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## Pathways--Patient-centered decision counseling for women at risk of cancer-related infertility: a protocol for a comparative effectiveness cluster randomized trial

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**Pathways--Patient-centered decision counseling for women at risk of cancer-related infertility: a protocol for a comparative effectiveness cluster randomized 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 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 to usual care on women’s fertility preservation knowledge and decision-making outcomes.

**Methods and analysis:** This cluster-randomized 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 a) up-to-date evidence and descriptions of fertility preservation and other family-building options, tailored to cancer type; 2) structured guidance to support personalizing 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 Fishers exact test. Secondary outcomes will be assessed using generalized linear mixed models, and sensitivity analyses will be conducted, as appropriate.

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**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:** NCT03141437, PI: Terri L. Woodard, M.D., 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 cancer 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 generalized linear mixed modeling methods and sensitivity analyses.
- This study will also 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.<sup>1</sup> Previous studies have shown that when women are referred to a fertility specialist for fertility counseling, regret and quality of life are improved (whether or not they choose to pursue fertility preservation).<sup>2-12</sup> However, recent reports indicate as little as 5% of eligible patients see a fertility specialist, and rates of long-term infertility-related distress remain high.<sup>2-20</sup> 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 counseling, and individualized decision support to foster informed, values-based decisions during the stressful time period leading up to initiation of cancer treatment.<sup>3 4 6 7 10 12 16-19 21-31</sup>

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 (i.e., feelings of being uninformed, unclear, unsupported, and uncertain that lead to delayed or poorly implemented decisions).<sup>26-28 30 32</sup> Over 115 randomized 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.<sup>30</sup> We previously developed a patient decision aid website called *Pathways* that provides a) up-to-date information about fertility preservation options and alternative pathways to family building; and b) 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 (manuscript under review). However, women report needing access to this information earlier in the cancer care pathway. Therefore, the next step in this program 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.

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Fertility preservation involves a multi-step decision-making process often complicated by uncertainty and a tight and variable timeline.<sup>4 6 9-12 15-17 24</sup> At the initial oncology consultation during which a woman 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 (e.g. 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 multi-step 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 counseling.<sup>6 7 10 12 24 33</sup> The following protocol describes the aims for the *Pathways* cluster randomized 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 to 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 counseling and to help facilitate referrals, as appropriate.
2. *Secondary:* To assess patients' decision-making process (e.g., preparation for decision making, decision self-efficacy, satisfaction) and decision quality (e.g., 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

(e.g., 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 randomized 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 counseling 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 program 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.<sup>27-32 34-45</sup> The core research team includes a reproductive endocrinologist (T.L.W.), women’s health advanced practice provider (D.A.H.), decision scientists (R.V., A.S.H.), and research assistant (L.C.C).A Stakeholder Advisory Panel composed of three female cancer survivors who had previously considered fertility preservation, two patient advocate leaders, and two oncology providers (gynecologic and pediatric).

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 tumor, female genital system tumor, colorectal tumor, and/or lymphoma or myeloma are eligible for inclusion in the study. These criteria were chosen to align

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with the current guidelines for fertility preservation discussions.<sup>1</sup> 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 centralized electronic health record for tracking referral and treatment utilization, and may be more generalizable to the U.S. population than the MD Anderson main campus. Providers of these clinics will be eligible for inclusion in the post-study provider discussions.

**Randomization**

We will generate a randomization list for the 4 oncology clinics using nQuery Advisor (©1995-2007, Statistical Solutions, Saugus, MA) with 2 study arms (control, multicomponent intervention) and a block size of 4.

**Treatment arms**

At the two sites randomized 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 randomized to the intervention, three components will be provided – provider seminar, access to *Pathways*, and follow-up telephone counseling. Dr. Woodard (a fertility specialist) will present a departmental seminar designed to: a) enable and motivate oncologists to address fertility issues in women at risk of cancer-related infertility and refer them to reproductive endocrinologists, if warranted; and b) introduce the *Pathways* patient decision aid; and c) 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, April 1, 2017) after their initial oncology consultation. Results of the formative studies (provider and patient needs assessments, user-centered design and production, and usability/acceptability pilot-testing) and efficacy study are published separately (manuscripts under

review). Selected screenshots and the overall architecture of the *Pathways* website are provided in figure 2; scores on the IPDAS Quality Checklist are provided in Supplementary File A.

**Figure 2. Components and features of the *Pathways*® patient decision aid website.**

*Pathways* provides women with an introduction to the effects of cancer on fertility; descriptions of the fertility preservation and other family-building options; and interactive My Personal Decision features that support women in personalizing 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 8<sup>th</sup>-grade language. Each woman's My Personal Decision information is provided in a printable summary.

Within the following week, follow-up telephone counseling 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). Supplementary File B provides the psychometric properties for each measure/instrument. The primary measure is decisional conflict, assessed pre/post-intervention using the 16-item Decisional Conflict Scale.<sup>46</sup> 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.

Table 1. Outcome measures and data collection time points.

| Measure  | Objective   | Baseline | During DA* | 1 Week | 2 Month |
|--|---|----------|------------|--------|---------|
| Eligibility: Age, sex, cancer status, Internet access, valid email, speaks English, has not viewed the 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) | Baseline characteristics                          | X        |            |        |         |
| Reproductive Concerns Scale  | Baseline characteristics                          | X        |            |        |         |
| Fertility Preservation Knowledge Scale <sup>17</sup>   | Baseline characteristics                          | X        |            | X      | X       |
| Intolerance of Uncertainty Scale <sup>19</sup>   | Baseline characteristics                          | X        |            |        |         |
| Brief Symptom Inventory <sup>18</sup>  | Baseline characteristics & data safety monitoring | X        |            | X      | X       |
| Decisional Conflict Scale <sup>46</sup>  | Primary   | X        |            | X      |         |
| Values Clarity Learning Scale for each relevant risk/benefit <sup>47</sup>   | Secondary   |          | X*         | X      |         |
| Strength of Treatment Preference Learning Scale for their favored option(s) <sup>47 48</sup>   | Secondary   |          | X*         | X      |         |
| System usage (e.g., time spent on website, error rates, revisit rates, viewing at home/clinic)   | Secondary   |          | X*         |        |         |
| Other fertility preservation resources viewed/used (5 open-ended questions)  | Secondary   |          |            | X      |         |
| Decision Self-efficacy Scale <sup>49</sup>   | Secondary   |          |            | X      |         |
| Preparation for Decision-making Scale <sup>50</sup>  | Secondary   |          |            | X      |         |
| Acceptability Learning Scales (length, clarity, ease of use, interesting, comprehensive) <sup>51</sup>   | Exploratory                                       |          |            | X      |         |
| Fertility preservation referral and/or fertility preservation scheduled/completed, type & estimated cost   | Secondary   |          |            |        | X       |
| Clinical factors: diagnosis, stage, & therapies, history of infertility, gravidity/parity, AMH, Antral follicle count  | Secondary   |          |            |        | X       |
| Decision-making factors: three primary influences on decision  | Secondary   |          |            |        | X       |
| Decisional Regret Scale <sup>52</sup>  | Exploratory                                       |          |            |        | X       |
| Client Satisfaction Questionnaire <sup>53</sup>  | Exploratory                                       |          |            |        | X       |
| Recommendations for improving decision-making process and referral process   | Exploratory                                       |          |            |        | X       |

\*For patients at intervention sites.

Baseline characteristics will include clinical (Reproductive Concerns Scale, Brief Symptom Inventory), decision-making (Decisional Conflict Scale, Intolerance of Uncertainty Scale) and sociodemographic factors.<sup>20 46 54-56</sup> 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 (e.g. three primary influences on their decision, role of spouse/partner in decision-making, etc.)<sup>49 50</sup> Decision quality will be assessed using the Fertility Preservation Knowledge Scale, Values Clarification Learning 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.<sup>21 47 48</sup>

In preparation for future planned dissemination and implementation studies, exploratory measures include the Patient Decision Aid Acceptability Scale (i.e. Learning Scales rating the length, ease of use, clarity, comprehensiveness, and meaningfulness of the decision aid), Client Satisfaction Questionnaire, system usage (e.g., preferences for viewing at home or at the clinic, time spent on the website, error rates, etc.) and preliminary testing of potential downstream measures (e.g., Decisional Regret Scale).<sup>51-53</sup> 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.

**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 (i.e., 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.<sup>54 55</sup> 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](http://www.project-redcap.org)) electronic data capture tools hosted at The MD Anderson Cancer Center.<sup>57</sup> 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 (that is, less uncertainty, anxiety, or distress).<sup>46 58</sup> 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 intra-cluster correlation was 0.011.<sup>59</sup> Assuming a similar intra-cluster correlation, 50 patients on each study arm (25 at each oncology clinic) will provide a ~80% power with a 2-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 (Hintze, J. 2005. NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah. [www.ncss.com](http://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 socio-economically, racially/ethnically, and clinically diverse population. Conservatively assuming a 50% participation rate, we anticipate enrolling 10-12 women/month from September 1, 2017 to May 30, 2018. Participants will be provided with \$25 gift cards at 2 months post-enrollment. If additional recruitment is needed, the MD Anderson main campus oncology clinics may be added, where previous studies in this program of research have observed a 75-90% participation rate.

The four oncology clinics will be assigned site identification numbers in alphabetical order, then randomized using nQuery Advisor 7.0. (©1995-2007, Statistical Solutions, Saugus, MA). The randomization 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 summarize 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, the statistical team will compare the two study arms using Fisher's exact test. They 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 generalized linear mixed model methods.<sup>46</sup> This model will include participant characteristics.

For the other instruments, the statistical team will use generalized linear mixed model 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 (e.g. preparation for decision making, decision self-efficacy, and satisfaction) and decision quality (e.g. fertility preservation knowledge, clarity of patients' values, and congruence of preferences with the decision about whether to accept fertility preservation and/or fertility preservation treatment).

Generalized linear mixed model 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.<sup>60</sup>

Finally, exploratory analyses will tabulate site usage and research feasibility outcomes (e.g. time on

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website, rates of completion of all data collection items, etc.). The research team will review open-ended responses and notes from the post-study discussions with providers to identify any suggested improvements to the decision aid or future implementation.

**Ethics and dissemination**

The University of Texas MD Anderson Cancer Center provided initial ethical approval and continues to provide ongoing review of any amendments to this protocol (#2017-0758, v.4.0, 07/31/2017).

Supplementary File C provides an example of the approved informed consent document (note: this manuscript 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 (CORG) 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.<sup>54</sup> 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-centered design and production, and usability/acceptability pilot-testing) and efficacy study are published separately (manuscripts under review). 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 randomized 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.

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.<sup>1</sup> Previous studies have demonstrated the value of fertility counseling in reducing women’s long-term distress, regardless of whether or not they pursue fertility preservation treatments.<sup>2-4 7-11 15 16 19</sup> However, referral rates for fertility preservation counseling remain low.<sup>5 6 8 10 12 15 17 22</sup> 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.<sup>3 7 10 12 14 16 23 24 33</sup> A few studies have developed and tested patient decision aids with encouraging results in select patient populations (e.g. women with breast cancer, parents of adolescent girls).<sup>7 16 18 23</sup> As part of a long-term research program, this comparative effectiveness trial will test a multicomponent intervention (provider education, *Pathways* patient decision aid website, and follow-up telephone counseling) 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-

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making preferences (e.g. preferred level of information detail and engagement in decision-personalization activities).

Further, this approach seeks to promote adherence to the American Society of Clinical Oncology 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.<sup>1</sup> 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 counseling referral.<sup>5 8 10-12 15 17 33</sup> 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 counseling to support decision making and referral, when desired.

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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**AUTHOR CONTRIBUTIONS**

Conceptualization, T.L.W., A.S.H., L.C.C. and R.J.V.; Methodology, T.L.W., A.S.H., L.A.C., D.A.H, D.B.H, J.M., R.L.B., and R.J.V.; Investigation (not relevant); Writing – Original Draft, T.L.W. and A.S.H.; Writing – Review & Editing, T.L.W., A.S.H., and L.A.C.; Funding Acquisition, T.L.W.; Resources, T.L.W., V.B.L., D.B.H., and R.J.V.; Supervision, T.L.W., A.S.H., and R.V.

COMPETING INTERESTS

The authors report that they have no conflicts of interest to declare.

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ETHICS APPROVAL

The University of Texas MD Anderson Cancer Center (#2016-0758).

DATA SHARING

Data sharing inquiries should be directed to the corresponding author.

FIGURES

Figure 1. Study Design.

R = Randomization, Shading = multicomponent intervention

Figure 2. Components and features of the *Pathways*® patient decision aid website.

For peer review only

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## FIGURES

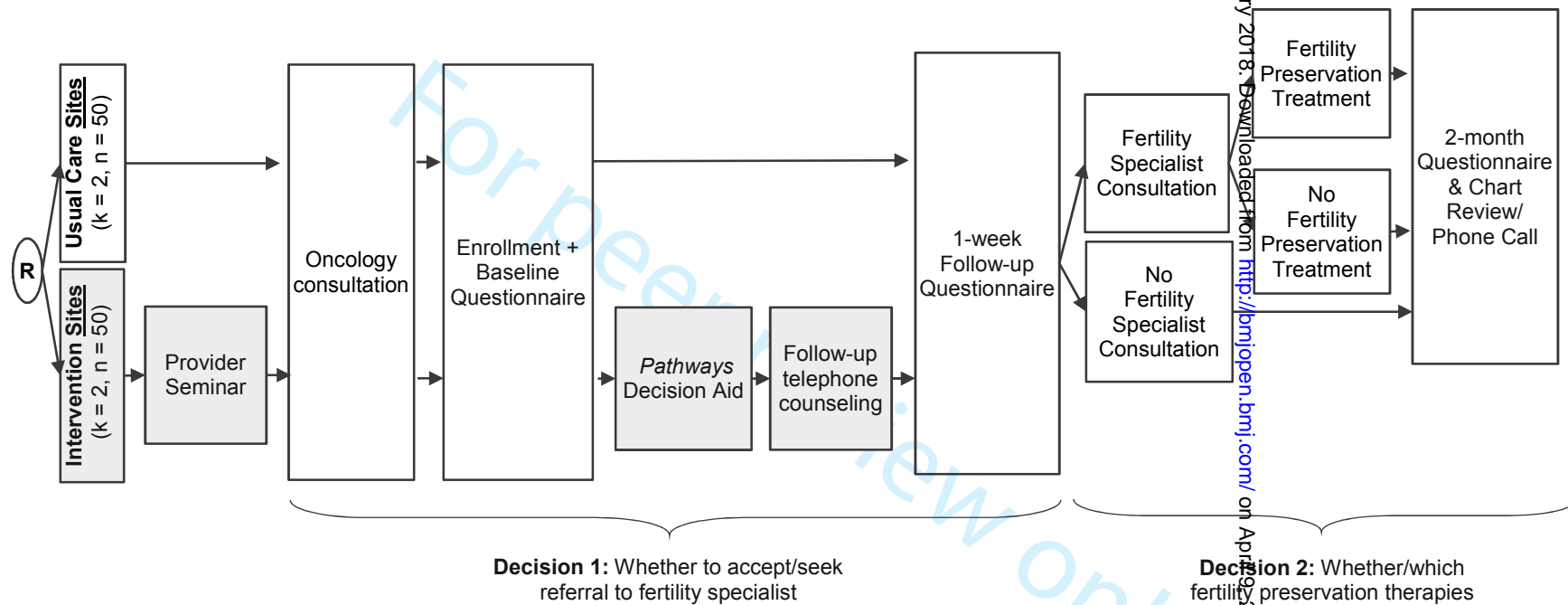


Figure 1. Study Design.

R = Randomization, Shading = multicomponent intervention

FIGURES



Figure 2. Components and features of the *Pathways*® patient decision aid website.

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\* = Includes an interactive personalization activity (e.g. open-ended goal-setting questions, values clarification rating scales, initial treatment leaning items); responses are collected in the My Personal Decision Summary

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## Appendix B. International Patient Decision Aid Standards (IPDAS) Collaboration criteria for high-quality patient decision aid development.

| Criteria  | Answer |
|---|--------|
| <b>Criteria to be defined as a patient decision aid</b>   |        |
| 1. The decision aid describes the condition (health or other) related to the decision.  | Yes    |
| 2. The decision aid describes the decision that needs to be considered (the index decision).  | Yes    |
| 3. The decision aid identifies the target audience.   | Yes    |
| 4. The decision aid lists the options (health care or other).   | Yes    |
| 5. The decision aid has information about the positive features of the options (e.g. benefits, advantages).   | Yes    |
| 6. The decision aid has information about negative features of the options (e.g. harms, side effects, disadvantages).   | Yes    |
| 7. The decision aid helps patients clarify their values for outcomes of options by: a) asking people to think about which positive and negative features of the options matter most to them AND/OR b) describing each option to help patients imagine the physical, social, and /or psychological effect. | Yes    |
| <b>Criteria to lower the risk of making a biased decision</b>   |        |
| 8. The decision aid makes it possible to compare the positive and negative features of the available options.   | Yes    |
| 9. The decision aid shows the negative and positive features of the options with equal detail.  | Yes    |
| 10. The decision aid compares probabilities (e.g. chance of a disease, benefit, harm, or side effect) of options using the same denominator.  | N/A    |
| 11. The decision aid (or available technical documents) reports funding sources for development.  | Yes    |
| 12. The decision aid reports whether authors of the decision aid or their affiliations stand to gain or lose by choices people make after using the decision aid.   | Yes    |
| 13. The decision aid includes authors/developers' credentials or qualifications.  | Yes    |
| 14. The decision aid reports the date when it was last updated.   | Yes    |
| 15. The decision aid (or available technical document) reports readability levels.  | Yes    |
| 16. The decision aid provides references to scientific evidence used.   | Yes    |
| <b>Other criteria for decision aids about screening or testing</b>  |        |
| 17. The decision aid has information about what the test is designed to measure.  | N/A    |
| 18. The decision aid describes possible next steps based on the test results.   | N/A    |
| 19. The decision aid has information about the chances of disease being found with and without screening.   | N/A    |
| 20. The decision aid has information about detection and treatment of disease that would never have caused problems if screening had not been done.   | N/A    |
| <b>Other criteria indicating quality</b>  |        |
| 21. The decision aid describes what happens in the natural course of the condition (health or other) if no action is taken.   | Yes    |
| 22. The decision aid has information about the procedures involved (e.g. what is done before, during, and after the health care option).  | Yes    |
| 23. The information about outcomes of options (positive and negative) includes the chances they may happen.   | Yes    |
| 24. The decision aid presents probabilities using event rates in a defined group of people for a specified time.  | N/A    |
| 25. The decision aid compares probabilities of options over the same period of time.  | Yes    |
| 26. The decision aid uses the same scales in diagrams comparing options.  | N/A    |
| 27. Users (people who previously faced the decision) were asked what they need to prepare them to discuss a specific decision.  | Yes    |
| 28. The decision aid was reviewed by people who previously faced the decision who were not involved in its development and field testing.   | Yes    |

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|--|--|------------|
| 29. People who were facing the decision field tested the decision aid.   |  | Yes        |
| 30. Field testing showed that the decision aid was acceptable to users (the general public & practitioners).   |  | Yes        |
| 31. Field testing showed that people who were undecided felt that the information was presented in a balanced way.   |  | Yes        |
| 32. There is evidence that the decision aid (or one based on the same template) helps people know about the available options and their features.  |  | Yes        |
| 33. There is evidence that the decision aid (or one based on the same template) improves the match between the features that matter most to the informed person and the option that is chosen. |  | N/A        |

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## Appendix B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts   | Timing, Scoring and Interpretation   | Psychometric properties  |
|--|---|--|--|
| <b>Participant Characteristics</b><br>Age, race/ethnicity, employment, religion, language, literacy, education, relationship status, insurance type, median household income, pregnancy and birth history                                    | Assessed using interview, paper, and online formats (e.g., REDCap questionnaire).   | Pre-decision Aid Multiple choice items, scored using standard procedures as binomial, ordinal or continuous variables.   | Not applicable   |
| <b>Reproductive Concerns Scale<sup>1</sup></b><br>Measures women's perceived importance and satisfaction with factors that may impact their fertility.   | Assessed using interview, paper, and online formats (e.g., REDCap questionnaire). Available in English and Dutch. Used in oncofertility, HIV, and general medicine.                 | Pre-decision Aid 0-56, with higher scores meaning more concern. 14-items, using Likert scales scored 0 "Not at all" to 4 "Very much". Item scores are summed for total score.  | Alpha coefficients 0.81 to 0.91.   |
| <b>Fertility Preservation Knowledge Scale<sup>2</sup></b><br>Measures women's knowledge of how cancer and cancer treatments may affect fertility; the fertility preservation options; and the procedures, risks and benefits of the options. | Assessed using interview, paper, and online formats (e.g., REDCap questionnaire). Used in oncofertility.  | Post-decision aid.<br>0-13 or 0-100% of questions scored correct, with higher scores meaning greater knowledge. 13 True/False items scored 0 (incorrect) or 1 (correct). Note: scoring modified to reflect updates in practice (Item X scored correct = True). Correlated with personal contact with fertility (p<0.01) and previous exposure to fertility preservation (p<0.01).          | Not reported.  |
| <b>Intolerance of Uncertainty Scale<sup>3</sup></b><br>Measures responses to uncertainty, ambiguous situations, and the future, including subscales of prospective and inhibitory anxiety.   | Used in interview, paper, computerized, and online formats (e.g., REDCap questionnaire). Available in English and French. Used in mental health, general health, and oncofertility. | 12-60 points or 0-100, with higher scores indicating greater anxiety about uncertainty (prospective or inhibitory). 12 or 27 items, using 5-point Likert scales scored 1 "Not at all characteristic of me" to 5 "Entirely characteristic of me". Can be scored as two sub-scales - prospective anxiety and inhibitory anxiety. IUS-12 strongly correlates with IUS-27 (rs = 0.94 to 0.96). | Alpha coefficients exceed 0.85. Good convergent and discriminant validity. |
| <b>Brief Symptom Inventory<sup>4 5</sup></b><br>Brief screening measure for psychological  | Used in interview, paper,   | 0-72 total Global Severity Index scores,   | Alpha coefficients exceed 0.80 in  |

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Appendix B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts  | Timing, Scoring and Interpretation   | Psychometric properties  |
|--|--|--|--|
| distress and psychiatric disorders in three dimensions: depression, anxiety, and somatization.   | computerized, and online formats. Available in English and Spanish. Used widely, across many general, mental, cancer, and population health contexts.  | with higher scores indicating greater distress. Recommended distress cutoffs of 10 in men, 13 in women, 50 in cancer survivors, and 62 in palliative care. 18 items scored on 5-point Likert scales of 0 "Not at all" to 4 "Extremely", summed for each subscale and for the total score.  | cancer survivors. Correlates with the Symptom Checklist 90 ( $r = 0.88$ to $0.94$ ). Internal consistency estimates of 0.74 somatization, 0.79 anxiety, 0.84 depression, and 0.89 global severity index.   |
| <b>Decisional Conflict Scale</b> <sup>6,7</sup><br>Assesses patients' perceptions of uncertainty about the options, modifiable factors contributing to uncertainty, and sense of effective decision making. Includes a Leaning Scale measuring strength of treatment preference and four subscales measuring uncertainty, informed, values clarification, and support. | Used in interview, paper, computerized, and online formats. 16-item, 10-item, Low Literacy, and 4-item "SURE" versions. Available in English, French, Danish, Chinese, Spanish, German, Japanese, Italian, and Chilean Spanish. Used across many musculoskeletal, genetic, cardiac, and oncological conditions, including oncofertility. | 0-100, with scores below 25 associated with making a choice and scores above 37.5 associated with delaying decisions. Additionally, for every unit increase, people are 59X more likely to change their mind, 23X more likely to delay decision, 5X more likely to express decisional regret, 3X more likely to fail knowledge test, and 19X more likely to blame doctor for any bad outcomes. 16 items scored on a 3-point Likert scale from 0 "yes" to 4 "no", summed, and divided by 10 to yield a total score. | Alpha coefficients >0.78. Discriminates between people who make and delay decisions; effect size ranges 0.4 to 0.8. Correlates to related constructs of knowledge, regret, and discontinuance.   |
| <b>Values Clarity Leaning Scale</b> <sup>8</sup><br>Assesses the desirability or personal importance a respondent places on the benefits and risks of an option.   | Used in interview, paper, computerized, and online formats. Available in English and French. Used in orthopedics, cancer, cardiology, genetics, geriatrics, etc. Adapted for each decision-making, clinical, and/or intervention context.  | At beginning and at end of Decision Aid; 10-point Likert scales for each relevant decision attribute (i.e., risk, benefits, procedures), scored 0 "not at all important to me" to 10 "extremely important to me", with higher scores indicating higher personal value for that attribute.  | Test-retest coefficients 0.79 to 0.91. Discriminates between those making different decisions. Correlations between choices and values change over time and differ between decision aids and comparison interventions, especially among those who are changing the status quo. |
| <b>Strength of Treatment Preference Leaning Scale</b> <sup>6-8</sup><br>Assesses choice disposition, (a person's leaning towards or propensity to, select an option) decision (a   | Used in interview, paper, computerized, and online formats. Available in English and French. Adapted for each decision-making, clinical,   | At end of Decision Aid; 11-point bi-directional leaning scale scored 0 "unsure/no preference" at the center anchor, to 10 "Strongly Leaning towards X/Y" at each end. Scores may be  | Test-retest coefficients exceed 0.90. Is sensitive to change and discriminates between interventions, particularly for the undecided group. Correlates with  |

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## Appendix B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts  | Timing, Scoring and Interpretation   | Psychometric properties  |
|--|--|--|--|
| person's stated choice among alternatives), or enacted decision (the implementation of a chosen options as determined by self-report and/or verification strategy). May also be used to identify undecided individuals for targeted recruitment or intervention. May also include reasons for, on influences on, decision making | and/or intervention context. Used in orthopedics, cancer, cardiology, genetics, geriatrics, obstetrics/gynecology, and internal medicine, etc.   | reclassified based on distribution (e.g. 0-3 "no/weak preference", 4-7 "moderate preference", 8-10 "strong preference". May also include open-ended questions to elicit reasons behind, and/or influences on, the leaning.   | values and expectations.   |
| <b>Decision Self-efficacy Scale<sup>9</sup></b><br>Assesses self-confidence or belief in one's ability in decision making, including shared decision making.   | Used in interview, paper, computerized, and online formats. Available in English and German. Used in orthopedics, mental health, cancer, and geriatrics.   | 0-100, with higher scores indicating higher self-efficacy. 11-item low literacy version, using 3-point Likert scale from 0 "Not Confident" to 4 "A Lot Confident".   | Alpha coefficient 0.86. Discriminates between individuals who make and delay decisions. Correlated with decisional conflict ( $r = 0.55$ ), especially the subscales of feeling informed ( $r = 0.61$ ) and supported ( $r = 0.61$ ).                              |
| <b>Preparation for Decision-making Scale<sup>10</sup></b><br>Assesses perspective of how well an intervention prepared them to communicate with their physician about a decision. Includes identifying a decision, preferred role, values clarification, communication.  | Patient and Practitioner versions. Used in interview, paper, computerized, and online formats. Available in English French, German, Italian.<br>Used in orthopedics, prostate cancer, breast cancer, autologous blood donation, hormone replacement therapy. | 0-100, with higher scores indicating better preparation. 11 multiple choice items scored on 5-point Likert scale from 1 "not at all" to 5 "a great deal", summed and multiplied by 2 to yield the total score.   | Alpha coefficients 0.92 to 0.96. Discriminates between people who do/do not find the decision aid helpful ( $p < 0.0001$ ). Correlates with informed ( $r = -0.21$ , $p < 0.01$ ) and support ( $r = -0.13$ , $p = 0.01$ ) subscales of Decisional Conflict Scale. |
| <b>Acceptability Leaning Scales<sup>11</sup></b><br>Assesses subjective rating of the decision aid's ease of use, clarity of information, length, level of detail provided, ability to hold one's interest, and satisfaction with "how the website prepared you for discussing this decision with your doctor(s)"                | Patient and Practitioner versions. Used in interview, paper, computerized, and online formats. Available in English and French. Adapted for each decision-making, clinical, and/or intervention context.   | Post-decision aid.<br>15 acceptability characteristics on 5-category Likert scales from (scored 1 Strongly Agree or Agree; 0 Neither, Disagree or Strongly Disagree), with the exception of the item assessing whether the decision aid favored either option (scored 1 Neither, 0 all other responses). | None reported.   |

Pathways oncofertility decision support trial protocol

Woodard TW

Appendix B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts   | Timing, Scoring and Interpretation   | Psychometric properties   |
|--|---|--|---|
|  | Various, from breast and prostate cancer to knee osteoarthritis to end-of-life.   |  |   |
| <b>Decisional Regret Scale<sup>12</sup></b><br>Measures distress or remorse after a health care decision.                                    | Used in interview, paper, computerized, and online formats. Available in English, French, Chinese, Spanish, and Japanese.<br>Used in cancer, orthopedics, and oncofertility.  | 0-100, with higher scores indicating greater regret. 5-items, using 5-point Likert scales from 1 "Strongly Agree" to 5 "Strongly Disagree". Items 2 and 4 are reverse coded. 1 point is subtracted from all items, then they are multiplied by 25, summed, and averaged for a total score. | Alpha coefficients 0.81 to 0.92. Correlates with satisfaction with the decision (r = -0.40 to -0.60), decisional conflict (r = 0.31 to 0.52) and overall quality of life (r = -0.25 to -0.27). Groups who differed on feelings about the decision (e.g. negative, mixed, positive) also differed on regret (p<0.001). Greater among individuals who change their decisions (p<0.001). |
| <b>Client Satisfaction Questionnaire<sup>13</sup></b><br>Measures and assesses overall consumer satisfaction with health and human services. | Used in interview, paper, computerized, and online formats. Available in a variety of languages, formats, and versions (e.g., CSQ-3, 4, 18, 18B, 31) and used in a wide spectrum of clinical , human services, educational, and governmental programs, legal services, police services, administrative settings, and research settings. | Total scores are the sum of item scores, using 4-point Likert scales 1 "Indifferent or mildly satisfied" to 4 "Very satisfied", with some items reverse scored to minimize stereotypic response sets.  | Alpha coefficients 0.83 to 0.97 with moderate correlation with the Brief Psychiatric Rating Scale and Client Checklist.   |
| <b>Usability<sup>11</sup></b><br>Assesses subjective perspectives on desired formats and modes of delivery                                   | Patient and Practitioner versions. Used in interview, paper, computerized, and online formats. Adapted for each decision-making, clinical, and/or intervention context. Used across a variety of  | Post-decision aid. 5 multiple-choice items scored as the percentage of positive responses to each item.  | Not applicable.   |

## Pathways oncofertility decision support trial protocol

Woodard TW

## Appendix B. Pathways trial evaluation measures.

| Measure | Formats, languages, and clinical contexts   | Timing, Scoring and Interpretation | Psychometric properties |
|---------|---|------------------------------------|-------------------------|
|         | clinical conditions, from breast and prostate cancer to knee osteoarthritis to end-of-life. |                                    |                         |

## REFERENCES

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**Informed Consent**

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Informed Consent Printer Database**

**INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN  
RESEARCH WITH OPTIONAL PROCEDURES**

Patient-centered decision counseling for women at risk of cancer-related  
infertility: efficacy study and comparative-effectiveness randomized trial  
2016-0758

Study Chair: Terri L. Woodard

Participant's Name

Medical Record Number or Study ID

This consent and authorization form explains why this research study is being done  
and what your role will be if you choose to take part. You may choose not to take  
part in this study.

**1. DESCRIPTION OF STUDY**

The goal of this research study is to learn if a decision aid website that provides  
information about fertility preservation (maintaining your ability to have children of  
your own after cancer treatment) can help women with cancer make  
fertility-preservation decisions. Researchers will also use information learned in this  
study to help improve the website. This website was developed at MD Anderson.

There are several ways to preserve fertility, including taking drugs to stop or control  
ovary function in order to freeze eggs and/or embryos. Freezing eggs and/or  
embryos may increase the chances of having a child of your own in the future. You  
may also choose to have children using other methods, such as adoption. This  
website is designed to help women learn more about these options and consider  
which of them may be best for them.

**NOT FOR USE IN CONSENTING PATIENTS**

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

**This is an investigational study.** The study will be performed at no cost to you.

Up to 160 participants will be enrolled in this multicenter study. Up to 160 may be enrolled at MD Anderson.

## 2. STUDY PROCEDURES

There are 2 parts to this study. In Part 1, researchers will learn if the fertility preservation website can help women make decisions about fertility. In Part 2, researchers will compare the current standard care to standard care in combination with the fertility preservation website.

If you are receiving treatment at MD Anderson, you will take part in Part 1 of the study. If you are receiving treatment at a Houston-area MD Anderson satellite office, you will take part in Part 2 of the study.

### **Part 1**

If you are in Part 1 of the study, you will be given the option to either view the decision aid website about fertility preservation at home or you can come to your routine fertility consultation visit about 30 minutes early and view the website at the office in a private room. Whichever you choose, you will complete a questionnaire before viewing the website about healthcare decision making and fertility. This questionnaire should take about 30 minutes to complete.

About 1 week after you view the website, you will complete another questionnaire about your opinions on the decision aid website and if you think the website is useful in making fertility preservation decisions. This questionnaire should take about 30 minutes to complete.

You will then have your fertility consultation visit as scheduled and you may or may not choose to use fertility preservation treatments or methods. About 2 months after your consultation visit, you will complete a questionnaire about which methods of fertility preservation you chose to use (if any), what influenced your decision-making, and if you have any ideas on how to improve the fertility preservation process. This will be completed online and may take about 30 minutes to complete.

### **Part 2**

If you agree to take part in this study, the type of educational information you receive will depend on where you are receiving treatment. You will either receive standard care or standard care plus the use of the decision-making website. Standard of care includes receiving patient education materials about fertility preservation from the Livestrong organization and receiving a referral for fertility preservation, if requested.

All participants will complete the questionnaires described below.

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You will complete 3 sets of questionnaires when you enroll in the study and then at 1 week and then 2 months after you enroll. These questionnaires include questions about your demographic information (for example, age, sex, and race). They also include questions about your preferred role in making healthcare decisions, your knowledge about fertility preservation, and any concerns you have about reproduction. Each set of questionnaires should take about 30 minutes to complete. All questionnaires will be completed online.

The research staff may call you to remind you to complete the questionnaires and/or to learn more information about your fertility status that may not be found in your medical record.

**All Participants**

The study staff may also review your medical records for information about what, if any, fertility preservation options you chose to do. The study staff will also review your medical record to collect data about your fertility status. The study staff may contact you to collect information that may not be included in your medical record.

**Length of Study Participation**

Your participation in this study will be over after you complete the 2-month questionnaire.

**3. POSSIBLE RISKS**

You should discuss the risks of questionnaires with the study chair. The known risks are listed in this form, but they will vary from person to person. Some questions may make you feel upset or uncomfortable. You may refuse to answer any question. If you have concerns after completing the questionnaires, you are encouraged to contact your doctor or the study chair.

Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen. All study data will be stored in password-protected computers, locked file cabinets, and/or on a secure online database named REDCap. Study data will not be destroyed but will be stored in a secure database at MD Anderson called REDCap after the study has been completed.

This study may involve unpredictable risks to the participants.

---

**OPTIONAL PROCEDURES FOR THE STUDY**

**Optional Procedure #1:** If you agree, the research staff may contact you by phone, email, or mail to ask you if you would be interested in taking part in future research studies.

There are no benefits to you for taking part in the optional procedure. Future patients may benefit from what is learned. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedure.

**Optional Procedure Risks:**

If you are **contacted about future studies**, other people may learn you have (had) cancer. This may be upsetting.

**CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES**

Circle your choice of “yes” or “no” for each of the following optional procedures:

**Optional Procedure #1:** Do you agree to allow the research staff to contact you by phone, email, or mail to ask you if you would be interested in taking part in future research studies?

YES                      NO

**4. POTENTIAL BENEFITS**

Future patients may benefit from what is learned. You may learn more about fertility preservation options by participating in this study. There **may be** no benefits for you in this study.

**5. OTHER PROCEDURES OR TREATMENT OPTIONS**

You may choose not to take part in this study. If you do not participate in the study, you will not have access to the website.

**6. STUDY COSTS AND COMPENSATION**

**NOT FOR USE IN CONSENTING PATIENTS**

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If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson, The Duncan Family Institute, or National Cancer Institute and Alliance for Clinical Trials in Oncology for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (health maintenance organization [HMO], health insurance company, etc.), will be your responsibility.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive a \$25 gift card in the mail two months after you enroll in the study.

Your gift card will be sent separately using the Bank of America Remuneration Program used at MD Anderson.

You will be given a reloadable debit card that will be electronically loaded with money at the end of the two months of the study. If this card is lost or stolen while you are on study, you may be required to pay a \$5.00 replacement fee to get a new one. Your name, address, date of birth, and social security number (if necessary) will be collected and every effort will be made to keep this information strictly confidential. It will only be shared with a third party for the purpose of processing your payment.

The money you receive may be taxable. If you receive more than \$600 in a calendar year for being in research studies, you will be given an IRS Form 1099-MISC for tax reporting purposes.

**ADDITIONAL INFORMATION**

- 7. You may ask the study chair (Dr. Terri L. Woodard, at 713-745-7591) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.
- 8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you withdraw from this study, you can

still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair, The Duncan Family Institute, National Cancer Institute and Alliance for Clinical Trials in Oncology, or the IRB of MD Anderson.
10. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.
11. MD Anderson may benefit from your participation and/or what is learned in this study.
12. This study is sponsored and/or supported by: The Duncan Family Institute and National Cancer Institute and Alliance for Clinical Trials in Oncology.

#### **Authorization for Use and Disclosure of Protected Health Information (PHI):**

- A. During the course of this study, MD Anderson may be collecting and using your PHI. For legal, ethical, research, and safety-related reasons, the research team may share your PHI with:
  - The OHRP
  - The IRB and officials of MD Anderson
  - The Duncan Family Institute and National Cancer Institute and Alliance for Clinical Trials in Oncology, who are sponsors or supporters of this study, and/or any future sponsors/supporters of the study
  - Study monitors and auditors who verify the accuracy of the information
  - Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

- B. Signing this consent and authorization form is optional but you cannot take part in this study if you do not agree and sign.
- C. MD Anderson will keep your PHI confidential when possible according to state and federal law. However, in some situations, health authorities could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, the data collected up to that point can be used and included in data analysis, but no further information about you will be collected.

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# Please Do Not Use for Patient Consent

Go to the PDOL Homepage to access the  
Informed Consent Printer Database

## CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

### **SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF PARTICIPANT

DATE

### **LEGALLY AUTHORIZED REPRESENTATIVE (LAR)**

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

### **SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF LAR

DATE

### **SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

RELATIONSHIP TO PARTICIPANT

### **WITNESS TO CONSENT**

I was present during the explanation of the research to be performed under Protocol 2016-0758.

### **SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF WITNESS TO THE VERBAL CONSENT  
PRESENTATION (OTHER THAN PHYSICIAN OR STUDY  
CHAIR)

DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

### **PERSON OBTAINING CONSENT**

### **NOT FOR USE IN CONSENTING PATIENTS**

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF STUDY CHAIR  
OR PERSON AUTHORIZED TO OBTAIN CONSENT

DATE

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**TRANSLATOR**

I have translated the above informed consent as written (without additions or subtractions) into \_\_\_\_\_ and assisted the people

(Name of Language)

obtaining and providing consent by translating all questions and responses during the consent process for this participant.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

NAME OF TRANSLATOR \_\_\_\_\_ SIGNATURE OF TRANSLATOR \_\_\_\_\_ DATE \_\_\_\_\_

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION \_\_\_\_\_ DATE \_\_\_\_\_  
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR)

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Supplementary File D: SPIRIT Checklist



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | 1                        |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | 3                        |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | 1-14                     |
| Protocol version                  | 3       | Date and version identifier  | 13                       |
| Funding                           | 4       | Sources and types of financial, material, and other support  | 16                       |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | 1                        |
|                                   | 5b      | Name and contact information for the trial sponsor   | 1,16                     |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16                       |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | 1,6,16                   |
| <b>Introduction</b>               |         |  |                          |
| Background and rationale          | 6a      | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention   | 2-5                      |

## Pathways oncofertility decision support trial protocol

Woodard TW

## Supplementary File D: SPIRIT Checklist

|   |     |  |        |
|---|-----|--|--------|
|   | 6b  | Explanation for choice of comparators  | 2-8    |
| Objectives  | 7   | Specific objectives or hypotheses  | 5      |
| Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  | 1, 5-7 |
| <b>Methods: Participants, interventions, and outcomes</b> |     |  |        |
| Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained   | 6-7    |
| Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)   | 6-7    |
| Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | 7-8    |
|   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)   | 11     |
|   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | 12     |
|   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | 7-8    |
| Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8-11   |
| Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)   | 8-11   |
| Sample size   | 14  | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations  | 11-12  |
| Recruitment   | 15  | Strategies for achieving adequate participant enrolment to reach target sample size  | 11-12  |

Methods: Assignment of interventions (for controlled trials)

|  |     |  |                          |       |
|--|-----|--|--------------------------|-------|
| Allocation:  |     |  |                          |       |
| Sequence generation                                | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions   |                          | 12    |
| Allocation concealment mechanism                   | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  |                          | 12    |
| Implementation                                     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  |                          | 12    |
| Blinding (masking)                                 | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  |                          | 11-12 |
|  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   |                          | N/A   |
| Methods: Data collection, management, and analysis |     |  |                          |       |
| Data collection methods                            | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 8-11, Supplementary File |       |
|  | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  |                          | 12    |
| Data management                                    | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol  |                          | 11-12 |

# Pathways oncofertility decision support trial protocol

Woodard TW

## Supplementary File D: SPIRIT Checklist

|                                 |     |   |       |
|---------------------------------|-----|---|-------|
| Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | 12-13 |
|                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 12-13 |
|                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | 12-13 |
| <b>Methods: Monitoring</b>      |     |   |       |
| Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14    |
|                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | 14    |
| Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | 11    |
| Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 11    |
| <b>Ethics and dissemination</b> |     |   |       |
| Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 13-14 |
| Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | 13-14 |
| Consent or assent               | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | 13-14 |
|                                 | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | N/A   |

|  |     |   |            |                    |
|--|-----|---|------------|--------------------|
| Pathways oncofertility decision support trial protocol |     |   | Woodard TW |                    |
| Supplementary File D: SPIRIT Checklist                 |     |   |            |                    |
| Confidentiality  | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  |            | 11                 |
| Declaration of interests                               | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   |            | 16                 |
| Access to data   | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   |            | 11                 |
| Ancillary and post-trial care                          | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   |            | 11                 |
| Dissemination policy                                   | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |            | 14                 |
|  | 31b | Authorship eligibility guidelines and any intended use of professional writers  |            | 16                 |
|  | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   |            | N/A                |
| Appendices   |     |   |            |                    |
| Informed consent materials                             | 32  | Model consent form and other related documentation given to participants and authorised surrogates  |            | Supplementary File |
| Biological specimens                                   | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  |            | N/A                |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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# BMJ Open

## Pathways--Patient-centered decision counseling for women at risk of cancer-related infertility: a protocol for a comparative effectiveness cluster randomized trial

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Manuscripts

**Pathways--Patient-centered decision counseling for women at risk of cancer-related infertility: a protocol for a comparative effectiveness cluster randomized trial**

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**Pathways oncofertility decision support trial protocol****Woodard TW**

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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 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 to usual care on women’s fertility preservation knowledge and decision-making outcomes.

**Methods and analysis:** This cluster-randomized 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 a) up-to-date evidence and descriptions of fertility preservation and other family-building options, tailored to cancer type; 2) structured guidance to support personalizing 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 Fishers exact test. Secondary outcomes will be assessed using generalized linear mixed models, and sensitivity analyses will be conducted, as appropriate.

**Pathways oncofertility decision support trial protocol****Woodard TW**

**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:** NCT03141437, PI: Terri L. Woodard, M.D., 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 cancer 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 generalized linear mixed modeling methods and sensitivity analyses.
- This study will also 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.<sup>1</sup> Previous studies have shown that when women are referred to a fertility specialist for fertility counseling, regret and quality of life are improved (whether or not they choose to pursue fertility preservation).<sup>2-12</sup> However, recent reports indicate as little as 5% of eligible patients see a fertility specialist, and rates of long-term infertility-related distress remain high.<sup>2-20</sup> 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 counseling, and individualized decision support to foster informed, values-based decisions during the stressful time period leading up to initiation of cancer treatment.<sup>3 4 6 7 10 12 16-19 21-31</sup>

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 (i.e., feelings of being uninformed, unclear, unsupported, and uncertain that lead to delayed or poorly implemented decisions).<sup>26-28 30 32</sup> Over 115 randomized 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.<sup>30</sup> We previously developed a patient decision aid website called *Pathways* that provides a) up-to-date information about fertility preservation options and alternative pathways to family building; and b) 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 (manuscript under review). However, women report needing access to this information earlier in the cancer care pathway. Therefore, the next step in this program 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.

## Pathways oncofertility decision support trial protocol

Woodard TW

Fertility preservation involves a multi-step decision-making process often complicated by uncertainty and a tight and variable timeline.<sup>4 6 9-12 15-17 24</sup> At the initial oncology consultation during which a woman 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 (e.g. 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 multi-step 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 counseling.<sup>6 7 10 12 24 33</sup> The following protocol describes the aims for the *Pathways* cluster randomized 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 to 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 counseling and to help facilitate referrals, as appropriate.
2. *Secondary:* To assess patients' decision-making process (e.g., preparation for decision making, decision self-efficacy, satisfaction) and decision quality (e.g., 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

(e.g., 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 randomized 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 counseling 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 program 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.<sup>27-32 34-45</sup> The core research team includes a reproductive endocrinologist (T.L.W.), women’s health advanced practice provider (D.A.H.), decision scientists (R.V., A.S.H.), and research assistant (L.C.C).A Stakeholder Advisory Panel composed of three female cancer survivors who had previously considered fertility preservation, two patient advocate leaders, and two oncology providers (gynecologic and pediatric).

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 tumor, female genital system tumor, colorectal tumor, and/or lymphoma or myeloma are eligible for inclusion in the study. These criteria were chosen to align

**Pathways oncofertility decision support trial protocol****Woodard TW**

with the current guidelines for fertility preservation discussions.<sup>1</sup> 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 centralized electronic health record for tracking referral and treatment utilization, and may be more generalizable to the U.S. population than the MD Anderson main campus. Providers of these clinics will be eligible for inclusion in the post-study provider discussions.

**Randomization**

We will generate a randomization list for the 4 oncology clinics using nQuery Advisor (©1995-2007, Statistical Solutions, Saugus, MA) with 2 study arms (control, multicomponent intervention) and a block size of 4.

**Treatment arms**

At the two sites randomized 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 randomized to the intervention, three components will be provided – provider seminar, access to *Pathways*, and follow-up telephone counseling. Dr. Woodard (a fertility specialist) will present a departmental seminar designed to: a) enable and motivate oncologists to address fertility issues in women at risk of cancer-related infertility and refer them to reproductive endocrinologists, if warranted; and b) introduce the *Pathways* patient decision aid; and c) 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, April 1, 2017) after their initial oncology consultation. Results of the formative studies (provider and patient needs assessments, user-centered design and production, and usability/acceptability pilot-testing) and efficacy study are published separately (manuscripts under

review). Selected screenshots and the overall architecture of the *Pathways* website are provided in figure 2; scores on the IPDAS Quality Checklist are provided in Supplementary File A.

**Figure 2. Components and features of the *Pathways*® patient decision aid website.**

*Pathways* provides women with an introduction to the effects of cancer on fertility; descriptions of the fertility preservation and other family-building options; and interactive My Personal Decision features that support women in personalizing 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 8<sup>th</sup>-grade language. Each woman's My Personal Decision information is provided in a printable summary.

Within the following week, follow-up telephone counseling 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). Supplementary File B provides the psychometric properties for each measure/instrument. The primary measure is decisional conflict, assessed pre/post-intervention using the 16-item Decisional Conflict Scale.<sup>46</sup> 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.

Table 1. Outcome measures and data collection time points.

| Measure  | Objective   | Baseline | During DA* | 1 Week | 2 Month |
|--|---|----------|------------|--------|---------|
| Eligibility: Age, sex, cancer status, Internet access, valid email, speaks English, has not viewed the 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) <sup>47</sup> | Baseline characteristics                          | X        |            |        |         |
| Reproductive Concerns Scale <sup>20</sup>  | Baseline characteristics                          | X        |            |        |         |
| Fertility Preservation Knowledge Scale <sup>21</sup>   | Baseline characteristics                          | X        |            | X      | X       |
| Intolerance of Uncertainty Scale <sup>48</sup>   | Baseline characteristics                          | X        |            |        |         |
| Brief Symptom Inventory <sup>49-50</sup>   | Baseline characteristics & data safety monitoring | X        |            | X      | X       |
| Decisional Conflict Scale <sup>46</sup>  | Primary   | X        |            | X      |         |
| Values Clarity Learning Scale for each relevant risk/benefit <sup>51</sup>   | Secondary   |          | X*         | X      |         |
| Strength of Treatment Preference Learning Scale for their favored option(s) <sup>51-52</sup>   | Secondary   |          | X*         | X      |         |
| System usage (e.g., time spent on website, error rates, revisit rates, viewing at home/clinic)   | Secondary   |          | X*         |        |         |
| Other fertility preservation resources viewed/used (5 open-ended questions)  | Secondary   |          |            | X      |         |
| Decision Self-efficacy Scale <sup>53</sup>   | Secondary   |          |            | X      |         |
| Preparation for Decision-making Scale <sup>54</sup>  | Secondary   |          |            | X      |         |
| Acceptability Learning Scales (length, clarity, ease of use, interesting, comprehensive) <sup>55</sup>   | Exploratory                                       |          |            | X      |         |
| Fertility preservation referral and/or fertility preservation scheduled/completed, type & estimated cost   | Secondary   |          |            |        | X       |
| Clinical factors: diagnosis, stage, & therapies, history of infertility, gravidity/parity, AMH, Antral follicle count  | Secondary   |          |            |        | X       |
| Decision-making factors: three primary influences on decision  | Secondary   |          |            |        | X       |
| Decisional Regret Scale <sup>56</sup>  | Exploratory                                       |          |            |        | X       |
| Client Satisfaction Questionnaire <sup>57</sup>  | Exploratory                                       |          |            |        | X       |
| Recommendations for improving decision-making process and referral process   | Exploratory                                       |          |            |        | X       |

\*For patients at intervention sites.

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.<sup>20-46-50</sup> Across time points, this study will assess women's

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3 decision-making processes using the Decision Self-efficacy Scale, Preparation for Decision Making  
4 Scale, and open-ended questions assessing other decision-making factors (e.g. three primary influences  
5 on their decision, role of spouse/partner in decision-making, etc.)<sup>53 54</sup> Decision quality will be assessed  
6 using the Fertility Preservation Knowledge Scale, Values Clarification Learning Scale, and Strength of  
7 Preference for Referral/Treatment(s) Scales, as well as an assessment of the concordance of  
8 participants' preferences with subsequent treatments scheduled or completed by 2 months.<sup>21 51 52</sup>

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11 In preparation for future planned dissemination and implementation studies, exploratory measures include  
12 the Patient Decision Aid Acceptability Scale (i.e. Learning Scales rating the length, ease of use, clarity,  
13 comprehensiveness, and meaningfulness of the decision aid), Client Satisfaction Questionnaire, system  
14 usage (e.g., preferences for viewing at home or at the clinic, time spent on the website, error rates, etc.)  
15 and preliminary testing of potential downstream measures (e.g., Decisional Regret Scale).<sup>55-57</sup> At the  
16 conclusion of the study, semi-structured discussions with clinicians at the intervention sites will assess  
17 clinician perspectives about the usefulness of the multicomponent intervention and suggestions for  
18 improvement. These exploratory measures will inform and guide the design of future longitudinal studies.

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34 **Adverse events**

35 The risk of adverse events are low. However, it is possible that discussion of fertility issues can cause or  
36 increase emotional distress. If a participant is identified as being significantly distressed (i.e., by notifying  
37 the study coordinator and/or scoring > 63 on the Brief Symptom Inventory), they will be reminded that  
38 they can end their participation at any time, and the principal investigator or research study coordinator  
39 will refer the participant to the appropriate psychosocial support resources.<sup>49 50</sup> An external Data  
40 Monitoring Committee is not commissioned for this protocol.

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49 **Data management**

50 Study data will be collected and managed using REDCap (Research Electronic Data Capture,  
51 [www.project-redcap.org](http://www.project-redcap.org)) electronic data capture tools hosted at The MD Anderson Cancer Center.<sup>58</sup> All  
52 protected health information (PHI) will be removed from the data when it is exported from REDCap for

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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 (that is, less uncertainty, anxiety, or distress).<sup>46 59</sup> 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 intra-cluster correlation was 0.011.<sup>60</sup> Assuming a similar intra-cluster correlation, 50 patients on each study arm (25 at each oncology clinic) will provide a ~80% power with a 2-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 (Hintze, J. 2005. NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah. [www.ncss.com](http://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 socio-economically, racially/ethnically, and clinically diverse population. Conservatively assuming a 50% participation rate, we anticipate enrolling 10-12 women/month from September 1, 2017 to May 30, 2018. Participants will be provided with \$25 gift cards at 2 months post-enrollment. If additional recruitment is needed, the MD Anderson main campus oncology clinics may be added, where previous studies in this program of research have observed a 75-90% participation rate.

The four oncology clinics will be assigned site identification numbers in alphabetical order, then randomized using nQuery Advisor 7.0. (©1995-2007, Statistical Solutions, Saugus, MA). The randomization 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 summarize 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 dichotomized decisional conflict score, the statistical team will first tabulate the counts and frequencies. To assess the effect of the proposed multicomponent oncofertility decision support intervention compared to usual care, they will use generalized linear mixed models (GLMM) with one covariate of the study arm and a random effect that takes into account the between-cluster variation. In analyzing cluster randomized trials, Klar and Darlington (2004) 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 randomized controlled trials with dichotomous outcomes.<sup>61 62</sup> Indeed, covariate adjustment is often recommended to achieve unbiased estimates and to improve the precision, thus increasing the power.<sup>63</sup> 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' socio-demographic, 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

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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 cutoffs (e.g. <37.5, since scores higher than 37.5 are associated with delaying decisions) and the differences in the change in score pre/post-decision aid.

For the other instruments, the statistical team will use generalized linear mixed model 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 (e.g. preparation for decision making, decision self-efficacy, and satisfaction) and decision quality (e.g. fertility preservation knowledge, clarity of patients' values, and congruence of preferences with the decision about whether to accept fertility preservation and/or fertility preservation treatment).

Generalized linear mixed model 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.<sup>64</sup>

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

**Ethics and dissemination**

The University of Texas MD Anderson Cancer Center provided initial ethical approval and continues to provide ongoing review of any amendments to this protocol (#2017-0758, v.4.0, 07/31/2017).

Supplementary File C provides an example of the approved informed consent document (note: this manuscript 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 (COrE) 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.<sup>49</sup> 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-centered design and production, and usability/acceptability pilot-testing) and efficacy study are published separately (manuscripts under review). 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 randomized 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.

Supplementary File D provides the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 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.<sup>1</sup> Previous studies have demonstrated the value of fertility counseling in reducing women's long-term distress, regardless of whether or not they pursue fertility preservation treatments.<sup>2-4 7-11 15 16 19</sup> However, referral rates for fertility preservation counseling remain low.<sup>5 6 8 10 12 15 17 22</sup> 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.<sup>3 7 10 12 14 16 23 24 33</sup> A few studies have developed and tested patient decision aids with encouraging results in select patient populations (e.g. women with breast cancer, parents of adolescent girls).<sup>7 16 18 23</sup> As part of a long-term research program, this comparative effectiveness trial will test a multicomponent intervention (provider education, *Pathways* patient decision aid website, and follow-up telephone counseling) 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 (e.g. preferred level of information detail and engagement in decision-personalization activities).

Further, this approach seeks to promote adherence to the American Society of Clinical Oncology 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.<sup>1</sup> 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 counseling referral.<sup>5 8 10-12 15 17 33</sup> 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 counseling 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 (e.g., 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 auto-notification of any distressing scores on the BSI scale. However, this distress may also be supportive of decision-making (i.e. “functional decisional conflict” that helps individuals take action) and similar studies have shown 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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## AUTHOR CONTRIBUTIONS

Conceptualization, T.L.W., A.S.H., L.C.C. and R.J.V.; Methodology, T.L.W., A.S.H., L.A.C., D.A.H, D.B.H, J.M., R.L.B., and R.J.V.; Investigation (not relevant); Writing – Original Draft, T.L.W. and A.S.H.; Writing – Review & Editing, T.L.W., A.S.H., and L.A.C.; Funding Acquisition, T.L.W.; Resources, T.L.W., V.B.L., D.B.H., and R.J.V.; Supervision, T.L.W., A.S.H., and R.V.

## COMPETING INTERESTS

The authors report that they have no conflicts of interest to declare.

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## ETHICS APPROVAL

The University of Texas MD Anderson Cancer Center (#2016-0758).

## DATA SHARING

Data sharing inquiries should be directed to the corresponding author.

FIGURES

Figure 1. Study Design.

R = Randomization, Shading = multicomponent intervention

Figure 2. Components and features of the *Pathways*® patient decision aid website.

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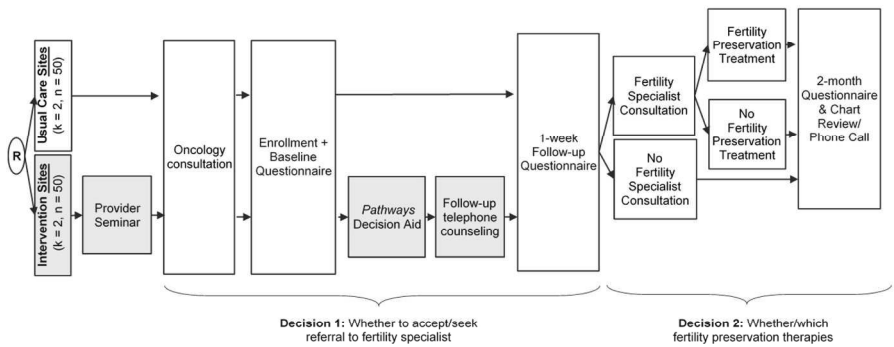


Figure 1. Study Design.  
R = Randomization, Shading = multicomponent intervention

Figure 1. Study Design

203x114mm (300 x 300 DPI)

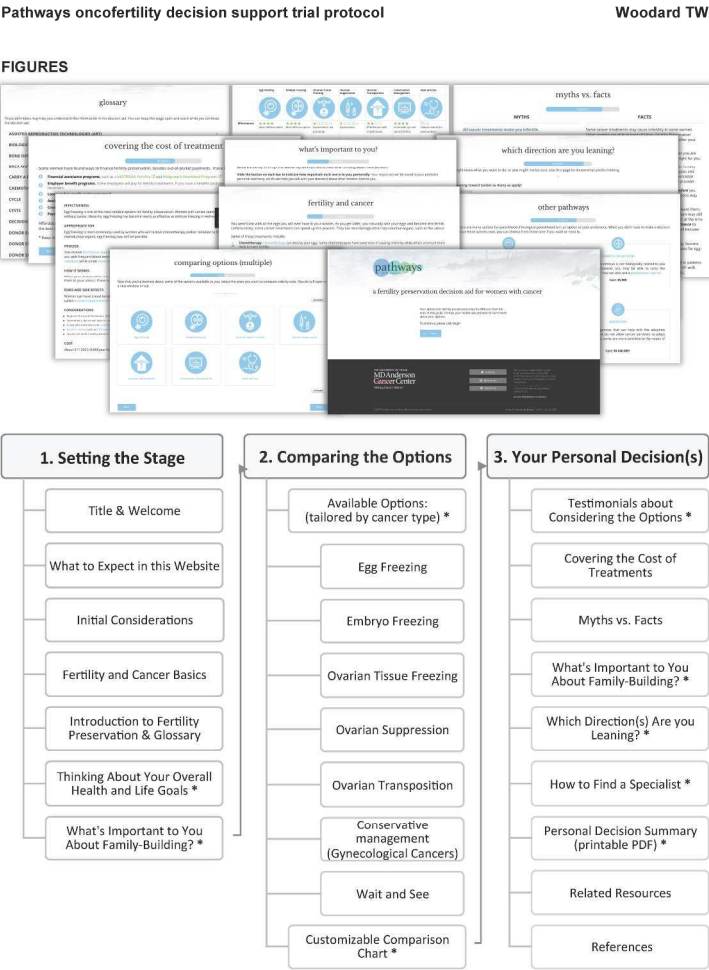


Figure 2. Components and features of the Pathways® patient decision aid website.\* = Includes an interactive personalization activity (e.g. open-ended goal-setting questions, values clarification rating scales, initial treatment leaning items); responses are collected in the My Personal Decision Summary

Caption : Figure 2. Components and features of the Pathways© patient decision aid website.

279x362mm (300 x 300 DPI)

**Supplementary File A. International Patient Decision Aid Standards (IPDAS) Collaboration criteria for high-quality patient decision aid development.**

| Criteria  | Answer |
|---|--------|
| <b>Criteria to be defined as a patient decision aid</b>   |        |
| 1. The decision aid describes the condition (health or other) related to the decision.  | Yes    |
| 2. The decision aid describes the decision that needs to be considered (the index decision).  | Yes    |
| 3. The decision aid identifies the target audience.   | Yes    |
| 4. The decision aid lists the options (health care or other).   | Yes    |
| 5. The decision aid has information about the positive features of the options (e.g. benefits, advantages).   | Yes    |
| 6. The decision aid has information about negative features of the options (e.g. harms, side effects, disadvantages).   | Yes    |
| 7. The decision aid helps patients clarify their values for outcomes of options by: a) asking people to think about which positive and negative features of the options matter most to them AND/OR b) describing each option to help patients imagine the physical, social, and /or psychological effect. | Yes    |
| <b>Criteria to lower the risk of making a biased decision</b>   |        |
| 8. The decision aid makes it possible to compare the positive and negative features of the available options.   | Yes    |
| 9. The decision aid shows the negative and positive features of the options with equal detail.  | Yes    |
| 10. The decision aid compares probabilities (e.g. chance of a disease, benefit, harm, or side effect) of options using the same denominator.  | N/A    |
| 11. The decision aid (or available technical documents) reports funding sources for development.  | Yes    |
| 12. The decision aid reports whether authors of the decision aid or their affiliations stand to gain or lose by choices people make after using the decision aid.   | Yes    |
| 13. The decision aid includes authors/developers' credentials or qualifications.  | Yes    |
| 14. The decision aid reports the date when it was last updated.   | Yes    |
| 15. The decision aid (or available technical document) reports readability levels.  | Yes    |
| 16. The decision aid provides references to scientific evidence used.   | Yes    |
| <b>Other criteria for decision aids about screening or testing</b>  |        |
| 17. The decision aid has information about what the test is designed to measure.  | N/A    |
| 18. The decision aid describes possible next steps based on the test results.   | N/A    |
| 19. The decision aid has information about the chances of disease being found with and without screening.   | N/A    |
| 20. The decision aid has information about detection and treatment of disease that would never have caused problems if screening had not been done.   | N/A    |
| <b>Other criteria indicating quality</b>  |        |
| 21. The decision aid describes what happens in the natural course of the condition (health or other) if no action is taken.   | Yes    |
| 22. The decision aid has information about the procedures involved (e.g. what is done before, during, and after the health care option).  | Yes    |
| 23. The information about outcomes of options (positive and negative) includes the chances they may happen.   | Yes    |
| 24. The decision aid presents probabilities using event rates in a defined group of people for a specified time.  | N/A    |
| 25. The decision aid compares probabilities of options over the same period of time.  | Yes    |
| 26. The decision aid uses the same scales in diagrams comparing options.  | N/A    |
| 27. Users (people who previously faced the decision) were asked what they need to prepare them to discuss a specific decision.  | Yes    |
| 28. The decision aid was reviewed by people who previously faced the decision who were not involved in its development and field testing.   | Yes    |

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|  |     |
|--|-----|
| 29. People who were facing the decision field tested the decision aid.   | Yes |
| 30. Field testing showed that the decision aid was acceptable to users (the general public & practitioners).   | Yes |
| 31. Field testing showed that people who were undecided felt that the information was presented in a balanced way.   | Yes |
| 32. There is evidence that the decision aid (or one based on the same template) helps people know about the available options and their features.  | Yes |
| 33. There is evidence that the decision aid (or one based on the same template) improves the match between the features that matter most to the informed person and the option that is chosen. | N/A |

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Supplementary File B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts   | Timing, Scoring and Interpretation   | Psychometric properties  |
|--|---|--|--|
| <b>Participant Characteristics</b><br>Age, race/ethnicity, employment, religion, language, literacy, education, relationship status, insurance type, median household income, pregnancy and birth history                                    | Assessed using interview, paper, and online formats (e.g., REDCap questionnaire).   | Pre-decision Aid Multiple choice items, scored using standard procedures as binomial, ordinal or continuous variables.   | Not applicable   |
| <b>Reproductive Concerns Scale<sup>1</sup></b><br>Measures women's perceived importance and satisfaction with factors that may impact their fertility.   | Assessed using interview, paper, and online formats (e.g., REDCap questionnaire). Available in English and Dutch. Used in oncofertility, HIV, and general medicine.                 | Pre-decision Aid 0-56, with higher scores meaning more concern. 14-items, using Likert scales scored 0 "Not at all" to 4 "Very much". Item scores are summed for total score.  | Alpha coefficients 0.81 to 0.91.   |
| <b>Fertility Preservation Knowledge Scale<sup>2</sup></b><br>Measures women's knowledge of how cancer and cancer treatments may affect fertility; the fertility preservation options; and the procedures, risks and benefits of the options. | Assessed using interview, paper, and online formats (e.g., REDCap questionnaire). Used in oncofertility.  | Post-decision aid. 0-13 or 0-100% of questions scored correct, with higher scores meaning greater knowledge. 13 True/False items scored 0 (incorrect) or 1 (correct). Note: scoring modified to reflect updates in practice (Item X scored correct = True). Correlated with personal contact with fertility (p<0.01) and previous exposure to fertility preservation (p<0.01).             | Not reported.  |
| <b>Intolerance of Uncertainty Scale<sup>3</sup></b><br>Measures responses to uncertainty, ambiguous situations, and the future, including subscales of prospective and inhibitory anxiety.   | Used in interview, paper, computerized, and online formats (e.g., REDCap questionnaire). Available in English and French. Used in mental health, general health, and oncofertility. | 12-60 points or 0-100, with higher scores indicating greater anxiety about uncertainty (prospective or inhibitory). 12 or 27 items, using 5-point Likert scales scored 1 "Not at all characteristic of me" to 5 "Entirely characteristic of me". Can be scored as two sub-scales - prospective anxiety and inhibitory anxiety. IUS-12 strongly correlates with IUS-27 (rs = 0.94 to 0.96). | Alpha coefficients exceed 0.85. Good convergent and discriminant validity. |
| <b>Brief Symptom Inventory<sup>4 5</sup></b>   |   |  |  |

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## Supplementary File B. Pathways trial evaluation measures.

| Measure   | Formats, languages, and clinical contexts  | Timing, Scoring and Interpretation   | Psychometric properties  |
|---|--|--|--|
| Brief screening measure for psychological distress and psychiatric disorders in three dimensions: depression, anxiety, and somatization.  | Used in interview, paper, computerized, and online formats. Available in English and Spanish. Used widely, across many general, mental, cancer, and population health contexts.  | 0-72 total Global Severity Index scores, with higher scores indicating greater distress. Recommended distress cutoffs of 10 in men, 13 in women, 50 in cancer survivors, and 62 in palliative care. 18 items scored on 5-point Likert scales of 0 "Not at all" to 4 "Extremely", summed for each subscale and for the total score.   | Alpha coefficients exceed 0.80 in cancer survivors. Correlates with the Symptom Checklist 90 ( $r = 0.88$ to $0.94$ ). Internal consistency estimates of 0.74 somatization, 0.79 anxiety, 0.84 depression, and 0.89 global severity index.                                     |
| <b>Decisional Conflict Scale<sup>6,7</sup></b><br>Assesses patients' perceptions of uncertainty about the options, modifiable factors contributing to uncertainty, and sense of effective decision making. Includes a Leaning Scale measuring strength of treatment preference and four subscales measuring uncertainty, informed, values clarification, and support. | Used in interview, paper, computerized, and online formats. 16-item, 10-item, Low Literacy, and 4-item "SURE" versions. Available in English, French, Danish, Chinese, Spanish, German, Japanese, Italian, and Chilean Spanish. Used across many musculoskeletal, genetic, cardiac, and oncological conditions, including oncofertility. | 0-100, with scores below 25 associated with making a choice and scores above 37.5 associated with delaying decisions. Additionally, for every unit increase, people are 59X more likely to change their mind, 23X more likely to delay decision, 5X more likely to express decisional regret, 3X more likely to fail knowledge test, and 19X more likely to blame doctor for any bad outcomes. 16 items scored on a 3-point Likert scale from 0 "yes" to 4 "no", summed, and divided by 10 to yield a total score. | Alpha coefficients >0.78. Discriminates between people who make and delay decisions; effect size ranges 0.4 to 0.8. Correlates to related constructs of knowledge, regret, and discontinuance.   |
| <b>Values Clarity Leaning Scale<sup>8</sup></b><br>Assesses the desirability or personal importance a respondent places on the benefits and risks of an option.   | Used in interview, paper, computerized, and online formats. Available in English and French. Used in orthopedics, cancer, cardiology, genetics, geriatrics, etc. Adapted for each decision-making, clinical, and/or intervention context.  | At beginning and at end of Decision Aid; 10-point Likert scales for each relevant decision attribute (i.e., risk, benefits, procedures), scored 0 "not at all important to me" to 10 "extremely important to me", with higher scores indicating higher personal value for that attribute.  | Test-retest coefficients 0.79 to 0.91. Discriminates between those making different decisions. Correlations between choices and values change over time and differ between decision aids and comparison interventions, especially among those who are changing the status quo. |
| <b>Strength of Treatment Preference Leaning Scale<sup>6-8</sup></b><br>Assesses choice disposition, (a person's leaning towards or propensity   | Used in interview, paper, computerized, and online formats. Available in English and French. Adapted for each  | At end of Decision Aid; 11-point bi-directional leaning scale scored 0 "unsure/no preference" at the center anchor, to 10 "Strongly Leaning towards  | Test-retest coefficients exceed 0.90. Is sensitive to change and discriminates between interventions, particularly for the   |

Pathways oncofertility decision support trial protocol

Woodard TW

Supplementary File B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts   | Timing, Scoring and Interpretation   | Psychometric properties  |
|--|---|--|--|
| to, select an option) decision (a person's stated choice among alternatives), or enacted decision (the implementation of a chosen options as determined by self-report and/or verification strategy). May also be used to identify undecided individuals for targeted recruitment or intervention. May also include reasons for, on influences on, decision making | decision-making, clinical, and/or intervention context. Used in orthopedics, cancer, cardiology, genetics, geriatrics, obstetrics/gynecology, and internal medicine, etc.   | X/Y" at each end. Scores may be reclassified based on distribution (e.g. 0-3 "no/weak preference", 4-7 "moderate preference", 8-10 "strong preference". May also include open-ended questions to elicit reasons behind, and/or influences on, the leaning. | undecided group. Correlates with values and expectations.  |
| <b>Decision Self-efficacy Scale<sup>9</sup></b><br>Assesses self-confidence or belief in one's ability in decision making, including shared decision making.   | Used in interview, paper, computerized, and online formats. Available in English and German. Used in orthopedics, mental health, cancer, and geriatrics.  | 0-100, with higher scores indicating higher self-efficacy. 11-item low literacy version, using 3-point Likert scale from 0 "Not Confident" to 4 "A Lot Confident".   | Alpha coefficient 0.86. Discriminates between individuals who make and delay decisions. Correlated with decisional conflict (r = 0.55), especially the subscales of feeling informed (r = 0.61) and supported (r = 0.61).                        |
| <b>Preparation for Decision-making Scale<sup>10</sup></b><br>Assesses perspective of how well an intervention prepared them to communicate with their physician about a decision. Includes identifying a decision, preferred role, values clarification, communication.  | Patient and Practitioner versions. Used in interview, paper, computerized, and online formats. Available in English French, German, Italian. Used in orthopedics, prostate cancer, breast cancer, autologous blood donation, hormone replacement therapy. | 0-100, with higher scores indicating better preparation. 11 multiple choice items scored on 5-point Likert scale from 1 "not at all" to 5 "a great deal", summed and multiplied by 2 to yield the total score.   | Alpha coefficients 0.92 to 0.96. Discriminates between people who do/do not find the decision aid helpful (p < 0.0001). Correlates with informed (r = -0.21, p < 0.01) and support (r = -0.13, p = 0.01) subscales of Decisional Conflict Scale. |
| <b>Acceptability Leaning Scales<sup>11</sup></b><br>Assesses subjective rating of the decision aid's ease of use, clarity of information, length, level of detail provided, ability to hold one's interest, and satisfaction with "how the website prepared you for discussing this decision with your doctor(s)"  | Patient and Practitioner versions. Used in interview, paper, computerized, and online formats. Available in English and French. Adapted for each decision-making,   | Post-decision aid. 15 acceptability characteristics on 5-category Likert scales from (scored 1 Strongly Agree or Agree; 0 Neither, Disagree or Strongly Disagree), with the exception of the item assessing whether  | None reported.   |

## Pathways oncofertility decision support trial protocol

Woodard TW

## Supplementary File B. Pathways trial evaluation measures.

| Measure  | Formats, languages, and clinical contexts  | Timing, Scoring and Interpretation   | Psychometric properties  |
|--|--|--|--|
|  | clinical, and/or intervention context.<br>Various, from breast and prostate cancer to knee osteoarthritis to end-of-life.  | the decision aid favored either option (scored 1 Neither, 0 all other responses).  |  |
| <b>Decisional Regret Scale<sup>12</sup></b><br>Measures distress or remorse after a health care decision.                                    | Used in interview, paper, computerized, and online formats. Available in English, French, Chinese, Spanish, and Japanese.<br>Used in cancer, orthopedics, and oncofertility.   | 0-100, with higher scores indicating greater regret. 5-items, using 5-point Likert scales from 1 "Strongly Agree" to 5 "Strongly Disagree". Items 2 and 4 are reverse coded. 1 point is subtracted from all items, then they are multiplied by 25, summed, and averaged for a total score. | Alpha coefficients 0.81 to 0.92. Correlates with satisfaction with the decision ( $r = -0.40$ to $-0.60$ ), decisional conflict ( $r = 0.31$ to $0.52$ ), and overall quality of life ( $r = -0.05$ to $-0.27$ ). Groups who differed on feelings about the decision (e.g. negative, mixed, positive) also differed on regret ( $p < 0.001$ ). Greater among individuals who change their decisions ( $p < 0.001$ ). |
| <b>Client Satisfaction Questionnaire<sup>13</sup></b><br>Measures and assesses overall consumer satisfaction with health and human services. | Used in interview, paper, computerized, and online formats. Available in a variety of languages, formats, and versions (e.g., CSQ-3, 4, 18, 18B, 31) and used in a wide spectrum of clinical, human services, educational, and governmental programs, legal services, police services, administrative settings, and research settings. | Total scores are the sum of item scores, using 4-point Likert scales 1 "Indifferent or mildly satisfied" to 4 "Very satisfied", with some items reverse scored to minimize stereotypic response sets.  | Alpha coefficients 0.83 to 0.97 with moderate correlation with the Brief Psychiatric Rating Scale and Client Checklist.  |
| <b>Usability<sup>11</sup></b><br>Assesses subjective perspectives on desired formats and modes of delivery                                   | Patient and Practitioner versions. Used in interview, paper, computerized, and online formats. Adapted for   | Post-decision aid. 5 multiple-choice items scored as the percentage of positive responses to each item.  | Not applicable.  |

Supplementary File B. Pathways trial evaluation measures.

| Measure | Formats, languages, and clinical contexts   | Timing, Scoring and Interpretation | Psychometric properties |
|---------|---|------------------------------------|-------------------------|
|         | each decision-making, clinical, and/or intervention context. Used across a variety of clinical conditions, from breast and prostate cancer to knee osteoarthritis to end-of-life. |                                    |                         |

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## Informed Consent

**Please Do Not Use for Patient Consent**

**Go to the PDOL Homepage to access the  
Informed Consent Printer Database**

### INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Patient-centered decision counseling for women at risk of cancer-related  
infertility: efficacy study and comparative-effectiveness randomized trial  
2016-0758

Study Chair: Terri L. Woodard

Participant's Name

Medical Record Number or Study ID

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

#### 1. DESCRIPTION OF STUDY

The goal of this research study is to learn if a decision aid website that provides information about fertility preservation (maintaining your ability to have children of your own after cancer treatment) can help women with cancer make fertility-preservation decisions. Researchers will also use information learned in this study to help improve the website. This website was developed at MD Anderson.

There are several ways to preserve fertility, including taking drugs to stop or control ovary function in order to freeze eggs and/or embryos. Freezing eggs and/or embryos may increase the chances of having a child of your own in the future. You may also choose to have children using other methods, such as adoption. This website is designed to help women learn more about these options and consider which of them may be best for them.

**NOT FOR USE IN CONSENTING PATIENTS**

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**This is an investigational study.** The study will be performed at no cost to you.

Up to 160 participants will be enrolled in this multicenter study. Up to 160 may be enrolled at MD Anderson.

**2. STUDY PROCEDURES**

There are 2 parts to this study. In Part 1, researchers will learn if the fertility preservation website can help women make decisions about fertility. In Part 2, researchers will compare the current standard care to standard care in combination with the fertility preservation website.

If you are receiving treatment at MD Anderson, you will take part in Part 1 of the study. If you are receiving treatment at a Houston-area MD Anderson satellite office, you will take part in Part 2 of the study.

**Part 1**

If you are in Part 1 of the study, you will be given the option to either view the decision aid website about fertility preservation at home or you can come to your routine fertility consultation visit about 30 minutes early and view the website at the office in a private room. Whichever you choose, you will complete a questionnaire before viewing the website about healthcare decision making and fertility. This questionnaire should take about 30 minutes to complete.

About 1 week after you view the website, you will complete another questionnaire about your opinions on the decision aid website and if you think the website is useful in making fertility preservation decisions. This questionnaire should take about 30 minutes to complete.

You will then have your fertility consultation visit as scheduled and you may or may not choose to use fertility preservation treatments or methods. About 2 months after your consultation visit, you will complete a questionnaire about which methods of fertility preservation you chose to use (if any), what influenced your decision-making, and if you have any ideas on how to improve the fertility preservation process. This will be completed online and may take about 30 minutes to complete.

**Part 2**

If you agree to take part in this study, the type of educational information you receive will depend on where you are receiving treatment. You will either receive standard care or standard care plus the use of the decision-making website. Standard of care includes receiving patient education materials about fertility preservation from the Livestrong organization and receiving a referral for fertility preservation, if requested.

All participants will complete the questionnaires described below.

You will complete 3 sets of questionnaires when you enroll in the study and then at 1 week and then 2 months after you enroll. These questionnaires include questions about your demographic information (for example, age, sex, and race). They also include questions about your preferred role in making healthcare decisions, your knowledge about fertility preservation, and any concerns you have about reproduction. Each set of questionnaires should take about 30 minutes to complete. All questionnaires will be completed online.

The research staff may call you to remind you to complete the questionnaires and/or to learn more information about your fertility status that may not be found in your medical record.

### **All Participants**

The study staff may also review your medical records for information about what, if any, fertility preservation options you chose to do. The study staff will also review your medical record to collect data about your fertility status. The study staff may contact you to collect information that may not be included in your medical record.

### **Length of Study Participation**

Your participation in this study will be over after you complete the 2-month questionnaire.

## **3. POSSIBLE RISKS**

You should discuss the risks of questionnaires with the study chair. The known risks are listed in this form, but they will vary from person to person. Some questions may make you feel upset or uncomfortable. You may refuse to answer any question. If you have concerns after completing the questionnaires, you are encouraged to contact your doctor or the study chair.

Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen. All study data will be stored in password-protected computers, locked file cabinets, and/or on a secure online database named REDCap. Study data will not be destroyed but will be stored in a secure database at MD Anderson called REDCap after the study has been completed.

This study may involve unpredictable risks to the participants.

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## **OPTIONAL PROCEDURES FOR THE STUDY**

**NOT FOR USE IN CONSENTING PATIENTS**

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**Optional Procedure #1:** If you agree, the research staff may contact you by phone, email, or mail to ask you if you would be interested in taking part in future research studies.

There are no benefits to you for taking part in the optional procedure. Future patients may benefit from what is learned. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedure.

**Optional Procedure Risks:**

If you are **contacted about future studies**, other people may learn you have (had) cancer. This may be upsetting.

**CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES**

**Circle your choice of “yes” or “no” for each of the following optional procedures:**

**Optional Procedure #1:** Do you agree to allow the research staff to contact you by phone, email, or mail to ask you if you would be interested in taking part in future research studies?

**YES                      NO**

**4. POTENTIAL BENEFITS**

Future patients may benefit from what is learned. You may learn more about fertility preservation options by participating in this study. There **may be** no benefits for you in this study.

**5. OTHER PROCEDURES OR TREATMENT OPTIONS**

You may choose not to take part in this study. If you do not participate in the study, you will not have access to the website.

**6. STUDY COSTS AND COMPENSATION**

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson, The Duncan Family Institute, or National Cancer Institute and Alliance for Clinical Trials in Oncology for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (health maintenance organization [HMO], health insurance company, etc.), will be your responsibility.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive a \$25 gift card in the mail two months after you enroll in the study.

Your gift card will be sent separately using the Bank of America Remuneration Program used at MD Anderson.

You will be given a reloadable debit card that will be electronically loaded with money at the end of the two months of the study. If this card is lost or stolen while you are on study, you may be required to pay a \$5.00 replacement fee to get a new one. Your name, address, date of birth, and social security number (if necessary) will be collected and every effort will be made to keep this information strictly confidential. It will only be shared with a third party for the purpose of processing your payment.

The money you receive may be taxable. If you receive more than \$600 in a calendar year for being in research studies, you will be given an IRS Form 1099-MISC for tax reporting purposes.

### **ADDITIONAL INFORMATION**

7. You may ask the study chair (Dr. Terri L. Woodard, at 713-745-7591) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-2933 with any questions that have to do with this study or your rights as a study participant.
8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you withdraw from this study, you can

still choose to be treated at MD Anderson.

9. This study or your participation in it may be changed or stopped at any time by the study chair, The Duncan Family Institute, National Cancer Institute and Alliance for Clinical Trials in Oncology, or the IRB of MD Anderson.
10. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.
11. MD Anderson may benefit from your participation and/or what is learned in this study.
12. This study is sponsored and/or supported by: The Duncan Family Institute and National Cancer Institute and Alliance for Clinical Trials in Oncology.

**Authorization for Use and Disclosure of Protected Health Information (PHI):**

- A. During the course of this study, MD Anderson may be collecting and using your PHI. For legal, ethical, research, and safety-related reasons, the research team may share your PHI with:
  - The OHRP
  - The IRB and officials of MD Anderson
  - The Duncan Family Institute and National Cancer Institute and Alliance for Clinical Trials in Oncology, who are sponsors or supporters of this study, and/or any future sponsors/supporters of the study
  - Study monitors and auditors who verify the accuracy of the information
  - Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson’s contracts require sponsors/supporters to protect this information and limit how they may use it.
- B. Signing this consent and authorization form is optional but you cannot take part in this study if you do not agree and sign.
- C. MD Anderson will keep your PHI confidential when possible according to state and federal law. However, in some situations, health authorities could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

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- D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, the data collected up to that point can be used and included in data analysis, but no further information about you will be collected.

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Go to the PDOL Homepage to access the  
Informed Consent Printer Database

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF PARTICIPANT

DATE

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF LAR

DATE

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2016-0758.

SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS

SIGNATURE OF WITNESS TO THE VERBAL CONSENT  
PRESENTATION (OTHER THAN PHYSICIAN OR STUDY  
CHAIR)

DATE

A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF STUDY CHAIR

DATE

OR PERSON AUTHORIZED TO OBTAIN CONSENT

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**TRANSLATOR**

I have translated the above informed consent as written (without additions or subtractions) into \_\_\_\_\_ and assisted the people  
(Name of Language)  
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

NAME OF TRANSLATOR \_\_\_\_\_ SIGNATURE OF TRANSLATOR \_\_\_\_\_ DATE \_\_\_\_\_

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

**SAMPLE -- NOT FOR USE IN CONSENTING PATIENTS**

SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION \_\_\_\_\_ DATE \_\_\_\_\_  
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR)

## Supplementary File D: SPIRIT Checklist



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | 1                        |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | 3                        |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | 1-14                     |
| Protocol version                  | 3       | Date and version identifier  | 13                       |
| Funding                           | 4       | Sources and types of financial, material, and other support  | 16                       |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | 1                        |
|                                   | 5b      | Name and contact information for the trial sponsor   | 1,16                     |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16                       |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | 1,6,16                   |
| <b>Introduction</b>               |         |  |                          |
| Background and rationale          | 6a      | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention   | 2-5                      |

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Pathways oncofertility decision support trial protocol

Supplementary File D: SPIRIT Checklist

Woodard TW

|  |     |  |        |
|--|-----|--|--------|
|  | 6b  | Explanation for choice of comparators  | 2-8    |
| Objectives   | 7   | Specific objectives or hypotheses  | 5      |
| Trial design                                       | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  | 1, 5-7 |
| Methods: Participants, interventions, and outcomes |     |  |        |
| Study setting                                      | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained   | 6-7    |
| Eligibility criteria                               | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)   | 6-7    |
| Interventions                                      | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | 7-8    |
|  | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)   | 11     |
|  | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | 12     |
|  | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | 7-8    |
| Outcomes   | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8-11   |
| Participant timeline                               | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)   | 8-11   |
| Sample size  | 14  | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations  | 11-12  |
| Recruitment  | 15  | Strategies for achieving adequate participant enrolment to reach target sample size  | 11-12  |

## Pathways oncofertility decision support trial protocol

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## Supplementary File D: SPIRIT Checklist

## Methods: Assignment of interventions (for controlled trials)

## Allocation:

|                                  |     |  |       |
|----------------------------------|-----|--|-------|
| Sequence generation              | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 12    |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | 12    |
| Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | 12    |
| Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | 11-12 |
|                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | N/A   |

## Methods: Data collection, management, and analysis

|                         |     |  |                          |
|-------------------------|-----|--|--------------------------|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 8-11, Supplementary File |
|                         | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | 12                       |
| Data management         | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol  | 11-12                    |

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Supplementary File D: SPIRIT Checklist

|                          |     |   |       |
|--------------------------|-----|---|-------|
| Statistical methods      | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | 12-13 |
|                          | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 12-13 |
|                          | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | 12-13 |
| Methods: Monitoring      |     |   |       |
| Data monitoring          | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 14    |
|                          | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | 14    |
| Harms                    | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | 11    |
| Auditing                 | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | 11    |
| Ethics and dissemination |     |   |       |
| Research ethics approval | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 13-14 |
| Protocol amendments      | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | 13-14 |
| Consent or assent        | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  | 13-14 |
|                          | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | N/A   |

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## Supplementary File D: SPIRIT Checklist

|                               |     |   |                    |
|-------------------------------|-----|---|--------------------|
| Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial  | 11                 |
| Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 16                 |
| Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   | 11                 |
| Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   | 11                 |
| Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 14                 |
|                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | 16                 |
|                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | N/A                |
| <b>Appendices</b>             |     |   |                    |
| Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | Supplementary File |
| Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  | N/A                |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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