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Original Article

Selection of endpoints in breast cancer clinical trials: a qualitative study of key trial stakeholders

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Abstract: Clinical trial endpoints are fundamental for evaluating the safety and efficacy of cancer therapies, yet it is not well understood how they are selected or the role of stakeholder groups in deciding endpoints. This study aimed to explore how clinical trial endpoints are selected in breast cancer trials of anti-cancer drugs through semi structured interviews with purposively selected stakeholders involved in breast cancer clinical trials (clinicians, consumers, pharmaceutical company representatives, and members of drug regulatory agencies). Participants were asked to describe the process of selecting trial endpoints. Interviews were transcribed verbatim and analysed using inductive thematic analysis supported by NVivo software. Saturation of the main themes was reached and the final sample included 25 participants from 14 countries (9 clinicians, 7 consumers, 5 members of regulatory agencies, 4 pharmaceutical company representatives). Pharmaceutical companies were almost always identified as the main decision maker. While most consumers and pharmaceutical company representatives felt clinicians and consumers influenced trial design, some clinicians and regulators reported consumers and clinicians had little influence. Factors identified as important considerations in determining trial endpoints included the main goal of the trial, established standardised endpoints, resources, and the investigational agent studied. All pharmaceutical advisors reported that meeting the requirements for regulatory approval was the major factor considered. Clinical trial endpoint selection is largely decided by the pharmaceutical industry, driven by requirements for regulatory approval. Given the limited influence from clinicians and consumers, guidance by regulatory agencies will be important for future inclusion of novel endpoints in clinical trials.

Keywords: Clinical trial, endpoints, breast cancer

Introduction

Clinical trials are needed to test the efficacy and safety of new cancer treatment regimens and are a requirement for drug approval by regulatory agencies [1]. Phase 3 randomised trials, which compare new treatment regimens with the available standard treatments, are traditionally considered the gold standard requirement for drug regulatory approval, and the findings of such trials shape clinical practice [2, 3]. The selection of trial endpoints is important in determining which data are collected during a clinical trial, and therefore what is eventually known, or not known, about the cancer therapy tested.

Previous studies have reported that many stakeholders are involved in the design of oncology clinical trials, including clinicians, regulatory bodies, consumers and industry [4, 5]. Involvement of clinicians and consumers in

study design has been shown to strengthen trial validity, and to provide valuable insight into the feasibility and acceptability of an intervention [6, 7]. Involvement of consumers in health research is well documented to enhance the quality and appropriateness of research, including developing patient-focused research objectives, user friendly information and more appropriate recruitment strategies [8].

Precision oncology, which matches therapeutics to specific molecular abnormalities in an individual's cancer, and immuno-oncology, which enhances the immune system for improved cancer control, have both revolutionised cancer care and have improved survival. As survival improves, understanding the impact of new therapies on the long term health of cancer survivors is becoming increasingly important. Data regarding the long term consequences of cancer treatment are increasingly needed so that choice of cancer therapy can balance anti-cancer efficacy with the risk of long term adverse events. For example, ovarian toxicity is a potential treatment-related adverse event which can result in the long term complications of infertility and premature menopause, yet it is infrequently an endpoint, or even assessed, in breast cancer clinical trials [9].

It is not well understood how decisions regarding the selection of trial endpoints are made in cancer trials, which stakeholders are most influential in the decision making process, and why ovarian toxicity data are not often collected. We aimed to explore these questions in this qualitative study. The barriers to and facilitators of assessment of ovarian toxicity have been reported separately [10], this manuscript reports the findings regarding endpoint selection and the role of key stakeholder groups in deciding endpoints in breast cancer trials.

Methods

Semi structured interviews with key decision makers in breast cancer clinical trials were conducted to explore the key themes I) how clinical trial endpoints are selected and II) the barriers to and facilitators of inclusion of fertility and ovarian toxicity endpoints in curative intent pharmacological breast cancer clinical trials which enrol premenopausal women. Analysis of theme II) has been previously reported [10]; this article reports on the analysis of theme I). This study was approved by the Peter MacCallum Cancer Centre Human Research and Ethics Committee (LNR/61921/PMCC).

Clinicians, consumers (patient advocates), employees of pharmaceutical companies and members of drug regulatory agencies who could speak English and had been involved in breast cancer clinical trials or in drug regulation in the last 10 years, were purposively sampled. Eligible participants were invited by email or social media, followed by letter if they did not respond. Consent was implied if the participant responded and provided contact details for the interview.

Participants were asked I) who contributes to trial endpoint selection, and II) what factors are considered during decision making. One author (WC, a medical oncologist, qualifications: MBBS, BMedSci, FRACP) conducted all semi structured interviews by phone or video conference using an interview guide until saturation of themes had been reached. All interviews were audio recorded and professionally transcribed verbatim, then deidentified after the transcription process. Grammatical changes were made to quotes for readability; changes are notated using the following legend: [ ] material added by author, [...] material omitted by author, xxx identifying details removed. Two researchers (WC and LK) independently coded several interviews. Inductive thematic analysis was performed facilitated using NVivo software [11].

Results

Participants

Two hundred and sixty stakeholders were invited by initial email invitation. Twenty eight people replied, of which 18 agreed to participate and 10 declined to participate (4 clinicians, 4 consumers, 2 members of regulatory agencies). After 18 interviews, 82 reminders were purposively sent to participants with demographics that were underrepresented; 6 participants replied, all agreed to participate. Interviews were conducted between 18th June 2020 and 27th April 2021. A coding framework was developed after 15 interviews; saturation was not reached at interview 15. After 21 interviews, saturation was reached with no new themes

Table 1. Demographics of participants

	Participants N = 25 N (%)
Age	
Median (years)	50
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%)
Member of drug regulatory agency	5 (20%)
Pharmaceutical company representative	4 (16%)
Years of experience	
Median (years)	16
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 cooperative trials group	
Yes	19 (76%)
No	6 (24%)
Member of pharmaceutical advisory committee	
Yes	16 (64%)
No	9 (36%)
Led a clinical trial	
Yes	10 (40%)
No	8 (32%)
NA (consumer)	7 (28%)
Training in clinical trial design	
Yes	12 (48%)
No	6 (24%)
NA (consumer)	7 (28%)

Abbreviation: NA, Not Applicable.

identified in subsequent interviews. A further 4 interviews were performed to confirm saturation had been reached. Twenty five interviews were performed in total (9 clinicians, 7 consumers, 5 members of drug regulatory agencies, 4 pharmaceutical company representatives). Participants were from North America (20%), Europe (52%), Australia (24%), Asia (4%); half were female. Median age was 50 years and median years of experience in breast cancer research or drug regulation was 16 years (**Table 1**).

Who contributes to the decision making process regarding endpoints in breast cancer clinical trials?

Table 2 summarises the themes related to who contributes to clinical trial endpoint selection. The main decision makers identified were pharmaceutical companies. Other stakeholders include clinicians, consumers, regulatory bodies, statisticians, cooperative trial groups and contract research organisations.

Almost all (17/25) participants reported that pharmaceutical companies were the main decision maker, particularly for industry funded clinical trials, including all pharmaceutical company representatives.

"What I see now is, I call it a pseudo involvement of academia. So, a pharmaceutical industry puts a clinical trial together, then they choose a steering committee. They choose a steering committee very carefully, so they take opinion leaders, opinion leaders they like. And then it's very attractive for academic people because they get the publications in the New England [Journal of Medicine], with very, very, very little effort that they have been doing themselves, and as I told you, very little impact at the end on what is really going on". (Clinician)

"We have several governance interactions within the company before the trial design is really finalised, and endorsed and approved. And at the end, [it] is the highest rank of the company that will endorse this investment decision and then proceed with the study". (Pharmaceutical company representative)

Table 2. Who contributes to the decision-making process regarding endpoints in breast cancer clinical trials?

Who contributes to decision making?	How do they contribute to decision making?	Number of participants who reported each reason				
		Clinician (n = 9)	Consumer (n = 7)	Pharmaceutical company representative (n = 4)	Member of drug regulatory agency (n = 5)	Overall (n = 25)
Pharmaceutical companies	Main decision maker	7	3	4	3	17
	Collaborate with clinicians	7	0	4	0	11
	Collaborate with consumers	1	3	3	0	7
	Collaborate with regulators	1	0	3	3	7
	Collaborate with cooperative groups	1	0	0	0	1
Clinicians	Influence trial design	6	1	1	0	8
	Little influence on trial design	3	0	0	1	4
Consumer/patient advocates	Influence trial design	4	7	1	0	12
	Have no influence on trial design	4	0	0	0	4
	Involvement depends on engagement of researchers	2	2	0	0	4
Regulatory bodies	Give advice on trial design	3	0	3	4	10
	Involvement depends on engagement of pharmaceutical company and/or clinicians	0	0	0	1	1
Other	Statistician	5	0	2	0	7
	Cooperative trials groups	1	0	0	0	1
	Contract Research organisation	1	0	0	0	1

Many participants reported that although pharmaceutical companies made the final decision regarding endpoints, they collaborate with clinicians including cooperative trial group researchers, consumers and regulators to reach this decision. Although almost all pharmaceutical company representatives reported they collaborate with consumers, less than half of the consumers interviewed reported this.

"It's not a voting process per se, but the sponsor will not want to embark on an expensive trial process where they've been advised that it's not the best designed by a [group] of [clinicians], who will then say, well, I don't want to put my patients on study". (Clinician)

"Not for every study, but for most of the studies, we will also have patients in the steering committee, and we almost for every study would consult with the patients or patient groups. I mean sometimes it's not with patients, but with patient advocacy groups, where we discuss the relevance of the study and we also discuss about endpoints as well". (Pharmaceutical company representative)

"[Regulatory agencies] have a pretty large impact. Certainly, from the regulator's perspective, we need to make sure that we're putting together a package that's going to be something that would potentially be acceptable to them. I think if we go to them for scientific advice and they give us advice, then, we have to seriously consider how we incorporate that. So, if we decide not to, then I think we're understanding that there may be some risks associated with that. [...] The other markets and other countries tend to look at what FDA [Food and Drug Administration] and what EMA [European Medicine Agency] do, they're good benchmarks for us to kind of put ourselves against, to make sure that we are designing the most appropriate studies". (Pharmaceutical company representative)

The perceived role of clinicians and consumers in clinical trial design varied between participants. While one third of participants reported that clinicians influenced trial design, in contrast, three clinicians and one drug regulator reported clinicians had little decision making power. However, one participant (clinician) felt that this was due to clinicians being too passive.

"Studies are broadcast. As investigators, we will choose whether or not we participate. We don't always know what goes in, in terms of the initial decision making, design process. That's sometimes a bit of a black box". (Clinician)

"I think sometimes you can have more influence than you really think. The majority of people sit on the steering committee and don't do anything and are not so involved. They leave that to the PIs [Primary Investigators] of the study, to the co-chairs of the study and the pharmaceutical company". (Clinician)

Similarly, half of participants, including all consumers interviewed, reported that consumers were now routinely included in trial steering groups, and this has increased over time. Participants felt that consumers and patient advocates were particularly valuable in reviewing study procedures, eligibility criteria and providing a patient perspective during trial design. However, the depth of consumer involvement depended on the engagement of researchers.

"It's actually changed in the last few years. [...] Since the last two years, there was a review of the practices and we're actually now involved at the concept stage. So as soon as a concept comes to the group as an idea, there's a committee set up to work through developing it and we have one member on that and we review all the documentation and all the aspects of the trial all the way through, and actually have some sort of input from the early stage". (Consumer)

"I think it's more getting the researchers on board of having a consumer at their meetings and that sort of things to really engage with them. I mean some of the researchers that I've been involved with have been engaging, but then others just basically talk about themselves and we are a bit of a tick box". (Consumer)

This view was not mirrored by other participants; half of clinicians felt that consumers were not involved in the trial design phase at all, but that they may be included in the later stages of clinical trial conduct.

"We have patient representatives in our steering committees but they have not been asked at the time of trial design what they thought". (Clinician)

Furthermore, participants reported that drug regulatory agencies can be consulted prior to and during clinical trial design for advice regarding appropriate endpoints. This relies on the sponsor(s) and/or investigator(s) to approach the regulators, and thus can vary between trials. Participants, particularly regulators and pharmaceutical company advisors report that scientific advice from drug regulators now occurs more frequently, and this may streamline drug approval after trial completion.

"There are a couple of companies who have come to us before doing anything, asking for advice, getting an agreement, then going for the trial. And we see that those companies that come in this way, they just go through the system without any problems. Because they've done things as we want them. And if their study's positive, xxx, it just goes through the system without any problems". (Member of drug regulatory agency)

What factors are considered during decision making about trial endpoints?

Factors identified as important considerations in determining trial endpoints are summarised in **Table 3**. These include the main goal of the trial (such as demonstrating clinical benefit and regulatory approval), preference to use established endpoints (such as endpoints which are already widely used in other trials, and endpoints which are listed in tools such as European Society of Medical Oncology Magnitude of Clinical Benefit scale (ESMO-MCBS)), resources (such as cost, time required to collect endpoint and burden on patients, investigators and trial sites), and the investigational agent studied (such as existing clinical and preclinical data regarding the agent, the setting in which the agent is used and the target population for the investigational agent). Participants mostly focused on the factors considered during selection of the primary endpoint. However, quality of life (QOL) and safety were identified as important factors to be considered in the selection of secondary and exploratory endpoints.

The aim of the trial and demonstration of clinical benefit were both major factors in endpoint decision making, particularly when selecting the primary endpoint, reported by more than half of participants, especially clinicians and members of drug regulatory agencies.

"We do think about what's clinically meaningful and, depending on the intent of the study and what the primary objective is, you try and have your endpoint then align with the primary objective; to make sure you're measuring something that is actually meaningful and that is going to, if you reach it, demonstrate success". (Clinician)

All pharmaceutical company representatives reported that meeting the requirements for regulatory approval was the major factor considered during endpoint selection. This was echoed by almost all the members of drug regulatory agencies, but just one quarter of clinicians.

"I think it depends on the objective of the study. In pharmaceutical companies, we do many studies which are for registration. So, when you have a study for registration then you have to consider what's in the regulatory landscape, what are the validated endpoints, what are those endpoints that are going to be acceptable from a regulatory standpoint, and that typically goes into the conversation for the primary endpoints for registration of studies. [These] are selected based on what is likely going to get your plans to registration". (Pharmaceutical company representative)

Half of participants reported that endpoints demonstrating the impact on QOL were frequent considerations. This was reported by most clinicians but less than half of consumers. However, QOL endpoints were often incorporated as secondary or exploratory endpoints.

"We're not just looking at the science only. We're looking at impact on patients' lives. And it's that reminder that as scientists and physicians you have to think about the fact that you have your goals in the treatment of the patient, but you might forget to ask what the goals of the patient are for the treatment. And they might not be the same thing". (Consumer)

"Generally, [the primary endpoint] is usually survival endpoints but they may also ask for quality of life data. They may go if you get three months in this disease, but people are miserable [during that time], then that's still not going to get you across the line. They want to see sur-

Table 3. What factors are considered when deciding on endpoints in breast cancer clinical trials?

Which factors are considered	Sub-themes	Number of participants who reported each reason				
		Clinician (n = 9)	Consumer (n = 7)	Pharmaceutical company representative (n = 4)	Member of drug regulatory agency (n = 5)	Overall (n = 25)
Aim of trial	To demonstrate efficacy and/or clinical benefit	7	0	2	4	13
	Impacts on quality of life	5	3	2	1	11
	To result in regulatory approval	2	0	4	4	10
	To incorporate what patients want	1	3	1	0	5
	To demonstrate safety	2	0	0	2	4
	To better understand the action of the drug	1	0	2	0	3
	Profitable investment	0	1	1	0	2
The agent studied	Treatment setting	4	1	2	0	7
	Existing clinical data	4	0	1	1	6
	Target population	4	0	0	1	5
	Existing preclinical data	1	0	0	0	1
Standard endpoints	Established endpoints which are widely accepted and used	4	0	2	0	6
	Guidelines regarding which endpoints to use	2	0	2	0	4
Study procedures and resources	Data collection and analysis considerations	5	0	1	1	7
	Cost of the trial	3	1	1	0	5
	Time required to reach endpoint	4	0	1	0	5
	Feasibility of trial	2	0	0	0	2

vival, but certainly secondary data may be quality of life". (Clinician)

Although survival endpoints were predominantly reported by participants as the main aim of clinical trials, and many believed they were the main endpoints assessed for regulatory drug approval, a member of a drug regulatory agency reported that QOL and patient preference is also considered during the drug approval process.

"From the point of view of the regulators, they [consider] approving any drug, any intervention, if the ratio between benefit and risk is positive. And the positivity of this benefit-risk ratio may be either because there is a higher [survival] benefit with respect to the standard treatment or because there is an advantage from the patient preference, from the quality of life point of view. So, benefit can be not necessarily only in terms of the classical definitions of benefit that we are used to, like prolongation of survival or disease-free survival". (Member of drug regulatory agency)

It was also acknowledged by two participants that clinical trials are ultimately an investment decision.

"Pharmaceutical [companies] do a lot of good, of course because with their medications a lot of lives are saved. But we have to remember that they are commercial entities, with stockholders that want the bottom line, they want the money". (Consumer)

Moreover, some participants reported that factors related to the investigational agent studied are important considerations, such as existing clinical and preclinical data, the target population and the treatment setting.

"When we are dealing with cancer products, of course the best thing would be to have a randomised study showing a survival gain. That's perfect scenario. But, as you probably know, drug development is becoming more and more targeted [...] Breast cancer is no longer breast cancer, it's hormone-receptor positive, it's triple negative, it's HER2 positive, it's HER2 positive hormone-receptor negative, and PIK3A mutated etc. So, the common diseases, the large cancer diseases like lung cancer and breast cancer, even these are becoming rare disease. [...] So, the good old fashioned, randomised study with a thousand patients in each arm, that train has left the station. We're dealing with single arm trials with 100 patients, and obviously it's difficult to make any conclusions on the survival or progression-free survival from single arm studies because of unmeasured confounding and bias. So, what do you do? You rely on endpoints that show a direct drug effect, for example, response rates. You will not see a response unless there is a drug effect". (Member of drug regulatory agency)

Clinicians and pharmaceutical company representatives also reported that certain endpoints are standardised for neoadjuvant or adjuvant trials of breast cancer therapies (reported by 6 participants), and existing guidelines such as the Standardised Definitions for Efficacy Endpoints (STEEP) criteria and the ESMO-MCBS can aid in decision making (reported by 4 participants).

"You don't want to demonstrate something different. So, for a classical adjuvant trial, you have time to event, a long term time to event endpoint such as an efficacy endpoint. And for a neoadjuvant study, you would rather go for the pathological complete response, either as primary or secondary endpoint". (Clinician)

"A few years ago, the Breast International [Group] and the North American Breast Cancer Group joined forces to review a little bit the endpoints in adjuvant clinical trials and produced a paper [...] the STEEP criteria, where we reviewed essentially all the endpoints and recommended invasive disease-free survival as the preferred endpoint in adjuvant studies. And what I could see of course is that companies have followed this and most of the time, it is what they are doing". (Clinician)

Lastly, factors related to study procedures are also considered. Participants, especially clinicians, reported that selection of endpoints of interest may be limited by available resources, such as money and time. Funding and burden on trial sites were identified as barriers to assessing secondary endpoints such as QOL and additional exploratory endpoints.

"Patient reported outcomes are really important, and I think they're underutilised in clinical research in breast cancer at the moment. But

obviously I am aware that there are barriers around that, particularly with funding trials which look at quality of life". (Consumer)

"The challenges, the point that always is made when you ask to have [additional] questions is that you need more time, you need more resources, [...] you need more money". (Clinician)

Data analysis and ability to interpret the data in a meaningful way were also reported as notable factors considered during endpoint selection.

"You can have a lot of very important questions but not every question which you want to answer is very important. You have to be careful not to overload a clinical trial because every endpoint you want to analyse. You need to collect data for that and in the end, you don't want to have a data graveyard. You want to use the data you have". (Clinician)

Discussion

To our knowledge, this is the first study exploring the role of key stakeholders in clinical trial endpoint selection, and the factors that are considered when deciding endpoints. Pharmaceutical companies were almost always identified as the main decision maker in selecting trial endpoints. Factors considered when selecting endpoints included the aim of the trial, the agent studied, resources, current endpoint standards and regulatory approval requirements. Furthermore, all pharmaceutical advisors reported that regulatory approval was the major factor considered during endpoint selection, highlighting the indirect influence that regulators also have on the design of clinical trials.

The pharmaceutical industry plays an important role in research and development of new cancer drugs. The landscape of clinical trials has changed rapidly since the Bayh-Dole Act passed in United States (US) Congress in 1980. It allows businesses to patent inventions (such as medications and devices) and profit from government funded research discoveries, thus incentivising the private sector to invest in translating scientific discoveries into pharmaceutical products [12]. Research spending by pharmaceutical companies surpassed that of the US National Institutes of Health in 1992 [13]; and between 2010 to 2020 89% of phase 3 randomised controlled trials in breast, colorectal and non small cell lung cancer received funding from the pharmaceutical industry, compared to 57% between 1995 to 2004 [14]. This is not unexpected given the cost of new anti-cancer agents and the high financial cost and resources required to perform clinical trials. This shift in funding may contribute to our study finding, that the pharmaceutical industry were key decision makers in clinical trial endpoint selection. However, we did not ask participants if the key decision maker was different between pharmaceutical led versus investigator initiated trials run by cooperative groups where the pharmaceutical industry may play less of a role in protocol development, even if they supply the drug.

Regulatory agencies and their evidence requirements were reported in our study to indirectly influence the selection of clinical trial endpoints. Drug regulatory agencies were identified as key collaborators when selecting endpoints, and all pharmaceutical company representatives in our study reported that regulatory approval was a major factor in deciding which endpoints to choose. Indeed, Food and Drug Administration (FDA) drug approvals are more common with industry funded phase 3 cancer randomised controlled trials compared to trials sponsored by national cooperative groups (one study reported that 97.3% of industry funded phase 3 randomised controlled trials resulted in drug approval versus 9.3% of cooperative group funded phase 3 randomised controlled trials, $P<0.001$) [2].

Almost half of participants in our study, especially clinicians and consumers, reported that QOL was a significant factor considered when selecting clinical trial endpoints, particularly secondary and exploratory endpoints. QOL is increasingly recognised as an endpoint of clinical benefit, particularly in the metastatic setting, and it is included in the ESMO-MCBS [15]. Regulatory agencies, such as the FDA, have now listed improvements in a patient's QOL as a recognised indicator of clinical benefit [16], and this was echoed by a member of a regulatory agency interviewed in our study. However, QOL is not often measured in early-stage breast cancer trials, and validated tools used to measure QOL do not assess long term treatment

toxicities such as ovarian toxicity, which can have profound impacts on enduring health and wellbeing [17]. Attention to these lasting treatment related adverse effects should be considered when evaluating the risk-benefit ratio of a new anti-cancer agent and its impact on QOL.

We found that participants had discordant views regarding the influence of consumers on clinical trial endpoint selection. Research co-design, where patients are involved in research design, is increasingly recommended in healthcare [18]. Qualitative research on cancer trial endpoint selection has reported that patients often do not understand commonly used surrogate endpoints such as progression-free survival (PFS), and can misunderstand the intent of their cancer treatment due to misperceptions about trial endpoints [19-21]. Although consumers are increasingly involved in cancer trials [22], the amount of influence consumers have on decision making needs to be examined, with many partipants in our study reporting their involvement to be tokenistic. This has been echoed by other studies from a range of different countries, which have reported that consumer involvement within trials can be cursory or engagement of consumers only occurs late, thus diminishing their value [23-25]. Barriers to consumer involvement in clinical trials included uncertainty regarding how to involve consumers effectively and systematically, a lack of resources and lack of consumer training; whereas facilitators include consumers feeling valued and respected [25, 26]. Meaningful consumer engagement is now a requirment by certain research funding groups [27], which may improve patient-centric endpoint selection for research funded by those groups. Ideally, all future clinical trials should be designed to reflect both scientific questions as well as patient priorities which, as a consumer in this study reported, may not be exactly the same.

In addition to demonstrating clinical benefit and regulatory requirements, the cost and resources required to perform clinical trials were reported by participants in our study to be major factors considered in clinical trial endpoint selection. There has been a change in clinical trial endpoint selection in breast cancer, with a trend towards using surrogate endpoints such as invasive disease-free survival (iDFS) and PFS as the primary clinical endpoint rather than overall survival (OS) [28, 29]. This coincides with a shift in the endpoints used to support FDA and European Medicine Agency (EMA) approvals in the last decade, with trials using surrogate primary endpoints making up the majority of trial data used to support drug regulatory approval applications [2, 3, 30, 31]. This change enables shorter duration clinical trials and a shorter time interval to data availability, a major factor considered during endpoint selection identified in our study, which may lead to drug approval more rapidly. However, the increasing use of surrogate primary endpoints may lead to flawed trials and misleading results, as surrogate endpoints may not translate to clinically meaningful outcomes such as improved OS or QOL [32, 33]. Medications approved on the basis of a PFS benefit may be later shown to have no OS benefit and adverse impacts on QOL longer term, thus their use may have actually caused overall harm [34].

As reported by participants in our study, there are tools that clinical trialists can use when designing a clinical trial. In non-metastatic breast cancer, the STEEP criteria proposed standard definitions for efficacy endpoints in adjuvant breast cancer trials [35, 36] and the Definition of the Assessment of Time to event Endpoints in Cancer Trials (DATECAN) initiative surveyed breast cancer experts to define standardised definitions of time to event endpoints in both metastatic and non-metastatic breast cancer randomised controlled trials [37]. The ESMO-MCBS is a tool developed to assess the relative magnitude of clinical benefit of new cancer treatments for solid tumours, where a score is assigned depending on which endpoints are assessed [15]. The World Health Organisation Cancer Essential Medicines working group have acknowledged the role of ESMO-MCBS as a screening tool when assessing cancer treatments considered for addition to the essential medicines list [38]. While these tools can be used as a guide, the decision regarding which endpoints are included in each individual trial is still determined trial by trial. Indeed, less than one third of randomised controlled trials for breast cancer, lung cancer, colorectal cancer and pancreatic cancer met the ESMO-MCBS thresholds for meaningful clinical benefit [39]. Furthermore, flaws in trial

design can lead to biases in the ESMO-MCBS score, which can overestimate the true benefit; one such limitation is the variable validity of surrogate outcome measures such as DFS, a commonly used primary endpoint in breast cancer trials [40]. Moreover, none of these tools address long term consequences of anticancer therapies such as ovarian toxicity.

There are a number of limitations to this study. Although we attempted to sample globally, only one participant from Asia was included; a major barrier to participation may be that the interviews were conducted in English only. Furthermore, this study was conducted during the Severe Acute Respiratory Syndrome Coronavius-2 (SARS CoV2, COVID-19) pandemic, which may have also impacted participation. Although we sampled stakeholders from different backgrounds, demographics and level of experience, there may be participation bias as participants may be more likely to have been more interested in the research question than non participants. Moreover, other stakeholders involved in trial design such as statisticians were not interviewed. We did not differentiate between endpoint selection for phase I, II or III trials; decision making processes may differ between phase I, II and III trials given the differences in trial design and trial aims. 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.

Conclusion

Clinical trial design and endpoint selection is rapidly changing in oncology, influenced by the changing therapeutic landscape and impact of key stakeholder groups. The pharmaceutical industry are the main decision makers when deciding clinical trial endpoints, and therefore hold foremost influence on current and future clinical trial design, drug development and drug approval. There needs to be increased attention to the role of clinicians and consumers in trial endpoint selection, and the depth of their involvement needs to be more than perfunctory and superficial given the vital role these stakeholders have in ensuring clinically relevant questions are answered in potentially practice changing clinical trials. Regulatory agencies and their evidence requirements shape the design of clinical trials. Drug regulatory agencies have considerable indirect influence on the pharmaceutical industry, and therefore have a key role in assuring the quality of future trial design and endpoint selection.

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Disclosure of conflict of 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.

RA Anderson: Professor Anderson reports personal fees and non-financial support from Roche Diagnostics, outside the submitted work.

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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