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

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AMENDMENT NUMBER	DATE	PROTOCOL VERSION

This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) 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
ARUK	Arthritis Research UK
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)
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
PROMIS PF20	Patient-Reported Outcomes Measurement Information System Physical function Short Form (20 items)
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
SSOTP	Staffordshire Stoke on Trent Partnership Trust
SUSARS	Serious unexpected serious adverse reaction
TMG	Trial management group
TSC	Trial steering committee
UKCRC	United Kingdom Clinical Research Collaboration

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2. Study synopsis

Title: Feasibility study of gait rehabilitation in patients with early rheumatoid arthritis: the Gait Rehabilitation in Early Arthritis Trial [GREAT-FS]

2.1 Duration of Study: 15 months

2.2 Objectives: The objectives of this feasibility study are to inform the design of a future randomised controlled trial through evaluation of primary outcome measures and refinement of a new gait rehabilitation intervention for adults with early rheumatoid arthritis. The specific objectives are:

2.2.1. To evaluate the measurement properties (responsiveness, minimal important difference) of candidate outcome measures to identify and select the most suitable primary outcome measure for the future main trial.

2.2.2. To evaluate the acceptability of the new gait rehabilitation intervention by exploring participants' and clinicians' views and experiences.

2.2.3. To monitor the safety of the new gait rehabilitation intervention by monitoring, recording and evaluating adverse effects/unintended outcomes.

2.2.4. To evaluate whether or not participants adhere to the new gait rehabilitation intervention and identify potential barriers/facilitators of adherence.

2.2.5. To evaluate whether or not the new gait rehabilitation intervention can be delivered as intended by participating physiotherapists and podiatrists.

2.2.6. To review and refine if necessary the new gait rehabilitation intervention prior to final development of the new gait rehabilitation intervention manual and training programme for participating physiotherapists and podiatrists for the future main trial.

2.2.7. To monitor and evaluate participant recruitment and retention rates.

2.2.8. To monitor and report data completion rates for candidate primary outcome measures.

2.3 Methodology: This feasibility study will be a multi-centre, single-arm repeated measures (pre- and post-intervention) design comprised of 3 evaluations:

2.3.1. An evaluation of measurement properties (using distribution and anchor based approaches) of primary outcome measure candidates for a future main trial;

2.3.2 A mixed-methods evaluation of intervention safety, acceptability and adherence (participants); and

2.3.3 A mixed methods evaluation of intervention fidelity (clinicians). This feasibility study will facilitate final amendments to the intervention and training programme for participating physiotherapists and podiatrists for the main trial.

2.4 Sample size:

2.4.1. 42 adults with early rheumatoid arthritis (studies 1 and 2)

2.4.2. All consenting intervention clinicians (up to n=12) (study 3)

2.5 Screening:

Screening will be conducted in either 1) NHS clinical research facilities or 2) NHS rheumatology, podiatry or physiotherapy outpatient settings within participating sites depending on local arrangements. Screening will be undertaken by the direct care team initially, prior to confirmation of eligibility by study research nurses or AHPs depending upon local arrangements for study personnel.

2.6 Inclusion criteria: Participants will be included if they fulfil all of the following criteria:

- They are 18 years of age or over.
- They have received a clinician diagnosis of RA (ACR 2010 criteria) and have disease durations of less than 2 years from diagnosis.
- They have 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 detected during clinical examination by the rheumatologist or rheumatology nurse specialist.
- They are willing to participate in the study and provide written informed consent.
- They have sufficient English language abilities to participate in a dialogue-based intervention and undertake completion of written questionnaires.

2.7 Exclusion criteria:

- Participants will be excluded if they fulfil any of the following criteria:
- They are not able to undertake or complete the intervention (e.g. due to severe co morbid disease) identified by their consultant rheumatologist prior to screening, or the research nurse at screening.
- They are unable or unwilling to provide informed consent
- 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.

2.8 Duration of treatment: The intervention period will be 12 weeks from the first clinical consultation with the physiotherapist/podiatrist.

2.9 Statistical and qualitative analyses: Evaluation of measurement properties of primary outcome measure candidates:-

- Minimal clinical important difference (MCID) [1] for each outcome measure will be calculated using participant's perceptions of the overall treatment effect at 12 week follow-up using a 7-point global rating of change scale. The minimal important difference for each measure will be calculated as the mean change score in participants who according to the anchor improved, minus the mean change score in participants who did not improve or whose symptoms worsened.
- Longitudinal validity of the primary outcome measure candidates relative to the global rating of change scale will be evaluated. Associations of change scores will be determined through regression analyses between candidate outcome measures and the anchor.
- Responsiveness of the primary outcome candidates to intervention from baseline to 12-week follow-up will be evaluated using four different effect size statistics: the paired t-test, Cohen's d, standardised response mean (SRM) and the Guyatt index (GI).

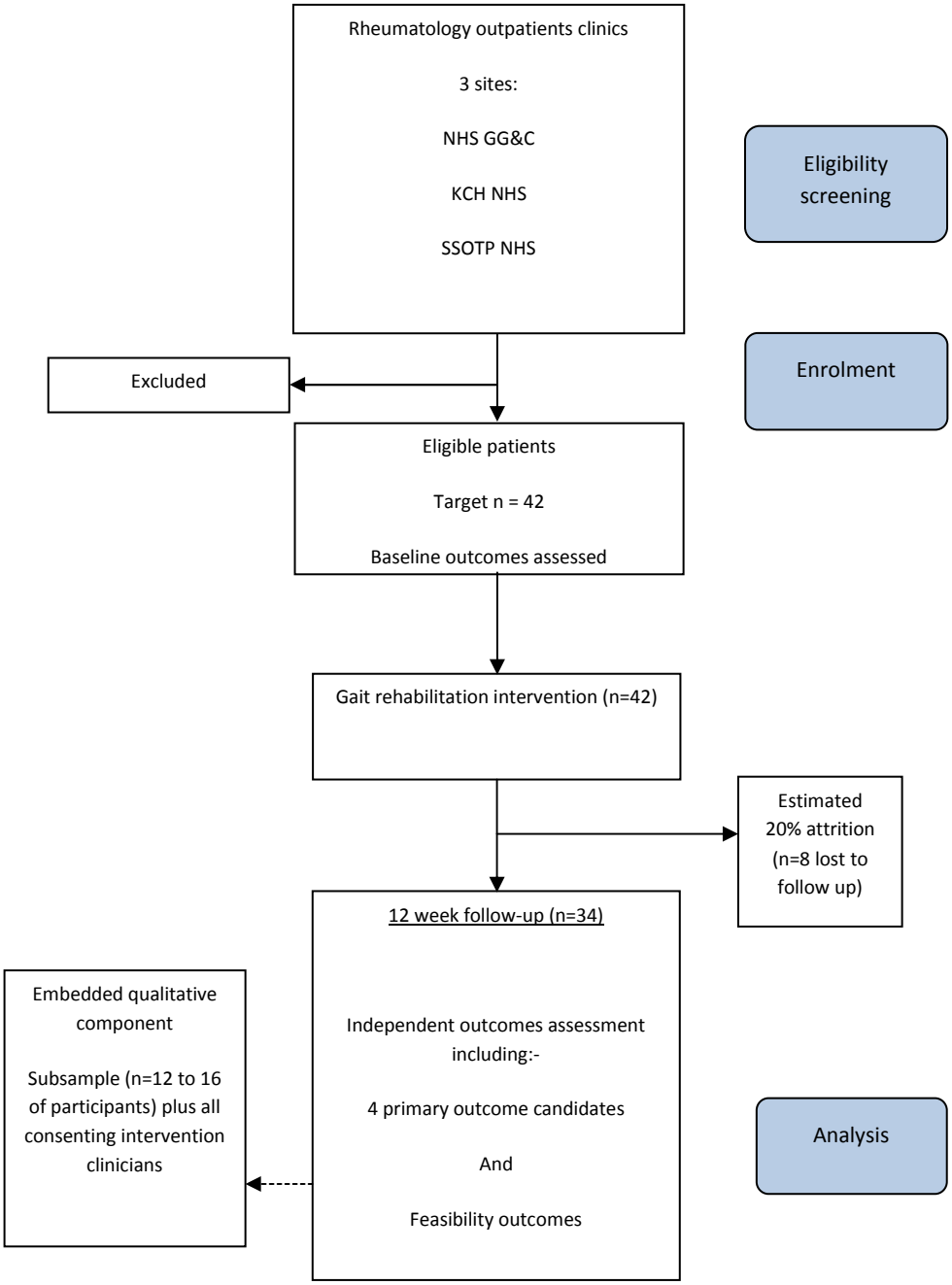
2.10 Remaining analyses will focus on process measures. Analysis will include the following aspects:-

- Acceptability of the intervention will be evaluated using a 3-item 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.

2.11 Intervention fidelity data will be gathered from participants and study intervention clinicians and analysed as follows:-

- Deviations from intervention protocols will be recorded using intervention checklists and will be analysed using descriptive statistics.
- Thematic analysis of qualitative data obtained from clinicians.
- 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.
- Behaviour beliefs will be evaluated before and after the intervention using the Theory of Planned Behaviour Questionnaire and will be analysed using descriptive and non-parametric statistics.

3. Study Flowchart:



4. Schedule of assessments

Study procedure	Description	Visit 1 Baseline	Visit 2 12 weeks	>12<16 weeks*
Review Inclusion/Exclusion Criteria and confirm eligibility	Initial screening will be conducted by a member of the direct care team. Review of inclusion/exclusion criteria to confirm eligibility will be conducted by a trained study research nurse/AHP and will be recorded on an Eligibility Screening Form	✓		
Obtain Informed Consent	Upon confirmation of the patient's willingness to participate, eligibility will be confirmed by telephone and participants will be invited to attend a appointment to check eligibility to participate and for the recruiting researcher to obtain written informed consent.	✓		
Demographics	Age, gender, employment status, height, weight and ethnicity will be recorded for each participant on the case report form.	✓		
Clinical data	Current medication regimen, current/previous AHP treatments, DAS28 score (from routine care via the direct care team), self-reported disease duration will be recorded for each participant on the case report form.	✓	✓	
Adverse Event Review			✓	
Foot function index disability subscale	9-item questionnaire with response by visual analogue scale	✓	✓	
Patient Reported Outcome Measurement Information System physical function short form (PROMIS PF-20)	20-item questionnaire with response by 5-point Likert scale	✓	✓	
10-metre walking velocity	Performance-based measure: 10-metre walking velocity using a marked unobstructed distance of 10-metres and a stopwatch	✓	✓	
Recent-onset arthritis disability questionnaire lower extremity subscale (ROADles)	4-item questionnaire with response by 5-point Likert scale	✓	✓	
Exercise adherence rating scale (EARS)	6-item questionnaire with response by 5-point Likert scale		✓	
Intervention acceptability questionnaire	3-item questionnaire with response by 5-point Likert scale		✓	
Client service receipt inventory	Adapted version of the 6-item form		✓	
Qualitative interviews	We will purposively subsample of between 12-16 participants for the generation of qualitative data using semi-structured, telephone-based interviews. All consenting intervention clinicians (up to approximately n=12 across all 3 sites) will also be invited to participate in semi-structured telephone-based interviews.			✓
*Qualitative interviews with sub-sample of participants and consenting intervention clinicians				

5.1 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 [2-4]. During the early post-diagnosis stage around 65% of patients experience foot pain and swelling and 60% report walking-related disability [5]. 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 [5]. Self-reported walking disability at 2 years post-diagnosis has been identified as the main predictor of persistent walking disability [6]. 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 [7-9]. Activity monitoring studies suggest that people with RA also take fewer steps, are more sedentary, and are less physically active [10-13]. 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 [14-16]. 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) [7,17-20]. Gait and walking activity pattern compensations in RA are consistent with the avoidance of pain, stiffness, fatigue and exacerbations of disease (flare) [7,17-20]. 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 [17,221-23]. 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 [12]. Avoidance of painful movements and activities appears to be the key contributor to functional decline in RA [24,25]. Resultant lower limb muscle weakness and poor muscle endurance are common and are associated with reduced walking speed and impaired physical function [8,9,26-31]. 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 [32]. There is an increased risk of falls in RA and impaired balance and fear-of-falling are associated with reduced walking speed and disability [32-35]. At present, it is unclear whether current usual care for people with early RA is sufficient to improve these functional impairments.

5.2 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 [36]. Improvements in disease characteristics following first-line medical management in early RA are well recognised [36,37], and lower limb function and walking ability generally improve for some patients [5,42,43]. However there is significant evidence demonstrating that foot pain, foot disease activity, gait problems and walking disability persist for a significant proportion of patients [10,38,39]. 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 [41-44].

Gait rehabilitation is a management strategy which is commonly used for improving independent walking capacity in neurological disorders such as stroke [45-49]. Definitions vary, but gait rehabilitation is largely considered to be the repetitive practice of gait cycles in order to improve walking ability [47,49]. There is good evidence that gait patterns can be improved as a result of gait rehabilitation in neurological disorders [45-50]. 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 [51,52]. However, gait rehabilitation is not recognised as a usual care intervention for early RA and evidence of efficacy and clinical protocols are lacking. Therefore a new gait rehabilitation intervention needs to be developed and tested.

There are several reasons why a feasibility study of gait rehabilitation is needed now: - 1) the current evidence suggests that there is a significant unmet need for therapeutic intervention in order to improve, maintain and/or prevent the deterioration of walking abilities of people with early RA [6,53]. Walking disability is one of the key drivers of sedentary behaviour and physical inactivity and is therefore linked to cardiovascular disease and morbidity and mortality in RA [10,54]; 2) there is a growing evidence base for earlier deployment of rehabilitation strategies in RA in order to exploit a therapeutic window of opportunity whereby prevention of walking disability can be achieved [10,54]; 3) gait rehabilitation has a strong evidence base for management of impaired gait in neurological conditions and has recently shown promise in established RA; 4) gait problems in RA are driven by joint pain, stiffness and fatigue [8,9,28-30,55], and are likely influenced by psychological factors such as fear avoidance and low exercise self-efficacy [7,17-20,28,56]. Resultant poor balance, proprioception, muscle endurance/weakness and psychological factors are credible therapeutic targets for prevention of deterioration of gait; 5) there have been no trials of gait rehabilitation in early RA; 6) it is not clear whether or not the addition of gait rehabilitation to usual care in early RA would be clinically and/or cost-effective relative to usual care provided alone.

This feasibility study will test the acceptability of a gait rehabilitation intervention in early RA and inform a future funded main RCT to investigate the clinical and cost-effectiveness of gait rehabilitation for people with early RA.

6. Study Objectives

The overall aim of this study is to develop and refine a new gait rehabilitation intervention for people with early RA in order to inform the design of a main RCT. Specific objectives are detailed as follows:

1. To evaluate the measurement properties (responsiveness, minimal important difference) of candidate outcome measures to identify and select the most suitable primary outcome measure for the future main trial.

2. To evaluate the acceptability of the new gait rehabilitation intervention by exploring participants' and clinicians' views and experiences.

3. To assess the safety of the new gait rehabilitation intervention by monitoring, recording and evaluating adverse/unintended outcomes.

4. To evaluate whether or not participants adhere to the new gait rehabilitation intervention and identify potential barriers/facilitators of adherence.

5. To evaluate whether or not the new gait rehabilitation intervention can be delivered as intended by participating physiotherapists and podiatrists.

6. To review and refine if necessary the new gait rehabilitation intervention prior to final development of the new gait rehabilitation intervention manual for the future main trial.

7. To monitor and evaluate participant recruitment and retention rates.

8. To monitor and report data completion rates for candidate primary outcome measures.

7. Design

There are three evaluations which comprise the feasibility phase: 1) evaluation of measurement properties of potential primary outcome measures; 2) mixed-methods evaluation of intervention acceptability, adherence and safety; and 3) qualitative evaluation of intervention fidelity. The design for all 3 studies will be a multi-centre, single-arm, repeated measures (pre- and post-intervention) design.

8.1 Study population

The target population from which the study population will be sampled for each phase of this project will be adults who have a clinician diagnosis of rheumatoid arthritis (meet ACR 2010 criteria for rheumatoid arthritis) [57] who have disease durations of less than 2 years and who also have disease-related foot impairments (either foot pain or synovitis). The research evidence strongly suggests that delivery of an effective gait rehabilitation intervention within the first 2 years of RA will provide the best opportunity to prevent walking disability, which strongly justifies our focus on patients within this critical window [6,53]. 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 and biologic drug therapies [58]. People with RA experience heterogeneous disease course and disability outcome trajectories during the first two years after diagnosis [58-60]. 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 [58-60]. To maximise external validity we have opted for a broad inclusion criteria, focusing on those with foot pain, which is associated with disrupted gait and walking disability [55].

8.2 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 (meet ACR 2010 criteria for RA [57]) and have disease durations less than 2 years from diagnosis.

3. They have 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.

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

5. They have sufficient English language abilities to participate in a dialogue-based intervention and undertake completion of written questionnaires.

8.3 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. Identification of participants and consent

Potentially eligible adults with early rheumatoid arthritis will be identified by one of two methods which will proceed in parallel and are described below:

9.1. Patients who are attending early arthritis outpatient clinics and who either self-report foot pain, 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 (research nurse or AHP as appropriate depending upon local site personnel arrangements) by the consultant rheumatologist where possible, or with the patient's consent will be referred to the recruiting researcher by the consultant rheumatologist by telephone/email. If the recruiting researcher is not available in clinic, then the patient will be asked to sign a form to say that they agree to have their identifiable data given to the researcher who will subsequently contact them by telephone. The recruiting researcher will provide verbal information about the study and will provide a participant information leaflet and will then ask for permission to undertake screening and confirm the patient's willingness to participate by phone after a minimum of 24 hours. Upon confirmation of the patient's willingness to participate, the patient will be invited to attend a baseline appointment where eligibility will be checked and the recruiting researcher will seek to obtain written informed consent. Consented and enrolled participants will then undergo baseline outcome assessment and will be referred to the intervention clinician to receive the intervention.

9.2. 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. Invitation packs will include an information leaflet, a screening survey for study inclusion and exclusion criteria to indicate willingness to take part; consent to be contacted and preferred method of contact. Participants will also be provided with study recruitment personnel contact details for seeking further information. Non-responders will be sent 1 further reminder two weeks later. 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 and will be referred to the intervention clinician at the relevant site to receive the intervention.

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.

11. Study schedule

This study will involve a maximum of two research-specific visits. A baseline measurements visit (including eligibility check), and a 12-week post-intervention follow-up visit for measurement of outcomes. The 12-week follow-up will ideally be undertaken at the end of the 12 week period commencing from the first clinical consultation for delivery of the study intervention. The details of study procedures for each visit are outlined below. A sub-sample of participants from the feasibility study as well as consenting intervention clinicians will be invited to participate in telephone-based interviews in order to undertake a deeper exploration of intervention acceptability, adherence, and safety.

11.1 Visit 1

- Final eligibility checks according to inclusion/exclusion criteria. Eligibility checks will be conducted by a trained research nurse/AHP and will be recorded on an Eligibility Screening Form.
- Obtain informed consent. The study team member will gain verbal and 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 score (from routine care), disease duration will be recorded for each participant on the case report form.
- Foot function index questionnaire
- Patient reported outcome measurement information system physical function short form (PROMIS PF-20)
- 10-meter walking velocity.
- Recent-onset arthritis disability questionnaire lower extremity subscale (ROADLes)

11.2 Visit 2

- 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.
- Foot function index questionnaire
- Patient reported outcome measurement information system physical function short form (PROMIS PF-20)
- 10-meter walking velocity

- Recent-onset arthritis disability questionnaire lower extremity subscale (ROADLes)
- Exercise adherence rating scale (EARS)
- Intervention acceptability questionnaire
- Client service receipt inventory

11.3 Telephone based interviews

- From the main sample (n=42) we will purposively subsample between 12-16 participants as is standard practice for the generation of qualitative data using an interpretative phenomenological approach (IPA) [61]. Semi-structured, telephone-based interviews will be conducted to minimise the potential burden on participants by avoiding the need for attending further research appointments [62].
- All consenting intervention clinicians (up to approximately n=12 across all 3 sites) will be invited to participate in semi-structured telephone-based interviews.

12. Study outcome measures

12.1 Feasibility study 1

Measurement properties of primary outcome measures: At present there are no recognised outcome measures for the measurement of lower limb function that have been used for the early RA population. Promising instruments exist but these have not been used specifically in the early RA population and therefore important information concerning measurement properties such as 'meaningful levels of change' and 'responsiveness' are lacking. To address this gap, responsiveness and meaningful levels of change of primary outcome measure candidates will be evaluated at 12 weeks from randomisation using anchor and distribution-based approaches [63-65].

The foot function index disability subscale (FFIdis) is a 9-item, foot-specific patient-reported outcome measure designed to measure self-reported foot-related disability and which was developed using classical test theory for people with RA. Item response is via 100mm visual analogue scales to indicate level of difficulty experienced in the previous week due to foot problems. The item scores are summed, divided by the maximum possible sum of the item scores and then multiplied by 100. The scores range from 0 to 100; higher the scores reflect more severe foot-related disability respectively. It has a high degree of internal consistency, good test –retest reliability, is considered to be responsive to change [66-70] and has been widely used in observational studies and trials of foot interventions in established RA [71,72]. Moreover, the FFIdis is quick and simple to use and has excellent face validity with the inclusion of items relevant to functional walking tasks such as "Walking outside", "Climbing stairs", and "Standing up from a chair".

The Patient Reported Outcome Measurement Information System physical function short form (PROMIS PF- 20) is a 20-item, generic patient-reported outcome measure designed to measure self-reported physical functional ability and which is based on item response theory (IRT) [73]. Item response is via 5-point likert scale to indicate current level of difficulty in undertaking tasks related to physical function, and scoring is conducted by summing raw item scores, multiplying them by the number of items in the short form, and dividing by the by the number of items that were answered. Raw scores are then translated to a T-score for each participant [74]. PROMIS PF-20 has emerged as a valid and reliable outcome measure of physical function in rheumatoid arthritis which is now considered to have greater responsiveness and precision relative to traditional legacy instruments such as the health assessment questionnaire (HAQ) and short form 36 (SF36) [75,76]. Moreover, short forms can be customised from a PROMIS PF item bank in order to more optimally reflect those aspects of physical function that are relevant for early RA patients with foot problems [75].

Walking velocity is an objective measure of walking capacity/functional mobility that has been used as an outcome measure in several studies in RA [7]. It appears to be one of the strongest independent predictors of higher disability scores in RA populations who have foot involvement [77]. Typically, time taken to walk a specified distance, or distance walked within a specified time are used to evaluate self-selected walking velocity [77]. For the purposes of this study we will seek to measure 10-metre walking velocity using a marked unobstructed distance of 10-metres and a stopwatch. Measurement of walking velocity is considered to be valid and reliable, and previous research suggests that it may be sensitive to change in the RA population [25,78-79].

The recent-onset arthritis disability questionnaire lower extremity subscale (ROADles) is a 4-item early RA specific questionnaire designed to measure lower extremity physical function [80-83]. In relation to the previous week, subjects are asked to rate the level of difficulty in performing lower extremity function tasks on a 5 point likert scale (0 without any difficulty, 4 unable to do). Scoring is by summating the 4 items (score 0-16) then normalisation to a 0-10 scale by multiplying the raw scores by 0.625. The ROADles is considered to be valid, reliable and responsive to change [80-83].

12.2 Feasibility study 2

Evaluation of intervention acceptability, adherence and safety: We will undertake a complementary mixed-methods evaluation of intervention acceptability, adherence and safety. These feasibility outcomes will be collected following completion of the 12-week intervention period.

Intervention acceptability will be evaluated using a 3-item questionnaire which utilises 5-point Likert scales for responses. This questionnaire has been adapted from previous literature and has been used by one of our co-applicants (NF) with success in previous trials [84,85]. Questions and responses include: “How confident are you that the treatment can help the

problem?" (not at all to very), "Would you recommend the treatment to a friend with a similar problem?" (not at all confident to very confident), "Does the treatment make sense to you?" (not at all logical to very logical). For analysis, responses will be dichotomised to positive (higher 2 responses) and negative (lower 3 responses) in order to evaluate percentages of participant acceptability for progression criteria.

Treatment adherence will be examined using the Exercise Adherence Rating Scale (EARS) which is a valid and reliable self-reported measure of adherence to exercise therapies developed by one of our co-applicants (EG) [86]. The EARS has 6-items generated from a systematic review and interviews with patients, physiotherapists and psychologists. Items are scored using a 5-point Likert scale (completely agree to completely disagree), resulting in a possible score between 0-24, where a higher score indicates greater adherence [86].

To monitor safety arising as a result of the intervention, serious adverse events (SAEs), and expected events will be recorded. The physiotherapists or podiatrists delivering the intervention will record SAEs during each intervention session, using a SAE reporting form according to the Glasgow CTU standard operating procedures for RCTs. Participants and the local personnel (intervention clinicians and outcome assessors) may report SAEs to the study team at any time. In addition, at the end of the intervention period the independent outcomes assessor will ask participants whether or not they have experienced SAEs over the 12-weeks intervention period. Expected events (defined as specific non-serious events that might be related to the intervention) will be monitored and recorded using a standard form as part of the case report form (CRF). These will be evaluated by the trial management group (TMG) to determine these are related to the intervention or study and will therefore be recorded as adverse events. Adverse events will then be reported to the trial steering committee (TSC). Given the study population, expected harms might include falling, fatigue, pain and post-exercise muscle soreness (see section 5. Assessment of Safety).

As part of this mixed methods evaluation, we will also undertake qualitative research according to the interpretive phenomenology approach (IPA) in order to elaborate, enhance and clarify the results from the quantitative component outlined above (complementary mixed methods approach) [87]. From the main sample (n=42) we will purposively subsample between 12-16 participants as is standard practice for the generation of qualitative data using an IPA [88]. Semi-structured, telephone-based interviews will be conducted to minimise the potential burden on participants by avoiding the need for attending further research appointments [62]. The interviews will be arranged on a date and at a time that is convenient to participants. The data collection will commence with an opening question which will allow the participant to talk freely about their experiences. This conversational style of one to one interview allows for the data to be generated more by the participant form their own perceptions and personal experiences. Further, it allows then to reveal their true feelings and opinions without the pressure or influence of a peer group. The opening question will be followed by several trigger questions in order to keep the conversation focussed. The interview will be recorded using an adapted digital recorder.

12.3 Feasibility study 3

- Evaluation of intervention fidelity: 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 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 all consenting intervention clinicians. Interviews will explore clinicians' experiences and perceptions of delivering the intervention.
- Audio-recordings of all clinician-participant consultations will be undertaken. A random sample of 10% of gait rehabilitation consultations from each site will be evaluated objectively by independent observers using an 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 [88].
- Participants' usual care will be recorded at the end of the 12 week intervention period using a modified version of the client service receipt inventory (CSRI). The CSRI provides a standardised method of collecting information on healthcare use including medications, admissions, referrals, consultations with and care provided by other healthcare professionals, and self-care [89].

13. Assessment and reporting of safety and serious adverse events

13.1 Study Safety Assessment

The gait rehabilitation intervention proposed for this feasibility study includes several walking task components which have been adopted previously in established RA as part of a walking circuit [55] and the Otago Exercise Programme [56]. However our intervention has not been used in early RA and as such our feasibility study will seek to monitor the safety of the intervention in a small group of people with early RA before proceeding to the main trial. 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 or potentially harmful procedures.

13.2 Definitions of Adverse Events

Adverse Event (AE) - Any untoward medical occurrence in a subject 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 investigator.

13.3 Recording and Reporting AEs/SAEs

Participants will be asked at clinical visits whether or not they have experienced any adverse effects from the study intervention or study procedures. All AEs will be recorded in participant's clinical notes.

- AEs and SAEs occurring before enrollment will not be recorded or reported.
- Participants will be asked at each study visit about the occurrence of any AEs.
- All SAEs occurring within the 12 weeks of the intervention will be recorded.
- All AEs must be assessed for seriousness. SAEs must be assessed for causality, expectedness and severity.
- 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, provided to the research sites. 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.

SAE forms should be completed and sent with 24 hours of becoming aware 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, 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 to the intervention and is unexpected, the SAE will be reported to the REC within 15 days of becoming aware of the event.

13.4 Expected Event of Special Interest

For SAE's that meet the criteria of Expected Adverse Events as detailed in the list below, completion of an SAE form is NOT required; however such events should be recorded on the appropriate CRF form as soon as possible.

For all Expected AEs details recorded on the CRF 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.

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
- 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.

14. 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 [50,90-92]. Preliminary evidence suggests that similar interventions are beneficial for improving walking ability in RA [51,52]. 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. It will consist of 3 main components in addition to usual care: -

14.1 Supervised intervention sessions

Supervised intervention sessions will be delivered by a 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 face-to-face supervised intervention sessions and up to a maximum of 6 over a 12-week period. Where participants are unable to attend further supervised sessions after the first 2, telephone-based sessions will be provided as required within office hours to maintain contact, promote adherence to the home programme, and/or to provide specific advice regarding progression. The content of all contacts will be audio recorded 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 [93,94]. 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. Progression will be advised at the discretion of the clinician and controlled 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) [93,94]. 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 [94]. 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) [51]. 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.

14.2 Support materials

Support for set up and completion of the gait circuit at home will be provided. Participants will be provided with a high quality illustrated educational booklet, an adherence diary and a DVD 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 DVD 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 web support will be developed (via patient and public involvement activities) and evaluated as part of the feasibility study before being revised as required for the pilot trial and main trial phases.

14.3 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 [17,21-23]. The theory of planned behaviour is recommended for behavioural change interventions in RA [95]. This model places emphasis on individuals' perceived ability to perform a given behaviour and their attitudes to initiate behavioural change [96]. The psychological elements of our intervention are based upon motivational interviewing (MI), which will be enhanced through development of implementation intentions to overcome barriers and facilitate translation of intentions into action [97].

The gait rehabilitation intervention is underpinned by the theory of planned behaviour (TPB) [98,99]. This has been widely used in health psychology to examine behavioural intentions, perceived behavioural control and subjective norms as precursors of actual behaviour. MI is a collaborative, goal oriented style of communication where particular attention is paid to the language of change [100]. It has 4 fundamental processes: engaging, guiding, evoking, and planning and is designed to strengthen personal motivation for, and commitment to, a specific goal by eliciting and exploring a person's own reason for change within an atmosphere of acceptance and compassion. Training in this empathetic and non-

judgemental approach to communication around health behaviour change is suitable for non-specialist health professionals and can therefore be included in the gait rehabilitation programme.

Clinicians will receive training on how to deliver the intervention over two full days. This training will also 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.

15. Statistical analysis plan

Calculation of meaningful levels of change: A two-step iterative approach will be adopted for the selection of the most suitable primary outcome measure for the main trial. To determine the minimal clinical important difference (MCID) for each outcome measure, participant's perceptions of the overall treatment effect will be recorded at 12 week follow-up using a 7-point global rating of change scale (defined as change in walking ability) as a patient-rated anchor [101,102]: "Overall how has your walking ability changed since the start of the study?", with a 7-point Likert scale response ("Very much worse", "Much worse", "A bit worse", "No change", "A bit better", "Much better", "Very much better"). In the absence of a gold reference standard for measurement of gait ability in early RA, the first iteration will be to evaluate the longitudinal validity of the primary outcome measure candidates relative to the global rating of change scale. Linear associations of change scores will be determined through correlation statistics between candidate outcome measures and the anchor. Candidate outcome measures will be excluded at the first iteration if they do not achieve the minimum threshold of association ($r \geq 0.65$) with the anchor [101,103]. The minimal important difference for each remaining measure, will be calculated as the mean change score in participants who according to the anchor, improved, minus the mean change score in participants who did not improve or whose symptoms worsened [101,103,105].

Calculation of responsiveness: Responsiveness of the primary outcome candidates to intervention from baseline to 12-week follow-up will be evaluated using four different effect size statistics: the paired t-test, Cohen's d, standardised response mean (SRM) and the Guyatt index (GI) [103-108]. To aid interpretation of the effect size statistics, the following benchmarks will be used: negligible (<0.15), small (≥0.15 and <0.40), medium (≥0.40 and <0.75), large (≥0.76 and <1.10), very large (≥1.10 and <1.45) and huge effect size s (>1.45) [104]. The larger the effect size, the more responsive the outcome measure.

Selection of primary outcome for the future randomised trial: For the second iteration, results of the analyses of the primary outcome candidates from the feasibility phase will be compiled in a report which will be presented to the both the TMG and the TSC who will be tasked with recommending which outcome should be taken forward to the main RCT. The TMG will be asked to consider the relative simplicity of the candidate outcome measures (to reduce participant burden), the strength of correlations with the anchor, and responsiveness.

16. 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: 3-item 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 using 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 [109].

17. Software for statistical analysis

Statistical analyses will be carried out using standard statistical software, such as SAS or R.

18. Sample size

For the purposes of evaluating measurement properties of primary outcome candidates, we have selected a minimum magnitude of association (correlation coefficient) between the selected anchor and outcome measures of r=0.65 [101,102]. With a feasibility study sample size of at least n=42, we can detect a correlation ≥0.65 at 5% significance with 80% power, accounting for 20% attrition.

19. Management and delivery

The Robertson Centre for Biostatistics which is part of the Glasgow Clinical Trials Unit and a fully UKCRC-registered Clinical Trials Unit, will manage and analyse data. All statistical analyses will be conducted according to the pre-specified Statistical Analysis Plan.

20. Study closure / definition of end of study

The study will end when the TSC agrees that one or more of the following situations applies:

- Last participant, last study visit (including qualitative interviews);

OR

i. The planned sample size for each aspect of the study (repeated measures plus embedded qualitative work) has been achieved;

ii. New information makes it inappropriate to continue to deliver the study intervention;

iii. Recruitment is so poor that completion of the study cannot reasonably be anticipated.

21. Case report forms

A paper-based case report form (CRF) will be used to collect study data. The CRF will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow. Site-specific personnel will complete the CRF for each participant and will subsequently securely mail completed CRFs to the Data Centre at the Robertson Centre for Biostatistics. Paper-based CRFs will be anonymised and will not include any identifiable information. Study personnel at the Data Centre will enter CRF data into an eCRF for analysis. Access to the eCRF will be restricted, with only authorised data centre personnel able to make entries or amendments to participants' data. It is the investigator's responsibility to ensure completion and to review and approve data captured in the CRF.

All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

22. Record retention

To enable evaluations and/or audit from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link

record), all original signed informed consent forms, serious adverse event forms, source documents,detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years.

23. 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.

Glasgow CTU: The study will be supported by Glasgow CTU (lead). 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.

24. Routine management of study: trial management group

The study will be co-ordinated from the Glasgow Clinical Trials Unit by the Trial Management Group. 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. Face-to-face meetings will be held at the beginning of the feasibility study. 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.

25. 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, Arthritis Research UK (ARUK), 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.

26. Protocol amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TSC and any required amendment forms will be submitted to the regulatory authority, REC and sponsor.

The CI and TSC will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.

Before the amended protocol can be implemented, favourable opinion/approval will be sought from the original reviewing REC and Research and Development (R&D) office(s).

27. Ethical conduct of the study

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).

Favourable ethical opinion will be sought from West of Scotland Research Ethics Service before participants are entered into this study. The CI will be responsible for updating the REC of any new information related to the study.

28. Informed consent

Written informed consent will be obtained from each study participant. The research nurse or investigator will explain the exact nature of the study in writing by provision of the participant information sheet and verbally. This will include the known side-effects that may be experienced and the risks of participating in this study. Study participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

29. Insurance and indemnity

The GREAT-FS study is sponsored by Glasgow Caledonian University. The sponsor will be liable for negligent harm caused by the design of the study. Glasgow Caledonian University will provide legal liability cover for their employed staff. NHS indemnity will apply for all patients treated within NHS sites.

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.

30. Funding

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

31. Timescales

October 2017 – December 2017 – develop and finalise the protocol for the feasibility study, first trial steering committee to finalise the protocol, finalise recruitment procedures and documentation for ethics application.

November 2017 – February 2018 – submit research ethics application and subsequently R&D applications, deliver intervention and protocol training to intervention delivery staff, set-up procedures and site initiation visits.

January 2018 – July 2018 – recruitment of study participants, delivery of intervention over 12 weeks, commence follow ups following completion of 12 week intervention period, data entry.

July 2018 – September 2018 – completion of study follow-ups, completion of qualitative data collection, data entry and analysis.

September 2018 – December 2018 – complete data analysis, write-up and finalise gait rehabilitation intervention for internal pilot trial. A separate protocol will be developed and submitted for approvals for the internal pilot and main trial.

32. References

1. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining minimal clinically important difference. Control Clin Trials 1989 10 (4): 407-15.
2. National Audit Office. Services for people with rheumatoid arthritis.2009.

3. Grondal L, Tengstrand B, Nordmark B, Wretenberg P, Stark A. The foot: still the most important reason for walking incapacity in rheumatoid arthritis: distribution of symptomatic joints in 1,000 RA patients. Acta Orthop 2008;79:257-261.
4. Michelson J, Easley M, Wigley FM, Hellma D. Foot and ankle problems in rheumatoid arthritis. Foot Ankle Int 1994;15:608-13.
5. van der Leeden M, Steultjens MP, Ursum J, Dahmen R, Roorda LD, Schaardenburg DV, Dekker J. Prevalence and course of forefoot impairments and walking disability in the first eight years of rheumatoid arthritis. Arthritis Rheum 2008;59:1596-1602.
6. Van der Leeden M, Dahmen R, Ursum J, Roorda LD, van Schaardenburg D, Knol DL, Dekker J, Steultjens MPM. Prediction of walking disability by disease-related factors in patients with rheumatoid arthritis. J Rehab Med 2010;42:506-510.
7. Carrol M, Parmar P, Dalbeth N, Boocock M, Rome K. Gait characteristics associated with the foot and ankle in inflammatory arthritis: a systematic review and meta-analysis. BMC MSK Disorders 2015,16:134.
8. Baan H, Dubbeldam R, Nene AV, van de Laar MAFJ. Gait analysis of the lower limb in patients with rheumatoid arthritis: a systematic review. Semin Arthritis Rheum 2012,41:768-788.
9. Weiss RJ, Wretenberg P, Stark A, Palmblad K, Larsson P, Grondal L, Brostrom E. Gait pattern in rheumatoid arthritis. Gait & Posture 2008,28:229-234.
10. Paul L, Rafferty D, Marshall-McKenna R, Gill JMR, McInnes I, Porter D, Woodburn J. Oxygen cost of walking, physical activity and sedentary behaviours in rheumatoid arthritis. Scan J Rheumatol 2014;43:28-34.
11. Piva SR, Almeida GJM, Wasko MCM. Association of physical function and physical activity in women with rheumatoid arthritis. Arthrit Care Res 2010;62:1144–51.
12. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum 2009;61:1726–34.
13. Tourinho TF, Capp E, Brenol JC, Stein A. Physical activity prevents bone loss in premenopausal women with rheumatoid arthritis: a cohort study. Rheumatol Int 2008;28:1001–7.
14. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Wilson M, Nevill AM, Koutedakis Y, et al. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. J Cardiovasc Risk 2009;16:188–94.
15. Turesson C, Matteson EL. Cardiovascular risk factors, fitness and physical activity in rheumatic diseases. Curr Opin Rheumatol 2007;19:190–6.

16. Sattar N, McInnes IB. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. Curr Opin Rheumatol 2005;17:286–92.
17. Van Zanten JJCSV, Rouse PC, Hale ED, Ntoumanis N, Metsios GS, Duda JL, Kitas GD. Perceived barriers, facilitators and benefits for regular physical activity and exercise in patients with rheumatoid arthritis: a review of the literature. Sports Medicine 2015,45:1401- 1412.
18. Nordgren B, Friden C, Demmelmaier I, Opava CH. Who makes it to the base? Selection procedure for a physical activity trial targeting people with rheumatoid arthritis. Arthritis Care Res 2014;66:662-670.
19. Brenton-Rule A, D'Almeida S, Bassett S, Carroll M, Dalbeth N, Rome K. The effects of sandals on postural stability in patients with rheumatoid arthritis: an exploratory study. Clinical Biomechanics 2014;29:350-353.
20. Turner DE, Helliwell PS, Emery P, Woodburn J. The impact of rheumatoid arthritis on foot function in the early stages of disease: a clinical case series. BMC Musculoskeletal Disorders 2006, 7:102.
21. Vervloesem N, van Gils N, Ovaere L, Westhovens R, van Assche D. Are personal characteristics associated with exercise participation in patients with rheumatoid arthritis? A cross-sectional explorative survey. Musculoskeletal Care 2012;10:90-100.
22. Crowley L, Kennedy N. Barriers to exercise in rheumatoid arthritis – a focus group study. Physiotherapy Practice and Research 2009;30:27-33.
23. Wilcox S, Der AC, Abbott J, et al. Perceived exercise barriers, enablers, and benefits among exercising and non exercising adults with arthritis: results from a qualitative study. Arthritis Rheum 2006,55;4:616–27.
24. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology 2002;41:157–166.
25. Hakkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. Arthritis and Rheumatism 2001;44:515-22.
26. Wilkinson TJ, Lemmey AB, Jones JG, Sheikh F, Ahmad YA, Chitale S, Maddison PJ, O'Brien TD. Can creatine supplementation improve body composition and objective physical function in rheumatoid arthritis patients? A randomised controlled trial. Arthritis Care Res 2016;68:729-37.

27. Challal S, Minichiello E, Boissier MC, Semerano L. Cachexia and adiposity in rheumatoid arthritis. Relevance for disease management and clinical outcomes. Joint Bone Spine 2016;83:127-33.
28. Lusa AL, Amigues I, Kramer HR, Dam T-T, Giles JT. Indicators of walking speed in rheumatoid arthritis: relative influence of articular, psychosocial, and body composition characteristics. Arthritis Care & Research 2015,67;1:21-31.
29. Kramer HR, Fontaine KR, Bathon JM, Giles JT. Muscle density in rheumatoid arthritis: associations with disease features and functional outcomes. Arthritis & Rheumatism 2012,64;8:2438-2450.
30. Giles JT, Bartlett SJ, Fontaine KR, Bathon JM. Association of body composition with disability in rheumatoid arthritis: impact of appendicular fat and lean tissue mass. Arthritis Rheum 2008,59;10:1407–1415.
31. Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr 2006;84:1463-72.
32. Rome K, Dixon J, Gray M, Woodley R. Evaluation of static and dynamic postural stability in established rheumatoid arthritis: exploratory study. Clinical Biomechanics 2009;24:524-6.
33. Morpeth T, Brenton-Rule A, Carroll M, Frecklington M, Rome K. Fear of falling and foot pain, impairment and disability in rheumatoid arthritis: a case-control study. Clinical Rheumatology 2015: DOI 10.1007/s10067-015-3124-6.
34. Stanmore EK, Oldham J, Skelton DA, O'Neill T, Pilling M, Campbell AJ, Todd C. Risk factors for falls in adults with rheumatoid arthritis: a prospective study. Arthritis Care & Research 2013,65;8:1251-1258.
35. Hayashibara M, Hagino H, Katagiri T, Okano T, Okada J, Teshima R. Incidence and risk factors of falling in ambulatory patients with rheumatoid arthritis: a prospective 1-year study. Osteoporosis International 2010;21:1825-33.
36. Smolen JS, Landewe R, Breeveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JWJ, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G, van Volenhoven R, Winthrop KL, Wong J, Zink A, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-975.

37. McInnes I, O'Dell JR. State-of-the-art: rheumatoid arthritis. Ann Rheum Dis 2010;69:1898- 1906.
38. Broström EW, Esbjörnsson A-C, von Heideken J, Larsson P, Wretenberg P, Iversen M. Change in gait deviation index after anti-tumour necrosis factor-α treatment in individuals with rheumatoid arthritis: a pilot study. Scandinavian Journal of Rheumatology 2013;42:356- 361.
39. Hamilton J, Brydson G, Fraser S, Grant M. Walking ability as a measure of treatment effect in early rheumatoid arthritis. Clinical Rehabilitation 2001;15:142-7.
40. Otter SJ, Lucas K, Springett K, Moore A, Davies K, Young A, Walker-Bone K. Comparison of foot pain and foot care among rheumatoid arthritis patients taking and not taking anti- TNFα therapy: an epidemiological study. Rheumatol Int 2010;31:1515-19.
41. Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology 2012,51:519-527.
42. Oldfield V, Felson DT. Exercise therapy and orthotic devices in rheumatoid arthritis: evidence based review. Curr Opin Rheumatol 2008;20:353-359.
43. Hurkmans E, van der Giesen FJ, Vliet Vlieland TPM, Schoones J, Van den Ende ECHM. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database of Systematic Reviews 2009,4: CD006853.
44. van den Ende, Vliet Vlieland TPM, Munneke M, Hazes JMW. Dynamic exercise therapy in rheumatoid arthritis: a systematic review. British Journal of Rheumatology 1998;37:677-687.
45. Mehrholz J, Kugler J, Storch A, PohlM,Hirsch K, Elsner B. Treadmill training for patients with Parkinson's disease. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD007830.
46. Mehrholz J, Pohl M, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev 2014;1:Cd002840 doi: 10.1002/14651858.CD002840.pub3.
47. Mehrholz J, Elsner B, Werner C, et al. Electromechanical-assisted training for walking after stroke. Cochrane Database Syst Rev 2013;7:Cd006185 doi: 10.1002/14651858.CD006185.pub3.
48. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD006676.

49. Mehrholz J, Friis R, Kugler J, et al. Treadmill training for patients with Parkinson's disease. Cochrane Database Syst Rev 2010(1):Cd007830.
50. Hollands KL, Pelton TA, Wimperis A, Whitham D, Tan W, Jowett S, Sackley CM, Wing AM, Tyson SF, Mathias J, Hensman M, van Vliet PM. Feasibility and preliminary efficacy of visual cue training to improve adaptability of walking after stroke. Multi-centre, single-blind randomised control pilot trial. PLoS ONE 2015;10: e0139261.
51. da Silva KNG, de Paiva Teixeira LEP, Imoto AM, Atallah AN, Peccin MS, Trevisani VFM. Effectiveness of sensorimotor training in patients with rheumatoid arthritis: a randomized controlled trial. Rheumatol Int 2012,33:2269-2275.
52. Williams SB, Brand CA, Hill KD, Hunt SB, Moran H. Feasibility and outcomes of a homebased exercise program on improving balance and gait stability in women with lower-limb osteoarthritis or rheumatoid arthritis: a pilot study. Arch Phys Med Rehabil 2010,91:106-114.
53. Woodburn J, Hennessy K, Steultjens MPM, McInnes IB, Turner DE. Looking through the 'window of opportunity': is there a new paradigm of podiatry care on the horizon in early rheumatoid arthritis? J Foot Ankle Res 2010;3:8.
54. Liao K, Solomon DH. Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. Rheumatology 2013;52:45-52.
55. Turner DE, Helliwell PS, Siegel KL, Woodburn J. Biomechanics of the foot in rheumatoid arthritis: identifying abnormal function and the factors associated with localised disease 'impact'. Clin Biomech (Bristol, Avon) 2008;23:93-100.
56. Demmelmaier I, Dufour AB, Nordgren B, Opava CH. Trajectories of physical activity over two years in persons with rheumatoid arthritis. Arthritis Care Res 2016; DOI 10.1002/acr.22799.
57. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
58. Norton S, Fu B, Scott DL, Deighton C, Symmons DPM, Wailoo AJ, Tosh J, Lunt M, Davies R, Young A, Verstappen SMM. Health assessment questionnaire disability

progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Seminars in Arthritis and Rheumatism 2014;44:131-44.

59. Barnaby C, Sun Y, Boire G, Hitchon CA, Haraoui B, Thorne JC, van der Heijde D, Curtis JR, Jamal S, Pope JE, Keystone EC, Bartlett S, Bykerk VP, CATCH Investigators. Heterogeneous disease trajectories explain variable radiographic, function and quality of life outcomes in the Canadian early arthritis cohort (CATCH). PLOS One 2015;10: e0135327.
60. Siemons L, ten Klooster PM, Vonkeman HE, Glas CAW, van de Laar MAF. Distinct trajectories of disease activity over the first year in early rheumatoid arthritis patients following a treat-to-target strategy. Arthritis Care Res 2014;66:625-30.
61. Brocki JM, Wearden AJ. A critical evaluation of the use of interpretative phenomenological analysis (IPA) in health psychology. Psychol Health 2006;21:87-108.
62. Fenig S, Levav I, Kohn R, Yelin N. Telephone vs face-to-face interviewing in a community psychiatric survey. Am J Public Health 1993;83:896-8.
63. Kazis LE, Anderson JJ, Meenan RF: Effect sizes for interpreting change in health status. Med Care 1989, 27:S178–S189.
64. Guyatt G, Walter S, Norman G: Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis 1987, 40:171–178.
65. Hays RD, Spritzer KL, Fries JF, Krishnan E. Responsiveness and minimally important difference for the patient-reported outcomes measurement and information system (PROMIS®) 20-item physical functioning short-form in a prospective observational study of rheumatoid arthritis. Ann Rheum Dis 2015,74;1:104-107.
66. Muradin I, van der Heijde HJL. The foot function index is more sensitive to change than the Leeds Foot Impact Scale for evaluating rheumatoid arthritis patients after forefoot or hindfoot reconstruction. International Orthopaedics 2016;40:745-9.
67. Madeley NJ, Wing KJ, Topliss C, Penner MJ, Glazebrook MA, Younger AS. Responsiveness and validity of the SF-36, Ankle Osteoarthritis Scale, AOFAS Ankle Hindfoot Score, and Foot Function Index in end stage ankle arthritis. Foot & Ankle International 2012;33:57-63.
68. Landorf KB, Radford JA. Minimal important difference: values for the foot health status questionnaire, foot function index and visual analogue scale. The Foot 2008;18:15-19.
69. Soohoo NF, Vyas R, Samini D. Responsiveness of the Foot Function Index, AOFAS clinical rating systems, and SF-36 after foot and ankle surgery. Foot & Ankle International 2006;27:930-4.

70. Landorf KB, Keenan AM. An evaluation of two foot-specific, health-related quality of life measuring instruments. Foot & Ankle International 2002;23:538-46.
71. Budiman-Mak E, Conrad KJ, Roach KE. The foot function index: a measure of foot pain and disability. J Clin Epidemiol. 1991;44:561-570.
72. Budiman-Mak E, Conrad KJ, Mazza J, Stuck RM. A review of the foot function index and the foot function index – revised. J Foot Ankle Res 2013;6:5.
73. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, DeVellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai J-S, Pilkonis P, Revicki D, Rose M, Weinfurt K, Hays, PROMIS Cooperative Group. The patient-reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. Journal of Clinical Epidemiology 2010;63:1179-94.
74. PROMIS. Instrument development and validation. 2013. http://www.nihpromis.com/Documents/PROMISStandards_Vers2.0_Final.pdf. PROMIS.
75. Voshaar MAHO, ten Klooster PM, Taal E, van de Laar MAFJ. Measurement properties of physical function scales validated for use in patients with rheumatoid arthritis: A systematic review of the literature. Health and Quality of Life Outcomes 2011,9:99.
76. Fries JF, Krishnan E, Rose M, Lingala B, Bruce B. Improved responsiveness and reduced sample size requirements of PROMIS physical function scales with item response theory. Arthritis Research & Therapy 2011,13:R147.
77. Hayes KW, Johnson ME. Measures of adult general performance tests: the berg balance scale, dynamic gait index (DGI), gait velocity, physical performance test (PPT), timed chair stand test, timed up and go, and tinetti performance-oriented mobility assessment (POMA). Arthritis & Rheumatism (Arthritis Care & Research) 2003,49;5S:S28–S42.
78. Ward MM. Clinical measures in rheumatoid arthritis: which are most useful in assessing patients? Journal of Rheumatology 1994;21:17-27.
79. Spiegel JS, Paulus HE, Ward NB, Spiegel TM, Leake B, Kane RL. What are we measuring? An examination of walk time and grip strength. Journal of Rheumatology 1987;14:80-6.
80. Salaffi F, Franchignoni F, Giordano A, Ciapretti A, Gasparini S, Ottonello M, on behalf of the “NEW INDICES” Study Group. Classical test theory and Rasch analysis validation of the Recent-Onset Arthritis Disability questionnaire in rheumatoid arthritis patients. Clinical Rheumatology 2013,32:211-217.

81. Salaffi F, Ciapetti A, Gasparini S, Migliore A, Scarpellini M, Corsaro SM, Lagana B, Mozzani F, Varcasia G, Pusceddu M, Castriotta M, Serale F, Maier A, Foti R, Scarpa R, Bombardieri S, on behalf of the NEW INDICES study group. Comparison of the recent-onset arthritis disability questionnaire with the health assessment questionnaire disability index in patients with rheumatoid arthritis. Clinical and Experimental Rheumatology 2010;28:855-865.
82. Salaffi F, Bazzichi L, Stancati A, Neri R, Cazzato M, Consensi A, Grassi W, Bombardieri S. Development of a functional disability measurement tool to assess early arthritis: the Recent-Onset Arthritis Disability (ROAD) questionnaire. Clinical and Experimental Rheumatology 2005,23:628-363.
83. Salaffi F, Stancati A, Neri R, Grassi W, Bombardieri S. Measuring functional disability in early rheumatoid arthritis: the validity, reliability and responsiveness of the recent-onset arthritis disability (ROAD) index. Clinical and Experimental Rheumatology 2005;23:S31-42.
84. Foster NE, Thomas E, Barlas P, Hill JC, Young J, Mason E, Hay EM. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ 2007; doi:10.1136/bmj.39280.509803.BE.
85. Vincent CA, Lewith G. Placebo controls for acupuncture studies. J R SocMed 1995;88:199-202.
86. Godfrey E, Weinman JA, Beinart NA. Development of a measure to assess adherence to exercise: the Exercise Adherence Rating Scale (EARS). International Journal of Behavioural Medicine 2014;21:S202.O684.
87. Wisdom JP, Cavaleri MA, Onwuegbuzie AJ, Green CA. Methodological reporting in qualitative, quantitative, and mixed methods health services research articles. HSR 2012;47:721-45.
88. Moyers TB, Martin T, Manuel JK, Hendrickson SML, Miller WR. Assessing competence in the use of motivational interviewing. Journal of Substance Abuse Treatment 2005,28:19-26.
89. Chisholm D, Knapp MRJ, Knudsen HC, Amaddeo F, Gaite L, Wijngaarden BV. Client socio-demographic and service receipt inventory – European version: development of an instrument for international research. The British Journal of Psychiatry 2000;177:s28-33.
90. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet 2011;377: 1693–1702.

91. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol 2009;8:741–754. doi: 10.1016/S1474-4422(09)70150-4 PMID: 19608100.
92. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, et al. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev 2007;CD006073.
93. Manning VL, Hurley MV, Scott DL, Coker B, Choy E, Bearne LM. Education, self-management, and upper extremity exercise training in people with rheumatoid arthritis: a randomised controlled trial. Arthritis Care Res 2014;66:217-27.
94. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2:92–8.
95. Larkin L, Kennedy N, Gallagher S. Promoting physical activity in rheumatoid arthritis: a narrative review of behaviour change theories, Disability and Rehabilitation 2015,37;25:2359-2366.
96. Ajzen I. The theory of planned behaviour. Organ Behav Hum Dec Process 1991,50:179–211.
97. Gollwitzer PM. Implementation intentions: strong effects of simple plans. The American Psychologist 1999,54;7:493-503.
98. Ajzen I. Attitudes, personality and behaviour. 1988, Milton Keynes, England.: Open University Press.
99. Ajzen I, Madden TJ. Prediction of goal-directed behaviour: attitudes, intentions, and perceived behavioral control. Journal of Experimental Social Psychology 1986;22:453-74.
100. Miller WR, Rollnick S. Meeting in the middle: motivational interviewing and self-determination theory. International Journal of Behavioural Nutrition and Physical Activity 2012;9:25.
101. Wrywich KW, Norquist JM, Lenderking WR, Acaster S, the industry advisory committee of international society for quality of life research (ISOQOL). Quali Life Res 2013;22:475-483.
102. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.
103. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of Clinical Epidemiology 2008;61:102–109.

104. Menz HB, Auhl M, Ristevski S, Frescos N, Munteanu SE. Comparison of the responsiveness of the Foot Health Status Questionnaire and the Manchester Foot Pain and Disability Index in older people. Health and Quality of Life Outcomes 2014;12:158.

105. Crosby RD, Kolotkin RL, Williams GR: Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003, 56:395–407.

106. Beaton DE: Understanding the relevance of measured change through studies of responsiveness. Spine 2000, 25:3192–3199.

107. Husted JA, Cook RJ, Farewell VT, Gladman DD: Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol 2000, 53:459–468.

108. Cohen J: Statistical Power Analysis for the Behavioral Sciences. 2nd edition. Hillsdale, NJ: Erlbaum; 1988.

109. Attride-Stirling J. Thematic networks: an analytic tool for qualitative research. Qualitative Research 2001;1:385-405.