FULL/LONG TITLE OF THE TRIAL

Multi-centre, randomised controlled trial of Vinehealth® digital health cancer solution for cancer patients commencing chemotherapy

SHORT TRIAL TITLE / ACRONYM

Randomised controlled trial of Vinehealth® digital health cancer solution /CTU-58

The Vinehealth® Digital App is being developed in accordance with the NICE MTEP guidelines. This document helps meet some of these guidelines and the results from this trial may help Vinehealth with their endeavours in fulfilling the requirements. The Vinehealth® Digital App will also be registered at HealthTech Connect

DOCUMENT VERSION NUMBER AND DATE Final Version 1.6 6th July 2023

The purpose of this document is to express the clinical investigation plan for the device described below.

The content of this document is based on the requirements of the relevant regulations, standards and guidelines as listed under Document References, above:

· United Kingdom Medical Device Regulation [UK MDR]

· European Union Medical Device Regulation (21CFR812)

· BS EN ISO 14155:2020

· BS EN ISO 14971:2019

· MHRA submission guide

· MHRA statistical considerations guide

FUNDER - UKRI-Innovate UK - Biomedical Catalyst 2020

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RESEARCH REFERENCE NUMBERS

IRAS Number:	300753
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SIGNATURE PAGE

The undersigned confirm that the following document has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved document and will adhere to the principles outlined and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.
I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this document will be explained.

For and on behalf of the Trial Sponsor:

Signature: P. Huckle

Date: 21 July 2023

Name (please print): Paula Huckle

Position: RIGO Manager

Chief Investigator:

Signature: Agnieszka Michael

Date: 6th July 2023

Name: (please print): Agnieszka Michael

Statistician:

Signature:

Date: 6th July 2023

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LIST OF ABBREVIATIONS

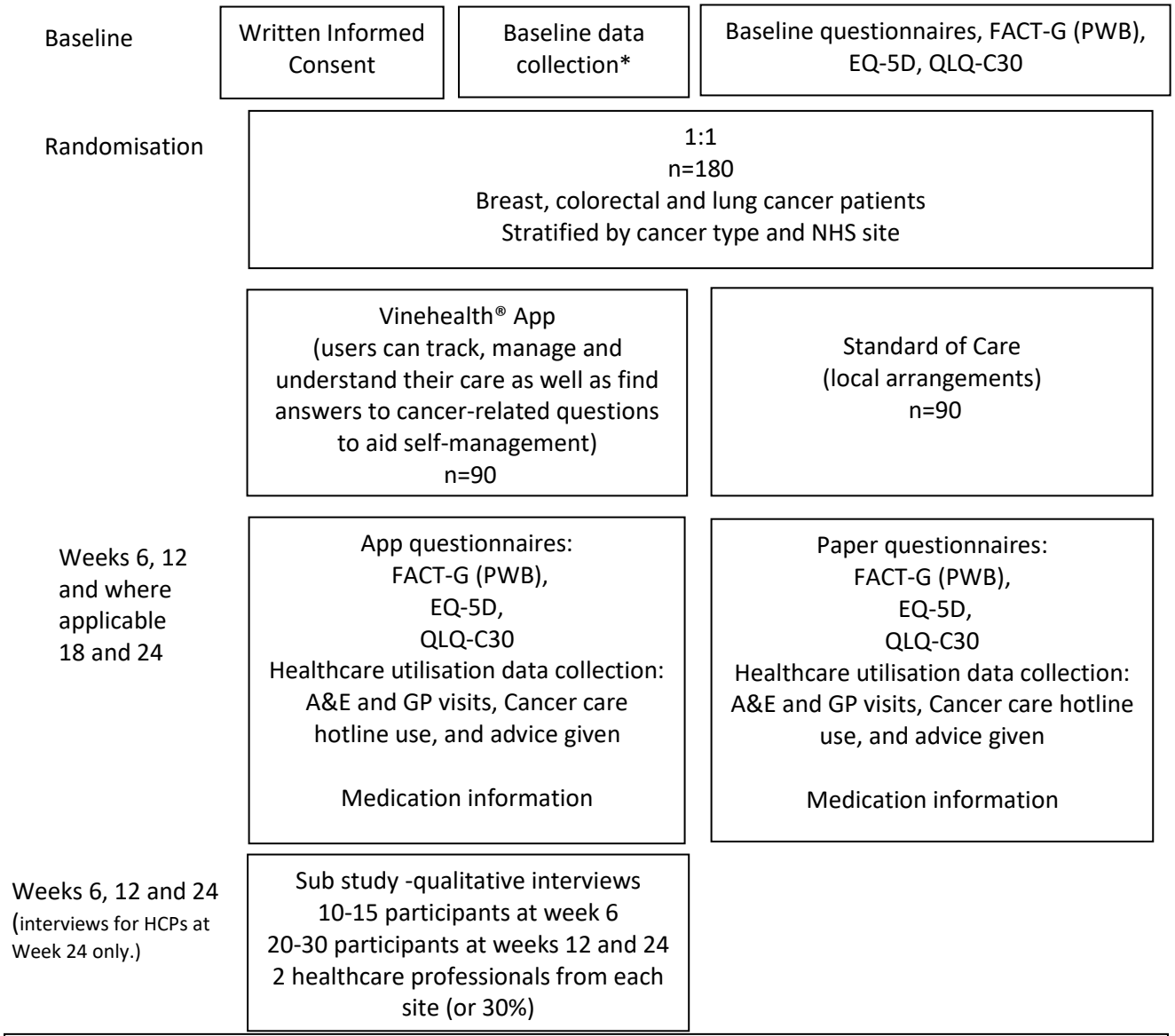
AE	Adverse Event
AI	Artificial Intelligence
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
FSCA	Field Safety Corrective Action
FSN	Field Safety Notice
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IFU	Instructions for Use
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
MHRA	Medicines and Healthcare products Regulatory Agency
MIR	Manufacturer Incident Report
ML	Machine Learning
NHS	National Health Service
PI	Principal Investigator
PIS	Participant Information Sheet
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	Randomised Controlled Trial of Vinehealth® Digital Health Cancer Solution	
Internal ref. no. (or short title)	CTU-58/Vinehealth	
Trial Design	Multi-centre two-arm parallel group randomised controlled trial	
Trial Participants	Colorectal, breast and lung cancer patients commencing adjuvant systemic treatment	
Planned Sample Size	180	
Intervention duration	12-24 weeks for each participant	
Planned Trial Period	July 2022-Nov 2023; recruitment to 31 July 2023 and 3-6 months follow-up during intervention	
Objectives		Outcome Measures
Primary	Undertake sufficiently large RCT to provide robust evaluation of claims that Vinehealth®'s digital platform (the app) can effectively: Demonstrate improvement in quality of life over standard of care by use of the platform	Health-related QoL; measured by FACT-G (PWB) over 12-24 weeks, at 6/12 and 18/24 weeks **The primary outcome will be determined at 12 weeks**, with data up to 24 weeks contributing to key secondary analyses.
Secondary	1. a. Improve patient compliance with PRO data collection b. Improve patient self-management of symptoms indicated via global quality of life (QoL) 2. Improve process of care and reduce emergency healthcare utilisation	1. a. FACT-G (PWB), EQ-5D-5L and EORTC QLQ-C30 at 6/12 and 18/24 weeks b. EQ-5D-5L and EORTC QLQ-C30 at 6/12 and 18/24 weeks 2. Medication adherence, A&E/GP visits/admissions. Acute oncology hotline utilisation, concomitant medications
Exploratory	To assess for those randomised to the Vinehealth® App: 1. Platform engagement 2. Patient and clinician views/opinions through semi-structured qualitative interviews	1. App/PRO platform usage data 2. Qualitative assessment tool
Device Name	Vinehealth® Cancer Companion & VinehealthPRO®	

Intervention	Patients will be randomised to the Vinehealth App or the standard of care. All patients will be asked to complete the FACT-G (PWB), EQ-5D-5L and EORTC QLQ-C30 at 6/12 and 18/24 weeks while the study remains open. At both weeks 12 and 24, 20-30 patients who have been randomised to the Vinehealth App will be asked to take part in the qualitative interview sub study and will be asked to participate in the remote interviews regarding the experience of using the app. In addition, a minimum of 2 healthcare professionals will be interviewed from each site (or 30%), depending on which is more. We will also speak to 10 - 15 patients around the 6-week timepoint in the study to gather qualitative feedback.
Manufacturer Name	Vinehealth® Digital Limited
Principal intended use	Cancer companion app allowing patients to easily report and monitor their symptoms, medication, and activity levels
Length of time the device has been in use.	CE mark applied in May 2021 (N.B the device is already CE marked so this is not a pre-market clinical investigation, rather a post-market clinical follow-up study of effectiveness per the objectives above.)

TRIAL FLOW CHART



Primary outcome measure: Health-related QoL measured by FACT-G (PWB) at 6/12 and 18/24 weeks.
Secondary outcome measures:

1. Patient compliance with PRO data collection; FACT-G (PWB), EQ-5D and EORTC QLQ-C30 at 6/12 and 18/24 weeks.
2. Patient self-management of symptoms indicated via global quality of life (QoL); EQ-5D and EORTC QLQ-C30 at 6/12 and 18/24 weeks.
3. Process of care and reduction in emergency healthcare utilisation; Medication adherence, A&E/GP visits/admissions, Acute oncology hotline utilisation, concomitant medications

Exploratory outcomes:

1. Platform engagement via App/PRO platform usage data
2. Collect patient and healthcare professionals' views through semi-structured qualitative interviews/focus groups

*Cancer diagnosis, cancer stage, type of cancer, concomitant medication, chemotherapy plan and treatment to date

1. BACKGROUND

Cancer care burden is growing; 1 in 2 people now develop cancer in their lifetime [1]. >2.5million in the UK were living with cancer in 2015 [2,3], reaching 4million by 2030 [4]. 44million are living with cancer worldwide [5]. Global cancer therapeutics spending reached £116 billion (2018), expected to reach £155-178billion by 2024; CAGR 11-14% [6].

Within cancer care generally, there is major unmet demand for personalisation, to improve patient self-management and Quality of Life (QoL) [7,8]. These are crucially important as rising survival means many patients remain on long-term toxic treatments for >10 years [9]. The NHS Cancer Taskforce reports improving cancer QoL through personalisation could mean 30,000 more patients/year surviving cancer for >10 years [10]. The National Cancer Survivorship Initiative finds cancer patients are not sufficiently supported as individuals to manage their treatment [11]. The NHS Long-Term Plan demands that all cancer patients should have access to personalised care, including health and wellbeing assessment, information and support, by 2021 [12]. 99% of cancer care experience occurs outside clinical environments [13], so this support must be available remotely, especially given the COVID-19 pandemic.

There is no effective solution yet to deliver scalable personalised cancer care. Vinehealth® uniquely provides a digital ecosystem comprising app, integrated wearables and central platform delivering personalised patient support. Initial pilot study data (including from UK's leading cancer centre, Royal Marsden) already demonstrate its patient benefits.

The proposed Randomised Controlled Trial (RCT) is needed to robustly evidence the clinical improvements.

2. RATIONALE

Global cancer deaths are projected to increase 45% by 2030[14]. Rising survival means many patients remain on long-term toxic treatments for >10 years, so improving QoL for cancer patients is crucial [15]. This presents an urgent and growing need for personalised tools to support cancer patient self-management and data collection to enable monitoring and remote follow-up [7,8].

Currently, patient information and support is dispersed, inaccessible and poorly personalised [15]. The majority of patients receive written information and a brief session with a doctor or a specialised nurse to explain the side effects of chemotherapy and the schedule of treatment. The management of side effects varies between the care providers with some hospitals offering access to a 24hr chemotherapy hotline and other hospitals providing only 9-5 hrs advice. Macmillan's Cancer Patient Experience Survey (2020) reported 39% patients stated treatment side-effects were not explained in a way they could understand [16]. 44% were not offered individual information and support in dealing with side-effects [17]. Macmillan reported that GPs are not able to take on this care, given workforce pressures [18].

Vinehealth® is a highly innovative solution meeting these unmet needs. Vinehealth®'s digital platform combines behavioural science and AI to improve cancer patient experience, care delivery and clinical outcomes. Vinehealth®'s patient-facing mobile app collates information from partners across the cancer ecosystem, deploying Machine Learning (ML) driven personalised support to enable better self-management of medications, side-effects, symptoms and lifestyles, seamlessly integrating with smartphones and wearables.

Vinehealth® brings all this information and support together to deliver an urgently needed single route through which patients receive care and information personalised to them, improving their care experience, self-management and ability to log and transfer patient-reported outcome (PRO) data to clinicians. PRO data collection confers up to 20% increased survival by improving self-management and allowing clinicians to see, pre-empt and rapidly address clinical deterioration [19].

Vinehealth® achieves personalisation using algorithms that distribute information based on type and severity of symptoms reported. It also uses Artificial Intelligence (AI) to analyse user app interactions in a "recommender system" similar to that used by Netflix, making recommendations based on user requirements and choices. Vinehealth® uses this to generate personalised behavioural nudges, evidence-based educational materials and psychological support.

3. OBJECTIVES AND OUTCOME MEASURES

The project objectives are to undertake sufficiently large RCT to provide robust evaluation of claims that Vinehealth®'s platform can effectively:

1. Demonstrate improvement in quality of life over standard of care by use of the platform
2. a. Improve patient compliance with PRO data collection
   b. Improve patient self-management of symptoms indicated via global quality of life (QoL)
   c. Improve medication adherence
3. Improve process of care and reduce emergency healthcare utilisation

3.1 Primary Objective

This trial will compare the intervention, the Vinehealth® digital app with standard of care, vs standard of care alone in this randomised controlled trial. The aim of the digital app is to bring together information and support for dealing with issues, such as side effects of chemotherapy, to deliver an urgently needed single route through which patients receive care and information personalised to them. Thus, improving patients' care experience, self-management and providing the ability to log and transfer patient-reported outcome (PRO) data to clinicians. PRO data collection confers up to 20% increased survival by improving self-management and allowing clinicians to see, pre-empt and rapidly address clinical deterioration.
The primary objective is to see if it is possible to undertake a sufficiently large enough RCT and provide robust evaluation claims that Vinehealth®'s digital platform (the app) can effectively demonstrate improvement in quality of life over standard of care alone by use of the platform. This will be measured using health-related QOL measured by FACT-G (PWB) over 12-24 weeks.

3.2 Secondary Objectives

The secondary objectives are to determine whether use of the Vinehealth® app:

- improves patient compliance with PRO data collection, medication adherence and self-management of symptoms.
- improves patient process of care and reduces emergency healthcare utilisation.

3.3 Outcome Measures/ Endpoints

Primary endpoint/outcome

Changes from baseline in the FACT-G (PWB) over 12/24 weeks; FACT-G (PWB) being measured at 6/12 and 18/24 weeks.

The primary outcome will be determined at 12 weeks.

Secondary endpoints/outcomes

1. a. Completion rates of FACT-G (PWB), EQ-5D and EORTC QLQ-C30 at 6/12 and 18/24 weeks.
   b. Global quality of life indicated by EQ-5D and EORTC QLQ-C30 at 6/12 and 18/24 weeks.

2. Process of care and reduce emergency healthcare utilisation; measured by medication adherence, A&E/GP visits/admissions, acute oncology hotline utilisation, concomitant medications

Exploratory endpoints/outcomes

The primary and secondary objectives of the study will be strengthened by consideration of the following exploratory outcomes.

1. Platform engagement via App/PRO platform usage data collected by Vinehealth®
2. Qualitative semi-structured interviews. A subset of clinicians (a minimum of 2 healthcare professionals from each site or 30% of healthcare professionals from each site depending on which is more) and 20 - 30 participants will be asked to take part in remote qualitative interviews to gather information on their experience dealing with the digital app versus standard of care, addressing quality of life, process of care and healthcare utilisation. The interviews will last no longer than one hour.

3.4 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the intervention, the Vinehealth® digital app with standard of care, vs standard of care alone on QoL	Health-related QoL FACT-G (PWB) will be collected at baseline, then 6, 12, and 18, 24 weeks.	Measured by changes in the FACT-G (PWB) from baseline to 6/12 and 18/24 weeks. The primary outcome will be determined at 12 weeks, with the data to 24 weeks providing a key secondary outcome
Secondary Objectives	1. Improve patient compliance with PRO data collection 2. Improve patient self-management of symptoms indicated via global quality of life (QoL)	1. FACT-G (PWB), EQ-5D and EORTC QLQ-C30 at 6/12 and 18/24 weeks. 2. EQ-5D-5L and EORTC QLQ-C30 at 6/12 and 18/24 weeks. 3. Medication adherence, A&E/GP visits/attendance

	3. Improve process of care and reduce emergency healthcare utilisation	Acute oncology hotline access, concomitant medications throughout the trial intervention period of 12/24 weeks
Exploratory Objectives	1. Platform engagement 2. Patient and clinician views/opinions through semi-structured qualitative interviews	1. App/PRO platform statistics over 12/24 weeks 2. Interviews with selected individuals

4. TRIAL DESIGN

This multi-centre randomised controlled two-arm parallel group trial is being conducted in several sites in the UK and will aim to recruit 180 people to evaluate the impact of the use of the Vinehealth® app to help manage symptoms and side effects and hopefully improve the quality of life of people with Breast, Colorectal or Lung Cancer. This is for patients who have just had surgery and are about to commence adjuvant chemotherapy for the cancer treatment. Participation for each patient will last for a minimum of twelve weeks (the primary endpoint) and a maximum of twenty-four weeks.
The aim of the trial is to determine whether the use of the Vinehealth® app is effective in encouraging completion of patient reported outcome (PRO) measures through questionnaires and is better or worse than local standard of care in supporting the self-management of chemotherapy related symptoms to help improve quality of life in the 12-24 weeks from starting chemotherapy.

5. TRIAL SETTING

5.1 Sites

Sites will be agreed prior to the start of the trial and the intention will be to use these sites only. If there are issues at any site(s) then other sites may be approached and their suitability for participation will be assessed by the Trial Steering Committee.

Once a site has obtained the necessary local approvals, following approval for the trial, they will be invited for trial-specific training which will cover all aspects of the trial. Once Surrey CTU and collaborators have performed this training and are satisfied that all documentation is in place they will give the site the green light to open to recruitment. The site is then able to approach participants and begin the informed consent process.

5.2 Participants

180 colorectal, breast and lung cancer patients commencing adjuvant systemic treatment (chemotherapy+/-targeted therapies or immunotherapy) will be enrolled into a prospective, multi-centre two-arm parallel group RCT over 12-24 weeks. Patients starting chemotherapy will be recruited across several clinical sites from outpatient oncology clinics and monitored for 12-24 weeks in total. All patients will be randomised 1:1 using an online randomisation service (SealedEnvelope.com) to minimise allocation bias to (a) current

standard of care or (b) current standard of care plus addition of Vinehealth® platform. Randomisation will be stratified by centre and cancer type. They will approach patients who are attending outpatient oncology clinics. These patients will have had surgery and will be due to commence adjuvant chemotherapy +/- targeted therapies or immunotherapy for the treatment of their primary cancer.

6. PARTICIPANT ELIGIBILITY CRITERIA

Patients with breast, colorectal and lung cancer who have just had surgery for their primary cancer and are about to commence adjuvant chemotherapy as part of their treatment will be approached in oncology clinics to see if they would like to participate.

6.1 Inclusion criteria

- Adult (age >=18 years) commencing adjuvant cytotoxic chemotherapy (+/-targeted therapies or immunotherapy) at participating site for minimum planned duration of 12 weeks, patients with breast cancer who require neoadjuvant chemotherapy for 12 weeks and have no cancer-related symptoms are also eligible
- Breast, colorectal or lung cancer diagnosis
- Primary disease completely excised (residual macroscopic disease allowed <2cm) for patients receiving adjuvant treatment
- Smartphone access that conforms to the following specifications:
  - Apple devices running iOS 12.5 (or later) or devices running Android 7.0 (or later).
  - Screen size of at least 4.7 inches (equivalent to an iPhone 6).
  - Reside in Great Britain
- Able to read and write in English (Information will be provided in the Welsh language if requested for the Welsh site)
- Able to provide informed consent

6.2 Exclusion criteria

- Systemic anti-cancer treatment to palliate incurable cancer for this malignancy (residual disease > 2cm)
- No longer undergoing systemic therapy
- No smartphone access
- Unable to read or write in English
- Significant cognitive impairment

7. TRIAL PROCEDURES

Following provision of written informed consent to join the trial, participants will be asked to complete three baseline questionnaires on paper. They will then be randomised by a member of their care team. Once randomised if allocated the intervention arm, they will be given appropriate training and be registered on the Vinehealth® digital app.

Visit/Weeks	Event	Vinehealth® Arm Location	Control Arm Location
Baseline/0 weeks	Consent, baseline questionnaires: FACT-G (PWB),	In oncology clinic	In oncology clinic

	EQ-5D and QLQ-C30 completed on paper Baseline data on paper* Randomisation	In oncology clinic Online: Sealed Envelope In oncology clinic Online - Sealed Envelope	 In oncology clinic Online - Sealed Envelope
V1/ 6 weeks V2/ 12 weeks V3/ 18 weeks V4/24 weeks (Window of + or - 5 days)	Questionnaires FACT-G (PWB), EQ5D and QLQ-C30 Current medication - Chemotherapy dose reductions/delays and reasons A/E and GP attendance and advice Chemotherapy hotline utilisation and advice	At home on Vinehealth® App In oncology clinic – completed on paper	In oncology clinic – completed on paper In oncology clinic – completed on paper
V1 – 6 weeks Week 12 and Post-trial	Qualitative remote interviews with 10-15 participants Qualitative remote interviews with 20-30 participants Electronic survey	Remote Remote Remote	N/A N/A N/A

*cancer diagnosis, cancer stage, type of cancer, concomitant medication, chemotherapy plan and treatment to date – prior to enrolment in the RCT

Clinical and treatment data (cancer stage, grade, date of diagnosis, and treatment received) will be collected at baseline, and updated at appointments in the oncology clinic.

Following randomisation participants will be asked to complete questionnaires for both arms at 6-weekly intervals, at baseline, weeks 6, 12 and where applicable 18 and 24 weeks.

A window of + or - 5 days is allowed for the completion of each 6-week timepoint, including all the associated visit procedures described in Section 7. Trial Procedures.
The 24-week questionnaire will be the final data collected from the majority participants and so completion of this will mark the end of their participation in the trial.

A subset of Vinehealth® arm participants, 20-30, will be asked to participate in remote qualitative interviews at 12 weeks to see how they are getting along with the app. 20-30 participants will then be asked to participate in another set of remote qualitative interviews following the end of the trial.

10 - 15 patients will be contacted around the 6-week timepoint in the study to gather qualitative feedback but also to understand whether they are having any major issues with usability or otherwise.

All Vinehealth participants and all healthcare professionals involved will be asked to complete an electronic survey post-trial to provide their reflections on the app. 2-3 healthcare professionals per site, or 30% whichever is more, will also be asked to participate in remote interviews for the same purpose.

7.1 Recruitment

Participants will be identified at outpatient oncology clinics and will be approached and informed about the trial. Members of staff listed on the trial site delegation log will be able to approach potential participants to discuss the trial will them.

Participant identification

The Principal Investigators (PIs) involved in recruiting participants for this trial have been involved in the trial since its conception and assisted with trial design. They and their delegated care team have been provided with appropriate training by both the CTU, for the trial, and Vinehealth for the use of the Vinehealth® digital app for the intervention arm.

Participants will be identified and approached by their usual care team, who have been trained for this trial, in oncology outpatient clinics, prior to commencing oral chemotherapy for treatment of their cancer at home. The care team will confirm eligibility and will explain the trial to them. Participants will be given time to think about the trial, discuss it with significant others and ask questions, then if agreeable they will need to provide written informed consent to participate in the trial. Screening logs will be kept by sites with details of those approached about the trial for recruitment purposes.

7.2 Payment

Patients will not be paid for participation in this trial. If randomised to the Vinehealth® app this will be provided free of charge.

Sites will be paid for participating in the trial to cover their costs for the additional workload and resources. A one-off payment is available for each site for use for staff time and resources on set-up, and an agreed per-patient payment for every patient randomised into the trial and complying with trial visits and data collection.

7.3 Consent

As mentioned in 7.1, participants will be identified and approached by their usual care team, who have been trained for this trial. The care team will be appropriately qualified for their role, trained appropriately to work on this trial, have up to date Good Clinical Practice (GCP) training, and must be delegated by the PI for their role. Appropriately trained staff will check eligibility of participants according to the latest version of the protocol and provide the latest versions of the patient information sheet (PIS) and informed consent form (ICF).

The trial will be explained thoroughly, by the trained care team, to participants and they will be given time to think about the trial, take away the PIS and ICF, discuss it with significant others and ask questions. If the participant is willing to consent to join the trial, they will need to provide written informed consent to participate.

Patients will be approached for both the main trial and the sub-study at the same visit, which will l take place in an oncology outpatient appointment. They will be approached and provided a copy of the PIS (for the study as well as for the qualitative interview for patients randomised to the Vinehealth® app) by a member of the research team, who has been adequately trained on the trial protocol and delegated by the Site PI. Vinehealth will select a list of patients for interview from those who have been randomised to the app arm, and who have also consented to the sub-study. These individuals will be selected randomly to prevent bias.

In order to comply with the Welsh Language Act 1993, the PIS and ICFs will be translated into Welsh or provided bilingually where this is requested by a participant at a research site.

The PI will take responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. Participants who are unable to read or write in English or have significant cognitive impairment are excluded from this trial.

Following consent, participants will be asked to complete the baseline questionnaires on paper. They will then be randomised via the Sealed Envelope randomisation system. Once randomised, if they are allocated the intervention, they will be asked for their email so that the recruiting PI can invite them to use the Vinehealth® App and consent will be taken for data sharing. Intervention arm participants will be given written and verbal information on using the app and treating PI's and their trained care team will be given access to Vinehealth®PRO to view patient-reported data.

Training will also be provided by the care team, both written and verbally for those in the standard of care arm for completion of the questionnaires.

7.4 The Randomisation Scheme

All patients will be randomised 1:1 using the online randomisation service (SealedEnvelope.com) to minimise allocation bias to (a) current standard of care or (b) current standard of care plus addition of Vinehealth® digital app. Randomisation will be stratified by NHS site and cancer type (colorectal/breast/lung), using a minimisation algorithm incorporating a random element to ensure balance between arms.

Method of implementing the randomisation/allocation sequence

After the patient has provided written informed consent and their eligibility for the trial has been confirmed, randomisation will be performed by the PI, or delegated member of the clinical investigating team, at local sites using the Sealed Envelope randomisation service stated above. Eligibility and consent will be verified before each patient is randomised.

At the baseline visit, a delegated member of the research staff will enter the patient's initials, gender, age, date of consent, criteria fulfilment, research site and cancer type into the Sealed Envelope secure database which will then allocate the appropriate PIN to the patient. Recruitment will continue until a total of 180 participants have been randomised. All participants will be randomly assigned to intervention group via the Sealed Envelope randomisation service.

7.5 Baseline Data

Baseline questionnaires will be completed prior to randomisation by all participants following the provision of written informed consent.

Clinical and treatment data (cancer diagnosis, stage, type of cancer, concomitant medication and chemotherapy plan - including planned reduction of dose intensity) will be collected from medical records. Participants who are randomised to the intervention arm will be asked for their email address in order to be invited by the PI to use the Vinehealth® App.

In order to create an account to use Vinehealth®PRO (VPRO), Clinicians and other staff at sites delegated the responsibility, will need to register to use the Vinehealth® App and will be asked to agree to the collection of their data:

- Name; to create a Vinehealth account
- Email address; to create a Vinehealth account
- Phone number; to create a Vinehealth account
- Clinical role; to give the appropriate permissions to view data on VPRO

Site staff will need to be registered in order to be able to invite participants to register for the Vinehealth® App.

If a participant is randomised to the Vinehealth® App they will be asked to agree to the collection of the following personal data, this is outlined in the Vinehealth Privacy Policy:
Mandatory data collected:

1. First Name
2. Last Name
3. Email address
4. Password
5. Cancer Type
6. Date of birth
7. NHS number
8. Gender/Sex

Optional data collected:

1. Phone number
2. Date of Diagnosis
3. Current stage of cancer
4. Ethnicity
5. Medication (unit, dosage, frequency, start date, end date, how to take it, notes)
6. Medical appointments (type, date, start time, end time, with who, location, notes)
7. Severity of symptoms
8. Mood/how you're feeling
9. Activity- type, duration & notes
10. Sleep - sleep start time, wake up time & feeling when you woke up
11. Blood pressure (& time taken)
12. Weight (& time measured)
13. Temperature (& time taken & notes)
14. Steps (from connected app)
15. Quality of Life Questionnaire responses

Participant's email addresses, for those randomised to the Vinehealth will be stored securely to provide linkage between pseudo-anonymised data collected via the Vinehealth® app and the trial database.

Any information about health and ethnicity is classed as sensitive Personal Information and Vinehealth ensures that additional safeguarding measures are in place to protect this information. Vinehealth's lawful basis for processing this sensitive Personal Information is consent. Consent can be withdrawn at any time by emailing privacy@vinehealth.ai.

7.6 Trial Assessments

6 weekly questionnaires, completed at baseline (prior to randomisation), 6 weeks post-randomisation, 12 weeks, and at 18 weeks and 24 weeks while the study remains open. These questionnaires are FACT-G (PWB), EQ5D-5L and QLQ-C30 and are methods of collecting Patient Reported Outcome's (PROs). FACT-G (PWB) is being used to collect data relating to physical well-being (27 items in total, 7-items for PWB, 5-point Likert-type scale), EQ-5D-5L is used as standardised measure of health-related quality of life (5 items - Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression, and 5 response levels), and QLQ-C30 is a 30 item validated questionnaire designed to measure cancer patients' physical, psychological and social functions. The questionnaire is composed of multi-item scales and single items.

Clinical and treatment data (cancer stage, grade, date of diagnosis, and treatment received) will be collected at baseline and treatments/medication updated at clinical visits.

The initial baseline questionnaires, prior to randomisation, will be completed by the patients on paper in clinic. Once randomised, the dates for completion of the PRO questionnaires will be generated from participant registration. Participants are given a window of + or - 5 days for the completion of each 6 weekly trial visit, which includes the completion of paper questionnaires.
Those participants randomised to the App will be given a + 5 day completion window for all questionnaires following baseline; this is automatically calculated from the date on which patients download and consent to the App. All other assessments for those patients randomised to the App as described in Section 7. Trial Procedures, should be completed within the + or - 5 day visit window

7.7 Qualitative Assessments

One of the exploratory endpoints is the assessment of platform engagement data including medication adherence and patient and clinician semi-structured interviews.

Recruitment

20 - 30 participants who are taking part in the RCT and have been randomised to use the Vinehealth® app, will be asked to participate in a qualitative interview. The interview will take a maximum of 1 hour and will be conducted remotely via audio or video on their phone/Computer. The interviews will be conducted by two employees of Vinehealth who have experience in user research, one of the researchers is a senior user researcher. The video/audio recording will be transcribed and stored on a secure server on google drive and on a secure cloud workspace called Confluence. The data from the interviews once transcribed, will be coded and analysed and stored for a minimum of 10 years according to Vinehealth policy. Arrangements for confidential destruction will then be made.

10 - 15 participants will be interviewed around week 6 through the study to gather qualitative feedback but also to understand whether they are having any major issues with usability of the app or otherwise (remote call) and 20-30 participants will be interviewed at week 12 and after the completion of the study, at around the week 24 timepoint.

When users first register, a welcome email will be sent to them, explaining how to contact Vinehealth with any queries or technical support if required. Midway through and at the end of the study, the number of participants mentioned above will be emailed to organise a time for interviews.

For the care team interviews, a minimum of 2 healthcare professionals will be interviewed from each site or 30% of healthcare professionals from each site, depending on which is more.

Methodology

Semi-structured remote interviews with participants and healthcare professionals will take place individually as described above to uncover their experience with using the Vinehealth® app/Vinehealth®PRO at week 12 and following the completion of the study. There will be a separate topic guide to structure the interviews for healthcare professionals and participants. All interviews will be video recorded.

Interviews will take place over a period of 3 - 6 weeks depending on availability of participants and based on the assumption that patients will not finish the study at the same time. We will also send an electronic survey to all participants who have been randomised to use the mobile app and all healthcare professionals involved to gather their thoughts on the usefulness of the Vinehealth® app. Details of this survey can be found in Appendix 6. The qualitative user research framework as well as topic guides for the qualitative interviews can be found in Appendix 7.

7.8 Withdrawal Criteria

Participants are free to withdraw from the trial at any time without it affecting the standard of care they receive. The treating clinician will discuss arrangements for continued treatment with the participant. Information that has already been collected may continue to be used for the purposes of the trial. It will be up to the participant to decide if data from the final visit can be used or not.

The care team may also decide to withdraw the participant from the trial if they feel this is in their best interests, for example if there is a change in medical health or treatment or if participants do not follow the study instructions given to them by the treating care team.

The Sponsor, the University of Surrey, the institution which has responsibility for the management of this study, or Funder (UKRI-Innovate UK), may decide to stop the trial at any time, for any reason.
Vinehealth® withdrawal info: patients are told when they consent that they can withdraw at any time by emailing privacy@vinehealth.ai. Also, a clinician/delegated representative can do this on the participant's behalf on the Vinehealth®PRO dashboard. Surrey CTU will need written confirmation whenever this occurs.

7.9 End of Trial

Within 90 days after the end of the trial, defined as the final visit of the last patient, Surrey CTU on behalf of the Sponsor will ensure that the REC are notified that the trial has finished. If the trial is terminated prematurely, those reports will be issued within 15 days after the termination date which is defined as the final patient visit. The Trial Steering Committee (TSC) will also be informed.

Surrey CTU, as delegated by the sponsor, will supply a summary of the final research report of the clinical trial to the REC within one year after the end of the trial. The report will also be communicated to the Trial Steering Committee.

8. TRIAL INTERVENTION

The Vinehealth® Cancer Companion Mobile App has two different platforms within it, a mobile application for patients and Vinehealth®PRO web app, a platform for healthcare and life science professionals.

The Vinehealth® mobile app is designed for use on smartphones that conform to the following specifications:

- Apple devices running iOS 12.5 (or later) or devices running Android 7.0 (or later).
- Screen size of at least 4.7 inches (equivalent to an iPhone 6).

8.1 Vinehealth®PRO© Platform

The Vinehealth®PRO© platform is designed for healthcare and life science professionals to accurately track high-quality patient-reported outcome and real-world data in real-time to support cancer care delivery, drug development and research. Once a patient has consented to sharing their data via the app, Vinehealth®PRO© allows healthcare professionals in this trial to:

- view the individual patient's personal identifiable information.
- view medications the patient has scheduled and logged via the Vinehealth® mobile app.
- view appointments the patient has scheduled and logged via the Vinehealth® mobile app.
- view the patient's symptoms, temperature, weight, activity, mood, blood pressure and other metrics that they're tracking via the Vinehealth® mobile app.
- acknowledge that clinician/care teams have discussed the patient's symptoms with them.

This data is not intended to replace elements of discussion with patients during routine appointments. The data is intended to facilitate a discussion with patients as part of shared decision making at clinic appointments. Also, Vinehealth®PRO© is not an urgent reporting tool. When using Vinehealth®PRO© to view high severity clinical metrics reported by patients, it is expected that any decisions about changes to patient care will result from a clinician discussing this with a patient at clinic appointments rather than through viewing the data in isolation. It is not the responsibility of the clinician to monitor the data in real-time though they can if they wish to.

Vinehealth®PRO© - Instructions for Use

The Instructions for Use (IFU) for healthcare professionals are here: https://www.vinehealth.ai/instructions-for-use-for-healthcare-professionals. The IFU is a controlled document that is held both on the Vinehealth website and within the VPRO product itself; its version and date are detailed in the document.

8.2 Vinehealth® Mobile App

The Vinehealth® mobile app is designed to support participants to track, manage and understand their care. The app lets participants:

- schedule and log medications and appointments.

- log symptoms and side effects and other important health measures such as weight, blood pressure, temperature and more.
- log activities.
- access personalised information to support self-management.

The Vinehealth® app is intended for use by adult (18+) patients with all types of cancer. The Vinehealth® app is available on the Apple App Store and Google Play store in the UK and Ireland.

Vinehealth® Cancer Companion – Instructions for Use

The Instructions for Use (IFU) for patients are here: https://www.vinehealth.ai/instructions-for-use-for-cancer-patients.

The IFU is a controlled document that is held both on the Vinehealth website and within the Vinehealth mobile app itself; its version and date are detailed in the document.

8.3 Regulatory Status

The Vinehealth® products (Vinehealth® Cancer Companion Mobile App and Vinehealth®PRO web app) are CE-marked in line with the Medical Devices Directive 93/42/EEC. They have both have been developed in compliance with the Medical Devices Directive 93/42/EEC for Class I devices. Vinehealth® Cancer Companion and Vinehealth®PRO are registered with the MHRA and CE marked as a Class I medical device in the United Kingdom and the European Union, including the Republic of Ireland and Northern Ireland. Further details are found in the Instructions for Use (IFU) as above.

Regulatory Information

- Software name: Vinehealth®: Cancer Companion & Vinehealth®PRO
- Version: The current version of the device is seen within the IFUs (3.7.0 and beyond). Any new versions of the device uploaded to the app store during the trial will be within the same intended use of the device and there will be no significant changes as per the MHRA definition; therefore, any software updates will not affect the integrity of the trial. Any change in intended use of the device would undergo an update to the ethics submission and we would also need to inform the notified body.
- Date of release: The date of release of the current version of the Vinehealth® mobile app can be seen on the Apple App Store for Apple devices and the Google Play Store for Android devices and the date of release of the current version of the Vinehealth® PRO app can be seen in the top left of the dashboard.
- Manufacturer and maintainer: Vinehealth® Digital Limited, Kemp House, 152 - 160 City Road, London, EC1V 2NX, England, United Kingdom
- The European Authorised representative is: Donawa Lifescience

8.4 Training and Download of the Vinehealth® App

Training will be provided to sites by the CTU and Vinehealth® in tandem. Sites will be shown how to use both Vinehealth® products so that they can use Vinehealth®PRO themselves to track participant data and they will also be trained themselves on how to use the Vinehealth® Cancer Companion app so that they can then train participants.

If a participant is randomised to use the Vinehealth® app, trained staff at participating sites will ask for an email address to be able to invite them to use the app. Participants will need to download the app during their visit so that they can be set up correctly for use. Once participants have downloaded the app, trained staff will show the participant how to use the app and will setup their medication schedules with them so that they are set up correctly, according to their cancer type and chemotherapy regimen. Participants will be given time to use the app for a short time and ask questions, once they are confident with using the app, they will be given a written copy of a "Getting Started One-pager" to take home with them (the Instructions for Use for the app is also built into the app), along with the usual care documentation.

The Vinehealth® Cancer Companion app is free to all cancer patients. Vinehealth®PRO will also be provided free of charge for all healthcare providers involved in this trial.

At the end of the trial participants using the Vinehealth® app will have the trial section disabled but will be free to continue to use the app in the usual way any cancer patient would if they had downloaded it publicly, outside of the trial.

8.5 Troubleshooting with the Vinehealth® App

If participants are randomised to the Vinehealth® App they will be given training both verbally and also a written user guide. The written user guide includes a link to the Vinehealth website for further information, which has numerous signposts for how to access support, an email for specific enquiries support@vinehealth.ai (Vinehealth® aim to respond within 1 working day), and a link to FAQs: https://support.vinehealth.ai/. There are also Instructions for Use for both the Vinehealth® App and Vinehealth® PRO that will be provided to participants and the trial teams at participating centres. Users of the Vinehealth product can also use the support feature in the Vinehealth® App to ask questions.

8.6 Timing of Questionnaires

The initial baseline questionnaires prior to randomisation will be completed by the patients on paper in clinic. Once randomised, the dates for completion of the PRO questionnaires will be generated from participant registration on the Vinehealth® App and completed on paper copies for those randomised to the Control arm. Participants are given a window of + or – 5 days for the completion of paper questionnaires, and a window of + 5 days for the completion of electronic questionnaires if randomised to the interventional arm. If those on standard of care miss this timeframe and compete their questionnaires out of window, then this will be recorded as a protocol deviation. If a patient in the intervention arm fails to complete a set of Visit questionnaires within + 5 days, the App will lock the questionnaires and they will be marked as not completed. For the Vinehealth® app, there are prompts on the home screen and schedule each day and a push notification at 9am to remind them to complete (if they have enabled the push notifications).

9. POST-MARKET SURVEILLANCE AND VIGILANCE

9.1 Overview

The Vinehealth® Digital app is a Class I, CE marked medical device.

Once a medical device has been placed on the UK and EU markets, the manufacturer must submit vigilance reports to the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the appropriate national competent authority in the EU (which is the Italian Ministry of Health as the product is, for the EU

market, registered in Italy) when certain types of incidents that involve their device occur in the UK and/ or EU, noting that for regulatory purposes Northern Ireland falls in to the EU jurisdiction. The manufacturer must also take appropriate safety action when required. The manufacturer will need to ensure their device meets appropriate standards of safety and performance for as long as it is in use.

The notification and evaluation of adverse incidents and field safety corrective actions (FSCA) involving medical devices is known as the medical device vigilance system. Comprehensive information on the medical device vigilance system is given in MEDDEV 2.12/1 rev 8 and the additional guidance under 'Post-Market Surveillance', and describes what, how and when to report adverse incidents involving medical devices on the UK and EU, including Northern Ireland, markets.

The manufacturer, in this case Vinehealth®, is responsible for reporting. The manufacturer shall notify the MHRA about incidents and FSCAs which meet the reporting criteria.

The manufacturer has the responsibility for investigating incidents and for taking any corrective action necessary.

The Patient Information Sheet will provide all patients with the name, address, and telephone number of a contact person at the participating site for information in the event of a problem with their participation in the study. The Patient Information Sheet will advise patients to keep this information safe and accessible should they need it at any time during their participation in the study.

9.2 Incident Reporting System

Manufacturers must report post-market vigilance reports to the MHRA via the MORE system or by sending an XML output of the Manufacturer Incident Report (MIR) form to aicxml@mhra.gov.uk.

Each initial report must lead to a final report unless the initial and the final report are combined into one report. Note that not every incident report will lead to a corrective action.

If there is any doubt about whether to report an incident, it should be reported. There should not be delays in reporting because of incomplete information. Further details can be provided in a follow up report.

9.3 Criteria for Incidents to be Reported

Any event which meets all three reporting criteria below is considered an adverse incident and must be reported to the MHRA:

- an event has occurred. This includes situations where testing performed on the device, examination of the information supplied with the device, or any scientific information indicates some factor that could lead, or has led, to an event
- the manufacturer's device is suspected to be a contributory cause of the incident
- the event resulted in, or might have resulted, in death or a serious deterioration in state of health of a patient, user or other person

Not all adverse incidents result in death or a serious deterioration in health. These may have been prevented because of other circumstances, or because of intervention. Therefore, you must still send us a report if:

- an incident associated with a device happened, AND
- if it occurred again, it might lead to death or serious deterioration in health

9.4 Timescale for Reporting an Adverse Incident to the MHRA

The manufacturer should notify the MHRA immediately upon becoming aware that one of its devices may have caused or contributed to an event meeting the above criteria.

The maximum permitted time between the manufacturer first becoming aware of the incident and notifying the MHRA are given below:

- Serious public health threat: No later than 2 calendar days after the manufacturer becomes aware
- Death or unanticipated serious deterioration in state of health: No later than 10 calendar days after the manufacturer becomes aware
- Others: No later than 30 calendar days after the manufacturer became aware

If after becoming aware of a potentially reportable incident it is unclear whether the event meets the reporting criteria above, the manufacturer must submit a report within the relevant timeframe.

9.5 Field Safety Corrective Actions (FSCAs)

FSCAs are actions affecting devices already distributed and which are taken by a manufacturer in order to reduce the risk of death or serious deterioration in health. It is the reason for the field action, not the type of field action, which decides whether it is reportable as a FSCA.
Some examples of FSCAs. This is not a full list:

- the return of a medical device to the supplier (recall)
- device inspection
- device modification
- device exchange
- device destruction
- retrofit by purchaser of manufacturer's modification or design change
- manufacturer giving advice about the use of the device and/or the follow-up of patients, users or others

FSCAs should always be communicated to all affected customers using a Field Safety Notice (FSN).
Manufacturers are encouraged to use the following templates and guidance for writing FSNs:

- FSN template
- FSN template Q&A
- FSN customer reply
- FSN distributor / importer reply
- The MHRA's published guidance on effective field safety notices

Manufacturers should notify the MHRA of FSCAs using the FSCA Report Form and are encouraged to submit via the MORE system. Notification should be made before or when the FSCA action is implemented in the UK.

The MHRA encourages manufacturers to inform them of intended actions before carrying them out so that they can provide advice on the FSCA implementation strategy or comments on the draft FSN.

9.6 Safety Reporting

A serious adverse event (SAE) is an untoward occurrence that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect.

A SAE occurring to a research participant will be reported to the CTU and subsequently will be reported to the main REC where in the opinion of Chief Investigator (CI) the event was:
• related – that is, it resulted from administration of any of the research procedures, and
• unexpected – that is, the type of event is not listed in the protocol as an expected occurrence

The SAE should be emailed to the REC using the Non-CTIMP safety report to REC form, found in Appendix 5. These should be sent within 15 days of the CI becoming aware of the event.

Device related serious adverse events will be notified to Vinehealth within 1 working day of receipt by the CTU.

Clinicians will continue to report adverse events as per normal clinical care. For the purposes of the trial, only serious adverse events potentially related to the Vinehealth® app will be recorded. These could potentially be distress caused by the content, or loss of service that may lead to a delay in contacting health support, or the misreporting of an adverse event or incident and relying on the information from the app and not contacting the health support despite clear advice to do so, through usual means resulting in delayed attention. As mentioned in the previous sections, Vinehealth will follow the regulatory requirements in terms of reporting any Class 1 medical device incidents that might lead to or might have led to the death of a patient or to a serious deterioration in their state of health.

10. STATISTICS AND DATA ANALYSIS

10.1 Sample Size Calculation

The target sample size is 180, to be randomly allocated in a 1:1 ratio between trial arms.

Our power calculation relates to the primary objective of demonstration of efficacy in improvement of QoL from access to the Vinehealth® platform, providing 80% power and at a significance level of 0.05. On this basis, 126 evaluable patients are sufficient to determine a difference of 2 points on the FACT- G (PWB) scale between the Vinehealth® app and standard of care groups at 12 weeks, adjusting for baseline using ANCOVA or similar. The calculation assumes a standard deviation of 4.57 [20], and accounts conservatively for a correlation of 0.5 between baseline measures and those observed after the initiation of treatment. 2 points on FACT-G (PWB) represents a small to medium effect size and is considered clinically meaningful [21]. To account for potential attrition (withdrawal/loss-to-follow up) of up to 30%, suggests a minimum of 180 patients are required.

Patients allocated to the Vinehealth® app will additionally provide continuous data during the trial to enable the ML-driven personalisation in the app that optimises patient self-management; and providing ongoing efficient machine learning personalisation across sites and cancer types.

The target sample size is considered sufficient to meet the aims of the project and is achievable with 20-30 patients being provided from 6-10 sites over the planned recruitment period.

10.2 Statistical Analysis Plan

All trial analyses will be according to the Statistical Analysis Plan (SAP), which will be prepared before the first substantive unblinded analysis and agreed in advance by the Trial Steering Committee (TSC). A single main analysis will be performed at the end of the trial when follow-up is complete.

The statistical analysis will be based on all participants as randomised, irrespective of subsequent compliance with allocated treatment.

A CONSORT diagram will be used to describe the course of participants through the trial. Baseline characteristics will be summarised by randomised group. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. The impact of missing data and non-compliance will be investigated.

Primary Outcome Analysis

The primary analysis will compare the quality of life, measured by the FACT-G (PWB) between arms over the trial intervention period of 12-24 weeks.

A mixed model approach will accommodate all observed outcome responses from patients at all time points. Analyses will adjust for cancer type and baseline FACT-G (PWB) score as fixed effects and include centre and participant random effects to accommodate the correlation between observations repeated on a subject and within centres. The model will be specified in the SAP.

Secondary Outcome Analysis

Analyses of the remaining secondary/exploratory outcomes will be undertaken similarly for the difference between groups according to treatment allocation over 12-24 weeks and adjusting for baseline values of each outcome.

AEs will be summarised by group, both by the number of events and the numbers of participants experiencing them. A full listing of events categorised by CTCAE classification will be presented.

10.3 Subgroup Analyses

Results on the primary outcome will be presented by stratum, according to cancer type (breast, colorectal, lung), and an interaction between cancer type and treatment will be added to the primary analysis model to investigate whether the effect of treatment differs according to cancer type. It is recognised that this analysis is exploratory, as the study is not powered to detect such differences.

10.4 Interim Analysis and Criteria for the Premature Termination of the Trial

No formal interim analyses are planned, however TSC members will convene at scheduled time points throughout the duration of the trial to review accumulating trial and safety data, without consideration of efficacy. The TSC may request an interim analysis if there are concerns with respect to patient safety.

10.5 Economic Evaluation

A formal health economic evaluation is not planned, however collection of EQ-5D would allow quality adjusted life years (QALYs) to be calculated to support a cost effectiveness analysis in combination with the resource use data collected.

10.6 Qualitative Data Analysis

To analyse the findings from the participant and clinician interviews, a framework analysis will be conducted by two researchers. This will involve initial familiarisation with the data, assigning codes, developing a working analytical framework. Then charting the data into the framework matrix and followed by interpretation of the data. Analysis will take place once interviews have been completed and over a period of 2 - 3 weeks upon collection of data.

Framework Analysis facilitates constant comparison through the review of data across the data matrices, thereby enabling systematic examination of how perspectives differ between the groups of people interviewed [22].

11. DATA MANAGEMENT

Data management processes will be described in a detailed Data Management Plan prepared by the Trial/Data Manager at Surrey CTU.

11.1 Data Collection Tools and Source Document Identification

Vinehealth App and Clinical Dashboard

The Vinehealth® App will be used by those trial participants randomised to the intervention, to enter patient-reported outcome (PRO) data. The App uses algorithms that distribute information based on type and severity of symptoms reported. The App will make recommendations based on user requirements and choices.

The Vinehealth® clinical dashboard/Vinehealth®PRO can be used by Clinical Administrator(s), at each site, to view the data and to invite trial team members to view the data. Participants can also be added, and questionnaires scheduled using this dashboard.

Promasys Database

A trial specific Promasys database will be created to capture the data collected on paper at baseline, for all participants, and then subsequent data collection for those in participants randomised to the standard of care arm.

Sealed Envelope

Web randomisation will be provided by Sealed Envelope. Site staff will logon to randomise the participants and will be notified immediately and via email with a notification stating that the participant has been randomised to either the intervention, i.e., Vinehealth® App or standard of care arm. The data entered into Sealed Envelope for randomisation will include the site, date of informed consent, patient's initials, date of birth, type of cancer and the inclusion/exclusion criteria for the study.

The randomised allocation, Vinehealth® or standard of care and the unique patient identification number (PIN) generated will be entered on the baseline CRF.

11.2 Data Handling and Record Keeping

The data collected on paper will be entered into a validated Promasys® database by appropriately trained members of the trial team at the CTU. The data management plan will document all trial specific processes, but the design, build testing and validation of the eCRF will be documented separately. All data will be handled and processed in accordance with applicable regulations, standards of GCP and Surrey CTU SOPs.

Participants will be given a unique trial PIN and the data collected on paper will be entered under the PIN onto the central database (Promasys® stored on the servers based at Surrey CTU). The servers are protected by firewalls and are patched and maintained according to best practice.

The trial database will be developed by a programmer based at the CTU and will be validated according to the SOPs. The database will only be available to specified users who will require a username and password for access. The database may also need to be accessed by delegated members of research teams at participating sites and external regulators if requested. Promasys® supports a role-based security model, granting different users different database privileges.

Promasys® implements data validations to assist data quality, including range checks on individual items and consistency checks between multiple items. This will be compliant with all necessary regulatory requirements including an audit trail to allow for date/time stamped corrections accompanied by justification/explanation for any data amendments.

After completion of the trial the database will be retained on the servers of Surrey CTU for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudonymised PIN will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by Surrey CTU.

11.3 Access to Data

The CI, Project Manager, Trial/Data Manager, Statistician, and other members of the Trial Team will have full access to the trial data during the trial, and Vinehealth Digital Limited will have access to data collected via the Vinehealth App. Following the predefined analyses on response to treatment, requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access are documented in the TSC Terms of Reference.

11.4 Archiving

The end of the trial for regulatory purposes is defined as the date of final database lock. At the end of the trial, Surrey CTU and Vinehealth Digital Limited will archive securely all centrally held trial related documentation for a minimum of 10 years. Arrangements for confidential destruction will then be made. It is the responsibility of Principal Investigators to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the site.
Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice (GCP) and all applicable regulatory requirements.

Surrey CTU will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

12. RISK ASSESSMENT AND MONITORING

12.1 Assessment and Management of Risk

The Vinehealth® digital app is a Class I, CE marked medical device. As such it is generally regarded as low risk. The use of the Vinehealth® app carries some technical and regulatory risks associated with sensitive data collection, error handling and security risks; the post-mitigation risk ratings are low given the experienced team, robust quality management system and extensive regulatory compliance. In addition, there are risks associated with working with NHS organisations in the post COVID environment, delays with patient recruitment and availability of skilled staff. The risks will be assessed at each step of the trial set up and the management will include careful assessment of the recruitment sites, and a close collaboration with Surrey CTU to avoid any delays. Vinehealth follows a robust risk management process to assess and mitigate any risks associated with its device.

12.2 Monitoring

As this is a low-risk study, it has been determined that each site shall be responsible for their own monitoring and ensuring the accuracy and quality of the data that is entered into the Sealed Envelope (randomisation), data collection sheets (paper CRF's subsequently entered into Promasys®) and Vinehealth® apps. The level and type of monitoring expected by the sites is not more than would be expected as part of standard procedures in research which sites should be performing as a matter of course to maintain oversight of the data and processes at their site. Examples of the types of information that sites would be expected to monitor are listed below. Please note sites may monitor additional information outside of this list should they feel it is necessary.

- The study is conducted appropriately and in accordance with the protocol and GCP
- All staff involved in the trial have the necessary qualifications for their delegated duties and have received the necessary training
- Only eligible participants are enrolled onto the study
- Informed consent is taken and documented accurately
- All data is entered accurately, completely and promptly
- Site files are maintained and kept up to date
- The Research Team is kept informed of any problems in a timely manner

The data entered into Sealed Envelope for randomisation, includes the site, date of informed consent, patient's initials, date of birth, type of cancer and the inclusion/exclusion criteria for the study. A participant will not be able to be randomised unless all these fields are completed; therefore, ensuring only eligible participants are enrolled. Surrey CTU will be a central point of contact during UK office opening hours should a site/participant have any problems with any system and Surrey CTU will liaise with the relevant personnel should there be repeated problems. Contact details will also be provided for office hours for both Vinehealth and Sealed Envelope in case of any issues.
Recruitment and enrolment at each site will be monitored by Surrey CTU. Monthly reports will be compiled listing the number of participant's recruited and enrolled for each type of cancer at each site. This information will be reported to the Trial Management Group (TMG), who will feedback to the sites regarding recruitment rates/concerns as appropriate.

Surrey CTU will keep a record of any recurrent issues and will notify the TMG so that they can decide whether additional training or other action at the site/sites is required.

Each site is responsible for keeping their own Investigator Site File (ISF). The Surrey CTU Project/Trial Manager in conjunction with the TMG will provide the sites as necessary with updates regarding the versions of documents that should be filed in their site files to ensure each site has the correct documentation.

If there are concerns regarding the data integrity at a site, then Surrey CTU will provide additional training/inspections/audits at the sites as required. The Sponsor, University of Surrey, and Vinehealth® are acting as joint data controllers for the purposes of the study. We will also have a data sharing agreement in place for this trial.

If a site discovers any major issues whilst monitoring (GCP breaches and Protocol deviations that may affect the safety of participants or the integrity of the data), then they must immediately notify Surrey CTU, who will notify the Sponsor, University of Surrey, as soon as possible, ideally within 2 working days. This communication should be documented in their site file. If applicable, the Trial Management Group (TMG) and Trial Steering Committee (TSC) should be notified of any significant issues. This may trigger additional monitoring requirements which may include, on-site monitoring by a member of Surrey CTU. If the level of monitoring required at a site changes during the trial, this will be documented in the monitoring plan.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH-GCP as well as ISO 14155:2020 and applicable regulatory requirements.

13.2 Patient Data Protection

The Informed Consent Form (ICF) will incorporate wording that complies with current data protection and privacy legislation. This will be agreed in our data sharing agreement that will be in place for this trial.

13.3 Ethics and Regulatory Review

The University of Surrey, as sponsor, will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Favourable Ethics Opinion from an approved Research Ethics Committee (REC) is acquired
- 'Adoption' into National Institute for Health Research (NIHR) portfolio
- National Health Service (NHS HRA) permission, obtained via the IRAS system
- Confirmation of sponsorship
- Adequate insurance provision

Surrey CTU will be responsible for providing the Research Ethics Committee (REC) with annual reports.

13.4 Informed Consent

Site investigators must ensure that patients are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

University of Surrey as sponsor will provide the Investigators with an appropriate sample Informed Consent Form (ICF) which will include all elements required by International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) and applicable regulatory requirements. The sample Informed Consent Form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide copies of the Informed Consent Forms to the patient and written information about the study in English (or Welsh for Welsh sites, when requested) prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for the patient to inquire about the details of the study - minimum 24 hours.
- Obtain an Informed Consent Form signed and personally dated by the patient and by the person who conducted the informed consent discussion.
- Obtain an Independent Ethics Committees (IEC's) written approval/favourable opinion of the written informed consent form and any other information to be provided to the patients, prior to the beginning of the study, and after any revisions are completed for new information.

The Chief Investigator (CI) can revise the Informed Consent Form whenever important new information becomes available that is relevant to the patients consent. Any changes will need to be submitted to the REC as a substantial amendment. Once a favourable opinion has been obtained, the Investigator, or a person designated by the Investigator, should fully inform the patient, of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication will be documented.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements.
The consent forms must also include a statement that sponsor and regulatory authorities have direct access to the patient records. The rights, safety, and well-being of the study patients are the most important considerations and should prevail over interests of science and society.

13.5 Peer Review

The project has been peer reviewed by 5 independent assessors as part of the funding application to UKRI Innovate UK with an overall feedback score of 86.8%.

13.6 Public and Patient Involvement

To date there have been patient representative panels at each NHS site and Vinehealth® Patient Board. They have been involved in the review of this project.

The Steering Group for the project will comprise patients, clinicians and developers and they will be involved in dissemination of results on completion of the trial.
The project proposal was presented and evaluated by NCRI's Living with and Beyond Cancer Methodology workstream. The constructive feedback informed the project application.

13.7 Regulatory Compliance

As stated in 13.3 and section 9, the study will be performed in accordance with and applicable regulatory requirements.

The University of Surrey will ensure that all trial documentation has been reviewed and approved by all relevant bodies including the legal manufacturer of the medical device under study, Vinehealth Digital Ltd.

Site Responsibilities

The site must not randomise any patients until the Sponsor and HRA approval are in place. The Sponsor approval is dependent on receipt of approval from the REC, and R&D site specific approvals.

It will be the responsibility of the site PI to ensure the accuracy of all data entered at his/her site. They must conduct the trial personally, or delegate to members of their research team specific tasks using a delegation log. They must ensure that each member of their research team is suitably qualified to perform delegated tasks by education, training and experience, and must ensure that written procedures are followed to enable the collection of high-quality data.

Research nurses/assistants/designated health professionals will inform the Sponsor of any protocol deviations that impact on patient safety or validity of the data. The CI will report to the REC any breaches or deviations that are, in his/her opinion, of major significance. Minor breaches and deviations will be summarised in the relevant reports and circulated to the REC.

13.8 Trial Oversight

Funding

Funding for the Project comes from UKRI-Innovate UK via the Biomedical Catalyst 2020: round 1, early and late-stage awards, application number: 88303. This RCT forms part of the project. The project will be monitored by the funders regularly through quarterly reports and meetings, ensure project delivery in terms of technical assurance, financial assurance, and project management assurance. The funder will be provided, within 90 days of the end of the project, with the final project report and any supporting documentation.

Innovate UK has the right to request access to any additional information they feel necessary in connection with this award. Any information collected will be managed according to this policy and is subject to data protection. This policy complies with the General Data Protection Regulation (EU 2016/679), or GDPR, introduced on 25 May 2018. 5. As a public sector organisation Innovate UK are also subject to some further data protection obligations under the UK Data Protection Act 2018.

The project must comply with all UK statutory framework legislation (including in the devolved administrations) where they apply and act in a way that does not affect the ability of Innovate UK, the funder, to comply.

Innovate UK requires the establishment of an exploitation plan in terms of project results and encourages the project to seek its own publicity.

Sponsorship

The University of Surrey is the legal sponsor with overall responsibility for this RCT, with Surrey CTU being delegated appropriate tasks associated with the sponsor's responsibilities. As such, Surrey CTU will ensure that there is appropriate use of patient, service user and public involvement, documentation for the RCT are scientifically sound (through independent expert review), safe, ethical, legal and feasible and remain so for the duration of the research project, taking account of developments while the research is ongoing.

Surrey CTU will also ensure that the trial sites are suitable, that their staff are appropriately trained for their roles and all of this is documented and delegated as appropriate.

Surrey CTU will ensure adequate provision is made for insurance or indemnity to cover liabilities which may arise in relation to the design, management and conduct of the research project; and appropriate arrangements are made for making information about the research publicly available before it starts (unless a deferral is agreed by or on behalf of the research ethics committee); agreeing appropriate arrangements for making data and tissue accessible, with adequate consent and privacy safeguards, in a timely manner after it has finished; and ensuring arrangements for information about the findings of the research to be made available, including, where appropriate, to participants.

The sponsor delegates responsibility to Surrey CTU for obtaining the necessary approvals from both ethics and regulatory bodies.

Surrey CTU shall ensure that the RCT is adequately financed and manage the RCT, through competent risk management and data management.

Surrey CTU will ensure that effective procedures and arrangements are in place and adhered to for reporting, such as progress reports and safety reports, and monitoring the conduct of the RCT, including the ongoing suitability of the approved protocol, in light of adverse events or other developments.

Trial Oversight Committees

The Trial Team will be comprised of core CTU trial staff (Project Manager, Trial/Data Manager, Data Systems Manager and Statistician), and will be convened to set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management.

They will be overseen by a formal Trial Management Group (TMG) whose role is to manage the day to day running of the trial, including monitoring the randomisation, accrual of participants, data collection, safety and compliance. This group will be comprised of CTU trial team, a representative from each site, the Chief Investigator, and a representative of Vinehealth®. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

The Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, CTU, the funder and sponsor on all aspects of the trial through its independent Chair. Including the chair, independent membership will include at least two experienced clinicians, a statistician and a patient representative. Given the low risk nature of the study, the TSC will additionally incorporate the functions of an Independent Data Monitoring Committee (IDMC), and will oversee patient safety and the accumulation of data. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

13.9 Protocol Compliance

Participating sites will inform the CTU as soon as they are aware of a possible serious breach of compliance, so that the CTU can fulfil its requirement to report the breach if necessary, within the timelines specified in the UK Clinical Trials Regulations. For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

Other deviations will be logged and dealt with appropriately. Any decisions relating to the inclusion or otherwise of such data in the analysis will be fully documented in accordance with the detailed statistical analysis plan.

13.10 Notification of Serious Breaches to GCP and/ or the Protocol

The MHRA have a definition of a serious breach of GCP: a 'serious breach' is a breach that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the participants; or
- the scientific value of the trial.

The Regulations define 'serious breaches' as any serious breach of:

- the conditions and principles of good clinical practice in connection with that study; or
- the protocol relating to that study, as amended from time to time in accordance with regulations 22 to 25 of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the UK Medical Device Regulations 2002 as well as the EU Medical Device Regulation (https://www.legislation.gov.uk/)

In the event of either a serious breach of GCP or the Protocol, Surrey CTU and relevant involved parties must be notified immediately so that they can take appropriate action. The Clinical Trials regulations state that the Sponsor is required to report serious breaches to the REC, and MHRA (where applicable) within seven days of becoming aware of the breach.

In the event that a serious breach is suspected at a site, the relevant NHS R&D Department must also be contacted so that an investigation of the concern can be undertaken as a matter of urgency.

Surrey CTU and local R&D departments can provide information on what should, or should not, be classified as a serious breach and on the practical arrangements for notifications.

13.11 Data Protection and Patient Confidentiality

Surrey CTU on behalf of University of Surrey

Surrey CTU, on behalf of the Sponsor, the University of Surrey, will comply with all aspects of current Data Protection legislation. All information collected during the course of the trial will be kept strictly confidential. All participants will receive a randomisation number which will replace the participant's name and provide anonymisation. Participants will not be identified in the results of the study.

All study staff sign a confidentiality statement where they are obliged not to disclose confidential information.
Standard Operating Procedures (SOPs) are in place to cover appropriate storage, restricted access and archive/destruction arrangements of participants personal and clinical details.

All non-anonymised information (i.e., personal data that can be used to identify participants, e.g., hospital number, name, date of birth, and contact details including home address and telephone numbers) will be stored securely for 10 years after the last contact between the research team and participant according to usual Information Governance (ISO 27001) and NHS Information Governance Toolkit safeguards. All anonymised information (e.g., responses to the trial questionnaires) will be stored securely for 10 years according to University of Surrey policy. The procedures that will be followed for the collection, storage, protection, retention and destruction of all information comply with national and EU legislation.

Vinehealth

Vinehealth is committed to protecting the security of Personal Information by endeavouring to ensure appropriate technologies and processes are maintained to avoid unauthorised access or disclosure. Vinehealth utilise, for all data storage and processing purposes, Amazon Web Services ("AWS"), Google's G Suite and Google Cloud. Specifically, all Vinehealth's AWS storage containers and databases are located in London (UK) (with possible transit through US/EU storage containers). All Personal Information collected by Vinehealth software products is encrypted to the highest possible degree both when it is stored in their databases and when it is being transmitted.

The Vinehealth Privacy Policy can be found online: https://www.vinehealth.ai/privacy-policy.

13.12 Financial and Other Competing Interests

The CI, PIs at Each Site and Committee Members for the Overall Trial Management

A CI statement and PI statements for all sites involved will be completed prior to sites being given the green light to begin recruiting participants into the trial. This will ensure that they know what their responsibilities and obligations are with regard to the trial and give them the opportunity to identify and disclose any competing interests that they might have, such as a professional interest, a proprietary interest or any other

conflict of interest. Any issues that arise from this will be reported to the Trial Steering Committee (TSC) and/or Sponsors to determine what further action is required.

All members of the TMG and TSC will also be required to complete a Members Agreement and Potential Competing Interests Form, under their agreed terms of reference. This will again ask if members have any potential conflict of interest such as

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor and Funder (including CI for other trials)
- Ongoing advisory role to a company providing the trial intervention
- Frequent speaking engagements on behalf of the intervention
- Intellectual conflict e.g. strong prior belief in the trial intervention
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products

Any issues arising will be dealt with by the Sponsor.

13.13 Indemnity

If participants believe they may have been harmed in anyway by taking part in this trial, they have the right to pursue a complaint and seek any resulting compensation through the University of Surrey which is acting as the research sponsor. Details about this are available from Surrey CTU who are running this trial on behalf of the University of Surrey.

Also, as a patient of the NHS, participants have the right to pursue a complaint through the usual NHS process. Note that the NHS has no legal liability for non-negligent harm. However, if participants are harmed and this is due to someone's negligence, they may have grounds for a legal action against NHS but the participant may have to pay their own legal costs.

13.14 Amendments

The trial protocol and related documents and procedures will not be changed without the mutual agreement of the Chief Investigator, Sponsor, Surrey CTU and Vinehealth.

Any 'substantial' protocol amendment(s) (meaning that it could have a significant impact on the safety or physical or mental integrity of the patients, the scientific value of the trial, or the conduct or management of the trial) must be submitted to the Research Ethics Committee (REC) and the NHS R&D prior to its implementation.

For non-substantial changes that do not affect the safety or validity, e.g., an administrative change, the EC must be notified. The amendment will be forwarded to the REC for their information, and the changes implemented immediately, unless otherwise instructed by the sponsor or REC.

In the case of changes consisting of urgent safety measures to protect the trial subjects, the sponsor should inform the REC as soon as possible after these measures have been implemented.
In the case of any non-substantial protocol amendments, it may be necessary to notify all sites. This will be decided on a case-by-case basis. In the case of any substantial protocol amendments, it will be necessary to notify all sites.

Surrey CTU will coordinate and prepare all necessary amendments.

13.15 Post-Trial Care

At the end of the trial participants will return to and/or continue with the standard of care that they would have received if they had not been part of this trial.

At the end of the trial participants using the Vinehealth® app will have the trial section disabled but will be free to continue to use the app in the usual way any cancer patient would if they had downloaded it publicly, outside of the trial.

The Vinehealth® Cancer Companion app is free to all cancer patients and so any participants who were randomised to the standard of care arm will also be free to download the app if they so wish for personal use.

Vinehealth®PRO will also be provided free of charge for all healthcare providers involved in this trial but will be disabled when all data is complete, and the database is locked.

13.16 Access to the Final Trial Dataset

The CI, Project Manager, Trial/Data Manager, Statistician, and other members of the Trial Team will have full access to the trial data. Following the predefined analyses on response to treatment, requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access are documented in the TSC Terms of Reference. On completion of the trial, full access to the trial data will be given to Vinehealth Digital Limited, as covered in the formal data sharing agreement.

14. PUBLICATION AND DISSEMINATION

A detailed publication plan will be developed and approved by the Trial Management Group (TMG), specifying what publications are planned and the person responsible for each. A writing committee will be established for each planned publication, being a subgroup of the TMG. Through peer reviewed publications, and presentations at policy and academic meetings, our findings will be disseminated widely. The results of the trial will be disseminated regardless of the direction of effect.

On completion of the trial, the data will be analysed and tabulated, and a final study report prepared following a medical device post market clinical follow-up report template (to be provided by Vinehealth Digital Limited). These results will be summarised on relevant trial registries, and a manuscript summarizing the main trial results will be submitted to a relevant medical journal within 12 months of trial completion, with authorship according to the criteria defined by the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org). These state that: Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. The results of this trial may also be publicised through Surrey CTU, the University of Surrey and Vinehealth's website and App, and using social media.

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16. APPENDICES

Appendix 1 - Trial Management Responsibilities

Surrey CTU is coordinating the trial on behalf of the sponsor and other collaborators and has been delegated the following responsibilities

(Large X is for main/primary responsibility and small x's are for input/other responsibility)*:*

Trial Task	Surrey CTU	Sites	CI	Comments/Clarification
Trial Management and Monitoring	x	X	x	Central monitoring by CTU, in conjunction with CI, assisted by sites self-monitoring. Review committee will have overall oversight.
Protocol and amendments	X	x	x	CTU will coordinate, in conjunction with CI, and obtain approvals and disseminate to sites
Patient Information Sheet/Informed Consent Form management	x	X		Central monitoring by CTU – regular request of logs, assisted by sites self-monitoring
CRF design and management	X			A database will be set up in Promasys to capture the data collected on paper. CTU will design this CRF. Standard validated questionnaires (EQ5D, QLQ-C30 and FACT-G) are to be used for QOL
Translations	X	x		Welsh translations are required. CTU will arrange this and ask for assistance from Welsh site to check back translation of documents.
Regulatory process *(if applicable i.e if trial is a CTIMP/ATIMP)*				N/A
Investigator selection	X		x	Vinehealth suggested collaborators, CTU has discussed necessary requirements with them and gone through selection requirements
Ethics committee process	X	x	x	CTU will coordinate, in conjunction with CI, and obtain approvals and disseminate to sites for local assessment
Trial registrations	X			CTU will obtain on behalf of trial
Management of Intervention	x	x	X	Sites will manage participant training and registration with intervention. Vinehealth can be contacted directly for any issues with the app. CTU will be central point of contact for any trial issues.
Trial specific training	X			CTU will provide overall trial training for sites including data collection for standard of care arm PRO collection. Vinehealth will provide training for sites on use of the app for site staff and for site staff to be able to train participants.
Provision of study supplies e.g. CRFs, Lab Kits other consumables	X			CTU will coordinate trial and provide means for standard of care data/questionnaire collection on paper. Randomisation is to be provided by Sealed Envelope

Trial Master File (TMF) set-up maintenance	X			CTU will maintain electronic and hard copy of TMF
Investigator Site File (ISF) set-up and maintenance	x	X		CTU will disseminate documentation once approved to sites. CTU will require sites to keep ISF up to date and will request self-assessment of this from sites as part of central monitoring.
Safety reporting and management	X	x	x	CTU will be central point of contact for trial. Vinehealth will be contact for any issues with the intervention. Sites should notify both parties if any safety issues occur.
Database Development	X			CTU will set up a database in Promasys® for standard of care arm data collection. Vinehealth will set up trial section in app for intervention arm.
Randomisation	x			CTU have a sub-contract with Sealed Envelope for the randomisation.
Quality Control/Monitoring	X	x	x	CTU will review data received and entered Promasys® and perform central monitoring with assistance from sites. Vinehealth will produce regular reports on compliance for TMG meetings for review.
Quality Assurance/Audit	X			CTU, as delegated sponsor responsibilities, will coordinate and review the quality assurance throughout the trial through QC and central monitoring and will perform audit if required. The funder (Innovate UK) and/or regulatory authorities may also audit if requested.
Data Management	X			CTU co-ordinate data management to ensure conformity for analysis. CTU will provide Promasys® database for standard of care data collection. Vinehealth will collect data via the intervention/app.
Statistical analysis and report	X			CTU is responsible for writing Statistical Analysis Plan (SAP) and will perform the analysis at the end of the trial.
Report writing and publications	X	x	X	The report writing will be a collaboration of all the main partners for the RCT, CI, CTU and Vinehealth, with contributions from PI's at sites.
Storage and archiving of TMF	X			CTU is responsible for storage and archiving of TMF
Storage and archiving of ISF		X		Sites are responsible for storage and archiving of ISF under the direction of PI's.

Appendix 2 - Protocol Contributors

The protocol was written and developed by key members of the Surrey CTU trial team, including Prof Simon Skene (Professor of Medical Statistics and Director), Dr Agnieszka Michael (Medical Director and Chief Investigator) who contributed to the trial design methodology and funding application. Beth May (Trial Manager) provided the draft with further input and review from Megan Roberts (Clinical Project Manager), Marie Williams (Data Systems Manager) and Kate Bennett-Eastley (Medical Statistician).

Rayna Patel (Co-Founder and CEO NHS Medical Doctor & Vinehealth® Caldicott Guardian) and Georgina Kirby (Co-founder and CTO Health Technology Specialist & Vinehealth® Data Protection Officer), have contributed extensively towards the production of this protocol for the trial, including trial design, data collection and trial intervention information.

The trial design and funding application were developed following research with trusted stakeholders such as cancer charities, healthcare professionals and patients, 6 months data collection from the Vinehealth® app from 1000 patients, and a feasibility study done in the NHS. Professional contributors included Dr. Liz O'Riordan - Consultant Oncoplastic Breast Surgeon, Ipswich NHS Trust & Breast Cancer Patient, Dr. Pauline Leonard - Consultant Medical Oncologist, Co-Chair of NCRI's Living With and Beyond Cancer Acute toxicities workstream, Dr. Geoff Hall - Consultant Medical Oncologist, CCIO Leeds Teaching Hospitals and Professor of Digital Health and Cancer Medicine, University of Leeds, Prof. Muntzer Mughal - Consultant General Surgeon & Clinical Chair, NCEL Cancer Alliance, Chief Medical Officer of UCLH Cancer Collaborative, Prof. Theresa Wiseman - Clinical Professor of Applied Health Research in Cancer Care, Royal Marsden, Dr. Michael Flynn - Consultant Medical Oncologist, University College London Hospital and Dr. Michael Kosmin - Consultant Clinical Oncologist, National Hospital for Neurology.

Methodology and further advice has been provided by numerous groups including the Vinehealth® Expert Patient Advisory Board (this is made up of patients across cancer types, treatments, ages and socio-economic backgrounds), Prof. Galina Velikova Study Advisor – a world-leading expert in cancer PRO data in trials & clinical practice, Dr. Christine Adams Innovate UK process expertise and 20yrs' R&D collaborations expert.

Technology input has been provided by Dr. Rayna Patel and Georgina Kirby, and other members of the Vinehealth®team; Owain Service, Behavioural Science Founder and Managing Director of the Cabinet Office's Nudge Unit, Dr Liz O'Riordan, Patient Advocate Breast cancer patient, thought leader, Daniel Karpinski - Tech Lead Anastasiia Kucherenko - Product Design Lead, Ravi Khiroya - Regulatory and Product Owner and Riccardo Mangiapelo - Data Scientist.

The proposal for the project was presented & evaluated by NCRI's Living with and Beyond Cancer Methodology workstream and constructive feedback informed the application to UKRI - Innovate UK.
The University of Surrey as sponsor will ensure procedures are in place for appropriate pharmacovigilance and safety monitoring, appropriate plans are written for data management, data analysis, monitoring and auditing/inspection and that the relevant submissions are made to ethics and the MHRA and appropriate guidelines and legislation are adhered to.

Appendix 3 – Schedule of Procedures

Procedures	**Visits**			
	Screening	**Baseline**	**Intervention Phase**	**Follow Up**
Informed consent	x			
Questionnaire's FACT-G, EQ5D and QLQ-C30		x		
Demographics		x		
Medical history				
Eligibility assessment	x			
Randomisation	x			
Training for app/standard of care		x		
Compliance			x	
Questionnaire's (FACT-G, EQ5D, QLQ-C30) weeks 6, 12, 18 and 24			x	
Interviews (subset of participants and clinicians only)			x	x

Appendix 4– Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SPON 2021 _ fhms Amendment 3	1.4	24th August 2022	Luke Smith Agnieszka Michael	Cytotoxic chemotherapy (+/-targeted therapies or immunotherapy) at participating site for minimum planned duration of 12 weeks added to inclusion criteria Primary disease completely excise (residual macroscopic disease allowed <2cm) added to inclusion criteria. Systemic anti-cancer treatment to palliate incurable cancer for this malignancy (residual disease > 2cm) added to exclusion criteria.
SPON 2021 _ fhms Amendment 7	1.5	12th December 2022	Simon Skene Luke Smith Agnieszka Michael	Sample size reduced and clarification of primary endpoint analysis at 12 weeks. Change to inclusion criteria to allow breast cancer patients who require neoadjuvant chemotherapy for 12 weeks and have no cancer-related symptoms Additional detail regarding the qualitative analysis, including addition of interview at 12 weeks. Completion Window for scheduled visits changed from +5 days, to + or -5 days Minimum Apple device iOS increased from iOS 9.2(or later) to iOS 12.5 (or later) Smartphone access that conforms to the following specifications, devices running Android 7.0 (or later). Previously 4.0.
SPON 2021 _ 17 fhms Amendment 12	1.6	13th July 2023	Luke Smith	Patients to be followed up for a minimum of 12 weeks (primary endpoint) and a maximum of 24 weeks.

Appendix 5 – Non-CTIMP SAE Form

Report of Serious Adverse Event (For all studies except Clinical Trials of Investigational Medicinal Products)

The Chief Investigator (CI) should report any SAE that is both related to the research procedures and is unexpected. The report should be emailed to the Research Ethics Committee that gave a favourable opinion of the research within 15 days of the CI becoming aware of the event

Details of the Chief Investigator

Question	Answer
Name:	Replace text here
Address:	Replace text here
Telephone:	Replace text here
Email:	Replace text here

Details of the study

Question	Answer
Full title of study:	Replace text here
Name of REC:	Replace text here
REC reference number:	Replace text here
IRAS ID:	Replace text here
Research sponsor:	Replace text here
Sponsor's reference for this report: (if applicable)	Replace text here

Type of event

Please categorise this event, ticking all appropriate options:

Death ☐

Life threatening ☐

Hospitalisation or prolongation of existing hospitalisation ☐

Persistent or significant disability or incapacity ☐

Congenital anomaly or birth defect ☐

Other ☐

Circumstances of event

Question	Answer
Date of SAE:	Replace text here
Location:	Replace text here
Describe the circumstances of the event: (Attach copy of detailed report if necessary)	Replace text here
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	Replace text here

Declaration
Signature of Chief Investigator:
Print name:
Date of submission:

Acknowledgement of receipt by REC (please insert name):
The [ ] Research Ethics Committee acknowledges receipt of the above.
Signed:
Name:
Position on REC:
Date:
Signed original to be sent back to Chief Investigator (or other person submitting report) Copy to be kept for information by REC.

Appendix 6 – Digital Survey Questions

Details of the digital survey to be sent by Vinehealth to participants of the Vinehealth arm of the trial and clinicians:

Survey Questions - Patients

To what extent do you agree with the following statements:

(all answers are a scale from: Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree)

1. Vinehealth has helped me to understand my care better than before I used the app.
2. Vinehealth has helped me to self-manage my care better than before I used the app.
   (* Self-management aims to empower you to take control of your condition and better manage your own health.)
3. Vinehealth has helped me to understand my condition better than before I used the app.
4. Vinehealth has helped me manage my condition better than before I used the app.
5. Vinehealth has allowed me to keep a more consistent record of my wellbeing
6. Vinehealth has improved my overall wellbeing
7. Vinehealth has helped to ensure that I adhere to my medications better than before I used the app.
8. Vinehealth has enabled me to communicate with my care team better than before I used the app.
9. Vinehealth has helped me to feel more in control of my care compared to before I used the app.
10. I am likely to recommend Vinehealth to my peers who also have cancer.
11. Vinehealth provides accessible, engaging and friendly digital content
12. Vinehealth is easy to use.
13. I will continue to use Vinehealth now that the study is complete.

Survey Questions - Clinicians

To what extent do you agree with the following statements:

(all answers are a scale from: Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree, Not Applicable)

1. Vinehealth has helped to improve patient-clinician communication.
2. Vinehealth has helped me to assess my patient's symptoms better.
3. Patient reported data presented in VinehealthPRO has supported me in making clinical decisions
4. Patient-reported data, sorted by the number of severe CTCAE symptoms in VinehealthPRO informed appropriate triage (i.e. deciding which order patients should be seen)
5. Patient-reported data through Vinehealth has helped me to provide better care for my patients.
6. Patient-reported data delivered through VinehealthPRO has decreased time to capture a patient's history.
7. I am likely to recommend VinehealthPRO to my colleagues.
8. I am likely to recommend the Vinehealth mobile app to my patients.
9. VinehealthPRO is easy to use.
10. VinehealthPRO is safe to use.

Appendix 7

Qualitative User Research Framework

Study Title: Multi-centre, randomised controlled trial of Vinehealth® digital health cancer solution for cancer patients commencing chemotherapy

Recruitment

We will speak to 10 - 15 patients (at week 6), who have taken part in the Surrey RCT and have been randomised to use the mobile app, to understand how they are getting along with the app and to find out whether they are having any major issues with usability or otherwise.
We will then also interview 20-30 patients at week 12 and 20-30 patients after they have completed the study.

When users first register, we send a welcome email explaining that if they have any questions how to use the app then to contact us for technical support. At the end of the study and mid-way through, we will email the number of patients mentioned above to organise time for interviews.
For healthcare professional interviews, we will run interviews with a minimum of 2 clinicians from each site or 30% of healthcare professionals from each site depending on which is more.

Methodology

At week 12 and at the end of trial, we will run semi-structured remote interviews with patients and clinicians individually to collect information relating to their experience with using the app/VPRO following the completion of the study. The interviews will be conducted by two employees of Vinehealth who have experience in user research, one of the researchers is a senior user researcher. The video/audio recording will be transcribed and stored on a secure server on google drive and on a secure cloud workspace called Confluence. The data from the interviews once transcribed, will be coded and analysed and stored for a minimum of 10 years according to Vinehealth policy.
10 - 15 participants will be interviewed around week 6 through the study to gather qualitative feedback but also to understand whether they are having any major issues with usability of the app or otherwise (remote call) and 20-30 participants will be interviewed at both week 12 and after the completion of the study, at around week 24.

Interviews will take place over a period of 3 - 6 weeks depending on availability of participants and based on the assumption that patients will not finish the study at the same time.

We will use a separate topic guide to structure the interviews for clinicians and patients. All interviews will be video recorded.

To analyse the findings, Framework Analysis will be conducted by two researchers. This will involve initial familiarisation with the data, assigning codes, developing a working analytical framework. Then charting the data into the framework matrix and followed by interpretation of the data. Analysis will take place once interviews have been completed and over a period of 2 - 3 weeks upon collection of data.

An electronic survey will also be sent out to all patients who have been randomised to use the mobile app and all clinicians involved, to gather their thoughts on the usefulness of the Vinehealth App.

Interview Questions at 12 weeks

Patients

1. How are you getting on with the app so far?
2. Would you like any support in learning how to navigate around the app, and the features within?
    a. Is there anything missing, or not working the way you'd expected?
    b. What can we do to make the app more helpful?
    c. Do you have any questions, comments or feedback so far?
    d. Are there any features you've found difficult to use?
3. How have you been using the app to: (if not answered by the first two questions)
    a. manage your medications?
    b. manage your appointments?
    c. keep track of your symptoms and wellbeing?
    d. See your progress over time through the reports?
    e. Access educational & support content?
4. What role has the app played so far in communicating with your care team and how have you found this?
    a. What would help you to communicate even better with your care team?
5. Do you have any other questions, comments or feedback so far?

Interview Questions at End of Trial

Patients

1. How would you describe your experience with the app during your treatment?
2. Are there areas you found useful in the app? What made them useful for you?
3. Are there any features that you never/ barely used? What made you not engage with them?

4. What are your thoughts about using the app to help you: (unless answered by previous two questions)?
    a. manage your medications?
    b. manage your appointments?
    c. keep track of your symptoms and wellbeing?
    d. See your progress over time through the reports?
5. What are your thoughts about the educational and support content in the app?
6. What role did the app play in communicating with your care team and how did you find this?
7. What do you think could be improved about the app to make it more helpful in managing your treatment and supporting you during and post-treatment?
8. Is there anything that is missing that you expected to be in the app, or something that's not working in the way you thought it would?
9. After the study has finished and you are not required to use Vinehealth anymore, how would you manage your medications and track your wellbeing/symptoms?
10. Out of a scale from 0-10 where 10 is the highest, how likely are you to recommend Vinehealth to other people suffering from cancer?
11. How would you feel if you couldn't use the Vinehealth app anymore?

Clinicians

1. How did you find using VPRO to recruit patients into the study?
2. What did you like about it? What were the biggest benefits of you using it?
3. Did you use VPRO during appointments with patients?
4. If so, how did you find it?
    a. How did it help in understanding your patients better?
    b. How did it help in understanding and assessing a patient's symptoms? And subsequent clinical decisions?
    c. How did you find the presentation of data? What format would be most useful for you?
    d. How did it affect how the appointment was run?
    e. How did it affect you time wise?
5. If not during appointments, then when else did you use the platform?
6. If you didn't use the platform after recruitment, what were the reasons for not using it?
    a. What would make it easier for you to use it/want to use it?
7. How do you see Vinehealth being used to inform clinical decisions?
    a. What sort of decisions?
    b. What could be improved to provide information to inform your decisions?
8. How do you see Vinehealth being used in triage?

9. Overall, how did you find VPRO, in terms of ease of use? How much time did it take for you to adopt using the platform?
10. What are your thoughts in terms of VPRO being safe to use?
11. Is there anything else you think could be improved that you haven't already mentioned?
12. How did you find patient's using the app beneficial in patient-HCP communication? Were there any noticeable differences in patients who were using the app?

13. Now that the study has finished, would you want to continue using VPRO if you could?
14. Out of a scale from 0-10 where 10 is the highest, how likely are you to recommend VPRO to your colleagues?
15. Out of a scale from 0-10 where 10 is the highest, how likely are you to recommend the Vinehealth app to your patients?

Survey Questions at End of Trial

Patients

To what extent do you agree with the following statements:
(all answers are a scale from: Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree)

1. Vinehealth has helped me to understand my care better than before I used the app.
2. Vinehealth has helped me to self-manage my care better than before I used the app. (* Self-management aims to empower you to take control of your condition and better manage your own health.)
3. Vinehealth has helped me to understand my condition better than before I used the app.
4. Vinehealth has helped me manage my condition better than before I used the app.
5. Vinehealth has allowed me to keep a more consistent record of my wellbeing
6. Vinehealth has improved my overall wellbeing
7. Vinehealth has helped to ensure that I adhere to my medications better than before I used the app.
8. Vinehealth has enabled me to communicate with my care team better than before I used the app.
9. Vinehealth has helped me to feel more in control of my care compared to before I used the app.
10. I am likely to recommend Vinehealth to my peers who also have cancer.
11. Vinehealth provides accessible, engaging and friendly digital content
12. Vinehealth is easy to use.
13. I will continue to use Vinehealth now that the study is complete.

Clinicians

To what extent do you agree with the following statements:
(all answers are a scale from: Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree, Not Applicable)

1. Vinehealth has helped to improve patient-clinician communication.
2. Vinehealth has helped me to assess my patient's symptoms better.
3. Patient reported data presented in VinehealthPRO has supported me in making clinical decisions
4. Patient-reported data, sorted by the number of severe CTCAE symptoms in VinehealthPRO informed appropriate triage (i.e. deciding which order patients should be seen)
5. Patient-reported data through Vinehealth has helped me to provide better care for my patients.
6. Patient-reported data delivered through VinehealthPRO has decreased time to capture a patient's history.
7. I am highly likely to recommend Vinehealth PRO to my colleagues.
8. I am highly likely to recommend the Vinehealth app to my patients.

9. Vinehealth PRO is easy to use.
10. Vinehealth PRO is safe to use.