Study of gait rehabilitation in patients with recently diagnosed rheumatoid arthritis: the Gait Rehabilitation in Early Arthritis Trial [GREAT]

Protocol version: 2.0

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AMENDMENT NUMBER	DATE	PROTOCOL VERSION
AM02	07th Sept 2020	V2.0

This study will be performed according to the UK Frame Work for Health and Social Care Research and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
AHP	Allied Health Professional
VA	Versus Arthritis
CRF	Case Report Form
CTU	Clinical Trials Unit
CSRI	Client Service Receipt Inventory
CTIMP	Clinical Trial of an Investigational Medicinal Product
DAS-28	Disease Activity Score for RA (28 joint count)
IDMC	Independent Data Monitoring Committee
DMARD	Disease modifying anti rheumatic drug
EARS	Exercise adherence rating scale
EOSI	Events of special interest
EU-FP7	European Union Seventh Framework Programme
FFIdis	Foot function index disability subscale
GCP	Good clinical practice
GGC	Greater Glasgow and Clyde
GI	Guyatt Index
HAQ	Health Assessment Questionnaire
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPA	Interpretative Phenomenological Approach
IRT	Item Response Theory
KCH	Kings College Hospital

MCID	Minimal Clinical Important Difference
MITI	Motivational Interviewing Treatment Integrity Scale
MRC	Medical Research Council
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROADles	Recent-onset arthritis disability questionnaire lower extremity subscale
RPE	Rating of perceived exertion
SAE	Serious adverse event
SAS	Statistical Analysis Software
SF36	Short Form 36
SOP	Standard Operating Procedures
SRM	Standardised Response Mean
SUSARS	Serious unexpected serious adverse reaction
TMG	Trial management group
TSC	Trial steering committee
UKCRC	United Kingdom Clinical Research Collaboration

1. Contacts

1.1 Trial Management Group (TMG)

The trial will be coordinated by the Trial Management Group (TMG). The TMG will consist of the chief investigator, other co-applicants, project manager and representatives from the Glasgow Caledonian University, Robertson Centre for Biostatistics and NHS GG&C. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

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1.2 Trial Steering committee

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will:

- Agree the trial protocol and substantial protocol amendments
- Provide advice to the investigators on all aspects of the trial
- Include an independent chairperson, at least 2 other independent members.

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the TSC who will advise the sponsor and study team. The TSC will meet at the start of the study, and 6 monthly or as required thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

Name	Role	Telephone	Email
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1.3 Independent Data Monitoring Committee

An IDMC will be established to include a minimum of two independent experts (covering the domains of Rheumatology and Physiotherapy or Podiatry; one of the academic clinicians will act as chair) and an independent biostatistician. The Robertson Centre for Biostatistics will liaise with the committee and ensure that the committee is provided with adequate information about study progress and results.

The IDMC will have a formal charter; this will outline the responsibilities of the IDMC members, Robertson Centre for Biostatistics and the Sponsor. Responsibilities include:

- To protect the safety of patients recruited to the trial.
- Advising the TSC and Sponsor if it is safe and appropriate to continue with the study.
- Examining information provided by the Robertson Centre for Biostatistics on study recruitment, adverse events and outcomes and providing recommendations for the Project Office to forward to the TSC, ethics committees, regulatory bodies and study sponsor.

- The IDMC will receive unblinded reports on study safety data and on study progress and outcomes. The IDMC may recommend to the TSC and sponsor that the study should stop prematurely because of concerns about patient safety. The IDMC will meet approximately every six months. The IDMC will take into account all results and the consistency and biological plausibility of the findings when making recommendations.

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1. 4 Sponsor

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1.5 Funding body

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) scheme (15/165/04).

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2. Study Summary

Trial Title	Study of gait rehabilitation in patients with early rheumatoid arthritis: the Gait Rehabilitation in Early Arthritis Trial
Internal ref. no. (or short title)	GREAT
Study Registration Identifier	ISRCTN 14277030
Trial Design	Multicentre randomised controlled trial (RCT) design where patients are individually randomised on a 1:1 allocation ratio stratified by recruitment site to account for variations between sites. Participants and clinicians will not be blinded and participants will complete self-reported questionnaires..
Trial Participants	Patients with a Rheumatoid Arthritis Diagnosis within the last 2 years and have or are currently experiencing foot pain.
Planned Sample Size	Internal pilot sample size: n=76 Main trial sample size: n=550 (including n=76 from internal pilot) Sample size may be revised following pilot phase
Treatment duration	12 weeks. Gait Rehabilitation Programme will be delivered over 12 weeks following the baseline appointment.
Follow up duration	12 Months from Baseline visit
Planned Trial Period	Approximately 40 months;
Investigational Intervention	Treatment sessions over 12 weeks to guide participants for undertaking a gait rehabilitation programme comprised of functional walking tasks. Intervention dose and progression will be individualised, and will include a supported home-based gait rehabilitation programme and an embedded psychological component to promote positive sustainable change.

Objectives		**Outcome Measures**
Primary	Does the addition of a specifically designed gait rehabilitation programme	Foot Function Index Subscale

	to standard care improve lower limb function in early rheumatoid arthritis patients?	Participant completed Questionnaire

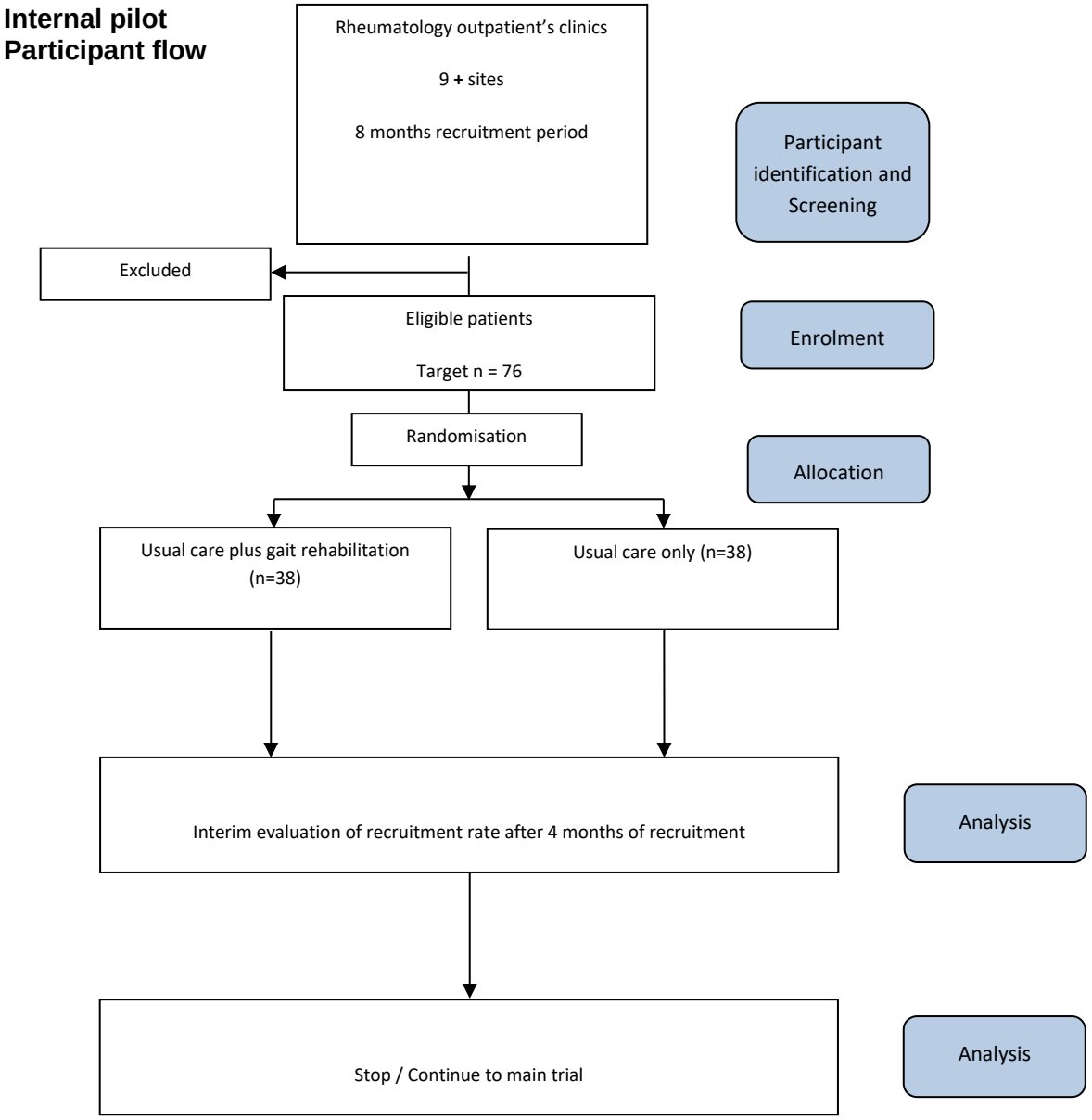
Objectives for Pilot phase

1. To revise and check the sample size calculation for the main trial using the feasibility study sample variance on the selected primary outcome.
2. To determine the feasibility of recruitment and retention of patients with early RA, including willingness to be randomised.

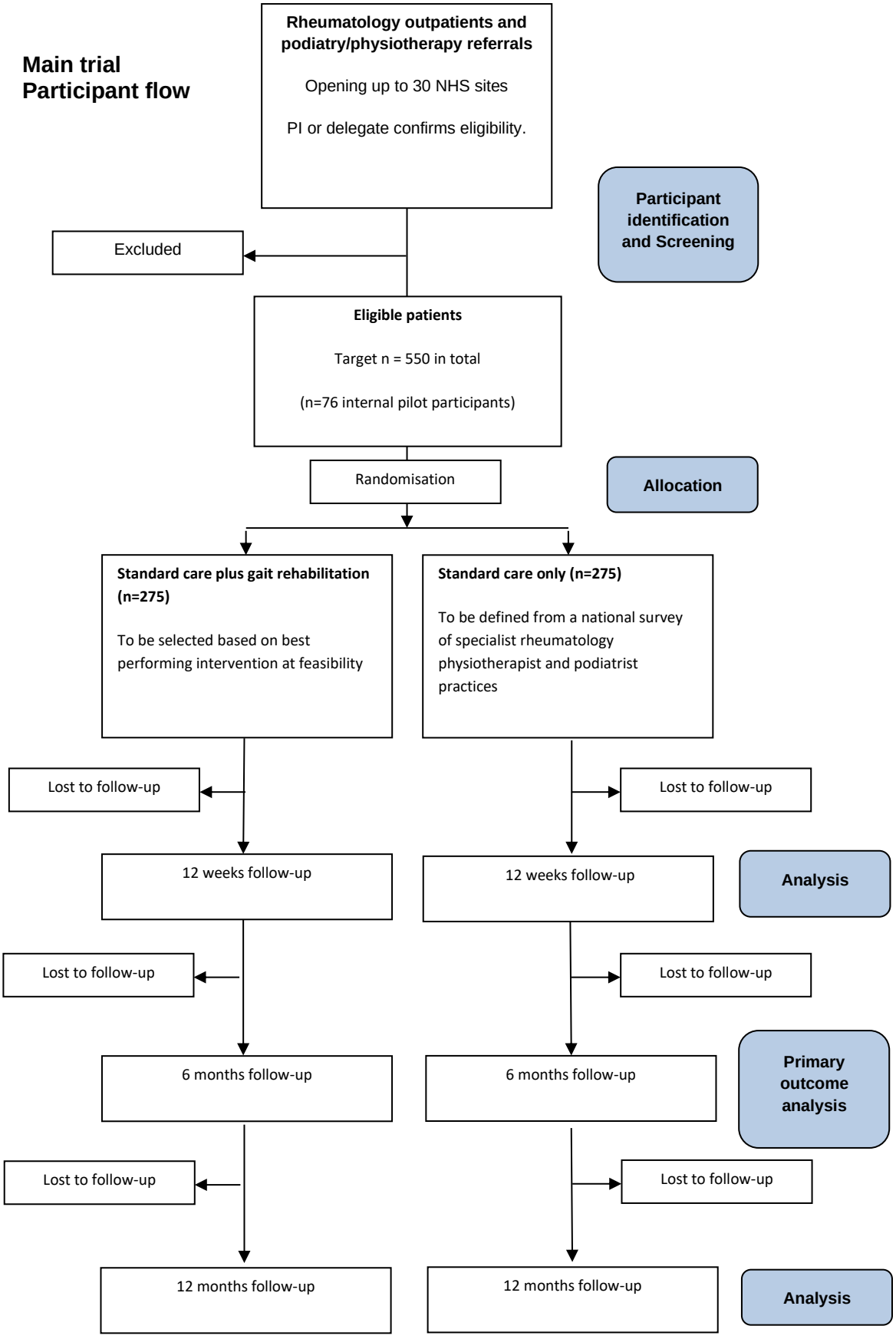
Objectives for Main Trial phase

1. To compare the clinical effectiveness of the addition of a new gait rehabilitation intervention to usual care versus usual care alone on lower limb function
2. To compare the cost-effectiveness of the addition of a new gait rehabilitation intervention to usual care versus usual care alone
3. To evaluate participants' view and experiences of the usual care and gait rehabilitation interventions.
4. To evaluate intervention therapists' (physiotherapists and podiatrists) view and experiences of the usual care and gait rehabilitation interventions and trial processes.

3. Study Flowchart:



Main trial
Participant flow



4. Schedule of assessments

Study procedure	Visit 1 Baseline	Week 1 – Week 12 *1	Follow-up 1 at 12 weeks *2	Following Intervention treatment/delivered	Follow-up 2 at 6 Months *2	Follow-up 3 at 12 Months*2
Review Inclusion/Exclusion Criteria and confirm eligibility	✓	Standard Care plus Gait Intervention programme or Standard Care alone				
Obtain Informed Consent	✓					
Demographics	✓					
Clinical Data	✓					
Adverse Event Review			✓			
Foot function index disability subscale	✓		✓		✓	✓
Patient Health Questionnaire - 4	✓		✓		✓	
EQ – 5D – 5L 5- item health Questionnaire	✓				✓	✓
Resource Use Questionnaire 4 section, 7 question form regarding the use of NHS services	✓		✓		✓	✓
Self-efficacy scale for exercise	✓		✓		✓	
MSK – HQ Musculoskeletal Health Questionnaire 14 – Item measuring health status.	✓				✓	
RADAI F5 Rheumatoid Arthritis Foot Disease Activity Index- 5	✓				✓	
Randomisation	✓					
EARS Exercise Adherence Rating Scale			✓		✓	✓
Theory of Planned Behaviour Questionnaire			✓			
Intervention acceptability questionnaire			✓		✓	
Qualitative interviews Qualitative interviews with sub-sample of participants and consenting intervention clinicians				✓		

SCHEDULE OF ASSESSMENTS

***1** – The period between week 1 and week 12 for each participant will likely be counted from different dates depending on the arm the participants is randomised to. For those randomised to routine/standard care this period will begin on the date of consent or Baseline visit. For those assigned to the standard care plus intervention arm this period will begin on the date of the initial Intervention consultation.

***2** - Follow-ups indicated with a ***²** should offer the option of being carried out face to face, by post with telephone support, or via electronic portal.All follow-ups should ideally be performed within +/- 4 weeks of the documented visit time (e.g. 12 weeks ± 4 weeks). The aim is to meet these visit windows but any that are out-with will be dealt with at the analysis stage, as appropriate, and therefore will not be considered protocol deviations

5. Background

There are an estimated 645,000 people with RA in the UK and almost all of them will experience foot and/or lower limb synovitis and mobility problems over the course of their disease [1-3]. During the early post-diagnosis stage around 65% of patients experience foot pain and swelling and 60% report walking-related disability [4]. With the early introduction of disease-modifying anti-rheumatic drugs (DMARDs) the prevalence of walking disability decreases to approximately 40% at 1 year post -diagnosis and thereafter [4]. Self-reported walking disability at 2 years post-diagnosis has been identified as the main predictor of persistent walking disability [5]. Importantly, this suggests that there may be a therapeutic 'window of opportunity' for prevention of persistent walking disability during the first 2 years of RA. Systematic reviews indicate that people with RA exhibit slow and unsteady gait patterns characterised by decreased walking speed, cadence, ankle power, step length, and increased double limb support time [6-8]. Activity monitoring studies suggest that people with RA also take fewer steps, are more sedentary, and are less physically active [9-12]. These sedentary characteristics are not trivial and have been associated with poor body composition (increasing fat, decreasing lean muscle), and patients with RA are at significantly increased risk of cardiovascular disease, likely to be worsened by poor mobility and physical inactivity [13-15]. Thus, walking disability in RA is prevalent and associated complications are likely to be costly to the NHS.

The current research evidence suggests that a progressive deterioration of gait in RA occurs due to a complex cycle of physical deconditioning which is negatively influenced by fear avoidance of activities (see figure 1) [6,16-19]. Gait and walking activity pattern compensations in RA are consistent with the avoidance of pain, stiffness, fatigue and exacerbations of disease (flare) [6,16-19]. For similar reasons people with RA commonly express safety concerns about undertaking exercise and physical activity, and these concerns are often exaggerated in those with higher levels of depression/anxiety and poor exercise self-efficacy [16,20-22]. Poor exercise self-efficacy (defined as low confidence in undertaking exercise) predicts persistently low physical activity levels in people with RA which in turn places them at a greater risk from associated functional decline, together with increasing their risk of important comorbidities such as cardiovascular disease. However there is strong evidence to suggest that weight-bearing exercises and physical activity are safe and do not cause disease exacerbations or joint damage [11]. Avoidance of painful movements and activities appears to be the key contributor to functional decline in RA [23,24]. Resultant lower limb muscle weakness and poor muscle endurance are common and are associated with reduced walking speed and impaired physical function [7,8,25-30]. Proprioception and postural stability are also commonly impaired in those with foot involvement, manifesting as balance problems during everyday activities such as walking and stair climbing [31]. There is an increased risk of falls in RA and impaired balance and fear-of-falling are associated with reduced walking speed and disability [31-34]. At present, it is unclear whether current usual care for people with early RA is sufficient to improve these functional impairments.

5.1 Rationale

The current medical approach to managing early RA involves early use of disease-modifying anti-rheumatic drugs (DMARDs) and/or biologic drugs which inhibit inflammatory cytokines to abrogate synovitis to maximise disease control and preserve function [35]. Improvements in disease characteristics following first-line medical management in early RA are well recognised [35,36], and lower limb function and walking ability generally improve for some patients [4,36,37]. However there is significant evidence demonstrating that foot pain, foot disease activity, gait problems and walking disability persist for a significant proportion of patients [8,38,39]. People with RA who experience ongoing problems may be referred to physiotherapy and podiatry for provision of muscle stretching/strengthening exercises, joint protection techniques, physical activity recommendations, footwear advice and foot orthoses as required. The effectiveness of strengthening exercises and foot orthoses are well underpinned by evidence for improving muscle strength and foot pain respectively in RA [40,41].

Gait rehabilitation is a management strategy which is commonly used for improving independent walking capacity in neurological disorders such as stroke [42-47]. Definitions vary, but gait rehabilitation is largely considered to be the repetitive practice of gait cycles in order to improve walking ability [48,49]. There is good evidence that gait patterns can be improved as a result of gait rehabilitation in neurological disorders [42-47]. Moreover there have been two small studies demonstrating benefits in walking ability and physical function in participants with established RA who underwent programmes of rehabilitation which included repetitive walking tasks [48,49]. However, gait rehabilitation is not recognised as a usual care intervention for early RA and evidence of efficacy and clinical protocols are lacking. We have developed a new gait rehabilitation intervention (the GREAT strides programme) and have evaluated its feasibility in terms of patient and clinician acceptability, safety and fidelity. Preliminary results from feasibility suggest that the intervention is acceptable to patients and clinicians, is safe, and can be delivered as intended by physiotherapists and podiatrists.

This study will involve an internal pilot trial to evaluate recruitment and retention rates, and subject to meeting a priori progression criteria, the main trial will involve investigation of the clinical and cost-effectiveness of gait rehabilitation for people with early RA.

6. Study Objectives

6.1. Objectives for the internal pilot trial phase:-

6.1.1 To determine the feasibility of recruitment and retention of patients with early RA, including willingness to be randomised.

6.2 To revise and check the sample size calculation for the main trial using the feasibility study sample variance on the selected primary outcome.

6.3 Objectives for the main trial phase:-

6.3.1. To compare the clinical effectiveness of the addition of a new gait rehabilitation intervention to usual care versus usual care alone on lower limb function (PRIMARY)

6.3.2. To compare the cost-effectiveness of the addition of a new gait rehabilitation intervention to usual care versus usual care alone.

6.3.3. To evaluate participants' view and experiences of the usual care and gait rehabilitation interventions.

6.3.4 To evaluate intervention clinicians' view and experiences of the usual care and gait rehabilitation interventions and trial processes.

7. Study Design

This is a UK multi-centre study. Participants will be randomised to either the standard care arm or standard care plus gait intervention arm.

All participants will require to attend 1 baseline research visit and have outcomes measured at the following time points;

Visit 1 - Baseline
Follow-up 1 - 12 weeks,
Follow-up 2 - 6 months
Follow-up 3 - 12 Months

Participants randomised to receive the GREAT gait rehabilitation programme will have up to 4 (2 compulsory, 2 optional) consultations with the podiatrist or physiotherapist delivering the intervention. The initial and first follow up intervention delivery visits will be mandatory and should be carried out as face to face visits where possible. The two additional visits are optional and will depend on therapist judgement and/or participant preference. The two additional visits have the option of being either telephone, video call or face to face visits depending on the clinician judgement and participant preference. All intervention visits, whether face to face or remote will be audio-recorded for the assessment of fidelity of the intervention. This is described later in the intervention section 12. Participating clinicians will be trained to deliver this technique.

In the event that a face to face visit cannot be performed for either or any of the following: Baseline research visit, Initial Intervention Session and/or 2nd Intervention session for any reason remote options may be utilised. Section 13 describes how the trial maybe adapted under COVID 19 restrictions and guidelines. Consideration to ensure the intervention fidelity is not compromised is required if remote Intervention Sessions are being carried out.

8. Study population

The target population will be adults who have a clinician diagnosis of rheumatoid arthritis, who have disease durations of less than 2 years, and who also have a documented or self-reported history of disease-related foot impairments (either foot pain or synovitis). Evidence suggests that delivery of a gait rehabilitation programme within the first 2 years of RA will provide the best opportunity to prevent walking disability, which justifies our focus on patients within this critical window [5,50]. At disease onset people with RA are typically of working age (mean, standard deviation, SD) 55 (15)), mostly female (approximately 65% of cases) and have moderate-to-high disease activity and disability scores prior to commencement of systemic DMARD or biologic drug therapies [51]. People with RA experience a heterogeneous disease course and disability outcomes during the first two years after diagnosis [51-53]. Most patients will improve with medical management; however, the rate of response to therapies can be variable, ranging from those who achieve remission quickly (within 6-12 months) to others who continue to experience at least moderately active disease after 2 years and worse functional outcomes [51-53]. To maximise external validity we have opted for a broad inclusion criteria, focusing on those with foot pain or synovitis, which is associated with disrupted gait and walking disability [54].

8.1 Inclusion Criteria

The following study inclusion/exclusion criteria will be adopted. Participants will be included if they fulfil all of the following criteria:

1. They are 18 years of age or over.

2. They have a clinician diagnosis of RA and have disease durations less than 2 years from diagnosis.

3. They have a history of disease-related foot impairments defined as at least one of: self-reported foot pain, and/or the presence of foot and/or ankle joint synovitis/tenosynovitis on clinical examination since diagnosis of RA.

5. They are willing to participate and provide written informed consent to participate in the study.

8.2 Exclusion Criteria

Participants will be excluded if they fulfil any of the following criteria:

1. They are not able to undertake or complete the intervention (e.g. due to severe comorbid disease) identified by their consultant rheumatologist prior to screening, or the research nurse at screening.

2. They are unable or unwilling to provide informed consent

3. They are currently taking part in other non-medical intervention studies where the goal of the intervention is to improve lower limb function and/or gait.

9. Trial Procedures

9.1 Participant Identification Screening and Recruitment

Patients will be identified from out-patient clinics including patients with a diagnosis of Rheumatoid Arthritis.

Patients will be identified by the local clinical and/or research team by two methods

9.1.1 Direct contact via clinic visit

Patients who are attending early arthritis outpatient clinics and who either self-report a history of foot pain since diagnosis of RA, or for whom foot/ankle pain and/or disease activity is detected during clinical examination will be identified as potentially suitable for the study. Patients who are interested in study participation will be introduced to the recruiting researcher, by the consulting physician or with the patient's consent will be approached by the recruiting researcher, research nurse or as appropriate depending upon local site personnel arrangements.

The recruiting researcher will provide verbal information about the study and will provide a participant information leaflet.

9.1.2. Mail shot

Patients with early rheumatoid arthritis will be identified from existing clinical lists/databases (depending on availability of these at participating sites) and will be invited to participate in the study using a mailshot approach.

Patients identified through clinic lists will be contacted by letter and invited to indicate their willingness to take part by returning a reply slip in a provided stamped addressed envelope.

Invitation packs will include an invitation letter, information letter, and an expression of interest form indicating consent to be contacted and preferred method of contact. Participants will also be provided with study recruitment personnel contact details for seeking further information.

Investigators will be permitted to issue up to 2 reminder letters a minimum of 3 weeks apart. Telephone contact is permissible to discuss the study.

Potential Participants will only be sent invitation letter and PIS once consent to do so has been provided by the patient clinician.

Regardless of the pathway, all potential participants will have at least 24 hours to review the patient information sheet before providing written, informed consent. Upon confirmation of the patient's willingness to participate, the patient will be invited to attend a screening appointment to confirm their eligibility to participate and for the recruiting researcher to obtain written informed consent. Consented and enrolled participants will then undergo baseline outcome assessment.

9.2 Study schedule

This trial will involve one research-specific visit, which will be an initial visit for screening and baseline measurements. All other outcomes will be collected remotely, either by post or electronic form completion.

The 12-week follow-up will be undertaken at the end of the 12 week period commencing from the first intervention visit. The details of study procedures for each visit are outlined below. Patients randomised to receive the GREAT intervention will have a mandatory intervention visits. These will be face-face or via video consultation (where face to face cannot be performed and agreed by patient and intervention therapist). There is the option for up to two additional follow up visits which can be conducted via preferred method.

A sub-sample of participants from the study as well as consenting intervention therapists will be invited to participate in telephone-based interviews to gain a deeper understanding of the experience and acceptability of the intervention and trial processes.

9.2.1 Visit 1 - Baseline

- Final eligibility checks according to inclusion/exclusion criteria. Eligibility checks will be conducted by a trained research nurse/AHP and will be recorded on Eligibility Screening Form.
- Obtain informed consent.
  A local study practitioner, delegated to do so, will obtain written informed consent from willing eligible patients by reading through each section of the consent form explicitly and clarifying each point the individual needs to confirm. Those who wish to take part in the study will be asked to sign and date the consent form.

- Demographics including gender, date of birth, employment status, height, weight and ethnicity will be recorded for each participant on the case report form.
- Clinical data including current medication, current/previous AHP treatments, DAS28 or most recent DAS 28 score from clinical care score (from routine care), any co-morbidities and disease duration will be recorded for each participant on the case report form.
- Participants will then complete a baseline questionnaire to include:
- Foot function index disability subscale
- Patient Health Questionnaire – 4
- EQ-5D-5L – Health Questionnaire
- Client service receipt inventory - Resource Use Questionnaire
- SEE – Self efficacy for exercise scale
- MSK-HQ – Musculoskeletal Health Questionnaire
- RADAI F5 – Rheumatoid Arthritis Foot Disease Activity Index
- Following collection of baseline measures, participants will be randomised. Randomisation will be achieved using an interactive voice response system (IVRS) or interactive web response system (IWRS). The investigator or person delegated to randomise will provide the participant identifier and the system will check the participant's eligibility from information already entered in the eCRF and the randomisation group will be allocated.
- Participants randomised to the Intervention Arm will then be referred in order to schedule an initial intervention consultation. The initial consultation date will act as Week 0 for participants in this arm. For those randomised to standard care, the Baseline visit date will act as Week 0.

9.2.2 Follow-up timepoint 1 at 12 weeks

- This visit can be carried out remotely. A participant's specific portal is available for participants to complete the questionnaire set remotely.
- Clinical data including current medication regimen, current/previous AHP treatments, care received during the 12 week intervention period, DAS28 score (from routine care via the direct care team) will be recorded for each participant on the case report form.
- Collection of relevant adverse events
- Foot function index disability subscale
- Patient Health Questionnaire – 4
- Client service receipt inventory - Resource Use Questionnaire
- SEE – Self efficacy for exercise scale
- Exercise Adherence Rating Scale (EARS)
- Theory of Planned Behaviour Questionnaire (TBPQ)
- Theoretical framework of acceptability questionnaire

9.2.3 Follow-up timepoint 2 at 6 Months

- This visit can be carried out remotely. A participant's specific portal is available for participants to complete the questionnaire set remotely. Clinical data including current medication regimen, current/previous AHP treatments, care received during

the previous 6 months, DAS28 score (from routine care collected by the direct care team via notes review) will be recorded for each participant on the case report form where possible.

- Collection of relevant adverse events
- Foot function index disability subscale
- Patient Health Questionnaire-4
- SEE – Self efficacy for exercise scale
- EQ-5D-5L – Health Questionnaire
- Client service receipt inventory - Resource Use Questionnaire
- MSK-HQ – Musculoskeletal Health Questionnaire
- RADAI F5 – Rheumatoid Arthritis Foot Disease Activity Index
- Exercise Adherence Rating Scale (EARS)
- Theoretical framework of acceptability questionnaire

9.2.4 Follow-up timepoint 3 at 12 Months

- This visit can be carried out remotely. A participant's specific portal is available for participants to complete the questionnaire set remotely.
- Clinical data including current medication regimen, current/previous AHP treatments, care received during the previous 6 months, DAS28 score (from routine care via the direct care team) will be recorded for each participant on the case report form.
- Collection of relevant adverse events
- Foot function index questionnaire
- EQ-5D-5L – Health Questionnaire
- Client service receipt inventory - Resource Use Questionnaire
- Exercise Adherence Rating Scale (EARS)

9.2.5 Telephone based interviews

From the main sample we will purposively subsample 10% of participants and consenting clinicians from each site (50% for internal pilot, 20% for main trial) who are delivering the intervention, for the generation of qualitative data using thematic analysis. Semi-structured, telephone-based interviews will be conducted to minimise the potential burden on participants by avoiding the need for attending further research appointments [55]

9.3 End of Study

Participation in the study ends at follow-up timepoint 3 (at 12 months) or at the post study telephone interview if selected and consented to take part in this. There are no further patient contacts after follow up time point 3 or telephone interview.

The end of the trial will be defined by the completion of the Month 12 follow up questionnaires by the last patient recruited or by a decision by the TSC and/or Sponsor to stop the trial prematurely because of a recommendation from the IDMC.

10. Withdrawal of subjects

Participants have the right to withdraw from the study at any point for any reason. The investigator can also withdraw participants from the study intervention in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations or any other relevant reasons. If a participant withdraws consent from further trial intervention and/or further collection of data their data will remain on file and will be included in the final study analysis, unless requested otherwise. Participants can be withdrawn from the intervention but can remain in the trial and still receive follow-ups unless they ask to be withdrawn from the study. A withdrawal page should be completed on the eCRF to record any participant withdrawals.

11. Assessment and reporting of safety and serious adverse events

11.1 Study Safety Assessment

The gait rehabilitation intervention proposed for this study includes several walking task components which have been adopted previously in established RA as part of a walking circuit [48] and the Otago Exercise Programme [49]. This intervention been evaluated with for acceptability, safety, fidelity and adherence in early RA. We anticipate that there will a very low risk of adverse effects associated with our intervention, which will be adapted according to individual needs. The study will not involve any invasive procedures.

11.2 Definitions of Adverse Events

Adverse Event (AE) - Any untoward medical occurrence in a participant to whom the intervention has been administered, including occurrences which are not necessarily caused by or related to the intervention.

Serious Adverse Event (SAE) - Any adverse event or adverse reaction that
a) results in death
b) is life threatening
c) requires hospitalisation or prolongation of existing hospitalisation
d) results in persistent or significant disability or incapacity
e) consists of a congenital anomaly or birth defect.
f) is otherwise considered medically significant by the person delegated to have clinical oversight at participating site

11.3 Recording and Reporting AEs/SAEs related to the intervention

AEs/SAEs will be collected from the date of consent until the Follow up 1 timepoint. This will be the 12 weeks following the consent date for those assigned to the routine care arm and 12 weeks following the initial intervention visit for those assigned to the Intervention arm.

Throughout the 12 week intervention period and at the 12 Week follow up time point, sites should ensure they are able to capture any relevant SAEs.
How this is managed will depend on the participating site set up and research experience of the intervention therapists. The responsibility of reporting SAEs during this time should be documented on the study delegation log.

During the 12 week intervention period, the intervention clinicians who will have contact with the participants will be responsible for reporting any relevant events they are made aware of. This may be performed in two ways:

1 - Directly into the eCRF and, if serious, completion and submission of the SAE form
2 - Reporting the SAE details to other members of the local research team for reporting in eCRF and SAE form, if needed.

How this is managed at sites will depend on the research experience of the intervention clinicians and delegation of responsibilities.

As the 12 week follow up time point will not include a face to face visit (unless necessary by participant or local investigator/Research nurse or assessor preference), a review of adverse events should be performed. This can be done by phone call to the participant and/or electronic medical record review.

All AEs should be recorded in participant's clinical notes as per standard practice.
Only AEs which fit any of the categories of an expected event in section 11.4 should be reported on the eCRF.

All AEs must be assessed for seriousness. SAEs must also be assessed for causality, expectedness and severity.

All SAEs or suspected SAEs should be reported to sponsor using the SAE form provided.

An SAE occurring to a research participant must be reported to the main Research Ethics Committee (REC) within 15 days of notification, where in the opinion of the Chief Investigator the event was:

"Related" that is, it resulted from administration of any of the research procedures
And
"Unexpected" that is the type of event is not an expected occurrence as a result of the intervention provided.

Causality - This should be assessed by the CI or PI and should be described using the following categories:

- Unrelated to intervention
- Possibly related to intervention
- Probably related to intervention
- Definitely related to intervention

Severity - This should be assessed by the CI or PI and should be described using the following categories:

Mild: awareness of event but easily tolerated

Moderate: discomfort enough to cause some interference with usual activity

Severe: inability to carry out usual activity

Details of SAE's arising during the trial should be entered in to the Non-cTIMP SAE reporting form within the eCRF.. The site must enter details in the form and submit to the sponsor contact provided within 24 hours of first becoming aware of the event and any follow up information should also be reported. Such events must be reported to sponsor in order to capture all potential related adverse events.

In the event that the eCRF is not available when reporting an SAE, paper SAE forms provided in the site file and electronically to sites can be completed and sent to a member of the GREAT study team at Glasgow Caledonian University, using the designated SAE form for non-CTIMPs using the designated email inbox.
The paper SAE form should be completed and emailed to: great.trial@gcu.ac.uk

The CI in conjunction with the local PI or person delegated to have clinical oversight, will assess the SAE form to determine whether or not the event is related to the intervention and whether or not the event is an expected occurrence. Given the low risk nature of this study, we do not expect any SAEs to be related to the intervention. If the event is considered to be related or potentially related to the intervention or participation in the study and is unexpected, the SAE will be reported to the REC within 15 days of becoming aware of the event.

11.4 Expected Event of Special Interest

All Expected Adverse Events that meet the serious criteria should be reported on the SAE form and submitted to sponsor at the email address above for assessment of causality.
For all Expected AEs details recorded on the eCRF will include the onset date; whether or not it was an SAE; level of severity (from 1 mild to 3 severe); whether or not medication was required (yes/no) and the AE outcome (unknown, ongoing, resolved, and if resolved the date of resolution).

The data centre will subsequently generate SAE and AE reports for review by the TSC and IDMC.

A list of expected adverse events in relation to the intervention and/or study participation (i.e. outcome assessment) is provided below:

- Transient post exercise soreness
- Post exercise stiffness
- Post-exercise fatigue
- Post-exercise trips, slips and/or falls
- Temporary exacerbation of disease-related inflammatory pain during exercises
- Trips, slips and/or falls during set-up of circuit, during exercises, and/or clearing away the circuit setup
- Temporary musculoskeletal pain from set-up of circuit at home

- Perceptions of new instance of disease flare resulting from undertaking gait rehabilitation circuit.

12. Gait Rehabilitation Intervention

There is strong evidence from the field of neurological rehabilitation suggesting that repetitive practice of walking tasks results in improvements in walking ability by improving lower limb function [47,56-58]. Preliminary evidence suggests that similar interventions are beneficial for improving walking ability in RA [48,49]. Our gait rehabilitation intervention is a complex intervention which can be described as individually tailored and progressed, which is to be supervised in clinic and practiced at home.

12.1 Supervised intervention sessions

Supervised intervention sessions will be delivered by a trained physiotherapist or podiatrist to guide participants on how to undertake a home-based gait rehabilitation programme. The delivery of intervention sessions will be pragmatic and flexible according to individual needs and preferences regarding additional attendances. Participants will be required to attend at least 2 supervised intervention sessions and up to a maximum of 4 over a 12-week period. Preferably, the initial 2 compulsory sessions should be carried out face to face. In the event that it is not possible to carry these out as face to face sessions, it is allowable that these sessions (either 1 or both) could be performed remotely by videocall. Both the intervention therapist and participants must agree and be comfortable with this approach in order to ensure the fidelity of the delivery of the intervention is maintained.

Where participants are not required to participate in further supervised sessions after the first 2 sessions, telephone-based sessions can be utilized to maintain contact, promote adherence to the home programme, and/or to provide specific advice regarding progression. These 2 optional additional sessions can be by telephone or other method Eg: video call. The content of all contacts will be audio recorded using supplied Dictaphones and recorded on an intervention checklist by the therapists.

To address the physiological principles of overload and specificity, the gait rehabilitation programme will involve a ‘gait circuit’ comprised of an adapted set of task-specific, weight-bearing, functional walking exercises previously employed in RA to target the main muscle groups used during walking [59,60]. Participants will be assessed by the clinician in order to determine baseline functional ability (i.e. can the participant complete each task?). The rationale for gait rehabilitation will be explained and gait circuit tasks will then be demonstrated by the clinician prior to an assessment of participants’ competency in undertaking gait circuit tasks. Gait circuit starting levels (dose) and a plan for progression will be established. A reduced circuit will be prescribed for those unable to complete specific tasks due to specific disease -related impairments. Participants will be instructed to complete the gait circuit at home in addition to their usual activities.

The 6-task gait circuit requires minimal set-up and space (at least 3x1 metre unobstructed floor space with two chairs and 4 evenly-spaced markers i.e. small household items such as socks) and uses bodyweight resistance only and which does not require any specialist equipment. A home-based session comprising 3 sets of the full 6-task circuit including a 2-minute warm-up (marching on the spot), 1 minute intervals of task completion and 30 second between-task rest periods would take 28.5 minutes to complete. Participants will be

encouraged to continue with the programme beyond the 12-weeks intervention period. They will also be encouraged to maintain their walking ability and will be sign posted to community walking groups. Support is provided in the illustrated patient intervention booklet on how to progress, regress and maintain their walking exercises.

Progression will be implemented in 4 ways: -

1) by increasing the number of gait circuit sessions, from 3 up to 5 times per week;

2) participants will be advised to monitor and progress intensity of task completion (by increasing speed) using a modified version of the Borg Rating of Perceived Exertion (RPE) scale (range 6-20) to maintain an RPE from 13 up to 17 (equivalent to 50-80% maximal exertion) [59,60]. Whilst the Borg RPE scale was originally developed to measure exertion of the aerobic system, our co-applicant (LB) has used this scale to guide participants' exercise exertion with success in a trial of upper limb training in RA [60]. This method of self-regulation of exercise exertion is beneficial as perceived rates of exertion are unique to each individual. Participants will be advised to complete tasks in a controlled and coordinated manner;

3) participants will be advised to complete more sets from 3 up to a maximum of 6 and;

4) participants will be advised to increase the duration of each task from 1 minute up to 1 minute and 15 seconds. Participants will be instructed to aim for approximately 10 repetitions within 1 minute and 12 repetitions in 1 minute and 15 seconds for each task (with the exception of task number 2; the heel-to-toe walk, which should be completed 5-6 times) [48]. Should participants successfully undertake a full gait circuit session at the upper limit of progression, they would complete 225 minutes of gait circuit tasks per week in addition to their usual activities.

12.2 Support materials

Support for set up and completion of the gait circuit at home will be provided. Participants will be provided with an illustrated educational booklet, an adherence diary and access to videos including educational material and step-by-step demonstrations of gait circuit home set-up and task completion. A secure trial website allowing online access to the video content will also be set-up so that those wishing to use smart phones, smart televisions, tablets, and/or personal computers to access support materials via the internet may do so. Home support materials including the DVD and website have been developed and evaluated as part of the feasibility study. The website includes all support materials content in downloadable form. The DVD and booklet can be used together to guide set-up, completion, adjustment of dose, maintenance, and monitoring of progress. Behaviour change components are included in the booklet and involve a goal setting and action plan worksheet, a barriers and facilitators worksheet, and an exercise diary.

12.3 Psychological/behavioural component

In order to address maintenance of progress and prevent reversibility, intervention sessions with the clinician will include an embedded psychological component. This is to address the barriers of adherence to exercise/physical activity based interventions commonly experienced

by people with RA such as fear avoidance of activity and poor exercise self-efficacy [16, 20-22]. The theory of planned behaviour is recommended for behavioural change interventions in RA [61]. This model places emphasis on individuals' perceived ability to perform a given behaviour and their attitudes to initiate behavioural change [62]. This has been widely used in health psychology to examine behavioural intentions, perceived behavioural control and subjective norms as precursors of actual behaviour [63,64]. The specific psychological components of our intervention are based upon Motivational Interviewing (MI), and behaviour change techniques (BCTs) to enhance motivation, overcome barriers and facilitate adherence to the Gait Rehabilitation Programme [65]. MI is a collaborative, goal-oriented style of communication, where particular attention is paid to resolving ambivalence by eliciting a person's own motivation to make positive changes, within an atmosphere of acceptance and compassion [66]. BCTs are defined as "observable, replicable, and irreducible component of an intervention designed to alter or redirect the causal processes that regulate behaviour" [67]. MI skills and BCT techniques are promising elements that have been successfully integrated into allied health professional practice to effectively support behaviour change in physical activity interventions.

Training in these empathetic, non-judgemental and effective approaches to health behaviour change is suitable for non-specialist health professionals and has therefore been included in the Gait Rehabilitation Programme. Prior to intervention delivery, physiotherapists and podiatrists will receive training that outlines the GREAT trial, demonstrates the initial set-up of the gait rehabilitation exercises, and provide an introduction on how to incorporate MI skills and BCT techniques in the supervised intervention sessions and how to facilitate long term behaviour change. This training will include practice of important elements of the study including; the recording of consultations and the recording of intervention delivery, starting dose and progression plan recorded on a checklist for fidelity assessment purposes.

12.4 Fidelity assessment

Fidelity of intervention delivery and uptake will be evaluated using a complementary mixed-methods design. Data will be gathered from participants and trial intervention clinicians from various sources as listed below:

- An intervention content checklist will be completed by all intervention therapists after each intervention session. The checklist will permit assessment of intervention protocol deviations.
- Semi-structured telephone-based interviews with consenting intervention clinicians. Interviews will explore clinicians' experiences and perceptions acceptability of therapist training they received and their experiences and acceptability of delivering the intervention, trial processes.
- Audio-recordings of all clinician-participant consultations will be undertaken. A random sample of 20% of gait rehabilitation consultations from each site will be evaluated objectively by independent observers using a bespoke content intervention fidelity checklist and the Motivational Interviewing Treatment Integrity Scale (MITI). The MITI is a valid and reliable measure designed to evaluate the clinicians' MI skills [68].

13. Covid-19 Mitigation

- In view of the Covid-19 pandemic, certain trial procedures may be changed where strictly necessary to reduce in person contact with participants. This will be consistently reviewed in view of the prevailing circumstances at the time, in line with local and national guidance and with the principle of protecting participants and study personnel. In the event of a second wave of infection this would be particularly important. In this context, consideration would be given to rearranging visits, changing to virtual visits using video technology or using additional phone calls to ensure patient safety. Consideration will also be given to how we can minimise face to face interaction with participants during the intervention period to ensure their safety as best we can.

- All visits in person will be subject to local and national guidance around the use of personal protective equipment including face masks and where appropriate when conducting procedures, the use of gloves and aprons.

14. Control intervention

Usual care will be the control intervention for the main trial and is defined as routine RA medical management led by a consultant rheumatologist and/or rheumatology nurse specialist with the potential for further referrals to members of the multidisciplinary team including physiotherapy, occupational therapy and podiatry as required. Treatments might include joint protection advice, lower limb strengthening exercises, foot orthoses and footwear advice as required. This 'usual care' definition meets the NICE and SIGN clinical guidelines for RA and early RA [3,4]. Usual care provision over the course of the trial will be monitored and documented via self-reported questionnaire (resource use questionnaire) so as to provide adequately detailed and accurate descriptions of the usual care intervention, and to estimate resource use for the economic evaluation.

15. Statistics and Data analysis

15.1 Sample size calculation

15.1.2 Feasibility Trial

Changes in the FFI disability subscale (a 9-item subscale with summary score ranging from 0-100) had the strongest correlation with self-reported change in walking ability (CWA) in the feasibility trial, and was chosen as the preferred primary outcome for the main trial. Taking the observed difference in FFI-DS change per 1-point increase in CWA as a minimally important difference, and the observed standard deviation of the FFI-DS at 12 weeks, this represents and effect size of 4.45/16.7, or 0.27. To have 90% power to detect an effect of this size would require a study of 290 participants, per group, with outcome data. The correlation between baseline and 12 weeks for FFI-DS was 0.43, with a 95% CI of (0.02, 0.72). Other pilot data from early RA patients showed a correlation between baseline and 6 months (the primary

outcome point for the main trial) of 0.61. Assuming a correlation between baseline and 6 months of 0.5, the sample size reduces by a factor if 0.75, giving a required sample size of 218 per group with 6-month outcomes. Allowing for 20% attrition at 6 months, the study would need to randomise 273 participants per group, or 546 in total. This agrees closely with the estimate of 550 made prior to the feasibility study.

15.1.1 Internal Pilot Trial

Data from the internal pilot trial will be used to derive a more precise estimate of the SD of the primary outcome, which will refine the sample size calculation for the main trial. We will use the one-sided upper 90% confidence limit (UCL) for the SD estimate in order to address the issue of imprecise SD estimates from a pilot study [69-71]. If the internal pilot has a sample size of 60, this corresponds to inflating the sample size by a factor of 1.138. To account for 20% attrition at 8 months we require an internal pilot trial sample size of n=76 participants in total (38 per arm). This SD estimate will, however, be for the primary outcome measured 3 months after randomisation, not at the primary analysis point of 6 months. The internal pilot will give primary outcome data at 6 months for approximately 30 participants, which will give some information about the stability of the SD of the primary outcome over time, as well as the correlation between measures taken at baseline, and at 3 and 6 months. At the end of the internal pilot trial, the TSC will make recommendations for the final sample size of the main RCT based on all available data. These recommendations may be in the form of a range of likely sample size requirements, and may include recommendations for additional (blinded) reviews of the distribution of the primary outcome during the trial.

15.2 Statistical analysis

A Statistical Analysis Plan (SAP) will be developed and updated as a version controlled document and will be approved by the CI and TSC before database lock. The SAP will contain full details of all analyses.

15.2.1 Pilot trial analyses

Recruitment rate over 8 months will be evaluated against a priori targets (n=76). Retention rates at 3 month follow up will be evaluated against a prior targets (80%).

15.2.2 Progression criteria from internal pilot trial to main trial

15.2.2.1 Decision rule 1 – recruitment:

For the trial to be a success, we anticipate that we need to recruit 76 participants during the internal pilot trial phase to allow for revision of the main trial sample size calculation, and to ensure that recruitment rates in 9 or more sites suggest that recruitment is feasible within the time and funding constraints to proceed to the main trial. Therefore, our progression criteria are outlined as follows: -

- Recruitment of n=76 participants at 9+ sites over 8 months (Proceed to main trial)
- Recruitment of n≥60<76 (≥80% of target) (Propose rescue plan, additional 1-2 months of recruitment, or increase number of recruiting sites)
- Recruitment of n<60 participants over 8 months (Stop, do not proceed to trial)

15.2.2.2 Decision rule 2 – retention:

For the trial to be a success, we need to retain at least 80% of participants at final follow-up to achieve our desired power for analysis of the primary outcome. If we cannot achieve 80% retention at 12-week follow-up, it is unlikely that we will be able to achieve suitable retention at 12 months. Retention of participants at 3 and 6-month follow-up will be evaluated after 8 months of recruitment, which means that retention rates will be analysed for those participants recruited during the first 4 months of the internal pilot trial recruitment period. Therefore, our progression criteria are outlined as follows: -

- Retention of ≥80% of participants at 3-month follow-up (Proceed to main trial)
- Retention of ≥70<80% of participants at 3-month follow-up (Develop and propose rescue plan)
- Retention of <70% of participants at 3-month follow-up (Stop, do not proceed to trial)

15.2.2.3 Decision rule 3 – revised sample size:

Should the revised sample size calculation significantly exceed n=550, the trial management group will evaluate the feasibility in terms of cost and time of recruiting additional sites and the recruitment period to boost overall recruitment rates as required. Accordingly, our progression criteria are outlined as follows: -

- Revised sample size calculation requires n ≤ 550 (Proceed with trial)
- Revised sample size calculation requires n >550 ≤ 675 (Propose rescue plan, additional 2 months of recruitment and/or recruitment of 1-3 additional sites)
- Revised sample size calculation requires n > 675 (Stop, do not proceed to trial).

15.3 Main trial analyses

The primary analysis will be a linear regression model of the primary outcome at 6 months in relation to intervention group, adjusted for the baseline measurement of the primary outcome and all variables used in the minimisation algorithm. Similar methods will be used for secondary outcomes. Subgroup analyses for the primary and selected secondary outcomes will be carried out with respect to the minimisation variables by inclusion of interaction terms within regression models. Changes in secondary outcomes, confounders and effect modifiers will be explored for any intervention effects on the primary outcome at 6 months by adding these variables to the primary analysis regression model. Similar methods will be used to assess whether the extent of adherence with the intervention is predictive of short- and long-term measures of the primary outcome. All analyses will be by intention-to-treat. No imputation will be carried for missing outcome data, but mixed effects regression models will be applied to model each outcome at all time-points simultaneously, as secondary analyses.

15.4 Analysis of process outcomes

Remaining analyses will focus on process measures. Analyses will include the following aspects:-

- Acceptability of the intervention will be evaluated using: the Theoretical Framework Acceptability questionnaire and analysed using descriptive statistics, and thematic analysis of qualitative data (from participants and clinicians).
- Treatment adherence will be evaluated using: the Exercise Adherence Rating Scale (EARS) and will be summarised using descriptive statistics and thematic analysis of qualitative data (obtained from participants and clinicians).
- Safety of the intervention will be determined by analysis of all reported adverse events and thematic analysis of qualitative data from participants and clinicians.
- Intervention fidelity data will be gathered from participants and trial intervention clinicians and analysed as follows:-

i) deviations from intervention protocols will be recorded by intervention therapists using paper-based intervention checklists and will be analysed using descriptive statistics.

ii) thematic analysis of qualitative data obtained from clinicians.

iii) audio samples of clinician-participant consultations will be evaluated objectively by independent assessors using an intervention fidelity checklist and the motivational interviewing treatment integrity scale.

For deeper explorations of intervention acceptability, adherence and safety the interview data will be transcribed verbatim. Thematic analysis will be undertaken using a thematic network approach whereby basic themes (lowest order premises) will be grouped together to summarise more abstract principles (organising themes) and global themes which wholly encapsulate the phenomena [74].

15.5 Health Economic Evaluation

The economic evaluation will determine the cost effectiveness of adding the gait rehabilitation intervention to usual care compared to usual care alone. Information on resource use will be collected using a modified version of the Client Service Receipt Inventory (CSRI) Resource Use Questionnaire at Baseline, 12 weeks, 6 and 12 months. This will include; contacts with primary and secondary care, medications, equipment and contacts with allied health professionals. Patients will also be asked to record personal expenditure on use of private health care and over the counter medications and/or equipment. Outcomes will be assessed using the primary trial outcome and from the EQ-5D 5L. The primary analysis will be undertaken at 12 months from an NHS and Personal Social Services perspective. A broader perspective including patient's personal expenditures will be included in a sensitivity analysis. Incremental cost effectiveness ratios (ICERS) will be computed by comparing the costs and outcomes of the intervention with the control arm of the trial. The difference in effectiveness will be expressed in terms of the change in score on the primary outcome measure (cost-effectiveness analysis). The difference in utility will be expressed in terms of quality adjusted

life years (QALYs) calculated using patient reported EQ-5D 5L data. This will be used in a cost utility analysis to calculate the incremental cost per QALY gained. A health economics analysis plan we be produced and agreed with the research team and TSC prior to data lock.

16. Randomisation and allocation concealment

At the baseline time point, data will be entered to the study eCRF, and if the participant is eligible, the eCRF system will be used to randomise the participant. Neither the researchers nor the participant will know the study group allocation prior to baseline data collection. Allocations will be made using a mixed minimisation/randomisation algorithm. Within every 10 participants, 8 will be allocated according to a minimisation algorithm, designed to minimise study group imbalance with respect to study site, age, gender and inflammatory foot disease using the RADAI-F5 in the case of neither allocation resulting in less imbalance, the allocation will be made at random. The remaining 2 participants in each block of 10 will be allocated at random, to prevent the allocation being deterministic. Once the participant has consented to participate, the participant will be registered in the trial by entering the data required for baseline timepoint using the eCRF system developed by the Robertson Centre for Biostatistics (RCB) at the Glasgow CTU. This will set off a chain of events, starting with randomisation of the participant, and notification of allocation will be provided to the site coordinator or staff delegated to perform randomisation who will subsequently inform the participant. Should the participant be allocated to receive gait rehabilitation, participating clinicians will be informed to book the participant in for their gait rehabilitation intervention session. Ideally a maximum of 4 weeks between baseline assessments and initial consultation should be achieved.

17. Blinding

Participants and clinicians will not be blinded, and participants will complete self-reported questionnaires. The statistical analysis plan (SAP) will be drafted early in the trial and approved in principle prior to any unblinded data being seen. The SAP will be finalised and approved by the trial statistician and TSC who will remain blind to treatment allocations throughout. All statistical analyses will be conducted by statisticians at the RCB within the Glasgow CTU, who will be blinded to group allocation. Unblinded reports will be stored in a secure area of the RCB network, with access to allocation codes and the secure network area revoked after production of reports.

18. Data Management and delivery

18.1 Data Collection

An electronic case report form (eCRF), developed by the Robertson Centre for Biostatistics, will capture the baseline and follow up data required to meet this protocol's requirements. Access to the eCRF will be restricted, via a study-specific web portal, and only authorised site-specific personnel will be able to make entries to their patients' data via the web portal. The Investigator, or his/her designee, will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete and verifiable. Data will be stored in a MS SQL Server database.

For the follow up visits at 12 weeks, 6 month and 12 months, as the data being collected will be participant reported via questionnaires, a data collection portal allowing participants to complete questionnaires electronically will be used. Participants will be offered the option of completing paper based questionnaires for these follow up points, if preferred. These will be posted to participants and returned. Data entry in to the eCRF of these returned questionnaires responses will be performed by local delegated site staff.

Site Staff should follow their local infection control guidelines with regard returned paper study documents to site.

18.2 Audio files

Sites will be provided with dictaphones for the trained intervention therapists to record the sessions with participants. These sessions will be anonymised by using study identifiers at the start of each sessions.

Recordings of these intervention sessions will be analysed for motivational interviewing and behavioural change techniques by study team member in Kings College. To facilitate the transfer of these files, the eCRF will function to allow audio files to be uploaded. Authorised researchers at Kings College will be able to download the files for analysis.

18.3 Source Documentation

In this study, source documentation will be from various sources.

For screening and baseline, participant's medical record will be used to confirm eligibility criteria, diagnosis, medications and any other relevant information. This source data, which will be transcribed into the eCRF from the medical records should be accurate and verifiable.

For the questionnaires completed by trial participants, the completed questionnaires will be regarded as the source data. These will be either electronically by the Data Centre or on paper at participating site

For the Audio files, the source data will be considered the file held on the Dictaphone, (or other stage location at site). Once these files have been loaded and acknowledged by sponsor and/or Kings College team, the source file will not be stored at site depending on the data storage facility available on the Dictaphone. In this case it's acceptable that the audio file copy at sponsor and/or Kings College is accepted as source.

In cases where data is transcribed directly into the eCRF and no other paper or electronic source exists, then the eCRF will be considered the source record. In these cases, these data should be prospectively documented in the medical records to ensure a full record of the trial is available at site.

18.4 Data Validation

Where it is practical, data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded to maintain a complete audit trail (reason for change, date change made, who made change).

18.5 Data Security

The Robertson Centre for Biostatistics systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and off-site to a commercial data vault weekly. The Robertson Centre for Biostatistics has an ISO 9001:2008 quality management system and ISO 27001:2013 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

18.6 Archiving

The Trial Master File will be archived by the Sponsor at the end of the trial for a minimum period of five years.

Archiving of Site Files will also be for a minimum of five years from completion of the trial, and this action will be delegated to the sites in the Clinical Trial Site Agreement that will be put in place between Sponsor and Sites. Sites will be notified by the Sponsor when Site files can be archived.

19. Ethical and Regulatory Considerations

19.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. GP information letters.
Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (it is noted that amendments may also need to be reviewed and accepted by NHS R&D departments before they can be implemented in practice at sites).
All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.
An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).
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.

19.2 Public and Patient Involvement

Patient and Public Involvement (PPI) will include a patient representative on the TSC and a PPI reference group who will be invited to contribute to this research. All patient–facing documentation will be reviewed in full and revised as necessary by our co-applicant patient representatives in order to ensure understanding and readability. Our PPI group will be

invited to comment on on-going issues pertaining to recruitment rates, and safety and adverse events. People with RA have contributed previously to the development of the intervention including its format and processes, provisional support materials (including patient facing documentation, DVD/website content and design, all self-management support materials).

19.3 Indemnity

The sponsor (Glasgow Caledonian University) will ensure that provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial in accordance with Part 2 (14) of Schedule 1 to SI 2004/1031.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a study involving exposure to new interventions and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

19.4 Amendments

Any change in the study protocol will require an amendment. Any proposed substantial protocol amendments will be initiated by the CI following discussion with the Sponsor and TSC and any required amendment forms will be submitted to ethics committee and Sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the Trial Management Group of all protocol amendments.

19.5 Clinical sites

A rheumatology department will be eligible as a recruitment site should they be able to offer access to physiotherapy and/or podiatry/orthotics services for treatments including joint protection, exercise therapies, foot orthoses and footwear advice as required for people with early RA. In order to facilitate recruitment, eligible sites will agree to a mailshot approach for invitation of eligible participants who would be identified from clinic lists. Eligible sites will be required to provide at least 2 therapists (either physiotherapists and/or podiatrists) who will undergo intervention training, and subsequently deliver the intervention for those allocated to receive it. We anticipate that 7-9 sites will be required for the internal pilot phase, and up to 30 sites will be required in total for the main trial phase.

20.0 Study management

Sponsorship: Glasgow Caledonian University will act as the sole sponsor for the trial.

Chief investigator: The CI has overall responsibility for the scientific quality, delivery and conduct of the study and will provide senior support to the GCU PI.

Principal investigator: The PI has responsibility for the scientific quality, delivery and conduct of the study at their site.

The study will be supported by Glasgow CTU. All trial procedures will adhere to respective CTU SOPs and support will be provided by the Project Manager based in Glasgow. The Glasgow CTU will provide a trial coordinator who will be supported by the Project Manager. The Project Manager will work closely with and will support study coordinators based at Keele University and KCL, for local site recruitment, setup and liaison. The CI will be responsible for overall delivery to target and to budget of the study, with support of the Project Manager, coordinators and the TMG.

20.1. Trial Management group

The study will be co-ordinated by the Trial Management Group (TMG). A TMG will be formed consisting of those individuals responsible for the day to day management of the study such as the CI, the PI, the project manager, lead coordinator, local study regional coordinators, representatives from each participating academic institute, data centre representatives, and the principal investigators from each site. Regular meetings at defined intervals will be held by conference call. The role of the group is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

20.2. Expertise in the team

Our team is internationally recognised for RA gait and disease-related foot and ankle pain research with a portfolio of studies previously funded from MRC, Versus Arthritis (VA) and EU FP7. The team is led by Prof Martijn Steultjens (Professor in Musculoskeletal Health), with support from Prof Woodburn (Professor of Rehabilitation) at GCU, as well as Prof Nadine Foster (NIHR Research Professor) at Keele, Prof Cath Sackley (Professor of Rehabilitation) at King's College London, and Prof McInnes (Professor of Experimental Medicine, Director of Research Institute) at the University of Glasgow. The study requires considerable knowledge and understanding of the impact of the RA disease process and associated symptomology on lower limb biomechanics, gait and management strategies delivered by the multidisciplinary rheumatology teams including physiotherapy and podiatry. The team have extensive expertise in the clinical care and assessment of RA patients with foot and lower limb problems and have delivered clinical services in previous trials. We have published extensively on the impact of RA and disease-related foot problems on gait, risk factors for walking disability, interventions for foot pain, development of disease, foot-specific outcome measures, recommendations for early intervention, systematic reviews of interventions, functional outcome measurement and clinical guidelines for the management of foot problems in RA.

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