarian toxicity is a potentially irreversible adverse effect of anti-cancer treatment for premenopausal women with breast cancer (BC).

It can result in infertility, and can have profound impacts on longer-term bone density, cardiovascular health and cognitive function [1–3]. As the incidence of BC in premenopausal women increases [4], and survival rates improve [5], minimising long-term treatment-related adverse effects in young women is paramount.

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The impact of cancer treatments on fertility and ovarian function is a significant concern for premenopausal women with BC [6,7] and is an important consideration when making treatment decisions [7]. Inter-

Abbreviations

BC	Breast cancer
COVID-19	Severe Acute Respiratory Syndrome Coronavirus-2
CRF	Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GnRH α	Gonadotrophin releasing hormone analogue
QOL	Quality of life
OS	Overall survival
PARP	Poly adenosine diphosphate-ribose polymerase

national guidelines recommend potential gonadotoxicity is addressed with all patients of reproductive age [8–14]. However, little is known about the ovarian effects of newer classes of anti-cancer therapies. A recent systematic evaluation demonstrated that ovarian toxicity is infrequently assessed in phase 3 (neo)adjuvant early BC clinical trials which enrolled premenopausal women [15], so the relevant information needed for informed decision-making for premenopausal women is usually not available when they are first used in practice.

Many stakeholders are involved in the design of clinical trials, including clinicians, drug-regulatory agencies, patient advocates (consumers) and pharmaceutical companies [16,17]. Phase 3 BC trials are often global multicentre studies, and stakeholders from different countries are involved in their design. It is not clear why ovarian toxicity endpoints are rarely assessed in trials enrolling premenopausal women. Existing qualitative research primarily focus on the barriers to ovarian preservation [18]. Qualitative research has been important for the incorporation of patient reported outcomes in clinical trials [19], and for examining trial design uncertainties [20]. Therefore, this international qualitative study was designed to determine the barriers and facilitators to ovarian toxicity assessment in BC clinical trials from the perspective of key decision-makers.

2. Methods

2.1. Design

Through semi-structured interviews with key decision-makers in BC clinical trials, this qualitative study explored the barriers to and facilitators of ovarian toxicity assessment in curative-intent pharmacological BC trials which enrol premenopausal women. Approval was obtained from the Peter MacCallum Cancer Centre Human Research and Ethics Committee (LNR/61921/PMCC).

2.2. Participants

Key decision-makers regarding clinical endpoints in BC trials are trial investigators (clinicians), consumers, pharmaceutical companies which produce BC anti-neoplastic agents [21], and drug-regulatory agencies. We purposively sampled for individuals from each of these groups, who had been personally involved in the design and conduct of BC trials or in drug regulation for BC anti-neoplastic agents in the last 10 years, and who were able to speak English and participate in an interview. We sought to include eligible participants from a range of countries.

Clinicians were eligible for the study if they were lead authors (first, second or last) of published phase 3 (neo)adjuvant BC trial manuscripts, or listed as the responsible party on clinicaltrials.gov or EudraCT

databases, or were scientific advisory committee members of collaborative trial groups. Consumers were eligible if they were consumer advisors for BC collaborative trial groups. Pharmaceutical company representatives (pharmaceutical company employees involved in trial design: medical advisors, chief scientific officers, chief research and development managers) and advisory committee members of drug-regulatory agencies (Food and Drug Administration (FDA), European Medicines Agency (EMA) or Pharmaceutical Benefits Advisory Committee) were eligible for inclusion and were identified through public internet search. To identify pharmaceutical company representatives, the website and LinkedIn page of each pharmaceutical company was searched. To identify regulatory agency members, the regulatory agency website and drug advisory committee meeting materials were searched. In order to extend the sample and identify other important stakeholders, snowball sampling was also conducted by asking participants to forward the email invitation to colleagues they believed would meet the inclusion criteria. Eligibility was checked by the researchers prior to interview for participants recruited through this process.

Eligible participants were sent an email or social-media invitation and a participant information sheet. If no response was received a reminder letter and a final email or social-media contact were sent. Consent was implied if the participant responded and provided contact details and a time for the interview.

2.3. Data collection and analysis

The study investigators included BC clinical trialists (clinicians), a reproductive specialist and a health sociologist. An interview guide was developed exploring the following questions: i) who contributes to trial endpoint selection, ii) what factors are considered during decision-making, iii) are ovarian toxicity endpoints included, iv) barriers to and/or benefits of ovarian toxicity assessment in BC trials, and v) strategies to improve ovarian toxicity evaluation. Only data related to themes iii), iv) and v) are reported in this paper, themes i) and ii) will be reported elsewhere. Interview questions were refined following piloting with colleagues initially, then one BC clinician who met the eligibility criteria; the pilot interview with the clinician who met the eligibility criteria was included in the overall analysis.

Semi-structured interviews were conducted by phone or video-conference by one author (WC, medical oncologist). The interviewer obtained verbal consent before each interview. Participants were initially asked closed-ended questions to collect demographic data. The themes covered in the interview were: the participant views on whether ovarian function endpoints were considered during trial design, whether these endpoints were important to include (why/why not), the barriers to their inclusion and the facilitators/strategies to improve their inclusion. All interviews were audio-recorded and professionally transcribed verbatim. Transcripts were de-identified after the transcription process. Transcripts were not returned to participants for comment after the interview. Grammatical changes were made to quotes for readability.

Inductive thematic analysis was performed by reading the transcripts in order to develop a coding framework, framework analysis was then undertaken to structure themes and to further analyse the emerging themes in light of the research question facilitated using NVivo software [22]. After five interviews, a summary of the emerging themes with supporting quotes was collated by one author (WC). Emerging themes were reviewed by co-authors LK (health sociologist) and KAP (medical oncologist) for feedback regarding the key themes and any refinements required for the interviews. After 15 interviews, a coding framework capturing the full range of comments was developed by WC and reviewed by co-authors LK and KAP. After interview 15, new interviews were reviewed in light of the coding framework to determine whether saturation of the main themes had been achieved. Two authors (WC and LK) independently coded several interviews and the coding framework was further refined. WC coded the remaining transcripts according to the coding framework. The final coding framework was discussed with

all study investigators (listed authors).

3. Results

3.1. Participants

Between June 2020 and April 2021, 260 stakeholders were invited to participate. 18 participants responded to the initial email invitation. Reminders were purposively sent to stakeholders who were from North American and Asian regions, members of drug-regulatory agencies and pharmaceutical company representatives, to broaden the range of participant demographics. Saturation was reached when no new themes were identified after interview 21. Another four interviews were conducted and no new themes were identified, therefore no further interviews were conducted after interview 25. The final sample included: 9 clinicians, 7 consumers, 5 members of drug-regulatory agencies, 4 pharmaceutical company representatives; half were female (Table 1). Interviews ranged between 24 and 46 min in duration.

Table 1
Characteristics of study participants.

	Participants
	N = 25
	N (%)
Age	
Median (years)	50 years
30–39 years	5 (20%)
40–49 years	7 (28%)
50–59 years	10 (40%)
60–69 years	3 (12%)
Gender	
Male	13 (52%)
Female	12 (48%)
Region	
North America	5 (20%)
Europe	13 (52%)
Australia	6 (24%)
Asia	1 (4%)
Stakeholder type	
Clinician	9 (36%)
Consumer	7 (28%)
Regulatory agency member	5 (20%)
Pharmaceutical company representative	4 (16%)
Years of experience	
Median (years)	16 years
1–5 years	3 (12%)
6–10 years	8 (32%)
11–20 years	5 (20%)
21–30 years	8 (32%)
>30 years	1 (4%)
Member of a cooperative trials group scientific advisory committee	
Yes ^a	19 (76%)
No	6 (24%)
Previously/currently a member of a pharmaceutical company advisory board^b	
Yes	16 (64%)
No	9 (36%)
Previously led a clinical trial as a lead investigator	
Yes	10 (40%)
No	8 (32%)
NA (consumer)	7 (28%)
Previously received training in clinical trial design	
Yes	12 (48%)
No	6 (24%)
NA (consumer)	7 (30%)

Abbreviation: NA - not applicable.

^a Three members of drug-regulatory agencies answered yes to this question.

^b This includes clinicians and consumers who have acted as advisors for pharmaceutical companies as part of an advisory board, as well as current employees of pharmaceutical companies.

3.2. Why are ovarian toxicity data infrequently included in breast cancer clinical trials?

Almost all participants reported that ovarian toxicity is rarely assessed in BC clinical trials. Four main barriers were reported. The main reported barrier was that this issue was rarely prioritised (barrier 1). Other important barriers included limited trial resources (barrier 2), lack of knowledge regarding how to assess treatment-related ovarian toxicity (barrier 3) and settings where these data were considered less relevant (barrier 4). Table 2 details the proportion of participants who reported each barrier, Appendix Table 1 describes the quotes to support each of these barriers.

3.2.1. Not prioritised

Almost all participants reported that ovarian toxicity was not prioritised and infrequently discussed during trial design. Ovarian toxicity was often deemed not the primary question of clinical trials and more than half of the participants reported that ovarian toxicity was considered less important than survival endpoints. Indeed, one consumer stated “There’s still that pervasive idea that if we keep you alive the rest doesn’t matter.” Furthermore, collection of ovarian toxicity data is not required for regulatory approval of cancer drugs; this was a key barrier identified by one pharmaceutical company advisor and almost all members of drug-regulatory agencies.

3.2.2. Considered too resource intensive

Many participants reported the pressure on trial resources required to assess ovarian toxicity, such as the cost and the additional burden on investigators and patients was perceived as prohibitive. Concerns regarding the duration of follow-up required to capture fertility events and loss of ovarian function, and the difficulty in collecting good quality data during the follow-up period were also distinctive barriers.

3.2.3. Lack of knowledge

Another barrier, particularly reported by clinicians, was the need for guidance regarding which ovarian markers are most useful to assess. Participants also reported that stakeholders designing clinical trials may not know the potential ovarian side-effects of the anti-cancer drugs they are studying.

3.2.4. Assessing ovarian toxicity may be less relevant in certain settings

Assessing ovarian toxicity was considered as less relevant in certain settings, such as trials where low numbers of premenopausal women are included. One quarter of participants reported that ovarian toxicity assessment may be difficult in trials where patients also receive concurrent gonadotoxic chemotherapy. Additionally, trials investigating hormone-receptor positive BC, where drugs are specifically administered to induce ovarian suppression [23], might make additional assessment of ovarian toxicity more challenging.

3.3. What are the perceived benefits of including ovarian toxicity endpoints?

Despite the perceived barriers, overall, participants felt that evaluating the impact of BC treatments on ovarian function was valuable. Indeed, one clinician stated that lack of ovarian toxicity assessment was “a failure of the entire research world”.

The two main benefits of including ovarian endpoints are these data are important to i) patients and ii) clinicians. Supporting quotes are provided in Appendix Table 2.

3.3.1. Data are important to patients

The importance of such data to patients was recognised by almost all clinicians and consumers, and half of the pharmaceutical company representatives and members of regulatory agencies. The impact of gonadotoxicity on a woman’s quality of life (QOL), and the importance

Table 2
Perceived barriers to and benefits of ovarian toxicity assessment in breast cancer clinical trials.

	Reason	Number of participants who reported each reason				
		Overall (n = 25)	Clinician (n = 9)	Consumer (n = 7)	Pharmaceutical company representative (n = 4)	Member of drug-regulatory agency (n = 5)
Why are ovarian toxicity data infrequently included in breast cancer clinical trials?						
1 Not prioritised	Not discussed or thought about	23	9	7	3	4
	Not the primary question or most important endpoint(s) studied by clinical trial	16	7	4	4	1
	Not required for regulatory approval	5	0	0	1	4
	More appropriate for a follow up/registry study	3	1	1	0	1
2 Considered too resource intensive	A burden on investigators and patients	9	4	1	2	2
	Time to obtaining results too long	7	1	3	1	2
	Assessment not considered feasible	5	3	0	2	0
	Too costly	5	2	2	1	0
3 Lack of knowledge	Difficult to collect good quality data	2	0	0	2	0
	Need for guidance regarding which markers to assess	6	5	0	0	1
	Lack of existing knowledge or preclinical data regarding ovarian toxicity side effects	4	3	0	1	0
4 Assessing ovarian toxicity may be less relevant in certain settings	Low numbers of premenopausal women enrolled	7	3	3	0	1
	Trials mandate contraception use	7	2	2	0	3
	Concurrent use of gonadotoxic chemotherapy	6	3	2	1	0
	Want to suppress ovarian function in some breast cancer phenotypes	6	1	2	2	1
What are the perceived benefits of including ovarian function endpoints?						
1 Data are important to patients	Infertility and early menopause are relevant and important to patients	18	7	7	2	2
	Improved ability to make informed cancer treatment and family planning decisions	11	3	6	1	1
	Preservation of ovarian function is important for quality of life	10	4	5	0	1
	To avoid potential harm to patients	4	2	2	0	0
2 Data are important to clinicians	Improved understanding of the investigational agent	9	3	2	1	2
	Improved understanding of the impact of ovarian function on disease outcomes	7	4	1	1	1
	Improved ability to counsel patients	7	5	1	1	0
	Prospective information is more valuable	3	2	1	0	0

of these data in informing cancer-treatment and family-planning decisions were leading reasons why these data should be assessed. Furthermore, information regarding the potentially irreversible impact of cancer treatments on ovarian function was seen as important to avoid unknown long-term side-effects.

3.3.2. Data are important to clinicians

Participants reported that ovarian toxicity assessment may help clinicians better understand the investigational agent and improve counselling their patient regarding treatment options. Indeed, one pharmaceutical company representative reported that “If you had two molecules that behaved in the same way, but one of them was able to result in better preservation of ovarian function than the other, then that would be a benefit that you could then make a claim in.” Moreover, there is increasing interest in the impact of ovarian suppression on disease outcomes, and these data may enrich interpretation of trial results. These data were also identified as best collected prospectively, as gonadotoxicity can be difficult to assess retrospectively.

3.4. What are strategies that might help to increase the inclusion of ovarian toxicity endpoints?

Participants identified two main strategies: i) increased awareness

and ii) increased stakeholder advocacy for these data to be assessed as important facilitators for the collection of these data in future trials (see [Table 3](#) for further detail and [Appendix Table 3](#) for supporting quotes).

3.4.1. Increased stakeholder awareness

Primarily, increased awareness through trial design guidelines was a central strategy reported by half of participants. One member of a drug-regulatory agency stated “Whenever we come up with a conundrum, that’s when we look at [National Comprehensive Cancer Network] guidelines or St Gallen’s [...] Having consensus with guidelines would be a great start.”

Other strategies to increase ovarian toxicity assessment included improving familiarity with ovarian function markers among trial design decision-makers and increased discussion regarding gonadotoxicity within the scientific community.

3.4.2. Increased stakeholder advocacy

A stronger consumer voice and clinician promotion were regarded as especially important by most participants. In addition, some participants felt that drug-regulatory agencies could also play an influential role in guiding sponsors and/or clinical trialists regarding the importance of ovarian toxicity assessment in trials. Other stakeholders identified as key to advocate for these data to be assessed included reproductive specialists and cooperative trials groups. Only two participants reported

Table 3
What are strategies that might help to increase the inclusion of ovarian toxicity endpoints?

What are strategies that might help to increase the inclusion of ovarian function endpoints?	Specific strategies	Number of participants who reported each strategy				
		Overall (n = 25)	Clinician (n = 9)	Consumer (n = 7)	Pharmaceutical company representative (n = 4)	Member of drug-regulatory agency (n = 5)
1 Increased stakeholder awareness	Trial design guidelines and recommendations	12	5	3	2	2
	Improved familiarity and ease of collecting these data	8	5	2	1	0
	Increased discussion and education	5	3	2	0	0
	Use of social media and internet resources	3	1	2	0	0
2 Increased stakeholder advocacy	Increased consumer voice	15	7	6	1	1
	Increased clinician promotion	12	6	3	1	2
	Increased regulatory buy in	5	2	0	0	3
	Increased reproductive specialist involvement	3	2	1	0	0
	Increased cooperative trial group interest	2	0	2	0	0
	Increased pharmaceutical company interest	2	1	1	0	0

increased interest from pharmaceutical companies as a strategy to increase the inclusion of ovarian toxicity assessment in BC trials.

4. Discussion

To our knowledge, this is the first study exploring the barriers and potential facilitators to assessment of ovarian toxicity in BC clinical trials. Despite the importance of avoidance of unnecessary treatment-induced menopause, we found that ovarian toxicity assessment was not prioritised and rarely even considered during trial design. Overall, key stakeholders of BC trials felt that assessing ovarian toxicity was important, and that these data were necessary to inform treatment decisions. We have identified a disconnect between what stakeholders desire to know, and what is currently assessed in BC trials.

Many participants in this study recognised that preservation of ovarian function was fundamental to a woman's QOL. Yet, the majority felt these data were currently under-prioritised during trial design. QOL is now considered an endpoint for clinical benefit by the FDA and leading oncology organisations [24,25], which has led to increased incorporation of QOL assessment in cancer clinical trials [26,27]. Similar to the experience of incorporating QOL assessment, increased awareness regarding the importance of ovarian toxicity data among trial design decision-makers was highlighted as a core strategy to increase assessment of ovarian toxicity.

We found that different stakeholders prioritised ovarian toxicity assessment differently. Although almost all clinicians and consumers reported that ovarian toxicity data were important, only half of the pharmaceutical company representatives and members of drug-regulatory agencies shared this view. Regulatory requirements may be an important strategy to ensure incorporation of ovarian toxicity assessment given their influence on the pharmaceutical industry. Further expansion of the FDA guidance for industry documents [28] and similar guidance from the EMA may lead to improved prioritisation of ovarian toxicity in trials enrolling premenopausal women.

A need for increased guidance regarding how to assess gonadotoxicity was considered another barrier to routine inclusion of these data. Indeed, in BC trials which do assess ovarian toxicity, including gonadotrophin-releasing-hormone analogue (GnRHa) trials where treatment-induced ovarian insufficiency was the primary endpoint, the ovarian measures used are variable, and arguably inadequate [29]. Furthermore, menstruation is often used to assess ovarian function [30]. Yet, reduced ovarian function can occur in women who are still menstruating and anti-cancer drugs may deplete the ovarian reserve without stopping menses [31].

Some participants considered that the gonadotoxic effects of the non-investigational chemotherapy clouds the interpretation of the ovarian toxic effects of novel cancer treatments. However, many novel agents may be given in a prolonged maintenance phase after chemotherapy has finished [32–35], at a time when “ovarian protection” measures may be discontinued. Therefore, ovarian toxicity assessment of these novel agents is still pertinent regardless of whether they are initially combined with chemotherapy or not. On the contrary, participants felt that assessing ovarian function may help assess the impact of these changes on cancer outcomes and enhance interpretation of trial results. This is particularly relevant for hormone-receptor positive BC where ovarian suppression has been shown to impact cancer outcomes [23]. Oestrogen also modifies the function of immune-cell populations [36]. This is relevant in triple-negative BC, where immunotherapy is now licenced [33,37]; trials assessing immunotherapy for other BC subtypes are also underway.

Another perceived barrier to ovarian toxicity assessment is the desire not to add excessive burden on the finite trial resources. There is a notable paradox between the detailed requirements in trial protocols to mandate often multiple contraceptive methods and pregnancy tests in women of potential child-bearing capacity throughout trial drug administration, but lack of attention to ovarian toxicity during and after treatment. Improved agreement regarding the most informative markers of ovarian toxicity could improve interpretation of such data and also minimise collection of unnecessary data and reduce resource intensity.

The duration of follow-up required was another perceived barrier. However, longer-term monitoring for late cancer-treatment toxicities is increasingly practiced [38,39]. Prospective cardiac surveillance is now often incorporated into trial protocols of cardiotoxic BC treatments, sometimes up to 10 years after treatment completion [40], demonstrating the feasibility to understand the existence of late treatment toxicities.

Guidelines are an important tool to guide best clinical practice, and were a key strategy suggested by participants to improve implementation of ovarian toxicity assessment. Current tools used for trial endpoint decision-making [25,41,42] do not address ovarian toxicity assessment. As reported by many participants in this study, development of clinical trial design guidelines which make recommendations regarding which ovarian measures to collect and when, may overcome many of the barriers we identified [43].

There were several limitations to this study. All interviews were conducted by phone or video-conference to allow international stakeholders to participate. Only one participant from Asia was included, and our findings may not be generalisable for this region; a barrier to

participation may be that the interviews were conducted in English and this study was conducted during the COVID-19 pandemic. Half of stakeholders included were involved in industry-sponsored trials, given these are generally more prevalent; but three-quarters were also involved in cooperative group coordinated trials and therefore our findings are relevant to both trial types. Although we sampled stakeholders from different backgrounds, there may be participation bias as participants may be more likely to have known more about or been more interested in the question of measuring ovarian toxicity than non-participants. Moreover, other stakeholders involved in trial design such as statisticians were not interviewed. Lastly, this study was exploratory in nature and represents the opinions of participants. Therefore, the data presented in this study is subjective, a caveat of our study design.

5. Conclusion

Despite the potential profound impact of treatment-related ovarian toxicity for premenopausal women, this qualitative study found that ovarian toxicity assessment in BC trials is currently not prioritised. Yet, stakeholders, particularly consumers, believe that assessing ovarian toxicity is important and these data are vital to inform treatment decisions. Stronger advocacy is needed to change practice. Clinical trial design guidelines may break down many of the existing barriers to ovarian toxicity assessment, raise awareness of this important knowledge gap and provide guidance on how to collect informative data while minimising the burden on trial resources. Inclusion of ovarian toxicity assessment in future trials will provide invaluable information regarding a potentially serious adverse effect of cancer treatment, to ultimately empower women to make fully-informed treatment decisions that will impact their family-planning choices and long-term health.

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Declaration of competing interest

W Cui: Dr Cui reports honoraria from AstraZeneca, Pfizer, Janssen and Merck.

KA Phillips: Professor Phillips reports two unpaid Advisory Boards for AstraZeneca in 2021. Breast Cancer trials Scientific Advisory Committee member. Breast Cancer Network Australia Strategic Advisory Committee member.

PA Francis: Professor Francis is the Breast Cancer Trials Australia & New Zealand Chair Scientific Advisory Committee. She reports travel to lecture overseas: Novartis, Ipsen.

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AH Partridge: Professor Partridge reports travel to lecture overseas: Novartis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2022.05.002>.

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