PROPEL

PeRsOnalised PrEhabilitation in AML

Evaluation of PeRsOnalised PrEhabilitation in people with acute myeloid Leukaemia

PROTOCOL

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This protocol has regard for current HRA guidance and content

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Protocol Amendments:

Amendment number	Date of amendment	Protocol version	Summary of changes
NSA14		3.0	• Updates to provide more guidance for sites to approach participants including consent based on blood count recovery and expected remission status. Remission status using bone marrow must still be confirmed prior to randomisation so the eligibility criteria remains unchanged. • Food diary at baseline will now be a 24hour recall only to support collection of baseline assessments. Updates to nutrition sessions format to allow nutrition topic information sessions currently available as Q&A sessions, to be provided as separate videos, with the opportunity for group Q&A sessions with a dietitian still available. • Additional advice provided to sites that may refer participants elsewhere for HSCT. • Additional advice for blinded physical outcomes collection. • Definition of 'End of Treatment' • Collection of AE's relating to trial intervention/control delivery to provide more oversight and clarity in SAE reporting. • General updates to contacts and consistency in terminology.

CONTACT NAMES AND NUMBERS

Role	Name, address, contact details
Sponsor:	**Lead sponsor:** University of Warwick (UOW) Head of Governance, University House, Coventry CV4 7AL Tel: 024 7657 5733 Email: sponsorship@warwick.ac.uk University Hospitals Coventry & Warwickshire (UHCW) Clifford Bridge Road, Coventry, CV2 2DX Tel: 024 7696 4000 Email: ResearchSponsorship@uhcw.nhs.uk
Chief Investigators:	**Professor Janet Dunn,** Professor of Clinical Trials Warwick Clinical Trials Unit, University of Warwick Tel: 02476 575 847 Email: j.a.dunn@warwick.ac.uk **Professor Simon Stanworth,** Consultant Haematologist Oxford University Hospitals NHS Foundation Trust, NHS Blood Transfusion and University of Oxford Email: simon.stanworth@nhsbt.nhs.uk

Clinical Trial Manager:	**Alice Longe** Warwick Clinical Trials Unit, University of Warwick Email: alice.longe@warwick.ac.uk
Clinical Trial Co-Ordinator	**Rosie Henvey** Warwick Clinical Trials Unit, University of Warwick Email: Rosie.Henvey@warwick.ac.uk
Statistician:	**Dr Andrea Marshall,** Associate Professor in Statistics Warwick Clinical Trials Unit, University of Warwick Email: andrea.marshall@warwick.ac.uk **Dr Gulnaz Iqbal,** Associate Professor Warwick Clinical Trials Unit, University of Warwick Email: G.Iqbal@warwick.ac.uk
Health Economist:	**Dr Hema Mistry**, Associate Professor in Health Economics Warwick Clinical Trials Unit, University of Warwick Email: hema.mistry@warwick.ac.uk **Dr Seyran Naghdi,** Research Fellow in Health Economics Warwick Clinical Trials Unit, University of Warwick Email: Seyran.Naghdi@warwick.ac.uk
Process Evaluation:	**Dr Claire Hawkes,** Senior Lecturer, Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College London Email: claire.hawkes@kcl.ac.uk
Patient and Public Involvement (PPI):	**Mrs Joanna Calder,** Individual PPI Member, Patient representative **Mrs Anna Mamwell,** Individual PPI Member, Patient representative **Eileen Stonock,** Individual PPI Member, Carer representative **Gillian Murphy,** Individual PPI Member, Patient representative

AML Specialist Collaborators:	**Clinical Advisors:**
	Dr Justin Loke, Clinical Research Fellow and co-lead clinical advisor Institute of Cancer and Genomic Sciences, University of Birmingham Email: justin.loke@nhs.net **Dr Victoria Potter,** Consultant Haematologist, Transplant physician Kings College Hospital NHS Foundation Trust Email: victoriapotter@nhs.net **Dr Priyanka Mehta**, Consultant Haematologist, AML specialist and expert in quality-of-life measures in AML Bristol Haematology and Oncology centre Email: Priyanka.Mehta@uhbw.nhs.uk **Dr Duncan Murray,** Consultant Haematologist, AML specialist and general clinician haematology University Hospitals Coventry and Warwickshire NHS Trust Email: duncan.murray@uhcw.nhs.uk **Dr Steven Knapper,** Clinical Reader School of Medicine, Cardiff University, lead AML national trials Email: knappers@cardiff.ac.uk
	Intervention Lead:
	Dr Gillian Prue, Reader Chronic Illness The Queen's University of Belfast Email: g.prue@qub.ac.uk

	Exercise component advisors:
	Dr Gordon McGregor (Lead), Associate Clinical Professor (Exercise Physiology & Rehabilitation) University Hospitals Coventry and Warwickshire NHS Trust Email: gordon.mcgregor@warwick.ac.uk **Dr Dominic O'Connor**, Assistant Professor in Physiotherapy and Sports Rehabilitation. School of Health Sciences, The University of Nottingham Email: dominic.o'connor@nottingham.ac.uk **Dr Malcolm Brown**, Research Fellow, School of Nursing and Midwifery, Queen's University Belfast Email: m.brown@qub.ac.uk
	Nutrition component advisors:
	Mrs Laura J Miller, Haemato-oncology Specialist Dietitian Nottingham University Hospitals NHS Trust Email: laura.miller44@nhs.net
	Behavioural Component advisors:
	Dr Rebecca Beeken, Associate Professor in Behavioural Medicine Leeds Institute of Health Sciences, University of Leeds Email: r.beeken@leeds.ac.uk **Dr Louise Hall,** Research Fellow, Leeds Institute of Health Sciences, University of Leeds Email: l.h.hall@leeds.ac.uk
	Psychological advisors:
	Dr Christopher Graham (Lead), Professor of Clinical Psychology School of Psychological Sciences & Health, University of Strathclyde Email: christopher.graham@strath.ac.uk **Dr John Pimm,** Consultant Clinical Psychologist Oxford Health NHS Foundation Trust Email: john.pimm@oxfordhealth.nhs.uk

	Nursing Advisor:
	Professor Annie Young, Professor of Nursing Warwick Clinical Trials Unit, University of Warwick Email: annie.young@warwick.ac.uk
	Qualitative researcher & PPI lead:
	Sophie Gasson, Senior Research Fellow, Warwick Clinical Trials Unit, University of Warwick Email: S.Gasson@warwick.ac.uk

For general queries and supply of trial materials please contact the coordinating centre:

PROPEL Team
Warwick Clinical Trials Unit (WCTU)
The University of Warwick
Gibbet Hill Road
Coventry
CV4 7AL
Tel: 02476 151 661
Email: PROPEL@warwick.ac.uk

For any queries regarding the intervention or control arm, please contact the central PROPEL specialist team on:

Email: PROPELspecialists@warwick.ac.uk

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TRIAL SUMMARY

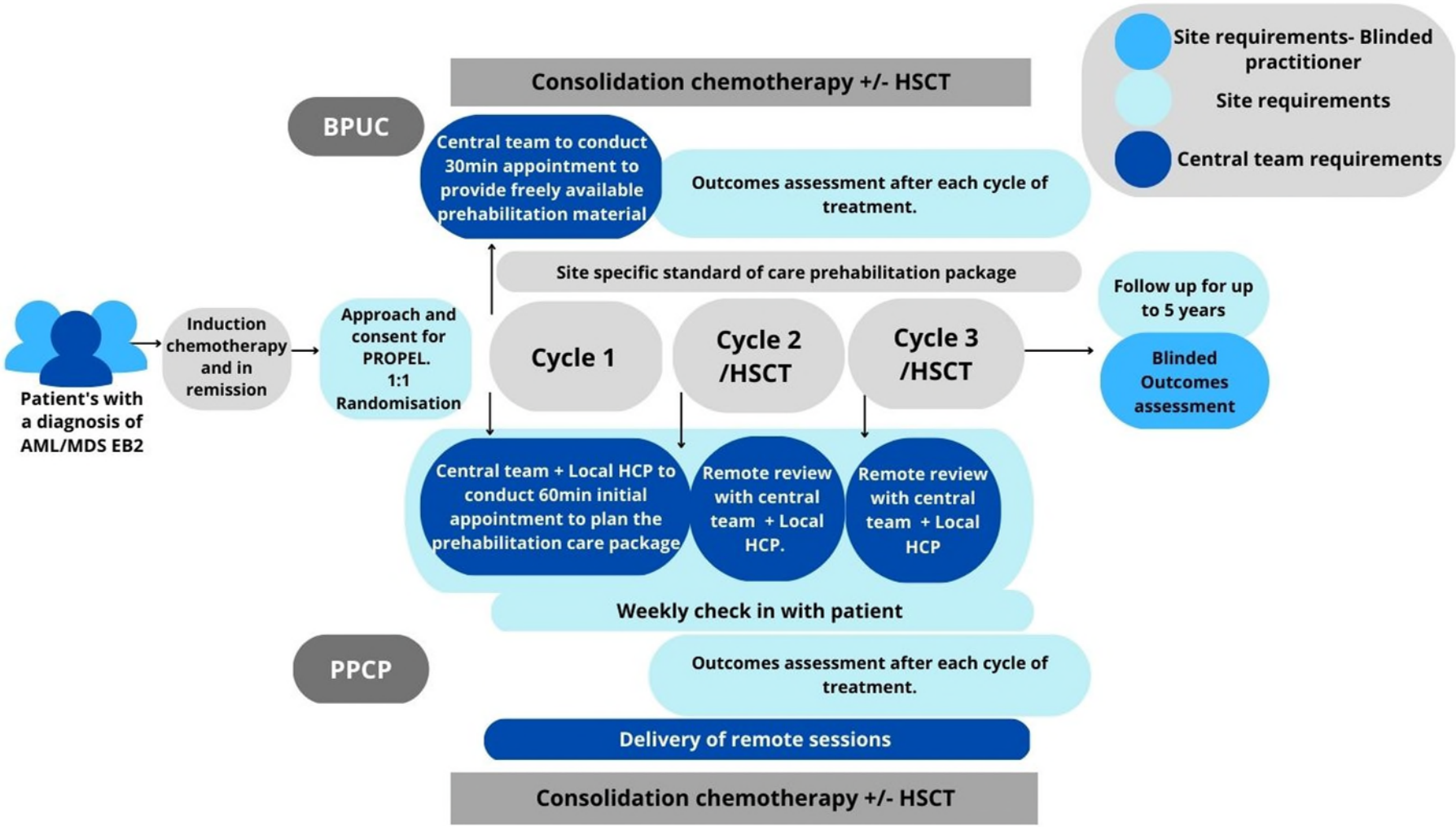
Trial Title	Evaluation of Personalised Prehabilitation in people with acute myeloid Leukaemia (AML)
Short title	PROPEL
Clinical Phase	Phase III
Trial Design	Multicentre, randomised controlled trial comparing best practice usual care (BPUC) with a personalised prehabilitation care package (PPCP) incorporating a 12-month internal pilot, parallel process evaluation and economic evaluation.
Research Question	What is the clinical impact and cost-effectiveness of BPUC compared to PPCP on fatigue, emotional wellbeing, and quality of life (QoL) in patients receiving remission consolidation treatment for AML or high-risk myelodysplastic syndromes with excess blasts (MDS-EB2)?
Hypothesis	PPCP will improve patients' experience of fatigue during treatment in comparison to BPUC, through supporting patients to manage their emotions, be physically active, and eat an appropriate diet.
Trial Participants	Diagnosis of AML or MDS-EB2, in complete remission following induction chemotherapy.
Inclusion Criteria	Aged ≥ 16 years with either: • Diagnosis of AML or MDS-EB2 (MDS with ≥10% blasts in the bone marrow), • In complete remission at completion of induction chemotherapy (defined <5% blasts in bone marrow), with an intention to undertake full consolidation treatment (chemotherapy +/- Haemopoietic Stem Cell Transplant (HSCT)), aimed at cure. ***or*** • Relapsed AML who have achieved a further complete remission with an intent to deliver further intensive consolidation treatment +/- HSCT.
Exclusion Criteria	• People with Acute Promyelocytic Leukaemia • Undergoing non-intensive treatment (e.g., single agent *Azacitidine*, low dose *Cytarabine*).
Planned sample size	600 patients; 300 per arm.

Treatment Duration	Treatment duration will vary according to number of cycles of chemotherapy and whether a HSCT is given. Each cycle of treatment and recovery is 4-6 weeks duration.
Follow-up Duration	Primary and secondary outcomes will be assessed at the first 3 months follow up post completion of treatment (either chemotherapy or HSCT) and at 24 months post randomisation. Annually up to 60 months for relapse free survival and overall survival.
Planned Trial Period	1st September 2022 – 31st August 2027. 60-month grant involves a 6-month set up period, recruitment over 30 months from 50 sites; 24 months is allotted for intervention delivery, follow-up, process evaluation, analyses, write up and dissemination.
Control	BPUC is in addition to prehabilitation care received as standard practice at site. It involves a 30-minute virtual prehabilitation discussion with a member of the central team, the participant +/- their caregiver where appropriate, once only and prior to the first cycle of consolidation chemotherapy. It will be based on the Maggie's Prehabilitation Guidance and provides the participant with online or printed generic and freely available prehabilitation information on emotional wellbeing, nutrition, and physical activity.
Intervention	PPCP is in addition to prehabilitation care received as standard practice at site. It involves information plus personalised support for emotional wellbeing, nutrition and physical activity. It will be offered before each consolidation cycle of chemotherapy and HSCT, if given. The PPCP will be developed based on screening and assessment of the person with AML by a central team of prehabilitation experts, with input from local staff and a caregiver (if appropriate). The PPCP will include advice on nutrition, physical activity and managing emotional well-being as required. Additionally, participants will be offered a range of remote support sessions delivered by a central specialist team (psychological wellbeing practitioners with clinical psychologist supervision, clinical exercise physiologist/physiotherapist/ Can-REHAB coaches and dietitians). Local staff will be trained to provide on-going behavioural support to participants via regular check-ins, to encourage adherence to the intervention. PPCP will mirror each consolidation cycle of chemotherapy and HSCT and should commence following blood count

	recovery, where possible, at least 8 days prior to commencing next consolidation cycle. Intervention will continue throughout each cycle and HSCT (if given).	
Aim	To establish the clinical impact and cost-effectiveness of best practice usual care (BPUC) compared to a multiphasic, multimodal personalised prehabilitation care package (PPCP) on fatigue, emotional wellbeing, and quality of life (QoL) in patients in remission following induction chemotherapy.	
	Objectives	**Outcome Measures**
Primary	To compare subjective levels of fatigue between patients in BPUC and PPCP arms	Functional Assessment of Chronic Illness Therapy (FACIT-F) fatigue scale
Secondary	To compare the following between participants in BPUC and PPCP arms:	
	Emotional wellbeing	Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)
	Anxiety and Depression	Patient Health Questionnaire 9-item (PHQ-9) General Anxiety Disorder 7-item (GAD7)
	Health Related Quality of Life	FACIT-F EQ-5D-5L
	Physical function	Karnofsky Performance Scale 6 min walk test Hand grip strength
	Presence or absence of sarcopenia	SARC-F Calf circumference
	Incidence of malnutrition and its determinants	MUST, Percentage weight change; BMI, dietary intake (food diary)

	Completion of treatment cycles	Number of cycles of chemotherapy completed +/- HSCT.
	Onward referrals for 'specialist' services	Number of onward referrals to local services for 'specialist' therapies
	Overall and relapse-free survival	Relapse, Death
	Readmissions to hospital, ICU admission, number of transfusions, complications of HSCT, adverse events and serious adverse events	Number of hospital admissions, transfusion, and complications of HSCT
	Cost, cost-effectiveness and cost utility	Resource use costs Cost EQ-5D-5L
	Parallel process evaluation: to understand the implementation and functioning of the intervention in context	Evaluation through qualitative interviews. Intervention delivery fidelity assessment of a proportion of sessions; patient intervention dose assessment through trial designed measurement tools
	Mechanisms of Action: Psychological Flexibility (PF), Motivation	CompACT-8 COM-B Questionnaire 1-item Motivation

Figure 1: Trial Schema



LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
ACT	Acceptance and Commitment Therapy
ACT-FM	Acceptance and Commitment Therapy Fidelity Measure
AE	Adverse Event
AHP	Allied health professional
AKI	Acute kidney injury
AML	Acute Myeloid Leukaemia
BMI	Body Mass Index
BPUC	Best Practice Usual Care
BCT	Behaviour change technique
CACE	Complier averaged causal effect
CI	Chief Investigator
CKD	Chronic kidney disease
COM-B-Q	Capabilities, opportunities, and motivations questionnaire
COMPACT	Comprehensive assessment of Acceptance and Commitment Therapy processes
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CRP	C-reactive protein
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ESPEN	European society for clinical nutrition and metabolism
EQ-5D	EuroQol-5 Dimension
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-G	Functional Assessment of Cancer Therapy – General
GCP	Good Clinical Practice
GAD-7	General Anxiety Disorder- 7
HSCT	Haematopoietic Stem Cell Transplant
HCP	Healthcare Practitioner
ICER	Incremental cost-effectiveness ratios
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number

LFT's	Liver function tests
MRC	Medical Research Council
MDS-EB2	Myelodysplastic syndrome With Excess Blasts
MDT	Multi-disciplinary team
MUST	Malnutrition Universal Screening Tool
NAHPs	Nurses/allied healthcare professionals
NHS	National health service
PAL	Physical Activity Level
PF	Psychological flexibility
PHQ-9	Patient Health Questionnaire 9-item
PI	Principal Investigator
PMH	Past medical history
PPCP	Personalised prehabilitation care package
PPI	Patient & Public Involvement
PSS	Personal social services
PWP	Psychological wellbeing practitioner
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SARC-F	Strength, Ambulation, Rising from a chair, Stair climbing and history of Falling
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
TDF	Theoretical domains framework
TMG	Trial management group
U&E's	Urea & Electrolytes
WCTU	Warwick Clinical Trials Unit
WEMWBS	The Warwick-Edinburgh Mental Wellbeing Scales

1 BACKGROUND

1.1 Epidemiology and treatment of AML

AML is the most common acute leukaemia affecting all ages in adults (2500 people/year in UK), often presenting as a medical emergency. Intensive chemotherapy forms the backbone of treatment in the NHS aiming at cure (over 1300 people/year), with an overall survival of 20% at 5 years in adults [1]. In 2019, across the UK, just over 600 patients were transplanted for AML and a related disease high-risk myelodysplastic syndrome (MDS with excess blasts; MDS-EB2), which is treated along the same pathway as AML. Completion of all cycles of treatment is important prognostically [1].

The first cycle of chemotherapy (induction) usually starts within days of diagnosis with little opportunity for conventional timing of prehabilitation, a point reiterated by our PPI panel. This first cycle is followed by an additional 2-3 cycles of consolidation chemotherapy, with ~40% requiring HSCT [curative intent & indicated by risk of relapse [2]]. Each cycle is 4-6 weeks, separated by 1-2 weeks for full blood cell regeneration. Overall treatment is either at home or in hospital and can be for a total of 6 months. Being able to tolerate HSCT is an important consideration when discussing treatment and cure options with patients.

PROPEL is addressing the challenge of how to reduce fatigue, increase emotional wellbeing and quality of life (QoL), enabling people with AML to prepare for and complete all intensive chemotherapy treatments.

1.2 Prehabilitation for People with AML

Prehabilitation aims to enhance general health and wellbeing prior to major treatments to enable completion of treatments. The benefits of prehabilitation may extend to reduced fatigue, better QoL, increased resilience to the effects of multiple cancer treatments, and an improvement in survival and long-term health [3].

Prehabilitation, as identified in our national survey (personal communication, Justin Loke, National Institute for Health Research [NIHR] AML Group), is not routinely offered to people with AML in the UK, and there is limited data on its value in patients with haematological malignancies. There are different layers of prehabilitation activity from information and self-management (akin to best practice usual care [BPUC]) to a more intensive multimodal personalised prehabilitation care package (PPCP) involving tailored support for emotional wellbeing, nutrition and physical activity. PPCP is conceptualised as a singular intervention that begins with an individual needs assessment and progresses to a personalised treatment programme integrating emotional wellbeing, nutritional and physical activity support, according to needs, underpinned by behaviour change strategies.

A relevant recent study funded by Blood Cancer UK (2021) reported on interviews with 200 people with blood cancers and healthcare professionals (HCPs) including doctors and nurses [4]. The results showed that fatigue and emotional wellbeing are key concerns, both points

reiterated by our PPI panel. Under half of HCP respondents in the survey agreed that their patients were well supported in terms of emotional wellbeing. Respondents described a wide range of emotional and psychological impacts throughout their blood cancer journey, including the need to address a major issue of fatigue, all reiterated in moving testaments provided by individuals in our PPI patient survey (n=43) [5]

Ensuring adequate emotional support has additional relevance and importance for blood cancer patients now treated during the COVID-19 pandemic. Emotional wellbeing plays an important role in how patients tolerate treatment and is also crucial for supporting engagement with other aspects of prehabilitation that are focused on enhancing patients' physical fitness via nutrition and physical activity. Randomised controlled trials in breast, colon and prostate cancer patients have shown psychological prehabilitation to have a positive effect on pain severity, fatigue and QoL [6] and evidence from surgical trials suggests prehabilitation focused on physical fitness can enhance patient outcomes post-treatment, including morbidity [7] and potentially, mortality [8].

Prehabilitation may help patients with AML get through all cycles of intensive chemotherapy, including critically to HSCT, which is an important curative therapy for obtaining disease remission, and improve survival outcomes.

1.3 Rationale

The outlook for many people who develop AML is poor, and as reiterated by our patient panel, their lives are hugely blighted by fatigue. Quality of life and functioning is very important to people with AML, alongside survival. Our PPI panel and the findings of our patient survey [5] confirm very limited access at present to interventions that can improve fatigue such as nutrition, physical activity and emotional wellbeing. Current usual care for prehabilitation, as reported in our two 2021 surveys of interested professionals [at different timepoints because of the pandemic], does not include standardised prehabilitation in any hospital setting of chemotherapy/HSCT for AML in the UK, except at two sites for HSCT only, delivered ad-hoc.

The majority of prehabilitation studies in cancer to date have focused on solid tumours and pre- and post-surgery. PROPEL therefore targets a population where limited patient-driven research on prehabilitation exists. Additionally, we have underpinned the PPCP arm with behavioural science which provides the best evidence for PPCP to be effective [9]. The PPCP will be delivered at a challenging time when people with AML are very unwell, and isolated in hospital for longer periods of time compared to patients with solid tumours, so sufficient behavioural support is crucial.

PROPEL addresses needs reported by a James Lind Priority Setting Partnership that identified fatigue, psychological wellbeing, diet, exercise and stress reduction as top 10 patient priorities for research [10]. Major charities working with people in haematological cancers,

including Anthony Nolan (involved with patients undergoing HSCT), Blood Cancer UK and Cure Leukaemia all support the need for this study.

In summary, PROPEL meets a large gap in evidence and practice and is extremely timely.

2 AIMS AND OBJECTIVES

To establish the clinical impact and cost-effectiveness, of BPUC compared to a multiphasic, multimodal personalised prehabilitation care package PPCP on fatigue, emotional wellbeing, and quality of life (QoL) in patients receiving remission consolidation treatment for AML and high-risk MDS-EB2.

2.1 Objectives

2.1.1 Primary objective

To compare fatigue measured by the Functional Assessment of Chronic Illness Therapy (FACIT-F) fatigue scale [11] in patients having consolidation chemotherapy +/- HSCT for AML or high risk MDS-EB2 receiving BPUC or PPCP.

2.1.2 Secondary objectives

Secondary objectives of the trial are to compare between arms:

- Emotional wellbeing, QoL, distress, physical function, performance status, incidence of malnutrition and sarcopenia.
- Number of completed chemotherapy and HSCT treatment cycles
- Onward referrals for 'specialist' services
- Overall and relapse-free survival

- To conduct a parallel process evaluation to understand the implementation and functioning of the intervention in context
- To assess whether the intervention works through the intended mechanisms of action
- To determine the cost, cost-effectiveness and cost-utility of PPCP in comparison to BPUC.

2.2 Outcome measures

2.2.1 Primary Outcome:

Fatigue will be measured by the FACIT-F [11], a validated 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function. It is appropriate for self-reporting or interview, takes approximately 10-15 minutes to complete, and is based on a 5-point Likert-type scale. Treating specialists will have no role in assessments of outcomes.

The rationale for the selection of primary outcome was informed by our PPI panel who placed the highest need on addressing fatigue. There is an extensive literature describing the real burden of fatigue in people with acute leukaemia. Whilst other measures of QoL were

considered relevant, our PPI kept returning to fatigue as the outcome that mattered the most.

2.2.2 Secondary Outcomes:

- Emotional wellbeing: the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) assesses participant's mental wellbeing and consists of 14 items, scored on a 5-point Likert scale score, giving an overall score [12].
- Anxiety and Depression: Patient Health Questionnaire 9-item (PHQ9) measures severity of depression and response to treatment. General Anxiety Disorder 7-item (GAD7) assesses the likelihood of the presence of the four most common clinical anxiety disorders [13, 14].
- Health-related quality of life:
    - FACIT F incorporates the 27 item FACT-G (Functional Assessment of Cancer Therapy – General) and measures four domains of health-related quality of life: physical, social, emotional and functional well-being.
    - EQ-5D-5L measures health status in 5 dimensions plus a visual analogue scale of self-rated health status [15].
- Physical function:
    - Performance Status: the Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment, used in (p)rehabilitation [16].
    - The 6-minute walk test [17].
    - Hand grip strength [18].
- Incidence of sarcopenia: SARC-F [19]; calf circumference [20].
- Incidence of malnutrition: Utilising Malnutrition Universal Screening Tool (MUST) [21] and its determinants; % weight change, Body Mass Index (BMI), energy and protein intake (food diaries via myfood24) [22].
- Completion of consolidation treatment plan (chemotherapy +/- HSCT)
- Number of onward referrals to local services for 'specialist' therapies.
- Overall and relapse-free survival.
- Readmissions to hospital, ICU admission, number of transfusions, complications of HSCT, adverse events and serious adverse events.
- Costs, cost-effectiveness and utility: costs, health resource use and EQ-5D-5L.
- Process Evaluation: fidelity to intervention delivery and dose of intervention received for each component.
- Mechanisms of Action:
    - Psychological flexibility – is the mechanism of action for ACT, and the model within which all intervention methods are delivered. This will be measured with a shortened version (8-items) of the CompACT questionnaires [23]
    - Motivation – measured using 1-item from the COMB-Q adapted for each component (3-items total) [24].

All questionnaires being used for the patient reported outcomes have been previously validated or have been adapted from validated questionnaires to fit this specific context and patient group.

3 ELIGIBILITY CRITERIA

Patients are eligible for inclusion in the trial if they meet the following criteria:

3.1 Inclusion criteria

- Age ≥ 16 years, treated on adult AML pathway

And either:

  - Diagnosis of either AML or MDS-EB2 (MDS with ≥10% blasts in the bone marrow)
  - In complete remission at completion of induction chemotherapy (defined <5% blasts in bone marrow)
  - Intention to undertake consolidation treatment (chemotherapy +/- HSCT),

** Patients undergoing Venetoclax based treatment are only eligible if a HSCT is planned.*

OR

  - Relapsed AML who have achieved a further complete remission, with an intent to deliver further intensive consolidation treatment +/- HSCT.

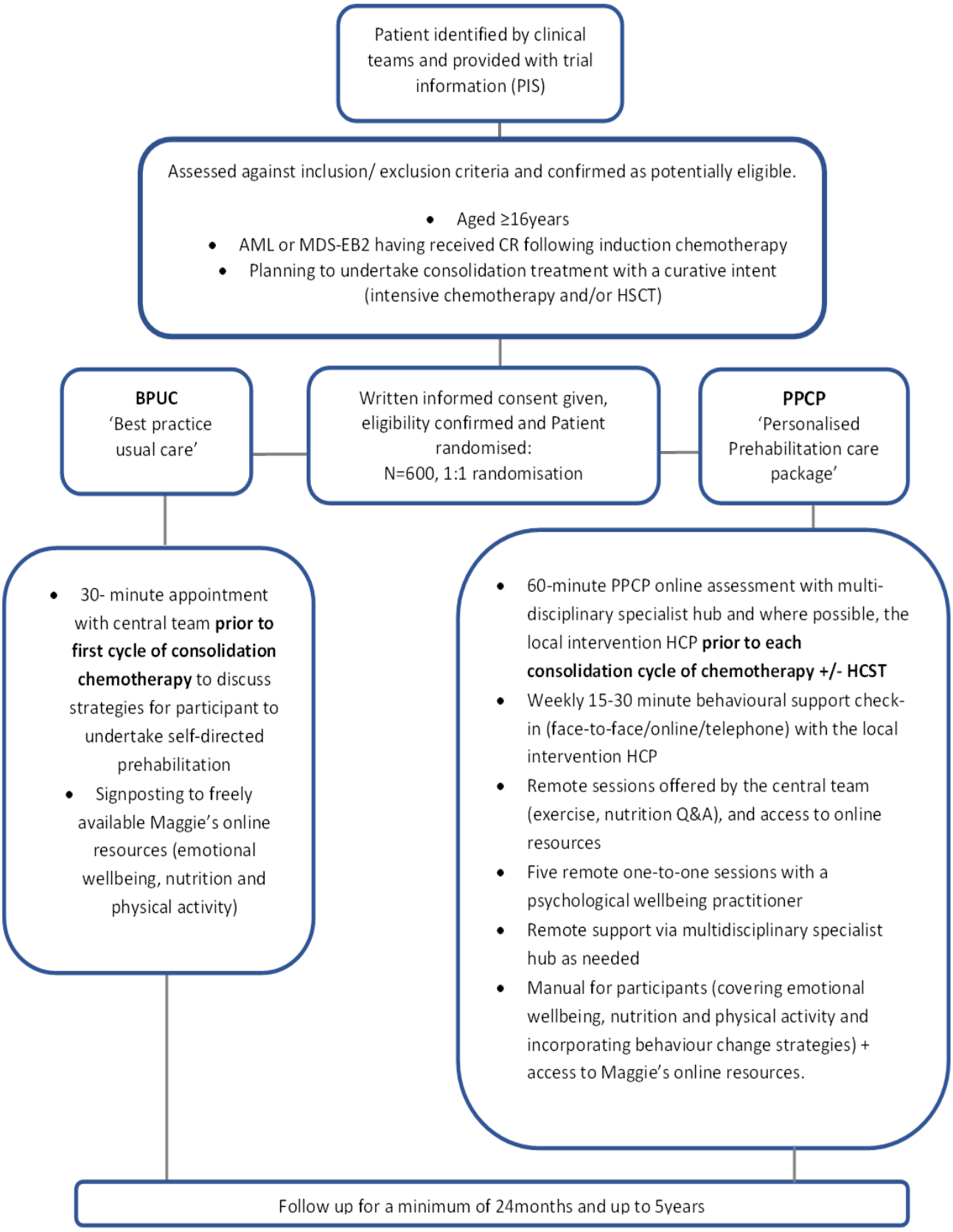
- Access to the internet and an email address.
- Willing to use videoconferencing to undertake the appointments and sessions.

3.2 Exclusion criteria

- Diagnosis of Acute Promyelocytic Leukaemia.
- Undergoing non-intensive treatment (e.g., single agent Azacitidine, low dose Cytarabine).

4 STUDY PROCEDURES

Figure 2 Trial flow diagram



4.1 Participant identification / Screening

Broad inclusion/exclusion criteria have been used to ensure the trial is as inclusive as possible. Patients will be identified by local site clinical teams based on their blood count recovery post-induction chemotherapy (indicating likely remission status) and provided with written trial information, either face to face or remotely (postal or electronic). A Patient Information Sheet (PIS) will be provided by the site research team, and patients given at least 24 hours where possible to consider their participation, prior to obtaining written informed consent.

A study summary sheet has been developed to ascertain interest in participants suffering from fatigue who may not feel able to read the full PIS in the first instance. However, all participants must receive a copy of the full PIS in order to make an informed decision about the study.

4.2 Informed consent

It is the responsibility of the local Principal Investigator (or trained designee as listed in the Site Signature and Delegation Log) to obtain informed consent in compliance with international requirements from each patient prior to entry into the trial. Discussions about trial participation may take place during an in-person consultation or remotely, i.e. during a telephone or video consultation. In all settings, the trial will be discussed in detail with the patient, and the patient will be provided with a copy of the Patient Information Sheet. Patients should be offered sufficient time to consider the trial, allowing time for discussion with family/friends/GP. The patient must be given the opportunity to ask questions and to be satisfied with the responses prior to consent being given. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time without giving reasons and without prejudice to any further treatment. Patients must also be provided with a contact point where they may obtain further information about the trial. Where possible, technical equipment such as tablets will be provided to participants that do not have the required technology to take part in the trial.

Ethically approved patient facing information such as printed leaflets and on-line information sources, designed to inform potential participants of the existence of the trial are not part of the formal informed consent process. Access to these sources will not be restricted to patients who have been approached about trial participation.

Full consent must be given in writing. The local Principal Investigator, or designee, or study team researcher receiving consent must countersign the consent form. The consent form should be signed and dated before conducting any study procedures. Sites are permitted to utilise third party translation services available as per local practices to support the consent process where required.

The Patient Information Sheet and Consent Form are available in electronic format to facilitate printing onto local headed paper. Signed original consent forms must be retained

on site and should be stored in the investigator site file with a copy filed in the patient's hospital notes. Completed Consent Forms must not be sent to the PROPEL Trial Office at Warwick Clinical Trials Unit (WCTU).

A copy of the fully signed consent form must be given to the patient. Copies may be in paper or electronic format according to site standard procedures. Sites must ensure that patients' participation in the trial is recorded in the patient notes and is communicated to the patient's General (or family) Practitioner. If the Patient Information Sheet and/or Consent Forms are modified during the course of the trial, sites will be notified of any required procedure to follow for patients already consented.

Process evaluation consent

Participants (and their carers if the patient wishes) local site propel trained HCPs, managers, central intervention delivery team and central team supervisors, who are approached to take part in process evaluation interviews will undergo a consent process with a researcher from the central team or by the site PI or their trained delegee. Participant information sheets, appropriate to the role in the study will be provided and will be available in electronic format and can be printed. The PROPEL team will ensure any completed consent forms completed by the central team researcher are returned to the recruiting site where possible, or stored securely at the PROPEL trial office.

4.3 Baseline

Primary and secondary outcome data will be collected prior to randomisation. Participant demographics, medical history and intended treatment pathway will be collected at baseline. A baseline participant questionnaire, with questions on health-related quality of life, and a 24hour dietary recall will be completed prior to randomisation.

4.4 Randomisation

Before randomising a participant, written informed consent must have been obtained and confirmation of trial eligibility documented in the patient's medical notes. Baseline assessments should also have been completed prior to randomisation. Where a participant is not eligible to proceed to randomisation post informed consent (i.e. if bone marrow results do not confirm remission), this information should be captured on the screening log.

Randomisation should occur at the end of induction chemotherapy, once remission status has been confirmed, and prior to the first cycle of consolidation chemotherapy.

Sites should log on to the PROPEL randomisation portal to randomise the participant. Sites should access the portal via the link below:

Patients can be randomised via the PROPEL database:

https://ctu.warwick.ac.uk/PROPEL

In the unlikely event the randomisation portal is not available, please contact the dedicated WCTU registration/randomisation line on 02476150402 (Mon-Fri 9am-5pm) excluding bank holidays & Christmas closure.

As part of the randomisation process, the participant will be assigned a unique trial number (TNO) that will be used to identify the participant and be recorded on all CRFs and on any correspondence with the PROPEL Trial Office.

Automated confirmation of the participant's randomisation details, TNO and trial arm allocation will be sent by email to the PI and main contact for the site research team (unblinded).

4.4.1 Method of Implementing the Trial Arm Allocation

Participants will be randomised on a 1:1 basis to best practice usual care (BPUC) or a personalised prehabilitation care package (PPCP). Trial arms will be allocated randomly using a computer minimisation algorithm held centrally at the Warwick Clinical Trials Unit and stratified by the following variables:

- age (<= 60; >60 years)
- baseline fatigue (none, mild, moderate, severe)
- performance status (Karnofsky performance status: 100-80; 70-50; 40-0) (17)
- intention to proceed to HSCT (yes; no).

4.5 Allocation concealment

Where possible, participant allocation should be concealed from the practitioners conducting the physical outcomes assessments throughout the trial. The practitioners conducting the physical outcomes assessments therefore should be different staff members to those supporting the intervention delivery. To maintain this allocation concealment, sites will divide staff members into two groups: 1) Those who support and deliver intervention and/or control (local intervention HCP); 2) Those who conduct physical outcome assessments (blinded physical outcomes assessor). Those in group 1 will be those that are permitted to receive notification at the point of randomisation revealing the participants allocation.

During the physical outcomes assessments, participants will be asked to not reveal their allocation to the assessing practitioner. If, however, an allocation is revealed, the practitioner will record this on the relevant CRF and inform the trial office on PROPEL@warwick.ac.uk. If an allocation is revealed, we ask that where possible the practitioner is changed for the next assessment visit in order to maintain blinded outcomes assessments.

Sites may request a blinded ISF for the blinded practitioners to use, which will only contain the documents relevant to their role.

4.6 Trial treatments / intervention

Table 1: Control and intervention composition		
	BPUC	**PPCP**
Timing	Once prior to first cycle of consolidation chemotherapy	Personalised prehabilitation MDT meeting prior to each consolidation chemotherapy cycle +/- prior to HSCT with support weekly throughout chemotherapy. The end of the intervention will be considered as up to 4 weeks following the final MDT.
Interventions	A single remote 30-minute appointment with a researcher from the central team to discuss strategies for the participant to undertake self-directed prehabilitation using the identified freely available support materials. Participants will continue to receive standard of care prehabilitation normally received as per site practices.	Pre-MDT clinical screening: collation of routinely available clinical data and project-specific assessments to inform the personalised prehabilitation MDT meeting. A 60-minute PPCP online prehabilitation MDT meeting with the multidisciplinary specialist hub in presence of person with cancer, a support person (if desired) and upskilled local intervention HCP. This will occur following blood count recovery, where possible, at least 8 days prior to commencing next consolidation cycle. PPCP will **not** be provided prior to maintenance chemotherapy such as Azacitidine or Cytarabine. Participants will be offered a range of remote support sessions via the central specialist team depending on needs. Where possible, the local HCP will provide a weekly check-in of 15-30 mins per week to the participant to provide behavioural support, discuss challenges and encourage adherence. Remote support from the multidisciplinary specialist hub can be accessed as needed. Participants will continue with PPCP prescription through their cycle and the process then repeats for each cycle of their consolidation chemotherapy +/- HSCT. Participants will continue to receive standard of care prehabilitation normally received as per site practices. At the end of the intervention, all participants will be signposted to relevant locally available resources and freely available online materials.

Support materials	Participant manual that includes signposting to freely available Maggie's Cancer Support online resources covering emotional wellbeing, nutrition, and physical activity. Standardised researcher script to facilitate call.	Manual for HCPs and for participants (covering emotional wellbeing, nutrition and physical activity and incorporating behaviour change strategies) in addition to access to Maggie's online resources.
Attendees	Participant +/- their nominated support person. A member of the central PROPEL specialist team (not involved in the PPCP where possible).	Participant +/- their nominated support person. Multidisciplinary specialist hub and upskilled local HCP.
Training		All PROPEL practitioners and local intervention HCP will be upskilled in Acceptance and Commitment Therapy (ACT) principles and key behavioural strategies to facilitate behaviour change. This involves a standardised ½ day training for HCPs, HCP support manual, educational video support and access to the multidisciplinary specialist hub for advice. Psychological Well-Being Practitioners delivering the emotional well-being intervention will receive two days' worth of training on delivering the intervention. They will be offered ongoing regular supervision with a qualified practitioner psychologist for the duration of the trial.

4.6.1 Best Practice Usual Care (BPUC)

Best Practice Usual Care (BPUC) consists of the provision of freely available online or printed information from Maggie's on self-directed prehabilitation on emotional wellbeing, nutrition, and physical activity, facilitated by a 30-minute scripted conversation with a trained member of the central team who, where possible, is not involved in PPCP, given once, before the first cycle of consolidation chemotherapy. This will be *in addition to* any routine referrals, and standard of care prehabilitation already offered at sites and ensures some level of standardisation.

4.6.2 Personalised Prehabilitation Care package (PPCP)

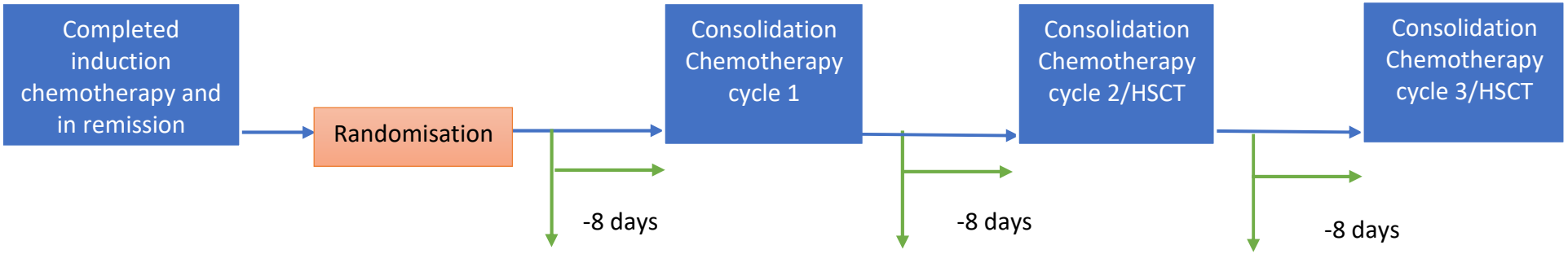
The PPCP is based on the NHS personalised care model [25] . The PPCP is underpinned by behavioural science and principles from Acceptance and Commitment Therapy (ACT). It is informed by our patient and carers experiences alongside the best available evidence for effective behaviour change techniques (BCTs) within interventions developed to support people living with cancer and beyond [26-28], and our own experiences of developing interventions in this area [29, 30]. BCTs to encourage engagement and adherence across the components will include goal setting, action planning, behavioural self-monitoring, and problem solving, alongside the promotion of psychological flexibility.

Screening, assessment, and planning of the PPCP will commence prior to each cycle of consolidation treatment, with remote sessions and compliance facilitated for the duration of that cycle of treatment. This process is repeated for each cycle of consolidation chemotherapy +/- HSCT. The end of the intervention will be considered as up to 4 weeks following the final PPCP meeting. PPCP will **not** be provided prior to maintenance chemotherapy such as Azacitidine or Cytarabine. PPCP will be *in addition to* any routine referrals, and standard of care prehabilitation already offered at sites. At the end of the intervention, all participants will be signposted to freely available online materials.

Figure 3 PPCP timeline

PPCP is a cyclical intervention that will mirror the consolidation cycles of chemotherapy undergone by each participant. PPCP should be commenced **PRIOR** to the commencement of any consolidation cycle, but it will continue throughout each cycle.

PPCP consists of a remote online 60 min personalised prehabilitation MDT meeting informed by pre-planning clinical screening. The patient will be provided with a personalised prehabilitation prescription to commence following the meeting and continue throughout the consolidation cycle (where possible) until the next assessment.



PPCP Cycle 1	**PPCP Cycle 2/ HSCT**	**PPCP Cycle 3/ HSCT**
Pre-planning clinical screening - Past medical history (PMH), meds, allergies; weight/height; food diaries; biochemistry; clinical screening questionnaire*	Pre-planning clinical screening- PMH, meds, allergies; weight/height; food diaries; biochemistry; clinical screening questionnaire*	Pre-planning clinical screening - PMH, meds, allergies; weight/height; food diaries; biochemistry; clinical screening questionnaire*
Personalised prehabilitation MDT meeting – following blood count recovery, where possible, at least 8 days prior to Cycle 1.	**Personalised prehabilitation MDT meeting** – following blood count recovery, where possible, at least 8 days prior to Cycle 2 +/- HSCT].	**Personalised prehabilitation MDT meeting** – following blood count recovery, where possible, at least 8 days prior to Cycle 3 +/- HSCT].
Post planning – commence intervention with local HCP supervision. Continue until PPCP prior to consolidation cycle 2.	Post planning – commence intervention with local HCP supervision. Continue until PPCP prior to consolidation cycle 3.	Post planning – commence intervention with local HCP supervision. Continue until treatment is completed.

**CORE-10 & Bespoke motivation questionnaire*

The PPCP has four integrated components delivered as one package:

Pre-MDT clinical screening: Clinical Screening involves the collation of routinely available clinical data by the local site team prior to each personalised prehabilitation MDT.

1. **Past medical history (PMH), current medications, and allergies**
2. **Nutrition** - Anthropometric measures (weight (kg), height (cm), dietary intake (food diary * – paper or electronic) & Full blood count and biochemistry results (U&Es, eGFR, LFTs, magnesium, corrected calcium, phosphate, CRP). This will be used to assess risk of refeeding syndrome/AKI/CKD; degree of malnutrition and enteral or parenteral nutrition requirements (out of scope for this study*).*
3. **Wellbeing** – CORE-10 [31] is a monitoring tool with items covering anxiety, depression, trauma, physical problems, functioning and risk to self. The measure has six high intensity/ severity and four low intensity/ severity items.
4. **Motivation -**1 item bespoke questionnaire for each component (exercise, diet, wellbeing) [24]. Three items total.

**Food diaries will be completed either on paper or directly onto myfood24, further details on this can be found in the practitioner manual.*

This information will be used to plan the prehab MDT meeting to ensure it is tailored to the participant. Screening will optimise delivery, safety and identify more complex needs, e.g., enteral or parenteral feeding, active psychosis, suicide risk where onward referral to local specialist allied health professional (AHP) services (i.e., physiotherapy, dietitian, psychology or psychiatry) may be required, and therefore PPCP may be inappropriate. Onward referral to local specialist services will be facilitated by the PROPEL specialist and local HCP. The need for a specialist referral in one domain (e.g., nutrition), will not preclude the participant from receiving PPCP remote delivery in the other two domains (e.g., exercise and psychological well-being). If the participant is under the care of, or receiving treatment from a speciality provided as part of the PPCP intervention, this should be discussed with the central team of PROPEL specialists to ensure there is no cross over.

Personalised prehabilitation MDT meeting: A remote 60-minute multidisciplinary (MDT) personalised care planning meeting, will be conducted by at least 2 members of a central team of specialists comprising of a psychologist, a CanRehab trained exercise specialist and dietitian. The meeting will be attended by the patient, their local PROPEL-trained intervention HCP (where possible)*, and a caregiver (if available and wished by the patient). It will be recorded and used to plan the participant's prehabilitation package for areas not requiring specialist referral, in line with the participant's values, needs and preferences. The personalised prehabilitation assessment will occur prior to each consolidation chemotherapy cycle and HSCT with changes made to the PPCP if indicated prior to each cycle.

**Where the local intervention HCP is unable to attend the MDT, they are able to request a follow-up conversation with the central PROPEL team for continuity of care.*

Personalised prehabilitation care plan: Following the prehabilitation MDT meeting, participants will be provided with their personalised plan for the treatment cycle, which will include advice on nutrition, physical activity and managing their emotional well-being as required. This will be supported by a manual providing further guidance on these areas, and incorporating behaviour change strategies. Additionally, where indicated participants will be offered a range of remote sessions delivered by the central PROPEL specialist team with no local HCP involvement required. PPCP participants will also have access to the Maggie's information provided as BPUC. Further details of each component of PPCP are described below:

Emotional wellbeing support: The intervention is informed by Acceptance & Commitment Therapy (ACT), which is particularly suited to cancer contexts [32, 33]. ACT will be delivered in a remotely guided self-help format that has proved effective with other long-term conditions [34]. It comprises of 4 self-help modules (available as podcasts or written material with audio files) that will be sent to participants, with follow-up phone/video calls from a therapist (Psychological Well-being Practitioner). The audio files contain brief centring/mindfulness exercises to correspond with each respective psychological skill. There are up to 5 telephone calls with a therapist; the first a 15-minute introduction call, and each module is followed-up with a 25-minute reflection call to help participants reflect on their experience and of trying the skills in everyday life. The modules contain opportunities for self-reflection and offer several psychological skills that participants can try. They include written materials, and audio files and cover the 4 skills of 'be present'; 'unhooking'; 'follow your values' and 'build a kind relationship with yourself'.

Training and ongoing supervision

Therapists will be qualified Psychological Well-being Practitioners (PWPs), employed within an NHS trust. Prior to delivering the intervention, therapists will receive training over 2 to 3 days. This will cover training in ACT, the context of AML, and the specific treatment package. PWP therapists will receive regular group supervision with registered practitioner psychologists.

Referral to specialist services

If, at any stage, it becomes clear the participant requires more intensive psychological support (i.e. suicide risk) they will be referred to local clinical psychology services.

Physical activity: A measurable dose of individualised multi-modality physical activity prescribed and supervised remotely by a specialist Clinical Exercise Physiologist in hospital or at home, to address general fitness, functional strength and fatigue [35], in accordance with American College Sports Medicine Guidelines [36]. To counter fatigue, focus will be on purposeful, prescribed and structured exercise [37], however, general physical activity recommendations will also be promoted. To accommodate transient changes in participants' wellbeing, the programme will adopt the principles of autoregulation whereby exercise is

progressed/regressed based on self-perceived daily variations in health, performance capability, recovery, and treatment [38].
The online, supervised, programme will consist of up to 30 minutes exercise two to three times per week. Participants will be encouraged to attend two live on-line sessions every week in discrete groups (max 6) or individually as required. Due to the complexity of health needs only Can Rehab professionals with suitable and recent experience in managing patients with complex conditions will supervise the intervention. Additionally, participants will be able to access online, pre-recorded sessions. A link will be provided to participants weekly for a specific session prescribed individually by the Clinical Exercise Physiologist.

Physical activity safety:
All participants will be assessed for any additional underlying health conditions or complications related to AML. All supervised sessions will be led by staff experienced in remote on-line assessment, prescription, and delivery of exercise for multi-morbid clinical populations. Pre-exercise session clinical screening will be completed. Staff will also monitor for adverse events during the sessions.

All participants will be advised to have another person nearby for the exercise sessions. When participants are joining from home, emergency contact information will be collected. In the event of an emergency, the practitioner will alert the designated 'co-pilot' for the session who will be able to communicate directly with the participant in question (via the live call or telephone) outside of the group and alert the emergency services if required.

Nutritional support: PPCP nutritional assessment will be delivered by a qualified dietitian as part of the central PROPEL specialist team utilising the dietetic care process [39] and informed by the pre-screening clinical data provided by the local HCP (see above for details). Intervention constituents will aim to facilitate improvements in cancer related fatigue via optimising dietary quality [40] and macronutrient provision tailored to individual requirements [41]. Energy and protein requirements will be based on ESPEN guidelines [42] and clinical expertise in AML at 25-30kcal/kg/d (utilising a Physical Activity Level (PAL) depending clinical appropriateness) and 1.2-1.5g protein/d. Recommendations and resources will be provided on timing of protein intake in relation to exercise in order to optimise muscle recovery [43]. Where appropriate patients will have access to nutritional supplements at site to meet energy or protein deficits in their intake. The PROPEL dietitian will work with local HCPs to support delivery (including supplement prescribing), in order to ensure parity in treatment access for intervention and control patients, accounted for in site agreements.

A rolling programme of group virtual support sessions, alongside online bite-sized nutrition education videos will be available to participants. The content will include principles of the PROPEL diet, known barriers to intake in this group informed by PPI and HCP experiences, for example, nausea/taste changes, altered bowels, protein and energy intake. Content will provide practical advice for managing these barriers and re-emphasise some of the

psychological skills from the emotional well-being modules that may be helpful (e.g.,unhooking). Use of behaviour change techniques such as goal setting and self-monitoring will also be encouraged. A virtual 1:1 dietetic appointment will be given each cycle to those requiring nutritional supplements. Additional 1:1 sessions may be offered on individual need where there is an identified concern raised, e.g. during their MDT, or by the local intervention HCP or patient during their weekly catch-up sessions. All prehab care plans will be updated as required.

Referral to specialist services:
Local PROPEL-trained HCPs will be supported to facilitate transfer to hospital based dietetic services where there is a clinical indication for enteral feeding, parenteral nutrition, specialist nutritional supplements (i.e. renal products, elemental diet) or the patient has refeeding syndrome at any stage in the trial. If a clinical risk then abates, nutrition advice can continue for subsequent cycles.

Local behavioural support: Local trained (unblinded) HCPs, where possible, will contact the participant (either face to face, by phone or video call) on a weekly basis for a brief check-in (15-30 minutes) to discuss any challenges and offer opportunities for reflections on their behaviour in relation to their goals and values. The HCP will support them to keep going by providing social support, the use of problem solving and action planning, and encouraging practice of their 4 psychological skills. The remote specialist team will act as an expert advice line to the local upskilled HCP.

Attendance to all sessions will be monitored, and participants or their local HCP will be contacted by a PROPEL practitioner in order to ascertain the participants welfare should any concerns arise due to non-attendance.

4.7 Resources and support materials:

4.7.1 Local practitioner manual

A practitioner manual will guide local practitioners through each component of the intervention and emphasise the ACT principles and behavioural strategies that will guide all practitioners throughout their delivery of the PPCP. The manual will reflect information provided during training and also include general information about the trial, key components of GCP, and contact details of the study team.

4.7.2 Participant manual

A participant manual will be a resource detailing, in a patient-friendly fashion, all information relating to the trial. Both the BPUC and PPCP manual will include:

1) general information about the trial
2) background information about AML
3) contact details and links to online resources.

The PPCP manual will additionally include

1) Information on emotional well-being, physical activity, and nutrition to support the remote sessions
2) Top tips for common problems
3) A logbook to support self-monitoring
4) Additional behaviour change strategies

4.8 Fidelity

Competency of those delivering the interventions will be assured through training which will include assessment of delivery at an early session, feedback and identification of additional training needed. These assessments will be included in the practitioner manual.

We will assess fidelity to each of the intervention components by those delivering them and how well patients are able to adhere to their programmes. Adherence will be assessed to calculate a measure of 'dose' of the intervention received and comprise of assessment of the proportion of prescribed sessions attended and, as appropriate, through assessment tools designed by the study team. The tools will be completed by those delivering the interventions at sessions. The assessment information will provide information about the amount of intervention participants were able to receive compared with published guideline recommendations, where available, or with a study standardised clinical assessment of how much of their prescribed dose they received. Delivery team practitioners will encourage patients to log their activities and bring these logbooks to sessions to inform the practitioners' assessment of intervention received. More information about the proposed content of these assessment is given below by intervention component. Participants ability to do their prescribed activities may fluctuate with how well they feel during their treatment cycles, so, where possible reasons for non-attendance at sessions or completion of activities will be noted.

An overall assessment of delivery team adherence to theoretical basis (behaviour change techniques and ACT) of the intervention package will be conducted. Thirty recordings, selected at random across the diet, exercise, and emotional wellbeing sessions will be listened to by the central team health psychologist and assessed for inclusion of pre-specified behaviour change techniques and broad adherence to ACT principles (e.g., using ACT-FM Stance items (4 prescribed and 3 proscribed) [44].

As this is a new way of delivering interventions together in a package, where possible, we will conduct analyses to see whether there were differences in key outcomes according to 'dose' received.

Table 2- Fidelity

Component and who delivers it	Delivery Fidelity	Patient adherence and assessments of "dose" of interventions received
Local behavioural support: Local PROPEL trained Health Care Professional (HCP) at site	Number of weekly check ins offered to each patient, detailing any with reasons that this was not offered. Health psychologist assessment of 30 recordings of randomly selected sessions, using a trial designed checklist of fidelity to the protocol.	Proportion of offered sessions received and reasons for non-attendance. The local HCP delivering the behavioural support will use the patient's logbook to assess what the participant was able to complete each week (including any BCTs used where relevant).
Exercise: Centralised Clinical Exercise Physiologist team	Proportion of planned sessions delivered and reasons for non-delivery. A randomly selected sample of 30 recordings of sessions will be assessed using a pre-specified checklist by an independent (where possible) clinical exercise psychologist.	Due to the changeable nature of how participants may feel in response to treatment, the aim of the exercise component assessment will be to compare dose received with existing guidelines recommendations for exercise in other similar cancer populations. **Live sessions:** we will calculate dose by recording frequency, intensity, time, and type of exercise for every participant at every live session. This will be documented by the practitioner after each session. **Pre-recorded/on-demand sessions:** participants will record in their logbook which sessions (if any) they compete each week. This will also be recorded by the practitioner.
Nutrition: PROPEL dietitian in central specialist hub (in collaboration with local PROPEL trained HCPs)	Delivery fidelity: • Proportion of planned nutrition sessions delivered and reasons for non-delivery. • No. of views for the online bite-size education videos • Proportion of patients being escalated to local care due to complex needs. • A random sample of recorded nutrition group sessions will be independently (where possible) assessed using a trial specific checklist to assess delivery of fatigue improving interventions.	Proportion of nutrition sessions attended plus assessment of requirement for additional queries made by patients, carers and local PROPEL trained HCPs outside the scheduled sessions (i.e., numbers of queries) The practitioner will use the following sources of information to make an assessment of "dose" received using a trial specific checklist/tool. Logbook: participants will be asked to log if they were able to adhere to their recommended nutrition treatment plan. Food diary: information from food diaries will determine patient capacity to adhere to nutritional treatment plans in the following ways:

		• Nutritional deficits between reported energy and protein intakes (calculated via myfood24 from 3-day food diaries) will be compared to recommended targets. • Number of recommended nutritional supplements versus those taken (also available from patient prescriptions).
Wellbeing: Central research team/PROPEL trained psychologists	Practitioner treatment fidelity will be assessed through independent (where possible) rating of a random sample of 30 tapes (of sessions 2 -5) using the ACT-Fidelity Measure (ACT-FM) [44]	Proportion of offered sessions received and reasons for non-attendance.

4.9 Schedule of assessments

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
		Consolidation Treatment: *To mirror the participant's planned treatment pathway*						
Visit Window (No. Weeks ± No. Days)	**Baseline***	**Cycle 1 (Day 0)** ***-8days***	**Cycle 2/HSCT** ***-8days***	**Cycle 3/ HSCT** ***-8days***	**EOT**	**3months post EOT**	**Month 24** *(post randomisation anniversary)*	**Annual follow up (up to 5 years)** *(post randomisation anniversary)*
Informed consent	x							
Medical history	x							
Confirm patient eligibility	x							
Randomisation		x[a]						
BPUC only: 30minute BPUC appointment		x						
PPCP only: MDT care planning sessions		x	x	x				
PPCP only: Participant check in		x Weekly check in						
Questionnaire booklet	x		x	x	x	x	x	
Health resource use questionnaire			x	x	x	x	x	

Visit	1	2	3	4	5	6	7	8
		Consolidation Treatment: *To mirror the participant's planned treatment pathway*						
Visit Window (No. Weeks ± No. Days)	**Baseline***	**Cycle 1 (Day 0)** ***-8days***	**Cycle 2/HSCT** ***-8days***	**Cycle 3/ HSCT** ***-8days***	**EOT**	**3months post EOT**	**Month 24** *(post randomisation anniversary)*	**Annual follow up (up to 5 years)** *(post randomisation anniversary)*
PPCP only: Clinical screening questionnaire booklet		x	x	x				
6minute Walk Test	x					x[b]	x[b]	
Performance status	x	x	x	x	x	x	x	
SARC-F & Calf circumference	x				x[b]	x[b]	x[b]	
Hand grip strength	x				x[b]	x[b]	x[b]	
Height	x							
Weight	x	x[c]	x	x	x	x	x	
Food diary[e]	x[d]	x[ce]	x[e]	x[e]	x[e]	x[e]		
Haematology and biochemistry[f]	x[f]	x[cf] **PPCP only**	x[f] **PPCP only**	x[f] **PPCP only**				
Adverse events / complications of treatment			x	x	x			

Visit	1	2	3	4	5	6	7	8
		Consolidation Treatment: *To mirror the participant's planned treatment pathway*						
Visit Window (No. Weeks ± No. Days)	**Baseline***	**Cycle 1 (Day 0)** ***-8days***	**Cycle 2/HSCT** ***-8days***	**Cycle 3/ HSCT** ***-8days***	**EOT**	**3months post EOT**	**Month 24** *(post randomisation anniversary)*	**Annual follow up (up to 5 years)** *(post randomisation anniversary)*
Review participant logbook			x[g] **PPCP only**	x[g] **PPCP only**	x[g] **PPCP only**			
Onward referrals		x *As required*[h]						
Survival status						x	x	x

**Where possible, baseline assessments should be completed at the end of induction chemotherapy, on blood count recovery, prior to hospital discharge*

a) Randomisation should occur at least 8 days prior to the planned start date of cycle one of consolidation chemotherapy.

b) Blinded outcome assessor

c) Where this has not been completed within 7 days of the first appointment (for participants randomised to PPCP only) this should be repeated.

d) The Baseline food diary will be a 24hour recall only, completed via paper

e) 3-day food diary, either completed via myfood24 or through paper food diaries

f) U&Es, FBC, neutrophils, eGFR, LFTs, magnesium, corrected calcium, phosphate, CRP, vitamin D to be taken on blood count recovery

g) Logbooks should be reviewed at each cycle of treatment, and a copy provided to the study team for participants on the PPCP arm only

h) Onward referrals as required throughout the treatment phase, supported by the central PROPEL specialist team and local HCP.

4.10 Follow-up assessments

To limit the burden on participants, only primary outcome and key secondary outcome data will be collected prior to each cycle of chemotherapy and at end of treatment (EOT). EOT within the PROPEL trial will be defined as following blood count recovery after the final cycle of intensive consolidation treatment (either chemotherapy or HSCT), where possible prior to discharge or at the EOT clinic review. Primary and secondary outcomes will be assessed in person at 3 months follow up post end of treatment (either chemotherapy or HSCT) and at 24 months post randomisation. Follow-up data for relapse and death will be collected up to 5 years from trial entry.

4.11 Referral to another centre for HSCT

In the most part for this trial, consolidation chemotherapy and HSCT will occur at a single hospital site, and therefore intervention delivery and follow up data collection will be seamless. In cases where chemotherapy and HSCT are delivered at different sites, trial follow up may require collaboration with the transplanting centre.

Where the transplanting centre is also open to PROPEL, the recruiting centre should notify the PROPEL trials office as soon as possible and prior to HSCT, and a hospital transfer CRF should be completed. The PROPEL trials office will contact the transplanting centre and organise the participant to be transferred via the PROPEL database. Although informed consent is an ongoing process, the original signed informed consent form will remain valid and does not require re-signing at the transplant centre at the point of transfer. The PROPEL trial office can advise if your nearest transplant centre is also open to PROPEL.

Where the transplanting centre is not open to PROPEL, post HSCT follow-up will involve close communication between the referring and transplant hospital. Sites should make every effort to collect data and questionnaires remotely where the participant does not return to the referring hospital at the relevant timepoint. If physical outcome assessments cannot be collected, the reason for this should documented on the relevant case report form. PROPEL specialists will be available to contact for advice, should the transplanting hospital have any questions about the care plan in place for participants on the PPCP arm.

4.12 Post-randomisation withdrawals, exclusions and moves out of region

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Patients may be withdrawn from their trial allocation at the discretion of the Investigator and/or Trial Management Committee. If a patient withdraws from their trial allocation, either by their choice or at the discretion of the investigator, they must be followed up in accordance with the protocol. For patients who are lost to follow-up, follow-up data should

continue to be collected from hospital or GP records, these patients should not be automatically withdrawn from the trial.

Patients moving away from the region of the local site should NOT be withdrawn from the trial. Should this occur, please contact the PROPEL Trial Office with the relevant details, and they will endeavour to assign the patient's follow-up to a site close to their new location.

4.13 Co-enrolment into other trials

The NIHR AML group including PPI are involved in the development of new protocols for treatment of AML. The CIs of these trials will be asked whether PROPEL can also be offered to patients in the treatment trials. As a non-CTIMP, it is expected that co-enrolment to PROPEL will be permitted. Patients randomised into PROPEL can be enrolled into other studies as long as this has been agreed with the TMG and they do not affect the PROPEL outcomes. Once agreed, these trials will be added onto a rolling list of trials permitted for co-enrolment.

4.14 Site Staff Training

PI's may be drawn from a range of health care professionals at participating sites, including haematologists. Nurses/allied healthcare professionals (NAHPs) are also actively encouraged to act as local PIs.

A standardised training package will be given face to face or virtually to nurses and AHPs who are supporting the PPCP for those people randomised to PPCP. Training includes:

- How to recruit and randomise participants
- Collection of data for pre-planning screening and onward referral for specialist services
- Structure of the weekly check-ins including ACT principles and behaviour change techniques to encourage adherence
- Contacting the central PROPEL specialist team for support (when and how to do this)

4.15 End of trial

The end of study will be defined as last data capture for the last participant, allowing three months after the last visit to return CRFs and answer data queries. The CI will notify the Sponsor, participating sites and REC within 90 days of the end of study, or within 15 days if the study is ended prematurely. The clinical study report will be written within 12 months of the end of study.

5 PARALLEL PROCESS EVALUATION

Guided by the MRC framework for evaluation of complex interventions [45], the mixed methods process evaluation will inform interpretation of trial results and wider implementation of the intervention package. It will provide understanding of the

implementation and functioning of the intervention, including intervention personalisation, in context. The PROPEL intervention model of delivery is through a combination of locally delivered aspects and remotely delivered aspects of the different components of the intervention. The process evaluation will assess this delivery model and consider the feasibility and practicalities of implementing this model of prehabilitation in practice.

Aims: To investigate issues that may affect the delivery and outcomes of the intervention and assess the feasibility of implementing the intervention widely in the NHS

Objectives:

1. To investigate intervention delivery fidelity and impact dose of the PROPEL intervention model.

2. To investigate patients', local site PROPEL Trained HCPs', managers', remote delivery practitioners and central PROPEL specialist team experiences of the intervention, how and why the intervention did or did not facilitate change among participants, at a sample of 6 sites, and

3. To explore how the intervention delivery was implemented by the remote delivery practitioners at the sample of 6 sites and how that implementation affected how the intervention package was delivered and received.

Design

A theoretically informed mixed methods process evaluation consisting of a fidelity and intervention dose assessment across all intervention sites, measurement of any behaviour change differences between intervention and control groups across all sites, and a qualitative interview study focused on six sites.

Theoretical framework

The multiphasic, multi-modal prehabilitation package intervention (PPCP) is informed by theoretically informed behavioural change determinants such as motivation and the principles of Acceptance and Commitment Therapy (ACT), which promotes psychological flexibility. These determinants associated behaviour techniques and principles will inform the study's intervention logic model. The behaviour change techniques can be identified in the Behaviour Change Taxonomy (BCT) [46] which focuses on the techniques or active ingredients in interventions that can lead to the desired behaviour changes. The Theoretical Domains Framework (TDF) [47] is associated with the BCT, and in turn is associated with the COM-B framework [24] and Behaviour Change Wheel [48].This will broaden our view from individual behaviour change to interactions with systems in order to frame our exploration of intervention implementation.

We will use the evaluation framework, as a lens to explore not only whether the intervention package works for the patients as hypothesised but also to identify barriers and facilitators

to implementing the intervention at different levels of the organisation. To do this we will explore the different layers of the context in which they receive the intervention. These include the existing structures of the organisation where the intervention is delivered, the management of the clinical service and any changes made to deliver both the remote and local components of the intervention, the experiences of the local PROPEL Trained HCP and the remote intervention therapists and the central PROPEL specialist team in delivering the intervention to the patient.

Samples for different components of the process evaluation

The investigation of intervention delivery fidelity and impact of the dose of the PROPEL intervention model (objective 1) has been described in section 4.8 'Fidelity' above.

All study participants will take part in an assessment of the intervention's underlying behaviour change techniques and ACT principles (in particularly psychological flexibility) to assess whether the intervention group was any different to the control group. The measures are selected to measure change expected with the intervention.

Psychological Flexibility

The 8-item brief CompACT will be used as a measure of psychological flexibility [23].

Motivation

The trial-adapted COM-B questionnaire item on Motivation will be used to measure motivation for each of the intervention components [24]. There will be 3 items in total (one for each intervention component).

Nutrition Impact Symptoms (NIS)

Modified unvalidated questionnaire based on the Omlin nutrition impact symptom (NIS) checklist [49] will be used to measure the impact of NIS on dietary intake. It includes 10 symptoms and 2 additional questions about food access on PPI request. Instead of severity of symptoms (which will be captured by adverse events) frequency of occurrence has been added to quantify burden more accurately. The questionnaire has been reviewed by 8 AML patients and 4 topic specialists for ease of understanding and relevance with updates made.

Six sites will participate in a more detailed evaluation (objective 2 and 3). They will be purposively selected to ensure the sample includes the following characteristics: whether or not they have a transplant service, previous routine provision of prehabilitation or not, and serving different populations (e.g., urban/rural, mixes of socio-economic areas and mix of ethnic groups). Two sites will be selected during the pilot phase and the remaining 4 in the main study. Having two sites in the pilot phase could allow opportunity to assess the feasibility of the planned data collection. Data from all six sites will be used in the final evaluation.

Sample recruitment and consenting for interview participants at the detailed evaluation sites.

Patient participants from each arm of the study at the selected process evaluation study sites will be given the opportunity to indicate they are willing to be contacted about the process evaluation when they are consented for the main study. If so, they will provide their contact details for this purpose. They will be informed that they may not be contacted as only a few people from each of only a few sites are needed. We will purposively select from those potential participants at each site and contact them to see if they would like to take part. We will provide potential participants with more detailed information about what will be involved, and they will be given the opportunity to ask questions. If they agree to take part, an interview will be arranged, and informed consent will be taken by the researcher conducting the interviews. This may be on the same day or beforehand. The patient sample will be purposively selected to achieve a sample of up to 4 participants per arm at each of the 6 sites. The participant sample will be selected to include a range of characteristics such as age, gender, ethnicity. Patients will be asked whether they wish a family member or key supporting person to be involved in the interviews or not. For those who do want this, the family member/key supporting person will also be given study information, the opportunity to ask questions and provide consent for participation in the interview.

The site research team and PI will be asked to identify the PROPEL Trained local HCPs involved in intervention delivery (up to 3) and key managers (up to 3) involved in implementation of the intervention. Although participation will be voluntary, to alert staff to the possibility, the site PI and research team will be asked to let their local teams know that they may be interviewed about their experiences of the intervention as part of the study, from the outset. This information may also be reiterated during the site initiation. The research team will approach the selected potential participants to obtain informed consent.

Members of the multidisciplinary specialist team delivering remote components of the interventions at the six sites will be interviewed. They will be selected to include up to three practitioners involved in each of wellbeing, diet and physical activity. Members of the research team supervising interventions will also be interviewed. Informed consent will be gained from all participants.

Mitigating risk:

We do not anticipate any serious adverse events arising from participation in interviews for the process evaluation. However, it is possible participants, particularly patients and their relatives may experience distress when talking about their experiences. Participants will be given the opportunity to take a break or end the interview should this happen. Participants will be referred to their clinical team, with their permission, should any areas that require further support be identified. Relatives will be signposted to sources of support such as their GP or charities supporting relatives of patients with cancer.

Interviewer's will also be given the opportunity to access debrief sessions, should they require it, if they find the interviews distressing and emotive.

Most interviews are expected to take place over the phone or via video call. If required, a face-to-face interview will be facilitated where possible, and would be subject to UoW lone working policy and relevant risk assessment.

Data collection

Data collection for the fidelity and intervention dose is described in section 4.8 Fidelity above. Data collection for the mechanisms of action will be through the patient completed CRF pre-, during-, and post-intervention.

The intervention description, logic model and underpinning theories including those underpinning Acceptance and Commitment Therapy (ACT) [32], the Theoretical Domains Framework (TDF) and associated Behaviour Change Taxonomy (BCT) [50] will inform data collection and analysis of the process evaluation interviews at sites and with members of the delivery teams. The interview topics for exploration with participants will be informed by the evaluation framework and will therefore cover perspectives of the intervention and how it worked (or did not work) and how it was implemented from patients', clinicians', managers', and multidisciplinary hub team members' viewpoints**.**

Starting during the internal pilot phase, at each site semi-structured online/telephone or face to face interviews will be conducted with participants.

Data analysis

To assess delivery fidelity, check list scores and the proportion of sessions delivered will be summarised for the different components of the intervention (nutrition, physical activity, emotional well-being and weekly behavioural support) alongside reasons for non-delivery. Self-reported participant adherence to the different components, logbook completion, and discussion of behaviour change techniques will be summarised based on data collected during the weekly check-ins. Intervention dose will be calculated for each component using the data outlined in Table 2. Associations between key study outcomes and adherence, and dose will be explored. A comparative analysis of behavioural mechanisms will be conducted to assess differences between study and intervention group, and if appropriate mediation analysis will explore whether differences in these mechanisms are related to study outcomes.

We will use data from the interviews to describe the approach to implementation taken at each of the six sites. We will conduct a thematic analysis of the qualitative interview data using an abductive approach. An analysis framework [47] will be iteratively developed. Initial development will be based on the study evaluation framework. Interview data will be coded, categorised and grouped into themes. These will be assessed for fit and explanatory value within the existing framework themes or will be used to create new themes within the framework. We will also analyse data from each site and across all sites, to enable

identification of differences and similarities and how the approach to implementation may have impacted on the delivery of or outcomes of the interventions.

Fidelity, adherence, dose and behavioural mechanism results will be narratively combined with the qualitative interview findings to inform interpretation of main trial outcomes and the process evaluation's aims and objectives.

Dissemination and further implementation
The process evaluation will include stakeholder meetings to discuss the results with commissioners who will be encouraged to implement prehabilitation should the results show benefit and cost effectiveness. This will help identify what implementation issues are the most important from a commissioner's perspective. The output from these meetings will aim to provide information for non-participating sites who may want to commission these services should the intervention been deemed effective.

6 ADVERSE EVENT MANAGEMENT

6.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant *participating in a clinical study* and which does not necessarily have a causal relationship with the treatment/intervention.

For the purpose of this study, the following events are regarded as expected AEs and **should not** be reported:

- AE's relating to chemotherapy, HSCT, blood transfusions or standard treatment delivery (outside of the PROPEL intervention). This information, where required, is collected on the treatment CRF's.
- AE's relating to recurrence or progression.
- Procedures which are elective or pre-planned, or for a pre-existing condition.

Any AE's which do not fall into the above categories, are considered as special interest as they may be related to the delivery of the intervention or control, and should be reported on the 'AE of special interest' CRF. Possible examples include musculoskeletal injuries related to exercise, or adverse events during the conduct of physical outcomes assessments.

Any AE's linked to the study outcomes will be collected on the relevant treatment CRF. Recurrence of and/or death from AML are outcome measures of the trial that will be collected via the CRF (the Event Form and Notification of Death Form) and are treated as expected events.

6.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Immediate intervention was required to prevent one of the above or is an important medical condition.

For the purpose of this study, the following are regarded as expected SAEs and **should not** be reported on an SAE Form:

- SAE's relating to chemotherapy, HSCT, blood transfusions or standard treatment delivery (outside of the PROPEL intervention). This information is collected on the treatment CRF's.
- SAE's relating to recurrence or progression.
- Procedures which are elective or pre-planned, or for a pre-existing condition.

This is not an exhaustive list and Investigators should use their own judgement when reporting SAEs.

6.3 Reporting procedure:

6.3.1 Site

Site events that meet the criteria for an SAE, per the protocol, should be reported to WCTU on the SAE form. When completing the form, the Investigator will be asked to confirm the following information:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- grade of severity (categorised using the Common Terminology for Adverse Events (CTCAE) version 5.0) [51].
- causality (i.e. relatedness to intervention), in the opinion of the investigator

On becoming aware that a patient has experienced a SAE, the Investigator (or delegate) must complete, date and sign the SAE Form (blank copies located in the ISF). The form must be sent by email to the Trial Office as soon as possible and no later than 24 hours after first becoming aware of the event.

To report an SAE, email the SAE form to WCTUQA@warwick.ac.uk

Patients should be followed up until resolution or stabilisation of the event. any change of condition or other follow-up information should be reported to WCTU using the method described above as soon as it is available. Follow-up information should be provided on a new SAE form.

6.3.2 Trial office (WTCU)

The Trial Office will report all events that are categorised as Unexpected and Related SAEs to the REC within 15 days of receipt. Details of all Unexpected and Related SAEs will also be reported to Principal Investigators at recruiting sites.

6.3.3 Reporting Period

Details of all SAEs (except those listed in Section 7.2) will be documented and reported from randomisation until 30 days post EOT. This reporting period should be sufficient to capture all SAEs associated with the trial protocol however, if a related SAE is identified after this period, the event should be reported to the Trial Office.

6.4 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

7 DATA MANAGEMENT

7.1 Data collection and management

The Case Report Form (CRF) will comprise of a set of forms capturing details of eligibility, baseline characteristics, treatment, and outcome details. This trial will use an electronic data capture (EDC) system which will be used for completion of the CRF. Access to the EDC system will be granted to approved site personnel via the Trial Office. If the use of a paper CRF is required, then original forms should be sent to the co-ordinating team at WCTU and copies retained on site. CRFs are expected to be completed within 4 weeks of their due date. Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. Missing

and ambiguous data will be queried in line with the WCTU data management plan, which will outline the requirements for CRF completion and return.

7.2 Source Data

Source documents are where data is first recorded, and from which participants' CRF data is obtained. These include, but are not limited to, hospital records (from which medical history and previous and concomitant medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number, not by name. Investigators should keep records of all participating patients, all original signed informed consent forms and copies of any paper CRFs. It is necessary for investigators to provide access to source document for monitoring and audit purposes to WCTU, Sponsor, any monitoring or regulatory authorities as deemed necessary.

7.3 Data Handling and Record Keeping

The database will be developed and managed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff. The database will meet industry standard security criteria and only be accessible to authorised personnel. Within the database, participants will be identified by the trial participant number only.

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

Interview data and recordings of appointments will be recorded using secure encrypted audio devices or using Microsoft Teams. Recordings will be downloaded as soon as possible to encrypted university laptops and subsequently to the secure study area on the university servers under the participants unique study identifier. Once downloaded, the original audio recording will be deleted from its source. Any data that are transferred out of the secure environment (for example audio files of interviews for transcription) will adhere to University of Warwick SOPs. Any transcription service used will be subjected to the University of Warwick's approved supplier review processes. Audio files will be fully pseudonymised at the point of transcription, with any participant identifiers removed. Pseudonymised transcriptions will then be saved to a secure encrypted folder, under the unique patient identifier. The study team will maintain a separate confidential and secure list of patient identifiable information (name, identification number and contact details) for the purposes

of the process evaluation research (e.g., organising interviews), co-ordinating appointments, audit / quality assurance. This will be securely held on the University of Warwick servers.

Personal data entered onto myfood24 (such as name and email address) for the purposes of sending the food diaries to the participants will be held externally, securely stored on the Amazon Web Services Europe 'cloud' servers located in Dublin, with back-up servers in London. It has physical and environmental security controls plus the network connection is encrypted and protected by a firewall. myfood24 has multiple data security accreditations including ISO27001, Cyber essentials plus and NHS Data Security and Protection Toolkit (DSPT) guidelines. Where participants are unwell or unable to input food diaries directly on to myfood24, paper versions will be made available. Pseudonymised paper copies will be transferred to the PROPEL trial office for data entry.

7.4 Access to data

Direct access will be granted to authorised representatives from the Sponsor, the WCTU monitoring team, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections. The CI, Process Evaluation Lead and the WCTU administrator (or delegate) will have access to the final study data set for the process evaluation.

7.5 Data access and quality assurance

The study will be conducted in accordance with the General Data Protection Regulation (GDPR). The investigator must ensure that participant's anonymity is maintained throughout the study and following completion of the study. To preserve anonymity, participants will be identified on all study specific documents (except for the informed consent form and enrolment log) by only the participants study specific identifier (and initials where deemed necessary to maintain patient safety). This identifier will be recorded on documents and the database. The Investigator Site File will hold an enrolment log detailing the study specific identifier alongside the names of all participants enrolled in the study.

All documents will be stored securely with access restricted to study staff and authorised personnel.

To support the remote intervention delivery, the participant will be asked for their consent to provide their name and contact details (email address and telephone number) and for this to be shared with the central PROPEL team of specialists. This is required for the organisation of remote appointments and to support participant safety.

In addition, patients will be asked if they would be willing to be contacted to be interviewed as part of the process evaluation. A sample of patients who agree to be contacted to be interviewed will be asked to provide their name and address to enable a qualitative researcher to contact the patient. Interviews will be audio recorded and will be stored electronically and identified by trial number only.

Personal data, including name, contact details will be stored securely on the database and security roles would be applied to ensure only those people who require access to participant identifying data are granted access. Participants should be assured that their confidentiality will be respected at all times.

UHCW and the University of Warwick will act as joint data controllers for this study.

7.6 Archiving

At the end of the study, following completion of the end of study report, UHCW and WCTU will securely archive all centrally held study related documentation for a minimum of 10 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure that data and all essential documents relating to the study are retained securely for a minimum of 10 years after the end of study, and in accordance with national legislation. WCTU will notify sites when study documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request. Trial documentation and data will be archived for at least ten years after completion of the trial.

8 STATISTICAL ANALYSIS

8.1 Power and sample size

A sample size of 300 patients in each arm (600 in total) will allow the detection of a standardised difference of 0.3 in the continuous fatigue subscale scores of the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-F) for the comparison of PPCP and BPUC with 90% power, 5% two-sided significance and allowing for 20% dropouts. The sample size calculation was determined using the POWER procedure within the SAS statistical software for a two-sample t-test.

A standardised difference of 0.3 equates to a minimally important clinical difference (MCID) of 4 points with a standard deviation of 13 using the FACIT-F fatigue subscale (which is a 13 item scale with scores 0-52) [11]. This MCID was based on the previous research from other studies [1] and considered acceptable after discussions with fatigue experts, AML clinicians and our PPI representatives.

8.2 Statistical analysis of efficacy and harms

8.2.1 Statistics and data analysis

A detailed statistical analysis plan (SAP) will be produced to provide full details of all statistical aspects of the study. All analyses and reporting of outcomes will be in accordance with CONSORT [52], with primary analysis conducted according to randomised allocation and intention to treat principles.

The primary analysis will be a pragmatic comparison of the PPCP versus BPUC on an intention to treat basis to preserve randomisation and avoid bias. Sensitivity analyses will investigate the effect of the personalised nature of the intervention on any treatment effects and the effect of compliance using a complier averaged causal effect (CACE) analysis.

All measures will be scored according to the appropriate scoring manual and summary measures obtained for each timepoint. A longitudinal mixed effects regression model will be used to estimate the effect of the intervention compared to standard care on fatigue adjusted for patient-level factors including age, performance status and treatment received. The specialist that delivers the interventions will also be considered for inclusion as a random effect in the model although we expect the variation to be negligible due to the large number of specialists across sites. The effect of red cell transfusion use on the outcome will be considered as time-dependent effect, considering haemoglobin levels and timing of transfusions, as anaemia is a universal complication in AML. The individual need, compliance and intensity of the intervention including the number and amount of each component delivered will be investigated and their need for inclusion in the mixed effects regression model evaluated. Exploratory analyses will investigate intervention and covariate interactions to identity any subgroups where the intervention may work differently to the whole population.

Similar longitudinal analyses will be performed for the secondary QoL outcomes. Time to event outcomes, including the overall survival and relapse-free survival, will be assessed using Kaplan-Meier curves and compared across trial arms using Cox proportional hazards models, adjusted for the stratification factors. The impact of fatigue on these time to event outcomes will also be evaluated using Cox models. Completion of consolidation treatment plan including chemotherapy and HSCT, readmissions to hospital, ICU admission, number of transfusions, complications of HSCT will be compared across trial arms using logistic regression models. Adverse events and serious adverse events will be tabulated and compared if appropriate.

A sensitivity analysis will be considered to determine the degree to which the conclusions may change with different missing data assumptions and mechanism models.

8.2.2 Planned recruitment rate

PROPEL aims to recruit 600 participants from approximately 50 centres across the UK over 30 months. Recruitment projections are based on a recruitment rate of 0.5 patients per month per site for the majority of the study to provide an average of 20 patients per month over the whole 30-month period. Our site surveys have demonstrated that at least 70 hospitals have expressed an interest in collaboration and estimated that around 1-2 patients per month may be eligible for recruitment. The projected rates allow for a 50% patient acceptance rate. A 12-month internal pilot phase has been incorporated into the trial to assess the willingness of clinicians and patients to participate.

8.2.3 Summary of baseline data and flow of patients

Descriptive statistics will be used to summarise the distribution of the baseline variables across trial arms. Continuous baseline variables will be reported with means and 95% confidence intervals (95% CI), if normally distributed, or otherwise with medians and Interquartile Ranges (IQR). Categorical variables will be reported with frequencies and percentages.

A CONSORT [52] flow diagram will be produced.

8.3 Health Economics Evaluation

The within trial analysis will be from the perspective of the NHS and personal social services (PSS) and will determine the cost-effectiveness and the cost-utility of a personalised prehabilitation (PPCP) compared to best practice usual care (BPUC). The primary effectiveness measure for the cost-effectiveness analysis will be change in FACIT-F and for the cost-utility analysis will be quality-adjusted life year (QALY). To estimate QALYs, health-related quality of life will be measured at baseline, post each chemotherapy cycle and three-months after completion of final cycle using the EQ-5D-5L measure. Using the trapezoidal rule, responses to the EQ-5D-5L will be converted into health utilities using the most appropriate utility algorithm as recommended by NICE [15]. The resource use questionnaire booklet will collect information on prehabilitation usage (including staff training, follow-up phone calls, weekly check-ins etc), specialist referrals, hospital admissions including readmissions and ICU admissions, number of transfusions, GP visits, complications of HSCT, and adverse events. This booklet will be first administered prior to cycle 2, and will collect the resource use data from baseline up until EOT. Unit costs will be estimated from local and national reference costs and reflated to current prices and will be applied to each resource item to value total resource use in each arm of the trial. These costs and outcomes will be aligned with the NICE-reference case using bivariate regression of costs and outcomes which will inform a probabilistic assessment of incremental cost-effectiveness including 95% confidence intervals around mean cost and QALY differences between the trial groups. The incremental cost-effectiveness ratios (ICERs) will be expressed as cost per improvement in FACIT-F and cost per QALY gained. Results will be shown on a cost-effectiveness plane and plotted as cost-effectiveness acceptability curves. Sensitivity analyses will be undertaken to explore cost-effectiveness uncertainty and generalisability. As part of the sensitivity analyses, using a societal perspective we will look at the broader implications of costs and benefits associated with the personalised plan to patients and their families.

If there are differences between the two arms, modelling will be undertaken to estimate the longer-term costs and benefits of the PPCP compared with BPUC. The model type and time horizon are still to be decided. The model will be populated using data from the trial, published literature and expert opinion. Any future costs and benefits will be discounted at 3.5%.

9 TRIAL ORGANISATION AND OVERSIGHT

9.1 Sponsor and governance arrangements

University Hospitals Coventry and Warwickshire (UHCW) and University of Warwick (UoW) will act as co-sponsors. The trial will be conducted in accordance with the principles and guidelines of the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) [53], UK legislation, WCTU SOPs and the Protocol. GCP-trained personnel will conduct the trial.

9.2 Ethical approval

9.2.1 Approvals

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of Capacity and Capability (CC&C) is received by WCTU and UHCW.

9.2.2 Amendments

All amendments will be documented by the PROPEL Trial Office. Substantial amendments will be submitted for HRA Approval, which includes NHS REC review, prior to communication to relevant participating NHS Organisations. Non-substantial amendments will be submitted to the HRA, and the applicable national coordinating functions in the devolved administrations, for review. Each trial site must ensure that they are using the most up to date version of the protocol, the Patient Information Sheet and Consent Form. All previous versions of the protocol, and other trial documents should be crossed out and marked as 'superseded', initialled and dated on the cover page.

9.2.3 Annual Reports

PROPEL Trial staff will send an annual trial update report to the NHS REC within 30 days of the anniversary date on which favourable opinion was given. This will be distributed to the local research team at each trial site. It is the responsibility of the local research team at each site to send a copy of this report to the research management function (e.g., R&D Office) in accordance with local requirements and recommendations made by the NHS REC. Any additional local information required must also be submitted. Additional data required by NHS Trusts is available from the PROPEL Trial Office on request.

NHS REC will be notified at the end of the trial, either at the planned end of study or prematurely. NHS REC will be notified within in writing within 15 days if the trial has been concluded or terminated early.

The CI will submit a final report to NHS REC with the results and any study publications within one year of the end of trial.

9.2.4 Peer review

This study has been independently peer reviewed as part of the NIHR's HTA application process.

9.3 Trial Registration

PROPEL is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register: 17655532

9.4 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the study; or

(b) The scientific value of the study.

If a serious breach is confirmed by clear and unequivocal evidence, the study Sponsor must notify the REC within 7 days of the matter coming to their attention. The Corrective and Preventative Actions Report template, supplied by WCTU, may be used for this purpose.

9.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

9.6 Trial timetable and milestones

Month	**1-6**	**7-18**	**19-24**	**24-36**	**37-53**	**54-60**
Grant activation						
Trial set up: protocol development						
Approvals						
Internal pilot						
Patient recruitment						
Data collection						

Patient follow-up						
Data cleaning						
Annual DMC/TSC meetings						
Data analysis						
Dissemination						
Trial close down						

9.7 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

9.8 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

9.9 Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (DMC) will be established for this trial.

DMC meetings will also be attended by the Chief Investigator(s) and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members. The trial will meet prior to commencement and then annually thereafter or more frequently if requested. The DMC will review the main trial for trial progress, recruitment, protocol compliance and interim assessment of outcomes, annually or more frequently if requested. The DMC will advise the TSC whether the trial should continue, be amended or stop prematurely based on the trial data monitored and any future publications or emerging worldwide evidence.

9.10 Essential Documentation

A Trial Master File will be set up according to Warwick SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

9.11 Financial Support

This project is funded by the National Institute for Health Research's Health Technology Assessment programme, project number: NIHR134257. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

9.12 Ethical considerations

The trial will be conducted in full conformance with Good Clinical Practice (GCP) guidelines [53] and the principles of the Declaration of Helsinki [54] . It will also comply with all applicable UK legislation and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the GDPR.HRA approval will be obtained, and the trial will be run in accordance with the UK Policy Framework for Health and Social Care Research; GDPR and the University of Warwick Sponsor and Quality Management system.

Sites will recruit patients once written confirmation of sites capacity and capability is received by WCTU and UHCW. Eligible patients will receive a patient information sheet and will be recruited after they have given informed consent. Consent to use their data for further research (optional) will also be requested and fully explained in the patient information.

10 MONITORING, AUDIT, AND INSPECTION

A Trial Monitoring Plan will be developed and agreed by the TMG and TSC based on the trial risk assessment. It is anticipated that monitoring activity will be predominantly central and remote.

The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the Research Ethics Committee (REC) or

equivalent local regulatory bodies for international centres. Authorised representatives of the Sponsor may visit the participating sites to conduct audits/ inspections.

All forms will be checked for completeness and consistency and any anomalies will be queried with the site. The trial staff will maintain regular communication with sites through routine calls, mailings and meetings. In the event of persistent issues with the quality and /or quantity of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. A representative from the Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and to determine the site's future participation in the trial.

11 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Our PPI group, as survivors of acute leukaemia and a caregiver, have been involved since the start of proposal development and continue to bring their voices through their lived experiences of acute leukaemia treatment (JC, AM, GM) or as a caregiver of a person with AML (ES), to the whole study. Our core PPI members have consulted widely through their many other established research networks, e.g., NCRI Supportive Care/Transfusion and AML Working Parties and in the voluntary sector including Anthony Nolan, Blood Cancer UK, MDS support group, Leukaemia Care, Cure Leukaemia. Our PPI team are well supported by a PPI collaborator (SG). Our PPI members have developed and circulated their own survey to people in their various networks on BPUC and thoughts on prehabilitation [5], in order to inform the project from a wider PPI perspective. PPI members are well versed in reviewing and writing written materials including the plain English summary. Our PPI panel have strongly reiterated the problem of fatigue as the key issue: a common lived experience was that they felt too poorly to 'fight' for access to any prehabilitation services. Their feedback has influenced and markedly strengthened PROPEL. Led by current PPI members, we continue to expand our PPI membership for diversity including striving to recruit different ages, genders and ethnicities. PPI members supported the use of document translation and translators. Our PPI members have therefore played a highly influential role on PROPEL design and will continue to support and advise on delivery.

12 DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The definitive research findings will be reported via a published HTA monograph (NIHR Library), alongside publications in open-access, high-impact, peer-review journals (trial protocol, primary clinical results, economic evaluation, process evaluation). These will be

linked with presentations at relevant conferences, nationally and internationally (haematology and other societies), to which our PPI members will be invited.

A strength of our outputs and dissemination plan will be the support from patients and caregivers and our established links to relevant cancer charities and organisations, e.g., Blood Cancer UK, Anthony Nolan, Cure Leukaemia, and NIHR Centre for Engagement and Dissemination.

The dissemination plan will ensure that the results are presented in additional relevant formats and media that are widely available and accessible for patients, commissioners, policy makers and other stakeholders including National AML and transplant networks, NCRI AML and Supportive care working parties.

12.1 Data Shared with Third Parties

The Trial Management Group supports the sharing of outcome data with other researchers wishing to undertake additional analyses such as meta-analysis once the primary analysis of the trial has been published. Any requests for access to the trial data should be sent to the CI and should describe the purpose, scope, data items requested, analysis plan and acknowledgment of the trial management team. Any data transfer would be in accordance with University of Warwick SOPs and require data sharing/processing agreements to be in place.

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