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Pathways: patient-centred decision counselling for women at risk of cancer-related infertility: a protocol for a comparative effectiveness cluster randomised trial

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ABSTRACT

Introduction National guidelines recommend that all reproductive-age women with cancer be informed of their fertility risks and offered referral to fertility specialists to discuss fertility preservation options. However, reports indicate that only 5% of patients have consultations, and rates of long-term infertility-related distress remain high. Previous studies report several barriers to fertility preservation; however, initial success has been reported using provider education, patient decision aids and navigation support. This protocol will test effects of a multicomponent intervention compared with usual care on women's fertility preservation knowledge and decision-making outcomes.

Methods and analysis This cluster-randomised trial will compare the multicomponent intervention (provider education, patient decision aid and navigation support) with usual care (consultation and referral, if requested). One hundred newly diagnosed English-speaking women of reproductive age who are at risk of cancer-related infertility will be recruited from four regional oncology clinics. The *Pathways* patient decision aid website provides (1) up-to-date evidence and descriptions of fertility preservation and other family-building options, tailored to cancer type; (2) structured guidance to support personalising the information and informed decision-making; and (3) a printable summary to help women prepare for discussions with their oncologist and/or fertility specialist. Four sites will be randomly assigned to intervention or control groups. Participants will be recruited after their oncology consultation and asked to complete online questionnaires at baseline, 1 week and 2 months to assess their demographics, fertility preservation knowledge, and decision-making process and quality. The primary outcome (decisional conflict) will be tested using Fisher's exact test. Secondary outcomes will be assessed using generalised linear mixed models, and sensitivity analyses will be conducted, as appropriate.

Ethics and dissemination The University of Texas MD Anderson Cancer Center provided approval and ongoing review of this protocol. Results will be presented at relevant scientific meetings and submitted for publication in a peer-reviewed journal.

Trial registration number NCT03141437; Pre-results.

Strengths and limitations of this study

► The proposed multicomponent intervention approach includes three evidence-based interventions to provide support across the multistep process of oncofertility awareness, referral, decision-making and treatment.

► The *Pathways* patient decision aid website provides lay language information about cancer-related infertility and family-building options, tailored to each woman's cancer type, and structured decision-making support with interactive activities to guide women in applying the information to their personal decision.

► The four sites chosen for this trial provide a diverse sample and allow for testing across multiple points in the fertility preservation decision-making and treatment process.

► The primary limitation of this protocol is the available number of clusters (k=4), which will be addressed in the data analytic plan by using generalised linear mixed modelling methods and sensitivity analyses.

► This study will be limited to English-speaking women; however, results will inform potential translation and cultural adaptation of the *Pathways* patient decision aid website in the future.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) guidelines recommend that fertility preservation be considered as early as possible during cancer treatment planning.[1] Previous studies have shown that when women are referred to a fertility specialist for fertility counselling, regret and quality of life are improved (whether or not they choose to pursue fertility preservation).[2–12] However, recent reports indicate that as little as 5% of eligible patients see a fertility specialist, and rates of long-term infertility-related distress remain high.[2–20] Barriers to

fertility preservation discussions and referrals need to be addressed, with a specific focus on issues such as timely delivery of evidence-based information, effective lay communication of this complex decision, facilitation of referrals for fertility counselling and individualised decision support to foster informed, values-based decisions during the stressful time period leading up to initiation of cancer treatment.[3 4 6 7 10 12 16–19 21–31]

Patient decision aids are tools that provide up-to-date clinical evidence in lay language and structured guidance in deliberation and decision-making to address patients' decisional conflict (ie, feelings of being uninformed, unclear, unsupported and uncertain that lead to delayed or poorly implemented decisions).[26–28 30 32] Over 115 randomised controlled trials have shown that patient decision aids improve patients' decisional conflict by improving knowledge, fostering realistic expectations, building self-efficacy and increasing engagement in decision-making.[30] We previously developed a patient decision aid website called *Pathways* that provides (1) up-to-date information about fertility preservation options and alternative pathways to family building and (2) structured approaches to support patient deliberation and preparation for discussion with their clinician(s). Field testing indicates that *Pathways* improves women's knowledge and decision-making when viewed in conjunction with a fertility specialist consultation.[33] However, women report needing access to this information earlier in the cancer care pathway. Therefore, the next step in this programme of research is to test the comparative effectiveness of *Pathways* when delivered upstream of the consultation with a fertility specialist—specifically, following the initial oncology consultation.

Fertility preservation involves a multistep decision-making process often complicated by uncertainty and a tight and variable timeline.[4 6 9–12 15–17 24] At the initial oncology consultation during which a women learns that she has cancer and cancer treatment options are discussed, guidelines recommend that she also be informed of the risk of infertility and offered a referral to a fertility specialist. At the fertility specialist consultation, she may discuss the relevant options and consider her initial preferences; however, key information may still be needed (eg, final cancer treatment plan(s) and/or fertility lab results). Hence, the final decision about which fertility preservation treatment is best for her, if any, is often made following her visit to a fertility specialist.

To support this multistep process, this study compares a multicomponent oncofertility intervention that includes an educational seminar for oncology providers and providing women with access to the *Pathways* decision aid website and follow-up telephone counselling.[6 7 10 12 24 34] The following protocol describes the aims for the *Pathways* cluster randomised trial, the intervention components and the rationale for the design elements chosen for this study.

1. *Primary*: To assess the effect of a multicomponent oncofertility decision support intervention (multicomponent DS intervention) compared with usual care with women of reproductive age at selected oncology clinics on patients' decisional conflict.
   a. Usual care includes an oncology consultation and an offer to refer for fertility preservation specialist, if desired.
   b. The multicomponent DS intervention will include (a) providing providers with an educational seminar about fertility preservation, the patient decision aid and the referral process and (b) providing patients with access to the *Pathways* patient decision aid website and follow-up telephone decision counselling and to help facilitate referrals, as appropriate.
2. *Secondary*: To assess patients' decision-making process (eg, preparation for decision-making, decision self-efficacy, satisfaction) and decision quality (eg, fertility preservation knowledge, clarity of patients' values and congruence of preferences with the decision about whether to accept fertility preservation referral and/or fertility preservation treatment).
3. *Exploratory*: To explore the feasibility of the multicomponent DS intervention and research methods (eg, clinician's perspectives of the educational session and referral process, website usage, rates of referrals, recommendations for improving the intervention and referral process) as delivered in the oncology clinics, in preparation for future planned dissemination and implementation studies.

METHODS AND ANALYSIS
Study design

To address the primary aim, this comparative effectiveness study involves a cluster-based randomised trial at four University of Texas MD Anderson Cancer Center Houston Area Location oncology clinics (see figure 1). Two control sites will be randomly assigned to continue with usual care; two intervention sites will receive provider training, access to the *Pathways* patient decision aid and follow-up telephone counselling for patients to facilitate decision-making and referral to a fertility specialist, if desired. At the end of the study, discussion sessions will be held with the providers at each site regarding their experience and recommendations for intervention improvement.

This protocol and the overarching programme of research is based on the underlying decision-making and cognitive psychology theories of the Ottawa Decision Support Framework, and follows the quality guidelines of the International Patient Decision Aid Standards (IPDAS) Collaboration.[27–32 35–46] The core research team includes a reproductive endocrinologist (TLW), women's health advanced practice provider (DAH), decision scientists (RV, ASH) and research assistant (LCC). A Stakeholder Advisory Panel included three female cancer survivors who had previously considered fertility preservation, two patient advocate leaders and two oncology providers (gynaecological and paediatric).
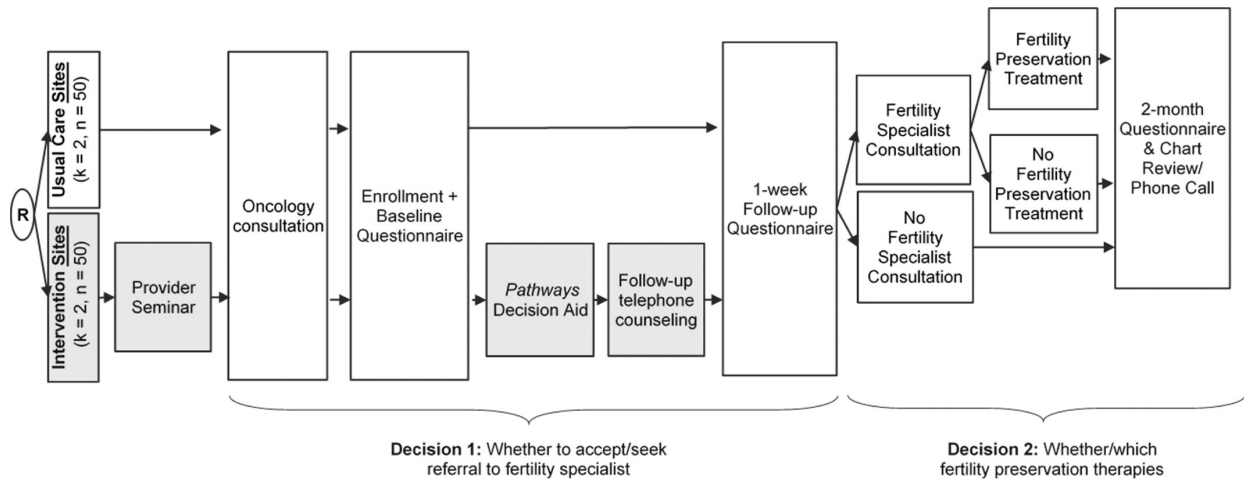
Figure 1 Study design.

Eligibility criteria

Women aged 18 to 45 years old who can read, write and speak English; are at risk of cancer-related infertility; and are newly diagnosed with a breast tumour, female genital system tumour, colorectal tumour and/or lymphoma or myeloma are eligible for inclusion in the study. These criteria were chosen to align with the current guidelines for fertility preservation discussions.[1] All women will be recruited from The University of Texas MD Anderson Cancer Center Houston Area Location oncology clinics. These clinics were chosen because they serve a large and diverse population, have a centralised electronic health record for tracking referral and treatment utilisation and may be more generalisable to the US population than the MD Anderson main campus. Providers of these clinics will be eligible for inclusion in the poststudy provider discussions.

Randomisation

We will generate a randomisation list for the four oncology clinics using nQuery Advisor (1995–2007, Statistical Solutions) with two study arms (control, multicomponent intervention) and a block size of 4.

Treatment arms

At the two sites randomised to the control condition, oncologists will proceed with usual care, which involves an oncology consultation and offering a referral to the fertility specialist, if desired.

At the two sites randomised to the intervention, three components will be provided—provider seminar, access to *Pathways* and follow-up telephone counselling. Dr Woodard (a fertility specialist) will present a departmental seminar designed to (1) enable and motivate oncologists to address fertility issues in women at risk of cancer-related infertility and refer them to reproductive endocrinologists, if warranted; (2) introduce the *Pathways* patient decision aid; and (3) describe the study procedures so that providers can introduce the study to eligible women.

Second, all participants at the intervention sites will be provided with access to the *Pathways* decision aid website (v1.0, 1 April 2017) after their initial oncology consultation. Results of the formative studies (provider and patient needs assessments, user-centred design and production and usability/acceptability pilot-testing) and efficacy study are published separately.[33] Selected screenshots and the overall architecture of the *Pathways* website are provided in figure 2; scores on the IPDAS Quality Checklist are provided in online supplementary file A.

Pathways provides women with an introduction to the effects of cancer on fertility; descriptions of fertility preservation and other family-building options; and interactive My Personal Decision features that support women in personalising the medical information, clarifying their decision-making values, comparing the relevant options and preparing for their discussions with their providers and family. *Pathways* tailors the information to each woman's cancer type and provides explanations of the oncofertility terminology and procedures in eighth-grade language. Each woman's My Personal Decision information is provided in a printable summary.

Within the following week, follow-up telephone counselling for participants will be offered to support informed, values-based decision-making as fertility laboratory results and cancer treatment plans become available, and to facilitate navigation and timely referrals to a fertility specialist, if desired.

Outcomes

Table 1 illustrates the study data collection for each objective and time point (baseline, 1 week and 2 month). Online supplementary file B provides the psychometric properties for each measure/instrument. The primary measure is decisional conflict, assessed pre/postintervention using the 16-item Decisional Conflict Scale.[47] All measures have been tested during the formative studies and pilot-testing, as well as in other fertility preservation or other patient decision aid research studies.

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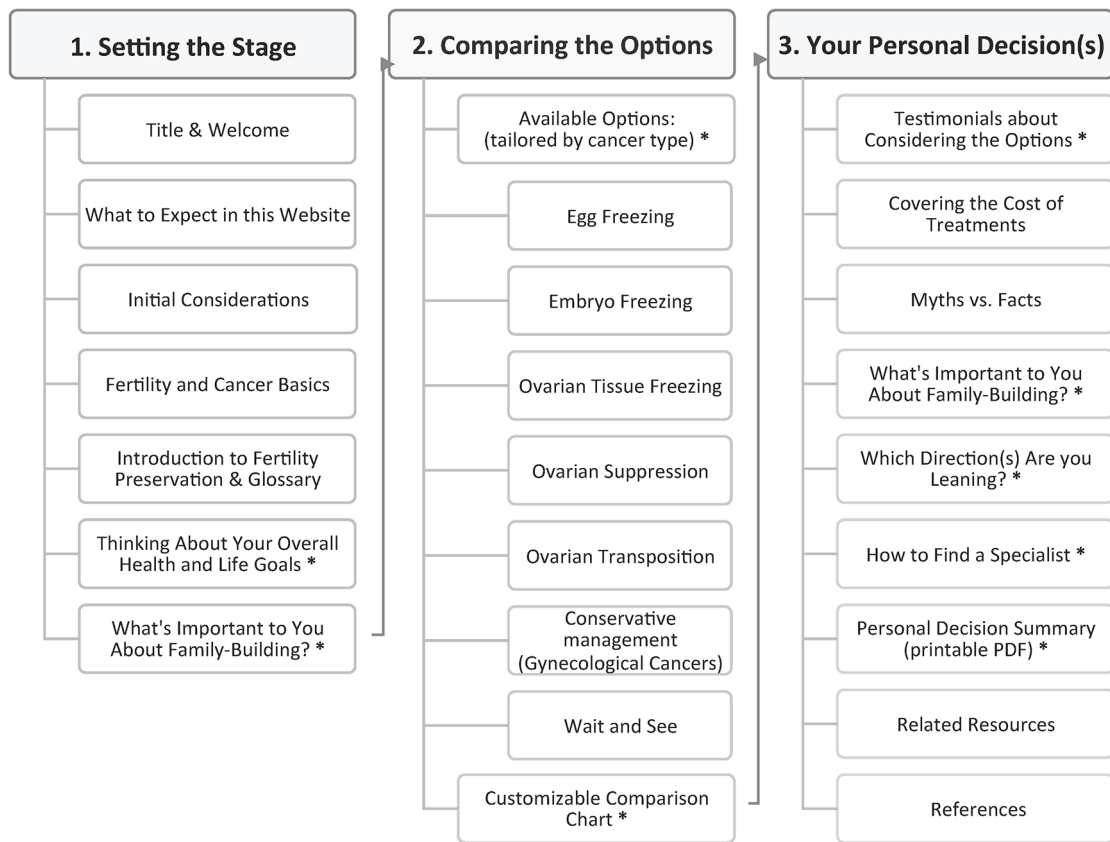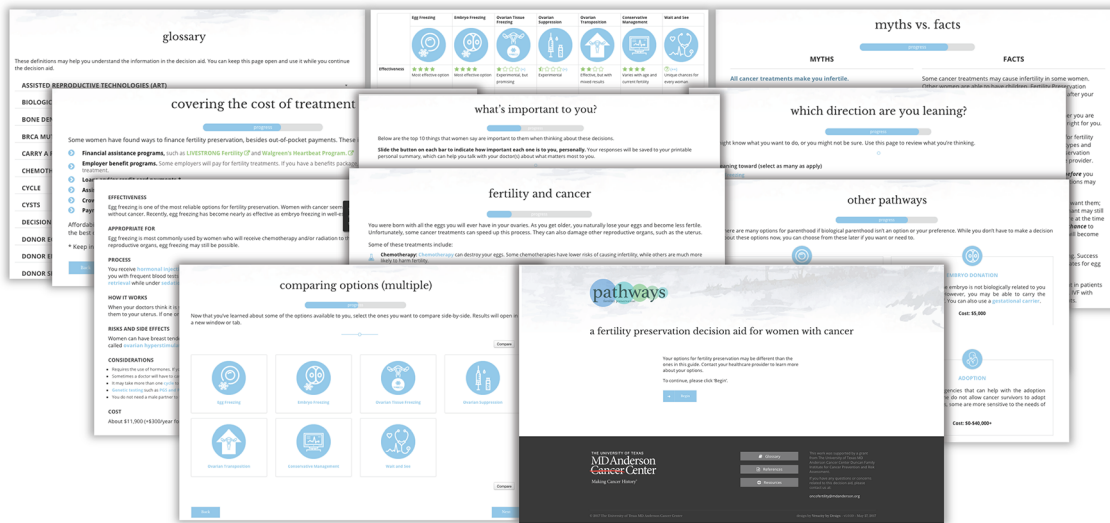
FIGURES

Figure 2   Components and features of the *Pathways* patient decision aid website. *An interactive personalisation activity (eg, open-ended goal-setting questions, Values Clarification Rating Scales, initial treatment leaning items); responses are collected in the My Personal Decision Summary.

Baseline characteristics will include clinical (Reproductive Concerns Scale, Brief Symptom Inventory), decision-making (Decisional Conflict Scale, Intolerance of Uncertainty Scale) and sociodemographic factors, including the Single Item Literacy Scale.[20 47–51] Across time points, this study will assess women's decision-making processes using the Decision Self-efficacy Scale, Preparation for Decision Making Scale and open-ended questions assessing other decision-making factors (eg, three primary influences on their decision, role of spouse/partner in decision-making, etc).[52 53] Decision quality will be assessed using the Fertility Preservation Knowledge

Table 1 Outcome measures and data collection time points

Measure	Objective	Baseline	During DA*	1 week	2 months
Eligibility: age, sex, cancer status, internet access, valid email, speaks English, has not viewed the decision aid (DA)	Eligibility	X			
Participant characteristics (age, race/ethnicity, employment, religion, language, literacy, education, relationship status, insurance type/coverage, median household income, decision-making preference, digital comfort, preferred viewing location)[48]	Baseline characteristics	X			
Reproductive Concerns Scale[20]	Baseline characteristics	X			
Fertility Preservation Knowledge Scale[21]	Baseline characteristics	X		X	X
Intolerance of Uncertainty Scale[49]	Baseline characteristics	X			
Brief Symptom Inventory[50 51]	Baseline characteristics and data safety monitoring	X		X	X
Decisional Conflict Scale[47]	Primary	X		X	
Values Clarity Leaning Scale for each relevant risk/benefit[54]	Secondary		X*	X	
Strength of Treatment Preference Leaning Scale for their favoured option(s)[54 55]	Secondary		X*	X	
System usage (eg, time spent on website, error rates, revisit rates, viewing at home/clinic)	Secondary		X*		
Other fertility preservation resources viewed/used (five open-ended questions)	Secondary			X	
Decision Self-efficacy Scale[52]	Secondary			X	
Preparation for Decision-making Scale[53]	Secondary			X	
Acceptability Leaning Scales (length, clarity, ease of use, interesting, comprehensive)[56]	Exploratory			X	
Fertility preservation referral and/or fertility preservation scheduled/completed, type and estimated cost	Secondary				X
Clinical factors: diagnosis, stage and therapies, history of infertility, gravidity/parity, serum Antimullerian Hormone (AMH), antral follicle count	Secondary				X
Decision-making factors: three primary influences on decision	Secondary				X
Decisional Regret Scale[57]	Exploratory				X
Client Satisfaction Questionnaire[58]	Exploratory				X
Recommendations for improving decision-making process and referral process	Exploratory				X

*For patients at intervention sites.

Scale, Values Clarification Leaning Scale and Strength of Preference for Referral/Treatment(s) Scales, as well as an assessment of the concordance of participants' preferences with subsequent treatments scheduled or completed by 2 months.[21 54 55]

In preparation for future planned dissemination and implementation studies, exploratory measures include the Patient Decision Aid Acceptability Scale (ie, Leaning Scales rating the length, ease of use, clarity, comprehensiveness and meaningfulness of the decision aid), Client Satisfaction Questionnaire, system usage (eg, preferences for viewing at home or at the clinic, time spent on the website, error rates, etc) and preliminary testing of potential downstream measures (eg, Decisional Regret Scale).[56–58] At the conclusion of the study, semi-structured discussions with clinicians at the intervention sites will assess clinician perspectives about the usefulness of the multicomponent intervention and suggestions for improvement. These exploratory measures will inform and guide the design of future longitudinal studies.

Adverse events

The risk of adverse events are low. However, it is possible that discussion of fertility issues can cause or increase emotional distress. If a participant is identified as being significantly distressed (ie, by notifying the study coordinator and/or scoring >63 on the Brief Symptom Inventory), they will be reminded that they can end their participation at any time, and the principal investigator or research study coordinator will refer the participant to the appropriate psychosocial support resources.[50 51] An external Data Monitoring Committee is not commissioned for this protocol.

Data management

Study data will be collected and managed using REDCap (Research Electronic Data Capture, www.project-redcap.org) electronic data capture tools hosted at The MD Anderson Cancer Center.[59] All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. A different randomly generated number will be used for each patient.

Sample size and rationale

The primary outcome measure is the percent of patients who score <25 on the Decisional Conflict Scale, as lower scores are associated with making decisions (ie, less uncertainty, anxiety or distress).[47 60] We will compare the two study arms (usual care, intervention) with respect to the change from baseline in the percent of patients who score <25 on the Decisional Conflict Scale. In a review of 31 cluster-based studies in primary care, Adams *et al* found that the median unadjusted intracluster correlation was 0.011.[61] Assuming a similar intracluster correlation, 50 patients on each study arm (25 at each oncology clinic) will provide an approximately 80% power with a two-sided significance level of 0.05 to detect a difference of 30% between study arms with respect to the change from baseline in the percent of patients who score <25 on the Decisional Conflict Scale. This sample size calculation was performed using Number Cruncher Statistical Systems Trial and Power Analysis and Sample Size Software 2005 (Number Cruncher Statistical Systems, Kaysville, Utah; www.ncss.com).

The four MD Anderson Houston Area Location oncology clinics see an estimated 250–300 potentially eligible patients per year (21–25/month), and observe a socioeconomically, racially/ethnically and clinically diverse population. Conservatively assuming a 50% participation rate, we anticipate enrolling 10–12 women/month from 1 September 2017 to 30 May 2018. Participants will be provided with $25 gift cards at 2 months postenrolment. If additional recruitment is needed, the MD Anderson main campus oncology clinics may be added, where previous studies in this programme of research have observed a 75%–90% participation rate.

The four oncology clinics will be assigned site identification numbers in alphabetical order, then randomised using nQuery Advisor 7.0 (1995–2007, Statistical Solutions). The randomisation list will be saved in a separate list by the study statistical team.

Statistical analysis plan

The data analytic plan begins with descriptive statistics and boxplots to summarise patients' characteristics and scores on each of the survey instruments at each assessment time point for each study arm.

With respect to the primary outcome of the dichotomised decisional conflict score, the statistical team will first tabulate the counts and frequencies. To assess the effect of the proposed multicomponent oncofertility DS intervention compared with usual care, they will use generalised linear mixed models (GLMMs) with one covariate of the study arm and a random effect that takes into account the between-cluster variation. In analysing cluster randomised trials, Klar and Darlington[62] showed that there could be considerable gains in power when covariates were adjusted, and a similar phenomenon was also observed in a peer-reviewed research study that investigated covariate adjustment in randomised controlled trials with dichotomous outcomes.[62 63] Indeed, covariate adjustment is often recommended to achieve unbiased estimates and to improve the precision, thus increasing the power.[64] As such, our statistical team will evaluate the intervention effect via GLMM with adjustment of baseline covariates that may further explain the variation in the primary outcome, hence resulting in potentially improved power. Covariate variables considered in this analysis include age, religion, relationship status, insurance type/coverage, median household income, gravidity, parity, Reproductive Concerns Scale and Fertility Preservation Knowledge Scale. Our selection of this list is based on the conceptual framework underlying patient decision-making, which includes patients' sociodemographic, clinical and decision-making characteristics as contextual factors that may potentially impact decision-making outcomes.

The statistical team will also model the logit of the probability of achieving a Decisional Conflict Scale score <25 as a function of study arm, assessment time and patient nested within provider using GLMM. The aforementioned covariate list will be considered first in this analysis. After a scientifically reasonable and mathematically stable model is constructed, the statistical team will further investigate other potentially important covariates including race/ethnicity, employment, education, Intolerance of Uncertainty Scale and Brief Symptom Inventory. Last but not least, if distributions allow, additional models will explore the probability of achieving other score cut-offs (eg, <37.5, since scores higher than 37.5 are associated with delaying decisions) and the differences in the change in score pre/postdecision aid.

For the other instruments, the statistical team will use GLMM methods to model scores as a function of study

arm, assessment time, patients nested within provider and patients' characteristics to address the secondary outcomes of decision-making process (eg, preparation for decision-making, decision self-efficacy and satisfaction) and decision quality (eg, fertility preservation knowledge, clarification of patients' values and congruence of preferences with the decision about whether to accept fertility preservation and/or fertility preservation treatment).

GLMM methods are designed to handle missing data and give unbiased estimates of effects provided that the probability of having missing data depends only on the covariates in the model (or data are missing at random). However, in the case that data are not missing at random, to avoid the bias due to the informative dropout, analyses will compare baseline information and reasons for dropout to examine whether the dropouts are systematically different from non-dropouts. In addition, a non-ignorable model, such as the pattern mixture model, will also be used to fit the data to account for possible informative missing data. As a sensitivity analysis, the results from the non-ignorable model will be compared with those from the standard mixed model.[65]

Finally, exploratory analyses will tabulate site usage and research feasibility outcomes (eg, time on website, rates of completion of all data collection items, etc). The research team will review open-ended responses and notes from the poststudy discussions with providers to identify any suggested improvements to the decision aid or future implementation.

Ethics and dissemination

Online supplementary file C provides an example of the approved informed consent document (note: this article refers to Part II activities). In addition, the MD Anderson Cancer Network Protocol Review, Integration, and Strategic Management (PRISM) provided initial approval and ongoing review for this study at the four Houston Area Location oncology clinics. Any amendments to this protocol will be reviewed and approved by both boards, and communicated to the collaborating sites, participants and journals, if appropriate. All eligible women who volunteer to participate will be asked to provide informed consent and will be registered in MD Anderson's Clinical Oncology Research System, and periodic audits may be performed to ensure adherence to protocol.

A Data Monitoring Committee is not required for this study due to low risk of adverse events; however, as a conservative measure, automatic notifications are sent to the core research team for any women who score high (indicating depressed feelings) on the Brief Symptom Inventory.[50] If that should occur, the clinical team will be notified and appropriate social services will be provided in accordance with clinical policies. The principal investigator maintains the authority to suspend or terminate the study at any time.

Results of the formative developmental studies (provider and patient needs assessments, user-centred design and production, and usability/acceptability pilot-testing) and efficacy study are published separately.[33] These results were also peer reviewed and presented at the scientific meetings of the American Society for Reproductive Medicine and the Society for Medical Decision Making.

Results of this comparative-effectiveness cluster randomised trial will be published in a peer-reviewed journal. Manuscripts will also be prepared for any significant findings for the secondary aim, as appropriate, in peer-reviewed journals. These results will be submitted for peer review for presentation at the scientific meetings of the American Society for Reproductive Medicine and the Society for Medical Decision Making.

Online supplementary file D provides the Standard Protocol Items: Recommendations for Interventional Trials checklist. On completion of the trial and publication of the primary manuscript, requests for access to the *Pathways* patient decision aid website and database may be made to the corresponding author.

DISCUSSION

Supporting women with cancer in making well-informed decisions about their fertility and family-building options is an important factor in providing high-quality cancer care.[1] Previous studies have demonstrated the value of fertility counselling in reducing women's long-term distress, regardless of whether or not they pursue fertility preservation treatments.[2–4 7–11 15 16 19] However, referral rates for fertility preservation counselling remain low.[5 6 8 10 12 15 17 22] As a result, significant gaps remain in providing effective communication of the potential for cancer-related infertility and facilitating informed decision-making about the potential risk/benefit trade-offs involved in these challenging decisions.

Several interventions, such as provider training, patient education and referral facilitation, have been tested and shown some success at increasing awareness, knowledge and engagement in fertility preservation discussions and decision-making.[3 7 10 12 14 16 23 24 34] A few studies have developed and tested patient decision aids with encouraging results in select patient populations (eg, women with breast cancer, parents of adolescent girls).[7 16 18 23] As part of a long-term research programme, this comparative effectiveness trial will test a multicomponent intervention (provider education, *Pathways* patient decision aid website and follow-up telephone counselling) delivered after an initial oncology consultation. This approach is novel, in that it combines several efficacious interventions, and in that the *Pathways* patient decision provides information and decision support tailored to a women's cancer type and decision-making preferences (eg, preferred level of information detail and engagement in decision-personalisation activities).

Further, this approach seeks to promote adherence to the ASCO guidelines recommendations that fertility preservation be discussed as early possible in the cancer treatment planning process to enable women to have the greatest opportunity for making informed decisions

among the greatest number of available options.[1] In current usual care, many women receive little information about their fertility preservation and other family-building options; when they do, it is often after the cancer treatment planning process and only for those women who seek a fertility counselling referral.[5 8 10–12 15 17 34] The *Pathways* approach seeks to shift the conversation upstream by (1) offering providers training to enable and motivate them to introduce the concept of fertility preservation, as well as a trusted, high-quality website to which they can refer women and (2) by providing women with high-quality information and personal decision-making activities, tailored to their cancer type, as well as telephone counselling to support decision-making and referral, when desired.

Limitations of this proposed study include possible retention challenges during cancer treatment; however, preliminary studies have observed 85% retention at 2 months. Additionally, unexpected distributions of responses (eg, bimodal or ceiling effects) may be seen as the delivery of the decision aid is shifted upstream; therefore, the statistical analysis plan includes sensitivity analyses. Increasing knowledge can increase decisional conflict (and anxiety and distress) temporarily, which is why the data management plan includes autonotification of any distressing scores on the Brief Symptom Inventory (BSI) scale. However, this distress may also be supportive of decision-making (ie, 'functional decisional conflict' that helps individuals take action) and similar studies have shown that it typically resolves once patients meet with their doctor. Finally, measurement of decisional regret at 2 months will only assess short-term regret for the initial decision; long-term regret will be assessed at 18 months in planned future longitudinal studies.

Results from this trial have the potential to improve care of women of reproductive age who are at risk of cancer-related infertility, in terms of their awareness, knowledge, communication, decision quality and satisfaction with their decision(s). These short-term gains may also translate into improved rates of long-term infertility-related distress, decision regret and dissatisfaction.

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