BMJ Open

Exploring the facilitators and barriers to using an online infertility risk prediction tool (FoRECAsT) for young women with breast cancer: A qualitative study protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033669
Article Type:	Protocol
Date Submitted by the Author:	16-Aug-2019
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Keywords:	Breast cancer, Premenopausal, Infertility, Risk prediction

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Abstract:

Introduction:

As cancer treatments may impact on fertility, a high priority for young breast cancer patients is access to evidence-based, personalised information for them and their healthcare providers to guide treatment and fertility-related decisions prior to cancer treatment. Current tools to predict fertility outcomes after breast cancer treatments are imprecise and do not offer individualised prediction. To address the gap, we are developing a novel personalised infertility risk prediction tool (FoRECAsT) for premenopausal breast cancer patients that considers current reproductive status, planned chemotherapy and adjuvant endocrine therapy to determine likely post-treatment infertility. The aim of this study is to explore the feasibility of implementing this FoRECAsT tool into clinical practice by exploring the barriers and facilitators of its use amongst patients and healthcare providers.

Methods and analysis:

A cross-sectional exploratory study will be conducted through semi-structured in-depth telephone interviews with 15-20 participants each from the following groups: (a) premenopausal breast cancer patients younger than 40, diagnosed within last 5 years, (b) breast surgeons, (c) breast medical oncologists, (d) breast care nurses (e) fertility specialists and (f) fertility preservation nurses. Breast cancer patients will be recruited from the joint Breast Service of three affiliated institutions of Victorian Comprehensive Cancer Centre in Melbourne, Australia– Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital, and clinicians will be recruited from across Australia. Interviews will be audio-recorded, transcribed verbatim and imported into qualitative data analysis software to facilitate data management and analyses.

Ethics and dissemination:

The study protocol has been approved by Melbourne Health Human Research Ethics Committee, Australia (HREC number: 2017.163). Confidentiality and privacy will be maintained at every stage of the study. Findings will be disseminated through peer-reviewed scholarly and scientific journals, national and international conference presentations, social media, broadcast media, print media, internet and various community/ stakeholder engagement activities.

Article Summary:

Strengths and limitations of this study:

1) Obtaining representative stakeholder feedback is an essential step in ensuring that a risk prediction tool is feasible and acceptable for use in clinical practice.
2) This tool could be adapted to newer breast cancer treatments and for other cancers.
3) Non-probability sampling may increase the risk of selection bias.
4) Recruitment is limited to breast cancer patients where fertility was discussed prior to cancer treatment, findings may not be applicable where fertility was not discussed.
5) This study will be conducted in the Australian setting, findings may not be generalisable to different health settings.

Introduction:

Globally, breast cancer is the most frequent cancer diagnosis in reproductive-aged women, with approximately 100,000 women younger than 40 years diagnosed annually worldwide, representing one-quarter of new breast cancer cases [1-3]. In Australia, most women are diagnosed with early-stage disease, and with current treatment, the five-year survival rate for women diagnosed with breast cancer is often excellent (90.8%) [4]. Recommended treatment can include gonadotoxic chemotherapeutic agents and thus poses a potential threat to fertility by destroying the number of eggs stored in the ovaries [5,6]. If the number of eggs is substantially depleted, early menopause and/or permanent infertility can result [7], and will commonly present as amenorrhoea (i.e. cessation of the menstrual cycle) [8]. Infertility and/or early menopause is a recognised long-term adverse effect of breast cancer treatment in premenopausal women and has serious implications for the survivorship experience of these women [8,9].

Fertility is well-established to be a priority for many young pre-menopausal breast cancer patients. More than half are concerned about their future fertility, and 50-76% wish to consider pregnancy following cancer treatment [10-12]. This number is likely to increase with the social trends of delayed motherhood until older reproductive ages [13,14]. Concerns about the potential risk of infertility and the inability to conceive in the future have direct implications for treatment efficacy and long-term physical and emotional health [10,15-19] – specifically it may influence patients to choose less optimal adjuvant therapies to reduce impact on fertility [10,11,20,21] or the uptake of fertility preservation options despite potential physical, emotional and financial burden [22-24]. Young women with breast cancer actively seek and desire knowledge, and improved information translates into better health outcomes[25,26]. Core to making informed fertility-related decisions is an understanding of the risk of infertility, but the currently available information about fertility outcomes following breast cancer treatment can only determine broad risk categories (e.g. intermediate risk: 30-70% risk of infertility) [27] and individual factors which are known to affect fertility in women (e.g. age, body mass index, smoking, previous fertility, serum ovarian markers) are not included in the risk prediction. There is a gap in personalised information to inform young breast cancer

patients about likely fertility outcomes after treatment [28-30]. Individuals increasingly use the internet seeking knowledge to meet their unmet information needs [31], therefore, an evidence-based online prediction tool may provide reliable, easy-to-access and personalised information of likely post-treatment infertility to address the gap and better manage the fertility-related needs [32,33].

Accurate prediction of infertility after breast cancer treatment is complex and requires consideration of baseline fertility and the likely impact of planned cancer treatments on fertility [28]. There is growing evidence that baseline fertility indicators prior to breast cancer treatment may predict the likelihood of developing amenorrhoea after treatment [29,34,35]. However, no previous studies have included baseline demographic and lifestyle factors, as well as serum ovarian markers and cancer treatment factors, all together, to predict fertility. To address this gap, we are developing the fertility after cancer predictor (FoRECAsT) tool for young breast cancer patients which considers both baseline fertility indicators and the impact of planned cancer treatment to provide an individualised risk of amenorrhoea at different time points after initial treatment (12 months, 24 months, 36 months, 48 and 60 months) to assess longitudinal changes in infertility risk, with amenorrhoea being a surrogate marker for infertility. The tool will allow users to input individual data (baseline demographic and lifestyle factors, serum ovarian markers and recommended breast cancer treatment) to determine a personalised risk of infertility after breast cancer treatment.

There are two key parts to the FoRECAsT tool – the algorithm development and the user interface. To develop the risk prediction algorithm (part one), authors from studies exploring variables related to fertility at baseline and impact of breast cancer treatment (Table 1) [29,36-44] have been invited to join the FoRECAsT Collaboration and contribute their data to the FoRECAsT database and these data are being used to build a predictive model. The algorithm will use Bayesian inference technique, which is the preferred method in complex algorithm development, in combination with Monte-Carlo Markov simulations [45-49]. From the algorithm, a working prototype of the tool will be developed (part two) as a proof-of-concept. To achieve part two and ensure that the tool is widely used clinically, the user interface will be developed in consultation with stakeholders including patients and patient advocacy groups. This protocol reports on a key aspect of this consultation process. Findings will be used to design the user interface of the FoRECAsT (prototype) tool ensuring it is easy to use and understand.

Objectives

The main purpose of this study is to explore perceptions, ideas and opinions from young breast cancer patients and clinicians regarding the feasibility of implementing the FoRECAsT tool including barriers and facilitators. Our findings will inform the development of FoRECAsT online infertility risk prediction tool.

Methods and analysis:

Study design

A cross-sectional exploratory study will be conducted through semi-structured in-depth telephone interviews with key stakeholders.

Study participants/ stakeholders

The following stakeholders will be included in our study:

a) Patient group: 15 -20 breast cancer patients.
b) Clinician group:
   - 15 -20 breast surgeons,
   - 15 -20 breast medical oncologists,
   - 15 -20 breast care nurses and
   - 15 -20 fertility specialists
   - 15 -20 fertility preservation (FPS) nurses.

The sample size is an appropriate minimum sample required for meaningful outcomes. However, as per qualitative methodology, participants will continue to be recruited until informational redundancy is achieved [50].

Eligibility Criteria

Breast cancer patients:

Inclusion criteria:

To be eligible to participate breast cancer patients must be

a) female,
b) diagnosed within the last five years.
c) aged 18-40 years
d) premenopausal at breast cancer diagnosis
e) have evidence of prior discussion with a health care provider about the risk of developing infertility after breast cancer treatment either through referral to a fertility specialist or documented discussion inpatient notes (so as not to cause distress in those who had not had a prior discussion about potential infertility),
f) concerned about future fertility after chemotherapy and/or have not completed their family (as identified by the treatment team),
g) able to give informed written consent and
h) able to speak and understand English.

Exclusion criteria:

Women with metastatic breast cancer.

Clinicians:

Inclusion criteria:

To be eligible to participate clinicians who:

a) have a valid Australian License for practice,
b) have at least one year of clinical experience in their respective discipline,
c) consult to women with breast cancer,

d) will be able to give informed written consent and
e) will able to speak and understand English.

Recruitment

Breast cancer patients will be recruited using purposive sampling by the breast care nurses from the joint Breast Service of Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital. Figure 1 illustrates the recruitment of breast cancer patients. Clinicians will be recruited using an e-flyer through their respective online communities across Australia (except northern territory and Tasmania due to ethics committee coverage), i.e. Breast Surgeons of Australia & New Zealand (BreastSurgANZ), Medical Oncology Group of Australia (MOGA), Fertility Society of Australia (FSA), Cancer Nurses Society of Australia (CNSA) and McGrath Foundation. Figure 2 shows the recruitment of clinicians. Participation is voluntary, and participants may choose not to participate in the study or may withdraw from the study at any time. There will be an opportunity for participants to ask the research team any questions regarding the study. Invited participants who do not respond, will be followed up with a second invitation two weeks after initial contact.

Data collection

In-depth telephone interviews will be guided by semi-structured interview schedules and will be carried out by the research team. The interview schedules are structured in consultation with clinical experts and qualitative research specialists based on Aizen's Theory of Planned Behaviour (TPB) [51]. They are customised to the level of stakeholders to allow questioning strategy and conversations to be more flexible. The study is supported by a consumer/patient who is a part of the working party and involved in the design of the study, and preparation of all the study materials from the patient's perspective.

Each interview is anticipated to last for 15-20 minutes. Interviews will be audio-recorded on a portable, electronic digital voice recorder (Olympus VN-731PC) and transcribed verbatim. The audio recordings and transcripts will be securely stored in a password-protected folder on The University of Melbourne server with access permitted to authorised personnel only. Verbal informed consent will be obtained for audio recording the interview. Interviews will be conducted until saturation is reached [50]. Patients and clinicians who consent to be interviewed will be offered the opportunity to view a copy of the transcripts prior to data analysis.

Outcome measures

Socio-demographic data will be collected from each participating breast cancer patient and clinician. Breast cancer patients will be asked about their current age, the highest level of education attained, employment status, stage of cancer, relationship status, and fertility history. Clinicians will be asked about their age, years of clinical experience, and proportion of patients seen with breast cancer.

Qualitative data will be collected focusing on five topics (Table 2):
1) Interest in using the tool;
2) Access and technical skills;

3) User attributes;
4) Potential impact of the tool on consultation;
5) Anticipated outcomes and benefits.

Data analysis

The processes of data collection and data analysis will be ongoing. Transcripts will be imported into a qualitative data analysis software (QRS NVivo version 12- QRS International Pty Ltd, Doncaster, Vic., Australia) to facilitate data management and analyses. The five broad areas are developed based on the theoretical framework of Planned Behaviour [51]**.** Transcripts will be coded line-by-line identifying keywords, concepts and reflections in accordance with the framework of Miles & Huberman [52], a widely used framework for qualitative research methodology. Coding will be conducted as an iterative process: starting with coding for broad themes, before coding into hierarchical categories and subthemes.

To ensure the integrity and consistency of the codes and reduce bias, codes will be reviewed by the qualitative research specialist. The research team will discuss the coding tree and reach consensus. Subsequently, content analysis will also be performed for each code, to support results from thematic analyses by identifying essential aspects of the content and highlighting the recurrence of themes, to present results clearly and effectively. A final list of themes and sub-themes will be determined through patterns as soon as further data that will emerge from the study add little to the emerging theory. Theoretical saturation is reached once no new themes emerge. Results will be reported according to the consolidated criteria for reporting qualitative research developed by Tong et al. [53].

Ethics and dissemination:

Ethics approval

The study protocol has been reviewed and approved by the Human Research Ethics Committee of the Melbourne Health, Australia (HREC number: 2017.163). This study will be conducted in compliance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research, the Australian Code for the Responsible Conduct of Research and the Declaration of Helsinki.

Confidentiality

Confidentiality and privacy will be maintained at every stage of the study. Individual participants will not be identifiable to any other members of their group or anyone else in the wider community. Participants will be approached, recruited and contacted in a confidential, one-to-one manner and no public dissemination of participants' details will occur. Contact details for the researchers and relevant ethics committee(s) will be provided to address any questions or concerns participants may have. Audio-recordings and individual transcripts will be stored on a password protected and secured The University of Melbourne server, which is backed up daily. Study-related records will be retained in a secure storage facility for at least seven years after the completion of the research as required by the Australian National Health and Medical Research Council.

Dissemination

All interested participants will be sent a summary report of the results via email or mail with de-identified aggregated findings. Only de-identified results will be published. The results will be actively disseminated through peer-reviewed scholarly and scientific journals, national and international conference presentations, social media, broadcast media, print media, internet and various community/ stakeholder engagement activities. The consumer/patient will also provide comment on the findings and contribute to the dissemination plan via consumer websites such as Breast Cancer Network Australia.

Strengths and limitations of this study:

This will be the first personalised tool considering baseline demographic and lifestyle factors, serum ovarian markers and cancer treatment factors all together in predicting the impact of breast cancer treatments on fertility. Strengths of this study include co-design the tool with patients' and healthcare professionals' needs and preferences in mind. This tool could potentially be implemented globally with adaptation to newer breast cancer treatment. Additionally, the tool could be adapted for other cancer treatments.

Limitations include the use of non-probability sampling to recruit breast cancer patients which may increase selection bias [54]. Recruitment is limited to breast cancer patients where fertility was discussed prior to cancer treatment and our findings may not be applicable to circumstances where fertility was not discussed. Also, our findings cannot be generalised to breast cancer patients from more diverse cultural and linguistic backgrounds and those with advanced breast cancer.

Authors' contributions:

MP conceived the research idea, participated in the design of the study, development of all study documents, ethical approval process and reviewed this manuscript. ZE participated in the design of the study, development of all study documents, ethical approval process, study coordination and drafted this manuscript. YJ participated in the design of the study, development of all study documents and reviewed this manuscript. MH, LS, RAA, HIS, KS, CS, AA, MMM, SC, PP, FA participated in the review of all study documents and the manuscript. LCL and SP participated in ethics approval process and reviewed the manuscript. WC and AG reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This Research Project/Program was supported by the Victorian Government through a Victorian Cancer Agency (Early Career Seed Grant) awarded to Dr Peate.

Competing interests

None.

Acknowledgements:

MP and YJ both are currently supported by an MDHS Fellowship, The University of Melbourne. At the time of this study, MP was supported by a National Breast Cancer Foundation Early Career Fellowship (ECF-15-005). MH is supported by a National Health and Medical Research Council of Australia (NHMRC) Practitioner Fellowship and is part of the Women Choosing Surgical Prevention (WISP) investigator team funded by Stand Up to Cancer. The authors would like to thank FoRECAsT Consortium for contributing their datasets to develop the infertility risk prediction algorithm.

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Table 1: Candidate predictors for fertility

Lifestyle factors	Age, race, body mass index, diet, exercise, smoking, alcohol, caffeine, drugs
Medical history	Prior (in)fertility and IVF, menstruation history, tubal and gynaecological disease, endometriosis, polycystic ovary syndrome, sexually transmitted infections, pelvic surgery, family history of (in)fertility and menopause
Serum markers of ovarian Function	Follicle stimulating hormone, luteinising hormone, estradiol, inhibin B, antimullerian hormone (AMH), antral follicle count, ovarian volume
Cancer factors	Age at diagnosis, stage, receptor status, type of treatment (dose and duration)

Table 2: Semi-structured interviews topic guides for participants

Broad topics	Specific topics
1. Interest in using the infertility risk prediction tool	Extent of information received/ delivered about risk of infertility, decision making with current infertility risk 'calculators', perceived satisfaction in using current calculators, interest in having a more accurate infertility risk prediction tool
2. Access and confidentiality	Requirements around access and user interface, security, confidentiality of input information, technical skill
3. User attributes	Perceptions of ease of use and preferences for data entry
4. Impact on fertility consultation	Perceptions of impact on fertility consultation
5. Anticipated outcomes and benefits	Benefits of using a more accurate tool, barriers and additional suggestions to better meet fertility-related needs.

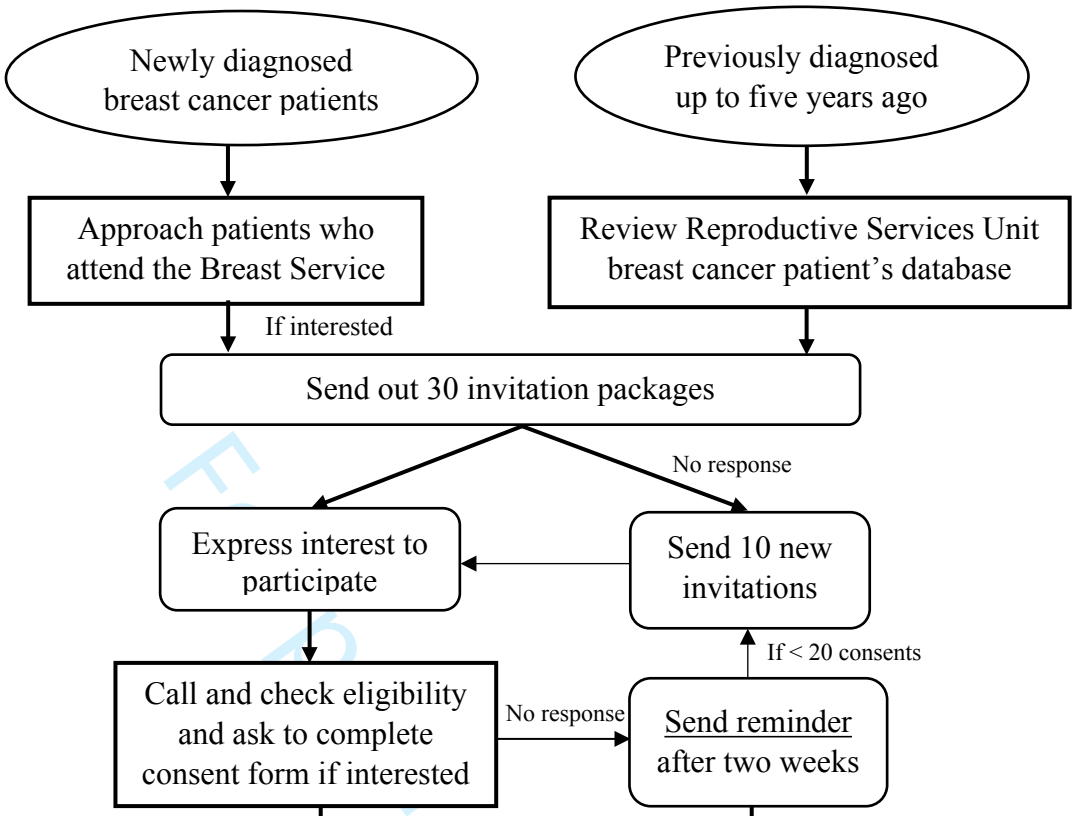

Figure 1: Illustration of the recruitment of breast cancer patients.

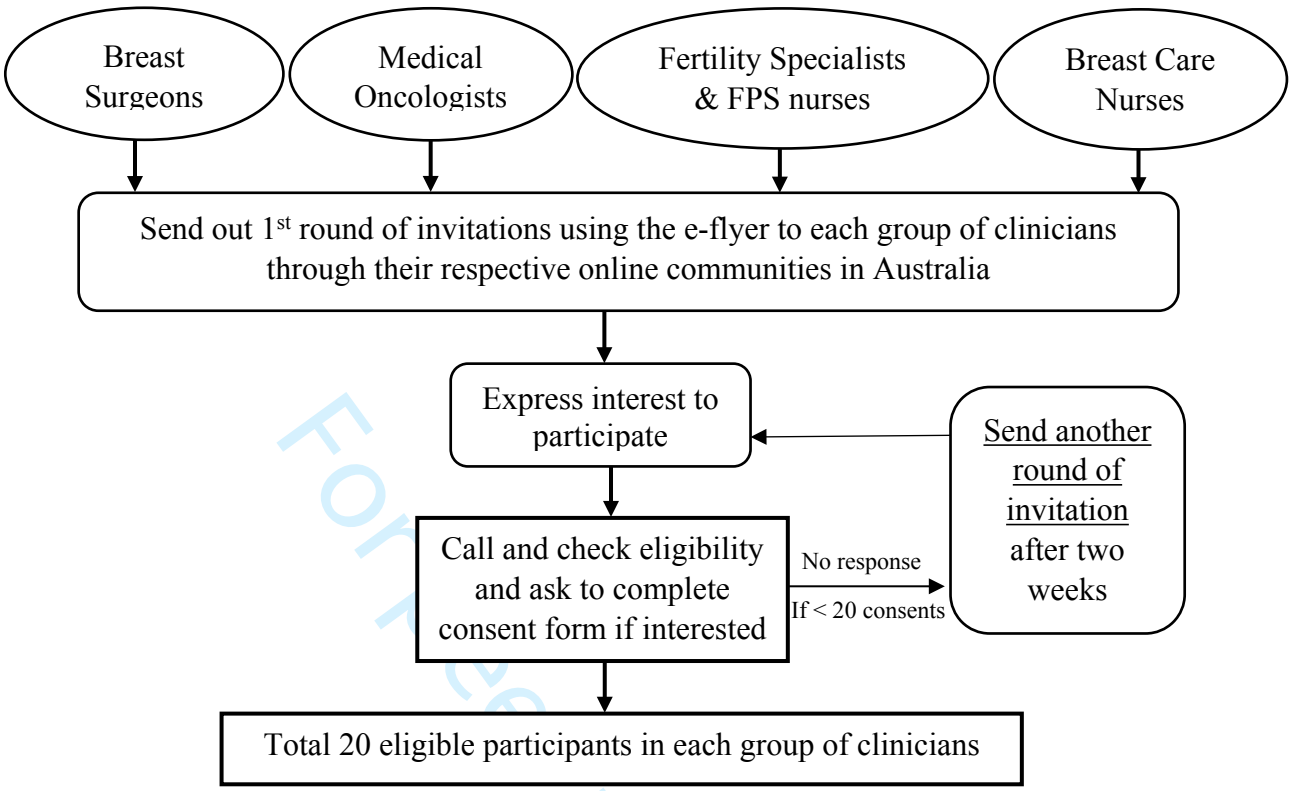

Figure 2: Illustration of the recruitment of clinicians.

FPS, Fertility preservation nurse

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	4
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	5,6
Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	7,8,9
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	7,8
Context - Setting/site and salient contextual factors; rationale**	7,8
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	8
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	9
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	8

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	8
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	7
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	8
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	9
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	9

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Not applicable
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Not applicable

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	5,10
Limitations - Trustworthiness and limitations of findings	10

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	10
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	10

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014 DOI: 10.1097/ACM.0000000000000388

BMJ Open

Exploring the facilitators and barriers to using an online infertility risk prediction tool (FoRECAsT) for young women with breast cancer: A qualitative study protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033669.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Dec-2019
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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Oncology, Obstetrics and gynaecology
Keywords:	Breast cancer, Premenopausal, Infertility, Risk prediction

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Title: Exploring the facilitators and barriers to using an online infertility risk prediction tool (FoRECAsT) for young women with breast cancer: A qualitative study protocol.

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Abstract:

Introduction:

As cancer treatments may impact on fertility, a high priority for young breast cancer patients is access to evidence-based, personalised information for them and their healthcare providers to guide treatment and fertility-related decisions prior to cancer treatment. Current tools to predict fertility outcomes after breast cancer treatments are imprecise and do not offer individualised prediction. To address the gap, we are developing a novel personalised infertility risk prediction tool (FoRECAsT) for premenopausal breast cancer patients that considers current reproductive status, planned chemotherapy and adjuvant endocrine therapy to determine likely post-treatment infertility. The aim of this study is to explore the feasibility of implementing this FoRECAsT tool into clinical practice by exploring the barriers and facilitators of its use amongst patients and healthcare providers.

Methods and analysis:

A cross-sectional exploratory study has been conducted through semi-structured in-depth telephone interviews with 15-20 participants each from the following groups: (a) premenopausal breast cancer patients younger than 40, diagnosed within last 5 years, (b) breast surgeons, (c) breast medical oncologists, (d) breast care nurses (e) fertility specialists and (f) fertility preservation nurses. Breast cancer patients are being recruited from the joint Breast Service of three affiliated institutions of Victorian Comprehensive Cancer Centre in Melbourne, Australia– Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital, and clinicians are being recruited from across Australia. Interviews are being audio-recorded, transcribed verbatim and imported into qualitative data analysis software to facilitate data management and analyses.

Ethics and dissemination:

The study protocol has been approved by Melbourne Health Human Research Ethics Committee, Australia (HREC number: 2017.163). Confidentiality and privacy are maintained at every stage of the study. Findings will be disseminated through peer-reviewed scholarly and scientific journals, national and international conference presentations, social media, broadcast media, print media, internet and various community/ stakeholder engagement activities.

Article Summary:

Strengths and limitations of this study:

1) Obtaining representative stakeholder feedback is an essential step in ensuring that a risk prediction tool is feasible and acceptable for use in clinical practice.
2) This tool could be adapted to newer breast cancer treatments and for other cancers.
3) Non-probability sampling may increase the risk of selection bias.
4) Recruitment is limited to breast cancer patients where fertility was discussed prior to cancer treatment, findings may not be applicable where fertility was not discussed.
5) This study will be conducted in the Australian setting, findings may not be generalisable to different health settings.

Introduction:

Globally, breast cancer is the most frequent cancer diagnosis in reproductive-aged women, with approximately 100,000 women younger than 40 years diagnosed annually worldwide, representing one-quarter of new breast cancer cases [1-3]. In Australia, most women are diagnosed with early-stage disease, and with current treatment, the five-year survival rate for women diagnosed with breast cancer is often excellent (90.8%) [4]. Recommended treatment can include gonadotoxic chemotherapeutic agents and thus poses a potential threat to fertility by destroying the eggs stored in the ovaries [5,6]. If the number of eggs is substantially depleted, early menopause and/or permanent infertility can result [7], and will commonly present as amenorrhoea (i.e. cessation of the menstrual cycle) [8]. Infertility and/or early menopause is a recognised long-term adverse effect of breast cancer treatment in premenopausal women and has serious implications for the survivorship experience of these women [8,9].

Fertility is well-established to be a priority for many young pre-menopausal breast cancer patients. More than half are concerned about their future fertility, and 50-76% wish to consider pregnancy following cancer treatment [10-12]. This number is likely to increase with the social trends of delayed motherhood until older reproductive ages [13,14]. Concerns about the potential risk of infertility and the inability to conceive in the future have direct implications for treatment efficacy and long-term physical and emotional health [10,15-19] – specifically it may influence patients to choose less optimal adjuvant therapies to reduce impact on fertility [10,11,20,21] or the uptake of fertility preservation options despite potential physical, emotional and financial burden [22-24]. Young women with breast cancer actively seek and desire knowledge, and improved information translates into better health outcomes[25,26]. Core to making informed fertility-related decisions is an understanding of the risk of infertility, but the currently available information about fertility outcomes following breast cancer treatment can only determine broad risk categories (e.g. intermediate risk: 30-70% risk of infertility) [27] and individual factors which are known to affect fertility in women (e.g. age, body mass index, smoking, previous fertility, serum ovarian markers) are not included in the risk prediction. There is a gap in personalised information to inform young breast cancer patients about likely fertility outcomes after treatment [28-30]. To meet their unmet information needs, young patients frequently use the internet to seek more accessible and consolidated

information about post-treatment reproductive consequences [31]. Therefore, an evidence-based and individualised online risk prediction tool may provide reliable and easy-to-access information to address the gap and better manage the fertility-related needs [32,33].

Accurate prediction of infertility after breast cancer treatment is complex and requires consideration of baseline fertility and the likely impact of planned cancer treatments on fertility [28]. There is growing evidence that baseline fertility indicators prior to breast cancer treatment may predict the likelihood of developing amenorrhoea after treatment [29,34,35]. However, no previous studies have included baseline demographic and lifestyle factors, as well as serum ovarian markers and cancer treatment factors, all together, to predict fertility. To address this gap, we are developing the fertility after cancer predictor (FoRECAsT) tool for young breast cancer patients which considers both baseline fertility indicators and the impact of planned cancer treatment on fertility. Based on the input information, it will provide an individualised risk of amenorrhoea at different time points after initial treatment (12 months, 24 months, 36 months, 48 and 60 months) to assess longitudinal changes in infertility risk, with amenorrhoea being a surrogate marker for infertility. The tool will allow users to input individual data (baseline demographic and lifestyle factors, serum ovarian markers and recommended breast cancer treatment) to determine a personalised risk of infertility after breast cancer treatment.

There are two key parts to the FoRECAsT tool – the algorithm development and the user interface. To develop the risk prediction algorithm (part one), authors from studies exploring variables related to fertility at baseline and impact of breast cancer treatment (Table 1) [29,36-44] have been invited to join the FoRECAsT Collaboration and contribute their data to the FoRECAsT database and these data are being used to build a predictive model. The algorithm will use Bayesian inference technique, which is the preferred method in complex algorithm development, in combination with Monte-Carlo Markov simulations [45-49]. From the algorithm, a working prototype of the tool will be developed (part two) as a proof-of-concept. To achieve part two and ensure that the tool is widely used clinically to facilitate onco-fertility decision making, the user interface will be developed in consultation with stakeholders including patients and patient advocacy groups. This protocol reports on a key aspect of this consultation process. Findings from this part of the study will be used to design the user interface of the FoRECAsT (prototype) tool ensuring it is easy to use and understand. There are successive steps to validate the predictive algorithm and evaluate the tool prior to implementation in clinical practice.

Objectives

The main purpose of this study is to explore perceptions, ideas and opinions from young breast cancer patients and clinicians regarding the design and feasibility of implementing the FoRECAsT tool including barriers and facilitators. Findings will inform the design, feasibility, and breast cancer patients' and clinicians' preferences, of where and when the FoRECAsT tool might be used.

Methods and analysis:

Study design

A cross-sectional exploratory study has been conducted through semi-structured in-depth telephone interviews with key stakeholders.

Study participants/ stakeholders

The following stakeholders are included in our study:

a) Patient group: 15 -20 breast cancer patients.
b) Clinician group:
   - 15 -20 breast surgeons,
   - 15 -20 breast medical oncologists,
   - 15 -20 breast care nurses and
   - 15 -20 fertility specialists
   - 15 -20 fertility preservation (FPS) nurses.

The sample size is an appropriate minimum sample required for meaningful outcomes. However, as per qualitative methodology, participants will continue to be recruited until informational redundancy is achieved [50].

Eligibility Criteria

Breast cancer patients:

Inclusion criteria:

To be eligible to participate breast cancer patients must be

a) female,
b) diagnosed within the last five years.
c) aged 18-40 years
d) premenopausal at breast cancer diagnosis
e) have evidence of prior discussion with a health care provider about the risk of developing infertility after breast cancer treatment either through referral to a fertility specialist or documented discussion inpatient notes (so as not to cause distress in those who had not had a prior discussion about potential infertility),
f) concerned about future fertility after chemotherapy and/or have not completed their family (as identified by the treatment team),
g) able to give informed written consent and
h) able to speak and understand English.

Exclusion criteria:

Women with metastatic breast cancer and women diagnosed with gestational breast cancer.

Clinicians:

Inclusion criteria:

To be eligible to participate clinicians who:

a) have a valid Australian License for practice,
b) have at least one year of clinical experience in their respective discipline,
c) consult to women with breast cancer,

d) will be able to give informed written consent and
e) will able to speak and understand English.

Recruitment

Recruitment started in September 2018 and is still ongoing. As per qualitative methodology, participants will continue to be recruited until informational redundancy is achieved. Breast cancer patients are being recruited using purposive sampling by the breast care nurses from the joint Breast Service of Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital. Figure 1 illustrates the recruitment of breast cancer patients. Clinicians are being recruited using an e-flyer through their respective online communities across Australia (except northern territory and Tasmania due to ethics committee coverage), i.e. Breast Surgeons of Australia & New Zealand (BreastSurgANZ), Medical Oncology Group of Australia (MOGA), Fertility Society of Australia (FSA), Cancer Nurses Society of Australia (CNSA) and McGrath Foundation. Figure 2 shows the recruitment of clinicians. Participation is voluntary, and participants may choose not to participate in the study or may withdraw from the study at any time. There will be an opportunity for participants to ask the research team any questions regarding the study. Invited participants who do not respond, will be followed up with a second invitation two weeks after initial contact.

Data collection

In-depth telephone interviews are guided by semi-structured interview schedules and have been carried out by the research team. Consented participants are asked to review the draft FoRECAsT tool to provide their feedback. The interview schedules are structured in consultation with clinical experts and qualitative research specialists based on Aizen's Theory of Planned Behaviour (TPB) [51]. They are customised to the level of stakeholders to allow questioning strategy and conversations to be more flexible.

Each interview is anticipated to last for 15-20 minutes. Interviews are audio-recorded on a portable, electronic digital voice recorder (Olympus VN-731PC) and transcribed verbatim. The audio recordings and transcripts have been securely stored in a password-protected folder on The University of Melbourne server with access permitted to authorised personnel only. Verbal informed consents are obtained for audio recording the interview. Interviews will be conducted until saturation is reached [50]. Patients and clinicians who consent to be interviewed have been offered the opportunity to view a copy of the transcripts prior to data analysis.

Patient and Public Involvement:

The study is supported by a consumer/patient who is a part of the working party and involved in the design of the study, and preparation of all the study materials from the patient's perspective. All interested participants will be sent a summary report of the results via email or mail with de-identified aggregated findings.

Outcome measures

Socio-demographic data are collected from each participating breast cancer patient and clinician. Breast cancer patients are asked about their current age, the highest level of education attained, employment status, stage of cancer, relationship status, and fertility history. Clinicians

are asked about their age, years of clinical experience, and proportion of patients seen with breast cancer.

Qualitative data are focusing on five topics (Table 2):
1) Interest in using the tool;
2) Access and technical skills;
3) User attributes;
4) The potential impact of the tool on consultation;
5) Anticipated outcomes and benefits.

Data analysis

The processes of data collection and data analysis are ongoing. Transcripts are being imported into a qualitative data analysis software (QRS NVivo version 12- QRS International Pty Ltd, Doncaster, Vic., Australia) to facilitate data management and analyses. The five broad areas are developed based on the theoretical framework of Planned Behaviour [51]**.** Transcripts are being coded line-by-line identifying keywords, concepts and reflections in accordance with the framework of Miles & Huberman [52], a widely used framework for qualitative research methodology. Coding is being conducted using an iterative process: starting with coding for broad themes, before coding into hierarchical categories and subthemes.

To ensure the integrity and consistency of the codes and reduce bias, codes will be reviewed by the qualitative research specialist. The research team will discuss the coding tree and reach consensus. Subsequently, content analysis will also be performed for each code, to support results from thematic analyses by identifying essential aspects of the content and highlighting the recurrence of themes, to present results clearly and effectively. A final list of themes and sub-themes will be determined through patterns as soon as further data that will emerge from the study add little to the emerging theory. Theoretical saturation is reached once no new themes emerge. Results will be reported according to the consolidated criteria for reporting qualitative research developed by Tong et al. [53].

Ethics and dissemination:

Ethics approval

The study protocol has been reviewed and approved by the Human Research Ethics Committee of the Melbourne Health, Australia (HREC number: 2017.163). This study will be conducted in compliance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research, the Australian Code for the Responsible Conduct of Research and the Declaration of Helsinki.

Confidentiality

Confidentiality and privacy are maintained at every stage of the study. Individual participants will not be identifiable to any other members of their group or anyone else in the wider community. Participants are approached, recruited and contacted in a confidential, one-to-one manner and no public dissemination of participants' details will occur. Contact details for the researchers and relevant ethics committee(s) are provided to address any questions or concerns

participants may have. Audio-recordings and individual transcripts are being stored on a password protected and secured The University of Melbourne server, which is backed up daily. Study-related records will be retained in a secure storage facility for at least seven years after the completion of the research as required by the Australian National Health and Medical Research Council.

Dissemination

Only de-identified results will be published. The results will be actively disseminated through peer-reviewed scholarly and scientific journals, national and international conference presentations, social media, broadcast media, print media, internet and various community/ stakeholder engagement activities. The consumer/patient will also provide comment on the findings and contribute to the dissemination plan via consumer websites such as Breast Cancer Network Australia.

Strengths and limitations of this study:

This will be the first personalised tool considering baseline demographic and lifestyle factors, serum ovarian markers and cancer treatment factors all together in predicting the impact of breast cancer treatments on fertility. Strengths of this study include co-design the tool with patients' and healthcare professionals' needs and preferences in mind. This tool could potentially be implemented globally with adaptation to newer breast cancer treatment. Additionally, the tool could be adapted for other cancer treatments.

Limitations include the use of non-probability sampling to recruit breast cancer patients which may increase selection bias [54]. Recruitment is limited to breast cancer patients where fertility was discussed prior to cancer treatment and our findings may not be applicable to circumstances where fertility was not discussed. Also, our findings cannot be generalised to breast cancer patients from more diverse cultural and linguistic backgrounds and those with advanced breast cancer.

Authors' contributions:

MP conceived the research idea, participated in the design of the study, development of all study documents, ethical approval process and reviewed this manuscript. ZE participated in the design of the study, development of all study documents, ethical approval process, study coordination and drafted this manuscript. YJ participated in the design of the study, development of all study documents and reviewed this manuscript. MH, LS, RAA, HIS, KS, CS, AA, MMM, SC, PP, FA participated in the review of all study documents and the manuscript. LCL and SP participated in ethics approval process and reviewed the manuscript. WC and AG reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This Research Project/Program was supported by the Victorian Government through a Victorian Cancer Agency (Early Career Seed Grant) awarded to Dr Peate.

Competing interests

None.

Acknowledgements:

MP and YJ both are currently supported by an MDHS Fellowship, The University of Melbourne. At the time of this study, MP was supported by a National Breast Cancer Foundation Early Career Fellowship (ECF-15-005). MH is supported by a National Health and Medical Research Council of Australia (NHMRC) Practitioner Fellowship and is part of the Women Choosing Surgical Prevention (WISP) investigator team funded by Stand Up to Cancer. The authors would like to thank FoRECAsT Consortium for contributing their datasets to develop the infertility risk prediction algorithm.

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Table 1: Candidate predictors for fertility

Lifestyle factors	Age, race, body mass index, diet, exercise, smoking, alcohol, caffeine, drugs
Medical history	Prior (in)fertility and IVF, menstruation history, tubal and gynaecological disease, endometriosis, polycystic ovary syndrome, sexually transmitted infections, pelvic surgery, family history of (in)fertility and menopause
Serum markers of ovarian Function	Follicle stimulating hormone, luteinising hormone, estradiol, inhibin B, antimullerian hormone (AMH), antral follicle count, ovarian volume
Cancer factors	Age at diagnosis, stage, receptor status, type of treatment (dose and duration)

Table 2: Semi-structured interviews topic guides for participants

Broad topics	Specific topics
1. Interest in using the infertility risk prediction tool	Extent of information received/ delivered about risk of infertility, decision making with 'current infertility risk calculator', perceived satisfaction in using current calculators, interest in having a more accurate infertility risk prediction tool
2. Access and confidentiality	Requirements around access and user interface, security, confidentiality of input information, technical skill
3. User attributes	Perceptions of ease of use and preferences for data entry
4. Impact on fertility consultation	Perceptions of impact on fertility consultation
5. Anticipated outcomes and benefits	Benefits of using a more accurate tool, barriers and additional suggestions to better meet fertility-related needs.

'Current infertility risk calculator' refers to the commonly used existing calculator for fertility risk prediction following breast cancer treatment [27].

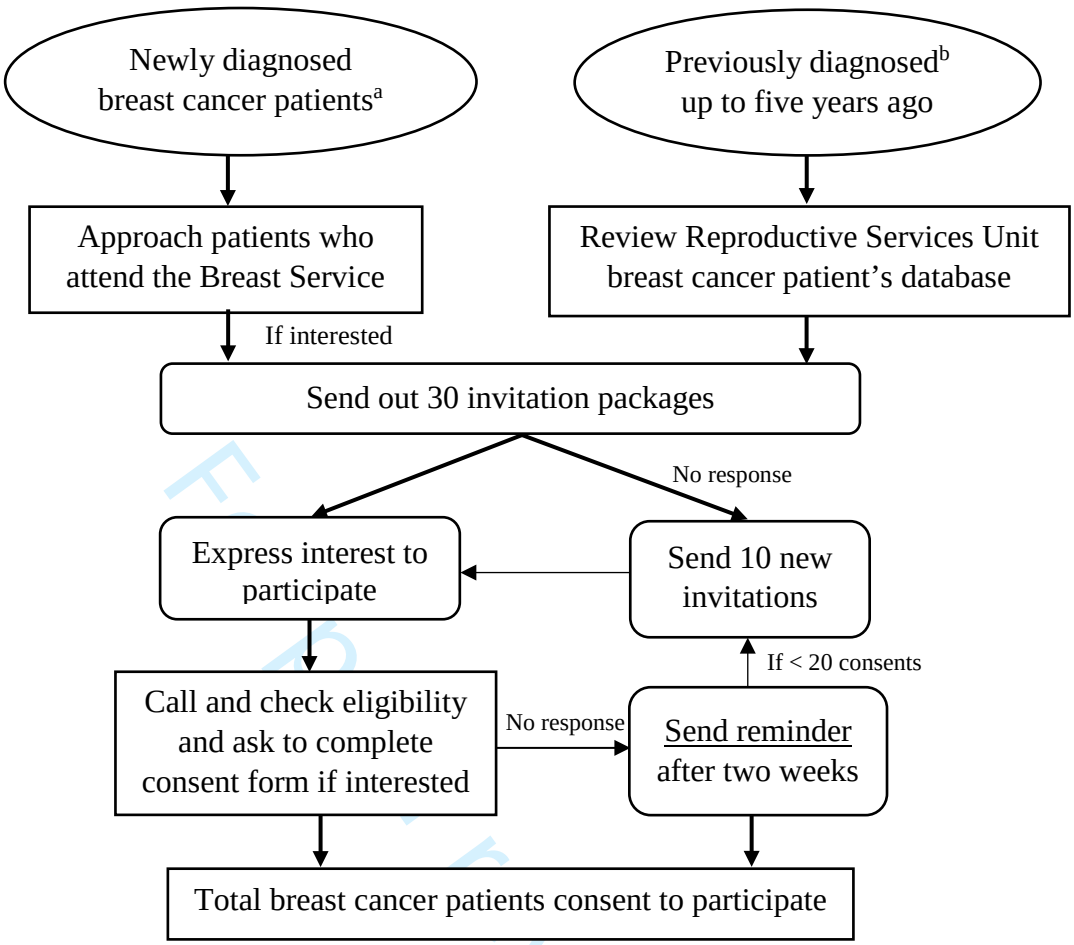

Figure 1: Illustration of the recruitment of breast cancer patients.

[a] Newly diagnosed patients are those who haven't started their chemotherapy yet.
[b] Previously diagnosed are those who have completed the chemotherapy and diagnosed within the last five years

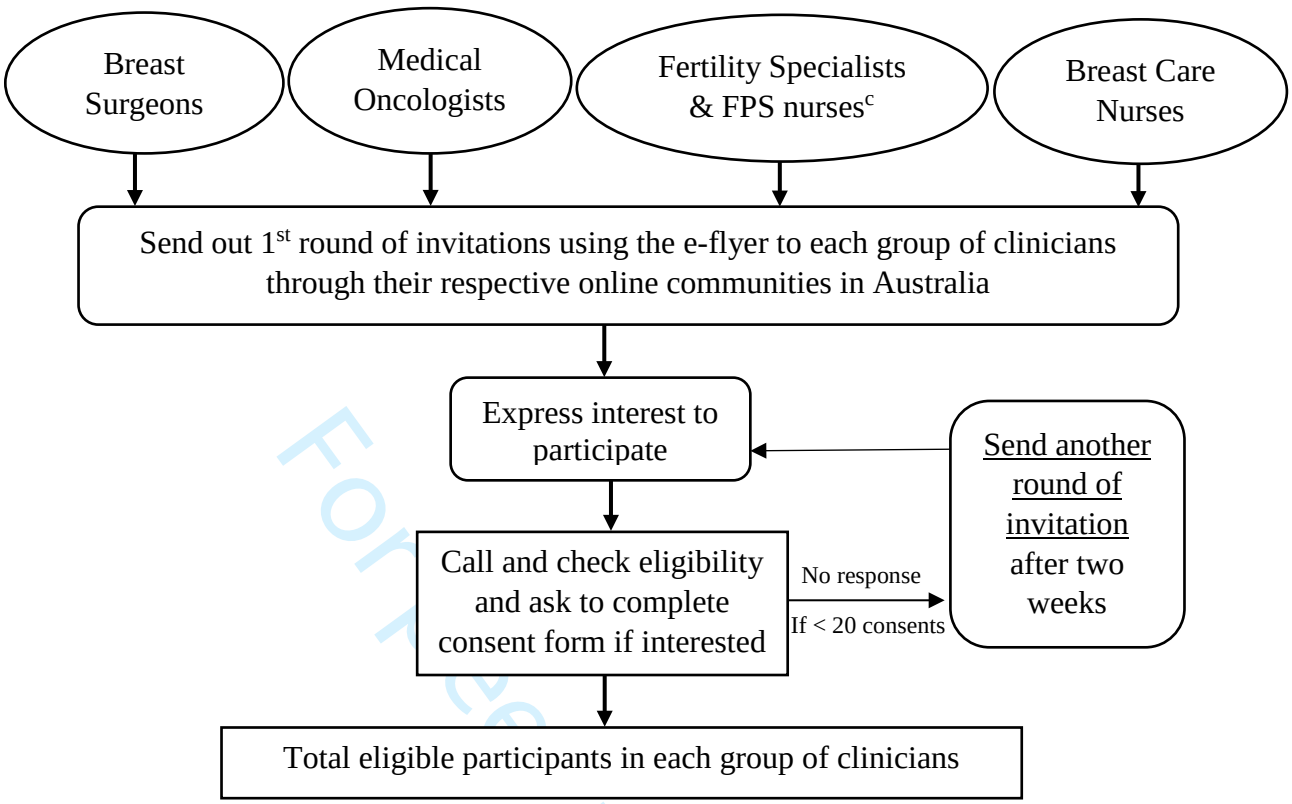

Figure 2: Illustration of the recruitment of clinicians.

[C]Fertility preservation nurses

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	4
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	5,6
Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	7,8,9
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	7,8
Context - Setting/site and salient contextual factors; rationale**	7,8
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	8
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	9
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	8

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	8
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	7
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	8
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	9
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	9

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Not applicable
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Not applicable

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	5,10
Limitations - Trustworthiness and limitations of findings	10

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	10
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	10

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014 DOI: 10.1097/ACM.0000000000000388

BMJ Open

Exploring the facilitators and barriers to using an online infertility risk prediction tool (FoRECAsT) for young women with breast cancer: A qualitative study protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033669.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Jan-2020
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Primary Subject Heading:	Health services research
Secondary Subject Heading:	Oncology, Obstetrics and gynaecology
Keywords:	Breast cancer, Premenopausal, Infertility, Risk prediction

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Title: Exploring the facilitators and barriers to using an online infertility risk prediction tool (FoRECAsT) for young women with breast cancer: A qualitative study protocol.

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Abstract:

Introduction:

As cancer treatments may impact on fertility, a high priority for young breast cancer patients is access to evidence-based, personalised information for them and their healthcare providers to guide treatment and fertility-related decisions prior to cancer treatment. Current tools to predict fertility outcomes after breast cancer treatments are imprecise and do not offer individualised prediction. To address the gap, we are developing a novel personalised infertility risk prediction tool (FoRECAsT) for premenopausal breast cancer patients that considers current reproductive status, planned chemotherapy and adjuvant endocrine therapy to determine likely post-treatment infertility. The aim of this study is to explore the feasibility of implementing this FoRECAsT tool into clinical practice by exploring the barriers and facilitators of its use amongst patients and healthcare providers.

Methods and analysis:

A cross-sectional exploratory study is being conducted using semi-structured in-depth telephone interviews with 15-20 participants each from the following groups: (a) premenopausal breast cancer patients younger than 40, diagnosed within last 5 years, (b) breast surgeons, (c) breast medical oncologists, (d) breast care nurses (e) fertility specialists and (f) fertility preservation nurses. Breast cancer patients are being recruited from the joint Breast Service of three affiliated institutions of Victorian Comprehensive Cancer Centre in Melbourne, Australia– Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital, and clinicians are being recruited from across Australia. Interviews are being audio-recorded, transcribed verbatim and imported into qualitative data analysis software to facilitate data management and analyses.

Ethics and dissemination:

The study protocol has been approved by Melbourne Health Human Research Ethics Committee, Australia (HREC number: 2017.163). Confidentiality and privacy are maintained at every stage of the study. Findings will be disseminated through peer-reviewed scholarly and scientific journals, national and international conference presentations, social media, broadcast media, print media, internet and various community/ stakeholder engagement activities.

Article Summary:

Strengths and limitations of this study:

1) Obtaining representative stakeholder feedback is an essential step in ensuring that a risk prediction tool is feasible and acceptable for use in clinical practice.
2) This tool could be adapted to newer breast cancer treatments and for other cancers.
3) Non-probability sampling may increase the risk of selection bias.
4) Recruitment is limited to breast cancer patients where fertility was discussed prior to cancer treatment, findings may not be applicable where fertility was not discussed.
5) This study is being conducted in the Australian setting, findings may not be generalisable to different health settings.

Introduction:

Globally, breast cancer is the most frequent cancer diagnosis in reproductive-aged women, with approximately 100,000 women younger than 40 years diagnosed annually worldwide, representing one-quarter of new breast cancer cases [1-3]. In Australia, most women are diagnosed with early-stage disease, and with current treatment, the five-year survival rate for women diagnosed with breast cancer is often excellent (90.8%) [4]. Recommended treatment can include gonadotoxic chemotherapeutic agents and thus poses a potential threat to fertility by destroying the eggs stored in the ovaries [5,6]. If the number of eggs is substantially depleted, early menopause and/or permanent infertility can result [7], and will commonly present as amenorrhoea (i.e. cessation of the menstrual cycle) [8]. Infertility and/or early menopause is a recognised long-term adverse effect of breast cancer treatment in premenopausal women and has serious implications for the survivorship experience of these women [8,9].

Fertility is well-established to be a priority for many young pre-menopausal breast cancer patients. More than half are concerned about their future fertility, and 50-76% wish to consider pregnancy following cancer treatment [10-12]. This number is likely to increase with the social trends of delayed motherhood until older reproductive ages [13,14]. Concerns about the potential risk of infertility and the inability to conceive in the future have direct implications for treatment efficacy and long-term physical and emotional health [10,15-19] – specifically it may influence patients to choose less optimal adjuvant therapies to reduce impact on fertility [10,11,20,21] or the uptake of fertility preservation options despite potential physical, emotional and financial burden [22-24]. Young women with breast cancer actively seek and desire knowledge, and improved information translates into better health outcomes[25,26]. Core to making informed fertility-related decisions is an understanding of the risk of infertility, but the currently available information about fertility outcomes following breast cancer treatment can only determine broad risk categories (e.g. intermediate risk: 30-70% risk of infertility) [27] and individual factors which are known to affect fertility in women (e.g. age, body mass index, smoking, previous fertility, serum ovarian markers) are not included in the risk prediction. There is a gap in personalised information to inform young breast cancer patients about likely fertility outcomes after treatment [28-30]. To meet their unmet information needs, young patients frequently use the internet to seek more accessible and consolidated

information about post-treatment reproductive consequences [31]. Therefore, an evidence-based and individualised online risk prediction tool may provide reliable and easy-to-access information to address the gap and better manage the fertility-related needs [32,33].

Accurate prediction of infertility after breast cancer treatment is complex and requires consideration of baseline fertility and the likely impact of planned cancer treatments on fertility [28]. There is growing evidence that baseline fertility indicators prior to breast cancer treatment may predict the likelihood of developing amenorrhoea after treatment [29,34,35]. However, no previous studies have included baseline demographic and lifestyle factors, as well as serum ovarian markers and cancer treatment factors, all together, to predict fertility. To address this gap, we are developing the fertility after cancer predictor (FoRECAsT) tool for young breast cancer patients which considers both baseline fertility indicators and the impact of planned cancer treatment on fertility. Based on the input information, it will provide an individualised risk of amenorrhoea at different time points after initial treatment (12 months, 24 months, 36 months, 48 and 60 months) to assess longitudinal changes in infertility risk, with amenorrhoea being a surrogate marker for infertility. The tool will allow users to input individual data (baseline demographic and lifestyle factors, serum ovarian markers and recommended breast cancer treatment) to determine a personalised risk of infertility after breast cancer treatment.

There are two key parts to the FoRECAsT tool – the algorithm development and the user interface. To develop the risk prediction algorithm (part one), authors from studies exploring variables related to fertility at baseline and impact of breast cancer treatment (Table 1) [29,36-44] have been invited to join the FoRECAsT Collaboration and contribute their data to the FoRECAsT database and these data are being used to build a predictive model.

Table 1: Candidate predictors for fertility

Lifestyle factors	Age, race, body mass index, diet, exercise, smoking, alcohol, caffeine, drugs
Medical history	Prior (in)fertility and IVF, menstruation history, tubal and gynaecological disease, endometriosis, polycystic ovary syndrome, sexually transmitted infections, pelvic surgery, family history of (in)fertility and menopause
Serum markers of ovarian Function	Follicle stimulating hormone, luteinising hormone, estradiol, inhibin B, antimullerian hormone (AMH), antral follicle count, ovarian volume
Cancer factors	Age at diagnosis, stage, receptor status, type of treatment (dose and duration)

The algorithm will use Bayesian inference technique, which is the preferred method in complex algorithm development, in combination with Monte-Carlo Markov simulations [45-49]. From the algorithm, a working prototype of the tool will be developed (part two) as a proof-of-concept. To achieve part two and ensure that the tool is widely used clinically to facilitate onco-fertility decision making, the user interface will be developed in consultation with stakeholders including patients and patient advocacy groups. This protocol reports on a key aspect of this consultation process. Findings from this part of the study will be used to design the user interface of the FoRECAsT (prototype) tool ensuring it is easy to use and understand.

There are successive steps to validate the predictive algorithm and evaluate the tool prior to implementation in clinical practice.

Objectives

The main purpose of this study is to explore perceptions, ideas and opinions from young breast cancer patients and clinicians regarding the design and feasibility of implementing the FoRECAsT tool including barriers and facilitators. Findings will also inform breast cancer patients' and clinicians' preferences of where and when the FoRECAsT tool might be used.

Methods and analysis:

Study design

A cross-sectional exploratory study is being conducted through semi-structured in-depth telephone interviews with key stakeholders.

Study participants/ stakeholders

The following stakeholders are included in our study:

a) Patient group: 15 -20 breast cancer patients.
b) Clinician group:
   - 15 -20 breast surgeons,
   - 15 -20 breast medical oncologists,
   - 15 -20 breast care nurses and
   - 15 -20 fertility specialists
   - 15 -20 fertility preservation (FPS) nurses.

The sample size is an appropriate minimum sample required for meaningful outcomes. However, as per qualitative methodology, participants will continue to be recruited until informational redundancy is achieved [50].

Eligibility Criteria

Breast cancer patients:

Inclusion criteria:

To be eligible to participate breast cancer patients must be

a) female,
b) diagnosed within the last five years.
c) aged 18-40 years
d) premenopausal at breast cancer diagnosis
e) have evidence of prior discussion with a health care provider about the risk of developing infertility after breast cancer treatment either through referral to a fertility specialist or documented discussion inpatient notes (so as not to cause distress in those who had not had a prior discussion about potential infertility),
f) concerned about future fertility after chemotherapy and/or have not completed their family (as identified by the treatment team),
g) able to give informed written consent and
h) able to speak and understand English.

Exclusion criteria:

Women with metastatic breast cancer and women diagnosed with gestational breast cancer.

Clinicians:

Inclusion criteria:

To be eligible to participate clinicians who:

a) have a valid Australian License for practice,
b) have at least one year of clinical experience in their respective discipline,
c) consult to women with breast cancer,
d) will be able to give informed written consent and
e) will able to speak and understand English.

Recruitment

Recruitment started in September 2018 and is still ongoing. As per qualitative methodology, participants will continue to be recruited until informational redundancy is achieved. Breast cancer patients are being recruited using purposive sampling by the breast care nurses from the joint Breast Service of Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital. Figure 1 illustrates the recruitment of breast cancer patients. Clinicians are being recruited using an e-flyer through their respective online communities across Australia (except northern territory and Tasmania due to ethics committee coverage), i.e. Breast Surgeons of Australia & New Zealand (BreastSurgANZ), Medical Oncology Group of Australia (MOGA), Fertility Society of Australia (FSA), Cancer Nurses Society of Australia (CNSA) and McGrath Foundation. Figure 2 shows the recruitment of clinicians. Participation is voluntary, and participants may choose not to participate in the study or may withdraw from the study at any time. There will be an opportunity for participants to ask the research team any questions regarding the study. Invited participants who do not respond, will be followed up with a second invitation two weeks after initial contact.

Data collection

In-depth telephone interviews are guided by semi-structured interview schedules and carried out by the research team. Consented participants are asked to review the draft FoRECAsT tool to provide their feedback. The interview schedules are structured in consultation with clinical experts and qualitative research specialists based on Aizen's Theory of Planned Behaviour (TPB) [51]. They are customised to the level of stakeholders to allow questioning strategy and conversations to be more flexible.

Each interview is anticipated to last for 15-20 minutes. Interviews are audio-recorded on a portable, electronic digital voice recorder (Olympus VN-731PC) and transcribed verbatim. The audio recordings and transcripts have been securely stored in a password-protected folder on The University of Melbourne server with access permitted to authorised personnel only. Verbal informed consents are obtained for audio recording the interview. Interviews will be conducted until saturation is reached [50]. Patients and clinicians who consent to be interviewed have been offered the opportunity to view a copy of the transcripts prior to data analysis.

Patient and Public Involvement:

The study is supported by a consumer/patient who is a part of the working party and involved in the design of the study, and preparation of all the study materials from the patient's perspective. All interested participants will be sent a summary report of the results via email or mail with de-identified aggregated findings.

Outcome measures

Socio-demographic data are collected from each participating breast cancer patient and clinician. Breast cancer patients are asked about their current age, the highest level of education attained, employment status, stage of cancer, relationship status, and fertility history. Clinicians are asked about their age, years of clinical experience, and proportion of patients seen with breast cancer.

Qualitative data are focusing on five topics (Table 2):
1) Interest in using the tool;
2) Access and confidentiality;
3) User attributes;
4) The potential impact of the tool on consultation;
5) Anticipated outcomes and benefits.

Table 2: Semi-structured interviews topic guides for participants

Broad topics	Specific topics
1. Interest in using the infertility risk prediction tool	Extent of information received/ delivered about risk of infertility, decision making with 'current infertility risk calculator', perceived satisfaction in using current calculators, interest in having a more accurate infertility risk prediction tool
2. Access and confidentiality	Requirements around access and user interface, security, confidentiality of input information, technical skill
3. User attributes	Perceptions of ease of use and preferences for data entry
4. Impact on fertility consultation	Perceptions of impact on fertility consultation
5. Anticipated outcomes and benefits	Benefits of using a more accurate tool, barriers and additional suggestions to better meet fertility-related needs.

'Current infertility risk calculator' refers to the commonly used existing calculator for fertility risk prediction following breast cancer treatment [27].

Data analysis

The processes of data collection and data analysis are ongoing. Transcripts are being imported into a qualitative data analysis software (QRS NVivo version 12- QRS International Pty Ltd,

Doncaster, Vic., Australia) to facilitate data management and analyses. The five broad areas are developed based on the theoretical framework of Planned Behaviour [51]. Transcripts are coded line-by-line identifying keywords, concepts and reflections in accordance with the framework of Miles & Huberman [52], a widely used framework for qualitative research methodology. Coding is being conducted using an iterative process: starting with coding for broad themes, before coding into hierarchical categories and subthemes.

To ensure the integrity and consistency of the codes and reduce bias, codes will be reviewed by the qualitative research specialist. The research team will discuss the coding tree and reach consensus. Subsequently, content analysis will also be performed for each code, to support results from thematic analyses by identifying essential aspects of the content and highlighting the recurrence of themes, to present results clearly and effectively. A final list of themes and sub-themes will be determined through patterns as soon as further data that will emerge from the study add little to the emerging theory. Theoretical saturation is reached once no new themes emerge. Results will be reported according to the consolidated criteria for reporting qualitative research developed by Tong et al. [53].

Ethics and dissemination:

Ethics approval

The study protocol has been reviewed and approved by the Human Research Ethics Committee of the Melbourne Health, Australia (HREC number: 2017.163). This study will be conducted in compliance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research, the Australian Code for the Responsible Conduct of Research and the Declaration of Helsinki.

Confidentiality

Confidentiality and privacy are maintained at every stage of the study. Individual participants will not be identifiable to any other members of their group or anyone else in the wider community. Participants are approached, recruited and contacted in a confidential, one-to-one manner and no public dissemination of participants' details will occur. Contact details for the researchers and relevant ethics committee(s) are provided to address any questions or concerns participants may have. Audio-recordings and individual transcripts are being stored on a password protected and secured The University of Melbourne server, which is backed up daily. Study-related records will be retained in a secure storage facility for at least seven years after the completion of the research as required by the Australian National Health and Medical Research Council.

Dissemination

Only de-identified results will be published. The results will be actively disseminated through peer-reviewed scholarly and scientific journals, national and international conference presentations, social media, broadcast media, print media, internet and various community/ stakeholder engagement activities. The consumer/patient will also provide comment on the findings and contribute to the dissemination plan via consumer websites such as Breast Cancer Network Australia.

Strengths and limitations of this study:

This will be the first personalised tool considering baseline demographic and lifestyle factors, serum ovarian markers and cancer treatment factors all together in predicting the impact of breast cancer treatments on fertility. Strengths of this study include co-design the tool with patients' and healthcare professionals' needs and preferences in mind. This tool could potentially be implemented globally with adaptation to newer breast cancer treatment. Additionally, the tool could be adapted for other cancer treatments.

Limitations include the use of non-probability sampling to recruit breast cancer patients which may increase selection bias [54]. Recruitment is limited to breast cancer patients where fertility was discussed prior to cancer treatment and our findings may not be applicable to circumstances where fertility was not discussed. Also, our findings cannot be generalised to breast cancer patients from more diverse cultural and linguistic backgrounds and those with advanced breast cancer.

Authors' contributions:

MP conceived the research idea, participated in the design of the study, development of all study documents, ethical approval process and reviewed this manuscript. ZE participated in the design of the study, development of all study documents, ethical approval process, study coordination and drafted this manuscript. YJ participated in the design of the study, development of all study documents and reviewed this manuscript. MH, LS, RAA, HIS, KS, CS, AA, MMM, SC, PP, FA participated in the review of all study documents and the manuscript. LCL and SP participated in ethics approval process and reviewed the manuscript. WC and AG reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This Research Project/Program was supported by the Victorian Government through a Victorian Cancer Agency (Early Career Seed Grant) awarded to Dr Peate.

Competing interests

None.

Acknowledgements:

MP and YJ both are currently supported by an MDHS Fellowship, The University of Melbourne. At the time of this study, MP was supported by a National Breast Cancer Foundation Early Career Fellowship (ECF-15-005). MH is supported by a National Health and Medical Research Council of Australia (NHMRC) Practitioner Fellowship and is part of the Women Choosing Surgical Prevention (WISP) investigator team funded by Stand Up to Cancer. The authors would like to thank FoRECAsT Consortium for contributing their datasets to develop the infertility risk prediction algorithm.

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Figure 1: Illustration of the recruitment of breast cancer patients.

Figure 2: Illustration of the recruitment of clinicians.

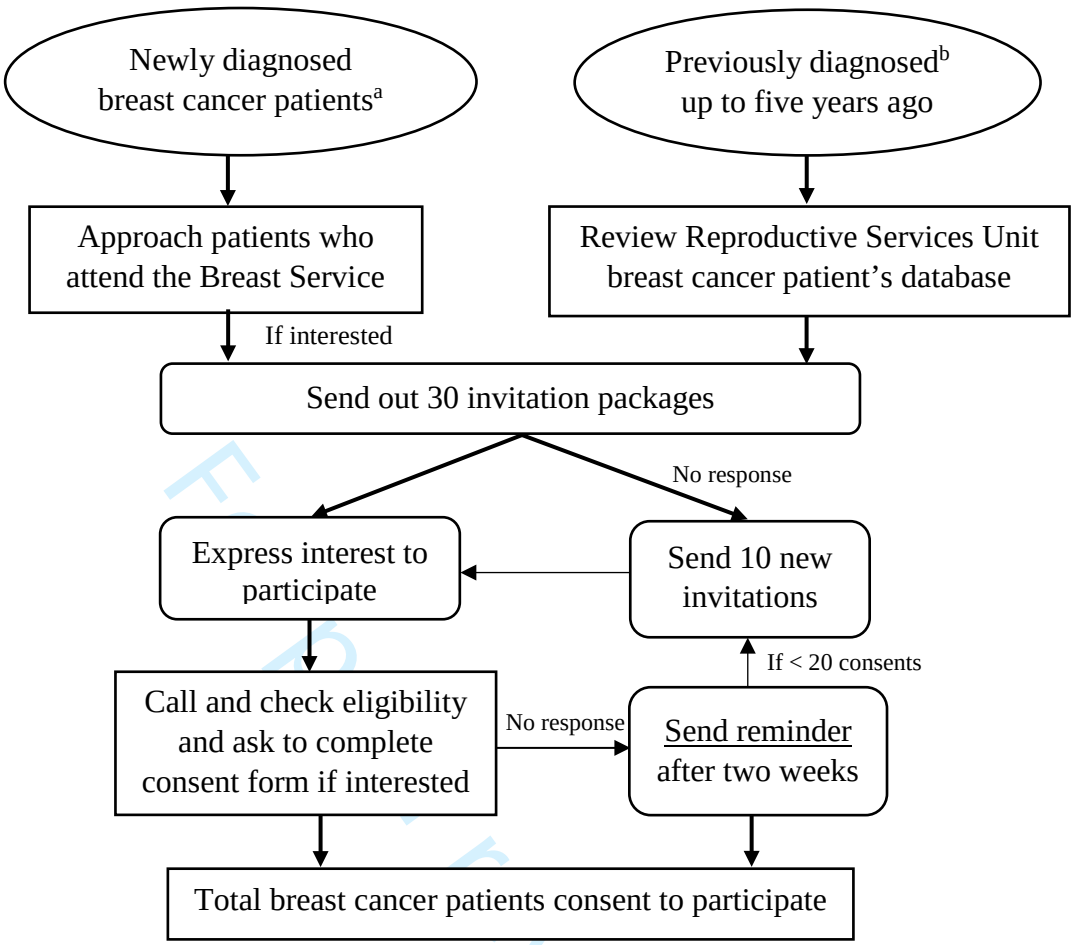

Figure 1: Illustration of the recruitment of breast cancer patients.

[a] Newly diagnosed patients are those who haven't started their chemotherapy yet.
[b] Previously diagnosed are those who have completed the chemotherapy and diagnosed within the last five years

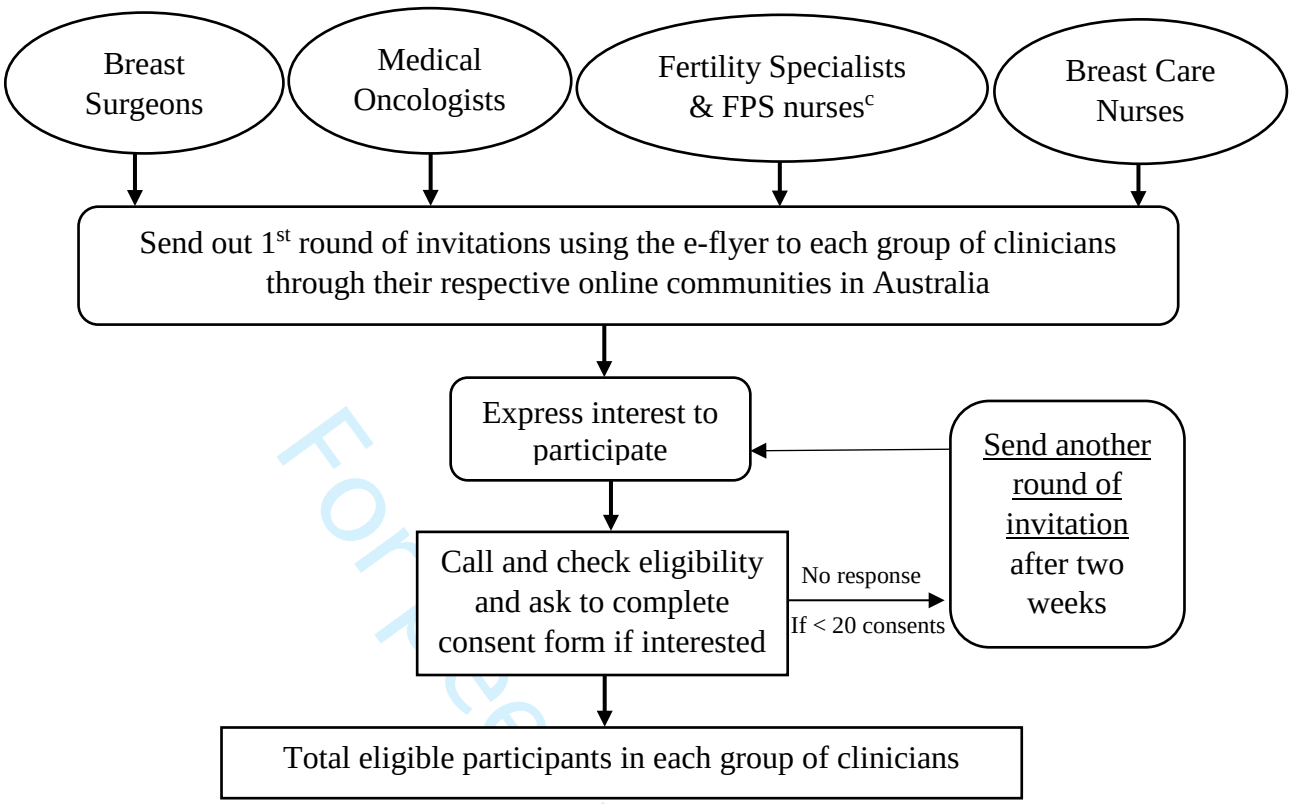

Figure 2: Illustration of the recruitment of clinicians.

[C]Fertility preservation nurses

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	4
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	5,6
Purpose or research question - Purpose of the study and specific objectives or questions	6
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	7,8,9
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	7,8
Context - Setting/site and salient contextual factors; rationale**	7,8
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	8
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	9
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	8

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	8
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	7
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	8
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	9
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	9

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Not applicable
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Not applicable

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	5,10
Limitations - Trustworthiness and limitations of findings	10

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	10
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	10

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014 DOI: 10.1097/ACM.0000000000000388