FULL/LONG TITLE OF THE STUDY:

User experience study of digital tools to collect data on wellbeing and side effects in cancer patients.

PROTOCOL VERSION NUMBER AND DATE V11.0 10 Apr 2024

RESEARCH REFERENCE NUMBERS

Name and Address of Sponsor:	Netherlands Cancer Institute on behalf of Cancer Core Europe (CCE) Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965397

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

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Position:

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Principal Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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TABLE of CONTENTS

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STUDY SUMMARY

Study Title	User experience study of digital tools to collect data on wellbeing and side effects in cancer patients.	
Study Design	Feasibility study	
Study Participants	• All patients enrolled in phase 1 or 2 anticancer drug trials and; • Healthcare professionals (medical oncologists, nurse practitioners) monitoring these patients.	
Planned Size of Sample	Patients included in investigational drug trials, expected number around 60. Also, a minimum of 1 Healthcare professional at each site in the study.	
Planned Study Period	4 weeks	
	Objectives	Outcome Measures
Primary	To evaluate the feasibility of using digital tools to report effects of drugs in patients on phase 1 or 2 anticancer drug trials	• Number of patients screen failing or withdrawing from study • Proportion of patients complying with agreed scheduled use of the tool (daily for 28 days).
Secondary	To evaluate user experience of using different digital tools to self-report on adverse events and quality of life.	• End of study questionnaire completed by patients. • Semi-structured interviews with healthcare professionals.

Exploratory	Explore the richness of the data reported by patients using digital tools and validated quality of life instrument.	• Output of PROACT 2.0 questionnaire and analysed videos. • Output of validated quality of life instrument – EQ5D5L
Selection criteria		
Inclusion Criteria	• Patients in screening for participation in a phase 1-2 anticancer drug trial • Written informed consent to participate in the study.	
Exclusion Criteria	• Not capable of using mobile phone applications, or no carer who is willing to and able to use the applications on the participants behalf. • Enrolled in a phase 1-2 anticancer drug trial that includes a QoL questionnaire, where inclusion of an additional QoL would interfere with the study's intended QoL measurements. This is at the investigator's discretion.	

FUNDING AND SUPPORT IN KIND

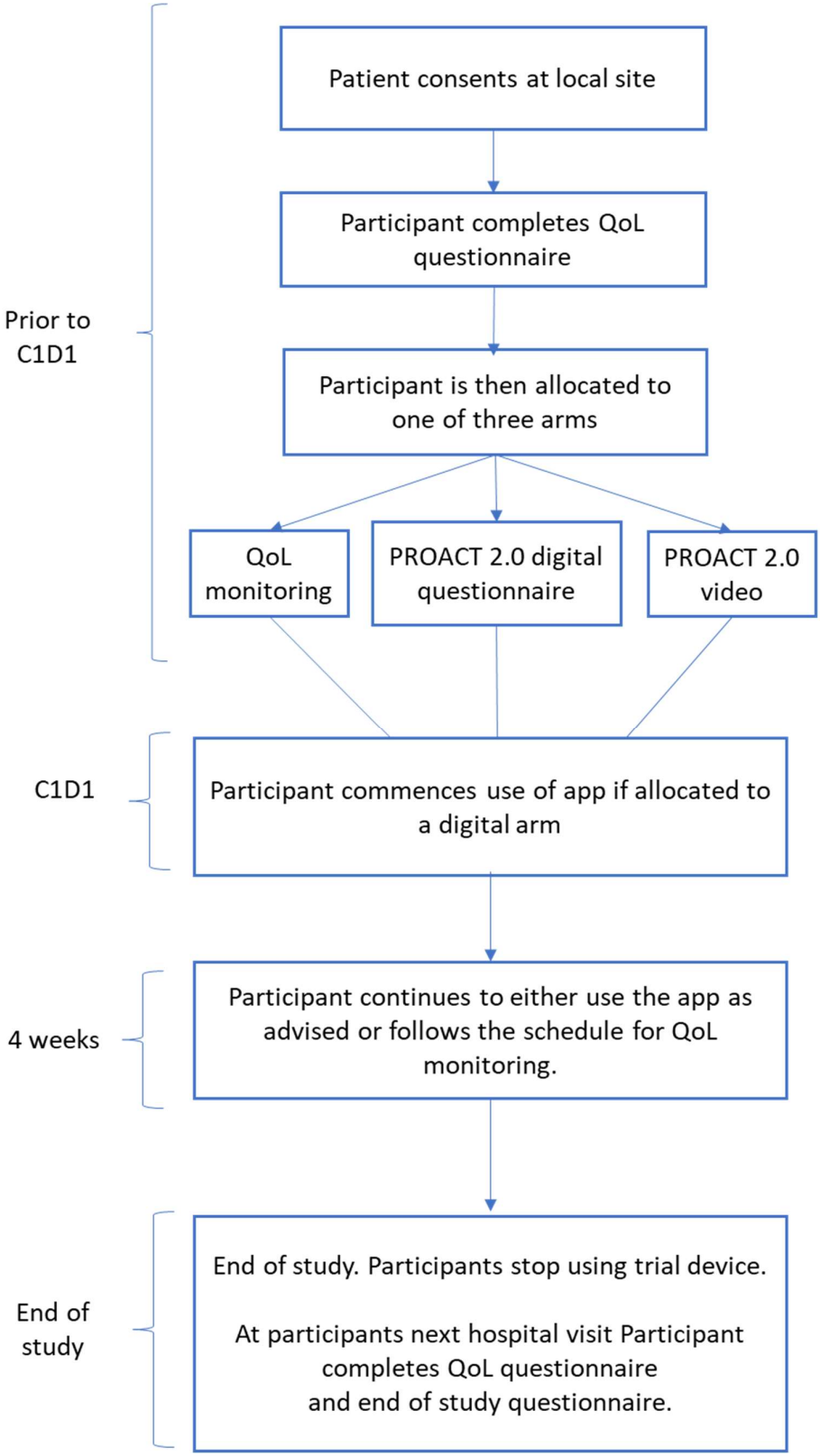
FUNDER(S)
Horizon 2020 European Union Funding for Research & Innovation program. Grant agreement number: 965397

KEY WORDS: Digital tools; PROACT 2.0; toxicity; phase 1; phase 2.

ABBREVIATIONS

AE	Adverse Event
CCE-DART	Cancer Core Europe – DATa Rich clinical Trials
CTIMP	Clinical trial of investigational medicinal product
DLT	Dose Limiting Toxicity
GCP	Good Clinical Practice
HRQoL	Health-related Quality of Life
IMP	Investigational medicinal product
NKI	Netherlands Cancer Institute
PIS	Patient Information Sheet
PROACT 2.0	Patient Reported Outcomes about Clinical Tolerability version 2.0
QoL	Quality of Life
PRO-CTCAE	Patient-Reported Outcome - Common Terminology Criteria for Adverse Events
GCP	Good Clinical Practise
GDPR	General Data Protection Regulation
eCRF	Electronic Case Report File
CRF	Case Report File
WHO	World Health Organsiation

STUDY FLOW CHART



1 BACKGROUND

1.1 Overview

Precision cancer medicine has created a rapid evolution of clinical research, with new types of adaptive, basket and umbrella clinical trials, amongst others, currently being developed with the aim of optimizing the biomarker-drug co-development process tailored to each disease setting[1]. However, all too often, cancer patients receive treatments which can be toxic, ineffective, or both[2]. Since cancer treatments often have a narrow therapeutic index, it is more important than ever to conduct smarter clinical trials which more effectively identify toxicities that significantly impact a patient's quality of life so we can truly deliver the right drug, for the right patient, at the right time, with the right tolerability profile.

1.2 Adaptive clinical trial designs

Clinical trials are the best source of clinical evidence but in many prospective trials, novel treatments are tested in large, unselected patient populations, the average effect size is modest, and the reasons for response / non-response in individual patients are poorly understood[2]. Platform trials enable the acquisition of prospective data from multiple patient cohorts and facilitate the study of biomarkers associated with chemosensitivity. However, current studies still are too rigid and have too many limitations that do not allow them to adapt to the speed of the discoveries in the oncology field, especially in the academic setting. In the digital age, new technologies can be adapted to clinical trials to enhance their performance in different ways[3].

With the aim of improving the design and implementation of clinical trials, and the use of newer, more effective methods, the CCE-DART project (Cancer Core Europe – Data Rich clinical Trials) was established to address a number of critical issues. Divided into four broad areas these are;

(i) use of more efficient clinical trial methodology.

(ii) incorporation of more accurate, integrated, and dynamic imaging and molecular markers of tumour drug response to treatment into the design and implementation of clinical trials.

(iii) development of digital tools facilitating the trial management and clinical-decision-making; and

(iv) patient empowerment/ engagement.

1.3 Health Related Quality of Life reporting

Side effects, or adverse events (AEs), arising from anticancer therapies can result in a diminished health-related quality of life (HRQoL). Inadequate symptom monitoring and reporting can lead to worsening of AEs, emergency department visits, hospital admissions and increased impact on HRQoL[4]. Studies have demonstrated the importance and value of direct patient involvement in developing an improved understanding of how cancer medicines impact drug tolerability and a patient's quality of life[5–7].

The ubiquity and high availability of low-cost smart devices and affordable broadband (4G) is now enabling the development and implementation of new clinical applications, which can enable improved drug side effect monitoring outside of the hospital[8-9]. Importantly, while the risk of inequality in the context of the digital divide still exists, it is significantly less in the mobile setting, with most of the public having access to technology[10]. The OFCOM 2020 report found that 82% of the public have a smartphone, and 87% of the population access the internet. 70% of adults 65-74 access the internet and 49% of 75+ adults[10]. Serial capture of these clinical data directly from patients has the potential to transform the patient's role in the clinical trial and provide important and vital information, which can guide optimal dosing and scheduling of cancer therapies.

Over the past 10 years, studies have shown that patient involvement in the reporting of their symptoms has demonstrated differences between what patients identify as important to their quality of life (QoL) compared with physicians[11–14]. Traditionally, the patient's QoL is assessed at different timepoints in a clinical study using a formally validated HRQoL instrument in the form of a questionnaire. The benefits of assessing patients HRQoL have been well described in the literature[15,16]. One study compared patient reporting of eight symptoms using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30 or QLQ), alongside physicians' reporting on the same eight symptoms in the study's adverse events log. This study showed that clinicians significantly under reported patient symptoms in a chemotherapy clinical trial[17]. Additionally, a phase 1 study evaluating dose limiting toxicities (DLTs) found that patient-reported assessment of tolerability and toxicity may help to better adapt the standard DLT definition to best define the recommended phase 2 dose[18]. Patient engagement and involvement in reporting symptoms is important and enriches the clinical understanding and impact of new and existing cancer therapies.

1.4 Digital solutions

Traditionally, digital solutions have focused on an online or mobile questionnaire-based tool to enable patients to provide information regarding their symptoms while on cancer treatment. These tools have demonstrated clinical utility[4,19]. The PRO-TECT study evaluated the implementation of electronic patient-reported outcomes (ePROs) utilising the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and their value in the management of patients. This study demonstrated how ePROs improved discussions with patients, empowered patients and improved physician decision making[20]. Additionally, the clinical utility of an artificial tool was demonstrated in a study showing a 69% reduction in risk of having a pain-related admission during the study for those who used the app[21].

Furthermore, the original PROACT study (PROACT 1.0 - Patient Reported Outcomes about Clinical Tolerability) demonstrated a new way for patients to interact with technology while on a clinical trial. The PROACT app enabled the capture of additional information by facilitating communication between patients, their clinical team, and feedback to the Sponsor, on specific topics such as safety, dosage administration and study design, while also providing added and complementary information on tolerability[19]. PRO-CTCAE is a patient-oriented digital tool to collect AEs from patients in real time. The National Cancer Institute developed the PRO-CTCAE to best capture 78 discrete toxicities in oncology clinical trials through direct patient reporting[4,22]. Subsequent evaluations of the PRO-CTCAE showed that patients grade symptoms up to 40% higher compared to clinicians[23]. The National Cancer Institute adapted these PRO-CTCAE into a diary questionnaire, which can be used on a daily basis for registration of toxicities.

For this study both the PROACT application and PRO-CTCAE questionnaire will be incorporated into the new PROACT 2.0 system to assess the multi-functionality of the system in assessing toxicities.

1.5 Study applications

Part of the CCE-DART project relies on the development and implementation of informatics tools that, alone, will involve important management improvements as they address unmet needs in current clinical trial designs. Some of these tools have already been developed and, under the CCE-DART umbrella, they will be validated, optimised, and refined for their use in a clinical setting. Specifically, the following tool has already been tested in other settings providing the adequate grounds for the estimation of their potential impact:

PROACT 2.0 is a digital healthcare platform which enables patients to self-report how they are feeling and functioning on a clinical trial via text, voice note, video or digital questionnaire. It can also be used to transmit information related to the trial to patients and caregivers through its broadcast functionality. Overall, the PROACT application has been trialled by 30 patients across two 'technology' clinical trials. PROACT 1.0 was trialled in an initial Proof-of-Concept study recruiting 8 patients in 2016 and then 22 patients were enrolled in the PROACT 1.0 study at The Christie NHS Foundation Trust and The Clatterbridge Cancer Centre. The first study reported 41 AEs. In the second study, 131 messages (14 video, 2 audios, 115 text) were sent by patients, 37 message events were associated with 43 AEs and in 32 message events the patients stated that they were in good health. The feedback from patients and nursing staff has been very supportive and positive. PROACT 2.0 has been developed by Fondazione IRCCS Instituto Nazionale dei Tumori di Milano, Italy as part of the Cancer Research UK UpSMART Accelerator Award, taking into consideration feedback from healthcare professionals and patients. Under this protocol the new PROACT 2.0 system will be implemented in a large heterogeneous clinical setting for the first time[19], focusing on two of the features of this digital tool – video and the digital questionnaire.

The PRO-CTCAE digital questionnaire will be uploaded into PROACT 2.0 for this study, and it will be the first time that this digital questionnaire will be implemented in a large clinical patient cohort.

1.6 Study Proposal

This is a feasibility, non-CTIMP study within CCE-DART, designed to investigate the feasibility of collecting QoL information from patients via digital tools. By feasibility, we mean the assessment of the uptake of the tool, the compliance to schedule and the quality of the data collected. Additionally, we aim to better understand the experience of patients and healthcare professionals in the use of digital tools to collect clinical data on well-being and adverse events. The study will be conducted alongside the patient's standard care and will not interfere in their trial-specific treatment.

This study will form part of a package of work within the CCE-DART project. This work package (WP12) aims to study and implement digital tools in clinical trials within Cancer Core Europe. It is important to note that this is not a Medical device Reporting (MDR) study.

1.7 Patient and Public Involvement

Over several years there has been continuous and extensive input from patients throughout the development of the PROACT tool and the development of this and previous protocols. The PROACT 1.0 application was originally designed with full patient involvement, and feedback on the utility of the

PROACT 1.0 tool was provided by patients and healthcare professionals at the end of the original study. Furthermore, the PROACT 2.0 system has been trialled in a feasibility study of 20 patients with positive feedback.

Additionally, patients were consulted on the usefulness of collecting HRQoL data and how they felt it would benefit them and their care. Feedback from interviews with patients indicated that they were enthusiastic about the prospect of monitoring HRQoL parameters that impacted areas of their life that were important to them, e.g., going for a walk every day. They wanted to have the opportunity to set these goals prior to the start of their treatment. Further patient engagement was carried out to assess the use of technology in the collection of HRQoL assessments. Understandably there were concerns about the potential to exclude technology illiterate patients from studies; however, they did concede that due to the COVID-19 pandemic older patients have become more technologically savvy. They stressed, in strong terms, their support for the study and its aims. The majority favoured the use of a video as a training method to show how to use the technology in the study.

2 OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

Objective	Measures
Primary Objective To evaluate the feasibility of using digital tools to report effects of drugs in patients on phase 1 or 2 anticancer drug trials	• Number of patients screen failing or withdrawing from study. • Proportion of patients complying with agreed scheduled use of the tool (daily for 28 days).
Secondary Objective To evaluate user experience of using different digital tools to self-report on adverse events and quality of life.	• End of study questionnaire completed by patients. • Semi-structured interviews with healthcare professionals.
Exploratory Objective Explore the richness of the data reported by patients using digital tools and validated quality of life instrument.	• Output of PROACT 2.0 questionnaire and analysed videos. • Output of validated quality of life instrument – EQ5D5L.

3 RESEARCH QUESTIONS

The aim of this study is to evaluate the feasibility of using digital applications to report the effects of investigational medicinal products (IMP) on the quality of life of cancer patients.

The research hypothesis is that using patient centered tools, such as PROACT 2.0, improves our understanding of QoL through proactive and dynamic engagement with patients. We hypothesise that this engagement will: help reduce recall bias; ensure we are capturing QoL data important to patients; and, more importantly, will allow healthcare teams to proactively engage with patients and intervene earlier where issues are reported. Furthermore, real time reporting of IMP toxicities will allow for a more comprehensive understanding of IMP profiles.

3.1 Objectives

3.1.1 Primary Objective

To evaluate the feasibility of using digital tools to report effects of drugs in patients on phase 1 or 2 anticancer drug trials.

3.1.2. Secondary objectives

To evaluate user experience of using the different digital tools to self-report on adverse events and quality of life.

3.1.3 Exploratory objectives

Explore the richness of the data reported by patients using digital tools and validated quality of life instrument.

3.2 Outcomes

3.2.1 Primary outcomes

The primary outcome measures for this study are:

- Number of patients screen failing or withdrawing from study
- Proportion of patients complying with agreed scheduled use of the digital tools (daily for 28 days).

Adherence to agreed usage schedule of at least 75% would be considered acceptable for feasibility for assessment of the digital tools.

3.2.2 Secondary outcomes

The secondary outcomes are

- End of study questionnaire complete by patients.
- Semi-structured interviews with healthcare professionals.

3.2.3 Exploratory objectives

The exploratory outcomes of this study are:

- Output of PROACT 2.0 questionnaire and analysed videos.
- Output of validated quality of life instrument – EQ5D5L

4 STUDY DESIGN

4.1 Overview

This is a feasibility study evaluating whether patients receiving anticancer treatment in phase 1 or 2 anticancer drug trials executed in Cancer Core Europe Centres will use digital applications to record HRQoL data. It will also assess the user experiences of patients and healthcare professionals of PROACT 2.0. The study will be performed in accordance with Good Clinical Practise (GCP), and all key trial personnel will be appropriately trained.

4.2 Trial Population

All potential study participants will be seen and assessed against eligibility criteria whilst already enrolled (cannot have started treatment) or attending for consideration for participation in a phase 1 or 2 clinical trials. Study participants will be selected by treating physicians from the several Cancer Core Europe centres participating in the DART WP12 project. Potential participants will be provided with a patient information sheet (PIS) and invited to voluntarily consent to participate in the feasibility study. It should be made clear to the potential trial participant that consent is voluntary and can be withdrawn at any time without any impact on their ongoing medical care.

If a potential participant declines entry into the study, the reasoning for this will be documented in the screening log where possible.

Potential study participants should be given sufficient time to consider participation in this study before consent is elicited. No activities for the study can be undertaken before consent had been obtained. After consent has been received the patient will be formally assessed for eligibility for the study against inclusion and exclusion criteria of the study protocol.

5 RECRUITMENT AND TRIAL PROCEDURES

5.1 Inclusion criteria

There will be no exception to the eligibility requirements at the time of registration. Patients are eligible if all inclusion criteria are met and none of the exclusion criteria apply.

1. Screening for participation in a phase 1-2 anticancer drug trials.
2. Written informed consent to participate in the study.

5.2 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

1. Not capable of using mobile phone applications, or no carer who is willing to and able to use the applications on the participants behalf.

2. Enrolled in a phase 1-2 anticancer drug trial that includes a QoL questionnaire, where inclusion of an additional QoL would interfere with the study's intended QoL measurements. This is at the investigator's discretion.

A patient can be supported in this study by a carer e.g. if the patient does not have access to a suitable device but a carer is willing to provide access to one for them. However, the role of the carer should be limited to support in accessing the tool and they should not complete the videos or questionnaires on the patients behalf.

5.3 Withdrawal

Possible reasons for withdrawal:

1. Withdrawal of consent.
2. Loss of capacity/ability to carry out study requirements as deemed by participant's primary medical team. Loss of capacity will be monitored by the patients Phase 1-2 trial team.
3. Safety reasons
4. Participant's decision to withdraw.

5. Severe non-compliance to protocol as judged by the investigator and/or Sponsor.

If at any time a participant expresses a wish to withdraw consent for ongoing study participation, the following procedures will be observed:

1. Withdrawal of consent will be clearly documented in the study documentation and the study participant's medical record.

2. No further clinical data will be collected from the study participant. However, existing clinical data held will be retained and may still be used in future research by researchers who have a legitimate interest in the study data.

3. The study participant's privacy will be respected and preserved.

If a participant consents to the study but subsequently becomes unable to give consent, they will be withdrawn from the study; the reason for withdrawal will be documented by the team but no further information will be collected. Previously obtained data will still be used in the study.

5.4 Recruitment

Patients in screening for a phase 1-2 trial will be informed of this feasibility study and given the PIS by their treatment team. Patients must not have commenced treatment in order to qualify to join the feasibility study. For trial entry a patient must fulfil all inclusion criteria and no exclusion criteria; this preliminary check against eligibility will be conducted by the patient's treating clinician.

A patient can be supported in this study by a carer e.g. if the patient does not have access to a suitable device but a carer is willing to provide access to one for them. However the role of the carer should be limited to support in accessing the tool and they should not complete the videos or questionnaires on the patients behalf.

5.5 Consent

All patients are required to sign an informed consent prior to taking part in this feasibility study. All potential participants will receive a PIS at first point of identification of the patient by the clinician and provided with sufficient time to consider this and ask questions. The PIS will outline the benefits and risks of taking part in this study. Once potential participants have had sufficient time to consider the information in the PIS they will be invited to consent for the study. Once consent is obtained the patient will be formally screened against eligibility criteria.

It should be made clear to the potential study participant that consent is voluntary and can be withdrawn without giving reasons and without prejudicing their ongoing/future care. If a potential participant fails screening or withdraws from the study, where possible, the reason for this will be documented.

Consent will be taken by a researcher who is appropriately trained and who has been delegated by the PI (Principal Investigator) to undertake this activity (and this is clearly documented on the delegation log). No study-related activities can be undertaken prior to consent.

The original, signed copy of the PIS and consent form(s) will be retained in the Investigator Site File, with a copy in the participant notes and a copy provided to the participant.

5.6 Prior to C1D1

The following information will be collected from patients at baseline in their screening period before being included in a specific phase 1-2 trial

- Patient demographics (age in years, year of birth, ethnicity, sex and tumour type)
- Quality of life questionnaire
- WHO performance status (World Health Organisation)
- Treatment start date
- Type of drug: targeted therapy/immunotherapy/other

5.7 Trial arms

After the screening period is complete, participants will be allocated to one of the three arms based on an allocation schedule assigned by site as follows:

- NKI - 1;2;3
- VHIO- Spain - 2;3;1
- INT - Italy: 3;1;2
- Cambridge - UK: 1;2;3
- Heidelberg - Germany - 3;1;2

Where (1) is PROACT 2.0 video; (2) is PROACT 2.0 digital questionnaire; and (3) is standard QoL monitoring. The arm they are allocated to will be recorded. All arms will last for 4 weeks.

5.7.1 Quality of Life paper questionnaire

This study will use a standard QoL monitoring questionnaire (EQ5D5L). Participants on all arms will complete a QoL questionnaire after consent but before C1D1, during any hospital visit in the 4-week trial period (only when allocated to the QoL arm) and at the end of the study.

5.7.2 PROACT 2.0

If allocated to an arm requiring the use of the app, participants will be provided with training on how to use PROACT 2.0.

PROACT 2.0 is a digital healthcare solution that allows users to record video, voice, text messages and undertake digital questionnaires which can be accessed directly by their care teams. For the purpose of this study, videos will not be reviewed by the patient's care team until after 30 days of receiving the message.

Participants on the PROACT 2.0 arms will be required to use the application every day for the duration of the 4-week study. Patients on the video arm will be asked to record any information on symptoms or impact of treatment – whether positive or negative. Participants on the digital questionnaire arm will answer questions about adverse events experienced in the previous 24 hours. If participants are concerned about their symptoms, they are to follow standard procedure and contact their care team directly and not through the PROACT 2.0 app.

5.8 Trial Visits

When a participant attends a standard trial visit whilst on a phase 1- 2 trial, both scheduled and unscheduled, the following information will be recorded for the feasibility study:

- End date of study treatment, if applicable.
- The reason to end participation in the study

5.9 End of study visit

After the 4-week study period, participants will attend for their end of study visit; this will be when they next attend for their drug trial visit. At the end of study visit, participants will be asked to complete a questionnaire to assess their experience of the study. Additionally, they will be required to complete one last QoL monitoring questionnaire.

The following information will also be collected from patients by the healthcare professional.

- WHO performance status

5.10 Qualitative assessments

At the end of the study period, eligible participants will be asked to complete the end of study questionnaire to assess their experiences with PROACT 2.0. Participants will be asked a series of questions relating to their experience of the process and all aspects of the study. The questions will broadly assess the following parameters:

- Overall impressions of the study.
- Opinions on the app functionality they were allocated to, if applicable.
- Adherence to and opinion of scheduling.
- Any further reflections or observations.

On completion of the study, eligible healthcare professionals (those involved in this study) will be requested to participate in a semi-structured interview to assess their experiences with PROACT 2.0. Participants will be asked a series of questions relating to their experience of the process and all aspects of the study. The questions will broadly assess the following parameters:

- Overall impressions of the study.
- Opinions on the app.
- Adherence to and opinion of scheduling.
- Any further reflections or observations.

All interviews should last no longer than 1 hour and will take place virtually. Interviews will be led by a member of the study team, who will transcribe the responses received to each question.

5.11 End of study

The study will close to recruitment with registration of the last trial participant. The study will close after all interviews with healthcare professionals have been completed and transcribed.

5.12 End of Study Notification

The end of study notification will be submitted in accordance with each country's ethical guidelines.

6 SCHEDULE OF ASSESSMENTS

Table 1 – Study schedule

	Pre-treatment period	Study period	End of study
	Prior to C1D1	**Day 1-28**	**Day 29 onward**
Informed consent	x		
Review of eligibility criteria	x		
PROACT 2.0 video		(x[1])	
PROACT 2.0 digital questionnaire		(x[1])	
End of study questionnaire			x
QoL questionnaire EQ5D5L	x	(x[2])	x

[1] Participants on PROACT 2.0 arms will use the application every day during this period. Patients will be allocated to use the video or the questionnaire, not both.

[2] Participants on the QoL questionnaire arm will complete QoL questionnaires when they attend for hospital visit.

5.13 Study Summary Report

The study team and Principal Investigator are responsible for compiling and submitting the final study report to the Sponsor and all relevant ethics committees within one year of study closure.

7 STATISTICS AND DATA ANALYSIS

7.1 Statistical Analysis

This is a feasibility study, therefore due to the exploratory nature of this study the sample size will be 60 patients. As there are 5 sites participating in the study, we will look to enrol up to 12 patients at each site.

Study feasibility calculation	
Number of participating sites	5
Number of patients per site per month (all have confirmed alteration)	1
Prevalence (All patients will have alteration	100%
Dropout rate	5%
Screen failure (cannot join study)	5%
# Enrolled patients	60
Start date	April-24
DURATION OF STUDY (months)	12
LSI (last Subject in)	April-25
Outputs	Oct-25
Total Pts Pre-screens required	66

For all objective outcomes we will use descriptive statistics: the outcomes of interest are dichotomous (e.g., cut-off scores from questionnaires indicating a clinical problem) and continuous (e.g., quality of life scores). Administered questionnaires will be quantitively analysed. Notes from interviews with healthcare professionals will be coded and thematically analysed.

8 DATA MANAGEMENT

Data collected from this study will be done so in line with CCE-DART SOPs (standard operating procedures) and processed in accordance with EU regulation 2016/679 (GDPR). For sites in the UK data will be processed in accordance with The Data Protection Act 2018, General Data Protection Regulations 2018 and Freedom of Information Act 2000. Storage will be secure; physically within a secure area with limited access and electronically on secure servers or in secure cloud environments, behind appropriate firewalls, with regular back up. Each centre participating in the project will be responsible for protecting the confidentiality of the participants data that are collected.

The protection of personal data will comply with the local, national and European or UK standards (as applicable) for protection of privacy and confidentiality. In all cases, this will include the pseudonymisation of each participant, by replacing their name by a code that will make any direct identification impossible. This code (trial identifier based on study, site and chronological order e.g. PRONL001; PRONL002) will be used in all exchanges of information related to this participant. Sensitive hard copy records such as medical and trial-related records will be kept in a key-locked, access-restricted place, and computer access to sensitive electronic data will be password protected.

Access to this information and to the identity of the study participants will be strictly restricted to the physicians in charge of the participant and with their explicit authorisation, to data managers in charge of the study, study monitors and authorised regulatory bodies.

The pseudonymised data (primary data and the data resulting from CCE-DART analyses) will be accessible only to project partners and to the scientific community under the controlled access mode. The applicant credentials, research purposes and commitment of preserving data confidentiality will be carefully checked by the project Steering Committee before allowing access to data. The project will design and implement a storage system for processed data (defined in the master Data Management Plan).

Under appropriate circumstances, representatives from the regulatory authorities will be given access to the records that relate to a specific study. They will have full access to the coded CRF (case report form) for the purposes of data validation. Results of a study may be communicated at scientific meetings and will contribute to the scientific literature. At no time will this be done in such a way that an individual participant may be identified.

Informed consent will be signed before enrolment in this study. Data will be pseudonymised. Key files with the trial identifier keys and hospital identifiers will be stored on a secured server, separately from the study file, which can be accessed by authorised persons only. All essential documents (including patient files, the Investigator Study File, CRFs and electronic study data), data management and statistical files will be retained and archived for 15 years after end of trial.

Videos and questionnaires submitted in PROACT 2.0 will not be reviewed until a minimum of 30 days has passed since the healthcare team receive them. After this time, delegated Healthcare professionals at site will access the videos via the PROACT 2.0 analyst console, to the videos and generate analyst tags using the predefined lexicon options within the analyst console. Analyst tags and the questionnaires will be stored in the Milan Microsoft Azure server until analysis at the end of the study.

If a Video or Digital Questionnaire is reviewed by an on-site Healthcare professional within the 30day window, they will have a duty of care to follow local SOPs for any concerns referenced in the communication.

To protect patient data privacy, The videos are only viewed, at the point of analysis, by an authorised member of the patient's local healthcare team (the reviewer). The patient will be known to them. No one else will be instructed to view the videos. From the Videos, the reviewer will identify symptoms and impacts and record these as analyst tags (following a predefined lexicon) in the analyst console (part of PROACT2.0). These analyst tags will be pseudonymised and only reference the trial ID. Only the pseudonymised analyst tags will be viewed and analysed by the research team (digital ECMT based in

the UK). No one outside of the Patient's Healthcare team will view the videos, thus protecting the patient's privacy.

A Data Transfer Agreement (DTA) will be signed before sharing data. Data will be treated in accordance with the provisions of the General Data Protection Regulation (GDPR). Videos generated from PROACT 2.0 will be managed in accordance with the master data management plan.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Assessment and management of risk

The study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).). Informed consent will be signed before enrolment in this study.

A potential risk from this study is the potential for a data leak. To mitigate this risk, data will be pseudonymised and linked only by a trial ID. The trials IDs will be assigned to enrolled patients and the files containing the trial IDs and hospital identifiers will be stored on a secured server at each site, separately from the study file, which can be accessed by authorized persons only. The trial ID files will never be transferred or shared outside of the study site.

Another potential risk is creating additional burden for the patients participating in this study. The task of filling in each questionnaire will be less than 5 minutes every day; this will be done during the study period. However, as this is a feasibility study, part of the process is to understand whether these questionnaires pose an additional burden, and this will be discussed with the participants at the end of the study.

Another potential risk is that an on-site Healthcare professional reviews a patient video or digital questionnaire within the 30 days of the healthcare team receiving them. If this occurred, they would have a duty of care to follow local SOPs for any concerns referenced in the communication.

The use of technology in this study excludes patients who do not have access to technology or who do not have a good grasp of technology. We plan to offer detailed instructions and training to help those who are less capable. Other than the potential for additional burden, there are no other direct risks for the patient associated with participating, nor are there any direct additional benefits.

9.2 Research Ethics Committee (REC) and other Regulatory review & reports

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC. The Sponsor is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Sponsor is also responsible for promptly informing the IRB/EC of any protocol amendments.

All participating sites must undergo site specific assessment of capacity and capability prior to their participation in the study. All investigators and key study personnel will be appropriately trained in GCP.

The study will be conducted in accordance with, but not limited to, the Human Rights Act 1998, The Data Protection Act 2018, General Data Protection Regulations 2018, Freedom of Information Act 2000 and the UK Policy framework for Health and Social Care research as amended from time to time, the Human Tissue Act 2004 and the Mental Capacity Act 2005.

Where participants agree to take part in the study, they will be informed of how data are recorded, collected, stored and processed and transferred to other countries, in accordance with The General Data Protection Regulation (EU-GDPR, 2016/679. Studies conducted in the EU or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC) as well as the European general data protection regulation (EU-GDPR, 2016/679). As the Sponsor of the study is a non-commercial organisation the legal basis for the handling and processing of data is 'task in the public interest'.

9.3 Amendments

Any changes in research activity will require an amendment and will be initiated by the PI. Proposed changes must be submitted in writing to the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB / EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

The research team will maintain an amendment history log to ensure that the most recent version of the protocol and supporting documents are used at all times.

9.4 Patient & Public Involvement

Several focus groups and studies have been held to discuss the PROACT 2.0 application. For more information on public and patient engagement in this study please see section 1.7.

9.5 Protocol compliance

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB / EC in accordance with established IRB / EC policies and procedures.

9.6 Data protection and patient confidentiality

8.6.1 GDPR and Data Protection

Sensitive participant data will be collected, stored and used in accordance with GDPR regulations.

9.6.2 Access to Data

Direct access will be granted to authorised representatives of the Sponsor. Participants of the study who wish to gain access to their own data will be provided with information on how to access this at the end of the trial period.

9.6.3 Archiving

All essential documents (including patient files, the Investigator Study File, CRFs and electronic study data), data management and statistical files will be retained and archived for 15 years after the end of the trial.

9.7 Dissemination policy

The data arising from this study will be owned by the CCE consortium. At the end of the study, all data will be analysed by the digital ECMT within their secure cloud environment. Once completed a final study report will be prepared and can be accessed at the CCE consortium No site or individual will publish this data without prior approval of the Sponsor.

The Sponsor is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from this study and for assuring the confidentiality and integrity of the study. The International Committee of Medical Journal Editors criteria will be used to ensure all those who have contributed to the study are appropriately acknowledged. The Sponsor will be informed prior to any intended publications.

10 FUNDING

CCE DART project is funded by the Horizon 2020 European Union Funding for Research & Innovation program.

11 REFERENCES

1. Park, J. J. H. *et al.* Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* **20**, 572 (2019).

2. Lin, A. *et al.* Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials. *Sci. Transl. Med.* **11**, (2019).

3. Inan, O. T. *et al.* Digitizing clinical trials. *npj Digit. Med.* **3**, 101 (2020).

4. Basch, E. *et al.* Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JNCI J. Natl. Cancer Inst.* **106**, dju244–dju244 (2014).

5. Baker, A. Book: Crossing the Quality Chasm: A New Health System for the 21st Century. *BMJ* **323**, 1192–1192 (2001).

6. Vodicka, E. *et al.* Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007–2013). *Contemp. Clin. Trials* **43**, 1–9 (2015).

7. Lemieux, J., Goodwin, P. J., Bordeleau, L. J., Lauzier, S. & Théberge, V. Quality-of-Life Measurement in Randomized Clinical Trials in Breast Cancer: An Updated Systematic Review (2001–2009). *JNCI J. Natl. Cancer Inst.* **103**, 178–231 (2011).

8. R. Maguire, M. Miller, M. Sage, J. Norrie, L. McCann, L. Taylor & N. Kearney. Results of a UK based pilot study of a mobile phone based advanced symptom management system (ASyMS) in the remote monitoring of chemotherapy related toxicity. *Clinical Effectiveness in Nursing*. **9**, 202-210 (2005).

9 D. Ryan, W. Cobern, J. Wheeler, D. Price & L. Tarassenko. Mobile phone technology in the management of asthma. *Journal of Telemedicine and Telecare*, 11, 43-46 (2005).

10. OFCOM. *Online Nation 2020 Report*. (2020).

11. Janse, A. J. *et al.* Quality of life: patients and doctors don't always agree: a meta-analysis. *J. Clin. Epidemiol.* **57**, 653–661 (2004).

12. Chandwani, K. D. *et al.* Lack of Patient-Clinician Concordance in Cancer Patients: Its Relation With Patient Variables. *J. Pain Symptom Manage.* **53**, 988–998 (2017).

13. Veitch, Z. W. *et al.* Underreporting of Symptomatic Adverse Events in Phase I Clinical Trials. *JNCI J. Natl. Cancer Inst.* **113**, 980–988 (2021).

14. Basch, E. *et al.* Adverse Symptom Event Reporting by Patients vs Clinicians: Relationships With Clinical Outcomes. *JNCI J. Natl. Cancer Inst.* **101**, 1624–1632 (2009).

15. Bottomley, A. & Aaronson, N. K. International Perspective on Health-Related Quality-of-Life Research in Cancer Clinical Trials: The European Organisation for Research and Treatment of Cancer Experience. *J. Clin. Oncol.* **25**, 5082–5086 (2007).

16. Atkinson, T. M. *et al.* Clinician vs Patient Reporting of Baseline and Postbaseline Symptoms for Adverse Event Assessment in Cancer Clinical Trials. *JAMA Oncol.* **6**, 437 (2020).

17. Fromme, E. K., Eilers, K. M., Mori, M., Hsieh, Y.-C. & Beer, T. M. How Accurate Is Clinician Reporting of Chemotherapy Adverse Effects? A Comparison With Patient-Reported Symptoms From the Quality-of-Life Questionnaire C30. *J. Clin. Oncol.* **22**, 3485–3490 (2004).

18. Henon, C. *et al.* Patient-reported tolerability of adverse events in phase 1 trials. *ESMO Open* **2**, e000148 (2017).

19. Hughes, A. *et al.* Development and Evaluation of a New Technological Way of Engaging Patients and Enhancing Understanding of Drug Tolerability in Early Clinical Development: PROACT. *Adv. Ther.* **33**, 1012–1024 (2016).

20. Basch, E. *et al.* Clinical Utility and User Perceptions of a Digital System for Electronic Patient-Reported Symptom Monitoring During Routine Cancer Care: Findings From the PRO-TECT Trial. *JCO Clin. Cancer Informatics* 947–957 (2020). doi:10.1200/CCI.20.00081

21. Kamdar, M. M., Centi, A. J., Fischer, N. & Jethwani, K. Artificial-Intelligence Smartphone App Significantly Reduced Severity of Cancer Patients' Pain & Hospital Admissions. *ASCO* (2018).

22. Dueck, A. C. *et al.* Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol.* **1**, 1051 (2015).

23. Basch, E. *et al.* Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol.* **7**, 903–909 (2006).