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# Health Risk Information Technology-Assisted Genetic Evaluation (HeRITAGE): A randomized controlled trial of digital genetic cancer risk assessment in a diverse underserved gynecology clinic



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**Title:** Health Risk Information Technology-Assisted Genetic Evaluation (HeRITAGE): A randomized controlled trial of digital genetic cancer risk assessment in a diverse underserved gynecology clinic

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## ABSTRACT

### Introduction

In the United States, up to 95% of individuals harboring cancer-predisposing germline pathogenic variants have not been identified despite recommendations for screening at the primary care level.

### Methods and Analysis

Our primary objective is to use a 2-arm, single-institution randomized controlled trial to compare the proportion of eligible patients that are recommended genetic testing for hereditary cancer syndromes using a digital tool versus clinician interview for genetic cancer risk assessment in an urban academic gynecology clinic. New gynecology patients will be consented and randomized 1:1 to either the intervention arm, in which a digital tool is used for genetic cancer risk assessment, or usual care, in which the clinician performs genetic cancer risk assessment. Individuals will be considered eligible for hereditary cancer syndrome genetic testing if criteria set forth by the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology are met. Eligible patients are 18 or older, speak and read English, have not yet undergone hereditary cancer genetic testing, and have access to a smartphone. Based on studies, >50% of patients identified as high risk though information technology are recommended genetic testing compared to <5% when cancer risk assessment is performed by the clinician. Enrolling 50 subjects into each study arm allows for 80% power with a two-tailed alpha of 5%. The primary outcome is the proportion of eligible individuals recommended genetic testing in the digital tool arm versus usual care arm. This will be analyzed using the chi-square test or Fisher's exact test, as appropriate for sample size.

### Ethics and Dissemination

This study has been approved by the Weill Cornell Institutional Review Board (Protocol # 21-11024123). Participants will be informed of the benefits and risks of participation prior to consent. Any dissemination of data will be de-identified.

## Registration Details

This trial is registered at clinicaltrials.gov (NCT05562778).

## STRENGTHS AND LIMITATIONS

1. The inclusion criteria of the HeRITAGE study are minimal, and thus the results of the study are anticipated to be largely generalizable to other practices.
2. A smartphone-based tool may address common genetic cancer risk assessment barriers such as limited appointment time and provider knowledge.
3. HeRITAGE is not designed to address language barriers which have also been shown to affect access to genetic services.[7] At this time, additional efforts are underway to explore the effect of the smartphone-based tool in non-English speaking populations through translation of the tool to other languages and implementation of the tool in urban clinics with significant non-English speaking patient cohorts.

## INTRODUCTION

Hereditary cancer syndromes, or the genetic predisposition to specific cancers caused by inherited germline pathogenic variants, cause an estimated 13% of cancers.[1] Among individuals with hereditary cancer syndromes, measures to reduce cancer risk have been shown to decrease cancer incidence, morbidity, and mortality.[2-4] However, in the United States, as many as 95% of individuals harboring cancer-predisposing germline pathogenic variants have not been identified despite recommendations for screening at the primary care level, and thus do not receive counseling regarding standard recommended risk reducing measures.[5] Further, under-recognition of cancer-predisposing pathogenic variants and a lack of receipt of genetic services is more pronounced among individuals identifying as racial or ethnic minorities or with public insurances.[6, 7] Common barriers to general population screening at the primary care level include limited appointment time with inadequate family history collection and lack of clinician knowledge regarding genetic testing eligibility criteria.[8]

Collection and interpretation of family cancer history is a cornerstone of genetic cancer risk assessment to determine national guideline-based eligibility for genetic testing for hereditary cancer syndromes. The use of digital tools has been demonstrated to be more effective than usual clinician interview for the collection of personal and family history, with high patient acceptance and satisfaction.[9, 10] Use of such a tool for collection of personal and family history may address clinician time limitations during genetic cancer risk assessment by allowing patients to input relevant family cancer information prior to appointments. Further, a tool with innate risk assessment capabilities may mitigate the need for clinicians to navigate complex genetic testing criteria, as well as reduce subjectivity and clinician bias.

Given that the use of a patient-facing tool has the potential to overcome several barriers to genetic cancer risk assessment, we hypothesize that implementation of a risk assessment tool in a gynecology clinic will improve receipt of appropriate genetic services. Thus, the purpose of this randomized controlled trial is to compare the rate of recommendation for genetic testing for hereditary cancer syndromes among eligible patients when genetic cancer risk assessment is performed via a digital tool versus usual clinician interview.

## METHODS AND ANALYSIS

### *Trial Design*

This single institution randomized controlled trial will compare the rates of recommendation for genetic testing among eligible patients compared to the standard of care (Figure 1). The study will be conducted in an urban, academic gynecology clinic in New York City, NY which serves patients with Medicaid and other government-based insurance plans. Enrolled patients will be randomly assigned to either the intervention arm or control arm. In the intervention arm, patients will be prompted to complete the digital tool: Ambry Genetics Comprehensive, Assessment, Risk, and Education (CARE) Program™ (Figure 2A). CARE™ is a digital, patient-facing, risk stratification tool with complex, rule-based, flow logic based on patient responses to pre-programed input options designed to collect relevant personal and family history. Patient responses are evaluated against the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) criteria for hereditary cancer testing.[11, 12] Clinicians receive a CARE™-generated clinical summary report denoting eligibility for genetic testing. CARE™ also provides optional educational videos on genetic testing to eligible patients. In the control arm, patients will receive usual care, in which genetic cancer risk assessment is performed via clinician-driven interview and assessment (Figure 2B). Eligible patients are offered same-day multigene genetic testing for hereditary cancer syndromes via mainstream genetic counseling and testing.

All enrolled patients complete pre- and post-appointment forms with questions relating to demographics, risk assessment experience, and social determinants of health such as health literacy. Those eligible for testing will be contacted at 1 month for follow up. Eligible patients who undergo genetic testing will be asked to complete a post-testing survey regarding attitude towards results. Eligible patients who decline genetic testing will be offered to participate in a focused interview exploring reasons for deferral of genetic testing.

The trial is registered at clinicaltrials.gov (NCT05562778).

*Participants*

Patients are eligible for enrollment if they meet the following criteria: (1) are scheduled for a new patient gynecology appointment, (2) are 18 years or older, (3) speak and read English, (4) have not yet undergone genetic testing for predisposition to hereditary cancers, and (5) have access to phone with internet access at the time of appointment.

*Primary Endpoints*

The primary objective is to evaluate the proportion of eligible patients recommended for hereditary cancer syndrome genetic testing when genetic cancer risk assessment is performed via a digital tool versus usual care with clinician interview. The secondary objective is to compare the rates of uptake of genetic testing among participants for whom genetic testing is recommended. Exploratory objectives include assessment of facilitators and barriers to utilization of genetic services and qualitative interviews to assess barriers to genetic testing among patients who decline genetic testing.

*Sample Size*

Approximately 30% of the general population meets eligibility criteria for genetic testing for hereditary cancer syndromes and thus warrants recommendation for genetic testing.[13] Based on prior studies of health information technology for personal and family history assessment, >50% of eligible patients are recommended for genetic testing compared to <5% of eligible patients when cancer risk assessment is performed by clinician interview.[9, 10] Based on this assessment, enrolling 50 patients into each study arm will allow for 80% power with a two-tailed alpha of 5% to detect a significant difference in recommendation for genetic testing among eligible patients in the intervention versus control arm, and also allow for exploration of secondary objectives.

*Randomization and Blinding*

Participants will be randomized 1:1 (using blocked randomization) to either the digital tool arm or usual care arm via a randomization module in Research Electronic Data Capture (REDCap). After enrollment, patients are randomized and unblinded to complete a digital tool or proceed with usual care. Clinicians are not blinded to enrollment arm as a tool-generated risk assessment summary is received for participants randomized to the intervention arm.

*Statistical Methods*

The primary aim, evaluating the proportion of eligible individuals recommended genetic testing in the digital tool arm versus usual care arm, will be analyzed using the chi-square test or Fisher's exact test, as appropriate for sample size, with a p-value of <0.05 indicating statistical significance. The secondary aim, comparing the rates of uptake of genetic testing among participants for whom testing is recommended in the digital tool arm versus the usual care arm, will also be analyzed with the chi-square test or Fisher's exact test, as appropriate for sample size. Associations between utilization of genetic services and participant characteristics will be explored with univariate tests as appropriate based on variable type (i.e., t-test, analysis of variance, Mann–Whitney U test, Kruskal-Wallace test).

*Patient and Public Involvement*

Prior to designing this randomized controlled trial, our study team performed a pilot study of patients regarding usability of the digital tool we proposed to use for genetic cancer risk assessment. The tool was met with high patient acceptance and satisfaction.[10]

## ETHICS AND DISSEMINATION

This study has been approved by the Weill Cornell Institutional Review Board (Institutional Review Board Protocol # 21-11024123). Participants will be informed verbally and in writing of the benefits and risks of participation prior to consent. Benefits include advancement of general knowledge as it applies to early identification of individuals at increased risk of certain cancers and the ability of participants to make informed decisions regarding risk-reduction measures they can choose to take if they are identified as high risk. Risks include psychological risks as a result of cancer risk assessment and/or social risks such as possible invasion of privacy, breach of confidentiality, and loss of community standing. Participants will be provided the opportunity to approve or deny whether their data is retained by the study team for use in future research as part of the consent process. All data will be deposited in REDCap. Any dissemination of data, as part of a publication or otherwise, will be de-identified.

## DISCUSSION

The results of this study will provide data regarding the effectiveness of a digital tool to collect and analyze personal and family history compared to usual clinician care. The primary outcome will be rate of eligible patients recommended for genetic testing for cancer-predisposing pathogenic variants. Given the longstanding barriers to genetic cancer risk assessment, we hypothesize that the digital tool will identify more patients as eligible for testing, and subsequently a higher rate of patients will be recommended for testing.

Similar tools have been integrated into clinical practices with publication of observational data. In Loving et al., authors report on the implementation of screening via CARE™ in women undergoing breast cancer imaging.[13] A total of 3345 patients were screened, and 1080 (32.3%) met genetic testing criteria. Patients who met genetic testing criteria received counseling by a pre-recorded video, and consent and sample collection was performed by medical assistants. Among those eligible for genetic testing, 416 (38.5%) proceeded with genetic testing, which identified 38 individuals with cancer-predisposing pathogenic variants. While the findings in Loving et al. support the feasibly of tool implementation, the study population was primarily non-Hispanic White (78.3%), which differs from the anticipated study population of the HeRITAGE study. Further, the observational design and study setting at an imaging center limit understanding of the effectiveness of the tool compared to usual care in office practice.

In Nazareth et al., authors report retrospectively on the implementation of a similar patient-facing digital health chatbot to perform genetic cancer risk assessment across 180 outpatient sites, including primary care clinics.[14] A total of 95,166 patients were invited to complete the chatbot, with 54,547 (89.4%) completing the chatbot risk assessment, and 14,850 (27.2%) meeting NCCN Guidelines® for genetic testing for cancer-predisposing pathogenic variants. In the study design, risk assessments were disclosed to patients by the clinician. Downstream data on the impact of the tool, such as number of patients who were appropriately recommended for genetic testing or received genetic testing was not included in the publication, except for a subset of 5,594 eligible patients among whom 1,622 (29.0%) had genetic testing ordered. Lack of comprehensive outcomes regarding counseling or utilization of genetic services after tool use limits the ability to make conclusions about the utility of the chatbot tool. In the HeRITAGE study, recommendation for genetic testing of eligible individuals was chosen as the primary outcome as this was felt to represent a clinically relevant milestone in which the genetic risk has

been communicated to the patient. Further downstream data, such as the rate of genetic testing, will also be reported.

While data regarding digital screening tools have generally supported feasibility and acceptance, the impact of the tool on disparities in genetic services warrants exploration as health systems begin to incorporate such tools into routine practice and smartphones become increasingly widespread.[15] An urban, academic, Medicaid-predominant clinic was chosen for the site of the HeRITAGE study due to the high proportion of patients that are historically underrepresented in genetics research. Data regarding the association of race, ethnicity, insurance status, health literacy, and other social determinants of health on the receipt of genetic services may allow insight of the impact of a smartphone-based tool on equitable care. Such data may also reveal vulnerable populations, such as those less comfortable with technology, that may require additional attention should a smartphone-based tool be incorporated as standard of care.

The inclusion criteria of the HeRITAGE study are minimal, and thus the results of the study are anticipated to be largely generalizable to other practices. While a smartphone-based tool may address common genetic cancer risk assessment barriers such as limited appointment time and provider knowledge, HeRITAGE is not designed to address language barriers which have also been shown to affect access to genetic services.[7] At this time, additional efforts are underway to explore the effect of the smartphone-based tool in non-English speaking populations through translation of the tool to other languages and implementation of the tool in urban clinics with significant non-English speaking patient cohorts.

Given the randomized study design and the urban Medicaid-predominant clinic setting, the results of HeRITAGE will provide informative data regarding the influence of screening technology in genetic cancer risk assessment on clinical outcomes, particularly among traditionally underrepresented populations.

## FIGURES

Figure 1. HeRITAGE study design. *Primary outcome; † secondary outcome; ‡ exploratory outcome. Created with BioRender.com.

Figure 2. HeRITAGE work flow; (A) Control arm; (B) Intervention arm. Created with BioRender.com.

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## AUTHORS' CONTRIBUTIONS

1. Bull – Formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization
1. Webster – Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, funding acquisition
3. McDougale – Conceptualization, methodology, software, resources, writing – review & editing, supervision, project administration, funding acquisition
4. Howard – Conceptualization, resources, data curation, writing – review & editing, visualization, supervision, project administration, funding acquisition
5. Ahsan – Conceptualization, methodology, formal analysis, investigation, resources, writing – review & editing
6. Levi – Investigation, data curation, writing – review & editing, project administration
7. Grant – Investigation, data curation, writing – review & editing, project administration
8. Chandler – Investigation, data curation, writing – review & editing, project administration
9. Christos – Conceptualization, methodology, formal analysis, writing – review & editing
10. Sharaf – Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, funding acquisition
11. Frey – Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, funding acquisition

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## COMPETING INTERESTS STATEMENT

The authors have no competing interests to disclose.

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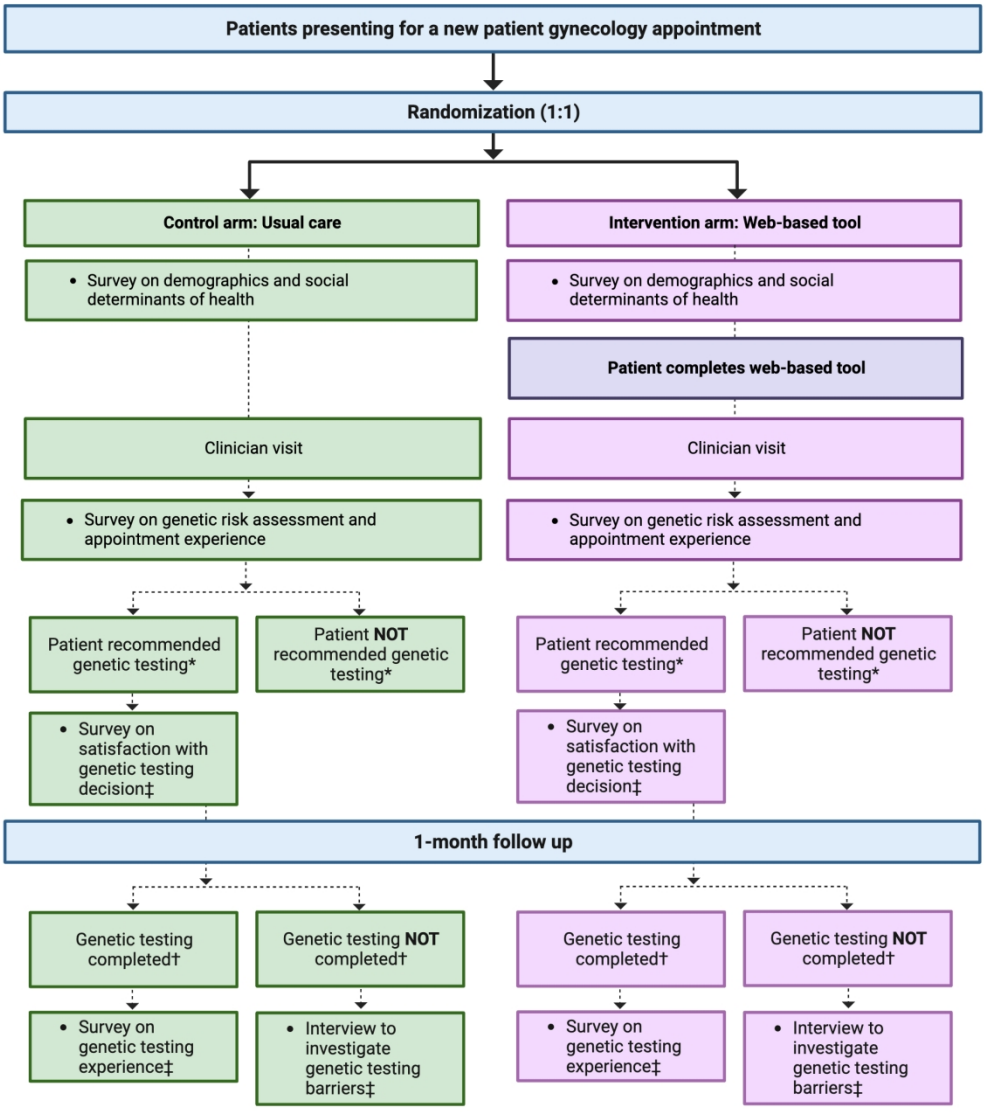


Figure 1: study flow

421x482mm (118 x 118 DPI)

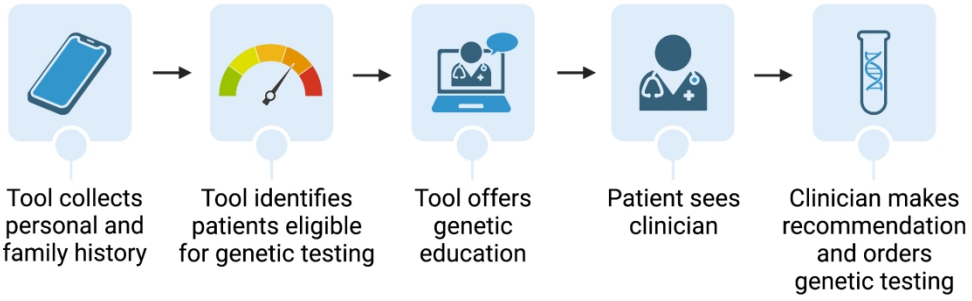


Figure 2A: Intervention Arm

202x67mm (300 x 300 DPI)

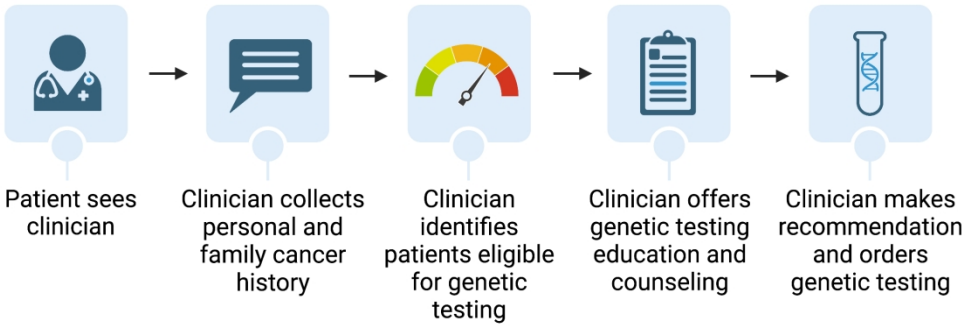


Figure 2B: Usual Care Arm

202x72mm (300 x 300 DPI)

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3 |
| | 2b | Specific objectives or hypotheses | 3 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 3 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | N/A |
| Participants | 4a | Eligibility criteria for participants | 3 |
| | 4b | Settings and locations where the data were collected | 4 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 4-5 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 5 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | N/A |
| Sample size | 7a | How sample size was determined | 5 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | N/A |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 5-6 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 5-6 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 5-6 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 5-6 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | 6 |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions – N/A | 6 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 6 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | N/A |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | N/A |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | N/A |
| | 14b | Why the trial ended or was stopped | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | N/A |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | N/A |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | N/A |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | N/A |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | N/A |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | N/A |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 7 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 7 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | N/A |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 5 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | N/A |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 1 |



*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

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**Public Title:** A protocol for a randomized controlled trial evaluating the use of a digital genetic cancer risk assessment tool in a gynecology clinic

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**Disclosures:**
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Abstract – 517

Main body text – 2385

## ABSTRACT

### Introduction

In the United States, up to 95% of individuals harboring cancer-predisposing germline pathogenic variants have not been identified despite recommendations for screening at the primary care level.

### Methods and Analysis

Our primary objective is to use a 2-arm, single-institution randomized controlled trial to compare the proportion of eligible patients that are recommended genetic testing for hereditary cancer syndromes using a digital tool versus clinician interview for genetic cancer risk assessment in an urban academic gynecology clinic. New gynecology patients will be consented and randomized 1:1 to either the intervention arm, in which a digital tool is used for genetic cancer risk assessment, or usual care, in which the clinician performs genetic cancer risk assessment. Individuals will be considered eligible for hereditary cancer syndrome genetic testing if criteria set forth by the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology are met. Eligible patients are 18 or older, speak and read English, have not yet undergone hereditary cancer genetic testing, and have access to a smartphone. The study aims to enroll 50 patients in each arm to allow for 80% power with two-tailed alpha of 5% to detect a 20% difference in proportion of eligible patients recommended for genetic testing. The primary outcome is the proportion of eligible individuals recommended genetic testing in the digital tool arm versus usual care arm, analyzed using the chi-square or Fisher's exact test as appropriate for sample size. The secondary outcome is completion of genetic testing, as well as exploration of patient factors, particularly social determinants of health, that may affect the receipt, utilization, and experience with genetic services.

### Ethics and Dissemination

This study has been approved by the Weill Cornell Institutional Review Board (Protocol # 21-11024123). Participants will be informed of the benefits and risks of participation prior to consent. Dissemination of data will be de-identified and conducted through academic conferences and journals. Patients identified to be eligible for genetic testing who did not receive counseling from their providers will be contacted; participants will not receive direct notification of trial results.

### Registration Details

This trial is registered at clinicaltrials.gov (NCT05562778) in September 2022.

### Protocol Version

This is protocol version 1, as of May 22, 2024.

### Countries of Recruitment and Recruitment Status

United States of America, currently recruiting

### Health Conditions/Problems Studied

Genetic predisposition to cancers such as breast, ovarian, uterine, and pancreatic.

**De-Identified Individual Clinical Trial Participant-Level Data (IDP) Sharing Statement**
IDP will not be shared.

## STRENGTHS AND LIMITATIONS

1. Randomized controlled design and comparison to usual care allows for evaluation of the impact a digital risk stratification tool may have on increasing counseling for patients eligible for genetic testing.
2. Study site at a racially and ethnically diverse, Medicaid-predominant clinic with a goal of capturing populations that have been historically underserved regarding genetic care.
3. Broad inclusion criteria were utilized to optimize generalizability. However, inclusion criteria requiring English speaking and reading patients and single study site limits generalizability of the tool in certain populations.
4. The focus of the study is to increase the number of patients receiving genetic cancer risk assessment, which is endorsed by national guidelines.

## INTRODUCTION

Hereditary cancer syndromes, or the genetic predisposition to specific cancers caused by inherited germline pathogenic variants, cause an estimated 13% of cancers.[1] Among individuals with hereditary cancer syndromes, measures to reduce cancer risk have been shown to decrease cancer incidence, morbidity, and mortality.[2-4] However, in the United States, as many as 95% of individuals harboring cancer-predisposing germline pathogenic variants have not been identified despite recommendations for screening at the primary care level, and thus do not receive counseling regarding standard recommended risk reducing measures.[5] Further, under-recognition of cancer-predisposing pathogenic variants and a lack of receipt of genetic services is more pronounced among individuals identifying as racial or ethnic minorities or with public insurances.[6-9]

Collection and interpretation of family cancer history is a cornerstone of genetic cancer risk assessment to determine national guideline-based eligibility for genetic testing for hereditary cancer syndromes. The use of digital tools has been demonstrated to be more effective than usual clinician interview for the collection and interpretation of personal and family history, with high patient acceptance and satisfaction.[10-13]

We hypothesize that implementation of a risk assessment tool in a gynecology clinic will improve receipt of appropriate genetic services. The primary objective of this randomized controlled trial is to compare the rate of recommendation for genetic testing for hereditary cancer syndromes among eligible patients when genetic cancer risk assessment is performed via a digital tool versus usual clinician interview.

## METHODS AND ANALYSIS

### *Trial Design*

This single institution randomized controlled trial will compare the rates of recommendation for genetic testing among eligible patients to the standard of care (Figure 1). The study will be conducted in an urban, academic gynecology clinic in New York City, New York which serves patients with Medicaid and other government-based insurance plans. A quality improvement initiative at this clinic site previously demonstrated a racially and ethnically diverse population.[11] Patients will be screened and approached by study personnel for consent in the clinic waiting room prior to scheduled appointments. All patients scheduled for new appointments during periods of study personnel availability will be screened. Enrolled patients will be randomly assigned to either the intervention arm or control arm. Enrollment is anticipated to be conducted between January 2023 and December 2024. The trial is registered at clinicaltrials.gov (NCT05562778) in September 2022.

In the intervention arm, patients will be prompted to complete the digital tool, Ambry Genetics Comprehensive, Assessment, Risk, and Education (CARE) Program™, in the waiting area prior to appointment (Figure 2). CARE™ is a digital, patient-facing, risk stratification tool with complex, rule-based, flow logic based on patient responses to pre-programed input options

designed to collect relevant personal and family history. Patient responses are evaluated against the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for hereditary cancer testing.[14] Patients who are unable to complete the tool in the waiting area prior to being called back to the exam room will be permitted to continue completion of the tool in the exam room. Completion of the tool is not mandated. Patients who complete the tool will be notified via the tool whether they met criteria for hereditary cancer testing, and clinicians will receive a CARE™-generated clinical summary report denoting eligibility for genetic testing. CARE™ also provides optional educational videos on genetic testing to eligible patients.

In the control arm, patients will undergo the usual clinic standard for new patients, in which genetic cancer risk assessment is performed via clinician-driven interview and assessment by their gynecologic provider (Figure 3).

At the clinicians' discretion, patients in both arms can be offered multigene genetic testing for hereditary cancer syndromes at the time of their appointment. Genetic counseling and testing will be performed by the patients' gynecologic providers, consistent with a "mainstreaming" model that is the standard of care for the study site.

All patients' personal and family history within the electronic medical records will be reviewed by study personnel to determine eligibility for genetic testing as per NCCN Guidelines®. Patients determined by study personnel to meet NCCN Guidelines® genetic testing criteria will be considered "eligible patients," which will serve as a denominator for the primary outcome (proportion of eligible patients recommended genetic testing) and the secondary outcome (proportion of eligible patients completing genetic testing).

All enrolled patients will be asked to complete paper pre- and post-appointment surveys which are designed to facilitate understanding of patient characteristics and facilitate exploratory analysis. The pre-appointment survey will include questions regarding patient demographics, social determinants of health, and health literacy. Social determinants of health will be assessed using several tools: the Health Leads Screening Toolkit,[15] encompassing 10 yes/no questions designed to screen for items which contribute to adverse social determinants of health; the Healthcare Distrust Scale,[16] a validated 9-item set which produces a numeric distrust score; and NCCN Guidelines® Distress Management,[17] in which patients answer yes/no questions regarding current stressors. Subjective health literacy will be assessed using the BRIEF Health Literacy Survey,[18] a validated 4-item survey which produces a health literacy assessment of "inadequate," "marginal," or "adequate," as well as the Subjective Numeracy Scale,[19] a validated 3-item survey which produces a numeric subjective numeracy score. The post-appointment survey will assess patient genetic cancer risk assessment experience and distress using the Hospital Anxiety and Depression Scale[20] and NCCN Guidelines® Distress Thermometer,[17] in which patients provide a numeric 0-10 value correlating with subjective distress, as well as 5-point Likert scale items (strongly agree / agree / neither agree or disagree/ disagree / strongly disagree) developed for the study to assess experience. Items include "I was satisfied with the genetic cancer assessment" and "The genetic cancer assessment was a waste of time."

Patients eligible for genetic testing will be contacted 1 month following their appointment to determine whether genetic testing for hereditary cancer syndromes was completed. All data will be entered into Research Electronic Data Capture (REDCap) by study personnel for the purpose of analysis.

*Participants*

Patients are eligible for enrollment if they meet the following criteria: (1) are scheduled for a new patient gynecology appointment at the trial site clinic, (2) are 18 years or older, (3) speak and read English, (4) have not yet undergone genetic testing for predisposition to hereditary cancers, and (5) have access to a phone with internet capability at the time of appointment. Patients not meeting the aforementioned criteria are excluded from the trial.

*Endpoints*

The primary objective is to evaluate the proportion of eligible patients recommended for hereditary cancer syndrome genetic testing when genetic cancer risk assessment is performed via a digital tool versus usual care with clinician interview. To determine the denominator of patients eligible for genetic testing, study personnel will review electronic medical records for personal and family history to determine eligibility per NCCN Guidelines®. To determine the numerator of patients recommended for genetic testing, study personnel will review electronic medical record visit documentation.

The secondary objective is to compare the rates of completion of genetic testing within 1 month of the appointment among participants for whom genetic testing is recommended. Additionally, associations between patient factors, with focus on social determinants of health, and the receipt of genetic services, such as counseling and testing, will be explored. Assessment of patient experience with genetic cancer risk assessment in the intervention arm versus the control arm will also be conducted.

*Sample Size*

Based on prior institutional experience and quality improvement investigations, we estimate less than 5% of patients would be eligible for genetic testing and recommended for hereditary cancer testing in our control group.[21] An increase of at least 20% more eligible patients being recommended for genetic testing within the intervention arm considered to be clinically meaningful. Thus, enrollment is planned for a total of 100 participants, with 50 participants in each study arm, allowing for 80% power with two-tailed alpha of 5% to detect a difference in proportion of eligible patients recommended for genetic testing.

*Randomization and Blinding*

Participants will be randomized 1:1 to either the digital tool arm or usual care arm via a preset computer-generated randomization scheme accessed through REDCap. After enrollment, patients are randomized and informed of their study arm. Clinicians are not blinded to enrollment

arm as a tool-generated risk assessment summary is received for participants randomized to the intervention arm.

*Statistical Methods*

The primary aim, evaluating the proportion of eligible individuals recommended genetic testing in the digital tool arm versus usual care arm, will be analyzed using the chi-square test or Fisher's exact test, as appropriate for sample size. The secondary aim, comparing the rates of uptake of genetic testing among participants for whom testing is recommended in the digital tool arm versus the usual care arm, will also be analyzed with the chi-square test or Fisher's exact test, as appropriate for sample size. Associations between risk assessment experience and utilization of genetic services and participant characteristics will be explored with univariate tests as appropriate based on variable type (i.e., t-test, analysis of variance, Mann–Whitney U test, Kruskal-Wallace test). For all analyses, a p-value of $<0.05$ will be used to indicate statistical significance.

*Patient and Public Involvement*

Neither patients nor the public have been involved in the design or implementation of this study.

## ETHICS AND DISSEMINATION

This study has been approved by the Weill Cornell Institutional Review Board (Institutional Review Board Protocol # 21-11024123). Participants will be informed verbally and in writing of the benefits and risks of participation prior to consent. Risks include psychological risks as a result of cancer risk assessment and/or social risks such as possible invasion of privacy, breach of confidentiality, and loss of community standing. Participants will be provided the opportunity to approve or deny whether their data is retained by the study team for use in future research as part of the consent process. All data will be deposited in REDCap. Dissemination of data will be de-identified and conducted through academic conferences and journals. Participants identified to be eligible for genetic testing who did not receive counseling from their providers will be contacted at the conclusion of their participation in the study. Participants will not receive direct notification of trial results. The authors report no conflicts of interest.

## DISCUSSION

The results of this study will provide data regarding the use of a digital tool for genetic cancer screening compared to usual clinician care. The primary outcome will be proportion of eligible patients recommended for genetic testing for cancer-predisposing pathogenic variants. We hypothesize that the use of the digital tool will be associated with a higher proportion of eligible patients being recommended for testing.

Similar tools have been integrated into clinical practices with the publication of observational data. In Loving et al., authors report on the implementation of screening via CARE™ in women undergoing breast cancer imaging.[22] A total of 3345 patients were screened, and 1080 (32.3%) met genetic testing criteria. Patients who met genetic testing criteria received counseling by a pre-recorded video, and consent and sample collection was performed by medical assistants.

Among those eligible for genetic testing, 416 (38.5%) proceeded with genetic testing, which identified 38 individuals with cancer-predisposing pathogenic variants. While the findings in Loving et al. support the feasibly of tool implementation, the study population was primarily non-Hispanic White (78.3%), which differs from the anticipated study population of the HeRITAGE study. Further, the observational design and study setting at an imaging center limit understanding of the effectiveness of the tool compared to usual care in office practice.

In Nazareth et al., authors report retrospectively on the implementation of a similar patient-facing digital health chatbot to perform genetic cancer risk assessment across 180 outpatient sites, including primary care clinics.[23] A total of 95,166 patients were invited to complete the chatbot, with 54,547 (89.4%) completing the chatbot risk assessment, and 14,850 (27.2%) meeting NCCN Guidelines® for genetic testing for cancer-predisposing pathogenic variants. In the study design, risk assessments were disclosed to patients by the clinician. Downstream data on the impact of the tool, such as number of patients who were appropriately recommended for genetic testing or received genetic testing was not included in the publication, except for a subset of 5,594 eligible patients among whom 1,622 (29.0%) had genetic testing ordered. Lack of comprehensive outcomes regarding counseling or utilization of genetic services after tool use limits the ability to make conclusions about the utility of the chatbot tool. In the HeRITAGE study, recommendation for genetic testing of eligible individuals was chosen as the primary outcome as this was felt to represent a clinically relevant milestone in which the genetic risk has been communicated to the patient. Further downstream data, such as the rate of genetic testing, will also be reported.

While data regarding digital screening tools have generally supported feasibility and acceptance, the impact of the tool on disparities in genetic services warrants exploration as health systems begin to incorporate such tools into routine practice and smartphones become increasingly widespread.[24] An urban, academic, Medicaid-predominant clinic was chosen for the site of the HeRITAGE study due to the high proportion of patients that are historically underrepresented in genetics research. Data regarding the association of demographics, health literacy, and other social determinants of health on the experience of genetic risk assessment and receipt of genetic counseling may allow for insight into the impact of a smartphone-based tool on equitable care.

The inclusion criteria of the HeRITAGE study are broad, and thus the results of the study have potential to be generalizable to other practices. However, the exclusion of non-English speaking and reading patients, those without access to phones with internet capability, and the location of the study at a single site may limit generalizability. While a smartphone-based tool may address common genetic cancer risk assessment barriers such as limited appointment time and provider knowledge, HeRITAGE is not designed to address language barriers which have also been shown to affect access to genetic services.[6] At this time, additional efforts are underway to explore the effect of the smartphone-based tool in non-English speaking populations through translation of the tool to other languages and recruitment of non-English speaking patient cohorts at multiple sites. Additionally, HeRITAGE requires in-person appointment attendance for recruitment, and does not address physical access to clinic spaces as a barrier to genetic testing.

Given the randomized study design and the urban Medicaid-predominant clinic setting, the results of HeRITAGE will provide informative data regarding the influence of screening technology in genetic cancer risk assessment on clinically relevant outcomes.

## FIGURES

Figure 1. HeRITAGE study outline. Bolded lettering indicates areas of study intervention; * primary outcome; † secondary outcome.

Figure 2. HeRITAGE patient and provider workflow for patients meeting eligibility criteria and proceeding with genetic testing on day of appointment: Intervention arm. Created with BioRender.com.

Figure 3. HeRITAGE patient and provider workflow for patients meeting eligibility criteria and proceeding with genetic testing on day of appointment: Control arm. Created with BioRender.com.

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## AUTHORS' CONTRIBUTIONS

1. Bull – Formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization
1. Webster – Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, funding acquisition
3. McDougale – Conceptualization, methodology, software, resources, writing – review & editing, supervision, project administration, funding acquisition
4. Howard – Conceptualization, resources, data curation, writing – review & editing, visualization, supervision, project administration, funding acquisition
5. Ahsan – Conceptualization, methodology, formal analysis, investigation, resources, writing – review & editing
6. Levi – Investigation, data curation, writing – review & editing, project administration
7. Grant – Investigation, data curation, writing – review & editing, project administration
8. Chandler – Investigation, data curation, writing – review & editing, project administration
9. Christos – Conceptualization, methodology, formal analysis, writing – review & editing
10. Sharaf – Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, funding acquisition
11. Frey – Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision, project administration, funding acquisition

Melissa K Frey is the guarantor.

## FUNDING STATEMENT

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## COMPETING INTERESTS STATEMENT

The authors have no competing interests to disclose.

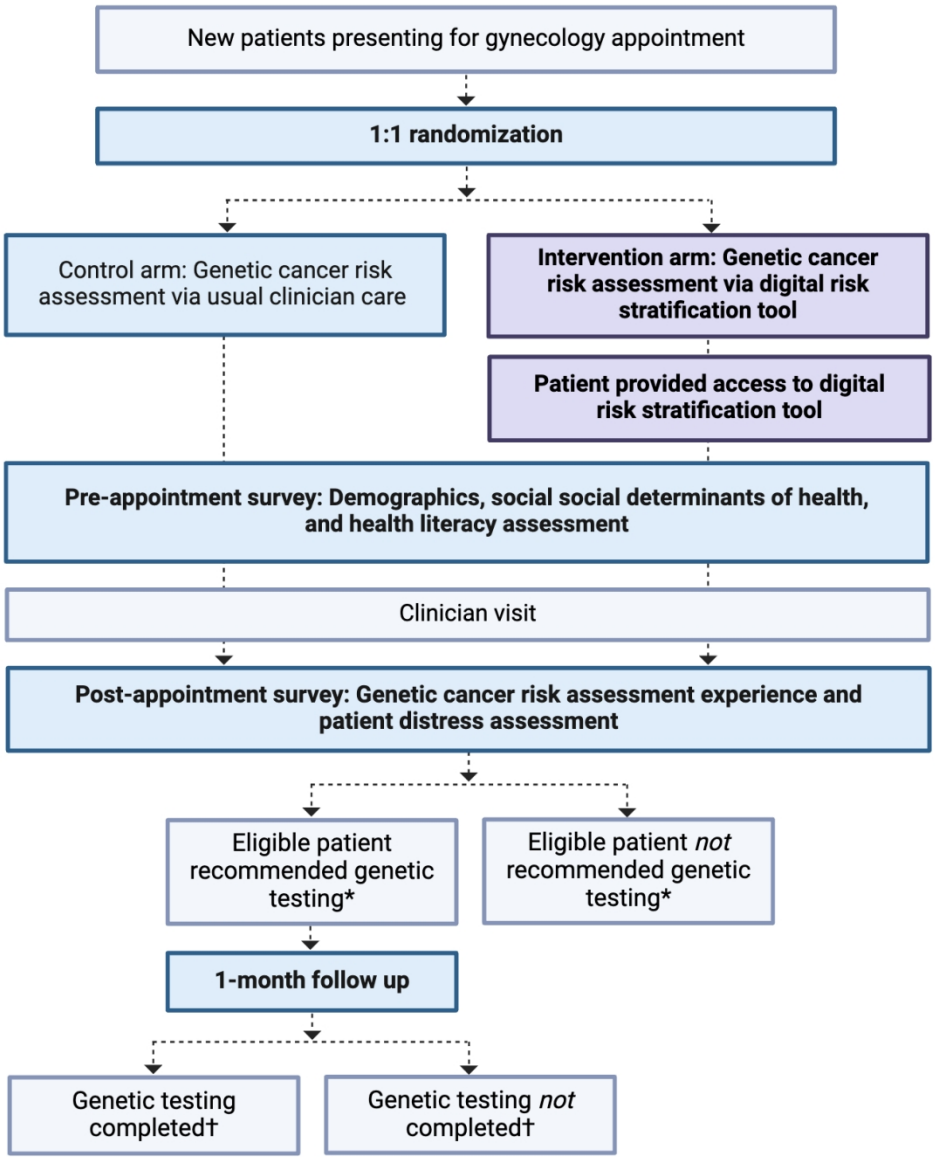


Figure 1. HeRITAGE study outline. Bolded lettering indicates areas of study intervention; * primary outcome; † secondary outcome.

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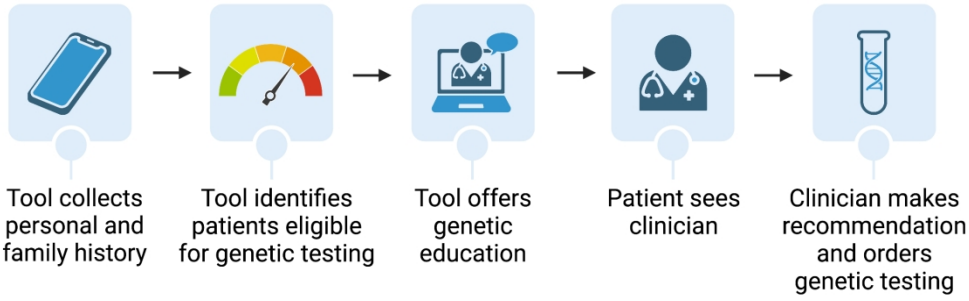


Figure 2. HeRITAGE patient and provider workflow for patients meeting eligibility criteria and proceeding with genetic testing on day of appointment: Control arm. Created with BioRender.com.

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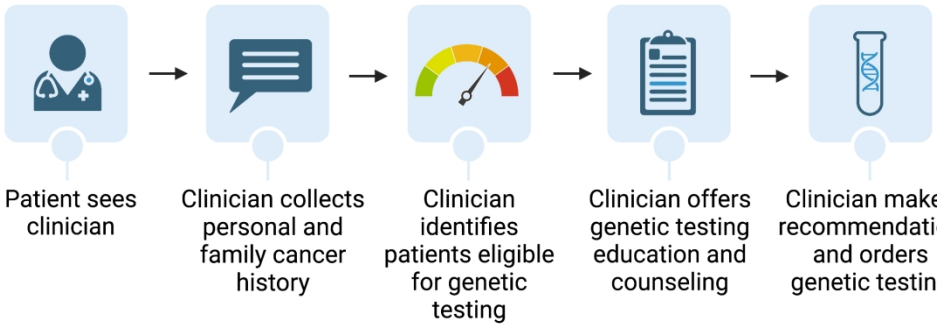


Figure 3. HeRITAGE patient and provider workflow for patients meeting eligibility criteria and proceeding with genetic testing on day of appointment: Intervention arm. Created with BioRender.com.

202x72mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym.<br>*Reported on page 1* |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry<br>*Reported on page 3* |
| | 2b | All items from the World Health Organization Trial Registration Data Set<br>*Reported on pages 1, 2, 3, and 4* |
| Protocol version | 3 | Date and version identifier<br>*Reported on page 3* |
| Funding | 4 | Sources and types of financial, material, and other support<br>*Reported on pages 1 and 2* |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors<br>*Reported on page 12* |
| | 5b | Name and contact information for the trial sponsor<br>*Reported on page 1* |
| | 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<br>*Reported on page 2* |
| | 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)<br>*Not applicable* |
| **Introduction** | | |

| | | |
|---|---|---|
| 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<br>*Reported on page 5* |
| | 6b | Explanation for choice of comparators<br>*Reported on pages 5 and 6* |
| Objectives | 7 | Specific objectives or hypotheses<br>*Reported on page 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)<br>*Reported on page 5* |
| **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<br>*Reported on page 5* |
| 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)<br>*Reported on page 7* |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered<br>*Reported on pages 5-7* |
| | 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)<br>*Reported on page 6* |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)<br>*Reported on page 7* |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial<br>*Not applicable* |

| | | |
|---|---|---|
| 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<br>*Reported on page 7* |
| 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)<br>*Reported on pages 5-7 and in figure 1* |
| 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<br>*Reported on page 7* |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size<br>*Reported on page 9* |
| **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<br>*Reported on pages 7-8* |
| 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<br>*Reported on pages 7-8* |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions<br>*Reported on pages 5 and 8* |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how<br>*Reported on pages 7-8* |

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| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial<br>*Not applicable* |
| **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<br>*Reported on pages 6-7* |
| | 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<br>*Reported on pages 6-7* |
| 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<br>*Reported on page 7* |
| 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<br>*Reported on page 8* |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)<br>*Reported on page 8* |
| | 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)<br>*Not applicable* |
| **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<br>*Reported on page 7* |

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| | 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<br>*Not applicable* |
| 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<br>*Not applicable* |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor<br>*Not applicable* |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval<br>*Reported on page 8* |
| 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)<br>*Reported on page 8* |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)<br>*Reported on page 5* |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable<br>*Included in consent form appendix* |
| 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<br>*Included in consent form appendix* |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site<br>*Reported on page 12* |
| 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<br>*Reported on page 7* |

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| 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<br>*Not applicable* |
| 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<br>*Reported on page 8* |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers<br>*Reported on page 12* |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code<br>*Not applicable* |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates<br>*Consent form attached as an appendix* |
| 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<br>*Included in consent form* |

*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.