Trial Protocol

F4S-2

Fit4Surgery 2:

A randomised controlled trial to investigate an App-based, motivation-theory grounded, personalised, comprehensive, prehabilitation programme in addition to usual care versus usual care alone to enhance recovery of physical function and reduce complications after lung cancer surgery

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number:	3.0
Version Date:	18 Apr 2023

Protocol development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

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This study is funded by the NIHR HTA programme as referenced above. The funder had no role in the trial design. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funder will have no role in the data collection, trial management, data analysis or interpretation of data, or in the writing of the final report.	

Protocol Sign Off

Chief Investigator Signature Page	
I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations. I agree to ensure that the 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 study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained	
Trial Name:	F4S-2
Protocol Version Number:	3.0
Protocol Version Date:	18 Apr 2023
CI Name:	Mr Babu Naidu _____ __ __ / __ __ __ / __ __ __ __
Sponsor statement: By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.	
Compliance statement: This protocol describes the F4S-2 trial only. This protocol should not be used as a guide for the treatment of patients not taking part in the F4S-2 trial. This trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.	

Principal Investigator Signature Page	
As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety. I agree to ensure that the 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.	
Trial Name:	F4S-2
Protocol Version Number:	3.0
Protocol Version Date:	18 Apr 2023
PI Name:	
Name of Site:	
Signature and date:	_____ __ __/ __ __ __/ __ __ __ __

Administrative Information

Reference Numbers	
Sponsor number	RG_21-046
ISRCTN reference number	<tbc>
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ABBREVIATIONS

Abbreviation	Term
AEs	Adverse Events
BCTU	Birmingham Clinical Trials Unit
CCI	Comprehensive Complication Index
CD	Compact disc
CEACs	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CRFs	Case Report Forms
CV	Curriculum Vitae
DAH30	Days alive and at home within 30 days
DCFs	Data Clarification Forms
DMC	Data Monitoring Committee
DMP	Date Management Plan
DSA	Data Sharing Agreement
EORTC-QLQ-LC29	EORTC-Quality of Life Questionnaire-LC29
EORTC-QLQ-C30	EORTC-Quality of Life Questionnaire-C30
F4S	Fit for Surgery app
F4S-2	The Fit for Surgery trial acronym
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratios
ICF	Informed Consent Form
ICU	Intensive Care Unit
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ISWT	Incremental Shuttle Walk Test
JSON	Java Script Object Notation
MCID	Minimum Clinical Important Difference
MP	Monitoring Plan
MP3	MPEC Audio Layer III

MDT	Multi-Disciplinary Team
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
ONS	Oral Nutritional Supplement
P	Probability
PA	Physical Activity
PG-SGA (SF)	Patient-Generated Subjective Global Assessment (Short Form)
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-Adjusted Life Years
RA	Risk Assessment
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SDT	Self Determination Theory
SoECAT	Schedule of Events Cost Attribution Template
SWAT	Study Within a Trial
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham
UK	United Kingdom
USM	Urgent Safety Measures
VAS	Visual Analogue Scales
WHO	World Health Organisation

DEFINITIONS

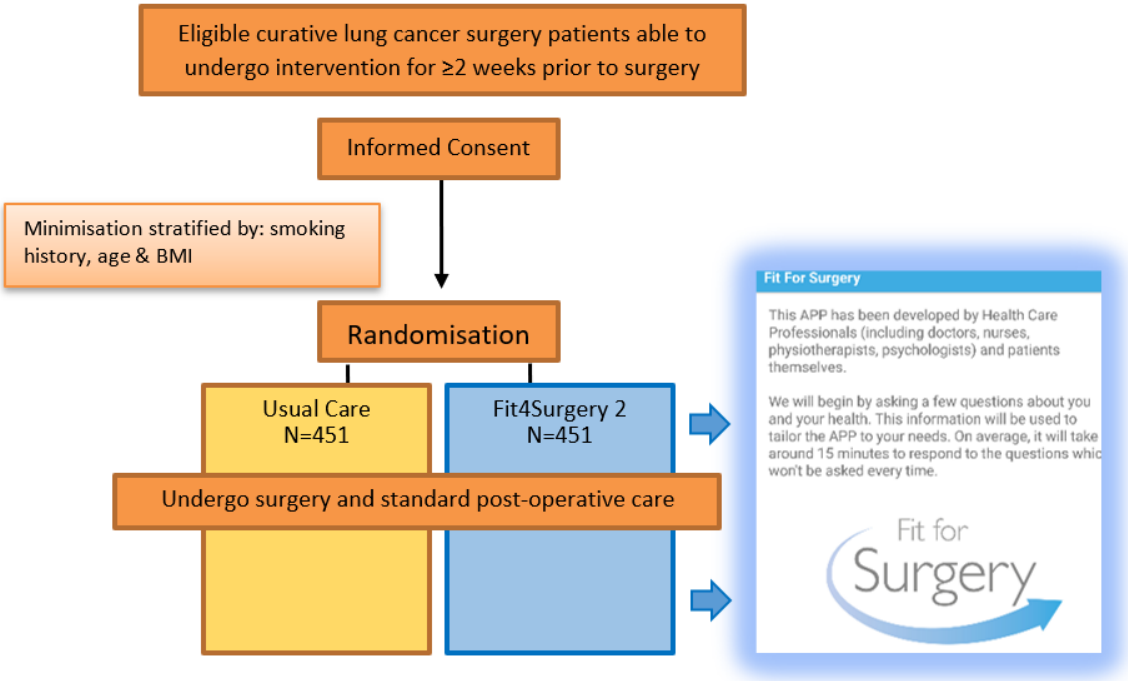
Term	Description
Patient	Person who has a suspected or confirmed clinical or pathological diagnosis of lung cancer and is awaiting surgery
Potential participant	Patient who has been approached about the F4S-2 trial and is considering participation
Participant	Patient who has given written informed consent and has been randomised to the F4S-2 trial

TRIAL SUMMARY

Title	Fit4Surgery 2 (F4S-2): A randomised controlled trial to investigate an App-based, motivation-theory grounded, personalised, comprehensive, prehabilitation programme in addition to usual care versus usual care alone to enhance recovery of physical function and reduce complications after lung cancer surgery.
Objectives	**Primary Objectives:** ● To establish the clinical and cost-effectiveness of the F4S App, a digital platform prehabilitation programme, consisting of personalised health information, a structured exercise programme and tailored nutritional conditioning in lung cancer surgery patients, in addition to usual care, when compared to usual care alone. **Secondary Objectives:** ● To examine the impact of prehabilitation on the overall quality of life and the mental health of the participant ● To use patient-submitted data to explore the trajectory of recovery with reference to muscle strength, physical endurance, nutritional status, symptoms and activities. **Economic Objectives** To establish cost-effectiveness of F4S compared to usual care, expressed as quality-adjusted life years (QALY).
Trial Design	Pragmatic, multicentre, open label, randomised controlled, two arm, parallel group trial with an internal pilot, an embedded SWAT, and health economic evaluation.
Participant Population/ Sample Size and Setting	902 patients who are about to undergo lung cancer surgery, recruited from approximately 20 sites across the UK.
Eligibility Criteria	**Inclusion Criteria** ● Adults aged 18 years or over ● With a suspected clinical or pathological diagnosis of primary lung cancer ● Selected for elective curative lung resection ● Able to undergo F4S-2 intervention for minimum of 2 weeks prior surgery ● Willing and able to provide informed consent ● Willing to use F4S app ● Willing to complete study questionnaires

	Exclusion Criteria ● Emergency surgery ● Patients requiring parenteral nutrition
Interventions	The F4S App & usual care versus usual care
Outcome Measures	**Primary Outcomes (dual primaries)** ● Patient-reported quality of physical function scale recovery (using the EORTC-QLQ-LC29) at 30 days after surgery ● Surgical complications (using the Comprehensive Complication Index (CCI)) at 30 days after surgery **Secondary Outcomes (Baseline, Day of surgery, 14 Days, 30 Days, 3 and 6 Months after surgery)** ● Days Alive and at Home Within 30 days (DAH30) ● Quality of Life (using the EORTC-QLQ-C30, LC29) ● Mental health/well-being (using the HADS) ● Symptom score (using a VAS) ● Motivation Processes ● Physical status assessed by the incremental shuttle walk test (ISWT), sit to stand test and hand grip test ● Patient-generated subjective global assessment short form (PG-SGA SF) **Health Economic Assessment** • Health Related quality of life (EORTC-QLQ-C30, LC-29 and EQ-5D-5L) • Health resource usage

Trial Schema



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1. BACKGROUND AND RATIONALE

1.1. Background

Surgery remains the best option for the cure of patients with lung cancer. Seven thousand such operations are performed in the United Kingdom (UK) each year, but post-operative complications occur in up to 45% of patients leading to readmission to hospital (13%), and up to a 5-fold increase in treatment costs. [1-4] Lung complications account for half of the post-operative complications. In these patients, 30 day mortality increases from 0.7 to 9%, Intensive Care Unit (ICU) admission rate from 1.9 to 28%, and hospital length of stay from 6 to 13 days. [5]

The burden to patients and to the National Health Service (NHS) continues to rise despite changes in surgery practice. Since 2015, there has been a sustained policy aiming to increase the numbers of patients receiving curative lung cancer surgery in order to improve the UK's poor ranking; 26th out of 29 European countries in lung cancer outcomes. [6] Thus, surgery is being offered to older and less fit patients, and the number of operations performed annually across the UK has increased by 12% over the last 3 years. [1,7]

1.2. Trial Rationale

The National Institute for Health and Care Research (NIHR) committees have prioritised "prehabilitation" in cancer care as an area of research needing attention. Prehabilitation is an important aspirational addition to the National Optimal Lung Cancer Pathway, which is being adopted across the UK. [8]

'Living With and Beyond Cancer' Priority Setting Partnership selected "specific lifestyle changes (e.g., diet, exercise and stress reduction) help with recovery from treatment, restore health and improve quality of life" among the top-ten research topics for the NHS.

Setting out NHS cancer outcome targets, the NHS Long Term Plan aims to facilitate patients recovering quickly and successfully from episodes of ill health, and improve survival from cancer.[9] Each year lung cancer costs the UK economy £2.4 billion, far higher than the cost of any other cancer.[10] Acute inpatient care accounts for more than 40% of this cost, and surgery is the biggest factor associated with increased cost.[11] The impact of delivering prehabilitation interventions on length of hospital stay, postoperative complications, ICU admissions and readmission rates will translate to NHS cost savings and improve patient-centred personalised care.[3,4]

The Health Technology Assessment (HTA) commissioning briefing (20/142) and MacMillan Cancer Support "prehabilitation evidence and insight review" highlights ***key gaps*** in cancer prehabilitation evidence and barriers to implementation in the pathway. [12] Currently, there is a lack of personalised, efficient and affordable programmes underpinned by the three fundamental prehabilitation stages: pre-assessment, intervention and post-treatment follow-up in the cancer care pathway.

1.2.1 Effectiveness of Exercise and Dietary Interventions

A systematic review and meta-analysis of 10 randomised controlled trials (RCTs) (involving 676 lung cancer surgery patients) showed that participants randomised to preoperative moderate intensity physical exercise for 1-4 weeks with 1-3 sessions per week had less dyspnoea and postoperative pulmonary complications, and shorter length of hospital stay compared with usual care participants.[13,14] About 1 in 10 preoperative lung cancer patients are underweight by World Health Organisation (WHO) definition, which doubles rates of mortality and morbidity compared with normal weight patients. [15-18] Meta-analysis confirms that oral nutritional supplements reduce complications after abdominal surgery. Combining exercise and nutritional conditioning in a multimodal approach seems to have an additive effect of further enhancing physical recovery after surgery. [19] Thus, national and international cancer, surgery and nutrition guidelines recommend prehabilitation and nutritional conditioning in lung cancer surgery patients. [20-23]

1.2.2 App Use in Healthcare

Smartphone Apps offer an opportunity to address healthcare challenges because of their widespread and ever-increasing use; 85% of the UK population own a smartphone, including 54% of >65 year olds. [24]

Evidence indicates Apps are successful tools for patient education, disease self-management, and remote monitoring. [25, 26] Systematic reviews and meta-analyses demonstrate that Apps have been used successfully as behaviour change tools to promote physical activity (PA). [26,27] One review highlighted enhanced efficacy when Apps are able to track PA/exercise behaviour, monitor progress toward PA goals, and incorporate options to undertake several types of PA. [28] To promote optimal and sustained behaviour change in PA, it is essential that interventions are theoretically grounded. [29-31] Self-Determination Theory (SDT) posits that where an individual feels a sense of autonomy (input, choice), competence (meets demands placed upon them) and connected (to others in a caring and supportive manner), in their attempts to change the targeted behaviour, this will promote greater autonomous motivation, which is linked to sustained engagement and well-being.[30] Meta-analysis of studies employing SDT has confirmed its utility as a viable

conceptual framework to study motivational processes, health behaviours and outcomes. Moreover, it is reported that health behaviour change interventions grounded in SDT are more cost-effective when compared to non-SDT grounded interventions. [31]

1.2.3 Justification for participant population

The target population in this trial is limited to adult patients (age ≥18) newly diagnosed with lung cancer referred for curative lung cancer surgery. This is because lung cancer is extremely rare in children, and they have a different overall health status to adults such that the intervention as formulated are not directed towards this patient cohort.

1.2.4 Justification for design

RCTs provide the highest level of evidence for clinical research.

The trial is designed to be as pragmatic as possible with wide inclusion criteria. To demonstrate generalisability against a wide range of practices using different "usual care", the trial is multi-centre, recruiting throughout the UK. The trial contains an internal pilot to both monitor the recruitment rate of the trial and to be able to respond to any issues with the usability of the intervention.

Given the nature of the intervention, it is not possible to blind the clinical teams or the participant to the randomisation allocation, so the participant reported outcomes will be completed with knowledge of treatment allocation.

In order to provide a more complete assessment of the effect of the F4S-2 intervention [32], we have selected dual primary outcomes, which are guided by

- The HTA commissioning brief
- Internationally recognised 'CORE OUTCOMES' in lung cancer [33]
- Existing literature
- Consultation with expert clinicians
- Views of patients and lay focus groups

The choice of dual primary outcomes encompassing both the patient-reported quality of life and the complication rate is to ensure capture of a signal in either area and were considered to be as equally important by a public and patient involvement (PPI) group convened for the trial.

1.2.5 Choice of intervention

A pilot study (ISRCTN: 00061628 funded by Health Foundation) was conducted in 65 lung cancer surgery patients comparing the Fit for Surgery App (F4S); a home rehabilitation structured exercise programme (with integrated patient and clinician bio-feedback), with conventional outpatient based prehabilitation. The F4S, developed by and for the NHS was designed "for all", "personalised" and adaptive to the "continuum" of the patient pathway, incorporating the three prehabilitation phases: assessment, intervention and follow up. [34] It includes tailored bespoke health information, e.g., on "your lungs, surgery, how to exercise, managing symptoms and recovery after surgery" (www.thoracicsurgery.co.uk). By presenting information in bite size snippets and being an individualised low resource programme that the patient can return to at their convenience, F4S mitigates many of the concerns and barriers raised about cancer prehabilitation programmes. [35]

The intervention was found to be highly acceptable to patients (even to those with minimal technology experience), deliverable within the lung cancer pathway and resulted in significant improvement in physical function before surgery. There were no adverse or serious events relating to using the App at home. Patients in the App group managed to complete 4 times the number of exercise sessions before surgery when compared to the group who received outpatient prehabilitation, their shuttle walk test increased on average by 100 metre ($P<0.05$) and the drop-out rate to recommence after surgery was halved. The cost of delivering the digital programme was significantly lower at £16 per patient versus £188 for conventional rehabilitation. [34, 36]

A single centre mixed method open label RCT "THIRSTY" was conducted in 64 lung cancer surgery patients (ISRCTN: 16535341 funded by Birmingham Health Partnership). This compared a nutritional intervention regime of pre- and post-operative oral nutritional supplements against standard care. Recruitment completed ahead of target and 97% of patients were compliant with nutritional drinks. The intervention was highly acceptable to patients. In addition, there was a trend towards less weight loss and symptom burden in the intervention group. [37]

The F4S App, combines both these interventions (exercise and nutrition) and embedded behaviour change principles grounded in SDT, with the aim to promote greater autonomous motivation for doing the exercises and taking the nutritional supplements, and encouraging uptake of exercise/PA that can be sustained in the long-term.

2. AIMS AND OBJECTIVES

The aim is to determine the clinical and cost effectiveness of F4S, a digital platform prehabilitation programme that can be used before and after surgery to enhance the recovery of physical function and/or reduce the risk of complications after major elective lung cancer resection surgery.

2.1. Internal pilot objectives

The aim of the internal pilot is to assess the ability to open sites, recruit/randomise and retain participants.
The aims of the internal pilot phase are:

- At least 17 sites open to accrual
- Accrual of 125 participants
- Average recruitment rate/ site/ month ≥2.2
- At least 80% of participants completing quality of life questionnaires 30 days after surgery in each arm of the study
- At least 80% of participant adherence to the F4S intervention

The internal pilot will also enable us to assess the usability of the intervention and address any issues.

2.2. Main Trial Objectives

Primary Objectives:

- To establish the clinical and cost-effectiveness of the F4S App, a digital platform prehabilitation programme, consisting of personalised health information, a structured exercise programme and tailored nutritional conditioning in lung cancer surgery participants, in addition to usual care, when compared to usual care alone.

Secondary Objectives:

- To examine the impact of prehabilitation on the overall quality of life and mental health of the participant.

- To use participants-submitted data to explore the trajectory of recovery with reference to muscle strength, physical endurance, nutritional status, symptoms and activities.

2.2.1 Clinical Aims and Objectives

To evaluate the clinical effectiveness of the F4S digital platform to enhance the recovery of physical function and/or reduce the risk of complications after major elective lung cancer resection surgery

2.2.2 Economic Aims and Objectives

To establish both the short and long-term cost-effectiveness of F4S compared to usual care, expressed as quality-adjusted life years (QALY) using within-trial and supplementary model-based economic analyses.

2.3. Study Within a Trial (SWAT) Objectives

The SWAT will investigate why patients who decline to participate in the clinical trial make this decision.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

Pragmatic, multicentre, open label, randomised controlled, two arm, parallel group trial with an internal pilot, an embedded SWAT, and health economic evaluation.

3.2. Trial Setting

Approximately 20 UK NHS acute hospitals; mixed Cardiothoracic and Thoracic hospitals performing lung cancer surgery will take part.

3.3. Assessment of Risk

All clinical trials can be considered to involve an element of risk and in accordance with Birmingham Clinical Trials Unit (BCTU) standard operating procedures, this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: No higher than the risk of standard usual care.

4. ELIGIBILITY

4.1. Inclusion Criteria

- Aged 18 years or over
- With a suspected clinical or pathological diagnosis of primary lung cancer
- Selected for elective curative lung resection
- Able to undergo F4S intervention for minimum of 2 weeks prior to surgery
- Willing and able to provide informed consent
- Willing to use F4S App
- Willing to complete study questionnaires

4.2. Exclusion Criteria

- Emergency surgery
- Patients requiring parenteral nutrition

4.3. Co-enrolment

Participants in F4S-2 can participate in other studies. Participants may be recruited to non-interventional trials such as observational or qualitative studies for rehabilitation and to all other trials in cancer treatment or surgery.

5. CONSENT

It will be the responsibility of the Principal Investigator (PI) or delegate to obtain informed consent for each potential participant prior to performing any trial related procedures. This task can be delegated by the PI to other members of the local research team, if local practice allows, and this responsibility has been documented in the **F4S-2 Trial Signature and Delegation Log.** Those obtaining consent will be medical professionals who are able to determine whether the patient has the capacity to consent to the trial.

5.1. Consent procedure

Eligible patients will be informed of the trial during a clinical appointment. However, on the rare occasions where clinical consultations are undertaken remotely, eligible patients can be informed of the trial during a remote consultation. Informed consent may also take place remotely following current authentication procedures used in clinical care for confirmation of the participant's identity.

In both cases, a Participant Information Sheet (PIS) (either in paper or electronic format) will be provided to facilitate the informed consent process. The PI or delegates will ensure that

they adequately explain the aim of the trial, the trial intervention, anticipated benefits and potential risks of taking part in the trial. They will also explain that participation is voluntary, and that the potential participant is free to decline to take part and may withdraw from the study at any time.

The potential participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The potential participant will be given the opportunity to ask questions.

Where English language is limited, an interpreter may be used to translate the study materials and ensure the potential participant understands all that is involved with participation in the trial prior to signing the Informed Consent Form (ICF). Where translation is required, this will be at the discretion of the local team using their provisions for translating material according to local practice.

5.2. Consent documentation

If the potential participant wishes to participate in the trial and has been confirmed as eligible to participate, they will be asked to sign and date the ICF

Where consultation is undertaken remotely, the potential participant will be asked to either:

- Provide consent in-person, and sign and date the ICF at their next clinic appointment; or
- Provide consent verbally, after the person taking consent has read out each of the statements on the ICF to the potential participant in presence of a witness. The witness will verify that informed consent was taken; the witness does not have to be named on the Site Signature and Delegation Log. As the potential participant agrees with each statement, the person taking consent will insert their initials in the associated box. The ICF will then be signed by both the person taking consent and witness.

A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the ISF. Agreement (or not) to each section of the ICF will be inputted onto the trial database. The potential participant must give explicit consent for the regulatory authorities, members of the research team and/or representatives of the sponsor to be given direct access to the participant's medical records.
In addition, the participant understands and acknowledges that, a copy of the signed ICF will be transferred to the Trial Office for review.

Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Copies of the PIS and ICF will be available from the Trial Office and will be provided on headed paper of the local institution. Details of all participants approached will be recorded on the **F4S-2 Participant Screening/Enrolment Log.**

5.3. Ongoing consent

At each hospital/clinic visit, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Where participant-reported data is sent directly to the Trials Office, or via the F4S App, the completion of this data will be taken as tacit consent that the participant wishes to continue in the trial.

Throughout the trial, the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

6. ENROLMENT, RANDOMISATION AND BLINDING

6.1. Identification, screening and enrolment

Patients with suspected or confirmed lung cancer who are being considered for surgery will be identified and screened for eligibility from preoperative clinics and Multi-Disciplinary Team meetings (MDTs), and through referral letters for surgery. Patients will be identified by the direct care team such as lung cancer nurses, dietitians, physiotherapists, physicians and surgeons and research teams in these centres as well as at lung cancer MDTs. Surgical trainee research networks will also be used to help identify patients as members attend

these MDTs. On occasion, this identification may take place at Patient Identification Centres (PICs). These PICs feed into the main sites where the surgery will take place.

Once potential participants have been initially identified and screened according to the eligibility criteria, a member of the clinical (surgery or cancer) team will approach the patient at their next consultation appointment, provide a PIS and ask if they are willing to speak to a member of the site research team to find out about the trial in more detail, and assess their willingness to take part in the trial.

Patients may also be contacted prior to surgery by the direct care team to discuss their willingness to take part in the study and in this situation each patient will be sent an ethically approved PIS and appropriate site contact details should they want any further information.

Regardless of the route of approach, the patient will be asked if they wish to participate in the trial (following the process below) and, if not, whether they would be willing to share their reasons for declining, for purposes of the SWAT.

An appropriately trained member of the team (healthcare professionals) delegated the task on the **F4S-2 Site and Signature Delegation Log** will confirm eligibility. If the potential participant meets all eligibility criteria and confirms they are willing to take part in the trial, they will be asked to formally consent to participate in the trial.

Details of all patients approached about the trial will be recorded on the **F4S-2 Participant Screening/Enrolment Log,** which will be kept in the ISF, and should be available to be sent to the Trials Office upon request.

6.2. Randomisation

6.2.1 Randomisation System

Randomisation will be provided by BCTU using a secure online system (available at *<insert web address>*), thereby ensuring allocation concealment. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study as detailed on the **F4S-2 Site Signature and Delegation Log**. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

In the event of the online system being unavailable the research team will contact the BCTU Trial Office (between 9am and 5pm) who will randomise the participant using a process on paper which will later be added to the database.

6.2.2 Randomisation Procedure

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial using the online system. All questions and data items on the online randomisation form must be answered prior to a potential participant being randomised into the trial and a trial number being issued.

Following randomisation, a confirmatory e-mail will be sent to the local PI and the person who carried out the randomisation.

The PI or delegate should add the participant to the **F4S-2 Participant Recruitment and Identification Log**, which links participants with their trial number. The PI or delegate must maintain this document securely at the NHS site, which is not for submission to BCTU, and should be held in strict confidence.

6.2.3 Randomisation Method

Participants will be randomised at the level of the individual in a 1:1 ratio to either the F4S App with usual care or usual care alone. A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Smoking History: current (within the last 14 days) or non/past smoker
- Age: 18-39, 40-69, 70-79, ≥80
- BMI: <18.5, ≥18.5-24.9, ≥25-29.9, ≥30

To avoid the possibility of the intervention allocation becoming predictable, a 'random element' will be included in the minimisation algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.3. Blinding

Given the nature of the intervention, it is not possible to blind the clinical teams or the participant to the randomisation allocation, so the participant reported outcomes will be completed with knowledge of treatment allocation.

6.4. Informing the participant's GP

The participant's General Practitioner (GP) will be notified that they are in F4S-2 trial, using the **F4S-2 GP Letter.**

7. TRIAL INTERVENTION

Participants will be randomised to receive:

- Usual care

OR

- F4S App and Usual care

7.1. Usual Care

This may be a range of healthcare services that provides all or one of the following: information for the participants (with or without links to further information), formal rehabilitation via physiotherapy, dietician support via dietician, and/or routine follow up as per standard of care.

7.2. F4S App and Usual Care

This will combine the usual care interventions as per section 7.1 and use of the F4S App (for a minimum of 2 weeks prior to surgery) with details described in the following sections.

7.3. F4S App

The advice given to the participant is determined by their unique, dynamic, personal health status. That is, as a participant engages with the App, the advice regarding exercise and nutrition adapts.

Specifically, the App collects baseline demographic data, comorbidities, symptom burden using simple questions and Visual Analogue Scales (VAS), and the outcome measures of Quality of Life, Health and wellbeing scores. This information is used to deliver personalised feedback, support and guidance when using the App. e.g. if diabetic, guidance on avoiding a hypoglycaemic event. This will not constitute trial data and is part of the data to inform the intervention itself.

The digital programme or 'App' comprises three prehabilitation interventions:

7.3.1 Structured Home Exercise Programme

Participants are guided through a series of screens to build their own programme, including a range of strengthening, mobility and cardiovascular exercises. Baseline suggestions on programme level/ intensity are made based on a 'sit to stand test' conducted within the App. Once the programme is built, participants are encouraged to exercise daily to achieve

150 minutes of exercise/week as per pulmonary rehabilitation guidelines [38]. Heart rate is recorded using a wearable sensor provided free of charge to the participants. Once each exercise is completed, the participant inputs their perceived intensity using the BORG perceived exertion scales to the App [40]. This data is used to encourage the participant via personalised messages to increase or decrease intensity at the next session to achieve the target intensity of BORG perceived exertion as per rehabilitation guidelines [38]. Regular data uploads allow health care professionals to view participants' progress, whilst the App allows the participant to request support from the health care professional if required. Only these health care professionals can view the information within the App. They will be able to see alerts from the participant through the admin page. The App app has safety messages to advise participants to seek medical advice when required (in the same way that usual care patients are directed to contact depending on the situation)

Participants are also able to record any other exercise they undertake e.g. swimming, running etc. Whilst the programme is focussed on pre-surgery, exercise can also benefit recovery post-surgery [41], so the participant will be permitted to use the programme after surgery for a period of 6 weeks, but it will be adapted/reset according to participants' post-surgery 'sit to stand test' performance (on postoperative day 1).

7.3.2 Individualised Nutritional Conditioning

At the time of enrolment, participants complete a nutritional screening questionnaire (Patient-Generated Subjective Global Assessment (PG-SGA score)) within the App [42], which tailors' nutritional advice and supplementation based on symptoms and nutritional risk. All participants in the F4S arm will be encouraged with the aid of a "ready reckoner" to intake a high protein (20g) snack within 90 minutes of exercise to stimulate muscle protein synthesis and a positive protein balance. Participants will record in the App when they have taken a protein snack. Participants deemed 'Medium risk' (PG-SGA score 4-9) will be started on a low volume, high calorie, high protein oral nutritional supplement (ONS) containing at least 18g of protein twice a day until surgery. High risk participants (score > 9) will be started on supplements as above and referred to a dietitian for optimisation of supplement prescription [42, 43].

While the recommendations above are aligned with national guidance, sites can adhere to local policies. Standard care will be followed regarding the supplementation and monitoring.

Whilst the programme is focussed on pre-surgery, it is acknowledged that after surgery, calorie and protein requirements are high at a time when intake may be impaired by the after effects of surgery. Therefore, nutritional intervention will continue for 4 weeks post-

surgery. Participants will complete the PG-SGA using the App on postoperative day 1 and based on this nutritional advice and supplementation will be tailored as described above.

7.3.3 Personalised Health Information

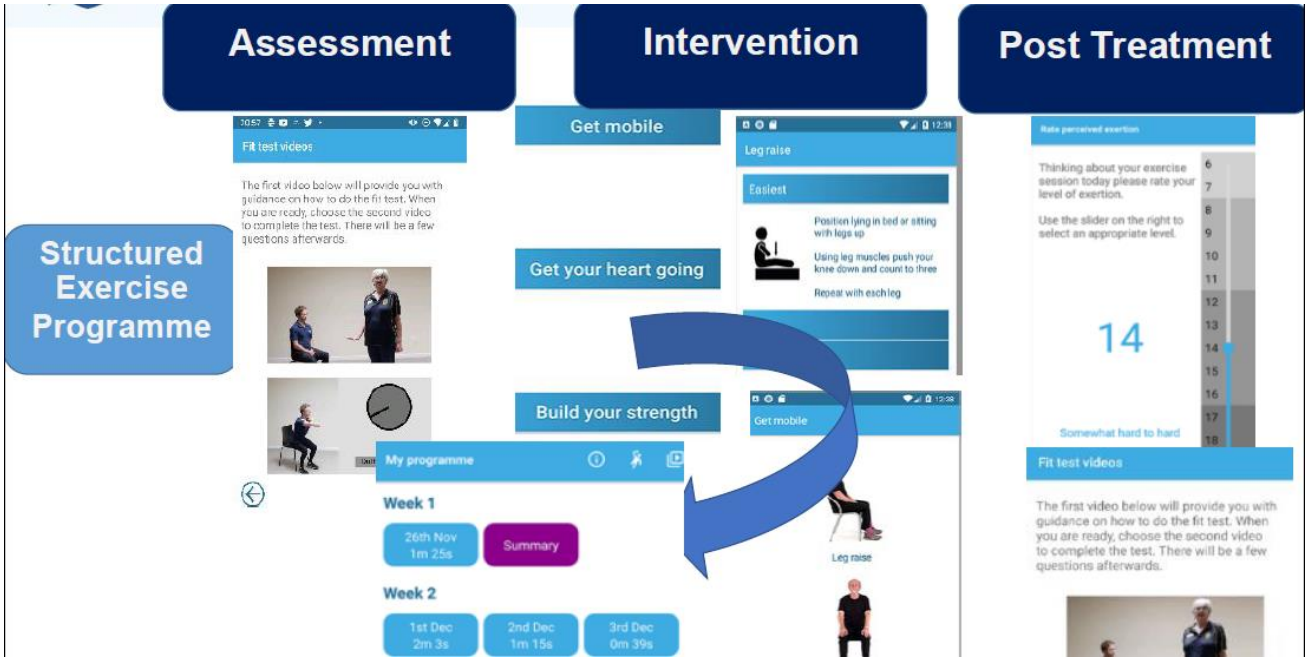
Displayed within the App as short informational videos with subtitles. Information is responsive, and guided by symptom data and whether the participant is pre- vs. post-surgery, as recorded in the App. For example, if the participant reports feeling breathless, information on how best to manage this is displayed. Information on surgery is prominent to the participant before surgery, whilst recovery and symptom management e.g., pain control are prominent after. Further details of the programme can be found on www.Fit4surgery.uk.

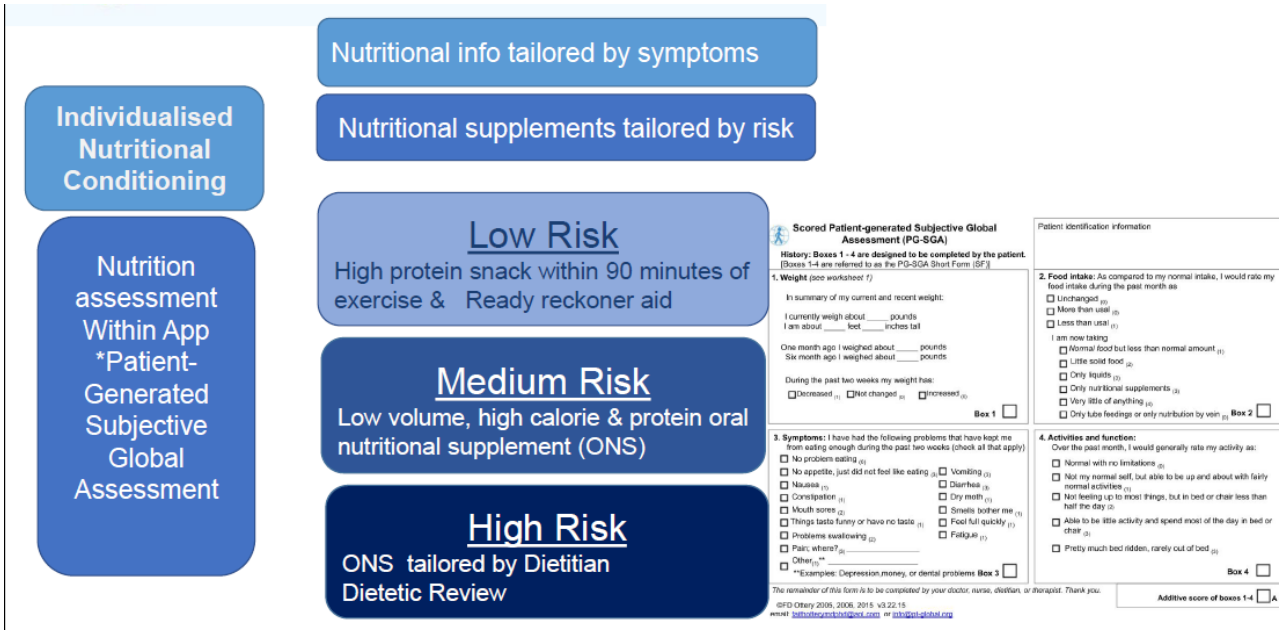
Motivational processes – In App data collection will include Motivational processes underpinning engagement with the App/behaviour change, autonomous and controlled motivation for engagement in exercise and physical activity and an assessment of autonomy, competence, and connection.

7.3.4 Technical training and competency for the intervention

Participants will receive initial training by the research team at recruitment on how to use the App (i.e., set up the programme, complete questionnaires, how to seek help), and will be provided with web links for short training and troubleshooting videos, as well as a pictorial paper guide. There is also a technical helpline that the participant can contact if they have difficulty with the App. Research staff will undertake web-based training to deliver the initial guidance, in which their competency will also be assessed and recorded.

Figure A and B: Screen shots of the Fit for Surgery App showing types of exercise, modifications, real-time feedback screen and exercise summary


Assessment
Intervention
Post Treatment
Structured Exercise Programme
Fit test videos
The first video below will provide you with guidance on how to do the fit test. When you are ready, choose the second video to complete the test. There will be a few questions afterwards.
Get mobile
Get your heart going
Build your strength
My programme
Week 1
26th Nov 1m 25s
Summary
Week 2
1st Dec 2m 3s
2nd Dec 1m 15s
3rd Dec 0m 39s
Leg raise
Easiest
Position lying in bed or sitting with legs up
Using leg muscles push your knee down and count to three
Repeat with each leg
Get mobile
Leg raise
Rate perceived exertion
Thinking about your exercise session today please rate your level of exertion.
Use the slider on the right to select an appropriate level.
14
Somewhat hard to hard
Fit test videos
The first video below will provide you with guidance on how to do the fit test. When you are ready, choose the second video to complete the test. There will be a few questions afterwards.


Individualised Nutritional Conditioning
Nutrition assessment Within App *Patient-Generated Subjective Global Assessment
Nutritional info tailored by symptoms
Nutritional supplements tailored by risk
Low Risk
High protein snack within 90 minutes of exercise & Ready reckoner aid
Medium Risk
Low volume, high calorie & protein oral nutritional supplement (ONS)
High Risk
ONS tailored by Dietitian
Dietetic Review
Scored Patient-generated Subjective Global Assessment (PG-SGA)
History: Boxes 1 - 4 are designed to be completed by the patient.
Patient identification information
1. Weight
2. Food intake:
3. Symptoms:
4. Activities and function:

7.4. Intervention Modification or Cessation

The F4S App will not be available to participants who are randomised to the usual care arm of the trial, so crossover will not be possible from usual care. It is possible that participants randomised to the F4S arm will cease to engage with the App completely. This will not however be considered a crossover, since this is part of the pragmatic nature of the trial.

As mentioned in section 7.3 the App is designed to adapt to the participant as they use it, or cease to use it. The variability in engagement with the App forms part of the trial and will be captured by the App.

7.5. Continuation of intervention after the trial

The App is designed specifically to assist participants in the weeks immediately prior to, and subsequent from, their surgery. Therefore, there is no further benefit expected after the 6 week trial period is completed.
The App will remain available for use where participants have used their own devices to download and access it, and may continue to use it. This will not be within the confines of the trial. It will be explained to participants that whilst use may continue, no further benefit is expected after the 6 week trial period is complete and it will not be monitored by the clinical team.
For participants who are provided with a tablet, the tablet will be returned and wiped of all data.

7.6. Intervention Access Supply and Storage

Participants will be asked to download the F4S App to their personal device. A link to register for the App will be provided to all participants randomised to the F4S arm. For those who do not have a mobile device, tablets will be provided before surgery and for approx. 6 weeks after. The tablet devices will be distributed to the recruiting sites from the Trial Office**,** where they should be safely secured until provided to a participant.
When provided to a participant the equipment log should be completed to record tablet use. At the end of each participant's participation in the trial the tablet will be returned to the recruiting site. The site will maintain a log of usage of the Tablet, set used throughout the study recording the lot number used against each participant (on an equipment log).
The hardware does not require any special storage conditions but should be handled with due care and in accordance with any instructions. Equipment failures will be replaced provided there is no evidence of inappropriate use or deliberate negligence, under which circumstances the Sponsor reserves the right not to re-supply the participant.

7.7. Device and Tablet support

Site staff will be trained on how to use the F4S App and training documents will be provided within the ISF. This will include informing participants how to set up, register and use the App.
The devices will be provided with no other software installed and only the F4S App pre-installed. Participants will be asked not to use the tablet for any other purpose than for trial participation.
Hardware support will be provided by the third-party App developer, with reference documentation provided to site staff to ensure the devices are wiped at the end of trial participation.

7.8. Adherence

Adherence to the intervention arm will be defined as using the app at least twice a week in the time before surgery and the completion of quality of life questionnaires 30 days after surgery.
Adherence to usual care will be the completion quality of life questionnaires 30 days after surgery.

8. OUTCOME MEASURES

8.1. Internal Pilot Outcome

The success of the 6-month internal pilot study will be based upon the recruitment rate (overall and at individual sites), completeness of primary outcome data (quality of life questionnaires 30 days after surgery in each arm of the study) and adherence to the intervention (adherence in the intervention arm will be defined as using the App at least twice a week in the time before surgery).

We will recruit 125 participants (14% of the total sample) during the 6-month internal pilot phase. We will open 2 sites in the first month, then 3 sites a month for the next 5 months until a maximum of 17 sites are open in the pilot phase.

Stop/Go Criteria
We have set criteria relating to number and rate of participants recruited, the number of sites, recruitment rate, data completeness/retention and adherence with the intervention (see Table 1 below):
• **GO**: progress to main trial; following pilot phase we would still review trial processes to assess whether any changes could/need to be implemented to improve the trial.

• **MODIFY**: review the trial processes to identify implementable changes. This may include recruiting additional centres and/or retraining centres in trial pathways and procedures. We would discuss with the trial oversight committees and funder about the need for a second internal pilot phase to verify resolution of issues, then if progress is satisfactory continue to the main trial.
• **STOP**: abandon the trial if the trial oversight committees and funder feel this is the appropriate course of action.

Progression criteria	**Stop**	**Modify**	**Go**
Trial recruitment % complete of pilot target (n=125)	<50%	50-99%	≥100%
Average Recruitment rate/ site/ month	<1	1.1-2.1	≥2.2
Number of sites opened	<8	9-16	17
Total number of participants recruited	<63	64-124	≥125
% of participants completing quality of life questionnaires 30 days after surgery in each arm of the study	<50%	50-79%	80-100%
% of participants adherence* with the F4S intervention	<50%	50-79%	80-100%

Table 1: **Internal pilot progression criteria (n=125)**

* Adherence defined as per section 7.8 Adherence.

8.2. Main Trial Outcomes

8.2.1 Primary Outcomes

- Patient-reported quality of physical function scale recovery (using the EORTC-QLQ-C30) at 30 days after surgery
- Surgical complications (using the Comprehensive Complication Index (CCI)) at 30 days after surgery

8.2.2 Secondary Outcomes

- Days Alive and at Home Within 30 days (DAH30)
- Patient-reported quality of life (using the EORTC-QLQ-C30 & LC 29) at 14 days, 30 days, 3 and 6 months after surgery
- Mental health/well-being (using the Hospital Anxiety and Depression Scale (HADS))
- Symptom score (using a 0-10 point VAS) (intervention only)
- Motivational processes
- Physical status assessed by the incremental shuttle walk test (ISWT), sit to stand test and hand grip test
- Patient-generated subjective global assessment short form (PG-SGA SF)

8.2.3 Health Economic Outcomes

- Health Related quality of life (EORTC-QLQ-C30, LC-29 and EQ-5D-5L)
- Health resource usage

8.2.4 Patient Reported Outcomes

Patient reported outcomes will be collected via paper booklets (unless stated) administered either during routine hospital visits or posted direct to the participants, they will consist of:

- Patient-reported quality of life (using the EORTC-QLQ-C30, LC 29)
- Mental health/well-being (using the HADS)
- Symptom score (using a VAS) (intervention only – obtained from the F4S App)

8.2.5 Clinical Outcomes

Clinical (objective) outcomes are collected at timepoints designed to match routine appointments. Data for these measures are entered by site staff directly onto the trial database.

The ISWT is a valid incremental field walking test to assess the functional capacity in patients with chronic airways obstruction [44,45]. It is a sensitive test that can be used on a wide range of patients with varying disability severity. Further, this validated field test has proven sensitive to changes in pulmonary rehabilitation programmes [46-48]. The equipment needed to perform the ISWT test is simple: CD or MP3 player and two markers (or small cones) placed 9 metres apart and it can be carried out in a flat hospital corridor with minimal blind turns or obstacles [49]. The ISWT has 12 levels; each level is measured by calculating the distance walked to the nearest 10m completed, and the time to complete that distance by the patient should also be recorded [49].

The hand grip strength test is performed using various equipment such as the Jamar Hand Dynamometer [50]. Previous studies have shown grip strength to predict current and future health [50]. When performing the hand grip test, the patient should be seated comfortably in a chair with back support and fixed arm rests, and three measurements for each hand, alternating sides should be recorded [50].

9. TRIAL PROCEDURES

Baseline (at least 2 weeks prior to surgery)

The following procedures and assessments should be performed:

- Medical history
- Informed consent
- Randomisation
- Nutritional assessment including weight and height (PG-SGA SF)
- Physical tests - Muscle strength hand grip, ISWT and sit to stand test
- Participant completed questionnaires to include IPAQ-E, EORTC-QLC-C30 & LC29, EQ-5D-5L, HADS, Technology Access Questions

F4S Arm only:

  - Instructions will be provided to the participants and/or care giver for use of the App

Day of Surgery

- Nutritional assessment including weight (PG-SGA SF)
- Physical tests - Muscle strength hand grip and sit to stand test
- Participant completed questionnaires to include EORTC-QLC-C30 & LC29, EQ-5D-5L, HADS
- Pre-operative questions assessing usual care
- Pre-operative Nutritional input assessment (drinks and dietitian)

F4S Arm only:

  - Motivational processes,
  - Shortened scales of behavioural change

Day of Hospital discharge post-Surgery

- Physical tests - Muscle strength hand grip and sit to stand test
- Assessment of in-hospital complications (Comprehensive Complication Index (CCI))

14 days post-Surgery

- Participant completed questionnaires to include EORTC-QLC-C30 & LC29, EQ-5D-5L, HADS

30 days post-Surgery

- Assessment of complications post hospital discharge (Comprehensive Complication Index (CCI))
- Nutritional assessment including weight (PG-SGA SF)
- Physical tests - Muscle strength hand grip, ISWT and sit to stand test
- Participant completed questionnaires to include EORTC-QLC-C30 & LC29, EQ-5D-5L, HADS
- Post-operative questions assessing usual care
- Post-operative Nutritional input assessment (drinks and dietitian)
- Health resource usage questionnaire

F4S Arm only:

  - Motivational processes,
  - Shortened scales of behavioural change

3 months post-Surgery

- Participant completed questionnaires to include EORTC-QLC-C30 & LC29, EQ-5D-5L, HADS

F4S Arm only:

  - Motivational processes,
  - Shortened scales of behavioural change

6 months post-Surgery

- Participant completed questionnaires to include EORTC-QLC-C30 & LC29, EQ-5D-5L, HADS
- Health resource usage questionnaire
- Assessment of disease recurrence/progression

Table 2: **Schedule of Assessments**

Trial Procedures and Assessments	Baseline	Day of Surgery (- 1 days)	Day of Discharge (+/- 2 days)	14 days Post op (+/- 3 days)	30 days Post op (+/- 7 days)	3 months Post op (+/- 2 weeks)	6 months Post op (+/- 4 weeks)
Medical history	X						
Informed consent	X						
Randomisation	X						
Patient and/or Carer Instructions for use of App	X						
Nutritional assessment (incl. height and weight) - PG-SGA SF	X	X			X		
Nutritional input assessment (drinks and dietitian)		X			X		
Physical tests (incl. hand grip, ISWT, sit to stand test)	X	X* (ISWT not collected)	X (ISWT not collected)		X		
Participant completed questionnaires (incl. EORTC-QLQ-C30 & LC29, HADS, EQ-5D-5L)	X	X*		X	X	X	X
Health Resource Usage questionnaire					X		X
Questions assessing Usual Care		X*			X		
Assessment of clinical complications (CCI)			X		X		
Technology Access Questions	X						
Assessment of disease recurrence/progression							X
(IN ADDITION TO ABOVE INTERVENTION ARM ONLY)							
Participant completed Motivational Processes		X			X	X	
Participant completed Shortened Scale of Behavioural Change		X			X	X	

** In instances where the participants surgery is cancelled and rearranged, the physical tests will need to be repeated if it is **more than 7 days** from the original surgery date. If the participant has already completed the Day of Surgery Participant Booklets they will be required to completed again.*

9.1. Participant withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

The changes in levels of participation within the trial are categorised in the following ways:

- **No trial intervention:** the participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis)

- **No trial related follow-up:** the participant no longer wishes to attend trial visits in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits (i.e., the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis)

- **No further data collection:** the participant is not willing to be followed up in any way for the purposes of the trial and does not wish for further data to be collected (i.e., only data collected prior to the withdrawal can be used in the trial analysis)

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

Participants can change their level of participation without giving a reason, although a reason would be very useful in the pilot to help assess whether it is related to the design of the trial.

BCTU should be informed of withdrawal or change in level of participation via the trial withdrawal/change of status form.

10. ADVERSE EVENT REPORTING

No related harms have been reported in the literature regarding App use to facilitate self-management of diet and exercise. Therefore, there is no reason to anticipate any safety concerns arising as a result of this intervention within F4S-2. Events that would be considered as adverse events (AEs) are being collected as part of the outcome measures data collection up to 30 days post-surgery this will include the following:

- Post-operative complications as per Claviden-Dindo classifications – see appendix I
- In-hospital mortality
- 30 day mortality

During follow-up, the systematic collection of self-reported data as part of the clinical outcomes will be conducted, this will take place alongside routine medical note review (at mandated time points: day of discharge and 30 days follow up). This will include participant reported summaries of health care visits including any admissions to accident and emergency. The team will also capture whether there have been any deaths and cause of death. The events listed above (with reference to Appendix I) will be reviewed by the Data Monitoring Committee (DMC) at regular intervals as part of the main data set.

11. Urgent Safety Measures

The Clinical Trials Regulations make provision for the Sponsor and PIs to take appropriate Urgent Safety Measures (USMs) to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the Research Ethics Committee (REC).

If any urgent safety measures are taken, BCTU shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

12. DATA HANDLING AND RECORD KEEPING

12.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the participants, source data will be accessible and maintained.

F4S-2 is a trial which is using an App, and therefore some of the data, e.g., App usage, will be generated in the App from participant's direct input

Table 3: **Source Data**

Data	Source
Participant Reported Outcomes (including Health Economics data).	The original completed participant reported outcome booklet is the source documentation. These will be either be stored with the participant's trial record: • at site, where the questionnaires have been administered by site in clinic • at Trial Office, where the questionnaires have been posted by and returned to the Trial Office
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical data reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Data uploaded to the F4S App	User usage and engagement data will be transferred to BCTU servers in the form of JSON files and will be the source documentation.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to change their level of participation, the conversation must be recorded in the medical records, and this will constitute the source data.

12.2. Case Report Form Completion

An electronic case report form (eCRF) should be completed for each individual participant, and these will be electronic with the exception of the participant completed questionnaires.

The eCRFs will include, but will not be limited to, the forms listed in Table 4.

Table 4: **List of trial specific CRFs**

Form Name	Schedule for submission
Randomisation CRF	At the point of randomisation
Baseline CRFs, including participant reported outcomes	At the point of randomisation

Follow-up CRFs, including participant reported outcomes	As soon as possible after each follow-up assessment time point
Trial withdrawal/Change of status Form	At the point of becoming aware of withdrawal/change of status or death

If data has not been provided within two weeks of the submission schedule detailed in the above table, a reminder email will be sent to sites. If data is consistently not provided, the Trial Office will directly contact the site to ascertain the reason for the delay. This may also be escalated to the site's senior management and can trigger a monitoring visit.

In all cases it remains the responsibility of the PI to ensure that the eCRF has been completed correctly and that the data is accurate. This will be evidenced by the electronic signature of the PI or delegate(s)The **F4S-2 Site Signature & Delegation Log** will identify all those personnel with responsibilities for data collection. The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the eCRF.

Data reported on eCRFs will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete eCRFs will be trained to adhere to trial specific working instructions on CRF Completion.

The following guidance applies to data:

- Rounding conventions - rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. (e.g. 3.8 rounded to the nearest whole number is 4). If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. (e.g. 3.4 rounded to the nearest whole number is 3).
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied.
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible.
- Repeat tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and Good Clinical Practice (GCP) non-compliances should be reported to the Trial Office when become aware.

12.3. Participant completed Questionnaires

A list of participant-completed forms can be found in Table 5.

Table 5: **Participants completed questionnaires included in the participant booklets**

Name of questionnaires
IPAQ-E
PG-SGA
EORTC-QLC-C30
EORTC-QLC-LC29
EQ-5D-5L
Hospital Anxiety and Depression Scale (HADS)
Subjective Vitality Scale (SVS)
EQ 5D VAS
Health Resource Usage Questionnaire
Motivational Processes (Intervention only)
Shortened scales of behavioural change (Intervention only)

The participant questionnaires listed above will be combined into booklets and completed by the participants on paper either in clinic or via postal paper questionnaire.

For questionnaires completed:
In clinic – questionnaires will be administered by sites in clinic at baseline, day of surgery and 30 day follow up visit. The research team will oversee completion and provide support if necessary. Where support is provided, the questions should be read to the participant verbatim and responses must not be led by the person assisting the form completion. Participant should be encouraged to respond to all questions but can refuse to answer any or all of the questions should they wish. Checks for missing data and completeness should be done by the researcher before the participant leaves the visit. Where questions are unanswered, the researcher should clarify whether the participant chooses not to answer or simply missed in error. Should they choose not to answer, this should be marked clearly on the paper and database.
Via post - questionnaires will be posted to the participants by the Trial Office ahead of each scheduled follow-up time point, except baseline, day of surgery and 30 day follow up visit. A return freepost envelop will included for participants to return the completed questionnaires back to the Trial Office. Questionnaires should generally be completed by the participant alone but physical assistance in completing the form can be given by the participant's friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and responses must not be led by the person assisting

with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance.
Upon receipt of a completed questionnaire, the Trial Office will check for unanswered questions or ambiguous answers. When completed questionnaires have not been returned by participants one reminder will be sent to them after the 3 month and 6 months' time points.

12.4. Data Management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan (DMP) and include the processes of data entry and data queries.

Data entry will be completed by sites via a BCTU-managed trial database, however, questionnaires returned to the Trial Office will be entered by a member of the trial team at the Trial Office via the same trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site (ideally) within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

Self-evident corrections will be only be permitted when entering participant completed questionnaires to correct date fields, or complete logic tree's to allow entry of participant reported data, within the returned forms, by the Trial Office.

12.5. Data Security

The University of Birmingham has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data.

The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). BCTU has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

- Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.
- System Management: the System will be developed by the Programming Team at BCTU, and will be implemented and maintained by the Programming Team.
- System Design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within BCTU.
- System Audit: The System will benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment

Data Protection Registration: The UoB's Data Protection Registration number is Z6195856.In relation to the F4S App:

- Fit4S application suite is stored within a Microsoft Azure data centre in the United Kingdom. All data hosted and stored securely within the data centre.
- No personal information from participants is accessible or viewed by the Sub-Contractor from the F4S App.
- F4S admin module access is granted to site staff and it is stored in the database securely within the Microsoft Azure data centre in the United Kingdom.

12.6. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISFs, participants' hospital notes, CRFs etc.) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The Trial Master File (TMF) will be stored at BCTU for at least 3 years after the end of the study. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Site Set-up and Initiation

All local PIs will be asked to sign the necessary agreements, including a **F4S-2 Site Signature and Delegation log**, between the PI and BCTU and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform BCTU of any changes in the site research team.

Prior to commencing recruitment, each site will undergo a process of initiation, either a meeting or a tele/video conference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping.

BCTU will provide each site with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The PI or delegate is required to keep the ISF up to date throughout the trial.

13.2. Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific Risk Assessment and are documented in the trial specific Monitoring Plan.

13.2.1 Onsite Monitoring

For this trial, no onsite monitoring is planned due to the low risk of the intervention and nature of the outcome data. Should any monitoring activities be required they will be conducted by BCTU/ UoB staff. PIs and site research teams will allow the BCTU/UoB staff access to source documents as requested. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution.

13.2.2 Central Monitoring

BCTU will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity as determined by the DMP. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

13.3. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The

investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections or local audits.

13.4. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

14. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and data cleaning. BCTU will notify the Sponsor and REC within 90 days of the end of the trial. Where the trial has terminated early, BCTU will inform the REC and sponsor within 15 days of the end of trial. BCTU will provide the Sponsor and REC with a summary of the clinical trial report within 12 months of the end of trial.

15. STATISTICAL CONSIDERATIONS

15.1. Sample size

Sample size has been calculated based on the dual primary outcomes measure of:

- Patient-reported quality of physical function scale recovery (using the EORTC-QLQ-C30) at 30 days after surgery
- Surgical complications (using the CCI) score at 30 days after surgery

For the assessment of the physical function domain of the EORTC-QLQ-C30 using the method of Frison and Pocock for repeated measure design (one Baseline and one Post-Randomisation score), 320 participants in each group (640 in total) will provide 90% power

at the 2.5% significance level (two-sided) to detect a 5 point difference (MCID), assuming a SD of 20, correlation of 0.6 and a 20% attrition rate. [53]

For the assessment of CCI score, previous studies have established that the minimum clinical important difference (MCID) is 5 points [51]. A total sample size of 902 (451 in each arm) will provide 90% power at 2.5% significance level (two-sided) to detect the MCID of 5 points in CCI score, considering that for the usual care mean and standard deviation (SD) at 30 days are 9.4 and 19.0, respectively and a 20% attrition rate. [52]

We will adopt the sample size associated with CCI score as it is considered dominant and requires a larger cohort of participants to detect a significant difference.

15.2. Analysis of outcomes

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those participants randomised to the F4S App and Usual Care versus those randomised to Usual Care alone. All analyses will be based on the modified intention to treat principle, i.e., participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised group or other protocol deviations, will only include those who received surgery.

For all outcomes, appropriate summary statistics and differences between groups, e.g. mean differences, will be presented. Where possible intervention effects will be adjusted for the minimisation variables listed in Section 6.2.3, and baseline values (where available). Given the structure of the data, nesting of patients by centre, centre will be included in the model in the primary analysis.

For the dual primary outcomes, differences between groups will be presented alongside 97.5% confidence intervals and p-values from two-sided tests also provided. To maintain an overall 5% Type I error rate, each comparison will be tested at a significance level of 2.5% to account for the increase in the risk of type I error associated with making two key comparisons. Thus, statistical significance will be set to $p<0.025$ (two sided). All secondary outcomes will be presented with 99% confidence intervals and no p-values.

15.2.1 Primary outcomes

The dual primary outcomes are:

- Patient-reported quality of physical function scale recovery (using the EORTC-QLQ-C30) at 30 days after surgery
- Surgical complications (using the CCI) score at 30 days after surgery

The primary outcome measures will be analysed using mixed effects GLM (General linear model) techniques to estimate the adjusted mean difference between groups and corresponding 97.5% confidence intervals

Supporting analysis based on the dual primary outcomes to assess differences between groups (F4S vs Usual Care) will use multivariate models, which will enable multiple outcomes to be analysed simultaneously, allowing for the correlation between them. Robust estimates will be generated, and type I error / family-wise error rate maintained at an acceptable level (5%).

15.2.2 Secondary outcomes

Continuous variables will be summarised using mean, standard deviation, median and range values as appropriate, and linear regression methods used to calculate an adjusted mean difference between groups along with a 99% confidence interval. Categorical data will be summarised using the number of patients, proportions, and log-binomial models used to obtain adjusted relative risks and 99% confidence intervals.

Repeated measures: Health / Mental health, Motivational processes, Physical Status/ exercise capacity: these numerical rating scores will be analysed using repeated measures techniques. The associated group differences will be calculated along with 99% confidence intervals.

15.2.3 Planned subgroup analyses

Subgroup analyses will be limited to the same variables as used in the minimisation algorithm (see section 6.2.3) and performed on the two primary outcomes only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 97.5% CI within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

15.2.4 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include a multiple imputation approach where missing data not at random will be imputed using multivariate imputations by chained equations following the methods of White and colleagues [56]. Twenty imputation cycles will be used, as this has previously been demonstrated to produce adequate results [57,58].

A compiler average causal effect analysis (CACE) (only those patients who are compliant with treatment allocation) will be carried out to assess the effect in those who adhered to their randomised allocation [55].

The different elements of the intervention (Nutrition, Exercise and Health information) and use/access to rehabilitation services (eg. Maggies centres) will be analysed to assess the effect is consistent across the treatment group. This will be performed with the inclusion of an interaction term.

15.3. Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 6 month assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis.

16. HEALTH ECONOMICS

The aim of the health economic analysis is to assess the cost-effectiveness of the F4S App in patients undergoing lung surgery. Following an agreed Health Economics Analysis Plan and in line with the National Institute for Health and Care Excellence (NICE) reference case [59], the analysis will be carried out from the perspective of the NHS and Personal Social Services. Subsequently, additional analyses will be carried out from a societal perspective.

16.1. Within-trial economic evaluation

A within-trial based economic evaluation will explore the cost-effectiveness of the 2 alternative interventions being compared i) usual care ii) F4S App.

Resource use and costs

Data collection will be carried out prospectively and will include resource use and costs due to delivering the intervention, including staff time, counselling, training costs and cost of medication; Use of health care and community services, including hospital admissions, length of hospitalisation, outpatient appointments, appointments with general practitioners, nurses and allied health care professionals; Patient out-of-pocket expenditure (e.g. travel costs), and time lost from work. Resource use will be obtained from patient completed questionnaires and through the App.

To obtain a total per-patient cost, resource use will be combined with the unit cost values obtained from national sources and tariffs, including the Unit Cost of Health and Social Care report, the British National Formulary and the NHS Reference Cost Schedules [60,61].

Quality of life

Quality of life will be derived from patients' responses to the EuroQol EQ-5D-5L instrument over the follow up period [62]. Each patient's health status descriptions obtained from the EQ-5D-5L will be translated into a single, preference-based index following NICE guidelines. QALYs will be calculated as the area under the curve approach.

Analysis

The trial-based analysis will be conducted on an 'intention to treat' basis. Missing data will be accounted for by using appropriate techniques, such as multiple imputation, depending on the extent and type of missing items. As the distribution of cost is usually skewed by the existence of patients with particularly high costs, the calculated mean per-patient cost will be given alongside confidence intervals obtained through non-parametric bootstrap methods. Incremental analysis will be undertaken to calculate the difference in costs and relevant outcomes of the interventions compared. Results will be presented in the form of incremental cost-effectiveness ratios (ICER), reflecting the additional cost per QALY gained. Where appropriate, the joint distribution of cost and outcomes derived from bootstrap simulations will be depicted on a cost-effectiveness plane and will be plotted as cost-effectiveness acceptability curves (CEACs) which will indicate the probability of F4S-2 intervention being cost-effective across a range of possible values of willingness to pay. Sensitivity analyses will be undertaken to explore the impact of alternative values and assumptions on the obtained results.

16.2. Model-based economic evaluation

In addition to the trial-based evaluation, a model-based analysis will be conducted to consider the long-term cost-effectiveness of F4S-2. The model will be populated with data from various sources, including patient level data obtained from the trial and information from a literature review. Estimates of the quality of life beyond the trial follow-up period

will be obtained from a review of the available literature. Costs and benefits accruing in the future will be discounted to reflect the impact of positive time preference. Both deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the obtained results to sample variability and plausible variations in key assumptions and employed analytical methods [63]

17. SWAT Qualitative Study

Reasons for refusing to take part in clinical trials can often be multi-dimensional but are not well understood. The qualitative SWAT will look to understand how patients who decline to participate in a rehabilitation and nutrition based clinical trial make this decision.

A survey has been created using feedback from PPI members and the RESOLVE group. This survey will be offered to patients who have declined to take part in the main F4S-2 trial. The survey will explore reasons for not wanting to participate in the trial. Questions will seek their opinion on method of recruitment, method of invitation to the trial and participation information. Data will also be gathered about how the recruitment process could be improved, to make it more appealing to encourage patients from varied backgrounds to feel comfortable to take up the offer of rehabilitation and nutrition support through a research trial.

Questions will consist of open and closed ended questions, including tick box options to learn what would encourage people to use the App or what barriers may be perceived by individuals. Findings gathered from the qualitative data will be analysed using thematic analysis; responses will be labelled with codes, and then grouped together into categories to create themes. Agreement on the final themes will be reached through discussion between the PPI co-applicants and qualitative researcher.

The SWAT survey will be completed on paper by the participant.
Participants will be approached by the research team after they have decided not to take part in the main trial. They will be given adequate time to think about whether they would like to complete the survey. If they wish to take it away with them to complete in their own time, they will be given a FREEPOST envelope to return it directly to Trial Office. If they are happy to complete there and then the form will be posted back to the Trial office by the research team. The surveys will be kept securely at the BCTU Trial Office.
Due to the nature of the SWAT, patients will not be asked to read a further PIS or sign a consent form. A short paragraph regarding confidentiality appears on the survey assuring the participants that their responses will be kept anonymous.
Implied consent through completion of the questionnaire will be used.

Data from the SWAT may guide future improvements in the study design and help develop strategies to increase participation into trials, especially from hard-to-reach groups.

18. TRIAL ORGANISATIONAL STRUCTURE

18.1. Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

18.2. Coordinating Centre

The trial co-ordinating centre (Trial Office) is the Birmingham Clinical Trials Unit, based at UoB.

18.3. Trial Management Group

The Trial Management Group comprises individuals responsible for the day-to-day management of the trial: the CI, co-investigators, statisticians, trial team leader, trial manager, PPI members. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

18.4. Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the trial and will meet as required depending on the needs of the trial.

Membership and responsibilities are outlined in the TSC Charter. In summary, the role of the committee is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. The TSC will operate in accordance with a trial specific TSC Charter.

18.5. Data Monitoring Committee

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and

(where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific charter, which will define the membership, roles and responsibilities of the DMC. The committee will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is much faster than anticipated or a safety issue is identified.

18.6. Finance

The research costs of the trial are funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA), REF NO 134214 . The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Schedule of Events Cost Attribution Template (SoECAT). These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

19. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018 and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

20. CONFIDENTIALITY AND DATA PROTECTION

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include: name, date of birth, NHS number, email address, postal address and mobile number.

Participants will only be identified by their unique trial identification number on the CRFs and on any correspondence with BCTU. Participants will acknowledge the transfer and storage of their informed consent form to BCTU. This will be used to perform central monitoring of the consent process.

No identifiable data is stored within the F4S App. Only the delegated clinical care team and research team can access any of this data during the trial. Any data stored on the borrowed tablet devise will be removed following use. Data will be stored on the server until the end of the trial and then will be removed.

If participants continue to use the app after the trial period has ended the data will only be held until the trial finishes.

Participants will acknowledge the transfer of their data to Intelex who will be processing data on behalf of the trial through administration of the F4S App. No participant data is stored with Intelex. No information from participants is accessible or viewed by Intelex from the F4S App. The data will be transferred at pre-defined intervals from Intelex to the UoB secure servers.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the F4S-2 trial team and sponsor may be required to have access to participants' medical notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party.

Electronic data will be stored on UoB servers. Paper consent forms and questionnaires will be stored securely at the NHS site and UoB.

The REDCap database system will be used for the trial. The BCTU has permission to use as members of the REDCap consortium.

21. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

22. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

23. POST-TRIAL CARE

At the end of the trial, the participants will continue standard of care with their usual clinical care team.

24. ACCESS TO THE FINAL TRIAL DATASET

The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses.

Any request for data generated in this trial will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing

Committee in discussion with the CI and, where appropriate (or in the absence of the CI) any of the following: the trial sponsor, TMG and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. The data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

25. PUBLICATION POLICY

The protocol will be made available within a trial registry.

On completion of the trial, the data will be analysed, and a Final Study Report prepared.

Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review.

In all publications, authors should acknowledge that the trial was performed with the support of the NIHR HTA and BCTU. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

Results will be made available to participants in a plain English summary.

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Appendix I

The Clavien-Dindo classification of postoperative surgical complications

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multiorgan dysfunction
Grade V	Death of a patient

**brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.*