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QIMR Berghofer
Medical Research Institute

Clinical Trial Protocol

PROMISE: Patient Reported Outcome Measures in cancer care: a hybrid effectiveness-Implementation trial to optimise Symptom control and health service Experience. A randomised controlled trial of electronic self-reporting of symptoms versus usual care during and following treatment in cancer patients to improve patient outcomes

Short title: PROMISE: Patient Reported Outcome Measures in cancer care: a hybrid effectiveness-Implementation trial to optimize Symptom control and health service Experience

Project No: P3622

Version: 1.1
Date: 22 September 2020

TRIAL REGISTRATION

ANZ Clinical Trials registry: ACTRN12620001290987

SPONSOR

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COORDINATING PRINCIPAL INVESTIGATOR

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This protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement 2013[1] and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol 2018.[2]

PROTOCOL AMENDMENTS/MODIFICATIONS AND APPROVALS

Protocol Amendment Number	**Date of Amendment**	**HREC Approval Required?** **YES/NO**	**Date of Nominee's or HREC's Approval**
V1.1	22-09-2020	YES (Initial approval)	25-09-2020 (Metro South HREC)
V1.2	07-12-2020	YES	06-01-2021 (Metro South HREC)

STUDY ACKNOWLEDGEMENT

By signing this Protocol, the Principal Investigator(s) acknowledges and agrees:
The Protocol contains all necessary details for conducting the study. The Principal Investigator will conduct this study as detailed herein, in compliance with the applicable legal and regulatory requirements, and will make every reasonable effort to complete the study within the time designated.
The Protocol and all relevant information will be made available to all physicians, nurses and other personnel who participate in the conduct of this study. The Principal Investigator will discuss this material with them to assure that they are fully informed regarding the conduct of the study.

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QIMR Berghofer will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this study are the sole property of QIMR Berghofer, which may utilise the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the study.

The conduct and results of this study will be kept confidential by the Principal Investigator and all study staff. Upon completion of the Study it is the intention of the parties to prepare a joint publication(s) regarding or describing the Study and all the results there from and all parties shall co-operate in this regard.

SIGNATURE PAGE

I have received and read this protocol. I agree to conduct the study in compliance with the protocol and the attachments, all applicable legal and regulatory requirements, and the following:

- World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants [3]
- NH&MRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018) [4]
-
- Current HREC approved Clinical Trial Protocol.

I will ensure that all study staff at my site comply with these requirements.

I acknowledge and agree that I am responsible for the conduct of the study and that I will personally conduct or supervise the conduct of the study.

Principal Investigator or Clinical Site Investigator:

Signed: Date:

Name:

Title:

LIST OF ABBREVIATIONS

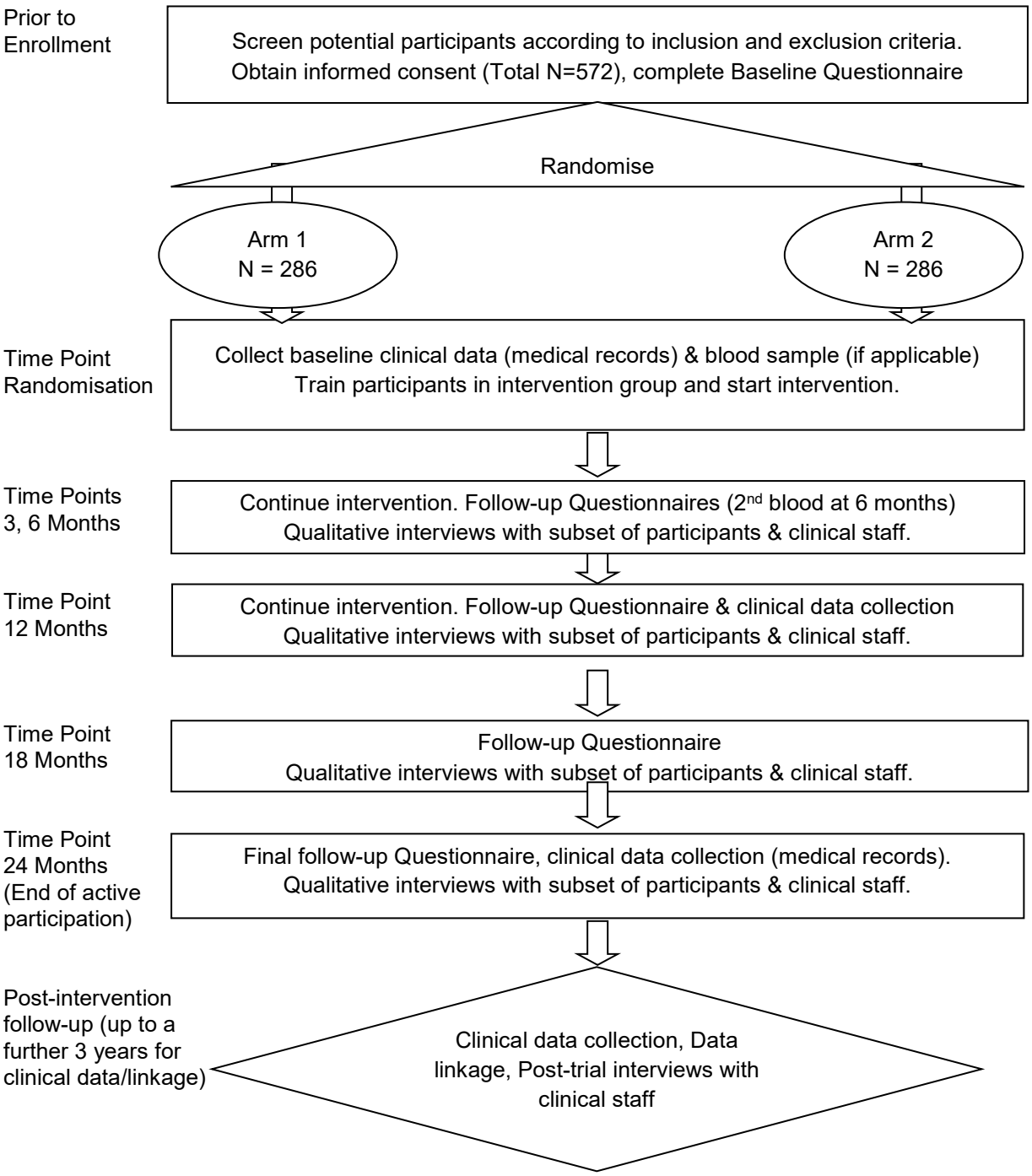
AHPEQS	Australian Hospital Patient Experience Question Set
CRF	Case Report Form
DT	Distress Thermometer
e-PROM	Electronic Patient Reported Outcome Measure
EDIS	Emergency Department Information System
EQ-5D-5L	EuroQol-5 Dimension 5 level
ESAS	Edmonton Symptom Assessment Scale
FACT	Functional Assessment of Cancer Therapy
GCH	Gold Coast Hospital
HREC	Human Research Ethics Committee
HR-QoL	Health Related Quality of Life
MBS	Medicare Benefits Schedule
MSAS	Memorial Symptom Assessment Scale
NHCDC	National Hospital Cost Data Collection
PAH	Princess Alexandra Hospital
PBS	Pharmaceutical Benefits Scheme
PI	Principal Investigator
PM	PROMISE Project Manager
PRO(M)	Patient Reported Outcome (Measure)
QCCAT	Qld Cancer Control Analysis Team
QIMR Berghofer	QIMR Berghofer Medical Research Institute
QHAPDC	Qld Hospital Admitted Patient Data Collection
QHNAPDC	Qld Hospital Non-Admitted Patient Data Collection
RA	Research Assistant (based at QIMRB)
RBWH	Royal Brisbane and Women's Hospital
SCNS-P&C	Supportive Care Needs Survey – Partners and Carers
TVH	Townsville Hospital

PROTOCOL SUMMARY

Full Title:	PROMISE: Patient Reported Outcome Measures in cancer care: a hybrid effectiveness-Implementation trial to optimise Symptom control and health service Experience. A randomised controlled trial of electronic self-reporting of symptoms versus usual care during and following treatment in cancer patients to improve patient outcomes
Short Title:	PROMISE: Patient Reported Outcome Measures in cancer care: a hybrid effectiveness-Implementation trial to optimize Symptom control and health service Experience
Project Number:	P3622
Synopsis:	The routine collection of patient-reported outcome measures (PROMs) has the potential to inform and improve cancer care. It is now feasible for patients to complete electronic PROMs providing information about their current levels of symptoms, side-effects of treatment and other concerns prior to each treatment /follow-up visit. PROM scores can be tracked over time allowing more timely identification of problems and more appropriate intervention. Studies show clear benefits in patient-clinician communication when PROMs are used but information about the effects on health outcomes and, particularly, the cost-effectiveness of incorporating this information into practice is limited. Trials in the USA and France found cancer patients randomised to complete regular e-PROMs reported better health-related quality of life, had fewer unplanned hospital visits and, importantly, significantly better survival than those randomised to usual care. e-PROM tools are being developed in Australia but whether they will be effective and, importantly, cost-effective in the Australian context is unknown. We propose a multi-centre, randomised hybrid effectiveness/implementation trial to evaluate the effectiveness and cost-effectiveness of using e-PROMs in routine cancer care to improve patient outcomes. We hypothesise that, compared to usual care, patients randomised to use an e-PROM tool will have fewer unplanned hospital presentations/admissions, report better health-related quality of life and greater satisfaction with their care, and that the e-PROM tool will be cost-effective compared with usual care. Two pre-planned sub-studies will assess the effects of the intervention on participants' partners and/or carers (PROMISE-Carers Substudy) and the relationship between genetic factors and symptoms/wellbeing/outcomes (PROMISE-Genetics Substudy).
Objectives:	To conduct a hybrid effectiveness-implementation trial to test the effectiveness/cost-effectiveness and implementation of the use of e-PROMs in routine cancer care to improve patient outcomes. Primary Outcomes: - Unplanned hospital presentations/admissions;

	- Physical and functional wellbeing at 6 months. Secondary Outcomes: - Rates of treatment completion; - Overall well-being and change in wellbeing; - Rates of distress; - Symptom burden; - Number of out-patient visits; - Cost-effectiveness. Exploratory outcomes: - Patient care experience; - Survival; - Partner/carer distress and unmet supportive-care needs (Carer Substudy); We will also assess measure implementation and process outcomes consistent with the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) Framework. In addition, we will invite participants to provide a small blood sample (~20ml) at two time-points to evaluate associations between genomic variation and patient outcomes (e.g., symptoms and health-related quality of life).
Population:	Patients aged 18+ years diagnosed with a solid cancer and starting treatment at one of the study hospitals.
Phase:	Hybrid Effectiveness-Implementation Trial
Number of Sites:	QIMR Berghofer (central coordination) + 4 clinical sites
Description of Intervention:	e-PROM tool (*My Health My Way* or *AboutMe*) comprising a short questionnaire administered via an electronic platform prior to clinic appointments (during treatment and follow-up) and monthly or as desired by the patient between follow-up appointments. <u>The tools provide information only and thus are not classed as medical devices.</u>
Study Duration:	4 years
Participant Participation Duration:	Up to 24 months
Estimated Time to Complete Enrollment:	12 months

SCHEMATIC OF STUDY DESIGN



1. KEY ROLES AND CONTACT INFORMATION

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Trial Coordinators PAH: To be appointed
RBWH: To be appointed
GCH: To be appointed
TH: To be appointed

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1.1 Study Locations

- **Trial Sites**

Princess Alexandra Hospital
Division of Cancer Services
199 Ipswich Road
Woolloongabba, Qld 4102

Townsville Hospital
100 Angus Smith Drive
Douglas, Qld 4814

Royal Brisbane and Women's Hospital
Cnr Butterfield St & Bowen Bridge Rd
Herston Qld 4029

Gold Coast University Hospital
1 Hospital Boulevard
Southport,
Qld 4215

- **Randomisation:** Statistics Group, Level 12 Bancroft Building, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston Qld 4006

- **Data management:** Gynaecological Cancers Group, Level 4 Central Building, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston Qld 4006
- **Blood processing/storage (PROMISE-Genetics):** Institute of Health and Biomedical Innovation, QUT

1.2 Study Management

1.2.1 *Sponsor*

QIMR Berghofer Medical Research Institute
300 Herston Road, Herston, Qld 4006
Tel: +61 7 33620281

Authorised signatory for the Sponsor
Deputy Director
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Phone: +61 7 3362 0207

1.2.2 *Roles of the Principal Investigator and Co-Investigators*

Name	**Role & Responsibilities**
Prof. Penelope Webb	Chief Principal Investigator; overall management of the trial.
Prof. Ray Chan	CIB and PAH Site PI; Support the CPI as Senior Investigator; deputise for the PI when PI/PM is not available; Oversee study operationalisation at the PAH (including recruitment, data collection and management of research nurses); Oversee implementation component and provide expertise in PRO and qualitative research (including supporting CI Nund in qualitative analysis)
Dr Bena Brown	CI; Provide support for *My Health My Way* and, with CI Chan, operationalise and oversee the study at PAH.
A/Prof David Wyld	RBWH Site PI; Operationalise and oversee the study at RBWH
Prof Sabe Sabesan	TVH Site PI; Operationalise and oversee the study at Townsville Hospital
A/Prof Jasotha Sanmurgarajah	GCH Site PI; Operationalise and oversee the study at Gold Coast University Hospital
A/Prof Louisa Gordon	CI; Study Health Economist
Prof Gunter Hartel	CI; Study Biostatistician
Prof Afaf Girgis	CI; Interstate Collaborator, input regarding trial design and conduct and PROs
A/Prof Melissa Eastgate	CI; with CI Wyld Operationalise and oversee the study at RBWH

Name	Role & Responsibilities
Dr Laurelie Wishart	CI; Provide support for *My Health My Way* with CI Brown at PAH
Dr Rebecca Nund	CI; Oversee the qualitative aspects of the study
Mr Martin Doyle	CI and Consumer representative; Input to all aspects of the trial as they relate to patients and carers
Ms Elizabeth Miller	CI and Consumer representative; Input to all aspects of the trial as they relate to patients and carers
A/Prof Kim Alexander	AI; Responsible for blood processing/storage and genetic analyses
A/Prof Larisa Haupt	AI; Responsible for blood processing/storage and genetic analyses
Ms Karen Martin	PM; Oversee: study ethics and compliance, site set ups, monitor study progress, organise meetings, liaise with data manager and the maintenance of study documents

1.2.3 *PROMISE Trial Committee*

The study will be managed by the PROMISE Trial Committee comprising the CIs who collectively bring experience in population health, randomised trials, implementation, clinical medicine, quantitative and qualitative studies as well as consumer representatives. The Project Manager will provide regular reports to the Trial Committee regarding recruitment rates; questionnaire completion rates; data collection, completeness and quality; and any issues or concerns arising regarding any aspect of the trial.

1.2.4 *Other members responsible for conducting the study*

- Institutional Ethics Committees
  Lead HREC: Princess Alexandra Hospital
  Other approving HRECs: QIMRB, RBWH, GCH, TH
- Independent Data and Safety Monitor
  Professor Rachel Neale, QIMR Berghofer
  A formal progress report will be submitted to Prof Neale every 6 months and she will provide feedback on the study progress and any concerns regarding this to the PROMISE Trial Committee.
- Medical Monitor: Not required.

1.3 Funding and resources

The study is funded by an Accelerating Collaborative Cancer Research Grant from the Cancer Council Queensland 2020-2023 (Grant number ACCR-0000000031) with a co-contribution from QIMR Berghofer. Access to the e-PROM tools will be provided by Princess Alexandra Hospital (*My Health My Way*) and Royal Brisbane and Women's Hospital (*AboutMe*).

1.3.1 *Conflict of Interest*

The funders will play no role in the design or conduct of the study, interpretation of the study results or in decisions regarding the reporting of study results.

1.4 Insurance and Indemnity

The study sponsor adheres to the Medicines Australia “Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial”; and holds a No-Fault Compensation for Clinical Trials insurance policy. The study sponsor agrees to indemnify the investigator(s) from any claims for damages for unexpected injuries, including death, that may be directly caused by the participant’s participation in the study, but only to the extent that the claim is not caused by the fault or negligence of the participants or investigator(s), hospital, institution, ethics committee.

2. INTRODUCTION

2.1 Background Information

Health problem: With the number of new cancer diagnoses increasing by ~2.5% per year and the number of cancer survivors in the Australian population predicted to reach 1.4 million by 2020, it is increasingly important we use our finite health dollars to care for those affected in the most cost-effective way. There is now considerable interest in the use of patient-reported outcome measures (PROMs), and particularly routine electronic collection of PROMs (e-PROMS) to inform cancer care in the hope this will improve timely identification and control of symptoms thereby enhancing physical and psychological well-being, improving health service experience, increasing treatment completion rates and, ultimately, improving survival. A recent national 'Think Tank' held by the Clinical Oncological Society of Australia (COSA) highlighted the importance of patient-reported outcome (PRO) monitoring in cancer and the need to evaluate the implementation of this [6].

Goal and Intervention: We propose a pragmatic hybrid effectiveness-implementation trial to test the effectiveness/cost-effectiveness and implementation of e-PROMs (comprising the ESAS and DT tools, administered via the *My Health My Way* platform developed at PAH and the AboutMe platform developed at RBWH) in routine cancer care in Queensland. The results have the potential to change practice, improve patient wellbeing and increase cancer survival rates.

Background and context: A PRO is an indicator of a patient's health status, as reported by the patient without amendment or interpretation by a health professional or other person [7]. PRO measures (PROMs) provide information about a patient's condition and response to treatment (e.g. side effects), functioning and wellbeing (e.g. physical functioning, social/emotional wellbeing) and psychological symptoms (e.g. depression, anxiety). Advances in technology and internet access now allow patients to complete PROMs electronically (e-PROMs) providing information about their current levels of symptoms, side-effects of treatment and other concerns prior to each treatment/follow-up visit. Their e-PROM scores can be tracked over time, potentially allowing more timely identification of, and intervention to resolve problems.

Relevant research: The routine use of e-PROM tools in cancer care has attracted considerable interest since a US trial reported that patients starting chemotherapy for metastatic solid cancers who were randomised to complete e-PROMs had significantly improved survival compared to those randomised to usual care (median 31 vs. 26 months, p=0.03) [8]. The authors had previously reported improved health-related quality of life (HR-QoL) and longer treatment duration among the intervention group [9]. A French trial has since reported that, among patients with non-progressive disease at the end of primary treatment for advanced stage lung cancer (N=121), survival was significantly better among the group randomised to complete weekly e-PROM measures compared to usual care (median 22.5 vs. 13.5 months, one-sided p=0.002) [10, 11] and the intervention was highly cost-effective [12]. These studies, both published in the high-profile Journal of the American Medical Association [8, 11], strongly suggest that routine use of e-PROMS has potential to improve patient survival. However, the French study had limitations as it was terminated early when the survival difference exceeded pre-set criteria in a pre-specified interim analysis and, although no other studies have yet published survival data, results for other patient outcomes are less consistent.

2.2 Objectives

To conduct a pragmatic hybrid effectiveness-implementation trial to test the effectiveness/cost-effectiveness and implementation of e-PROMs (comprising the ESAS and DT tools, administered via the *My Health My Way* platform developed at PAH and the AboutMe platform developed at RBWH) in routine cancer care in Queensland. The trial will be evaluated using the RE-AIM framework (See Section 14, Appendix B) [13, 14]. This assesses five separate aspects of the intervention: Reach; Effectiveness, assessed via a series of primary, secondary and exploratory objectives; Adoption; Implementation; and Maintenance.

2.2.1 ***Primary:***

To evaluate the effect of the use of e-PROM tools (*My Health My Way* and *AboutMe*) in adult patients undergoing primary treatment or follow-up for cancer compared to usual care on:

(i) The rate of unplanned hospital presentations/admissions; and
(ii) Physical and functional wellbeing at 6 months.

2.2.2 ***Secondary:***

To evaluate the effect of the use of e-PROM tools (*My Health My Way* and AboutMe) on:

(i) Rates of treatment completion;
(ii) Overall well-being and change in wellbeing;
(iii) Participant distress;
(iv) Symptom burden;
(v) Numbers of out-patient visits.

2.2.3 ***Exploratory:***

To evaluate the effect of the use of e-PROM tools (*My Health My Way* and AboutMe) on:

(i) Patient care experience;
(ii) Survival;
(iii) Partner/carer distress and unmet supportive-care needs (PROMISE-Carers Substudy);
(iv) To evaluate the role of genetics in the outcomes above (PROMISE-Genetics Substudy).

2.2.4 ***Implementation Objectives:***

To evaluate the extent to which the PROMISE Intervention (the use of e-PROMS and associated implementation strategies):

(i) Reaches the target population;
(ii) Is adopted by clinicians and patients;
(iii) Is implemented within the clinics;
(iv) Is cost-effective compared to usual care; and
(v) Continues to be used beyond the end of the trial (maintenance).

2.3 Outcome Measures

The trial outcomes will be assessed according to the RE-AIM framework (See Section 14, Appendix B) which includes five key components: Reach, Effectiveness, Adoption, Implementation and Maintenance [13, 14]. Effectiveness will be measured via a series of primary (2.3.1), secondary (2.3.2) and exploratory (2.3.3) outcomes at the patient and system level. Reach, Adoption and Implementation will be assessed via recruitment and

process data and qualitative data from stakeholder interviews (2.3.4) with a formal cost-effectiveness analysis (2.3.5). Maintenance will be assessed by clinician surveys and e-PROM platform usage statistics during the passive follow-up period after the end of the intervention (2.3.4).

The individual outcomes and the source(s) of the information that will inform them are summarised in Table 1 and below.

Table 1. Information to be collected to address each of the five RE-AIM Indicators

RE-AIM Indicator & Level of Analysis		Collection method / instrument
1. REACH & Representativeness		
Study & Centre	Participation rate (%), comparison of participants and eligible non-participants	Study database, Hospital record audit
	Patient clinical & demographic characteristics (overall & by participation)	Study database; Hospital records; Comparison to state-wide data from QCCAT
2. EFFECTIVENESS		
Primary outcomes:		
System	Emergency presentations & unplanned admissions	Hospital records; linkage to QHAPDC; MBS
Patient	Physical & functional wellbeing	Self-report: FACT-G: physical & functional wellbeing subscales [15]
Secondary Outcomes:		
Patient	Rates of treatment completion & proportion of planned treatment received	Medical records
	Overall wellbeing	Self-report: FACT-G (33 items) [15]
	Anxiety and depression	Self-report: HADS (14 items) [16, 17]
	Symptom burden	Self-report: MSAS (32 items) [18]
	Proportion of planned treatment received (dose reductions, delays)	Hospital records
	Numbers of out-patient visits	Hospital records; linkage to EDIS and MBS
Exploratory Outcomes:		
Patient	Patient experience of care	Self-report: AHPEQS (12 items) [19]
	Survival	Hospital records
3. ADOPTION		
Centre	Numbers of clinics, medical and nursing clinicians invited to participate and number participating in implementing e-PROMs	Hospital and study records
	Health providers' (all) & patients' feedback on system usability and implementation	Stakeholder interviews, System Usability Scale [20]
4. IMPLEMENTATION		
Patient	e-PROMs completed prior to each medical appointment (N, %)	e-PROM platform
	e-PROM items completed (%)	e-PROM platform
Centre	Frequency of clinician access to e-PROM data (N, %)	e-PROM platform
	Length of medical appointments at the cancer centre	Hospital records
	Clinical responses related to e-PROMs	Hospital records
	GP & specialist visits (N, timing)	MBS; Hospital records
	Costs including costs of the intervention and all healthcare interactions	QHAPDC, QHNAPDC, EDIS, MBS, PBS, NCDC

	Benefits measured as quality-adjusted life years	Self-report: EQ-5D-5L[21]
5. MAINTENANCE & Sustainability		
	Proportion of the clinics, clinicians and intervention participantsusing the e-PROMs at the end of the study, 6 months and 12 months after study completion	Clinician surveys and e-PROM platform usage statistics.

Abbreviations: AHPEQS, Australian Hospital Patient Experience Question Set; EDIS, Emergency Department Information System; EQ-5D-5L, EuroQol-5 Dimension 5 level; MBS, Medicare Benefits Schedule; MSAS, Memorial Symptom Assessment Scale; NCDC, National Cost Data Collection; PBS, Pharmaceutical Benefits Scheme; QCCAT, Qld Cancer Control Analysis Team; QHAPDC/QHNAPDC, Qld Hospital Admitted/Non-Admitted Patient Data Collection.

2.3.1 *Primary outcomes*

(i) The rate of unplanned hospital presentations/admissions. This information will be obtained from hospital records and linkage to the Queensland Health Admitted Patients Data Collection (QHAPDC), Emergency Data and Medical Benefits Scheme (MBS) data.

(ii) Physical and functional wellbeing measured by the Physical Wellbeing and Functional Wellbeing subscales of the Functional Assessment of Cancer Treatment – General (FACT-G) scale [15].

2.3.2 *Secondary outcomes*

The secondary objectives will assess differences in a range of other key health-related outcomes that could be affected by the intervention.

(i) Rates of treatment completion: proportion of planned treatment received; information about planned treatment, dose reductions and delays will be obtained from medical records.
(ii) Overall wellbeing measured by the Functional Assessment of Cancer Treatment – General (FACT-G) scale [15].
(iii) Levels of patient distress measured by the Hospital Anxiety and Depression Scale (HADS) using cut-points of ≥10 to indicate clinical anxiety or depression and 8-10 to indicate sub-clinical anxiety or depression [16, 17].
(iv) Symptom burden measured by the Memorial Symptom Assessment Scale (MSAS) which assesses the presence, severity and distress caused by 32 individual symptoms [18].
(iii) Numbers of out-patient visits; information will be obtained from hospital records and linkage to Emergency Data and Medical Benefits Scheme (MBS) data.

2.3.3 *Exploratory outcomes*

Although power will be lower for some of these analyses, they are included because of their importance in improving cancer outcomes.

(i) Patient care experience measured by the Australian Hospital Patient Experience Question Set (AHPEQS) [19]
(ii) Survival; information about date and cause of death or date last known to be alive will be obtained from medical records. This will be assessed passively from medical records and via data-linkage after the main trial is complete.
(iii) Partner/carer distress and unmet supportive-care needs measured by the HADS and Supportive Care Needs Survey – Partners and Carers (SCNS-P&C) [22].

2.3.4 ***Implementation outcomes***

(i) REACH: we will assess the 'Reach' of the intervention via the participation rate (numbers of eligible participants, those invited to participate and those who consent, N and %) and by comparison of basic clinical and demographic characteristics of participants and eligible non-participants,

(ii) ADOPTION: we will assess this by:
- The numbers of clinics, medical and nursing clinicians invited to participate and those who do participate (N, %)
- Healthcare providers' (all) & patients' satisfaction and feedback via Stakeholder interviews and the System Usability Scale [20].

(iii) IMPLEMENTATION: will be assessed via:
- The number and proportion of e-PROMs completed prior to each medical appointment & the number of e-PROM items completed (%), measured via the e-PROM platform
- The frequency of clinician access to e-PROM data (N, %) measured via the e-PROM platform
- The length of medical appointments measured via hospital records
- Clinical responses related to e-PROMs measured via hospital records
- The numbers of GP & specialist visits (N, timing) measured via hospital records and linkage to MBS

(iv) MAINTENANCE: we will:
- Quantify the proportion of the clinics, intervention participants, and clinicians using the e-PROMs at the end of the study, 6 and 12 months after study completion. The latter time-points will be assessed passively from medical records and the e-PROM platforms during the 'Follow-up Extension' after the main trial is complete.

2.3.5 ***Cost-effectiveness***

We will also evaluate the cost-effectiveness of the e-PROM tools by quantifying: (a) the costs of the intervention and all healthcare interactions (using data from QHAPDC, QHNAPDC, EDIS, MBS, PBS, NHCDC) and (b) the benefits of the intervention measured as quality-adjusted life years using EQ-5D-5L [21].

2.4 Hypotheses:

We hypothesise that, compared to usual care, routine self-reporting of e-PROMs will result in:

1. Primary Outcomes:
   - Fewer emergency presentations/unplanned hospital admissions;
   - Better physical and functional well-being at 6 months;
2. Secondary Outcomes:
   - Higher rates of treatment completion;
   - Better health-related quality of life (HRQOL);
   - Lower rates of distress;
   - Lower symptom burden;
   - Fewer out-patient visits;
3. Exploratory Outcomes:
   - A better patient care experience;
   - Better survival;
   - Lower rates of distress and unmet supportive care needs among partners/carers.

We also hypothesise that use of the e-PROM tools will be cost-effective compared to usual care.

2.5 Potential Risks and Benefits

2.5.1 *Potential Risks*

There are no known physical risks associated with the intervention. The only possible psychological risk to participants is that they may become distressed when answering questions within the e-PROM tools or the study questionnaires. If participants in the intervention group report high levels of distress when they complete the e-PROM tool this will be identified and managed as part of clinical practice. If participants in either group appear to be severely distressed based on their answers to the study questionnaires (e.g. HADS anxiety or depression score >10) we will pass this information on to their clinical team. In practice, it is highly unlikely such distress would be related to their participation in the study, it is much more likely to be a consequence of their disease and/or treatment.

PROMISE-Carers Substudy: if partners or carers report high levels of distress (HADS score >10) on their study questionnaires we will recommend that they talk to their GP or, if they provided contact information for a medical practitioner on their consent form, we will contact the practitioner directly.

2.5.2 *Potential Benefits*

Potential benefits to participants in the intervention group (and their partners/carers) include enhanced communication with their clinical team, earlier identification of potential problems, more timely intervention and thus a better outcome.

There is unlikely to be any direct benefit to participants in the control group although, as described in 2.5.1, if control participants report severe distress on a study questionnaire we will report this to their clinical team and this may result in more effective management of the problem.

3. STUDY DESIGN

3.1 Type of Study

This is an investigator-initiated multi-site, two-arm randomised controlled hybrid effectiveness-implementation trial of two e-PROM tools designed to help clinicians better manage patient care. The tools provide information only and thus are not classed as medical devices.

The traditional route to translation requires a study of clinical effectiveness and then a separate study to evaluate the implementation of the intervention in practice. This stepwise process is necessarily time-consuming and has led to the development of designs that allow both steps to be conducted in a single study [23]. We therefore propose a hybrid study that will test both effectiveness/cost-effectiveness and implementation.

3.2 Study Sites and Study Population

The study population will be adult (age ≥18 years) cancer patients about to start their first systemic anti-cancer therapy or radiation therapy at one of the trial sites. The trial will be run at PAH, RBWH, Townsville (TVH) and Gold Coast Hospitals (GCH) in Queensland. These sites were selected because PAH and RBWH are quaternary public health hospitals that provide integrated cancer care and, together, deliver outpatient care to ~3000 cancer patients each week. They have developed e-PROM tools (*My Health My Way* and *AboutMe*) and are well set up to evaluate these in a trial context. TVH and GCH are large regional hubs and have expressed an interest in using the e-PROM tools. Collectively, these public hospitals are well-placed to optimise and influence cancer care delivery in Queensland, and to inform a statewide approach to the use of e-PROMs.

3.3 Number of Participants

The study will recruit a minimum of 572 participants, 286 in each arm, across the four study sites. The recruitment target for each site is below but the exact numbers may vary:

PAH & RBWH	150-175
GCH & TVH	110-145

3.4 Expected Duration of Study

The active component of the study is expected to run for up to 3 years. It is anticipated that it will take 12 months to recruit participants and that the intervention and active follow-up will continue for up to 2 years. [Funding is currently available for 1.5 years follow-up but, if additional funding can be secured, we will continue active follow-up for an additional 6 months for a total of 2 years.]

3.4.1 *Extended passive follow-up*

After the end of the active follow-up period, we will continue to monitor ongoing use of the e-PROM tools for an additional 12 months and will follow participants passively (through medical records and routine data linkage) for up to an additional 5 years. There will be no further contact with participants during this period. We will also conduct a brief survey with a sample of clinicians at each of the study sites at 6 and 12 months after study. This will ask whether the clinicians are still using the tools, how many and which patients they use them with (e.g. only former trial participants or also new patients), how often they use them and how they use the results.

4. PARTICIPANT ENROLMENT AND WITHDRAWAL

4.1 Eligibility Criteria

4.1.1 *Inclusion Criteria*

- Age at least 18 years;
- Diagnosed with an invasive solid cancer;
- About to start or recently started treatment at one of the study sites.

4.1.2 *Exclusion Criteria*

An individual who meets any of the following criteria will be excluded from participation:

- A tumour type or characteristic that is not appropriate for inclusion at the discretion of the Site Investigator and Coordinating PI e.g.:
    - Will not return to the site for regular treatment/follow-up;
    - Already using or would normally use an e-PROM tool at that site;
- Life expectancy less than 3 months
- Treated with surgery only;
- Current participation in another study that requires completion of similar PROMs;
- Unable to provide informed consent;
- Unable to complete the e-PROM tools remotely (e.g. a comorbid condition affecting vision, cognition or dexterity or no internet access at home)
- Unable to complete the study questionnaires in English;
- Unwilling to consent to data linkage.

In addition, participants who consent but do not complete the Baseline Study Questionnaire will be excluded post-consent.

4.2 Recruitment

The Study Coordinator at each site will identify all patients attending participating clinics during the study period who meet the inclusion criteria. Patients who clearly meet one of the exclusion criteria will be flagged and the reason for exclusion recorded. The Study Coordinator will approach the remaining patients and briefly explain the study to them. If patients are interested in the study, the Study Coordinator will perform a final eligibility screen and record any additional reasons for exclusion. The Study Coordinator will conduct the informed consent discussion. They will give patients who pass all of the exclusion criteria the PROMISE Participant Information sheet and Consent Form (PICF) and will explain the study to them and answer any questions. The PICF will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The Study Coordinator will check that the participant understands the information provided. Patients will be advised that if they decline to participate, or initially consent but then choose to withdraw, this will not affect their future healthcare. All participants will also be asked to provide consent to obtain MBS and PBS data from Services Australia (PROMISE Medicare Consent Form).

Consent will be voluntary and free from coercion. When a patient consents to participate they will be given a copy of the consent form, they will be assigned a unique Study ID number and their consent will be recorded in the Study Database. When their consent is recorded, this will prompt the Database / Study RA (based at QIMR Berghofer) to send them a personalised link to complete the Baseline Study Questionnaire.

Basic information (age, gender, postcode, cancer type and stage, study site) will be recorded in the Study Coordinator's Log and the Study Database for patients who are excluded or who decline to participate, together with the reason for exclusion/non-participation. This is to allow participation rates to be calculated, both overall and within key demographic/clinical groups. The patient's name will also be recorded but this information will only be accessible to the Study Coordinator (to ensure the same participant is not approached twice) and it will be deleted at the end of the recruitment period.

4.2.1 *PROMISE-Carers Substudy*

After they consent to participate in the main study, participants will be invited to nominate their partner/carer to participate in the Carer Sub-Study. They will be advised that this is optional and that they do not have to nominate a partner or carer. Nominated partners/carers will be approached, given a copy of the PROMISE Carer PICF and invited to participate.

4.2.2 *PROMISE-Genetics Substudy*

Consenting participants will also be invited to participate in the Genetic Substudy. The Study Coordinator will describe the purpose of the Substudy and what it will involve. They will give the participant a copy of the PROMISE Genetic PICF and will answer any questions that the participant has. Participants will be advised that this aspect of the study is optional and if they choose not to participate this will not affect their participation in the main PROMISE trial. They will also be advised that they can withdraw from this aspect of the study at any time and that any blood samples already collected will be destroyed if they request this.

4.3 Treatment Assignment Procedures

4.3.1 *Randomisation Procedures*

Randomisation will be at the patient level, with a 1:1 ratio between groups, using randomly varied permuted blocks, stratified by sex, hospital, treatment intent (curative/palliative) and computer literacy (defined as regular access to a computer/tablet/smart phone and use of email ≥1/week vs. less often) as this was shown to be important in previous trials [8, 9]. When a participant completes the Baseline Study Questionnaire, the central web-based database will automatically apply the next relevant record in the allocation sequence, as we have done previously [24-26].

4.3.2 *Blinding Procedures*

All study staff/investigators will be blinded to the allocation sequence ensuring allocation concealment until study entry. Due to the nature of the intervention, participants, their treating clinicians and the Trial Coordinators at each site will not be blinded to group allocation; however, the other investigators and project staff, including those collecting outcome data and conducting analyses, will remain blinded until after the main analyses have been finalised and the first papers are being prepared for publication (see 10.3 Statistical Analysis).

4.4 Participant Withdrawal

Participants may withdraw voluntarily from the study at any time upon request without this affecting their future treatment or care. Withdrawal may be complete (no further participation or follow-up) or partial (no further active participation but ongoing passive follow-up). If participants withdraw completely, their data will be deleted if they request this.

4.4.1 *Reasons for Withdrawal*

Participants may choose to withdraw from active participation in the study if:

- They no longer want the study investigators to access their medical records and/or revoke their consent for data linkage (complete withdrawal).
- They no longer wish to complete the study questionnaires (partial withdrawal).

An investigator may terminate a study participant's participation in the study if:

- It is identified that they meet an exclusion criterion (not previously recognised, or e.g. altered mental capacity) that would have made them ineligible to participate.
- A participant experiences a clinical adverse event (AE) or other medical condition or a situation occurs such that continued participation in the study would not be in their best interest.

4.4.2 *Handling of Withdrawals/Discontinuation & Loss to Follow-up*

When participants consent to take part in the study they will be advised that they have the right to withdraw at any stage if they choose to do so and that this will not affect their future medical care. The PICF will also explain that, if they do withdraw, any data already collected will be retained and passive follow-up via their medical records and data linkage will continue unless they specifically request that the data be destroyed and/or passive follow-up cease.

If a participant chooses to withdraw from the study they will be invited to complete the final Study Questionnaire. The withdrawal and, where possible, the reasons for this will be recorded on the relevant page of the CRF by the Investigator or Site Coordinator. A participant will be withdrawn completely if they revoke their consent to allow access to their medical records/information or if they request information previously collected from them be deleted. All other withdrawals will be deemed 'passive'. Participants will not be asked to complete any other study questionnaires but ongoing passive collection of clinical data will inform analyses of key end-points that do not require patient-reported information.

Participants in the intervention group who withdraw will be able to continue to use the e-PROM system if they choose to do so. If participants in the intervention group decide they no longer want to use the e-PROM tool they will be encouraged to continue to complete the study questionnaires and/or to allow ongoing access to their medical records.

4.4.3 *Replacements*

If participants withdraw completely while recruitment is ongoing we will seek to recruit additional participants to maintain the sample size. If participants withdraw completely after recruitment has ceased they will not be replaced. Participants who withdraw but allow continued passive follow-up will not be replaced.

4.4.4 *Continuation of Therapy*

When participants in the intervention group complete their active participation in the study it will be up to them and their treating clinician to decide if they wish to continue to use the e-PROM tool while the trial is ongoing. At the end of the study, participants at PAH and RBWH will be able to continue to use the tool. At TVH and GCH, use of the tools is currently only supported during the trial. Ongoing use beyond this will require the hospitals to enter into an agreement with PAH (for *My Health My Way*) or RBWH (for *AboutMe*). If the clinics wish to continue using the tools beyond the study we will try to facilitate this.

4.5 Premature Termination or Suspension of Study

The study may be suspended or prematurely terminated if there is sufficient reasonable cause. The Sponsor, Principal Investigator, Human Research Ethics Committee (HREC) and Regulatory Authorities independently reserve the right to discontinue the study at any time for safety or other reasons; however, this should be discussed between the relevant parties beforehand and the reason for such a decision recorded. In the occurrence of premature trial termination or suspension, the above mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension. After such a decision, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the participants' interests.

Circumstances that may warrant termination include, but are not limited to:

- Inability to recruit sufficient participants
- Insufficient adherence to protocol requirements
- Excessive rate of withdrawal

5. STUDY INTERVENTION

5.1 Intervention

The full PROMISE intervention combines the e-PROM tools that participants will complete (5.1.1 and 5.1.2) and the associated implementation strategies (5.1.3). The e-PROM tools use validated instruments (DT and ESAS) that have been used in previous studies, are currently being used in the PROMPTCare system in New South Wales [27-29] and are recommended for use nationally by the Cancer Survivorship Group of the Clinical Oncology Society of Australia (COSA).

In addition to their usual care (Section 5.2), participants randomised to the intervention will be oriented to the use of the e-PROM tool (*My Health My Way* at PAH, TVH; *AboutMe* at RBWH, GCH) at their first treatment visit post-randomisation. A reminder service built into the e-PROM systems will prompt participants to complete the tool 48-72 hours before each subsequent clinic visit (for treatment or follow-up), as previous reports identify this as a feasible time frame for health services to action e-PROM data entered [30]. Participants will also be encouraged to complete the tool monthly between clinic visits to monitor their own progress and facilitate early detection of new problems or exacerbation of existing problems.

When participants arrive for their appointment, the site nurse will check the summary report, to ensure the tool has been completed and, if not, they will help the participant to complete it prior to seeing their clinician. Where feasible, they will give the participant a print-out of the report to take in when they see their clinician; the clinician will also be able to access the report electronically. The report will detail the most recent symptoms entered and their severity (severe, moderate, normal/mild according to standard cut-points) as well as trends over time. Hospital-specific protocols (co-designed with clinical staff – see Section 5.3) will also be used to generate a summary patient-risk profile (e.g. urgent, high, medium, low [30]) and provide recommendations for review/referral . Clinicians will then decide on and prioritise management according to individual patient need.

5.1.1 *My Health My Way*

My Health My Way operates via a secure Qualtrics platform and is managed by PAH. The tool can be accessed from anywhere by patients (via a unique link sent to them) and approved healthcare providers. The system has been adapted for PROMISE to identify participants on the study, flag their study site and to allow access by appropriate staff at Townsville Hospital.

If a patient's responses to the e-PROM tool exceed predefined thresholds for various disciplines (Nursing, Medical, Dietetics, Speech Therapy, Physiotherapy, Social Work etc.) the system automatically sends an email alert to the relevant discipline who will review this and take appropriate action. These alerts are routinely monitored and actions performed in response to the alert are recorded. As a safeguard, patients who enter scores that exceed the thresholds are advised that the e-PROM tool is not monitored outside working hours and they should also contact their clinical team.

5.1.2 *AboutMe*

AboutMe is managed at RBWH and operated via a Queensland Government QGov account to ensure data are stored and transmitted securely. When participants are randomised to the intervention group the site nurse will help them set up a QGov log-in and will show them how to use the *AboutMe* system. As for *My Health My Way*, the tool

can be accessed from anywhere by patients (via a unique link sent to them) and their approved healthcare providers.

5.1.3 *Implementation*

In addition to evaluating the effectiveness of e-PROM tools, we will also evaluate their implementation. The process we will follow to implement the tools and the project personnel responsible for each stage in this process are summarised below.

Pre-Trial:

Step 1: Establishment of the project and preparation of the environment (Responsible Personnel: PIs)

- Identify and describe the characteristics of the sites (current workflows and use of PROMs)
- Use a co-design approach to finalise the core content of the e-PROM tools with site PIs
- Obtain support from relevant key opinion leaders (e.g. medical and nursing executives)
- Present an overview of the PROMISE intervention to the clinical staff
- Begin the preparation for on-boarding/training
- Conduct a group-based approach to strategise actions and maximise Reach, Effectiveness, Adoption, Implementation and Maintenance (medium and long term sustainability)

Step 2: Implementation planning with site PIs and additional key clinical champions (Responsible Personnel: PIs)

- Co-design and reach consensus on detailed procedures and recommendations for clinical actions based on e-PROM responses
- Ensure IT and paper-based infrastructure in in place to facilitate implementation of e-PROMs

Step 3: Development of guidance and procedures documentation (Responsible Personnel: PM)

- Ensure the documentation (practice guidance, trial and implementation procedures flowcharts etc.) are congruent with those agreed in Step 2.

Step 4: Implement on-boarding/training program with all clinic staff (Responsible Personnel: PM and Site nurses)

- Undertake group-based, face-to-face meetings with all participating clinicians (offering individual sessions to those who cannot participate in the group sessions)

During Trial:

Step 5: Clinical implementation of e-PROMs (Responsible Personnel: PM and Site nurses)

- Facilitate and implement clinical workflow
- Provide clinical support to maximise the uptake of agreed clinical workflows
- Maintain contact with Site PIs and key clinical champions to identify implementation issues and resolve them within an agreed time interval

Step 6: Periodic audit and review of RE-AIM outcomes (Responsible Personnel: Investigators, PM & PROMISE Team)

- Report to the Site PI, clinical champions and clinicians at agreed time intervals.
- Oversee the implementation process, monitor challenges and provide feedback and strategies to maximise intended implementation

Post-Trial:

Step 7: Facilitate maintenance beyond the trial (Responsible Personnel: Investigators and PM)

- Apply trial learnings to improve implementation of e-PROMs (this may be site specific)
- Facilitate the establishment of e-PROMS as a routine procedure at the clinics.

5.2 Usual care

Prior to commencing treatment, all participants will receive education regarding the possible side-effects relevant to their cancer type and treatment, as per standard care. They will attend their routine medical and supportive care appointments during treatment and follow-up, with regular medical reviews (by the treating oncologist) and nursing/allied health intervention at standard intervals depending on cancer type and treatment. As per standard care, any participants who experience treatment-related side effects will be advised to contact their treating nurse who will then directly manage the concerns or refer them to appropriate medical or allied health professionals.

5.3 Assessment of Participant Compliance

The e-PROM tools will capture information including (i) when and how often links were sent to participants to complete the tools; and (ii) if and when (prior to their clinic visit, in clinic) participants completed the tools. This will be used to assess patient compliance e.g. the proportion of times they completed the tool prior to their scheduled clinic visit. Usage data will also provide information about how often different types of healthcare provider accessed patient records in the system.

If participants do not complete the tool before arriving at clinic for follow-up the site nurses will encourage them to complete it when they arrive at the clinic, providing assistance if required. They will record (i) that the participant had not previously completed the tool; (ii) the reason(s) for this; and (iii) the level of persuasion/help required to help the participant complete the tool in the clinic. They will also encourage the participant to complete the tool prior to their next visit and, where possible, will address the reasons given for non-completion (e.g. if the participant did not receive the link).

6. STUDY SCHEDULE

6.1 Screening

The Trial Coordinator at each site will check the lists of patients scheduled to attend the participating clinics in order to identify those who meet the eligibility criteria (See section 4.1). At this time they will also ascertain whether the patient will need to be excluded because they will not return to the treatment centre, are participating in another conflicting study or are unlikely to be able to provide informed consent, do not have the physical or cognitive capacity to complete the e-PROM tool or would not be able to complete the Study Questionnaires in English. This information will be recorded on an eligibility checklist.

The Trial Coordinator will approach potential participants who pass these criteria when they attend their appointment and introduce the study to them. They will complete the eligibility checklist to confirm the patient does not meet any of the exclusion criteria and has appropriate internet access. Participants will then be invited to consent to participate in the study.

If a patient does not meet all of the criteria or they do not consent to participate in the study, their name will be retained in the database (accessible only to the Site Coordinator. This information will be deleted when recruitment is complete and only basic information will be accessible to the study staff.

6.2 Enrolment/Baseline (T=0)

When they consent to participate in the study, and prior to randomisation, participants will be sent a link to complete the Baseline Study Questionnaire (See Appendix D) on-line. If they do not complete this within 7 days they will be sent a reminder. If the questionnaire has still not been completed after a further 7 days, the participant will be withdrawn from the study. Participants who complete the Baseline Questionnaire and consented to provide a blood sample for the Genetic Substudy will also be asked to provide a blood sample (~20 ml).

6.3 Intermediate Time Points (T=3, 6, 12, 18 months)

Participants will not be required to make any specific visits for the study. At 3, 6 and 12 months (+ 18 months if funding is obtained for additional follow-up, see Section 3.4), all participants (Intervention and Control) will be sent a link and asked to complete the appropriate Follow-Up Questionnaire (Appendix D) on-line. If they do not complete this within 7 days they will be sent a reminder. If the questionnaire has still not been completed after a further 7 days, a project officer at QIMR Berghofer (who is blinded to the participant's study group) will call the participant and help them complete the questionnaire over the phone.

At 6 months, participants who consented to the Genetic Substudy will also be asked to provide a blood sample (~20 ml).

During the study, a subset of participants who consented to being contacted for an interview will be invited to complete an interview (in person, by telephone or videoconference) about their experience using the e-PROM tool (see Section 6.5). They will be free to decline if they no longer wish to do this.

6.4 End of Study (T=18/24 months)

When a patient's participation in the study is complete (at 18 months or 24 months if funding is obtained for additional follow-up, see Section 3.4) they will be asked to complete a final Questionnaire (Appendix D).

While the study is ongoing, participants in the Intervention group will be asked if they wish to continue to use the e-PROM tool after their active participation in the study is complete. At the end of the study, participants at PAH and RBWH will be able to continue to use the tool if they and their clinician want this. At TVH and GCH, use of the tools is currently only supported during the trial. Ongoing use beyond this will require the hospitals to enter into an agreement with PAH (for *My Health My Way*) or RBWH (for *AboutMe)*.

Patients randomised to the Control group will not routinely be offered the intervention when they complete their participation in the study to facilitate long-term follow-up of the groups for survival. If, however, participants become aware of the tool and wish to use it with the support of their treating clinicians, this will be facilitated.

At both 18 at 24 month time points, a subset of participants who consented to being contacted for an interview will be invited to complete an interview (in person, by telephone or videoconference) about their experience using the e-PROM tool (see Section 6.5). They will be free to decline if they no longer wish to do this.

When they complete their study participation, participants (or their next of kin) will be asked if they wish to receive a copy of the study results when these are available. Those who request this will be sent a summary of the main results, written in lay language, to coincide with the first formal presentation of the scientific results.

6.5 Stakeholder Interviews

Participants for the qualitative interviews will be selected for their unique knowledge and experiences in using/implementing the e-PROM tool/system. A sample of patients and partners or carers will be invited to take part in a one off, individual interview regarding their experiences using the e-PROM tool. In addition, healthcare workers involved with implementing the e-PROM system will be invited to participate in a one-off, individual interview. When they initially consent to the study, participants and partners/carers will be advised that they may be invited to participate in an interview but that they are not obliged to agree to this (see Appendix C: PICF and PICF-Carers). Healthcare providers invited to take part in interviews will be given a separate PIS explaining what this will involve. By agreeing to being contacted for the interview they will be providing implied consent and in addition, they will be requested to give verbal consent at the commencement of the interview.

Participants will be selected for interview based on maximum variation sampling. Maximum variation sampling is used when a broad range of participants is required and involves selecting information-rich cases to capture a broad range of perspectives. The following characteristics will be sought to achieve variation within the sample: role (patient, carer, health professional [medical, nursing, allied health); clinical site; cancer type. Recruitment will continue until a minimum of two participants who meet the criterion in each category is recruited. It is anticipated that approximately 30 participants will be required.

7. STUDY PROCEDURES AND EVALAUTIONS

7.1 Study Procedures/Evaluations

7.1.1 *Baseline*

After consent and prior to randomisation, participants will sent a link and asked to complete an on-line questionnaire (Appendix D) to provide information about: sociodemographic variables (e.g., education level, post-code of usual residence, marital and employment status, household income, private health insurance status, dependents/household structure) and their medical/health history (e.g. height, weight, existing comorbidities). This information will be captured using standard questions based on those used in the Australian census and/or used by the CI team in previous studies [31].

Participants who have consent to the Genetic Substudy and completed the baseline questionnaire will also be asked to provide a small sample of blood (approximately 20ml). As far as possible this will be collected when the participant is already having blood drawn; samples will either be collected at the hospital or participants will be given a blood collection kit containing the blood tubes and full instructions, to take to their local pathology lab. Samples will be collected in EDTA and PAXgene tubes and transferred to QUT where they will be stored at -80^{O}C.

7.1.2 *Follow-Up*

Participants will be asked to complete questionnaires (Appendix D) at 3, 6, 12, 18 and, if funding is obtained to continue follow-up to two years, 24 months after starting treatment. They will be emailed links to complete the questionnaires on-line and, if they do not complete them, a research officer at QIMR Berghofer who is blinded to the participant's group allocation, will telephone them to complete or help them complete the questionnaires over the phone.

At 6 months, participants who consented to the Genetic Substudy will also be asked to provide a second blood sample (approximately 20ml). As far as possible this will be collected at the hospital when the participant is already having blood drawn. Samples will be collected in PAXgene tubes and transferred to QUT where they will be stored at -80^{O}C.

7.1.3 *Clinical data*

Information about the participant's cancer (histology, grade and stage of disease at diagnosis), date of diagnosis, treatment (surgery, chemotherapy and radiotherapy doses and dates, side-effects experienced, response to treatment), recurrence of disease (basis of diagnosis, dates, treatment) and vital status (date and cause of death, if relevant) will be obtained from medical records at baseline and annually after this.

7.1.4 *Data linkage*

Participants will be asked to consent to linkage of their personal data to routine health-related data collections. Information about hospital admissions, emergency department presentations, procedures and prescriptions will be obtained via linkage to the Queensland Hospital Admitted and Non-Admitted Patient Data Collections (QHAPDC, QHNAPDC), the Emergency Department Information System (EDIS), the Queensland Cancer Registry and other linked data managed by the Queensland Cancer Control Analysis Team (QCCAT) (facilitated by our QCCAT collaborator Danica Cossio), and the national Medicare Benefits

Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and National Hospital Cost Data Collection (NHCDC) databases.

7.1.5 *Stakeholder interviews*

Individual, semi-structured interviews will be conducted either face-to-face or via tele/video conferencing by a researcher skilled in qualitative interview techniques. Participants will be encouraged to speak openly and to describe their experience using/implementing the e-PROMs tools/system. The interview guide will be informed by the CFIR Interview Guide Tool (https://cfirguide.org/guide/app/#/). Where appropriate, interview questions may be adapted, omitted and/or elaborated on an individual basis to encourage participants to reflect openly about their experience. On request, participants will have the opportunity to review their interview transcripts. It is anticipated that interviews will take no longer than 30 minutes). Following completion of interviews and data analysis, participants may be given an opportunity to comment on the researchers' interpretation of the data.

7.2 Laboratory Procedures/Evaluations

7.2.1 *Specimen Preparation, Shipping and Storage*

Blood samples will be identified by the participant's name, date of birth and study identification number. Following collection at room temperature and storage at $4^{O}C$ for up to 24 hours, a courier from the pathology collection centre or cancer clinic will deliver the participant's blood sample to laboratory technicians at QUT. Upon receipt of the blood sample, a laboratory technician will relabel each tube with the participant's unique identification number only and place it in a freezer storage box for storage at -80 degrees in preparation for DNA and RNA extraction and analysis. The storage position of each tube will be recorded. All paperwork including the documentation from the pathology collection centre and blood processing information such as the blood tube's storage position will be passed on to a research assistant who will enter this data into a secure database designed for this project. This will be stored on a secure drive and only accessible by study personnel. After the data have been entered, the documentation will be stored in a locked filing cabinet in a locked office and only accessible by study personnel.

8. ASSESSMENT OF SAFETY

8.1 Definition of an Adverse Event & Serious Adverse Event

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavourable and unintended sign, including an abnormal laboratory finding, symptom, or new or exacerbated disease) in a study participant, temporally associated with the use of an investigational product, whether or not it is considered related to the investigational product. A serious adverse event (SAE) is any untoward medical occurrence that results in death; is life threatening; requires hospitalisation or prolongation of an existing hospitalization; or results in persistent or significant disability/incapacity.

Any event, side effect, or other medical occurrence that is anticipated because of the normal course of treatment (standard care) is not considered an adverse event.

8.2 Relation to the study intervention

The proposed intervention does not have any known side effects or likely adverse events. There is a small possibility that participants might experience distress as they answer study questions relating to their symptoms, disease, or experience of care. While the research team is not expecting any distress caused specifically by this research, if a participant does suffer distress as a result of this trial, we will refer them to the relevant clinical team at their treating centre for appropriate action. We will also provide information on the free, confidential telephone information and support service run by the Cancer Councils in each state and territory (phone 13 11 20).

8.3 Recording and reporting of adverse events

AEs and SAEs will generally be clinical in nature and resolved according to usual medical procedures.

8.3.1 *Study sites*

All reported and observed AEs or SAEs that occur during the study must be recorded in the participant's case report form (CRF) and summarised on an AE log that will be reviewed by the site PI every 3 months. If necessary, they must also be notified to the participant's treating oncologist and/or GP (most information about AEs/SAEs will come from the clinician to study staff so notification will not be necessary).

SAEs and AEs potentially related to the intervention must also be reported to the Coordinating PI (or delegate) within 24 hours of becoming aware of the event.

It is the responsibility of the research team member who is initially made aware of the AE/SAE to complete the CRF and AE log, and, for events potentially related to the intervention, to report the information to the Coordinating PI.

8.3.2 *Coordinating PI*

The Coordinating PI will report all SAEs possibly related to the intervention to the Sponsor within 24 hours of first becoming aware of the event.

All AEs possibly related to the intervention must be reported to the Sponsor in a line listing at least every 3 months. On conclusion of data collection, a line listing of all AEs will be provided to the Sponsor.

8.4 Follow-up of adverse events and serious adverse events

Any AEs or SAEs potentially related to the intervention will be followed until resolution or the condition stabilises. The participant's oncologist and/or GP will be kept informed of the outcome of any follow-up for adverse events potentially related to the intervention. All other AEs and SAEs will be followed up by the participant's clinical team according to usual clinical care at that site.

9. STUDY OVERSIGHT AND MONITORING

Study oversight will be provided by the PROMISE Management Group which comprises the Chief Investigators who collectively have skills in managing large-scale research studies, clinical trials, clinical medicine, nursing and allied health, and consumer representatives.

The PROMISE Project Manager will conduct regular site visits to monitor the conduct of the study and will report back to the Principal Investigator and the PROMISE Management Group.

9.1 Curriculum Vitae

All Investigators signing the Protocol and all trial staff will provide a current, signed and dated Curriculum Vitae including name, title, occupation, education, research experience and present and former positions (AppendixE). A Staff Signature List is required.

10. STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

We hypothesise that, compared to usual care, routine self-reporting of e-PROMs will result in:

1. Primary Outcomes:
   - Fewer emergency presentations/unplanned hospital admissions;
   - Better physical and functional well-being at 6 months;
2. Secondary Outcomes:
   - Higher rates of treatment completion;
   - Better health-related quality of life (HRQOL);
   - Lower rates of distress;
   - Lower symptom burden;
   - Fewer out-patient visits;
3. Exploratory Outcomes:
   - A better patient care experience;
   - Better survival;
   - Lower rates of distress and unmet supportive care needs among partners/carers.

We also hypothesise that use of the e-PROM tools will be cost-effective compared to usual care.

10.2 Sample Size Considerations

Our sample-size has been calculated to achieve a minimum 80% power (a=0.05) for our primary outcomes.

- Emergency presentations (measured from linked data that will be close to complete): Previous studies have reported reductions of 17-30% ([9] and personal communication). Assuming a similar baseline rate (1.09/person-year), we require 242 participants per group to detect a 20% reduction with 18 months follow-up.

- HR-QOL: To detect minimally-important differences (where there is no defined minimally-important difference we have used 0.5 standard deviations as recommended [32] we require 70-150 patients per group depending on the outcome. A sample of 200 per group will give >90% power for the primary outcomes in the full population and ~80% power for analyses stratified by e-PROM tool.

Allowing for up to 30% drop-outs (death or withdrawal), we will recruit a minimum of 572 participants (286 per group). We estimate that more than 2000 eligible patients will attend the study hospitals during a 12-month period (data from the Queensland Oncology Analysis System) thus this target is feasible.

10.3 Statistical Analysis Plan

Data analysis will be guided by a formal statistical analysis plan that will be finalised prior to any analyses being conducted. All analyses will be intention-to-treat but compliance with the intervention will be assessed and, if there is substantial non-compliance, per-protocol analyses will also be performed. In exploratory sub-group analyses, we will also conduct analyses stratified by e-PROM tool, study site, gender, computer literacy, cancer type and cancer stage (early vs. advanced).

To preserve the blinding during preliminary analyses, the Data Manager will generate datasets with participants' true allocation code replaced by a random dummy code. This will

be replaced by the true code when we perform the final analyses (as in the D-Health trial [26]).

10.3.1 *Primary Outcomes*

Fewer emergency presentations/unplanned hospital admissions: we will use Poisson regression to calculate and compare the rate of unplanned hospital presentations (per 10,000 patient days) during follow-up in each group.

Better physical and functional wellbeing: we will calculate FACT-G physical and functional wellbeing scores at each time point. If there are missing items, subscale scores will be prorated as per the FACT-G scoring manual. We will compare mean scores in the two groups at 6 months using t-tests followed by general linear models to incorporate baseline covariates, including site, e-PROM tool, type of cancer, type of treatment (e.g. radio or chemotherapy). A difference of 0.5 standard deviations on each scale is considered clinically meaningful.

Differences at other time-points will also be assessed and we will explore changes over time and differences between treatment arms using a multilevel repeated measures model. The model for each post-randomisation point will be adjusted for baseline score and stratification factors.

10.3.2 *Secondary Outcomes*

Higher rates of treatment completion: we will calculate the fraction of planned primary treatment that participants actually received. We will compare the mean (or median, as appropriate) fraction received and the proportion of participants who received >85% of their planned treatment between the groups using t-tests and chi-squared tests, respectively.

Better overall HR-QoL, lower rates of distress and lower symptom burden: we will calculate overall FACT-G (to measure HR-QoL), HADS anxiety and depression (to measure distress) and MSAS (to measure symptom burden) scores at each time point. If there are missing items, subscale scores will be prorated as per the relevant scoring manuals. We will use t-tests to compare the intervention and control groups with respect to absolute levels at each time-point (with 6 months being the primary time-point) and will use mixed effects repeated measures models to assess change over time from baseline. The models for post-randomisation point will be adjusted for baseline score and stratification factors. A difference of 0.5 standard deviations on each scale is considered clinically meaningful.

We will also assess differences in social and emotional wellbeing using these subscales of FACT-G.

Fewer out-patient visits: we will use Poisson regression to calculate and compare the rate of unplanned hospital presentations (per 10,000 patient days) during follow-up in each group.

10.3.3 *Exploratory Outcomes*

Survival: we will calculate and the mortality rate (per person-year) in each group and use Cox proportional hazards regression to compare mortality in the two study groups.

A better patient care experience: the AHPEQS askes patients to rate 9 aspects of care on a 5-point scale from never (worst) to always (best) and their overall care from very poor to very good. We will use chi-squared tests to compare the proportions of participants in each group that answer mostly or always to each individual item (or good/very good to overall care) and t-tests to compare the mean number of items rated as mostly/always. We will also

compare the proportions of participants who report experiencing physical and/or emotional distress and, among those who report distress, the proportions who reported that healthcare staff discussed this with them.

Partner/Carer distress and unmet supportive-care needs: HADs data from carers will be analysed as for participants (above). Analyses of supportive-care needs will compare the frequency of individual needs and specific domains (information needs, healthcare needs, psychological and emotional needs, social and work needs). Parametric and non-parametric tests, as appropriate, will be used to compare the intervention and control groups.

Sub-group analyses: We will repeat the primary and secondary analyses above for sub-groups of participants defined by (i) study site, (ii) e-PROM tool (*My Health My Way* vs. *AboutMe*), (iii) cancer type (high vs. low mortality), (iv) type of treatment (curative/palliative), (v) sex, and (vi) computer literacy. This is to examine effect modification and identify scenarios where e-PROM tools are potentially most effective and those where their effectiveness could be improved. We recognise that statistical power will be more limited for some of these stratified comparisons.

10.3.4 *Genetic Analyses*

This study also seeks to obtain blood samples at baseline and 6 months to evaluate associations between genes, demographic and clinical characteristics and patient outcomes (e.g., HRQoL response/non-response, symptoms). While it is becoming increasingly clear that genetic variation plays a role in HRQoL and symptom experience, the current evidence is limited so investigators have called for the incorporation of biological data in new symptom science research [33]. By collecting and storing samples from PROMISE participants we will generate a valuable resource to answer questions about the association between genotype, gene expression and DNA methylation and HRQoL and symptom experience. These analyses (to be funded separately) will use the most up-to-date methods. They will help us to interpret the magnitude of the intervention effect and to identify possible reasons for heterogeneity in the outcomes of participants. We also hope the results will inform future development of personalised supportive care interventions that meet the varied individual needs of people with cancer. For example, the results may lead to the development of a prognostic test for whether an individual is likely to experience debilitating side effects from treatment. This information can then be used in treatment decision making as well as identifying those who may need greater supportive care or vigilance in disease monitoring.

10.3.5 *Implementation Outcomes:*

These analyses will be largely descriptive combining usage statistics and the results from the qualitative stakeholder interviews. The goal is not to prove superiority but to show that it is feasible for sites to implement the tools and to identify barriers and enablers to this. Interview transcripts will be analysed inductively and deductively through content analysis and using the Consolidated Framework for Implementation Research (CFIR) {Ref}, thereby enhancing our ability to explore reasons for successes and challenges to effective implementation. Coding will be performed with the assistance of the NVivo12 software program. To ensure rigour and agreement in the data, two researchers will code the transcripts independently and discuss any discrepancies. After all interviews have been coded, the analysis will be reviewed by a third researcher. Final results will be discussed between the three researchers involved in the analysis to reach consensus on data interpretation and major themes.

REACH & Representativeness: We will describe participation rates, compare the characteristics of the study population to state-wide statistics and describe factors associated with non-participation.

ADOPTION: We will describe patient, partner/carer and healthcare provider perspectives on the e-PROM tools and will assess their ease of use using the System Usability Scale.

IMPLEMENTATION: CFIR will allow a detailed exploration of the following implementation domains: Intervention Characteristics, Outer Setting, Inner Setting, Characteristics of Individuals, and the Process of Implementation. Within the intervention group, we will also calculate the total numbers and proportions of eligible e-PROMs completed prior to each medical appointment (N, %), the proportion of e-PROM items completed (%), the frequency of clinician access to e-PROM data (N, %), overall and by subgroups defined as above. We will also calculate the average length of medical appointments at the cancer centre and the rate (per patient-year) of GP and specialist visits made by participants and compare these across the intervention and control groups.

MAINTENANCE (Sustainability): We will calculate the proportion of the clinics, intervention participants, and clinicians using the e-PROMs at the end of the study, 6 months and 12 months after study completion. We will also assess whether the implementation of the e-PROM tools was cost-effective as this will be key for sustainability (See 10.3.6).

10.3.6 *Economic Outcomes:*

We will compare the costs and health benefits associated with the e-PROM intervention from the health system perspective. The health benefits will be: (1) quality-adjusted life years quantified using the EQ-5D (QALYs); and (2) hospitalisations avoided. Incremental cost-per-effect ratios will be generated which represent the additional cost and health benefits (QALYs, hospitalisations avoided) for the intervention, compared with usual care. Generalised estimating equations will assess both time and treatment effects and allow for non-parametric and missing data. Using the area-under-the-curve method and health utility scores at each time point, a single QALY for each person will be calculated at the last time point[34]. One-way and probabilistic sensitivity analyses to address data uncertainty will be performed using TreeAge Pro for Healthcare (TreeAge Software Inc). We will consider a Markov microsimulation model informed by our clinical data.

11. ETHICAL CONSIDERATIONS

11.1 Ethical Standards

The investigators will ensure that this study is carried out according to the Declaration of Helsinki,[3] and the NHMRC National Statement on Ethical Conduct in Human Research (2018).[4]

11.2 Ethical Review

The Protocol and all relevant documents will be submitted for approval to the PAH HREC (the lead HREC), for waiver of review by QIMR Berghofer, QUT and UQ HRECs, and to the Governance Offices at the four participating sites. Written approval will be obtained before participants are enrolled. If approval is suspended or terminated at any site, the Principal Investigator will notify the PAH HREC immediately.

It is the responsibility of the Investigator to report study progress, including a safety report, to the HREC as required or at intervals not greater than one year. Informed Consent

Before enrolment into the study, each prospective candidate will be given a full explanation of the nature and purposes of the study, and a copy of the PICF (Appendix C) to review. The site nurse will explain (either in person, telephone or web-based communication such as skype or face time) the nature of the study, its purpose, procedures, expected duration, and the potential benefits, risks and inconveniences in participation. Once the essential study information has been provided, and the Investigator is assured that the individual understands the implications of participating in the study, they will be asked to give consent to participate in the study by signing and dating the Consent Form. A note that written informed consent has been obtained will be made on the participant's CRF. The completed consent form will be retained by the Investigator and a copy will be given to the participant.

11.3 Blood Sampling & Communication of Genetic Results

Participants will be asked to provide a blood sample at baseline and 6 months for future genomic analyses to evaluate associations with the study outcomes (e.g., symptoms, HRQoL, survival). Participants do not have to provide a blood sample to participate in the main PROMISE study. This part of the study is exploratory and aims to identify possible markers of HRQoL and symptom experience in this cohort.

This study will not measure known markers of disease risk so there is a low risk of identifying information that is important for participants' or other family members' health. The findings will also have no health significance to an individual participant as they already know their outcomes (e.g. symptom experience, HRQoL). Any findings from this work would need to be validated by future research before diagnostic tests for such outcomes could be developed thus any findings of potential genetic predictors of poorer outcomes would have no impact on current clinical care decisions for patients or their relatives. This part of the project is very unlikely to benefit participants or their relatives directly and the results will not be communicated with participants individually.

Although the results of the planned genetic analyses will not be communicated with participants individually there is one exception when genetic information may be communicated with participants via their nominated medical contact. In future, new markers of disease may be identified thus it is possible, although unlikely, that we may discover such information inadvertently during our genetic research. Information about a medically-

significant genetic variant may have nothing to do with a participant's reasons for taking part in the study and may involve a completely different genetic condition. Some people find the news that their family has a genetic condition to be distressing and may not wish to know that it could be present in themselves, or other family members. Participants will, therefore, be able to choose whether or not they wish to receive information about any potentially significant genetic variants. If they wish to receive this information, they will need to confirm this on their consent form when consenting to the genetic analyses. Participants will also need to nominate a medical doctor who will receive a report about what is discovered, and will pass the information back to them. A medical doctor must be involved so that the participant can be fully informed of the implications of the genetic result on their health and that of their family. Analyses will be conducted within the Genomics Research Centre at QUT and this also operates a diagnostic clinic and so can facilitate contact between the participant's doctor and specialist counsellors and geneticists who will assist in the management of any condition that is identified. Participants will also be informed that some forms of health insurance or employment might require them to reveal any results of this research that are returned to them, or whether or not they have undergone testing of any kind for a known genetic condition.

For participants who decide to provide a blood sample, there are only minimal risks (e.g. some participants may experience minor bruising or discomfort in their arm) associated with having blood taken by a trained phlebotomist. The sample will in most cases be taken during routine blood collection as part of usual follow-up care at a cancer clinic and therefore it does not pose any additional risk to the participant. If this is not possible, the blood collection will take place at a time and pathology centre convenient to the participant at no cost to the participant. The phlebotomist will take a small sample of blood (approximately 20mL) from the participant at baseline and 6 months. The blood samples will be transported to the Genomics Research Centre at QUT for processing and storage and will be used for approved projects to evaluate genetic associations with patient outcomes (e.g. HRQoL, symptom experience).

11.4 Protocol Amendments

Neither the Site PI nor the Coordinating PI may modify the Protocol without first obtaining the agreement of the other party in writing. No amendments to the Protocol may be implemented without prior approval of PAH, QIMR Berghofer and other appropriate HREC(s). If a Protocol amendment requires changes to the PICF, the revised PICF must be approved by the PAH, QIMR Berghofer and appropriate site HREC(s) prior to use.

It is the responsibility of the Principal Investigator to submit the amendment to the HRECs for their approval; written approval should be obtained and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority must be notified of the Protocol change. Completed and signed Protocol amendments will be circulated to all those who were on the circulation list for the original Protocol. Any training that is required by the amendment must be provided to study staff by the Principal Investigator.

The original signed copy of amendments will be kept in the Study File with the original Protocol. Where an amendment to the Protocol substantially alters the study design or the potential risks to the participants, each participant's consent to continue participation should be obtained.

11.5 Protocol Deviations

All protocol deviations and reasons for them must be recorded on the CRF and must be reported to the Principal Investigator as soon as is reasonably practicable and within 7 days of first becoming aware of the deviation. Protocol deviations will be assessed for significance by the Principal Investigator and any deemed to have a potential impact on the integrity of the study results or the ethical acceptability of the trial will be reported to the HREC. Where deviations to the protocol identify issues for protocol review, the protocol may be amended as per section 11.5.

11.6 Retention of Other Study-Specific Samples

Blood samples will be kept securely at QUT. The samples and genetic material will be given a unique identification number and the participant's name will be removed to protect their privacy. Data will be stored securely and only authorised persons, who understand it must be kept confidential, will have access to it.

Samples will be retained beyond the end of the main trial (with update HREC approval as required) as the genetic analysis will continue after this. When no further projects are planned, the samples will be destroyed as per NHMRC and QUT guidelines.

12. DATA HANDLING, RECORD KEEPING AND PUBLICATION POLICY

12.1 Data Management Responsibilities

The study database will be maintained at QIMR Berghofer. Personal information will be kept separate from questionnaire data and access will be restricted to authorised project staff. Questionnaire data will be stored by study ID with no personal information attached and will be made available to approved project staff for analysis.

Information about the blood samples (study ID number, date of collection and processing etc.) will be stored securely at QUT. This will not include any information that would allow the lab to identify individual participants.

12.2 Access to Source Documents/Data

Source data include all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, and pharmacy dispensing records. Study staff will maintain appropriate medical and research records for this study (consistent with Good Clinical Practice), and regulatory and institutional requirements for the protection of confidentiality of participants.

Each participating site will maintain appropriate medical and research records for this study. Each site will permit authorised representatives of QIMR Berghofer to examine research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity. Upon request, the Investigators and Institutions will permit direct access to source data/documents for trial-related monitoring, audits, HREC review, and regulatory inspection(s) by the Sponsor (or their appropriately qualified delegate) and regulatory authorities. Direct access includes examination, analysis, verification and reproduction of records and reports that are important to the evaluation of the trial.

12.3 Data Confidentiality

All study participants will be assigned a unique identifier and all information collected from participants will be treated with strict confidentiality. Data will be stored in a secure environment (electronic controlled access buildings, locked filing cabinets and password protected computer files) at QIMR Berghofer. Tracking data, which will contain participant identifying details, will be stored separately from all other information and only be accessible to the Principle Investigator and designated study staff who need access to the information to manage participants during the study. All other data will be identified only by the participant's unique identifier and accessible only to approved researchers involved in this study.

Information about the blood samples (study ID number, date of collection and processing etc.) will be stored securely at QUT. This will not include any information that would allow the lab to identify individual participants.

QIMR Berghofer or regulatory or health authorities may review medical records of study participants for validation or audit purposes or to ensure compliance with this protocol but QIMR Berghofer will not disclose the identity of any research participant to a third party, unless permitted or required by law.

12.4 Data Capture Methods

Data capture methods will include:

- On-line questionnaires: Participants and participating partners/carers will be sent unique electronic links to allow them to complete the Study Questionnaires on-line. The data-entry interface will include in-built checks and prompts to maximise data quality and minimise missing data.

- Telephone interviews with participants and participating partners/carers: *these will only be required if the Study Questionnaires have not been completed on-line and/or the participant needs assistance*. A Research Assistant (blinded to the participant's group allocation) based at QIMR Berghofer will call relevant participants and either help them to complete the questionnaire or complete it with information by entering the information directly into the study database.

- In-person, telephone or videoconference interview with participants (patients, partners/carers and healthcare providers): to capture qualitative information about experience using the tools. These interviews will be recorded and transcribed at the end of the study by a professional transcriber.

- Clinical information from medical records: where possible, this will be entered directly into the study database via an interface that will include in-built checks and prompts to maximize data quality and minimise missing data. If direct entry is not possible, the information will be recorded onto a paper CRF by the site nurse and entered into the database as soon as possible after this. The paper record will then be shredded.

- Other health-related information will be obtained electronically via linkage to routine data collections and the e-PROM systems. An electronic list of study participants with key identifying information (e.g. name, date of birth, address, URN number) will be sent securely to the relevant data custodian who will return the resulting linked dataset according to their established protocols. Data transfer will be performed with assistance from QIMR Berghofer IT Department and following requirements of the various Data Custodians to ensure all electronic transfer of electronic data is secure.

12.5 Types of Data

Data collected will include:

- Personal information to identify participants, facilitate tracking of participants and allow linkage to other health databases; this will be stored securely and separate from all other information.

- Participant responses to questionnaires and interviews; these will be stored securely and identified only by study ID number.

- Clinical information collected from medical records; this will be stored securely and identified only by study ID number.

- Other health-related information obtained via linkage to routine data collections; this will be stored securely and identified only by study ID number.

12.6 Study Record Retention

All study related documents and records will be retained for a minimum of fifteen years after trial completion. Paper records will be stored in locked filing cabinets at QIMR Berghofer with access restricted to designated project staff. Electronic records will be stored securely in password protected files on QIMR Berghofer servers with appropriate back-up. Personal information (e.g. contact information, consent forms) will be stored separately from all other study information. Written agreement from the Sponsor will precede destruction of documents or records. When disposed of, paper records will be shredded and electronic records deleted with assistance from QIMR Berghofer IT Department.

12.7 Publication Policy

A publication policy will be developed and approved by the investigators before the data analysis begins.

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency and in accordance with QIMR Berghofer's Policy on Criteria for Authorship. Publication of results will be subjected to fair peer-review. Authorship will be given to all persons providing significant input into the conception, design, execution or reporting of the research according to QIMR Berghofer Policy on the Criteria for Authorship. No person who is an author, consistent with this definition, will be excluded as an author without their permission in writing. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation. All conflicts arising through disputes about authorship will be reviewed by the QIMR Berghofer Director. Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organisations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with QIMR Berghofer's Corporate Media Strategy Policy.

13. LITERATURE REFERENCES

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14. LIST OF APPENDICES

14.1 Appendix A: Schedule of Events

14.2 Appendix B: RE-AIM Planning Approach to Enhance Translation

14.3 Appendix C: Patient Information and Consent Forms

14.3.1 ***Master PICF***
PROMISE PICF_Master_V1.1_2020-09-22

14.3.2 ***Medicare Consent Form***
PROMISE PICF_Medicare_V1.1_2020-09-22

14.3.3 ***Medicare Withdrawal Form***
PROMISE_Medicare_Withdrawal_V1.0_2020-09-22

14.3.4 ***Genetic PICF***
PROMISE PICF_Genetic_V1.1_2020-09-22

14.3.5 ***Carer PICF***
PROMISE PICF_Carer_V1.1_2020-09-22

14.3.6 ***Healthcare PICF***
This component of the study will not begin until 2023. We will submit the PICF for ethical review prior to commencing.

14.4 Appendix D: PROMISE Questionnaires

14.4.1 ***Participant Questionnaire: Text of questions for on-line interface***
PROMISE Questionnaire_V1.0_2020-08-06

14.4.2 ***Carer Questionnaire: Text of questions for on-line interface***
PROMISE Questionnaire-Carers_V1.0_2020-08-06

14.5 Appendix E: Curriculum Vitae

APPENDIX A: SCHEDULE OF EVENTS

	T0	T3	T6	T12	T18	T24	>T24
Informed study consent	✓						
MBS/PBS data consent	✓						
Carer & Genetic Substudy consent	✓						
Medical history/co-morbidities	✓						
Cancer diagnosis/treatment	✓						
Intervention (Intervention Group only)							
Blood sample	✓		✓				
Collect clinical data	✓			✓		✓	✓
QUESTIONNAIRES							
Demographics (Participants & Carers)	✓						
FACT-G (Participants)	✓	✓	✓	✓	✓	✓	
HADS (Participants & Carers)	✓	✓	✓	✓	✓	✓	
MSAS (Participants)	✓	✓	✓	✓	✓	✓	
EQ-5D (Participants & Carers)	✓	✓	✓	✓	✓	✓	
Patient Experience (AHPEQS) (Participants)			✓	✓	✓	✓	
System Usability Survey (Participants)			✓				
Supportive Care Needs Survey (Carers)	✓	✓	✓	✓	✓	✓	
QUALITATIVE INTERVIEWS							
Participants & Carers					✓		
Clinicians					✓		✓
DATA LINKAGE							
Health resource utilisation				✓		✓	✓

APPENDIX B. RE-AIM PLANNING APPROACH TO ENHANCE TRANSLATION

Dimensions for Dissemination	Questions to Ask of Potential Programs	Strategies to Enhance Future Translation and Dissemination
Reach (individual level)	• What percentage of the target population would come in contact with your program? • Will you reach the most needy? • Will research participants reflect the targeted population?	• Formative evaluation with potential users and nonusers • Small-scale recruitment studies to enhance methods • Identify and reduce participation barriers • Use multiple channels of recruitment
Effectiveness (individual level)	• Will the intervention likely affect key targeted outcomes? • What unintended adverse consequences may occur? • How will impact on quality of life be assessed?	• Incorporate tailoring to individuals • Reinforce messages via repetition, multiple modalities, social support and systems change • Consider stepped care approaches • Evaluate adverse outcomes and quality of life for program revision and cost-to-benefit analysis
Adoption (setting or organizational level)	• What percentage of target settings and organizations will use the program? • Do organizations include high-risk or underserved populations? • Does program fit with organizational goals and capacities?	• Conduct formative evaluation with adoptees and non-adoptees • Recruit settings that have contact with the target audience • Develop recruitment materials outlining program benefits and required resources • Provide various cost options and customization of the intervention
Implementation (setting or organizational level)	• Can different levels of staff successfully deliver the program? • What proportion of staff within a setting will agree to program delivery? • What is the likelihood that various components will be delivered as intended?	• Provide delivery agents with training and technical assistance • Provide clear intervention protocols Consider automating all/part of the program • Monitor and provide staff feedback and recognition for implementation
Maintenance (individual and setting levels)	• Does the program produce long-term individual behavior change? • Will organizations sustain the program over time? • What are characteristics of persons and settings showing maintenance?	• Minimize level of resources required • Incorporate “natural environmental” and community supports • Conduct follow-up assessments and interviews to characterize success at both individual and setting levels • Consider incentives and policy supports