ACE: Active, Connected, Engaged

A multi-centre randomised controlled trial of a peer volunteer led active ageing programme to prevent decline in physical function in older people at risk of mobility disability.

STUDY PROTOCOL

Version: 5 22th July 2022

Trial registry number and date ISRCTN17660493 30th Sept 2021

NIHR Project Reference Number 130156

Study Sponsor: University of Birmingham

Chief Investigator: Professor Afroditi Stathi (University of Birmingham)

This protocol has regard for the HRA guidance and order of content

FULL TITLE OF THE TRIAL

ACE: Active, Connected, Engaged. A multi-centre randomised controlled trial of a peer volunteer led active ageing programme to prevent decline in physical function in older people at risk of mobility disability.

SHORT STUDY TITLE / ACRONYM	ACE: Active, Connected, Engaged (Known in Wales as ACTIF)
PROTOCOL VERSION V 5	22/07/22
IRAS Number:	290332
ISRCTN Number:	17660493

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol, GCP guidelines and the Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

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

For and on behalf of the Study Sponsor:		
Sponsor statement: Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.		
Chief Investigator:		
Signature:  .		
Name: Professor Afroditi Stathi		22/07/2022
Statistician: Signature 		
Name: Dr Rebecca Playle		22/07/2022
Position: ACE Senior Statistician		

KEY TRIAL CONTACTS

Chief Investigator	Professor Afroditi Stathi, University of Birmingham, Birmingham Edgbaston B15 2TT. a.stathi@bham.ac.uk +44 (0) 121 415 8389
Trial Co-ordinator	Dr Janet Withall University of Birmingham, Birmingham Edgbaston B15 2TT j.withall@bham.ac.uk +44 (0) 121 415 8389
Sponsor	Dr Birgit Whitman

	Head of Research Governance and Integrity University of Birmingham, Edgbaston B15 2TT Email: researchgovernance@contacts.bham.ac.uk Tel: 0121 4158011
Joint-sponsor(s)/co-sponsor(s)	None.
Funder(s)	National Institute for Health Research - Public Health Research programme The Royal Voluntary Service, Beck Court, Cardiff Gate Business Park, Cardiff CF23 8RP sarah.roche@royalvoluntaryservice.org.uk Tel 0845 608 0122 Sport Cardiff, Cardiff Metropolitan University Cyncoed Road Cardiff CF23 6XD Bwilliams2@cardiffmet.ac.uk University of Birmingham (PhD Scholarship), Dr Jet Veldhuijzen van Zanten, Life and Environmental Sciences College Director of Graduate Research Edgbaston, Birmingham B15 2TT veldhujj@bham.ac.uk Tel: 01214143379 Greater Manchester Applied Research Collaboration (ARC) (PhD Scholarship) Prof Chris Todd Professor Primary Care & Community Health Oxford Road, Manchester, M13 9PL Chris.Todd@manchester.ac.uk Tel 0161 306 7865
Clinical Trials Unit	Centre for Trials Research University of Cardiff, Park Place, Cardiff CF10 3AT
Key Protocol Contributors	Professor Afroditi Stathi and Dr Janet Withall
Statistician	Dr Rebecca Playle 029 2074 4821 playlera@cardiff.ac.uk
Committees	**Trial Steering Committee** Chair Professor Sharon Simpson Tel 0141 353 7500 Email Sharon.Simpson@glasgow.ac.uk **Data Monitoring Committee** Chair Dr Gladys Pearson Email G.Pearson@mmu.ac.uk **Trial Management Group** Chair Professor Afroditi Stathi Tel: 0121 415 8389. Email a.stathi@bham.ac.uk

TRIAL SUMMARY

Trial Title	**ACE: Active, Connected, Engaged. A multi-centre randomised controlled trial (RCT) of a peer volunteer led active ageing programme to prevent decline in physical function in older people at risk of mobility disability**	
Short title	ACE: Active, Connected, Engaged (Known in Wales as ACTIF)	
Research sites	West Midlands, Greater Manchester, South Wales and Bristol*. *The Bristol site was approved and included in the main trial in September 2022.	
Trial Design	ACE is a multi-centre individually randomised, parallel group, single-blind RCT with an internal pilot study and a whole-systems oriented process evaluation and an economic evaluation.	
Trial Participants	Participants will be men and women aged 65 or older, not in full-time work, who are at risk of mobility disability, but are still ambulatory, defined as scoring 4-9 (inclusive) on the Short Physical Performance Battery (SPPB). Peer volunteers will be community-dwelling older people, aged 55 years and older, with SPPB scores of 4 and above, not in full-time employment (unless with the flexibily to volunteer during weekdays), available to volunteer in the daytime during the week.	
Planned Sample Size	Total of 515 participants across all trial sites, plus 150 peer volunteers	
Intervention duration	6 months	
Follow up duration	18 months	
Planned Trial Period	Internal pilot Recruitment commences November 2021 Intervention delivered Nov 2021 – Sept 2022 Full trial Recruitment commences May 2022 Intervention delivered June 2022 – Aug 202	
	Objectives	Outcome Measures
Primary	To assess the effectiveness of the ACE intervention for preventing decline in lower limb physical function in community-dwelling older people at risk of mobility disability	The primary outcome will be the Short Physical Performance Battery (SPPB) score at 18 months. SPPB assesses lower limb physical function in terms of observed ability to complete a repeated sit-to-stand task, a standing balance test and a gait speed assessment. (1)

Secondary	To test the hypotheses that: compared with the control group, participants allocated to the ACE programme will significantly increase their levels of physical activity, psychological functioning, well-being, social networks health-related quality of life, cognitive function, ability to perform the activities of daily living, and have reduced sedentary time, falls, pain, loneliness, adherence to muscle strengthening exercise, health and social care usage at 18 months. In addition, a full economic evaluation will estimate the incremental cost-effectiveness of the ACE intervention	Weekly volume of physical activity accounting for both physical activity intensity and duration. Average number of times a participant transitions from sitting to standing per hour of the day. The number of times a participant transitions from sitting to standing each hour of the day Average proportion of each waking hour spent in active events. Average proportion of each waking hour spent inactive Muscle-Strengthening Exercise - Adherence scale Psychological functioning and well-being measured by Warwick-Edinburgh Mental Well-being Scale [WEMWBS] (2); Ageing-Well Profile (3). **Participants only** Health-related quality of life (EQ-5D-5L (4), ICECAP-O (5) Capability (ICECAP-O) (5) Activities of Daily Living (EQ-5D-5L (4), ICECAP-O (5) Medical history, Health and Social Service Usage, trips out of the house Falls Inventory, Short Falls-Efficacy scale-international (Short FES-I) (6) Pain (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) (7) Fried Frailty Phenotype score (8) to assess progression of frailty, including the following components: For the assessment of the Fried phenotype o Grip strength in kg (highest score out of three trials), using a dynamometer o Gait speed (4M walk from Short Physical Performance Battery)

		o Physical activity (International Physical Activity Questionnaire-Elderly (PASE) (9) o Exhaustion (exhaustion questions from Centre for Epidemiological Studies Depression Scale (10) o Unintentional weight loss Cognitive function will be measured using the Montreal Cognitive Assessment (MoCA) (11) Loneliness (3-item Revised UCLA loneliness scale) (12) Social networks (Lubben's Social Network Scale) (13) **Peer volunteers only** Motivation to volunteer and volunteering outcomes (Short Volunteer Functions Inventory) (14) Diary of contacts with ACE participant(s) **Process Evaluation (Participants only)** Muscle-Strengthening Exercise - Perceived importance, confidence and adherence scale Physical Activity - Perceived confidence and benefits scale Community activities - Perceived confidence, benefits, autonomy, relatedness, competence and adherence scale Feedback on ACE intervention (Intervention participants only) Evaluation of local environment Local activities attended *Interviews with participants, volunteers and volunteer managers:* They will explore experiences of ACE, barriers to and enablers of the targeted behaviours, quality of peer-volunteer relationship, and goal interdependence between participant and peer volunteer in relation to activity goals Intervention fidelity (from coding of audio-recorded intervention sessions)

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute for Health Research - Public Health Research programme The Royal Voluntary Service Beck Court, Cardiff Gate Business Park, Cardiff CF23 8RP Sarah Roche sarah.roche@royalvoluntaryservice.org.uk Tel 0845 608 0122 Sport Cardiff, Cardiff Metropolitan University Cyncoed Road Cardiff CF23 6XD Bwilliams2@cardiffmet.ac.uk University of Birmingham (PhD Scholarship) Edgbaston, Birmingham B15 2TT Dr Jet Veldhuijzen van Zanten, Life and Environmental Sciences College Director of Graduate Research Tel: 01214143379 Greater Manchester Applied Research Collaboration (ARC) (PhD Scholarship) Prof Chris Todd Professor Primary Care & Community Health Oxford Road, Manchester, M13 9PL Chris.Todd@manchester.ac.ukTel 0161 306 7865	£1,834,090.09 Financial support £98,950. Management and delivery of the ACE intervention Financial support: £59849 Award of one PhD Scholarship to support the ACE study Financial support: £63,866 Award of one PhD Scholarship to support the ACE study

ROLE OF STUDY SPONSOR AND FUNDER

The University of Birmingham will act as sponsor for the trial. The Chief Investigator (CI) and Trial Manager are employees of the University of Birmingham and will oversee the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

ACE is funded by the National Institute for Health Research - Public Health Research Programme. The funder expects the research team to conduct the study according to the trial as described and as set in the NHS ethics application. NIHR has the right to publish itself any non-confidential material generated from this project. NIHR will however consult with the CI if this is to occur.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Committees

- Trial Steering Committee (TSC)

  The TSC will consist of an independent Chair with expertise in ageing and public health (Professor Sharon Simpson, University of Glasgow); the CI; at least one Advisory Group representative from one or more of the delivery sites, an independent medical advisor (Dr Wilby Williamson, Global Brain Health Institute, Trinity College Dublin), an independent statistician, an expert in health economics, a research expert from UKActive, plus two independent academics experienced in the design, delivery and evaluation of health promoting interventions in primary care and in the community. Representatives from the NIHR PHR programme will be invited to all TSC meetings and the trial statisticians, site PIs and health economist may be called on to attend as needed. The TSC will meet every 6-9 months from the start of the trial, providing overall supervision of the trial, monitoring trial progress and advising on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring and Ethics Committee (DMEC) and will have responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy. The TSC will be blinded to all information regarding treatment assignments until the database is locked for final analysis or if the DMEC recommends that results need to be reviewed.

- Data Monitoring and Ethics Committee (DMEC)

  A fully independent DMEC will be appointed and will report to the TSC. This will comprise of an independent chair plus two senior academics including a statistician. The CI, PIs and Senior trial statistician may be invited to attend to provide specific input by the DMEC Chair with the CI and statistician usually expected to attend the 'open session' section of the meetings. The DMEC will be responsible for the interests of the participants and its main role will be to make recommendations to the TSC as to whether the trial needs to be stopped for any ethical or safety reason (based on review of accumulating safety data). The DMEC will undertake safety data reviews every 12 months after recruitment begins, unless otherwise deemed necessary. This will include data on any adverse advents reported during the trial. Analysed data will be blinded, unless the DMEC identifies a specific need for unblinding. The DMEC will meet shortly before the TSC and will provide a report for review during the TSC meeting.

- Trial Management Group (TMG)

  The TMG will consist of the CI, all co-applicants, the trial manager, two people from our service user advisory group and the researchers at each trial centre. It will meet 4 times per year to ensure accurate implementation of the study protocol and the successful conduct and completion of the trial. The trial manager will also meet with the Chief Investigator and site leads for the three sites as needed, and each site will have its own site-specific meetings to discuss day to day project management issues. In accordance with the NIHR carbon reduction guidelines, those members of the TMG not based in Birmingham will usually join these meetings remotely. TEAMS or other online communications tools will be used to minimise environmental impact.

- Advisory Groups (AG)

  The AGs will consist of a small group of older adults. There will be an AG at each of the three ACE sites, representing geographical diversity and inclusion of diverse experiences. AGs will include people with volunteering experience. The groups' responsibilities are to review study materials and processes and engage with the study oversight groups as described in the PPI section below. AG members will receive £20/meeting reimbursements and their travel costs will be paid.

Protocol contributors

The protocol was prepared by Professor Afroditi Stathi, Chief Investigator (University of Birmingham) and Dr Janet Withall, ACE Trial Manager (University of Birmingham). The statistical analysis was prepared by Dr Rebecca Playle (University of Cardiff) and the economic evaluation by Professor Emma Frew (University of Birmingham).

The funder (NIHR) expects the research team to conduct the study according to the trial as described and as set out in the NHS ethics application and took no part in the development of the protocol.

PPI involvement

ACE builds on several years of multidisciplinary work by this team aimed at understanding influences on the adoption and maintenance of physical activity in community-based activity programmes. Our Avon Network for the Promotion of Active Ageing in the Community (AVONet) (MRC Lifelong Health and Wellbeing – Collaborative Development Network (Ref 90543)) used focus groups and workshops with service providers, older people, international experts and service commissioners to assess the needs of older people and their communities for physical activity promotion. The ACE study was considered by our AVONet service user, service provider and commissioner stakeholders to be suitable for delivery across a range of socio-economic and cultural populations. The ACE protocol has been developed based on this input. Following the INVOLVE guidelines (involve.org.uk), we will have Advisory Group representatives on our Trial Management Group and Trial Steering Committee. The Trial Management Group was closely involved in the development of the study protocol including two people from our Advisory Group who form part of that committee. The Trial Steering Committee which approved the protocol prior to submission included Advisory Group representatives. In addition, the draft protocol was reviewed by our delivery partner, the Royal Voluntary Society, and members of their volunteer community.

KEY WORDS:	Physical activity, disability prevention, older adults, randomised control trial, intervention, mobility, physical function, peer volunteering

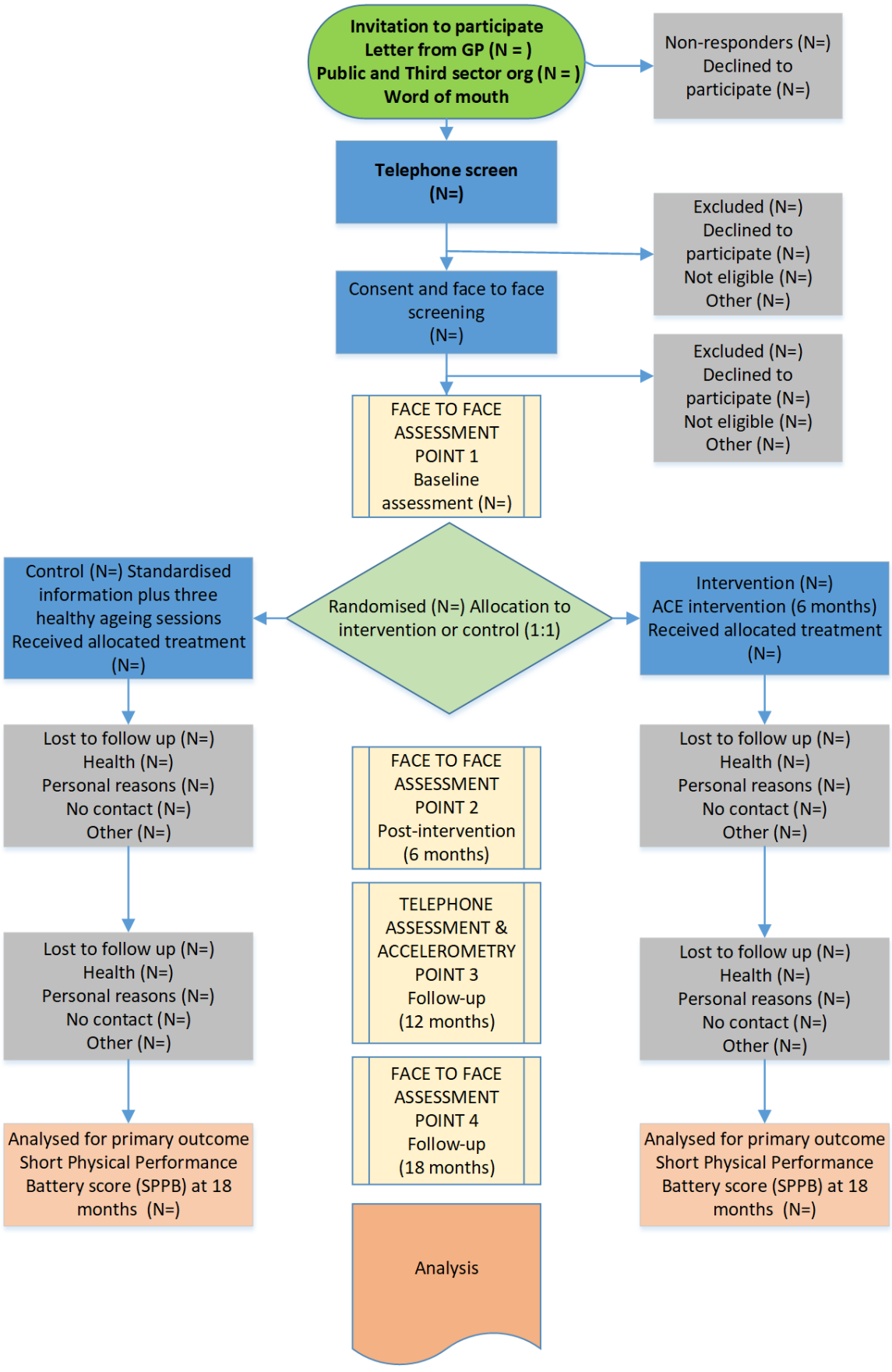
LIST of CONTENTS

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AG	Advisory Group
CI	Chief Investigator
CRF	Case Report Form
CTR	Centre for Trials Research
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-Adjusted Life Year
RA	Research Assistant
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

ACE Participant Flow



1 BACKGROUND AND SCIENTIFIC RATIONALE

The ACE intervention mobilises community resources (peer volunteers) to prevent decline in physical function in older people by supporting them to become more physically and socially active within their communities. During old age, people gradually transition from independence and adequate physical function to frailty and mobility disability (15, 16). Mobility disability, defined as a reduced ability to walk or balance, increases rapidly with age and generates major societal challenges. These include costs for people with mobility disability, loss of independence, risk of falls, greatly reduced quality of life, costs to friends/family who provide care and increased health and social care costs (17, 18). Among adults aged over 70, 38% are classed as frail or pre-frail (defined as scoring 9 or less on the Short Physical Performance Battery (SPPB)) (1,5). Frail or pre-frail older people have a substantially higher risk of major mobility disability (OR = 8.3 (95%CI: 3.3 to 20.7) (19) and mortality (HR 2.6 to 5.3) (20) compared with non-frail older adults. Interventions that can delay or prevent this functional decline would therefore have substantial public health value. This study will: a) evaluate an intervention that mobilises community assets to improve health; and b) use a systems approach to identify mechanisms influencing the implementation, scalability and sustainability of the intervention.

Review of existing evidence

Increasing physical activity can prevent or delay progression of frailty and mobility disability (21, 22). However, there is a clear trend of declining physical activity over time in people aged over 65 (23). Reasons for this include the lack of a companion to go out with, low confidence to engage with community initiatives, and perceived safety of engaging with activity (24). A recent systematic review of reviews of interventions for increasing uptake of physical activity in older people (17 studies; N = 79,650) and for examining barriers to and facilitators of active ageing (9 studies; N = 22,413) supported the effectiveness of a variety interventions in the short-term . Access to role models, peer and community support, individual tailoring of interventions, making exercise enjoyable and sociable and feeling of ownership of interventions were identified as key enablers of physical activity (25).

Our AVON network, a multidisciplinary consortium of service users, public health policy and service provider stakeholders which ran from 2009 to 2010, identified the potential of peer volunteers to promote active ageing in the UK (26). This was ranked as one of two “best bet“ approaches for promoting physical activity in older people that was likely to be both deliverable and scalable in real-world public health services. A rapid review conducted to inform a recent NIHR study identified nine studies employing a peer-led model to promote physical activity, with only four targeting inactive or sedentary older adults. None were UK-based, only one used a dyadic (peer-participant pair) intervention and none targeted people at risk of mobility disability. A 2019 systematic review and meta-analysis of 59 trials of dyadic physical activity interventions identified six peer-led interventions (27). Only one study targeted people aged over 50. This study reported that peer-delivered telephone-based interventions were as effective at increasing physical activity as professionally delivered interventions. The review concluded that peer /friend dyads and having shared target-oriented goals were associated with larger effect sizes. A 2019 NIHR review of UK-based

physical activity interventions for older people (28) identified only two volunteering programmes, a peer-led walking group feasibility trial (29) and our ACE feasibility trial (30). This review highlighted the need for more robust evidence for such approaches ensuring that they incorporate theories of behaviour change; focus on social enablers of exercise; and target people with poor lower limb strength and/or weaker social networks.

More generally, there is a need for systems-oriented intervention evaluation approaches that go beyond the individual level and also consider the role of family, community and population-level systems in motivating and sustaining health behaviour change (31, 32).

The above overview was informed by literature searches including groups of terms representing "older people", "physical activity", "volunteering", "randomised controlled trials" and "peer support" applied to Google Scholar, the Cochrane database of systematic reviews, the NIHR library and Pubmed focussing on recent systematic reviews and meta-analyses. We also reviewed RCTs reported in the WHO trials site (http://apps.who.int/trialsearch/) using the terms "older" and "volunteering". The search returned 10 relevant hits. Only one study used a peer volunteering scheme, supporting frail people in the community (33). However, that was a small study (N=120), targeting very frail people who were unable to leave home on their own. The intervention lasted only for three months with no follow-up assessment. The authors reported some benefits in quality of life and highlighted the need for more evaluation of peer volunteering interventions. Our application builds on learning from our Medical Research Council-funded feasibility study of the ACE intervention, which used peer volunteers to promote active ageing. The study demonstrated the feasibility of delivering a full-scale RCT (34).

In 2014, ACE was one of only two (of 952) UK initiatives to be rated "promising practice" by Public Health England (35), with the recommendation that robust evidence of effectiveness and cost-effectiveness is required for this programme to progress to the status of " established practice" We now want to generate this evidence in a definitive full-scale multi-site trial. We will also extend the study using systems approach methods to include a consideration of how public health and community /population level systems impact on the operation of the intervention and on participant engagement in the intervention (31, 32). The evidence produced will inform public health guidelines, policy and practice on how the voluntary sector (and community systems/policies) can be best engaged to prevent decline in the physical functioning of frail/pre-frail older adults.

At the delivery site in Wales, the study will be known as ACTIF, with the qualifier 'known in England as ACE' on documentation. This is in order to avoid any confusion with the high profile ACE (Adverse Childhood Experiences) programme in Wales.

Description of the ACE Intervention

Control Arm:

The control arm will receive written materials on healthy ageing. They will be invited to two social events with a presentation on healthy ageing (excluding any physical activity component). One event between 0 and 6 months and one between 12 and 18 months post-randomisation at each trial site. Newsletters will be distributed to all participants at the end of each project year. This 'staying in touch' retention strategy resulted in 83.5% retention at 12 months (post-intervention) and 81% retention at 24 months (follow-up) in our NIHR-funded REACT trial, with no differences in dropout rates between the trial arms. The session content

may include healthy eating in older age or dementia awareness, both of which were well received by the REACT trial control group.

Intervention Arm:

The intervention arm will receive the same information as the control arm and a quarterly 'catch-up' meeting of ACE volunteers and participants (at each site) to be delivered by the local volunteer management partner i.e. the Royal Voluntary Service (RVS) or Sport Cardiff ACE is a 6-month active ageing programme using peer volunteers to deliver individually tailored and person-centred support to help inactive, less mobile older people to 'get out and about', improve their mobility, increase physical activity and confidence, and engage with their local community (34). ACE draws on the Process Model of Lifestyle Behaviour Change (PMLBC) and Self Determination Theory (36, 37), two overlapping and mutually compatible theoretical frameworks which provide the main principles and processes for supporting behaviour change in the ACE intervention.

1. Peer volunteers meet participants twice in one-to-one meetings supporting them to identify local activities of interest and address barriers to participation (Motivation stage: first 2 weeks). The particular relevance/benefits of activities that might improve lower limb physical function (i.e. those including a significant strength and balance component) will be discussed.
2. The volunteer-participant pair attend at least three local initiatives chosen by the participant (Action stage: month 1−3). We are collaborating with exercise providers for older adults in all three sites to encourage participants to attend activities that specifically target lower limb physical function.
3. Weekly telephone support to continue attending local activities. At least two further joint visits are scheduled as support "tails off" (Maintenance stage: month 3−6).

Peer Volunteers Training and Support

A realist synthesis of theoretical frameworks of community health volunteering has provided a useful conceptualisation of community level factors affecting volunteer performance (Fig.1) which will inform both our systems mapping and our process evaluation (38). It has highlighted individual-level theoretical processes that may sustain the motivation and engagement of the volunteers, including self-efficacy, positive feedback and fulfilment of the volunteer's needs and expectations. These factors are consistent with qualitative feedback we obtained from volunteers in the ACE feasibility study and they will guide the preparation of the manual and training programme of peer volunteers (34).

Peer volunteers will attend a one-day training course delivered by senior ACE researchers. The course will be developed, tested and further refined in the ACE feasibility study including: i) skills for developing and reinforcing motivation (person-centred counselling for supporting fundamental (SDT-related) needs; ii) how to identify local activity options and develop tailored plans based on individual needs /preferences; iii) the need to build lower limb function (strength and balance) and types of exercise /activity associated with this; iv) solution-focused methods for avoiding /overcoming barriers and v) maintenance support techniques. Drawing on key principles of person-centred counselling (which is recommended by both SDT and the PMLBC), the training programme emphasizes that the ACE volunteer's role is to support the individual becoming autonomous and responsible for making

decisions. The training course will also include statutory training in safeguarding and confidentially and will be further refined during the first phase of the trial in consultation with the Royal Voluntary Service, ensuring that it aligns with the organisation's principles of training and supporting volunteers.

ACE volunteers will be managed and supported by local volunteer management partners such as RVS or Sport Cardiff, whose Volunteer Coordinators will be partner employees experienced in managing volunteers. NHS/government COVID-19 guidelines will be adhered to throughout all phases of the ACE intervention.

Description of the ACE population

Participants will be community-dwelling older people, aged 65 and older, not in full-time employment, who are at risk of mobility disability, but still ambulatory.

Inclusion criteria: a) SPPB score between 4 and 9 inclusive. This is based on definitions of physical frailty from the European Medicines Agency for identifying people with (or at risk of) physical frailty in clinical trials (15). This guidance defines pre-frailty as an SPPB score of 8-9 and frailty as a SPPB score of 7 or less; b) Planning to reside in the target area for intervention delivery for at least 18 months.

Exclusion criteria: a) Self-reported inability to walk across a room without help (use of a stick for support is acceptable); b) Being too physically active (defined by four verbal screening questions, as used in the REACT study (How would you find walking across a room? How easy would you find getting out of a low chair? How easy would you find walking up a flight of stairs with no handrail or wall to lean on? How easy do you find walking on an uneven pavement without losing your balance? Responses Easy/A little Difficult/Very difficult) (30); c) Having an existing major mobility limitation (SPPB of 3 or less); d) Living in residential or nursing care; e) Having any of the medical conditions (see 6.2 for full details) that would preclude participation.

ACE will be delivered in four areas of the UK: West Midlands, Greater Manchester, South Wales, and Bristol. These sites all include areas with complex challenges in relation to area deprivation, health inequalities and ethnic diversity. All also have a diverse range of community activities within their localities. Within each site, community settings with high numbers of older adults will be purposively selected to recruit a sample that is representative of area deprivation and ethnic diversity (in older adults) in England and Wales.

2 RATIONALE

2.1 Trial justification

Breaking the spiral of decline that is characterised by loss of physical and cognitive function, reduced capacity to independently manage daily tasks, and reductions in social interaction is fundamental to healthy ageing. It also has the potential to substantially reduce reliance on health and social care services. This is particularly true for those who are at risk of mobility-related disability resulting from low levels of physical activity as they settle into changed routines after their primary working years.

Prospective cohort studies and trial data demonstrate that both moderate and lighter intensity physical activity are associated with lower risk of mobility disability (39). An active older person has 36% lower risk of developing functional limitations and 38% lower risk of hip fracture (40). A large-scale clinical trial in the US has shown that increasing light to

moderate physical activity by a modest amount (40-50 minutes per week) can significantly reduce the onset of mobility disability in at-risk older adults (41). The wider health and wellbeing benefits associated with physical activity in older age are well documented (42). However, in the UK, levels of activity decrease with age, with 47.9% of people aged 65 years and older being classified as inactive in a national survey conducted by Public Health England (43).

Recent policy documents, including the NHS Long Term Plan, call for new service models to proactively support older people living with frailty in the community (44, 45). A consensus statement led by Public Health England identifies five key commitments towards healthy ageing: prioritising prevention initiatives; removing barriers and creating more opportunities for older adults to contribute to society; adopting a range of community-centred approaches that support and encourage community participation; narrowing inequalities and challenging ageism (46). The ACE study aligns with these commitments, is relevant to policies targeting living independently in the community and has strategic importance for social and health care policy across the UK. Community-based, social capital-building approaches are well-placed to address health inequalities (47). The voluntary sector is an untapped resource, ideally placed to deliver low-cost and effective interventions and to increase access to disadvantaged populations (41, 48). However, there have been few high-quality trials evaluating community approaches that mobilise peer volunteers to promote active ageing, and none that specifically target people at risk of mobility disability (49). Promoting independence in older people is also one of the priority areas of a further commissioned call by NIHR (call 17/55) seeking evidence of programmes that have the potential to be delivered at scale and produce greater impact. To address this, we are collaborating with the Royal Voluntary Service (RVS) and Sport Cardiff to deliver the Active, Connected, Engaged (ACE) intervention in the West Midlands, Greater Manchester, South Wales and Bristol.

Delivery will be supported by a range of other community providers at each site and organisations with national infrastructures including Public Health England, Sport England and Age UK. ACE therefore has a strong potential to be rolled out in the UK, once the research is complete.

2.2 Assessment and management of risk

The benefits of moderate intensity physical activity for older people vastly outweigh the risks (50). The UK Chief Medical Officer's [CMO] guidelines for physical activity for older adults concluded that "engaging in physical activity carries very low health and safety risks for most older adults. In contrast, the risks of poor health as a result of inactivity are very high" (42). Risks occur predominantly among those undertaking vigorous activity or contact sports. In rare cases, inactive and unfit individuals who start doing vigorous physical activity may face increased cardiovascular risks and there are some important counter indications such as unstable cardiovascular illness or uncontrolled hypertension.

Both the CMO's guidance and NICE guidelines (51) emphasise that increasing engagement with physical activity would provide considerable benefit in terms of both human welfare and savings in social and health care costs. As well as preventing mobility-related disability, the evidence is strong that physical activity protects against cardiovascular disease, diabetes, and some cancers (52). Prospective cohort studies indicate that activity in later years also delays cognitive decline, and reduces the risk of depression, dementia and Alzheimer's disease (53). Intervention studies indicate that in older adults, exercise also improves

cognitive abilities (54), reduces risk of falls in those at risk (55), and alleviates depression (56). Engaging in any kind of group activity facilitates social interaction and helps address social isolation which has itself been shown to positively impact physical and mental health in addition to improving quality of life.

- A preliminary phone screening will exclude participants who have unstable or uncontrolled cardiovascular or musculoskeletal health issues, a diagnosis of dementia, serious mental illness.

Participants will be asked to consent to allowing the research team to contact their GP if any concerns about their health or well-being arise.

The Trial Steering Committee and the Data Monitoring and Ethics Committee will oversee all patient safety issues, which the study medical advisor will review in detail.

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH Good Clinical Practice will apply. The University of Birmingham standard operating procedure for reporting research related Adverse Events (AEs) will be adopted.

All AEs will be examined by our medical advisor to see if they are related to the study intervention or measurement procedures. The ethics committee, the sponsor and the TSC or DMEC will be notified promptly (within 24 hours) of all Serious Adverse Events (SAEs). All AE and SAE data will be passed to the Chief Investigator who will compile a 12-monthly report for the Trial Steering Committee. Adverse events will be recorded at all follow-up data collection timepoints and further data may accrue through patient-reporting to research staff. If a participant does not attend two consecutive intervention sessions with their peer volunteer, they will be contacted by telephone and if the reason for non-attendance is an adverse event this will be recorded.

The detailed process for the reporting of Adverse Events is outlined in Section 9, Safety Procedures. The DMEC will monitor and analyse data on any adverse events reported during the trial.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 ACE hypotheses

Primary hypothesis

Compared with an information-only control group, participants allocated to the ACE programme will have significantly reduced mobility-related limitations, as indicated by SPPB score, at 18 months of follow-up.

Secondary hypothesis

Compared with the control group, participants allocated to the ACE programme will significantly increase their levels of physical activity, psychological functioning and well-being, health related quality of life, capability, activities of daily living, cognition, social networks and reduce sedentary time, loneliness, pain, falls, fear of falling and utilisation of health and social care.

3.2 ACE research questions

Primary research question

What is the effectiveness of the ACE intervention compared with an information-only control group for preventing decline in lower limb physical function in community-dwelling older people at risk of mobility disability?

Secondary research questions

a) What is the cost-effectiveness of the intervention from a societal perspective (including the costs and consequences from the perspective of multiple public health systems /stakeholders) both within the trial timeframe and over a lifetime horizon?

b) How do effectiveness and cost-effectiveness vary with area deprivation, ethnicity and other socio-demographic factors?

c) What process or systems influence outcomes and how? How can systems /policy /processes active within the community be optimised to support effectiveness, maximise the reach of the intervention and reduce inequalities in either uptake or effectiveness?

d) What is the impact of the intervention on peer volunteers?

3.3 ACE outcomes and measures

Primary Outcome and measure

Primary outcome: Changes in lower limb functional ability of participants measured by the Short Physical Performance Battery (SPPB) score at 18 months post baseline (12 months after the end of the intervention). SPPB is an objective battery of functional performance tests (observed ability to complete a repeated sit-to-stand task, a standing balance test and a gait speed assessment) (35). The resulting score ranges from 0 to 12. The SPPB can usually be completed in 5-8 minutes with the use of a stopwatch, a 4-m tape and a chair. Inter-rater reliability is reported as 0.9 and test–retest reliability is 0.72. The SPPB has been shown to predict both mobility-related disability (inability to complete a 400m walk in 15 minutes) and activities of daily living disability (using Barthel Index ADL scores) (54). SPPB also provides a reliable estimate of future risk of hospitalisation and decline in health and function in older adults (55,56). Risk of mobility-related disability over a three-year period shows a strong graded response across the range of SPPB scores (OR = 26.9; 7.7; 8.3; 3.4 for SPPB ≤ 7; SPPB ≤8, and SPPB ≤9; SPPB ≤10, respectively. Based on these associations and other data, a 0.5 difference (effect size 0.25) is considered to be a clinically meaningful change in SPPB score.

Secondary outcomes and measures

1. Physical activity (Weekly volume of physical activity, both intensity and duration; average hourly transitions from sitting to standing; count of hourly transitions from sitting to standing; average proportion of each waking hour spent in active events; average proportion of each waking hour spent inactive) assessed objectively via accelerometer, using a protocol successfully used in previous studies (57). We will use wrist-worn accelerometers as they provide high compliance rates, minimal burden to participants, and they are waterproof minimising the risk for participants to forget to put them back on after swimming or having a shower (common problems with waist worn accelerometers).

2. Muscle-Strengthening Exercise - Adherence scale

3. Psychological functioning and well-being (Warwick-Edinburgh Mental Well-being Scale [WEMWBS] (2); Ageing-Well Profile (3).

Participants only

1. Health-related quality of life (EQ-5D-5L (4), ICECAP-O (5)).

2. Capability (ICECAP-O) (5).

3. Activities of daily living (ADL) will be measured with the ICECAP-O (5), and EQ-5D-5L (4).

4. Medical history, Medications, Falls Inventory, Fear of falling Short FES-I (58) and Health and Social Service Usage.

5. Fried frailty phenotype index (8).

6. Cognitive function will be measured using the Montreal Cognitive Assessment (MoCA) (11).

7. Loneliness (Revised UCLA loneliness scale) (12).

8. Social networks (Lubben's Social Network Scale) (13).

9. Pain (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) (7)

10. Trips out of the house

Peer volunteers only

1) Motivation to volunteer and volunteering outcomes (Short Volunteer Functions Inventory) (14).

Process evaluation

1) Muscle-Strengthening Exercise - Perceived importance, confidence and adherence scale

2) Physical Activity - Perceived confidence and benefits scale

3) Community activities - Perceived confidence, benefits, autonomy, relatedness, competence and adherence scale

4) Feedback on the ACE intervention (Intervention participants only)

5) Evaluation of local environment

6) Attendance at local activities

7) Interviews with participants, volunteers and volunteer managers: They will explore experiences of ACE, barriers to and enablers of the targeted behaviours, quality of peer-volunteer relationship, and goal interdependence between participant and peer volunteer in relation to activity goals

8) Intervention fidelity (from coding of audio-recorded intervention sessions)

Demographic data

Participants and volunteers Age, sex, ethnicity, level of education attainedpostcode (for the calculation of deprivation index for residence), marital status, housing type, ownership/rental status, number of people in household and caring responsibilities. Participants only Height and weight (BMI) and co-morbidities.

4 TRIAL DESIGN

The ACE study is an individually randomised, parallel group, single-blind RCT with an internal pilot phase, a whole-systems oriented process evaluation and an economic evaluation. Outcome data will be collected at baseline, 6, 12 and 18 months (see ACE Trial Flow chart). Following identification and recruitment, 515 patients who meet the study inclusion criteria will be randomised to receive either the ACE intervention, delivered over a period of 6 months by peer volunteers or a minimal control intervention. Participants will be individually randomised to the intervention and control arms in a 1:1 ratio stratified by site, using a centralised web-based system run by the Cardiff Centre for Trials Research.

4.1 Stopping rules or discontinuation criteria

The TSC, with advice from the Data Monitoring and Ethics Committee, will assess the feasibility of the trial during the internal pilot phase, taking into account findings on the acceptability of trial procedures, intervention adherence and recruitment and retention rates. Based on our recruitment rates in previous UK-based physical activity interventions with similar target populations (Project ACE (pilot), Retirement in Action (REACT)) and with equivalent of 1FTE research assistants at each of three sites, in the pilot study we anticipate a recruitment rate of 7-8 participants/month/site, (90 participants will be recruited in total over 4 months). If the recruitment rate is less than predicted in a given month, we will take actions to increase it (increasing the number of people approached and/or increasing the geographical area, adapting recruitment procedures). Recruitment data will be reviewed by the TSC and any required changes in the recruitment strategy and/or introduction of new recruitment avenues will be discussed and agreed. Retention rates (proportion of people providing follow up data) will also be checked. Receipt of strong negative feedback from the majority of either participants or intervention providers about the intervention or trial methods will be considered as a stopping criterion. The participants recruited in the pilot study will be included in the trial analysis.

4.2 Internal pilot study and progression criteria

Acceptability and feasibility of the proposed trial methods and of the ACE intervention have been established in a feasibility study with 39 participants and 15 ACE activators (peer volunteer facilitators) (34). This showed that the ACE intervention was well accepted and easy to administer, with excellent attendance of intervention sessions and retention of 82% (100% in ACE activators) at six months follow-up. However, recruitment was challenging. Recommendations to improve this included recruiting via primary care, linking to social prescribing systems and working with community providers of social care, pharmacists, physiotherapists and occupational therapists to identify suitable participants.

Since the ACE feasibility study, the REACT trial has demonstrated feasibility of recruitment and retention of the target population at scale across multiple sites (including Birmingham, Devon, Bristol and Bath). In REACT, we used searches of GP databases in combination with telephone screening (and then face-to-face screening using SPPB) to recruit 777 people aged over 65 and with SPPB scores of 4-9. The ACE trial involves the same target population, the same recruitment and retention methods and similar measures as the REACT trial. However, the ACE intervention and its delivery methods are very different. Therefore, we propose to conduct an internal pilot study to confirm recruitment feasibility at scale and to allow (if needed) fine-tuning of our recruitment and intervention delivery strategies. The pilot will run at all three trial sites with progression criteria assessed after 4

months of recruitment and intervention delivery. The progression criteria will be assessed by the independent members of the Trial Steering Committee who will advise the funder on any recommendation to stop the trial.. If any of the criteria are in the red zone, we will consider stopping the trial.

Progression Criteria	Clear to progress	Modifications needed	Do not progress
Recruitment rate (N randomised per month)	>= 30 /mth*	15-29 /mth	< 15 /mth
Intervention delivery rate (new participants starting per month by end of pilot phase))	Up and running at all sites with >= 15 /mth new starters	Not running at any one site or 10-14 /mth new starters overall	Not running at 2 sites or < 10 /mth new starters

*NB: The feasibility targets are set below the rates required for full-scale delivery to allow for building of capacity during the pilot phase.

To facilitate the decision making process for continuation of the ACE trial we will also collect and report the following data:

1. % of participants who had a first meeting
2. No of meetings per month,
3. % of meetings re-scheduled
4. Retention figures for participants and for volunteers

During the internal pilot phase, 3 months after starting the intervention we will administer a brief feedback survey (based on the feedback section of the CRF (Page 42-43)) by post to intervention participants and peer volunteers. Participants will be asked to report their views anonymously to encourage disclosure of any issues and or negative feedback.

The organisations supporting the volunteers will also report to the study team:

- No of participants who have asked for a change of volunteer
- No of volunteers who have asked for a change of participant

Volunteers will be asked to report any issues regarding acceptability with the volunteer manager and any issues will be discussed with the research team in a timely manner. This information will be shared with the TSC at regular intervals (monthly at the internal pilot study, every two months at the main trial study).

5 STUDY SETTING

5.1 Trial sites

The ACE trial will take place at sites in four areas of the UK: West Midlands, Greater Manchester, South Wales and Bristol[1]. These sites have been selected as they all include areas with complex challenges in relation to area deprivation, health inequalities and ethnic diversity. They also have a diverse range of community activities within their localities. Conduct of the trial at each site will be led by a local Principal Investigator supported by a Research Assistant who will receive training in the requirements of the study protocol.

Within each site, community settings with high numbers of older adults will be purposively targeted to recruit a sample that is representative of area deprivation and ethnic diversity (in

[1] The Bristol site was added in September 2022

older adults) in England and Wales. Participation and types of physical activity undertaken will also be dependent on the cultural norms and beliefs of different ethnicities.

5.2 Intervention Setting

Peer volunteers and ACE participants will initially meet in community centres/cafes/parks or at the participant's home (Motivation stage). They will then jointly attend activities in the participant's local area at a range of venues (Action stage). During the Maintenance stage attendance at activities at local centres will continue (minimum of two joint visits to community activities) plus telephone contact to support the participant to attend independently. Current Government safety guidelines and applicable sponsor procedures and risk assessments in relation to COVID-19 will be adhered to at all times.

5.3 Peer volunteer/participant pairing

Peer volunteers and participants will be paired on the basis of geographical proximity, common language and shared interests. These data will be collected from volunteers by local volunteer management partners during the recruitment process and from participants during the recruitment and screening processes (See Participant Reply Form and Participant Screening Form)

6 ELIGIBILITY CRITERIA

6.1 Participant Inclusion criteria

- Men and women aged 65 or older who are not in full-time employment
- Planning to reside in the target area (West Midlands, Greater Manchester South Wales and Bristol) for at least 18 months
- Participants must score between 4 and 9 (inclusive) on the Short Physical Performance Battery (SPPB) (1). This is based on definitions of physical frailty from the European Medicines Agency for identifying people with (or at risk of) physical frailty in clinical trials (15). This guidance defines pre-frailty as an SPPB score of 8-9 and frailty as a SPPB score of 7 or less. Evidence demonstrates a strongly increased 3-year risk of major mobility disability for older adults with SPPB of 9 or less (OR 8.3 (95% CI: 3.3-20.7); During the pilot phase we will monitor the baseline profiles of participants and consider whether the inclusion /exclusion criterion or recruitment procedures need refinement (e.g. if they lead to over-exclusion of participants).

6.2 Participant exclusion criteria

- A documented or patient-reported medical condition that would preclude participation, including
  - a) arthritis so severe it would prevent participation in physical activity,
  - b) Parkinson's disease,
  - c) diagnosed dementia;
  - d) lung disease requiring use of oral corticosteroids or supplemental oxygen (not inhalers),
  - e) severe kidney disease that requires dialysis;
  - f) any severe heart condition that would prevent participation in physical activity (for example unstable cardiovascular disease including unstable angina);
  - g) an implanted cardiac defibrillator,

- h) a cardiac arrest which required resuscitation;
- i) major heart surgery (including valve replacement or bypass surgery) or spinal surgery in the last six months
- j) severe uncontrolled psychiatric illness;
- k) currently receiving radiation therapy or chemotherapy treatment for cancer;
- l) awaiting knee or hip surgery;
- m) using a wheelchair or Zimmer frame
- n) terminal illness

-
- Any other clinical condition that their GP or clinician considers would make them unsuitable for potential participation in physical activity to prevent decline of lower-limb functioning.
- Self-reported inability to walk across a room without help (use of a stick for support is acceptable).
- Existing major mobility limitation. This will be defined using a SPPB lower cut-off score of 3 or less). In addition, being unable to complete the 4m walk component of SPPB will result in exclusion
- Living in residential or nursing care
- Reported lower limb functionality (defined by four verbal screening questions, as used in the REACT study) (30) likely to produce an SPPB score of 9 or more.

6.3 Peer volunteer inclusion criteria

Peer volunteers will be

- Community-dwelling
- Aged 55 years and older
- SPPB scores of 4 and above
- Not in full-time employment (unless with the flexibility to volunteer during weekdays)
- Available to volunteer in the daytime during the week

6.4 Systems mapping participants inclusion criteria

- People living and working in the area local to each site (see 7.8.1 for full description)

7 TRIAL PROCEDURES

For Trial Project Management Plan see Appendix 3

Jan 2021 – August 2021: Study set-up
April 2021 – July 2021: Confirmation of ACE delivery sites (within study sites in West Midlands, Greater Manchester, South Wales and Bristol[2])
May 2021 – Aug 2021: Refine peer volunteer training manual
Feb 2021 – July 2021: Ethics application/approval

[2] The Bristol site was added in September 2022

May 2021 – Feb 2022 Engage with CRN, identify partner GP practices and set up recruitment processes (pilot and main trial)
May 2021 – July 2021: Research Assistants' recruitment
1st Sept 2021 Trial Manager starts in post
1st Sept 2021: Researcher Assistants in post in West Midlands, Manchester and Cardiff.
November 2021: INTERNAL PILOT- Recruitment of participants and peer volunteers starts
90 participants - 30 per site (45 intervention - 45 control)
Nov 2021 – Mar 2022: INTERNAL PILOT- Baseline measures
90 participants - 30 per site
June 2022 – Sept 2022: INTERNAL PILOT- 6-month measures
Nov 2022 – Feb 2023: INTERNAL PILOT- 12-month measures (reduced measurement pack)
June 2023 – Sept 2023: INTERNAL PILOT- 18-month measures
April 2022: EVALUATION OF PILOT AND DECISION TO CONTINUE TO MAIN TRIAL
May 2022 – Feb 2023: MAIN TRIAL- Recruitment of participants and peer volunteers and baseline measures
(515 sample size, 90 recruited for the pilot) = 425 remaining participants to be recruited
14.6/per site/per month * 3 sites = 10 months for recruitment
Nov 2022 – Aug 2023 MAIN TRIAL – 6-month measures
May 2023 – Feb 2024 MAIN TRIAL – 12-month measures (reduced measurement pack)
Nov 2023 – Aug 2024 MAIN TRIAL – 18-month measures
Jan 2022 - Sept 2024: Data entry
Sept 2024 - Nov 2024: Data cleaning and analysis
Nov 2024 – Feb 2025: Writing up
28th Feb 2025: Official study end date. Total duration: 42 months

7.1 Recruitment

The goal of the study is to enrol 515 participants across the fourtrial sites, West Midlands, Greater Manchester South Wales, and Bristol. Using community demographic data, we will purposively select areas by postcode to ensure representativeness in terms of area deprivation and ethnic diversity within each locality. We will monitor sample demographics bi-monthly and, if needed we will increase recruitment activity in higher area deprivation or more ethnically diverse areas.

All recruitment related activities will be overseen by the CI, Trial Manager and TMG. The Trial Manager will coordinate press and media releases and assist the sites in the preparation of recruitment materials.

Each trial site will develop a site-specific recruitment plan built around three main strategies to accommodate the variability across centres in catchment area characteristics and routes to access potential participants. All recruitment materials will be reviewed by the appropriate PI before being used.

7.1.1 Patient identification

ACE will use four main recruitment strategies:

1) Via Primary Care
2) Via Third Sector organisations
3) Word-of-mouth and snowball sampling techniques with the assistance of bi-lingual community champions (via existing community contacts).

4) These recruitment approaches will be supported by a low-cost public relations campaign targeting local newspapers, social media, magazines, radio and community events.

1) Via Primary Care

Recruitment of GP practices

General practitioner (GP) Practices in the Clinical Commissioning Groups will be invited to participate through their local Clinical Research Network (CRN) and through existing networks. Where possible we will select practices to maximise diversity in terms of ethnicity socio-economic status and rurality. Practices who agree to participate will be contacted by a member of the local research team (PI, Trial Manager or RA) for an appointment with the practice manager or IT administrator to arrange to discuss the study and the details of the database search.

GP register search

Practice or CRN staff will search the practices' electronic patient databases for potentially eligible patients using those inclusion/exclusion criteria that are coded in the database. Lists generated from the searches will be screened by GPs to ensure there is no reason why the patient should not participate in ACE.

Search details:

All people aged 65 years and older

Where possible using search codes: Exclude people with; a) arthritis so severe it would prevent participation in physical activity, b) Parkinson's disease, c) dementia; d) lung disease requiring use of corticosteroids or supplemental oxygen, e) severe kidney disease that requires dialysis; f) severe heart disease that would prevent participation in physical activity; g) an implanted cardiac defibrillator, h) a cardiac arrest which required resuscitation; i) severe uncontrolled psychiatric illness; j) currently receiving radiation therapy or chemotherapy treatment for cancer; k) awaiting knee or hip surgery, l) major heart surgery or spinal surgery in the last 6 months m) using a wheelchair or Zimmer frame n) terminal illness o) living in residential care or nursing home

NB: if the field for any of the above exclusion criteria is not completed, the assumption should be that the exclusion does not apply (only a positive recorded event or condition should result in exclusion).

GP or his/her appointed representative to review the list to a) exclude anyone who is known to already have a major mobility limitation (being unable to walk 4 metres or being unable to do this without a Zimmer frame or support from another person - using a walking stick is OK) and b) exclude anyone with any other clinical condition (or other reason i.e. recent bereavement) that their GP considers would make them unsuitable for participation in a programme potentially including physical activity to prevent decline of lower-limb functioning.

Patient Approach Letter

The mailing database generated from the GP register search will be sent by the practice to an NHS approved secure mailing house. The approved mailing house will print and mail the Patient Approach Letter (PAL), the Participant Summary sheet, a reply form and the Participant Information Sheet (PIS)) printed on the Practice headed notepaper enclosing a reply-paid envelope addressed to the research team at the local trial site. The PAL will make

it clear that we wish to recruit people who have some difficulty doing daily activities such as walking, getting out of a chair, and climbing stairs but are still able to do these things. This constitutes the first phase of the screening process – Initial self-screening. Patients will be asked to return the reply form to the research team if they feel they meet the study criteria and are interested in talking to a member of the research team about the study. If the target recruitment rate is not achieved general practices will be asked to send out follow-up approach letters to the same patients 14-21 days. The follow-up approach letters will include an acknowledgement that the follow-up letter may be ignored by those patients who have responded to the initial letter. GPs will be provided with a list of their patients who are taking part in the study.

2) Via Third Sector organisations

Mailed invitations from the Royal Voluntary Service and our extensive network of third sector (Age UK, Sport England) and community partners in all the trial settings who work with adults over the age of 65. Our partners include: health development co-ordinators from local care organisations, district nurses, active case managers based in neighbourhood teams, Likely partners include: Cardiff City Council Independent Living Services, Cardiff community pharmacy schemes committed to promote healthy lifestyles, social prescribing schemes, community connectors, Ageing Well coordinators, Healthcare assistants, link workers, Good Neighbours schemes, Be-well Social prescribing and Buzz Ageing Well schemes in Greater Manchester Mental Health Trust, Coventry City Council, Birmingham Voluntary Services Council, Birmingham City Council Adult Social Care Commissioning, Neighbourhood Network Scheme Facilitators, Healthy Ageing Project in Sandwell Council. Many of these proposed partners are already engaged and support the project. Professionals in these services will either approach potentially eligible service users and provide a brief summary of the study or invite the study researchers to give a presentation about the study, followed by provision of the study information/invitation materials, if deemed appropriate.

3) Via word-of-mouth and snowball sampling techniques

To enhance recruitment, we will use word-of-mouth and snowball sampling techniques and employ the assistance of multi-lingual community champions to help with recruitment and retention initiatives. This strategy has been previously used successfully by members of the ACE study team and is particularly useful for engaging with ethnically diverse groups. The local PI or RA will work closely with community champions already known to the research team to identify ethnic minority groups or individuals who may meet the ACE inclusion criteria. The initial approach would be made by the community champion who would provide a brief summary of the study, followed by provision of the PAL, reply form, PIS and reply-paid envelope (if deemed appropriate). This material would be translated where necessary.

4) **Low cost media campaign**

Low cost media campaigns will target local newspapers, magazines, radio and community events (See Appendix 5).

Recruitment response rates

ACE recruitment response rates are based on the recruitment statistics from the recent REACT study, conducted by this research team, which recruited from the same target population (59). In REACT 12.6% of those invited to participate responded and were

telephone screened; 38.9% of those telephone screened were consented and screened face-to-face; 64% of those screened face-to-face were randomised into the trial. Applying these percentages to the ACE recruitment target of 515, we predict we would need to contact approximately 21,000 people over the 14-month recruitment period (4 months Internal Pilot, 10 months Main Trial).

Based on our experiences in REACT we estimate the recruitment plan will require recruitment of 8-10 GP practices per site.

Recruitment Monitoring and Assistance

Participants arising from all methods of recruitment will be documented by each of the ACE trial centres by means of coded reply slips. In addition, during the telephone screening interview, potential participants will be asked about where they heard about the study. These data are used to generate regular reports through the whole recruitment period to track the method(s) that provide the greatest yield of eligible participants. These reports will be provided to the Trial Manager on a weekly basis and to the Trial Management Group members on a bi-monthly basis and provide data on the number of potential participants screened from each of the recruitment sources, eligible participants from the various recruitment sources, and eligible ethnically diverse participants from the recruitment sources. Recruitment procedures will be refined based on this feedback during the course of the pilot study to correct any deviations from sampling targets and target response rates.

Recruitment numbers will be reported monthly to NIHR and the TSC.

Initial response

Older adults who are interested in participation based on the initial invitation will instigate contact with the research team by returning the approach letter reply slip. Participant Approach letters and reply slips will undergo Research Ethics Committee review and approval prior to use.

Provision of study information

Once an approach letter reply slip has been received from a potential participant, an RA will telephone the patient using the contact details provided on the reply form. The telephone call will be used by the research team member to provide further information if necessary and to confirm ongoing willingness and to conduct the second, phone-based phase of the screening process. If the call establishes that the patient is potentially eligible and willing to participate, arrangements will be made for them to attend a baseline recruitment session. Transport to this session can be offered.

Recruiting for Diversity

Sedentary behaviour and mobility limitations in older people are more prevalent in socio-economically deprived sectors of the population (60). Ethnic minorities experience significantly greater risk of a range of physical and mental health problems as compared to their white counterparts, and subsequently suffer higher rates of morbidity and premature mortality (61, 62). Self-reported data from the HSE indicate that older (55+yrs) Bangladeshi, Pakistani, and Indian adults are less likely to meet physical activity guidelines compared to

their Caucasian counterparts (61). Thus, interventions that increase physical activity in sedentary and ethnically diverse populations will help reduce health inequalities. The geographical areas in the West Midlands and Greater Manchester targeted in ACE were chosen to recruit sedentary older people from diverse socioeconomic and ethnic backgrounds. Our team has successfully recruited people with diverse SES status to a number of previous projects (30, 63, 64). Within each study location, we will target areas for recruitment that include a broad range of deprivation and diversity utilising our established links with community groups, faith leaders, and GP surgeries that serve ethnically and economically diverse communities. We will monitor the Index of Multiple Deprivation (IMD) scores of postcodes of the recruited sample quarterly as the study progresses and will seek to over-sample in higher deprivation areas if the pilot study shows that the recruited sample is not broadly representative of the UK population.

Each ACE trial site will track recruitment methods to determine the most successful strategy for recruiting minority groups in order to ensure socio-economic diversity amongst the cohort.

Translation

In order to maximise recruitment and retention from ethnically diverse populations, interpreters will be provided at key points in the study. Using an approach employed successfully in REACT and the Community-based Prevention for Diabetes (ComPoD) trial, the Patient Approach response form will contain a tick box inviting potential participants to inform the research team if they would need an interpreter in order to participate in ACE, and if so in what language. For these participants, telephone screening will be conducted by an interpreter using the screening script, with oversight provided by the site-based Research Assistant. Interpreters will also translate at the point of consent and scheduling of data collection events, at the face-to-face screening and at baseline, 6 months, 12 months (by telephone) and 18-month data collection events. Interpreters will also translate at the social event/presentation offered to the Control group. These interpreters will be recruited from our established links with local interpreter services and we will provide additional training of interpreters to assist with data collection as needed. Participants will be paired with volunteers who speak the same language so that their involvement with the intervention will be a peer to peer experience. Welsh language versions of key documents (Consent Form, Participant Information Sheet, Recruitment Poster) will be made available.

Recruitment launch event

At the beginning of the recruitment process, we will hold a one day event where collaborators, partners, potential recruiters and community groups which focus on the ACE study population will be invited to discuss ACE and their potential engagement in the study.

All these actions will be evaluated during the internal pilot stage and any necessary changes on recruitment and sampling framework will be discussed, identified and agreed by the Trial Management Group and Trial Steering Committee prior to the start of the main phase of the study.

Peer volunteer recruitment

The Royal Voluntary Service [RVS] or Sport Cardiffwill be largely responsible for recruiting and managing ACE peer volunteers. One or two other partner organisations may be sought in order to target volunteer recruitment in ethnically diverse areas. Peer volunteers will be

community-dwelling older people, aged 55 years and older, with SPPB scores of 4 and above, not in full-time employment (unless with the flexibility to volunteer during weekdays) and available to volunteer in the daytime during the week. Our volunteer recruitment partners) will conduct an initial screening of volunteers based on the above criteria. They will not conduct a full SPPB test (to avoid volunteer burden) but will assess by observing ease of walking the likelihood of an SPPB score of less than 4. If recruitment takes place over the phone/Zoom they will use the Four Easy questions (see ACE Screening Form) to assess physical function. The full SPPB will be conducted at baseline assessments by the research team and may result in a very small number of volunteers being excluded from the study at this point.

We will recruit volunteers via:

a. Our volunteer management partners including via the large volunteer database of the Royal Voluntary Service. Our extensive network of health, public health and third sector organisations have all expressed their support to the ACE study and their willingness to support the recruitment process. After expression of interest, they will receive a volunteer Information Sheet and Volunteer Role Description and complete the Volunteer Information form where they will provide information on previous volunteering experience (if any), demographic information, languages spoken and their interests and hobbies. Prior to completing the form, they will be asked for verbal consent to allow the data collected (in anonymised form) to be used as part of the study. Volunteers' data will be managed in accordance with the local volunteer management partner's Privacy Notice and terms and conditions. This data will be shared with the local research site, via password protected communications, for entry onto the study database.

b. The GP participant recruitment letter will include a request to those who think they are too highly functioning to participate in ACE to consider becoming a peer volunteer. The reply slip will contain an option to allow them to do that and will explain that they will be contacted directly by the local volunteer management partner. Potential participants who are excluded at the point of telephone screening as they appear to be too highly functioning (Q10-13) will be asked if they would consider participating as a peer volunteer. If they are interested, they will be asked to verbally consent to their contact details being shared with the local volunteer management partner. The research team will then post or email a Volunteer PIS to potential volunteers who have returned reply slips or expressed interest during the screening process. Their contact details will then be forwarded to the local volunteer management partner point of contact who will continue the recruitment process.

Retention

Loss to follow up is modelled on an attrition rate of 20% at 18 months. This is based on an attrition rate of 19% at 24 months in our REACT study. The internal pilot study will demonstrate that recruitment and retention rates are satisfactory and established at each site before we progress to the full-scale trial. To maximise retention, we will offer a voucher-based incentive for completion of assessments at 6 and 18 months (one of the most effective strategies identified by a Cochrane Review (65) and we will follow recommendations for good practice for retention in trials provided by the NIHR School for Primary Care Research (66). These include emphasising the meaningfulness of the research, regular contact, use of incentives and involving Advisory Groups in the development of study materials.

The following information will be calculated based on the volunteers' Time and Travel diary

- % of participants who had a first meeting
- No of meetings per month,
- % of meetings re-scheduled,

The organisations supporting the volunteers will also report to the study team:

- No of participants who have asked for a change of volunteer
- No of volunteers who have asked for a change of participant

This information will be shared with the TSC at regular intervals (monthly at the internal pilot study, every two months at the main trial study).

If participants fail to attend two consecutive meetings, without prior notice, the volunteering organisation will inform the research team who will contact the participant to explore potential issues/barriers to participation.

1. Every two months, we will report the retention figures for participants and for volunteers
2. During the internal pilot phase, 3 months after starting the intervention we will administer a brief feedback survey (based on the feedback section of the CRF (Page 42-43)) by post to intervention participants and peer volunteers. Participants will be asked to report their views anonymously to encourage disclosure of any issues and or negative feedback.
3. Volunteers will be asked to report any issues regarding acceptability with the volunteer manager and any issues will be discussed with the research team in a timely manner.

7.1.2 Screening

Peer volunteers will be initially screened by the local volunteer management partner. They will then join the research screening process at the point of face-to-face screening (Point (3 below).

Current Government safety guidelines and applicable sponsor procedures and risk assessments in relation to COVID-19 will be adhered to at all times.

The eligibility of respondents will be assessed in a three-step sequential screening process:-

1. Initial self-selection: The Patient/Participant Approach letters, PIS, Study invitation letters and promotional materials will make it clear that we wish to recruit people who have some difficulty doing daily activities such as walking, climbing stairs and getting out of a chair but are still able to do these things. The first two criteria have been shown to strongly predict SPPB scores (67) and the third is a self-report of one of the components of the SPPB test battery which correlates strongly with SPPB total score.

2. Telephone based screening: After gaining verbal consent a preliminary telephone screen will check inclusion and exclusion criteria that can be assessed by telephone (e.g. self-reported inability to walk across a room, ability to attend intervention sessions) Participants who do not meet the eligibility criteria will have the reasons for their exclusion explained (see Telephone Screening script) and will be thanked for their time.

3. Face-to-face screening sessions: Potentially eligible participants will then be invited to a group-based assessment session where they will be asked for written informed consent. This method involves having several 'stations' for each step in the assessment process which participants work their way through and has been successfully piloted in prior studies

(34, 64). Attendees will have an opportunity to ask questions about the study and be asked to give written informed consent (including consent for a longer-term follow-up at up to 10 years). They will then be administered the SPPB. The gait speed test will be conducted first and those who fail to complete the 4-metre walk will be screened out of the study and will not continue to the other SPPB tests. Participants who meet the eligibility criteria will be invited to complete the remainder of the baseline assessments. Participants who do not meet the eligibility criteria will be thanked for their time and provided with an information pack.

7.2 Consent

Older adults who are willing to take part in ACE will be asked to provide verbal informed consent at the beginning of the telephone screening call and written informed consent prior to commencement of the face-to-face screening sessions.

Consents to be Obtained

The ACE trial has two points of informed consent: one verbal and one written.

1) Verbal consent

The verbal consent is requested prior to the beginning of the phone screening interview. If the participant fails to give consent, then a phone screen will not be done. If a participant provides verbal consent, then the assignment of a study ID number and completion of the phone screening interview will be taken as positive evidence that initial consent was obtained.

The Phone Screening form may be administered as a face-to-face interview if the situation warrants it.

Peer volunteers will be asked for verbal consent for the use of the data collected on the volunteer application form as part of the study. This will be done by the local volunteer management partner staff during the application process (see RVS application form). Where staff are not experienced in taking consent, the local RA will provide training based on the NIHR's Good Clinical Practice (GCP) using the elements designed for the voluntary sector.

2) Written Consent

The Environment for Consent

The setting in which written consent is obtained at the face-to-face screening session will be as private as possible so that participants can freely ask questions without embarrassment. To avoid pressuring the participant, only one person associated with the study will be present when the participant reviews the consent forms.

The Consent process

The consent process will involve a full explanation of the study given by the person taking consent (RA or other authorised researcher) prior to any of the face-to-face screening processes commencing. Potential participants will be informed that they may, at any time, withdraw their consent to participate in the study without giving a reason, and without it affecting their relationship with their GP or the referring organisation and/or their future treatment and care. The PIS will also provide details of a contact point where participants may obtain further information about the study. Participants will also be informed that although they are under no obligation to provide a reason for withdrawing from the study, it would be helpful information when assessing the study's success.

Following these discussions people who are willing to participate will be asked to complete, sign and date the study consent form, which will also be signed and dated by the person obtaining consent.

Capacity to consent

To be eligible for participation in the ACE study, participants must have the capacity to give their own informed consent. If a member of the research team considers that a participant is incapable of understanding what is expected of him or her as a subject in the study, it is not permissible for informed consent to be obtained from a guardian. The study requires daily responsibilities that cannot be easily assumed by other people.

Storage of consent forms

The original signed consent form will be retained in the relevant Site File. A copy of the form will be scanned and stored at the local trial site.

Data Entry of Informed Consent Documents

Pertinent information from the informed consent forms will be entered into the secure ACE database.

7.3 The randomisation scheme

Eligible participants will be randomised to one of the two arms in a 1:1 ratio stratified by site, using a centralised web-based system run by the Cardiff Centre for Trials Research (CTR).

To perform randomisation an authorised member of the research team will access the randomisation website using unique username and password log-in details. The website will require entry of patient's initials, date of birth and stratification variable. The randomisation website will also generate a unique study ID number for the participant when they are randomised. In the relatively unlikely event that two people from the same household present for screening, to avoid potential for contamination (if they were allocated to different groups), only the first would be included in the study.

7.3.1 Method of implementing the allocation sequence

Confirmation that randomisation has been performed will be communicated to the appropriate site RA. Communication will be achieved via emails automatically generated by the randomisation website.

The RA will telephone participants to inform them of their allocation and will send them a confirmation letter using the contact details collected at the baseline assessment. The local site RA will therefore not be blinded to allocation.

The control group will be invited to two social events with a presentation on healthy ageing (excluding any physical activity component). One event between 0 and 6 months and one between 12 and 18 months post-randomisation at each trial site. Newsletters will be distributed to all participants at the end of each project year.

RVS, or the local volunteer management partner, will manage the process of pairing peer volunteers and participants based on the information collected during recruitment and screening (vicinity, language, interests and hobbies). Letters to participants in the intervention group will advise them when and how their peer volunteer will contact them. They will follow this

up with a telephone call shortly before the day of the first meeting to re-confirm the arrangements and discuss any practical issues.

7.4 Blinding

Allocation concealment: We will ensure allocation concealment until the point of randomisation which will be after collection of all baseline measures.

Blinding: It is not possible to blind study participants to treatment allocation in behavioural intervention studies and this is not a problem in pragmatic trial designs, which aim to estimate the benefits of the intervention over and above usual or standardised care. However, we will take steps to ensure that data collectors, statisticians and the majority of the research team remain blinded to group allocation. The CI will not be blinded due to her involvement in assessing and reporting any Serious Adverse Events. The local site RA will not be blinded to allocation (see above) so will not conduct the primary outcome measure (SPPB) at assessment sessions. The SPPB will be assessed by a researcher who was not involved in randomisation (each site will have either part-time or 'casual hours' SPPB-trained data collecting research assistants, so that this can be achieved). Participants will be asked not to reveal to which group they were allocated. Any instances of unblinding will be recorded in the Trial Site File. Allocation codes will be locked away by the CI until the database is closed for analysis.

Data will be coded so that those performing the statistical and economic analyses will also be blinded. Given the study design, we do not anticipate a substantial risk of contamination (i.e. exposure of the control participants to the ACE intervention). However, as part of their briefing on entry to the study (and at follow up measurement visits), participants in the intervention arm will be asked not to share or discuss the content of the intervention sessions with any control participants they may be in touch with, for the duration of the study. Attrition bias will be minimised by having robust trial procedures to prevent data loss and also analysing the data by intention to treat (ITT).

7.5 Unblinding research

The DMEC will undertake safety data reviews every 12 months after recruitment begins, and all SAEs will be reported to them. The DMEC will be responsible for identifying any need for unblinding. The DMEC will also periodically review unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

7.6 Methods for data collection

Quantitative measures will be collected at meetings in community venues and with home-visits for participants who cannot attend, at baseline, 6, and 18 months.

At each data collection point, participants will be fitted with a GENEActiv accelerometer worn on the non-dominant wrist (https://www.activinsights.com/actigraphy/geneactiv-original/). They will be asked to wear the accelerometer for 24-hours per day for 16 consecutive days. Sixteen days have been selected to ensure 14 complete days of wear. Two weeks of wear time has been selected to get a representative estimate of physical activity behaviour. Participants will be given brief written instructions for wearing the accelerometer to supplement the verbal guidance. They will also be given a pre-paid padded envelope to return the accelerometer. This protocol has been successfully implemented in the REACT trial with over 90% adherence to wear time guidance.

To limit participant burden the 12 month assessment will not be face-to-face but will be a posted CRF (with return envelope) and a follow-up telephone call to all participants to complete some short but key secondary measures: (Warwick-Edinburgh Mental Well-being Scale [WEMWBS] (14 items); loneliness (Revised UCLA loneliness scale) (3 items) and social networks (Lubben's Social Network Scale) (6-items), Health-related quality of life (EQ-5D-5L, ICECAP-O (62)), Medications, Medical History and Process Evaluation measures. An accelerometer will also be mailed to them and they will be requested to wear it for 16 days.

For peer volunteers, measures will be administered at the same time points as for participants.

Detailed instructions for conducting the SPPB, using a digital dynamometer (grip strength) issuing accelerometers and conducting the questionnaires will be provided to researchers as part of the Site File. Research staff at all sites will also receive study-specific training in each of these procedures delivered by members of the study team.

Details of the baseline assessment visit will be recorded in the baseline Case Report Form (CRF).

The person conducting the assessments will be responsible for checking completed questionnaires before participants leave the assessment premises and will make every effort to ensure missed or spoiled questions are addressed in the interests of maximising data completeness.

Qualitative data collection is described in the process evaluation section 7.8.

NHS/UK government COVID-19 guidelines, and any COVID-19 guidance issued by NIHR, will be adhered to throughout all phases of the ACE data collection process.

7.7 Trial assessment schedule

The primary outcome (SPPB score) will be assessed at baseline, 6 and 18 months. Other secondary outcomes will be assessed at either baseline, 6, 12, and 18 months or baseline, 6 and 18 months (see above regarding 12 month assessment). Process evaluation questionnaires assessing mechanisms of change will be conducted at baseline, 6, and 18 months.

Table 1 Assessment schedule

Visit type	Scr	Scr	Fu	Fu	Fu
Visit code		SV1	F06	F12	F18
Visit number		1	2	3	4
Telephone call	1				
Activity/assessment Month	-0.5	0	6	12	18
Form Name					
Verbal consent	X				
Telephone screening (some elements of inclusion and exclusion criteria)	X				
Written informed consent		X			
Contact information update	X	X	X	X	X

Demographics					
Age	X				
Sex	X				
Ethnicity	X				
Highest Education Level	X				
Marital status	X				
Home ownership	X				
Index of Multiple Deprivation (from postcode)	X				
Caring responsibilities		X	X		
Height (Baseline and 18M only) and Weight (BMI)		X	X		X
SPPB battery		X	X		X
Accelerometry		X	X		X
MoCA – Montreal Cognitive Assessment		X	X		X
Fried frailty phenotype index (5 measures)		X	X		X
Loneliness (Revised UCLA loneliness scale) (63)		X	X	X	X
Social networks (Lubben's Social Network Scale) (64)		X	X	X	X
Psychological functioning and well-being (Warwick-Edinburgh Mental Well-being Scale [WEMWBS])		X	X	X	X
Ageing Well profile		X	X		X
Health-related quality of life (EQ-5D-5L, ICECAP-O (5))		X	X	X	X
Trips out of the house		X	X	X	X
Time and resource costs for volunteers and participants			X		
Medical history		X	X	X	X
Falls Inventory		X	X		X
Fear of falling (Falls-Efficacy scale-international)		X	X		X
Medications		X	X	X	X
Health and Social Service Resource Use		X	X	X	X
Short Volunteer Functions Inventory (volunteers only)		X	X		X
Process measures					
Muscle-Strengthening Exercise - Perceived importance, confidence and adherence scale		X	X	X	X
Physical activity–Perceived confidence and benefits scale		X	X	X	X
Community activities - Perceived confidence, benefits, autonomy, relatedness,		X	X	X	X
Evaluation of local environment		X	X	X	X

Attendance at local activities			X	X	X
Feedback on the ACE programme (intervention group only)			X		
Interviews: Will explore patient and volunteer experiences of ACE, barriers and enablers to the targeted behaviours, quality of peer-volunteer relationship, goal interdependence between participant and peer volunteer in relation to activity goals and other life goals			X		X
Intervention fidelity (from coding of audio-recorded intervention sessions)			X		

7.8 Process Evaluation

A mixed methods process evaluation designed to test and inform refinements of the ACE logic model (Appendix 4) will be delivered, as detailed below:-

7.8.1 Systems Level Process Evaluation

We will conduct a mixed methods process evaluation including a systems mapping approach.

Systems mapping: This part of the study will be managed by Nick Cavill of Cavill Associates (www.cavill.net) who will be contractually obliged by the Sponsor to adhere to the protocol and sponsor requirements and will work in conjunction with the research team. To facilitate a comprehensive understanding of this complex public health intervention, the researchers, service users and a wide range of stakeholders will co-produce a systems map (32, 34), as described below.

1. Community-led systems mapping: During the first 3 months, two half-day workshops will be held in each implementation site; one with older people representing the target group (age, sex, functional ability, deprivation, ethnicity) and one with people with experience of volunteering to support older people. Up to 15 people will take part at each of the 6 workshops, up to a total of 90 participants. Recruitment will rely on methods described in the recruitment section and focus particularly on third sector organisation, word of mouth and snowball sampling techniques.

The maps will be produced through workshop-style methods, in which small groups of older people will identify factors that they think are important influences on their involvement in physical activity and community-based exercise and/or other initiatives; discuss and agree them; and put them forwards for mapping. Two facilitators will then transcribe these onto a system map, using STICKE (Systems Thinking in Community Knowledge Exchange) software (https://sticke2.deakin.edu.au/). This enables the system map to be produced in real time, with the active participation of the older people. The second task is then to make connections between the factors, identifying how the factors interact. This is again done through group consensus. The output is then a systems map of influences on older people's participation, which will be used to 1) help to refine the ACE intervention-delivery and recruitment strategies; and 2) feed into the stakeholder systems mapping (see below).

These two workshops at each site will be repeated after intervention completion (with the same group of participants (the 'map makers') as well as with a group of up to 15 actual ACE participants and peer volunteers). They will aim to identify individual level and systems level factors that have changed over the course of the intervention. These will use the system maps from the pre-intervention phase as prompt materials for qualitative discussions of the ways in which any factors influencing physical activity have changed during the intervention, how the participants (the 'navigators)' have experienced the system-level barriers and facilitators represented on the map (e.g. what barriers were overcome by the ACE intervention, what barriers remain, how could they be overcome).

All four workshops at each site (12 in total) will be audio-recorded for analysis purposes.

2. Stakeholder system mapping and Social Network Analysis:

During the first three months, two half-day workshops will be held in each site for key active ageing agencies and stakeholders. These will be identified by site leads and will include any key agencies that might have an influence on older people's physical activity. (e.g. local authority service managers, voluntary sector, public health, social care workers, activity session leaders, GPs and community nurses). Recruitment strategies will include invitations and word-of-mouth nomination via existing local contacts. Each workshop will have up to 20 people (up to a total of 120 across all workshops). At the first event we will use the community-led systems maps (above) to stimulate discussion among the participants about the agencies' and stakeholders' response to the barriers and enablers (influencing factors) identified. Following the first session, we will draft a stakeholder system map that shows the organisations working in this space, and how they are connected. At the second session, the same set of stakeholders will refine and agree this map. This system map will then be used to identify gaps and opportunities for enhanced joint action to support the ACE delivery. None of the participating agencies and stakeholders will be specifically named in any of the systems maps reports and subsequent ACE outputs. Both workshops will be audio-recorded for analysis purposes.

At the first stakeholder workshop, participants will be given a brief survey of relationships. This will ask them to identify the names and organisations of people who they consider important in their work in promoting physical activity with older people. This will be turned into a Social Network Analysis diagram using KUMU software (https://kumu.io/). This shows the extent and strength of relationships across the network and identifies key agencies or individuals who are central to the effectiveness of the network.

Both the processes above will be repeated post-intervention (the same participants will be invited, but they can delegate a colleague to attend if needed), to identify changes and mechanisms of change in the system and any strengthening of social networks. We will particularly seek to identify changes relating to the introduction of the ACE intervention into the community (if any). Changes in systems will be assessed qualitatively through consensus among workshop participants. Changes in social networks will be shown through changes in key Social Network Analysis measures including degree; closeness; and betweenness measures.

All four workshops at each site (12 in total) will be audio-recorded for analysis purposes.

Analysis

Transcripts of all workshops will be subjected to thematic analysis (68, 69) to: a) support the generation of system maps at each time point describing influences of participation in physical activity and community-based initiatives, systems in place and the dynamics of their interactions around promoting physical activity in frail/pre-frail older people at each site; b) explore the participants', volunteers' and stakeholders views on or experiences of the ACE intervention; and c) identify systems-level mechanisms that might mediate or moderate the effects of the ACE intervention. We will seek to enhance the trustworthiness and depth of the analysis by inviting participants' feedback on summaries of the analysed data. Our PPI group will also be involved in the interpretation of the data through workshops to discuss transcripts and the researchers' interpretations of the data.

There are many advantages to considering the issue of physical inactivity from a systems perspective. This will allow us to develop a detailed, nuanced understanding of the nature of the issue: the way that physical activity is realised in people's lives; the way that factors operating at different levels (individual, family, social /community and societal /cultural) are related to each other; and the nature of the complex adaptations that occur as older people, and the systems in play around them, respond to interventions such as ACE. This will help to inform both the initial delivery and the future implementation of the ACE intervention, enabling agencies and partners to plan a system-wide response to the challenge.

7.8.2 Qualitative Process Evaluation

The qualitative process evaluation will address five overarching questions:

RQ1. Was the intervention delivered as planned? Variations in intervention delivery by peer volunteers, including feedback on ACE training and implementation challenges by volunteers and volunteer managers will be investigated and recorded, as will variability in the acceptance/ receipt of the intervention by participants.

RQ2. Do any observed variations in delivery explain effectiveness / ineffectiveness of the intervention on physical function outcomes? What were the factors associated with engagement with ACE? What made participants adhere to or drop-out from the programme?

RQ3. Do theorised mechanisms explain any observed impact on physical function and physical activity? Theorised change mechanisms, including key human needs (autonomy-relatedness-competence) identified in the Self Determination Theory, and other psychological and behaviour change processes will be investigated as mediators of intervention effects on physical function and physical activity.

RQ4. What other factors are associated with variation in intervention effectiveness among intervention recipients? Factors to be explored will include differences in participant characteristics (e.g. context/circumstances, ethnicity, deprivation index, beliefs and cognitions), perception of social connectedness and bonding within (and external to) groups, engagement with partner organisations, involvement with other activities offered by the same provider.

RQ5. In what ways did the ACE intervention help to support ongoing PA and exercise after the 6 months intervention period (i.e. between 6 and 18 months)?

Study 1 Tracking the Experiences of Participants throughout the study: Repeated interviews addressing RQs 2,3,4,5

Participants: 30 participants (10 at each site).

Data collection: Thirty participants will be purposively selected by members of the process evaluation team. These participants will represent a range of age, ethnicity and functional status and will include men and women and participants at all three four sites. Selection will be facilitated by review of baseline data as provided by Cardiff Centre for Trials Research (CCTR) via the web-based database. Topic guides will be developed for the 6, and 18-month interviews. The interviews will be conducted by the two PhD student appointed to the ACE study and the research assistants at each site. Verbatim meeting and interview transcripts will be categorised and organised using computer software NVIVO. The research team will, with permission, interview each of these 30 participants, preferably on their own, 6 months (post-intervention) and 18 months (follow-up) after the baseline visit, and audio record these interviews. All recorded meetings and the two interviews will be recorded verbatim. The researchers will summarise the content of the interview at the end of the discussion and invite the participants to add anything else they would like to share. The interviewees will be asked if they would like a copy of the summarised findings. This will be sent through the postal system and the participants will be invited to add comments if they wish.

Study 2 Investigation of Experiences of peer volunteers and provider organisations addressing RQs 1,2, 5.

Participants: Up to 30 peer volunteers (up to 10 from each site seeking diversity on age, sex, ethnicity and area deprivation) including volunteers who drop out of the programme to capture their individual experiences in more depth and build on the theoretical perspective on volunteer motivation/engagement. The whole sample of volunteers will also complete open-ended questions on their experiences of delivering ACE in the 6-month follow-up questionnaire. All volunteer managers at partner organisations at each site will be invited to one-to-one interviews.

Data collection: Interviews and focus groups will be conducted at 12 months from the time of intervention commencement in a mutually convenient venue. The interviews/focus groups are expected to last between 60-90 minutes. They will be conducted using a semi-structured interview guide allowing and encouraging participants to express their views. The researcher will summarise the content of the interview at the end of the discussion and invite the participants to add anything else they would like to share. The interviews will be carried out by the PhD students and the research assistants. All provider organisations will be assigned a code to ensure they remain anonymous. All other interviewees will have already been assigned a code.

Analysis: The audio recordings from Study 1 and Study 2 interviews or focus groups will be transcribed verbatim and stored on encrypted laptops and a secure data base at the University of Birmingham. In transcripts, all identifiable information will be removed. No participant will be identified in any publication. Verbatim meeting and interview transcripts will be categorised and organised using computer software NVIVO. Data analyses will use similar methods as applied in study 1. The analysis will be conducted by the PhD students and the process evaluation research team. All qualitative data will be analysed using thematic analysis.

7.8.3 Intervention Fidelity Assessment

Aim: To assess the quality of delivery of the ACE intervention by peer-volunteers.

We will audio-record all participant-volunteer consultation meetings for a purposive sample of c30 peer volunteers, selected to achieve diversity in terms of age, sex and prior physical activity promotion experience. Encrypted digital audio recording devices will be used to record the consultations. Filenames for the recordings will include date, time and study number, but no identifiable participant information. We will apply a fidelity checklist to code the data. The checklist will include items to assess the quality and quantity of delivery of intervention processes that are part of the theory underpinning the ACE intervention. Scoring will be based on the scoring system for assessing clinical consultation skills developed by Dreyfus et al (70). This approach worked well in our NIHR-funded EARS, REACH-HF and REACT trials. We will also record facilitator-participant contact time (intervention dose) and relate this to outcomes. Scoring will be completed by two coders independently.

7.8.4 Quantitative Process Evaluation

Aim: To explore possible mechanisms of action of the ACE intervention.

Brief questionnaire measures will be administered to participants and peer-volunteers at the baseline, 6, 12 and 18-month data collection points (see measurement schedule, Table 1). The questionnaire data will be used to test hypotheses derived from the ACE logic model (Appendix 4). This will include checking for between-group changes in the process variables listed in the model (e.g. autonomy, enjoyment, perceived benefits) and mediation and moderation of the effects of the ACE intervention on the primary outcome by changes in the process variables. Hypotheses will be derived from the logic model by the process evaluation researcher (to be appointed) and the ACE process evaluation team. Analyses will vary depending on the hypotheses, but will include Analysis of Covariance (ANCOVA) and multiple regression analyses.

7.9 *Economic Evaluation*

The economic evaluation will:

- Estimate the intervention costs from a societal perspective

- Estimate changes in costs related to health and social care usage and volunteers' and participants' time caused by the intervention.

- Assess if the intervention leads to improved HRQOL and wellbeing

- Estimate the incremental cost-effectiveness at 18 months from a societal perspective, and if appropriate over a longer term (lifetime) horizon.

The costs related to the intervention will be collected using a diary completed by the volunteers during meeting times (See ACE Time and Travel Diary). Participants will report any health and social care resource use during the past 6 months in the baseline questionnaire, and in the 6, 12 and 18 month follow up questionnaires. A simple diary based on the relevant questions in the Participant CRF (Page 23-) will be given to participants at the baseline assessment for recording resource use between assessments to increase the accuracy of resource use data collected at follow-up. The resource use will be combined with the Unit Costs of Health and Social Care and with NHS reference costs (71). Any prescribed medication will be costed using the British National Formulary. Volunteer time spent attending the one-to-one meetings and the local initiatives will be recorded and this will be converted to costs using the value of leisure time. Costs will be reported transparently including how they are distributed across health and social care, and wider society.

Additional costs related to training the volunteers will be collected by RVS and other volunteer management partners and reported separately.

HRQOL and wellbeing effects will be measured at baseline and at 6, 12 and18 months using the EQ-5D-5L (4) and the ICECAP-O (5), respectively. Both QALYs and Capability will be measured for the participants and volunteers. The responses to these questionnaires will be combined with the respective tariff scores to estimate the incremental QALY and wellbeing effects at 18 months, for the intervention versus the control arm.

Costs will then be combined with outcomes to form a cost-utility analysis (CEA) where the result will be expressed as a cost per QALY. In addition, a 'cost per capability' (CCapA) achieved will be estimated by combining the cost with improvements in wellbeing, measured using the ICECAP-O. All of the above analyses will be conducted as within trial-based economic evaluations and will therefore only use data collected over the 18-month period. The analysis will report results of the CEA and CCapA from a health and social care perspective, including costs related to health and social care and QALYs/Capabilities accruing to the participants. Then, the analysis will be broadened to take a societal perspective including societal costs and outcomes for both participants and volunteers. Missing data will be explored and imputed using the most appropriate imputation technique and sensitivity analysis will be conducted.

If the ACE intervention shows superiority in terms of improvements in mobility, we will conduct evidence synthesis and decision-analytic modelling to assess the lifetime cost-effectiveness of the intervention versus control, including consequences in terms of health and social care costs. Methods will follow best practice guidelines for decision-analytic modelling in health technology assessment (72).

Data collected via primary care

GPs will be asked to provide a summary of the biological sex, age, ethnicity and Index of Multiple Deprivation score or postcode of all patients receiving an ACE invitation to establish the representativeness of our study sample.

7.10 Data collected by peer volunteers

Peer volunteers will be asked to record the date and duration of each meeting with their participant, each telephone call, each attendance at an activity and the type of activity (See ACE Time and Travel Diary). A sample of approximately 30 volunteers will record their one-to-one meetings with participants for purposes of checking delivery fidelity.

7.11 End of trial

The Research Ethics Committee which gives a favourable opinion of the research will be notified of its conclusion, in writing, using the appropriate form within 90 days of the end of the study. A summary of the final research report will be submitted to the REC within 12 months of the end of the study.

A draft final report will be provided to NIHR within 14 days of the project end date following the NIHR guidance: www.journalslibrary.nihr.ac.uk/authors

This report will be sent by NIHR for external peer review and a revised report will be submitted within six weeks.

8 TRIAL INTERVENTION

The intervention arm will receive a 6-month active ageing programme using peer volunteers to deliver individually tailored and person-centred support to help inactive, less mobile older people to 'get out and about', improve their mobility, increase physical activity and confidence, and engage with their local community (29). ACE draws on the Process Model of Lifestyle Behaviour Change (PMLBC) and Self Determination Theory (36, 37), two overlapping and mutually compatible theoretical perspectives which provide the main principles and processes for supporting behaviour change in the proposed intervention.

The PMLBC was developed from a wide-ranging systematic review of evidence of components associated with success in interventions to change diet and/or physical activity (38) and it has been used in several lifestyle change interventions that have been subject to trial evaluations (39-40). It is an adaptation of the Health Action Process Approach model (41) and proposes that behaviour changes through a motivational phase, and a volitional phase (involving the phases of planning, action and maintenance), for which belief in ability to perform an activity (self-efficacy), perceptions of risk, and outcome expectancies are identified as primary mediators of change during the motivation phases. This theory has informed the phases of the ACE intervention. Self Determination Theory (SDT) is a leading theory of motivation in the field of physical activity promotion (42). SDT highlights the importance of three psychological needs which motivate people to initiate and sustain behaviour. These needs are universal and innate and include the need for competence (feeling capable and confident), autonomy (feeling in control of decisions /goals, having motivation that is intrinsic /self-generated), and relatedness (social engagement, social acceptance /approval of the behaviour, giving support to others). ACE aims to support the fulfilment of these needs by helping them to build competence and confidence and remove social barriers in their efforts to engage with community initiatives they choose to participate in. Improvement in these needs (and the accrual of positive physical, social and emotional benefits following engagement in activities), contributes to more active involvement within local communities and more daily activity. The ACE intervention therefore integrates support for the needs of competence, autonomy and relatedness at each of the Process Model of Lifestyle Behaviour stages.

Peer volunteers meet participants twice in one-to-one meetings supporting them to identify local activities of interest and address barriers to participation (Motivation stage: first 2 weeks). The particular relevance/benefits of activities that might improve lower limb physical function (i.e. those including a significant strength and balance component) will be discussed.

The volunteer-participant pair attend at least three local initiatives chosen by the participant (Action stage: month 1–3). We are collaborating with the Move it or Lose it exercise provider for older adults in all sites (see letter of support) to encourage participants to attend activities that specifically target lower limb physical function.

Weekly telephone support to continue attending local activities. At least two further joint visits are scheduled as support "tails off" (Maintenance stage: month 3–6).

Peer volunteers will attend a one-day training course developed, tested and further refined in the ACE feasibility study including: i) skills for developing and reinforcing motivation (person-centred counselling for supporting fundamental (SDT-related) needs; ii) how to identify local activity options and develop tailored plans based on individual needs /preferences; iii) the need to build lower limb function (strength and balance) and types of exercise /activity

associated with this; iv) solution-focused methods for avoiding /overcoming barriers and v) maintenance support techniques. Drawing on key principles of person-centred counselling (which is recommended by both SDT and the PMLBC), the training programme emphasizes that the ACE volunteer's role is to support the individual becoming autonomous and responsible for making decisions. The training course will be further refined during the first phase of the trial in consultation with the Royal Voluntary Service, ensuring that it aligns with the organisation's principles of training and supporting volunteers.

Assessment of intervention

We will include a range of the strategies outlined by the NIH Behaviour Change Consortium to assess and reinforce intervention training delivery fidelity (69). To maximise and monitor trial fidelity we will: (i) Recruit trainers with appropriate skills and experience, (ii) Develop an accessible, standardised (albeit flexible for individual tailoring) ACE intervention manual, (iii) Implement standardised ACE 'trainer training', (iv) Document any co-interventions in both the control and intervention groups (v) Monitor delivery fidelity by recording of consultation meetings for a sample of meetings with peer volunteers and applying a fidelity checklist. The checklist will include items to assess the quality and quantity of delivery of intervention processes that are part of the theory underpinning the ACE intervention, using a procedure for assessing clinical consultation skills developed by Dreyfus et al (70). This approach worked well in our NIHR-funded EARS, REACH-HF and REACT trials. We will also record facilitator-participant contact time (intervention dose) and relate this to outcomes.

9 SAFETY REPORTING

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH Good Clinical Practice will apply. The University of Birmingham standard operating procedure for reporting and responding to research related Adverse Events (AEs) will be adopted. All AEs will be examined by an independent medical advisor to see if they are related to the study intervention or measurement procedures. The ethics committee, the sponsor and the Trial Steering Committee or DMEC will be notified promptly (within 24 hours) of all related Serious Adverse Events (SAEs). All AE and SAE data will be passed to the Chief Investigator who will compile a 12-monthly report for the Trial Steering Committee. Adverse events will be recorded on a pro-forma at all follow-up data collection timepoints and further data may accrue through patient-reporting to research staff. If a participant does not attend two consecutive intervention sessions, they will be contacted by telephone and if the reason for non-attendance is an adverse event this will be recorded.

9.1 Recording and reporting of SAEs

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH Good Clinical Practice will apply. The University of Birmingham standard operating procedure for reporting research related Adverse Events (AEs) will be adopted.

9.2 Definitions

Adverse Event (AE) is any untoward medical occurrence, elective hospitalisation/surgery, unintended disease or injury or any untoward clinical signs in subjects, users or other persons **whether or not related to any research procedures or to the intervention.**

Non-serious adverse events which are not related to study procedures or to the intervention will **not** be reported in this study.

The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship. PIs or Research Assistants will assess the causal relationship between reported events and trial participation according to the standardised guidance given below:

Table 2 Causal relationship between reported events and trial participation	
Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. The event did not occur within a reasonable time after the study period). There is another reasonable explanation for the event (e.g. The participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. Because the event occurs within a reasonable time after the study period) However, the influence of other factors may have contributed to the event (e.g. The participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Seriousness

Any adverse event or adverse reaction will be regarded as serious if it:

i. results in death;

ii. is life threatening;

iii. requires non-elective hospitalisation, prolongation of existing hospitalisation or elective hospitalisation that may be related to taking part in the study;

iv. results in persistent or significant disability or incapacity

If the description of the event leading to an elective hospital admission suggests in any way that the cause might be related to taking part in ACE, this will be investigated using the normal SAE pathway. Therefore, an adverse event meeting any one of these criteria will be a **Serious Adverse Event (SAE).** In this study, only SAEs related to the study will be reported. All SAEs will be followed until resolution where possible or until the end of the data collection period. The CI will maintain a register of all reported serious adverse events.

Non-serious AEs will not be recorded or reported, regardless of relatedness.

All **SAEs** occurring from the time of **written informed consent until** 30 days post the final assessment will be recorded on the University of Birmingham report of serious

adverse event form (See Appendix 7) and sent to the CI **within 24 hours** of the research staff becoming aware of the event. SAE forms will also be shared with the Trial Medical Advisor.

For each **SAEs** the following information will be collected:

full case description

event duration (start and end dates, if applicable)

action taken

outcome

seriousness criteria

causality (i.e. relatedness to trial), in the opinion of the investigator

whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information will be sent to the CI as soon as it is available or at least within 24 hours of the information becoming available.

9.3 Reporting related and unexpected SAEs

Adverse events will be collected at the research measurement events at six and 18 months, via telephone at 12 months and via reports by peer volunteers. Volunteers will inform their manager/coordinator of any participant illness or injury. The manager/coordinator will inform the local PI/RA who will contact participants about the adverse events and complete a NRES report of serious adverse event form if required. This will be forwarded to the CI who will liaise with the Trial Medical Advisor to judge if there is any relationship to the study procedures.

The PI and CI will review the form and when happy with the content the CI will sign the form.

If the SAE is judged to have been, or likely to have been, related to the study the CI will send the following to chair of the DMEC who will decide if the ethics committee who gave favourable opinion and the Sponsor (Research Governance Office) need to be informed.

(i) A cover letter including the REC number.

(ii) The NRES report of serious adverse event form

(iii) A copy of the SAE form.

(d) The RA will file a copy of the form and cover letter in the site file. If there is no missing data and the event has been resolved the SAE form will also be filed in the site file.

Processing serious adverse event forms

On receipt of a completed SAE form, the CI will assign a unique SAE number and confirm receipt of the event to the reporting site. If complete information is unavailable at the time of reporting, all appropriate information relating to the SAE will be forwarded to the CI as soon as possible.

Summary reports listing all serious adverse events will be compiled by the CI and sent to the DMEC and the TSC on a quarterly basis.

9.4 Responsibilities

The Chief Investigator is responsible for:

Reporting details of all potentially related SAEs to the DMEC using the study specific SAE Form within 48 hours of becoming aware of the event.

Providing the follow up report (if required) to the DMEC.

Providing any further information that has been requested to the DMEC.

In conjunction with the study medical advisor reviewing the SAEs for seriousness, causality and expectedness; classifying the SAE related).

Reviewing and signing the NRES “Report of SAE Form”.

Sending the quarterly SAE reports to the DMEC and TSC.

The Principal Investigators are responsible for:

Completing (with the RA) the SAE form

Reviewing the SAE form with the CI.

The /Trial Steering Committee are responsible for:

Discussing all SAEs that have been received.

When required: giving consensus to a SAE classification (consensus reached when at least the Chair and 1 member have agreed).

TSC will periodically review safety data and liaise with the DMEC regarding safety issues.

Data Monitoring and Ethics Committee are responsible for:

Discussing all potentially related SAEs that have been received.

When required: giving consensus to a SAE classification (consensus reached when at least the Chair and 1 member have agreed.)

Deciding which SAEs need to be reported to the Sponsor and the ethics committee.

The DMEC will periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

The Research Assistants are responsible for:

Following up any reported SAEs.

Contacting any participants whose illness or injury has been reported to the local ACE volunteer management partner by a peer volunteer to discover if this is due to an SAE.

Scanning/typing and verifying the SAE on to the Study database and chasing missing information.

Filing all documentation in the site file.

Sponsor

Reviewing potentially related SAEs for relatedness

9.5 Notification of deaths

All deaths, including deaths deemed unrelated to the trial will be reported to the CI immediately.

9.6 The type and duration of the follow-up of subjects after adverse events.

Following up SAEs (where data is missing or event not resolved)

(a) Where there is missing data/queries or the event is not yet confirmed as resolved, the RA will manage the event/chase the data until the form is complete.

(b) RA will update the database with all new information received.

(c) When the SAE form is complete the RA will file the SAE form in the site file.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The ACE trial will recruit a total of 515 participants across four study sites[3].

Effect Size: The primary aim is to assess the long-term (18 month) effect of a peer volunteering/ physical activity intervention on changes in Short Physical Performance Battery (SPPB) scores.

A difference of 0.5 points in SPPB score has been defined as a minimum clinically meaningful change (11,57). Based on data from the LIFE-P study, changes in SPPB of 1.2 points (with a difference between intervention and an active control group of 0.6 points) are feasible at 12 months in response to a community-based exercise intervention (84). Using baseline data from 777 adults with the same inclusion criteria as we propose for this study (from our REACT trial (31,52), the standard deviation for SPPB scores in this population is 1.56. This is identical to the standard deviation observed for SPPB scores in the US-based LIFE trial (SD = 1.6, N=1635). To detect a difference of 0.5 points in SPPB with 90% power and 5% significance, 206 participants are required per arm. Assuming 20% loss to follow-up at 18 months [based on 19% loss to follow-up at 24 months in our REACT study], the total sample size required is 515.
We will recruit a minimum of 130 volunteers (aged 55+ years) to support two intervention participants each (n=258). Since the cluster sizes in the intervention arm are minimal (less than two participants to each volunteer on average) any effect of clustering will be very small. Moreover, statistical power will be gained by including the baseline measure as a covariate in the primary analysis model. Therefore, we will not inflate the intervention arm to account for clustering. The analytic strategy will utilise a partial cluster model to investigate clustering in the intervention arm only in the first instance but if the ICC is zero we will revert to a general linear model. We have assumed a 20% drop out therefore the total sample size to randomise is 515 and the randomisation ratio will be 1:1 intervention to control.

[3] A fourth site (Bristol) site was added in September 2022 for the main trial

10.2 Planned recruitment rate

For details of the planned recruitment rate see Section 7.1.1 (Recruitment response rates)

10.3 Statistical analysis plan

All quantitative analyses will be conducted by the trial statistician from Cardiff Centre for Trials Research, who will be blinded to group allocation. The data will be analysed and reported in accordance with the CONSORT guidelines for randomised controlled trials (72). A detailed statistical analysis plan (SAP) will be signed off by the Chief Investigator, the Senior Statistician and Trial Statistician prior to database locking. As the study includes an internal pilot, an interim SAP will be prepared and signed prior to database locking for interim analysis (recruitment data only). Input from the TSC will sought for both the interim and main SAP.

10.3.1 Summary of baseline data and flow of patients

For details of data collected at baseline see Section 7.7 (Baseline data). The flow of participants through the study is illustrated by the Participant Flow Chart on Page 14. Baseline demographic checks for drop out bias will be performed using descriptive statistics of tabulated data for non-completers. Distributions of primary and all secondary outcomes will be examined and transformed where necessary.

10.3.2 Primary outcome analysis

The primary analysis will follow an intention to treat basis with participants remaining in their allocated group irrespective of intervention receipt and use the complete case population to compare SPPB scores at 18 months between the groups. A linear mixed model with the random effect applied just to the intervention arm will be used to account for clustering (73, 74). Covariates will include baseline SPPB, site and any prognostic variables that are substantially unbalanced at baseline.

A general linear mixed model will be used to investigate any possible clustering effects of peer volunteers using a partial cluster model accounting for intracluster correlation in the intervention arm only. The level of clustering is expected to be small (less than two participants to each volunteer on average) and any loss of statistical power will be ameliorated by the inclusion of baseline SPPB for the primary analysis.

10.3.3 Secondary outcome analysis

Secondary analysis of the primary outcome will utilise a linear mixed model incorporating the repeated measurements of SPPB at 6 months.

Secondary outcomes will be analysed using similar methods to the primary analysis depending on the distributional properties of the outcome and including any available interim timepoints in the partial cluster models. If the level of clustering is negligible general linear models will be used. Transformations towards linearity or generalised modelling will be used where appropriate if outcomes are categorical in nature.

Accelerometer data will be processed using custom R code (developed by the University of Exeter). Initial processing will include auto calibration, detection of abnormally high values and non-wear. Data will be averaged over one second epochs. Non-wear will be determined over 60 minute windows using 15 minute increments, and if two of the three axes have a data range <50 mg and a SD <13 mg non-wear will be recorded.[21] To be included in

analysis, participants will be required to have ≥16 hours per day and ≥7 days of wear. Total wear time will be accounted for in the analysis.

All active behavioural events will be extracted from the raw acceleration data. An active behavioural event is defined as the average acceleration throughout the event being greater than 40mg, a threshold which discriminates between purposeful and incidental movement. Twenty percent of the acceleration in any event is allowed to be under the 40mg threshold, to allow for brief pauses in an otherwise continuous event. Each event will then be characterised by its duration, volume of work done and average intensity. In addition, again using custom code, the number of sit-to-stand and stand-to-sit transitions each hour will be recorded along with the proportion of each hour spent active/inactive.

Qualitative analyses are described in the process evaluation section.

10.4 Subgroup analyses

Subgroup analyses are not powered for in this trial analysis but will be included and interpreted as exploratory only. Key pre-specified moderators of interest are area deprivation and ethnicity. Area deprivation is measured by the Index of Multiple Deprivation (IMD) and the Welsh equivalent (WIMD). If numbers allow, a group*moderator interaction term will be added to the primary analysis model to investigate area deprivation effects on treatment effectiveness by quintile. However, collapsing quintiles into fewer categories may be required. Similarly, for ethnicity the number of categories to examine will be determined by baseline frequencies. We will incorporate a further analysis to examine variations in outcome between groups with different levels of intervention exposure. This may take the form of a CACE (Complier Average Causal Effect) analysis. Full details will be written into the statistical analysis plan.

10.5 Adjusted analysis

Using appropriate descriptive statistics, we will assess any imbalance between the trial arms at baseline and describe the characteristics of participants. As the sample size is over 500 participants we are not expecting significant imbalance between groups.

10.6 Criteria for the premature termination of the trial

A full data analysis protocol including stopping criteria will be developed by the senior trial statistician (Dr Rebecca Playle) in collaboration with the Chief Investigator and agreed with the Project Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee prior to any data analysis.

10.7 Population

ACE participants will be sedentary, community living, older persons aged 65 and over, with functional limitations (i.e. who are at risk of major mobility limitations), but who are still ambulatory, i.e. can still walk. The West Midlands, Greater Manchester, South Wales and Bristol will be target areas for recruitment.

10.8 Procedure(s) to account for missing or spurious data

The mechanism of missingness for the primary outcome data will be explored and if determined to be either missing at random (MAR) or missing not at random (MNAR), as opposed to missing completely at random (MCAR), then the possible bias due to loss to

follow-up will be estimated via multiple imputation and associated sensitivity analyses for departures from MAR towards MNAR.

10.9 Other statistical considerations.

The Statistical analysis plan (SAP) will be specified as part of the publication of the trial protocol. Hence any changes to the SAP will be noted as amendments to the original protocol such that both the original intention the changes and the purpose of the changes will be clear. All changes will be approved by the Trial Steering Committee.

10.10 Economic evaluation

The economic evaluation will aim to:

- Estimate the incremental intervention costs from a societal perspective (including health and social care resource use and volunteer or participants time-use)

- Assess if the intervention leads to improved HRQOL and wellbeing when compared to the control arm

- Estimate the incremental cost-effectiveness at 18 months from a societal perspective, and if appropriate over a longer term (lifetime) horizon.

The costs related to the intervention will be collected using logbooks (See ACE Time and Travel Diary) completed by the participants and volunteers during meeting times. Participants will report any health and social care resource use at baseline, and then again at 6, 12 and 18 months follow up. The resource use will be combined with the Unit Costs of Health and Social Care and with NHS reference costs. Any prescribed medication will be costed using the British National Formulary. Both volunteer and participant time spent attending the one-to-one meetings and the local initiatives will be recorded and this will be converted to costs using the value of leisure time. Costs will be reported transparently including how they are distributed across health and social care, and wider society. Additional costs related to training the volunteers will be collected and reported separately.

HRQOL and wellbeing effects will be measured at baseline and at 6, 12 and 18 months using the EQ-5D-5L (4) and the ICECAP-O (5), respectively. Both QALYs and Capability will be measured for the participants and volunteers. The responses to these questionnaires will be combined with the respective tariff scores to estimate the incremental QALY and wellbeing effects at 18 months, for the intervention versus the control arm.

Costs will then be combined with outcomes to form a cost-utility analysis (CEA) where the result will be expressed as a cost per QALY. In addition, a ‘cost per capability’ (CCapA) achieved will be estimated by combining the cost with improvements in wellbeing, measured using the ICECAP-O. All of the above analyses will be conducted as within trial-based economic evaluations and will therefore only use data collected over the 18-month period. The analysis will report results of the CUA and CCapA from a health and social care perspective, including costs related to health and social care and QALYs/Capabilities accruing to the participants. Then, the analysis will be broadened to take a societal perspective including societal costs and outcomes for both participants and volunteers. Missing data will be explored and imputed using the most appropriate imputation technique and sensitivity analysis will be conducted. If the ACE intervention shows superiority in terms of improvements in mobility, we will conduct evidence synthesis and decision-analytic modelling to assess the lifetime cost-effectiveness of the intervention versus control,

including consequences in terms of health and social care costs. Methods will follow best practice guidelines for decision-analytic modelling in health technology assessment (75).

11 DATA HANDLING

11.1 Data collection tools and source document identification

Study Numbering

Each participant will be allocated a unique study number on consenting to the study and will be identified in all study-related documentation by their trial number.

Data Collection

Data will be recorded on study specific data collection forms, the Case Report Forms (CRFs), by the research team at each site. All persons authorised to collect and record trial data at each site will be listed on the trial site delegation logs, signed by the relevant PI. Source data will include all data recorded straight into the CRF, SPPB results, accelerometer data and grip strength data. Audio files and transcriptions of the data will be collected by the Process Evaluation Team, including the ACE PhD students, PIs and RAs.

11.2 Data handling and record keeping

Data handling

Completed CRFs will be checked and signed at the assessment sites by a member of the research team before being taken to the local research site. Data from the original CRF pages and SPPB result forms will be entered on to a password-protected website designed and maintained by the Cardiff Centre for Trials Research. All CRF pages and data collection forms will be tracked using the website. 10% of data will be double-entered and compared for discrepancies using a report available on the website. Discrepant data will be verified using the original paper data sheets and incorrect values will be updated. A discrepancy report will be provided to the chair of the DMEC who will decide if the level of discrepancy is acceptable or if further double entry is required. Audit trails will be used to record all changes to study data. Accelerometry data will be imported directly into the study database at each site.

Data Confidentiality

Local contact databases containing participant and volunteer names and addresses will be created at each site for the purpose of managing appointments, questionnaires, intervention delivery and process evaluation interviews. These will be stored at each site (one database per site) in a SQL server database, housed on a restricted access, secure server. Data in the databases will be backed up daily by IT services at the Universities of Birmingham, Manchester and Cardiff Metropolitan.

Investigators will ensure that the participants' anonymity is maintained on all paper documents through the use of Participant IDs and the storing of anonymised and identifiable study data separately. Identifiable study data will be stored in locked filing cabinets within a locked office. Access to this data will be restricted to members of the research team and will be overseen by the CI and Trial Manager. Copies of original study data retained at trial sites will be securely stored for the duration of the study prior to archiving. Audio recordings and

participant names and addresses will be stored on a restricted access, secure servers at the Universities of Birmingham, Manchester and Cardiff Metropolitan.

Data collected via the ACE screening form and the CRF will be entered, by members of the research team, onto one central data entry website developed by Cardiff Centre for Trials Research and will be encrypted using SSL. Data will be collected and stored in accordance with the General Data Protection Regulation 2018. Direct access to the trial data will be restricted to members of the research team, with access granted to the Sponsor on request. Access to the website will be overseen by the CI and Trial Manager.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institutions and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.4 Archiving

Following completion of trial data analysis, the Sponsor will be responsible for ensuring the study data and essential documentation is archived in a secure location in accordance with the sponsor's archiving procedures. No trial-related records will be destroyed unless or until the Sponsor gives authorisation to do so. The NIHR's Policy on Open Access will be adhered to and data supporting published findings will be made accessible. Data will be archived for 15 years following the end of the trial.

12 DATA MONITORING, AUDIT & INSPECTION

The PI or RA will check completed case report forms for missing data or obvious errors before the forms are sent for data entry. Data will be monitored for quality and completeness by each site and every effort will be made to recover data from incomplete forms where possible. The PIs will oversee data tracking and data entry and initiate processes to resolve data queries where necessary.

Participating sites will be required to permit a representative of the TSC or representative of the sponsor, to undertake study-related monitoring to ensure compliance with the approved study protocol and applicable SOPs, providing direct access to source data and documents as requested.

All study procedures will be conducted in compliance with the protocol and according to the principles of the International Conference on Harmonisation Good Clinical Practice (ICH GCP). Procedures specifically conducted by the CTR team (e.g. randomisation) will be conducted in compliance with CTR standard operating procedures (SOPs).

13 ETHICAL AND TRIAL ADMINISTRATION

13.1 Research Ethics Committee (REC) review & reports

The study protocol, informed consent form, participant information sheet and proposed recruitment materials will be submitted to an appropriate Research Ethics Committee (REC) for approval within two months of ACE project commencement.

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, Second edition (2005). The study will be supported by the UKCRC-registered Cardiff Centre for Trials Research (Registration Number 63), sponsored by the

University of Birmingham and approved by a recognised NHS REC and the HRA. The study will be adopted by the NIHR Clinical Research Network (CRN).

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP. Any amendments to the protocol will be submitted for REC approval as appropriate.

On request, the Chief/Principal Investigators will make available relevant trial-related documents for monitoring and audit by the Sponsor, the TSC and the relevant Research Ethics Committee.

Annual progress reports will also be submitted to the REC using the recognised National Research Ethics Service (NRES) template. An end-of-trial declaration will be provided to the REC within 90 days of trial conclusion or within 15 days of trial termination in the event the trial is prematurely terminated.

The Sponsor will draw up an agreement with the Cardiff CTR regarding study responsibilities, which will be agreed and signed by the authorised representatives of each party.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study.

All correspondence with the REC will be retained in the Trial Site File.

The Chief Investigator will produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

The ACE draft trial protocol was reviewed by the TMG, the TSC and the DMEC prior to submission. Their comments were incorporated into the final version of the protocol. The ACE grant application was given favourable review by the NIHR panel.

13.3 Public and Patient Involvement

This study was co-created with service users and service providers at each stage of the development, feasibility testing and refinement of our ACE peer volunteering, active ageing community programme. In 2009, we established an advisory group of older people participating in local community initiatives (26). They participated in focus groups and decision-making workshops, as part of a network of academic experts, service users, service providers, charities and local government policy makers. These workshops identified three ‘best bet’ community-based activity programmes for promoting active ageing. They ranked different possible intervention models based on their likely value for money, feasibility, attention to maintenance of physical activity, and potential to meet older people’s needs. ACE was one of the three ‘best bet’ interventions (one of the others being the NIHR-funded REACT study). ACE was subsequently tested for feasibility and acceptability in a study funded by the Medical Research Council. The extensive PPI work in the refinement of the ACE programme has been described in detail in a dedicated peer-reviewed publication (76).

This evaluation and resulting recommendations, further feedback received by the Royal Voluntary Service and organised stakeholder group meetings which took place at each of the proposed ACE sites (West Midlands, South Wales, Greater Manchester) led to further refinement of the ACE programme into its current form for testing in a definitive trial.

Each site will set up an Advisory Group (AG) who will meet twice in Year 1 then annually. Three of the participants from our REACT study (Birmingham site) have already agreed to serve on the ACE Advisory Group (West Midlands site). They reviewed the Stage 1 and Stage 2 applications, recommended changes in the lay abstract and raised concerns about the measurement frequency and its potential for participant burden. In response to their feedback, we further refined the lay abstract to ensure good readability levels and we removed one face-to-face assessment point (12 months) as it was deemed unnecessary and burdensome for the participants. Two of our Manchester PPI reps chosen specifically to represent the relevant areas of Manchester and populations we will target, reviewed key participant documentation, giving advice on wording and appearance. The documentation was also reviewed by an experienced member of the Greater Manchester Applied Research Collaboration PPIE group. In Cardiff the materials were reviewed by n=3 older people representatives. All three were over 65 years. They were opportunistically recruited through a neighbourhood social media account. Our extensive PPI work has therefore fed directly into the design of the ACE programme which has received a great deal of support by a range of service providers, primary care and public health leads at each site. This increases the likelihood of successful implementation of the ACE programme, if it is found to be effective. Nationally, the support of Royal Voluntary Service (co-applicant in this application and provider of the ACE programme), Public Health England, Sport England and Age UK will also increase the potential of ACE potential for scalability and long-term impact.

The Trial Management Group (TMG) and the Trial Steering Committee (TSC) will include a member from each of the three local Advisory Groups who will then report back to the Advisory Group in their area. Advisory Groups will also review study processes and materials.

Members of our PPI group will be active partners in the dissemination process, advising on presentation and content of messages, routes to maximise reach to older adults and as co-presenters of our findings.

In order to evaluate the PPI input to the trial all PPI meetings will be recorded and minutes focusing on actions for improvements to the study will be prepared and shared.

We will organise brief PPI group zoom meetings at the end of year 1, year 2 and after study completion. We will treat this as action research and will address PPI feedback throughout the trial.

ACE co-applicants, Professor Stathi, Professor Crone and Dr Hawley-Hague will lead the training of 10 citizen scientists at each site. The citizen scientists will directly contribute to assessment, dissemination and impact activities during the ACE trial, and increase their own scientific understanding. This training programme will be one of the outputs of the ACE trial. We have developed a comprehensive systems mapping process which will include meetings with a range of stakeholders, citizen scientists, peer volunteers and older adults at each site at the beginning of the study and post-intervention. The ACE participants and peer volunteers will help present the study findings and will share their experiences of taking part in the ACE study at the three half-day dissemination events and at local and national events.

In accordance with the Involve guidance (www.involve.org.uk/) all service users and citizen scientists will be reimbursed for their involvement.

13.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol will not be allowed, e.g. subjects who do not meet the eligibility criteria or restrictions specified in the trial protocol will not be enrolled.

Any accidental protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator immediately.

Deviations from the protocol which occur frequently will be addressed immediately and if appropriate will be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree – the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase in accordance with the sponsor’s serious breaches reporting procedures. Guidance for reporting potential serious breaches of good clinical practice / trial protocol in clinical research sponsored by the University of Birmingham will be adhered to (See Appendix 8).

13.7 Data protection and patient confidentiality

Participant names and addresses will be collected for the purpose of managing questionnaires, intervention delivery and process evaluation interviews. Investigators will ensure that the participants’ anonymity is maintained on all other documents.

Local contact databases containing participant names and addresses will be created at each site for the purpose of managing appointments, questionnaires, intervention delivery and process evaluation interviews. These will be stored at each site (one database per site) in a SQL server database, housed on a restricted access, secure server. Data in the databases will be backed up daily by IT services at the Universities of Birmingham, Manchester and Cardiff Metropolitan.

Investigators will ensure that the participants’ anonymity is maintained on all paper documents through the use of Participant IDs and the storing of anonymised and identifiable study data separately. Identifiable study data will be stored in locked filing cabinets within a locked office. Access to this data will be restricted to members of the research team and will be overseen by the CI and Trial Manager. Copies of original study data retained at trial sites will be securely stored for the duration of the study prior to archiving. Audio recordings and participant names and addresses will be stored on a restricted access, secure servers at the Universities of Birmingham, Manchester and Cardiff Metropolitan.

Data collected via the ACE screening form and the CRF will be entered, by members of the research team, onto one central data entry website developed by Cardiff Centre for Trials Research and will be encrypted using SSL. Data will be collected and stored in accordance

with the General Data Protection Regulation 2018. Direct access to the trial data will be restricted to members of the research team, with access granted to the Sponsor on request. Access to the website will be overseen by the CI and Trial Manager.

Access to data

Access to the data will be strictly limited to members of the research team; however participating sites will permit a representative of the Cardiff CTR or representative of the sponsor, to undertake study-related monitoring to ensure compliance with the approved study protocol and applicable SOPs, providing direct access to source data and documents as requested.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator, site PIs and TMG members have no competing interests that might influence trial design, conduct, or reporting. Any that occur during the period of the trial will be noted to the TMG meetings and minuted. All co-applicants will sign a competing interest form at the beginning of the trial and at the end of the trial unless there is a need for an updated form during the trial.

13.9 Indemnity

The University of Birmingham has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University.

The University of Birmingham holds Professional Indemnity insurance to cover the legal liability of the University as Research Sponsor and/or as the employer of staff engaged in the research, for harm to participants arising from the design of the research, where the research protocol was designed by the University.

The University of Birmingham's insurance policies do not provide an indemnity to collaborators. As Research Sponsor we will ensure as far as reasonably practicable at the outset of the study that collaborators hold appropriate legal liability insurance.

The University of Birmingham has not made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

Evidence of insurance cover is available to download at intranet.birmingham.ac.uk/finance/insurance/liability

13.10 Amendments

Any amendments to the protocol will be submitted for REC approval as appropriate. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study.

13.12 Access to the final trial dataset

Prior to the first report/publication being made (the publication(s) reporting the results of the research as a whole), the collaborators cannot report on the results (those collected at their site and from the project as a whole) without first gaining consent from the CI. Thereafter the collaborators can independently publish the results subject to provisions of confidentiality.

The NIHR's Policy on Open Access will be adhered to and data supporting published findings will be made accessible.

Subject to data protection provision (data to be anonymised), the Secretary of State for Health has the right to have access and use data collected and used for the purpose of the project.

14. KEY OUTPUTS AND DISSEMINATION POLICY

14.1 Key outputs

1. An ACE delivery toolkit (including the manualised ACE programme and training course, an economic 'business case' and guidance on setting up and running the ACE programme). This will be developed with in-kind support by RVS and Sport England and hosted on the RVS website while being adopted by RVS and delivered nationwide;

2. A citizen science training programme;

3. Research capacity through two funded PhD studentships (in-kind support by Universities of Birmingham and Manchester) and a base of 30 trained and experienced citizen scientists;

4. A detailed systems mapping analysis protocol which will provide a useful framework for research and community programmes interested in using this approach in similar populations; (v) Academic papers and conference presentations (see below);

5. A recruitment report providing a rigorous account of the different strategies used to recruit older people with functional limitations.

14.2 Dissemination plan

Dissemination will commence from project initiation with the creation of a project website and will be planned according to NIHR guidance (https://www.nihr.ac.uk/funding-and-support/documents/fundingfor-research-studies/managemy-study/How-to-disseminate-your-research/dissemination-guidance.pdf).

1. Our ACE/Active Ageing website (https://www.activeageingresearch.org/about-ace) will be updated to include a section for publishing ACE news and progress. All research presentations and reports will be uploaded and made available for public comments;

2. A one day launch event will be co-hosted with the partner organisations inviting all key audiences and organisations involved in recruitment;

3. Showcase events will be delivered at all sites after completion of ACE to present the findings and celebrate successful lifestyle change stories as told by peer volunteers and participants themselves

4. ACE Infographics will be developed to provide an appealing and accessible, graphical description of the study;

5. A Pop-up ACE stand will be created to increase visibility at events, conferences, exhibitions;

6. At least 5 papers will be submitted for publication in peer reviewed journals, including 3 open access journals (e.g., International Journal of Behaviour Nutrition & Physical Activity), subject-specific journals (e.g., Journal of the American Geriatrics Society) and medical journals (e.g., Annals of Behavioural Medicine, NIHR PHR Journal);

7. Presentations will be delivered at at least two academic conferences directly concerned with ageing and physical activity (e.g. UK Society of Behavioural Medicine and International Society of Physical Activity and Health); at the Public Health England annual meeting; and at third sector organisation annual meetings: RVS, Sport England and Age UK (with in-kind support via fee-waiving from these organisations); and events organised by local partner organisations:

8. Three half-day events to announce the study results to our extensive network of stakeholders and identify actions for scalability and sustainability;

9. A brief promotional piece to be mailed to all UK Directors of Public Health and other key decision makers in voluntary sector organisations promoting the use of the delivery toolkit;

10. Newsletters will be distributed to participants at the end of each project year and to academic and non-academic partners;

11. Social media (including Universities' Twitter accounts and Facebook pages) and local media (newspapers, magazines) will be used to publish news briefings prepared by the Universities' press offices.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The International Committee of Medical Journal Editors' authorship criteria (detailed below) will be used as the basis for granting authorship of the ACE final trial report.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A detailed publication plan with proposed authorship will be developed and agreed by the TMG during the first year of the Trial.

Professional writers will not be used in the development of the ACE trial reports

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16. APPENDICES

Appendix 1 ACE Intervention group programme

Appendix 2 Control group programme

Appendix 3 Trial Project Management Plan

Appendix 4 ACE Logic Model

Appendix 5 Press release

Appendix 6 Publicity materials

Appendix 7 University of Birmingham report of serious adverse event form

Appendix 8 Guidance for potentially serious breaches of GCP

Appendix 1 ACE Intervention programme

Objectives	ACE aims to support the fulfilment of three important psychological needs (1). These needs are universal and innate and include the need for competence (feeling capable and confident), autonomy (feeling in control of decisions /goals, having motivation that is intrinsic /self-generated), and relatedness (social engagement, social acceptance /approval of the behaviour, giving support to others). ACE aims to motivate people to initiate and sustain behaviour.by helping them to build competence and confidence and remove social barriers in their efforts to engage with community initiatives they choose to participate in. Improvement in these needs (and the accrual of positive physical, social and emotional benefits following engagement in activities), contributes to more active involvement within local communities and more daily activity. The 6-month programme aims to “kick start” participants’ personal physical fitness and give them the skills and motivation they need to stay fit and active and engaged with their community throughout this phase of their lives (retirement /older age). Participants should be encouraged to see the programme as a stepping-stone to ongoing health, rather than a time-limited programme that lasts 6 months
Mechanisms of Change	ACE draws on the Process Model of Lifestyle Behaviour Change (PMLBC) and Self Determination Theory (1, 2), two overlapping and mutually compatible theoretical perspectives which provide the main principles and processes for supporting behaviour change in the intervention. The PMLBC was developed from a wide-ranging systematic review of evidence of components associated with success in interventions to change diet and/or physical activity (4) and it has been used in several lifestyle change interventions that have been subject to trial evaluations (5). It is an adaptation of the Health Action Process Approach model (6) and proposes that behaviour changes through a motivational phase, and a volitional phase (involving the phases of planning, action and maintenance), for which belief in ability to perform an activity (self-efficacy), perceptions of risk, and outcome expectancies are identified as primary mediators of change during the motivation phases. This theory has informed the phases of the ACE intervention. Self Determination Theory (SDT) is a leading theory of motivation in the field of physical activity promotion (1). SDT highlights the importance of three psychological needs which motivate people to initiate and sustain behaviour. These needs are universal and innate and include the need for competence (feeling capable and confident), autonomy (feeling in control of decisions /goals, having motivation that is intrinsic /self-generated), and relatedness (social engagement, social acceptance /approval of the behaviour, giving support to others). ACE aims to support the fulfilment of these needs by helping them to build competence and confidence and remove social barriers in their efforts to engage with community initiatives they choose to participate in. Improvement in these needs (and the accrual of positive physical, social and emotional benefits following engagement in activities), contributes to more active involvement within local communities and more daily activity. The ACE intervention therefore integrates support for the needs of competence, autonomy and relatedness at each of the Process Model of Lifestyle Behaviour stages. We have identified a realist synthesis of theoretical frameworks of community health volunteering (3). This synthesis provides a useful conceptualisation of community level factors affecting volunteer performance which will help to inform both our systems mapping and our process evaluation. Furthermore, this realist synthesis suggests individual-level

	theoretical processes that may sustain the motivation and engagement of the volunteers, including self-efficacy, positive feedback and fulfilment of the volunteer's needs and expectations. This theoretical perspective is consistent with qualitative feedback we obtained from volunteers in the ACE feasibility study (76). These ideas help to expand our theoretical perspective and will be examined further in the process evaluation. The ideas on volunteer engagement will also be incorporated in the training and supervision of the peer volunteers.
Peer Volunteers	Peer volunteers will attend a one-day training course developed, tested and further refined in the ACE feasibility study including: i) skills for developing and reinforcing motivation (person-centred counselling for supporting fundamental (SDT-related) needs; ii) how to identify local activity options and develop tailored plans based on individual needs /preferences; iii) the need to build lower limb function (strength and balance) and types of exercise /activity associated with this; iv) solution-focused methods for avoiding /overcoming barriers and v) maintenance support techniques. Drawing on key principles of person-centred counselling (which is recommended by both SDT and the PMLBC), the training programme emphasizes that the ACE volunteer's role is to support the individual becoming autonomous and responsible for making decisions. The training course will be further refined during the first phase of the trial in consultation with the Royal Voluntary Service, ensuring that it aligns with the organisation's principles of training and supporting volunteers.
Sessions (Intervention group only)	
Intervention group only	**Weeks 1-2** Weekly one-to-one meetings (participant and peer volunteer) **Weeks 3-12** The participant/peer volunteer pair attend at least three local initiatives together **Weeks 13-26** At least two further joint visits to activities plus telephone support
	Content Peer volunteers meet participants twice in one-to-one meetings supporting them to identify local activities of interest and address barriers to participation (Motivation stage: first 2 weeks). The particular relevance /benefits of activities that might improve lower limb physical function (i.e. those including a significant strength and balance component) will be discussed. The volunteer-participant pair attend at least three local initiatives chosen by the participant (Action stage: month 1–3). We are collaborating with the Move it or Lose it exercise provider for older adults in all sites to encourage participants to attend activities that specifically target lower limb physical function. Weekly telephone support to continue attending local activities. At least two further joint visits are scheduled as support "tails off" (Maintenance stage: month 3–6).

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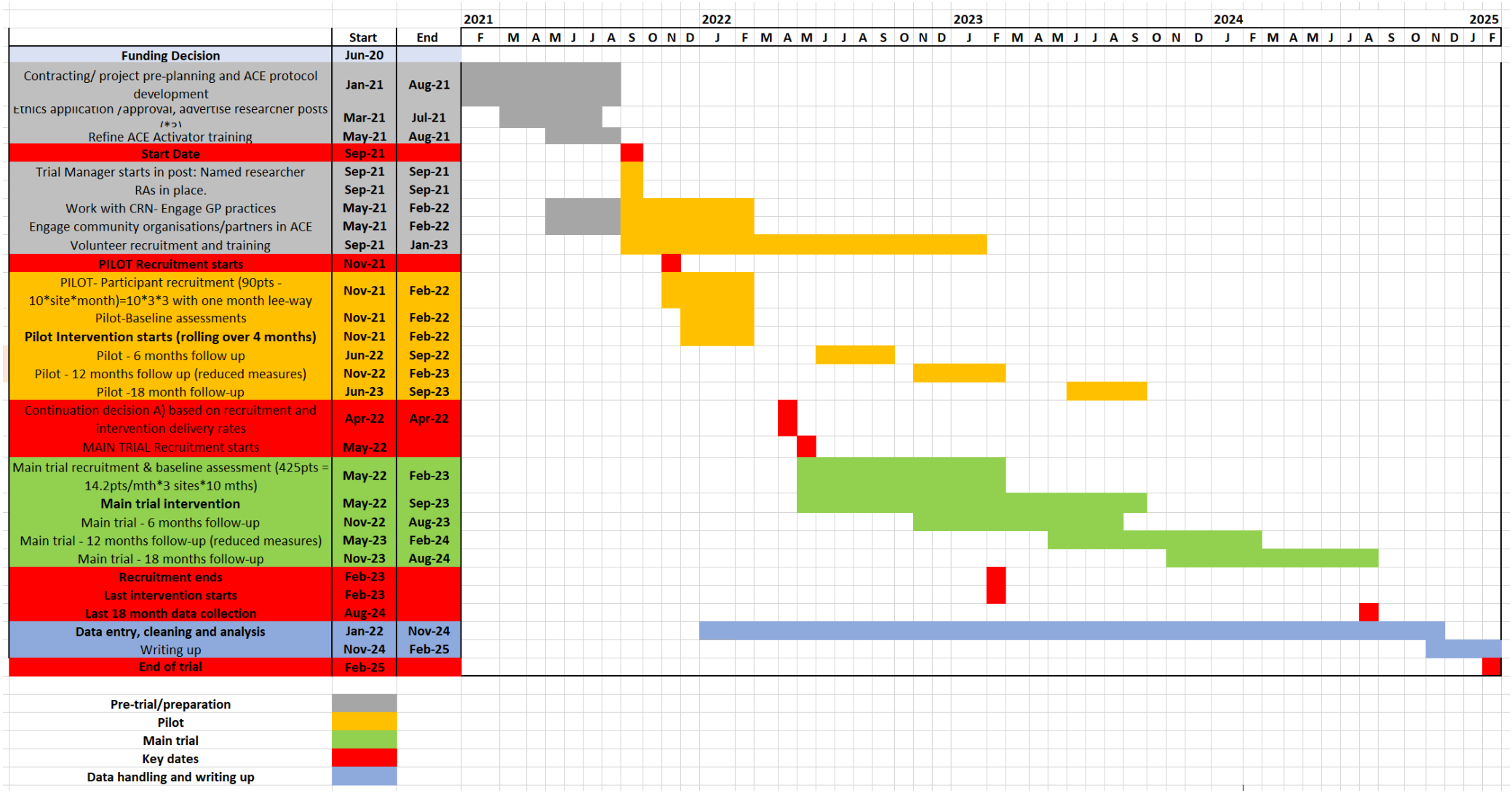
Appendix 2 Control group programme

Objectives	The REACT control group will receive information relating to healthy ageing and attend two events incorporating health education presentations 1-2 months after the baseline and 12 month assessment sessions. The goal is to provide a positive experience and promoting engagement and retention. The presentation is designed to educate participants about the benefits of healthy eating and other health-related behaviours.
Mechanisms of Change	Self-Determination Theory Three psychological needs motivate people to initiate and sustain behaviour. These needs are said to be universal and innate and include the need for competence (feeling capable and confident), autonomy (feeling in control), and psychological relatedness (feeling part of something bigger). In the case of the control group, we aim to promote the behaviours of engaging with ACE data collection events at baseline 6, 12 (telephone only) and 18 months, and also to increase Control Group participants' awareness of various health topics.
Key Competencies	Health Education booklets: all health education booklets will adhere to the principles of Plain English, with both the language and layout designed to optimise readability, and will be tailored to meet the needs of literacy- and ethnically-diverse older adults. Health education session: Select members of the research team and from our local delivery partner organisations will be trained in the key competencies required to deliver session in accordance with Self-Determination Theory: Active Listening ("Attending") and Empathic Communication Asking Open-Ended Questions Paraphrasing Giving and Receiving Feedback Handling Emotions Summarizing Problem-Solving Group Leadership Skills Dealing with the Difficult/Challenging Participant

Appendix 3 Trial Project Management Plan



Appendix 4 ACE Logic Model

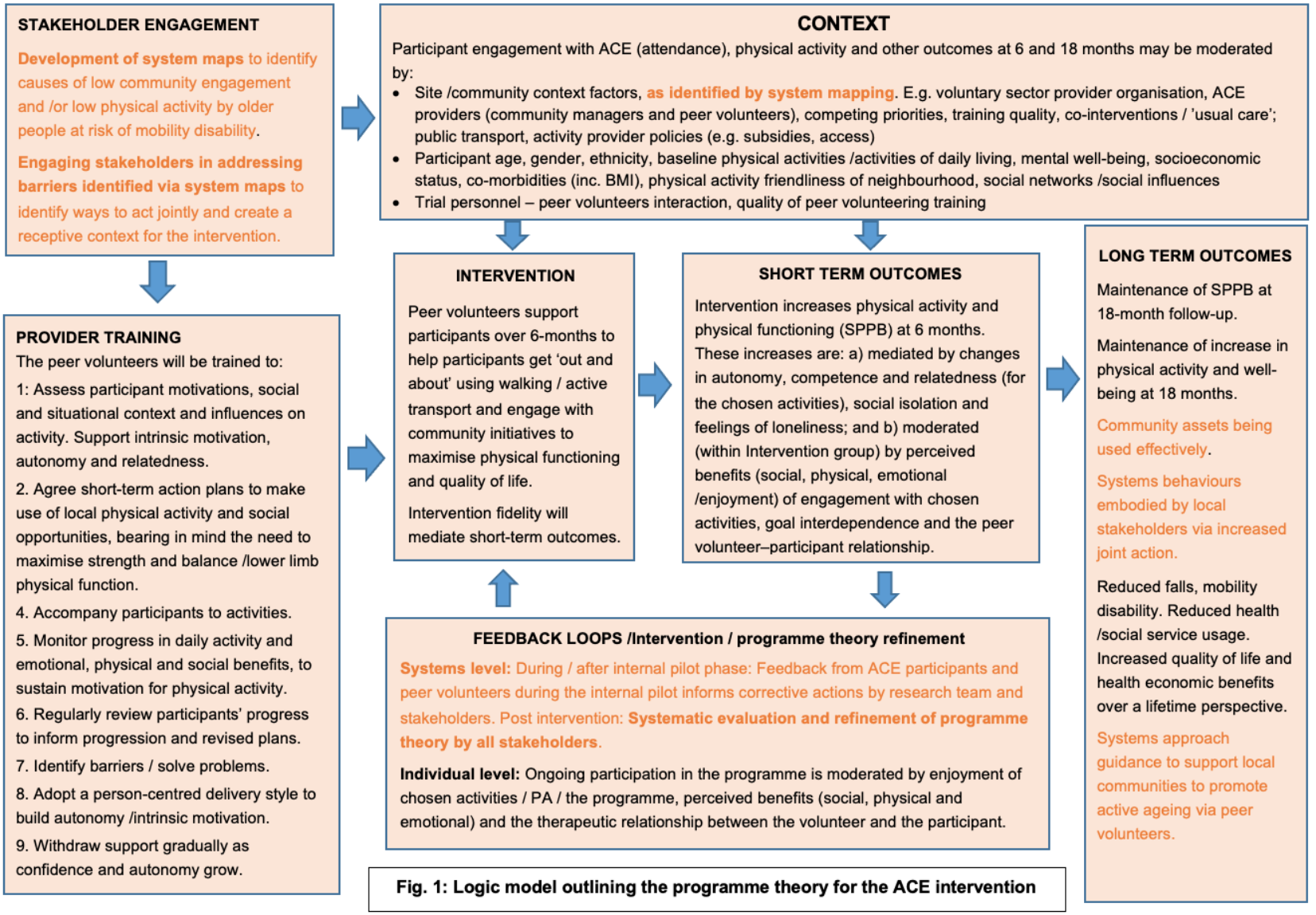


Fig. 1: Logic model outlining the programme theory for the ACE intervention

Appendix 5 Press release

University of (local site) News Release

Embargo: TBC

Could a volunteer 'buddy' scheme be key in supporting older adults to get out and about more and stay healthy and active?

Researchers at the University of (local site) are launching a new study aimed at maintaining mobility in older adults. They are looking for 200 people over 65 years old in (local site) to take part. The study is designed for older adults who are starting to find everyday activities such as getting up from a chair, climbing the stairs and walking to the shops harder than it used to be (*https://www.activeageingresearch.org/about-ace*). If that sounds like you, a family member or friend, they would love you to get in touch.

As people get older, everyday activities, like walking and climbing the stairs, can become more difficult. The Covid-19 pandemic has made this issue even worse as many people haven't been able to get out and about as much as normal and so have become less fit and active. This 'deconditioning' can affect people's ability to live independently and make life a lot less enjoyable. However, there is lots of research showing that it is possible to stop this physical decline, even reverse it, by just keeping active. But we know this is a lot easier said than done.

Called **ACE** (Active, Connected and Engaged), the new volunteer buddy scheme is going to pair people 65 and above with a volunteer, themselves 55+ years. The pair will choose some local activities to try out together over a three-month period. It could be an exercise class, dancing, a choir or just a local walk. Over the next three months, the volunteer will support the participant to continue these activities independently, through phone calls and further face-to-face visits.

The ACE study will see whether getting out and about with a volunteer, and so being more active, can help older people maintain their mobility and independence for longer.

The ACE team will follow up with people who are taking part after 6, 12 and 18 months, to find out how successfully they have been in maintaining their new levels of activity allowing them to live independently and to get the most out of life.

Project lead Professor Afroditi Stathi, explains: "Not being physically active makes losing your mobility in later life much more likely. An older person who remains fit and active is more likely to stay healthy – both mentally and physically – and to enjoy their independence and a higher quality of life for longer. We think using volunteers to support people to get out and about and become more active, could have really positive results."

"I would encourage anyone who might be interested in taking part in or volunteering for ACE, to contact us on Tel XXXX or email XXXX or visit our website (*https://www.activeageingresearch.org/about-ace*). We can explain a bit more about ACE and help people decide if they would like to take part".

ACE volunteers will be managed through local volunteer management partners such as the Royal Voluntary Service (RVS), a UK-wide volunteering organisation. The study will take place in four areas: West Midlands, Greater Manchester, Wales and Bristol. If the programme is shown to be effective, RVS will roll it out nationally.

ACE is funded by the National Institute for Health Research (NIHR) and researchers in the University's School of (local site), are testing ACE in a study which starts in September 2021.

ENDS

For media enquiries please contact (Local University Press Office, tel: / email:)

Notes to editor:

Insert local University boilerplate

Appendix 6 Publicity materials (Poster)

ACE ACT CONNECT ENGAGE

Are you starting to have difficulty with everyday activities like climbing stairs, carrying the shopping or getting up from the sofa?

Did you know that it is possible to stop this physical decline, even reverse it, by just keeping active?

ACE is a study which is looking at ways we can support people who are 65 years and older to stay mobile and maintain their independence for longer. The way we plan to do this is by matching older adults with volunteers who are themselves over 55 years old so they can get out and about and enjoy taking part in local activities together.

If you are **65 years or older** and interested in taking part, please contact us.

Email ACE@xxx.ac.uk or call the research team at the University of xxx on: **XXXX XXX XXXX**

Local University logo

NHS National Institute for Health Research

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Active, Connected, Engaged (ACE) XXXX XXX XXXX ACE@xxx.ac.uk

Appendix 7 University of Birmingham report of serious adverse event form

Serious Adverse Event Form

E-mail: researchgovernance@contacts.bham.ac.uk

A serious adverse event (SAE) is any medical occurrence that results in death, is life-threatening, requires or prolongs unplanned hospitalisation, causes persistent or significant disability, results in congenital abnormalities or represents potentially serious harm to research patients and others.

Please complete this form using black ink and BLOCK capitals. Options should be selected by placing a cross (X) in the appropriate box.

Once complete please scan and send electronically to the above email [University of Birmingham] as soon as possible, ideally within 24 hours, of the event taking place. If you have any questions related to this form or reporting please ring the Research Governance Office on: 0121 4147618.

Study Details

Study Name	ACE (ACTIVE, CONNECTED, ENGAGED)	**MREC:**	**TBC**
ISCRTN:	**TBC**	**UKCRN:**	TBC

Details of Chief Investigator (CI)

Name	AFRODITI STATHI
Address	UNIVERSITY OF BIRMINGHAM, EDGBASTON, BIRMINGHAM B15 2TT
Telephone	0121 415 8389
Email	A.STATHI@BHAM.AC.UK

Section 1 – Participant & Site Details

Study Name: **ACE**

1. **Patient ID:**
2. **Patient Initials:**
3. **Date of Birth:**
4. **Site Name:**

Section 2 – Serious Adverse Event (SAE) Details

5. SAE Onset Date: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

6. Seriousness Criteria (check all that apply):

- ☐ Resulted in Death
- ☐ Life Threatening
- ☐ Persistent / Significant Disability / Incapacity
- ☐ Congenital anomaly / Birth defect
- ☐ Hospitalisation / Prolongation of Hospitalisation
- ☐ Other medically important condition

Admission date ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

Discharge date ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

7. Relationship to research procedures:

☐ None ☐ Possible ☐ Probable ☐ Definite

If related to Research Procedures (possibly, probably or definitely), expectedness:

☐ Expected ☐ Unexpected

8. Severity: ☐ Mild ☐ Moderate ☐ Severe

9. Outcome: ☐ Recovered ☐ Recovered with sequelae (Date of recovery ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)) ☐ Recovering ☐ Not Recovered ☐ Unknown ☐ Fatal

Section 3 – Serious Adverse Event Narrative

10. Please provide a description of the SAE and follow-up infomration as required:

Include presenting signs and symptoms, course of events, treatments for the event and outcomes. Continue on separate sheet if necessary and attach relevant medical notes (remembering to sign and date).

11. Has the event resolved: ☐ Yes ☐ No ☐ On going

12. Date resolved: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

Section 4 – Form Details

13. Type of report: ☐ Initial ☐ Follow-up

13. Date SAE form completed: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

14. Signature of reporting person:

16. Please Print Name:

17. Please Print Position:

For [University] use ONLY

1. Date received: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y)

2. Date entered on database: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y) **3. Entered by:** ☐☐

4. Name of reviewer: (CI or Medical Monitor)

5. Date of review: ☐☐ ☐☐ ☐☐☐☐

6. Type of event: SAE ☐ SAR ☐ SUSAR ☐

7. Further action required: NO ☐ YES ☐

8. Comments:

Reviewer, Signature: **Date:**

CI, Signature: **Date:**

Section 5 – Acknowledgement of receipt by main REC (South West – Frenchay)

The [ ] Research Ethics Committee acknowledges receipt of the above.

Signed:	
Name:	
Position on REC:	
Date:	

Signed original to be sent back to Chief Investigator (or other person submitting report).

Appendix 8 Guidance for potentially serious breaches of GCP

University of Birmingham

Standard Operating Procedure: Deviations and Serious Breach Reporting

Purpose:

This Standard Operating Procedures (SOP) describes the procedures to manage deviations relating to the trial or study specific protocol and plans, Good Clinical Practice (GCP) or any other Good Practice guidelines (GxP), any applicable regulatory requirements and/or the University of Birmingham (UoB) Quality Management System (QMS). The SOP also describes the procedure for serious breach reporting.

Scope:

This SOP applies to clinical research where the UoB is the Sponsor, or takes on Sponsor responsibilities for deviations and serious breach reporting. This includes where clinical research is required by the Health Research Authority (HRA) to report serious breaches to the Research Ethics Committee (REC). This SOP also applies to clinical research approved by UoB REC that are required to follow UoB Principles of GCP.

Where clinical research is (co-) sponsored by another institution, this procedure should be followed as far as possible, and in line with the contractual agreement between the UoB and the other institution.

Implementation plan:

This SOP will be implemented directly after the effective date.

Stakeholders:

Note that where the UoB takes on the Sponsor responsibility for deviations and serious breach reporting, the UoB will delegate the majority of these duties to the CI and/or to a Clinical Trials Unit, who may delegate these duties further to their trials team(s). All delegation of duties will be documented using either the CI declaration and/or the Clinical Trials Task Delegation Log; see *UoB-CLN-CTM-QCD-002 Clinical Trial Task Delegation Log*.

- ☐ Principal Investigator (PI) / UoB Lead / Manager (or delegate); these terms are used to define the role that has the responsibility for oversight of deviations and serious breach reporting. This may include the Chief Investigator (CI) for clinical trials, or the supervisor for postgraduate research students.
- ☐ Clinical research staff member; refers to any person who has a role in clinical research either sponsored by UoB or located at UoB premises, either directly or indirectly. This may include those working with honorary contracts or not directly employed by the UoB but who contribute to research either sponsored and/or located at UoB.Head of Research Governance and Integrity (or delegate)
- ☐ Research Governance and Ethics Team (RG&ET)
- ☐ Chair of Clinical Trials Oversight Committee (CTOC; or delegate)
- ☐ UKCRC registered UoB Clinical Trials Units (UoB CTU)
- ☐ Advanced Therapies Facility (ATF); the ATF will take responsibility for non-conformance and deviation reporting, except where a serious breach occurs. The study/trial management team will be responsible for serious breach reporting as detailed in the ATF study/trial-specific communication plan.

Background and Rationale:

For the purposes of this SOP the terms 'clinical trials' or 'trial' will cover Clinical Trials of Investigational Medicinal Products (CTIMPs), other interventional trials (e.g. surgical trials, device trials and non-CTIMP trials, and any other projects deemed to be 'interventional' by the Sponsor), and clinical studies.

Deviations

A deviation is a departure from a framework such as an agreed process, principle, procedure or protocol which may, or may not, be intentional. A deviation is also known as a non-compliance, breach or violation. Deviations include major or critical findings and serious breaches of GCP or the trial protocol. Deviations can be either planned or detected e.g. during on-site monitoring. For consistency, the term 'deviation' is used within UoB to mean all of the above.

Deviations from agreed processes or practice can affect the safety of participants and/or quality of the output of that process. The *UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research* states that research is designed, reviewed, managed and undertaken in a way that ensure integrity, quality and transparency, and it is expected that those conducting trials have systems and procedures in place to manage deviations.

Serious Breaches

A serious breach is defined as a breach which is likely to affect to a significant degree:

☐ The safety or physical or mental integrity of the participants of the trial; or

☐ The scientific value of the trial.

For CTIMPs, the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 require that the sponsor of a clinical trial shall notify the licensing authority and REC in writing within 7 days of becoming aware of any serious breach of:

☐ The conditions and principles of GCP in connection with that trial; or

☐ The protocol relating to that trial, as amended from time to time.

Examples of what constitutes as serious breach can be found in Appendix II of the MHRA's Guidance for the notification of Serious Breaches of GCP or the trial protocol (PDF - 211 KB).

For non-CTIMPs and clinical studies, the HRA SOPs for RECs defines the requirements for reporting of serious breaches to the REC, utilising the process defined by the MHRA above.

Procedure:

Significant research related events or serious breaches may be identified by clinical research staff through various means, including monitoring, audits, team meetings, feedback from site staff or participants. Members of the research team may also receive allegations of deviations from the protocol, the principles of GCP (or applicable GxP requirements), or legal requirements that may affect the safety of participants or the integrity of the trial. This information may be received directly or indirectly from whistle blowers or complaints from within or outside of UoB.

All deviations follow the procedures described below in the section 'Deviations'. For (suspected) serious breaches, these are additionally addressed in the section below marked 'Serious breach reporting outside the UoB CTUs' and 'Serious breach reporting in the UoB CTUs' respectively.

Information regarding deviations from the protocol, GxP or legal requirements and possible serious breach reports should be treated as confidential to relevant UoB staff and site. All relevant documentation should be kept as part of the Trial Master File (TMF) and relevant site/lab file including any emails. Details of the ensuing investigation will be made available to staff at UoB and site on a need to know basis. All individuals interviewed during the investigation will be asked to respect this confidentiality.

Deviations

Deviation administration

1. The PI / UoB Lead / Manager (or delegate) will set up a process for deviation management, which will include:

   A written procedure detailing deviation reporting, review, investigation and escalation (where appropriate) who has been delegated what duties from the PI / UoB Lead / Manager within this procedure. See *UoB-DSB-QCD-001 Deviation Management*.

Tools to capture deviations (where applicable); see *UoB-DSB-QCD-002 Deviation Form* for an example template.

2. Where appropriate, the PI / UoB Lead / Manager (or delegate) will set up a process to ensure any Corrective Action and Preventative Action (CAPA) plans arising from deviations are executed within the set timeframe.
3. For clinical research in the laboratory, the PI / UoB Lead / Manager (or delegate) will follow the procedures as described in *UoB-CRL-SOP-005 Reportable Issues*.
4. The PI / UoB Lead / Manager (or delegate) will ensure clinical research staff members are appropriately trained on the process for deviation management; see also *UoB-CRG-SOP-003 Training*.

Deviation management

5. The clinical research staff member identifying a deviation, will follow the local procedure for deviation reporting, ensuring the deviation is documented (e.g., in e-mails, a note to file or a deviation form, see *UoB-DSB-QCD-002 Deviation Form*).
6. The PI / UoB Lead / Manager (or delegate) will review the deviation, assessing whether the deviation could be categorised as a serious breach and is likely to affect participant safety, participant confidentiality and/or data integrity, and whether it is relating to a significant GxP non-compliance and/or a failure to comply with applicable regulations. For serious breaches also refer to the serious breach reporting section below.

   The recording of the deviation will include the impact of the deviation as well as any corrective action(s) required and the preventative action(s) required to prevent reoccurrence (CAPA plan, where appropriate).

   The assessment of the impact may require communication with the relevant trial team or other stakeholders involved.
7. The PI / UoB Lead / Manager (or delegate) will identify if the deviation is recurring and whether the deviations suggest a systematic quality assurance failure.
8. The PI / UoB Lead / Manager (no delegation allowed) will assess the impact of the deviation and where appropriate approve the appropriate CAPA plan, and provide oversight that the agreed CAPA plan has been completed.
9. For serious breaches, the PI / UoB Lead / Manager (or delegate) will adhere to all applicable regulations and reporting requirements.
10. The PI / UoB Lead / Manager (or delegate) will file evidence of the deviation in the relevant TMF and site/lab file as applicable.

Serious breach reporting outside the UoB CTUs

Initial receipt of information

11. Immediately upon identification of an event that is a deviation of the protocol, the principles of GCP (or applicable GxP requirements), or legal requirements and that may affect participant safety, participant confidentiality and/or the integrity of the trial, the PI / UoB Lead / Manager (or delegate) will liaise with a member of the RG&ET (for contact details please see References below), providing as much detail as possible, for example:

    Location where the deviation occurred

    Name of the PI at the site where the deviation occurred (if applicable)

    Full title of the clinical trial

    Name of the CI for the trial

    Whether the trial is sponsored or co-sponsored by UoB

    Internal UoB ERN/RG Number, REC and/or EudraCT references (where applicable)

    An explanation of how the deviation was identified

    Details of the deviation

    Details of any initial corrective action

    Assessment of the impact the deviation will have on the participants and/or the scientific integrity of the trial

12. Where the events identified raise the likelihood of any sort of legal action, disciplinary procedure or other dispute, the PI / UoB Lead / Manager (or delegate) will inform Legal Services and follow any instructions with respect to investigation.
13. The RG&ET will liaise with the Legal Services as required, providing an initial report of the breach and requesting their advice on the matter.
14. The RG&ET will request further information from the reporter, and may ask the reporter to include Legal Services in their correspondence.

Review of suspected serious breaches, reporting of serious breaches and follow-up

15. The Head of Research Governance and Integrity (or delegate) will discuss if the deviation is a suspected serious breach that requires further referral. Where this is not the case, the PI / UoB Lead / Manager (or delegate) will work with RG&ET to develop a CAPA plan, and the PI / UoB Lead / Manager (or delegate) will ensure the relevant members of the trials team are informed accordingly.
16. Where it has been decided that the deviation is a suspected serious breach that requires further referral: the Head of Research Governance and Integrity (or delegate) will provide information about the suspected serious breach to the Chair of the CTOC. Note that Legal Services may stay involved in the communication loop as per their request.
17. The Chair of the CTOC (or delegate) will convene a Serious Breach Referral Panel and then refer the deviation to them to determine whether it constitutes a serious breach under the regulations within 5 days of initial receipt of the information and consulting colleagues as necessary. The format of the meeting will be determined based on the timeline.
18. The Serious Breach Referral Panel will enquire after more information as necessary, and determine if:

    The deviation is a serious breach and should be reported as such; or

    The deviation is not a serious breach under the regulations.
19. For CTIMPs - In the event that the Serious Breach Referral Panel is unable to agree on whether to classify the event as a Serious Breach, or in the eventuality that there are not enough members of the panel available to make a decision, the Head of Research Governance and Integrity (or delegate) will liaise directly with the MHRA for advice.
20. If the event is determined to be a serious breach the Head of Research Governance and Integrity (or delegate) or the PI / UoB Lead / Manager (or delegate) will complete a Serious Breach Report, in liaison where a site is involved with the site's PI and Research and Development (R&D) department. This will include feedback from the Chair of CTOC as appropriate. The report will be submit to the REC, and for CTIMPs, with the Competent Authority, within 7 days of becoming aware of the breach. It is expected that the 7-day timescale commences at the moment there is a strong suspicion of a serious breach.

    For CTIMPs in the UK, the Notification of Serious Breaches of GCP or the Trial Protocol Form (Word - 205 KB) should be used and a copy provided to the REC.
21. The Chair of CTOC (or delegate) will monitor the CAPA plan through CTOC meetings.
22. The PI / UoB Lead / Manager (or delegate) and the Head of Research Governance and Integrity (or delegate) will ensure any relevant essential documents are filed appropriately in the TMF and Sponsor File respectively.

Serious breach reporting in the UoB CTUs

23. In the UKCRC-registered UoB CTUs, the UoB CTUs will be responsible for investigating, reporting and following up suspected serious breaches within the CTU:

    The UoB CTUs will send a copy of the Serious Breach Report to the RGT and CRCT at the time the Serious Breach Report is submitted to the REC and Competent Authority if applicable. The RGT and CRCT will review the Serious Breach Report to ensure the proposed CAPA plan is appropriate, and liaise directly with the UoB CTU where further actions are required.

    The UoB CTUs will inform the CTOC of any reported serious breaches in 6 monthly reports to CTOC.

List of expected outputs:

☐ Evidence of a documented process for the identification, recording and review of deviations and escalation, where appropriate

- ☐ Evidence of the process for recording and reviewing being followed
- ☐ Evidence that reporting timelines have been followed, and that appropriate staff have been contacted
- ☐ Evidence of the serious breach process described above being followed, where applicable

Related documents:

- ☐ UoB-CLN-CTM-QCD-002 Clinical Trials Task Delegation Log
- ☐ UoB-CRG-SOP-003 Training
- ☐ UoB-CRL-SOP-005 Reportable Issues
- ☐ UoB-DSB-QCD-001 Deviation Management
- ☐ UoB-DSB-QCD-002 Deviation Form
- ☐ UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research

Note the UoB QMS documents can be found on the Clinical Research Compliance Team website. The RGT can be contacted via researchgovernance@contacts.bham.ac.uk and the CRCT can be contacted via crct@contacts.bham.ac.uk for a copy of their internal Work Instructions.

References and Frameworks:

- ☐ Contact details for serious breach reporting:

  CRCT: crct@contacts.bham.ac.uk

  RG&ET: phone; +44 (0)121 415 8011 (Ext. 58011), email; researchgovernance@contacts.bham.ac.uk

  Legal Services: https://intranet.birmingham.ac.uk/legal-services/who-we-are.aspx

  MHRA: https://www.gov.uk/guidance/contact-mhra
- ☐ HRA SOPs for RECs: https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/
- ☐ Medicines for Human Use (Clinical Trials) Amendment Regulations 2006: http://www.legislation.gov.uk/uksi/2006/1928/contents/made
- ☐ MHRA Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/705179/Guidance_for_the_Notification_of_Serious_Breaches_of_GCP_or_the_Trial_Protocol_Version_5.1__04-05-2018_.pdf
- ☐ Notification of Serious Breach of Good Clinical Practice or Trial Protocol Form: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/779472/Notification_of_serious_breaches_of_GCP_or_the_trial_protocol_form__V6__18-02-19_.odt

Abbreviations and Definitions:

Term	Description
Chief Investigator (CI)	The person who takes overall responsibility for the design, conduct and reporting of a study if it is at one site; or if the study involves researchers at more than one site, the person who takes primary responsibility for the design, conduct and reporting of the study, whether or not that person is an investigator at any particular site. Note that for CTIMPs the Chief Investigator must be an authorised health professional.
Clinical Research Compliance Team (CRCT)	The Clinical Research Compliance Team (CRCT) forms part of the College of Medical and Dental Sciences Research and Knowledge Transfer Office, and is responsible for developing an infrastructure for researchers involved in clinical studies. In addition, the team takes on responsibilities relating to Sponsor oversight such as audits and quality checks.
Clinical trial	**For clinical trials of an Investigational Medicinal Product(s):** Any investigation in human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more Investigational Medicinal Product(s), and/or to identify any adverse reactions to one or more Investigational Medicinal Product(s) and/or to study absorption, distribution, metabolism and excretion of one or more Investigational Medicinal Product(s) with the object of ascertaining its (their) safety and/or efficacy. See also 'Clinical Trial of an Investigational Medicinal Product (CTIMP)'. **For all other clinical trials:** Prospective biomedical research on human participants that are conducted to allow safety (or more specifically, information about adverse drug reactions and adverse effects of other treatments) and efficacy data to be collected for health interventions. Examples include devices, surgery and radiotherapy trials.
Clinical Trials Oversight Committee (CTOC)	The Clinical Trials Oversight Committee (CTOC) is responsible for overseeing the activities undertaken by UoB in its role as a Sponsor, co-sponsor, host institution or partner with other organisations for clinical research. This includes Clinical Trials of Investigational Medicinal Products (CTIMPs), trials conducted through the UoB's Clinical Trials Units (CTUs), any clinical research where UoB Ethics Committee has stipulated that the research must be conducted to the Principles of GCP. The CTOC reports to the Pro-Vice Chancellor for Research & Knowledge Transfer through the UoB Research Governance, Ethics and Integrity Committee (RGEIC).
Clinical Trials Unit (CTU)	A specialist unit which have been set up with a specific remit to design, conduct, analyse and publish clinical trials and other well-designed studies. The University of Birmingham has two UKCRC fully registered Clinical Trials Units; the Cancer Research UK Clinical Trials Unit (CRCTU) and the Birmingham Clinical Trials Unit (BCTU).
CTIMP	A Clinical Trial of an Investigational Medicinal Product. See also 'clinical trial'.
CTU managed study/trial	A study/trial for which the overall study management or the majority of study/trial management duties has been delegated to the CTU on behalf of a Sponsor. Examples include all or most of the activities of Registration, Site Initiation, Monitoring, IMP supply, Pharmacovigilance, Data Management and Statistical Analysis.

Term	Description
Medicines and Healthcare Products Regulatory Agency (MHRA)	The UK government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe.
Principal Investigator	An individual responsible for the conduct of the research at a research site. There should be one PI for each research site. In the case of a single-site research project, the chief investigator and the PI will normally be the same person.
Quality Management System (QMS)	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
RG&ET	Research Governance and Ethics Team, consisting of the Research Governance Team and the Research Ethics Team.

See also the Glossary of Terms.

APPENDIX A

Purpose:

A deviation is a departure from a framework such as an agreed process, principle, procedure or protocol which may, or may not, be intentional. Any deviation (planned or otherwise) must be documented, for example; in emails, a note to file or a deviation form.

This document contains a template which can be used to create a deviation form in order to document deviations if it is required, and instructions for how to complete this form. For clinical research in the laboratory, see the procedures as described in *UoB-CRL-SOP-005 Reportable Issues*.

Instructions:

Remove this first instruction page.

Update header and footer

Documenting a deviation

The person who discovered the deviation will complete Section 1 of the 'Deviation Form' with a detailed description of the deviation, any immediate actions taken, their name and the date on which the event occurred. See also *UoB-DSB-QCD-001 Deviation Management* for defining the project-specific procedure to deviation reporting.

The person responsible for reviewing the deviation will sign and date in Section 1 of the 'Deviation Form'.

Where the instance constitutes a serious breach (or is suspected) the procedures for serious breach reporting outlined in *UoB-DSB-SOP-001 Deviations and Serious Breach Reporting* must be followed.

The person performing the root cause analysis will completed Section 2 of the 'Deviation Form'.

Where appropriate, document any proposed corrective actions and preventive actions (CAPA) in Section 3 of the 'Deviation Form' with details to the person(s) responsible for the action and the agreed completion date.

Consideration should also been given to the root cause of the deviation. There are a range of methods/tools that can be used to perform a root cause analysis, each of which are appropriate for different situations. For example: 'The 5 Ways', 'Fishbone Diagram', or 'Eight Disciplines of Problem Solving (8D)'.

If applicable, follow up action points from the CAPA plan by completing Section 4 of the 'Deviation Form'. If the action point has not been completed at the point of checking, provide an update in the comment section and perform another check at a later date.

File completed versions of this form and all related correspondence in the relevant Trial Master File and site/lab file as applicable.

Related documents:

UoB-DSB-SOP-001 Deviations and Serious Breach Reporting

UoB-DSB-QCD-001 Deviation Management

UoB-CRL-SOP-005 Reportable Issues

Note the UoB QMS documents can be found on the Clinical Research Compliance Team webpages. The RGT can be contacted via researchgovernance@contacts.bham.ac.uk and the CRCT can be contacted via crct@contacts.bham.ac.uk for a copy of their internal Work Instructions.

Purpose:

Where deviations (planned or otherwise) arise, robust and documented processes must be in place to enable the impact of the deviation to be assessed and the appropriate actions are executed within the set timeframe.

This document provides a tool for detailing the process for deviation management. For clinical research in the laboratory, see the procedures as described in *UoB-CRL-SOP-005 Reportable Issues*.

Instructions:

Remove this first instruction page.

Update trial/study ID in header.

Update footer.

Defining process for deviation reporting

Document the procedure for deviation reporting, review, investigation and escalation (where appropriate).
See *UoB-DSB-QCD-002 Deviation Form* for an example template to capture deviations.

Record to whom the deviation should be reported. Consider whether this should be:

The Sponsor (or their representative)

The Chief Investigator and/or

The co-ordinating centre.

Select an appropriate staff member to perform a root cause analysis to identify the factors that contributed to the deviation (if applicable).

File this written procedure in the relevant Trial Master File and site/lab file as applicable.

Related documents:

UoB-DSB-SOP-001 Deviations and Serious Breach Reporting

UoB-DSB-QCD-002 Deviation Form

UoB-CRL-SOP-005 Reportable Issues

Note the UoB QMS documents can be found on the Clinical Research Compliance Team webpages. The RGT can be contacted via researchgovernance@contacts.bham.ac.uk and the CRCT can be contacted via crct@contacts.bham.ac.uk for a copy of their internal Work Instructions.

Deviation reporting procedure:

Provide details on how deviations are reported (e.g., email/CRFs/deviation form), who these deviations should be reported to (contact details provided below) and where to file evidence of the deviation.

See also *UoB-DSB-SOP-001 Deviations and Serious Breach Reporting*.

Staff member(s) to review deviation:

Name	Role	Contact details:

Staff member(s) to perform root cause analysis (where appropriate):

Name	Role	Contact details:

Staff member(s) to agree CAPA plans (where appropriate):

Name	Role	Contact details:

Section 1. Deviation Details

Date deviation noted:		DD / MON / YYYY			
Date that deviation occurred:		DD / MON / YYYY			
☐ **Relating to a UoB QMS document:**					
☐ **Relating to a trial**		☐ **Relating to a study**			
Trial/study identifier (if applicable):					
Site (if applicable):					
Participant identifier (if applicable):		ID:	Initials:	DoB:	
Planned deviation:	☐	**Detected deviation:**	☐		
Further details of the deviation and immediate action taken:					
Deviation details:					
Immediate action taken:					
Person(s) notified:		**Role(s):**			
Does the deviation fulfil one or more of the following criteria:					
Likely to affect patient safety, patient confidentiality and/or data integrity?	☐ Yes	☐ No	If yes to any, consider if the deviation meets the criteria of a Serious Breach and process accordingly, see *UoB-DSB-SOP-001 Deviations and Serious Breach Reporting*.		
Relating to significant GxP non-compliance?	☐ Yes	☐ No			
Shows failure to comply with regulations?	☐ Yes	☐ No			
Is a recurring deviation and deviations are minor departures of GxP suggesting a systematic quality assurance failure?	☐ Yes	☐ No			

Reported by:		**Signature:**	DD / MON / YYYY
Job title/Role on trial:			
Reviewed by:		**Signature:**	DD / MON / YYYY
Job title/Role on trial:			

Section 2. CAPA Plan

Corrective Actions			
Action no.	**Action identified**	**Person(s) responsible**	**Agreed completion date**

Preventive Actions			
Action no.	**Action identified**	**Person(s) responsible**	**Agreed completion date**

	CAPA Identified by:	CAPA Agreed by:
Name:		
Function:		
Date:	DD / MON / YYYY	DD / MON / YYYY
Signature:		

Section 3. Follow Up

CAPA Plan Follow Up

Action no.	Checked by	Date	Complete?	Comment
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	
			☐ Yes	