PROJECT PROTOCOL

Title of Project	Remote monitoring of disease and physical activity in rheumatoid arthritis: a pilot study
Sponsor	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funding	NIHR Newcastle Biomedical Research Centre
Chief Investigator	Dr Kenneth Baker
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1. GENERAL INFORMATION

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1.4 Research Site

This study will be conducted at one single research site:

Newcastle upon Tyne Hospitals NHS Foundation Trust,
Musculoskeletal Outpatients Department,
Level 2,
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NE7 7DN.

1.5 CONFLICTS OF INTEREST STATEMENT

The investigators have no conflicts of interest to declare for this study.

2. STUDY SUMMARY

Trial Title	Remote monitoring of disease and physical activity in rheumatoid arthritis: a pilot study
Summary of Study Design	Observational longitudinal cohort study
Summary of Participant Population	Participants with established rheumatoid arthritis with active disease commencing a new disease-modifying anti-rheumatic drug
Planned Sample Size	20 participants
Planned Number of Sites	1
Follow Up Duration	3 months
Planned Study Period	11 months
Primary Objectives	To demonstrate the feasibility of remote disease activity monitoring in participants with rheumatoid arthritis, to support a future clinical efficacy trial.
Primary endpoint:	Correlation and agreement of remote methods of disease activity measurement (patient reported outcome measures, and activity/gait/cardiorespiratory monitors) compared to face-to-face assessments of disease activity in 28 joints with C-reactive protein (DAS28-CRP) scores.
Study Intervention:	Nil (standard clinical care, observational only)

3. BACKGROUND INFORMATION

Rheumatoid arthritis (RA) is a common disease affecting 1 in 100 adults in the United Kingdom,[1] and is characterised by joint pain and swelling, and general features such as fatigue.[2] Patients with RA are prescribed disease modifying anti-rheumatic drugs (DMARDs) in order to prevent joint damage and improve symptoms.[3] In current clinical practice, the response to DMARD therapy is assessed by a clinician who assesses the number of tender and swollen joints, together with a laboratory marker of inflammation, to calculate a disease activity score in 28 joints (DAS28) (Appendix A). The need for face-to-face hospital clinic reviews makes such disease activity monitoring a time-consuming and expensive process, further compounded by reduced outpatient clinic capacity as a result of the COVID-19 pandemic. Furthermore, DAS28 monitoring has been criticised for under-representation of subjective symptoms such as fatigue, and potential insensitivity to impact on physical function.

In contrast to traditional DAS28 monitoring, various patient reported outcome measures (PROMs) have been developed which utilise self-completed patient questionnaires to quantify a range of disease activity parameters including fatigue, pain, mood and physical function.[4] Such PROMs can be completed remotely without the need for hospital visits, and can quantify subjective parameters not explicitly captured by DAS28. Furthermore, recent technological advances in sensor technology now form the basis of a range of wearable devices, which can remotely record and quantify physical activity, gait characteristics, and physiological parameters such as heart rate.[5] PROMs have been shown to correlate closely with DAS28,[4] and activity tracker data has been shown to correlate with arthritis flares,[5] but the clinical efficacy of both approaches in remote RA disease activity monitoring is yet to be confirmed.

In this pilot study (**Figure**), we propose to recruit 20 participants with RA with active disease who are newly starting a DMARD. Participants will be followed for 3 months, with monthly face-to-face visits to measure DAS28 score. Throughout the study, participants will complete weekly PROM measurements in the form of the simple 5-question RA Disease Activity Index 5 (RADAI-5, Appendix D), captured electronically using the British Society for Rheumatology ePROMs online portal,[6] with weekly email reminders to support participant uptake. In addition, at each monthly visit participants will be provided with activity trackers (lower back and wrist – Axivity AX6) and a combined activity and cardiorespiratory monitor (VitalPatch) to be worn for 7 days. Additional PROMs including FACIT-F[7] and MFS[8] (fatigue), HAQ-DI[9] (physical function), PHQ-2[10] (anxiety/depression) and EQ-5D-5L[11] (general health) will be captured at the monthly visits, in order to collect information necessary for interpretation of the activity monitor data. Importantly, participant acceptability will be assessed through questionnaires, and by invitation of participants to an optional participant focus group to identify areas of potential improvement. Ultimately the findings of this pilot study will support further funding applications both for a definitive randomised clinical trial to demonstrate the clinical efficacy of remote monitoring in RA management, and for further research to refine and validate potential digital biomarkers of disease activity.

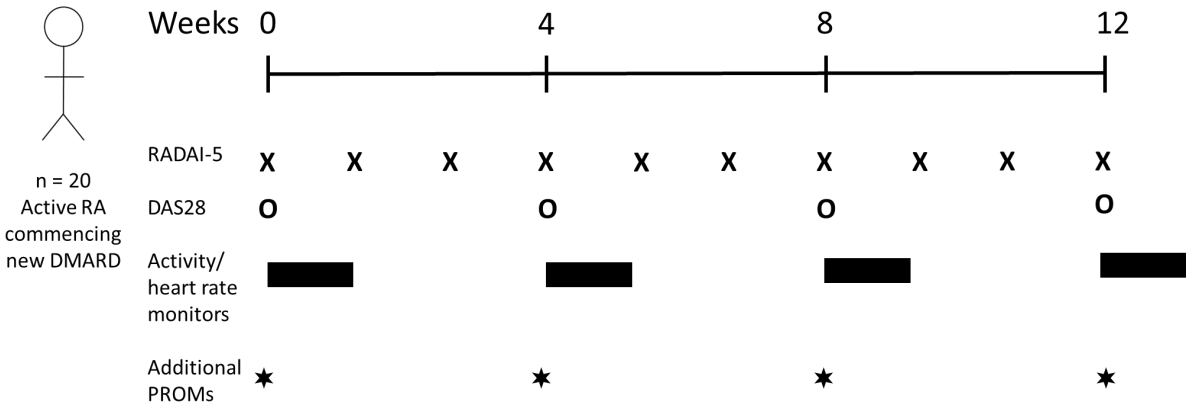

Figure – Study design. Participants will be reviewed at monthly intervals for DAS28 assessment, completion of additional PROMs, and provision of activity and heart rate monitors to be worn for 7 days and then returned by post.

4. STUDY DESIGN

4.1 Aims

1. To demonstrate the feasibility of remote RA disease activity monitoring, to support a future clinical efficacy trial
2. To identify digital biomarkers of disease activity based on wearable monitoring devices, for future development and validation

4.2 Primary objectives

1. To assess the correlation and agreement between paired DAS28 and RADAI-5 measurements
2. To assess the longitudinal responsiveness and minimal detectable change in repeated RADAI-5 measurements
3. To assess the acceptability of remote PROM capture and activity/gait/heart rate monitoring, through the use of participant questionnaires and focus groups

4.3 Secondary objective

1. To use validated algorithms and novel machine-learning methods to identify activity, gait and heart rate monitor signatures that correlate with, and are predictive of, DAS28- and RADAI-5-defined disease activity

4.4 Study type

This will be a prospective observational cohort study conducted at a single study site.

5. RECRUITMENT OF PARTICIPANTS

5.1 Inclusion criteria

1. Diagnosis of rheumatoid arthritis according to the 1987 American College of Rheumatology (ACR) (Appendix B) or 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria (Appendix C) applied at any time since diagnosis.
2. Participant about to commence (i.e. planned within next 4 weeks), or recently commenced (i.e. within past 8 weeks), a new disease-modifying anti-rheumatic drug (i.e. conventional synthetic DMARD, Janus-kinase inhibitor or biologic therapy)
3. Able to walk at least four metres independently without walking aids
4. Participant willing to commit to complete remote monitoring measurements and wear monitoring devices

5.2 Exclusion criteria

1. Unable to read or communicate in English
2. Current participation within an interventional clinical trial (participation in another observational trial is permitted)

3. Inability to provide informed consent
4. Age less than 18 years
5. Current diagnosis of a movement disorder
6. Current pregnancy

5.3 Recruitment strategy

Potentially eligible patients attending rheumatology outpatient appointments will be identified by the doctor or nurse specialist that they see in clinic. If a research nurse is available, then they will provide the participant information leaflet and discuss the study with the patient. If the patient is interested in joining the study, then either the research nurse or the patient can book the initial study appointment. Alternatively, and with the patient's verbal consent as documented in the clinical records, the referring healthcare professional may provide contact details (name, address and telephone number) of the patient by secure NHS.net email to a study researcher, who will contact the patient by telephone to discuss the study further. If the patient would like to join the study, a participant information sheet will be posted to the patient. Potentially eligible patients who are retrospectively identified by their clinical team (by review of electronic clinical records and/or clinical databases) may also be recruited to the study.

Within the Newcastle Hospitals rheumatology department, “Change of Medication” forms are completed by clinicians when patients change their arthritis drug treatment. In addition to the recruitment strategy above, these Change of Medication forms will be reviewed by the Chief Investigator (or other clinician working within the department who is appropriately delegated on the study delegation log) to identify patients with rheumatoid arthritis who have (or will shortly) start a new arthritis drug, and thus be potentially eligible to enrol in the study. Identified patients will then be sent a letter to invite them to contact the research team to discuss the study and participate if they so wish.

5.4 Target recruitment size

This is a pilot study, designed to support a future definite clinical efficacy trial. As such this pilot study is not statistically powered, but rather is intended to provide preliminary data to estimate the feasibility and acceptability of remote monitoring in patients with RA, and generate an exploratory dataset for derivation of putative digital biomarkers of arthritis activity. A target of 20 participants will be recruited to the study, based upon the limited available resources for purchasing monitoring equipment in this small pilot study.

5.5 Closure of study

Recruitment to the study will close upon recruitment of the 20th participant or on 30/06/23, whichever is earlier. The study will close on 30/09/23.

6. STUDY VISITS

6.1 Initial study visit

Participants attending their initial appointment will undergo the following procedures.

1. All participants will have the opportunity to discuss the study further with a study investigator before signing the consent form.
2. Participant eligibility for study enrolment based on the inclusion and exclusion criteria will be confirmed.
3. Participants will be asked to provide baseline information including age, sex, address, telephone number, email address, past medical history, Clinical Frailty Score,[12] Charlson Comorbidity Index,[13] current medications, smoking status and alcohol intake.
4. The participant's height and weight will be recorded.
5. A researcher will then examine the participant to ascertain the 28-joint tender and swollen counts, a patient visual analogue scale, and a physician visual analogue scale, required to assess disease activity using the DAS28-CRP score (Appendix A).
6. The participant will then complete a RADAI-5 questionnaire (Appendix D).
7. The participant will then be asked to complete the following paper questionnaires:
    a. Health Assessment Questionnaire Disability Index (HAQ-DI)
    b. FACIT-F and MFS
    c. PHQ-2
    d. EQ-5D-5L
8. Participants will then be shown how to access the ePROMs portal. Written information will be provided to participants to explain this further.
9. Participants will then be instructed on how to wear and activate the remote monitoring digital tracker devices. Written information will be provided to explain this further. The following devices will be provided, and should be worn simultaneously for 7 days following the study visit:
    a. Axivity AX6 monitor and adhesive dressing – for application to lower back
    b. Axivity AX6 monitor and wrist strap – for application to wrist
    c. VitalPatch self-adhesive monitor – for application to left upper chest wall
    d. A study mobile phone and charger – for data linkage and downloading from the VitalPatch device
10. Blood tests will be taken as per below, thus avoiding additional hospital attendances for mandatory routine clinical blood monitoring during the study period. These results will be passed on to the local clinical DMARD monitoring service, and any necessary action taken by the local clinical team. In the event that a participant has blood monitoring more frequently than once every 4 weeks, then any blood tests required before the date of the next study visit will be performed by the clinical DMARD monitoring service as per usual routine practice.
    a. Full Blood Count (FBC)
    b. Erythrocyte sedimentation rate (ESR)
    c. C reactive protein (CRP)
    d. Urea and electrolytes (U&Es)
    e. Liver function tests (LFTs)
11. Participants will be provided with the following documents at the end of the visit:

a. Blank paper questionnaires, for completion within the 48 hours prior to their next study visit
    i. Health Assessment Questionnaire Disability Index (HAQ-DI)
    ii. FACIT-F and MFS
    iii. PHQ-2
    iv. EQ-5D-5L
b. A pre-paid addressed envelope, to post back the reusable Axivity AX6 devices to the researcher team after 7 days

6.2 Week 4 and week 8 visit

1. Participants will be asked to verbally confirm their willingness to continue in the study.
2. Any change in concurrent medications will be recorded.
3. Any adverse events occurring since the last clinic visit will be recorded.
4. A researcher will then examine the participant to ascertain the 28-joint tender and swollen counts, a patient visual analogue scale, and a physician visual analogue scale, required to assess disease activity using the DAS28-CRP score (Appendix A).
5. The participant will then complete a RADAI-5 questionnaire.
6. Remote self-entered RADAI-5 data will be reviewed on the ePROMs platform (see 6.4 below)
7. The pre-filled questionnaires provided to the participant at their last visit will be collected. If the participant has not had the opportunity to complete these or has not brought them to the appointment, then they will be asked to complete the questionnaires during the study visit:
    a. Health Assessment Questionnaire Disability Index (HAQ-DI)
    b. FACIT-F and MFS
    c. PHQ-2
    d. EQ-5D-5L
8. Participants will then be reminded on how to wear and activate the remote monitoring digital tracker devices, and how to access the ePROMs portal.
9. Participants will be provided with the following devices, to wear simultaneously for 7 days following the study visit:
    a. Axivity AX6 monitor and adhesive dressing – for application to lower back
    b. Axivity AX6 monitor and wrist strap – for application to wrist
    c. VitalPatch self-adhesive monitor – for application to left upper chest wall
10. Blood tests will be taken as per below, thus avoiding additional hospital attendances for mandatory routine clinical blood monitoring during the study period. These results will be passed on to the local clinical DMARD monitoring service, and any necessary action taken by the local clinical team. In the event that a participant has blood monitoring more frequently than once every 4 weeks, then any blood tests required before the date of the next study visit will be performed by the clinical DMARD monitoring service as per usual routine practice.
    a. Full Blood Count (FBC)
    b. Erythrocyte sedimentation rate (ESR)
    c. C reactive protein (CRP)
    d. Urea and electrolytes (U&Es)

    e. Liver function tests (LFTs)
11. Participants will be provided with the following documents at the end of the visit:
    a. Blank paper questionnaires, for completion within the 48 hours prior to their next study visit
        i. Health Assessment Questionnaire Disability Index (HAQ-DI)
        ii. FACIT-F and MFS
        iii. PHQ-2
        iv. EQ-5D-5L
    b. A pre-paid addressed envelope, to post back the reusable Axivity AX6 devices to the researcher team after 7 days

6.3 Week 12 visit

1. Participants will be asked to verbally confirm their willingness to continue in the study.
2. Any change in concurrent medications will be recorded.
3. Any adverse events occurring since the last clinic visit will be recorded.
4. A researcher will then examine the participant to ascertain the 28-joint tender and swollen counts, a patient visual analogue scale, and a physician visual analogue scale, required to assess disease activity using the DAS28-CRP score (Appendix A).
5. The participant will then complete a RADAI-5 questionnaire.
6. Remote self-entered RADAI-5 data will be reviewed on the ePROMs platform (see 6.4 below)
7. The pre-filled questionnaires provided to the participant at their last visit will be collected. If the participant has not had the opportunity to complete these or has not brought them to the appointment, then they will be asked to complete the questionnaires during the study visit:
    a. Health Assessment Questionnaire Disability Index (HAQ-DI)
    b. FACIT-F and MFS
    c. PHQ-2
    d. EQ-5D-5L
8. Participants will then be reminded on how to wear and activate the remote monitoring digital tracker devices, and how to access the ePROMs portal.
9. Participants will be provided with the following devices, to wear simultaneously for 7 days following the study visit:
    a. Axivity AX6 monitor and adhesive dressing – for application to lower back
    b. Axivity AX6 monitor and wrist strap – for application to wrist
10. Blood tests will be taken as per below, thus avoiding additional hospital attendances for mandatory routine clinical blood monitoring during the study period. These results will be passed on to the local clinical DMARD monitoring service, and any necessary action taken by the local clinical team. In the event that a participant has blood monitoring more frequently than once every 4 weeks, then any blood tests required before the date of the next study visit will be performed by the clinical DMARD monitoring service as per usual routine practice.
    a. Full Blood Count (FBC)
    b. Erythrocyte sedimentation rate (ESR)
    c. C reactive protein (CRP)

   d. Urea and electrolytes (U&Es)
   e. Liver function tests (LFTs)
11. The study smartphone and charger will be collected from the participant.
12. Participants will be asked to complete a feedback questionnaire on acceptability of remote ePROMs and wearable digital monitoring devices. Participants will be asked whether they would be willing to take part in an optional focus group to discuss issues around acceptability of remote monitoring (see section 6.5 below).
13. Participants will be provided with the following documents at the end of the visit:
    a. A pre-paid addressed envelope, to post back the reusable Axivity AX6 devices to the researcher team after 7 days

6.4 *ePROMs remote capture and review*

1. All participants will be asked to complete a RADAI-5 questionnaire via the secure online ePROMs portal once every week for the 12 week follow-up duration of the study
2. Automated weekly reminder emails will be sent via the ePROMs platform to participants to remind them to complete a RADAI-5 assessment.
3. ePROMs RADAI-5 data will be reviewed at each monthly visit, and any missing data discussed with the participant to identify any difficulties in accessing or using the ePROMs platform.

6.5 Optional focus group

Participants at their week 12 visit who express an interest in providing additional feedback on their experience of taking part in the study will be invited to take part in an optional focus group. Participants will join a meeting, either face-to-face or virtual, lasting for approximately 60 minutes. Individual (i.e. one-on-one) meetings may be arranged where participants would otherwise feel uncomfortable or inhibited in providing feedback in a group setting.

The session will be led by a study researcher, who will invite participants to reflect on their experience (positive and negative) of participating in the study, with a specific focus on:
1. Ease of use of ePROMs portal
2. Acceptability of frequency of ePROMs measurements
3. Ease of use and acceptability of Axivity AX6 and VitalPatch monitors

The meetings will not be recorded, but rather the researcher will take written notes during the meetings. Participant feedback may be transcribed verbatim, but participant feedback will be recorded in an anonymous fashion.

6.6 Participant autonomy

Participants will have full autonomy throughout this study. The participant, informed of the full information as detailed in the participant information sheet, may withdraw their consent at any time. The wishes of the participant will be respected, and would result in them exiting the study at

that point. Any data collected up to that point would be retained and analysed by the study team in line with the terms of the original participant consent form.

6.7 Digital monitoring device availability

Owing to the pilot nature of this study, limited funds are available for the purchase of monitoring devices, and supply of these devices is constrained by disruption to global supply chains. In the event that a monitoring device (i.e. Axivity AX6 monitor or VitalPatch device) or a component required for proper device use (i.e. study smartphone/charger, wrist strap, or fixation dressing) is unavailable, then provision and/or use of the affected monitoring device will be omitted from the study visit schedule. This will be recorded on the visit case report form, but will not constitute a breach of study protocol.

6.8 End of study

If the participant declines to take part in the optional focus group (section 6.5), then the week 12 visit will be their final study visit. The participant will exit the study 7 days after this visit (i.e. at the end of their final remote monitoring device measurement period).

If the participant agrees to take part in the optional focus group (section 6.5), then a further optional focus group visit will occur no later than 180 days from the date of their week 12 visit. No additional study visits are permitted between the week 12 and optional focus group visits. No blood monitoring or disease activity measurements (remote or otherwise) will be performed as part of the research study beyond 7 days after the week 12 visit. The participant will exit the study at the end of the optional focus group visit.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.1 Adverse event (AE)

Any untoward medical occurrence experienced by the participant during their participation within the study. The severity of adverse events is defined as follows:

i. **Mild:** Symptoms noted but no disruption to normal daily activities
ii. **Moderate:** Symptoms sufficient to disrupt normal daily activities
iii. **Severe:** Symptoms sufficient to prevent normal daily activities

Causality: All adverse events should be assessed by the principal investigator or their medically qualified delegate for any causal relationship with a study procedure, namely remote ePROM or activity/physiological monitoring. Causality is defined as:

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed

	to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.2 Serious adverse event (SAE)

Any adverse event which:

a. Results in death
b. Is life-threatening (i.e. an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
c. Requires hospitalisation, or prolongation of existing hospitalisation
d. Results in persistent or significant disability or incapacity
e. Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.3 Expected symptoms

This study will recruit participants with active rheumatoid arthritis, and as such are expected to have joint pain, joint swelling and joint stiffness. Symptoms can be expected to improve (though not necessarily completely resolve) after initiation of DMARD therapy in approximately half to three-quarters of participants, with continuation or even worsening of symptoms in the remainder of participants.

7.4 Protocol specifications

i. Joint pain, joint swelling and joint stiffness will not be recorded as an adverse event
ii. An adverse event will not be classified as a serious adverse event if it is a hospitalisation, surgical procedure or other medical intervention (whether as an inpatient, day-case, outpatient or in primary care) that was planned before the recruitment of the participant to the study

7.5 Reporting AEs and SAEs

1. *All AEs* will be recorded on AE case report forms at the research site
2. Site staff should report any *SAE immediately* to the Chief Investigator. Upon receipt of the SAE report the Chief Investigator must:
    a. *All SAEs*: Immediately inform the Sponsor (within 1 working day)
        i. Inform the REC on behalf of the Sponsor as soon as possible, and no later than fifteen calendar days for non-fatal and non-life threatening SAEs

b. *Unexpected SAEs related to a study procedure (SUSAR – suspected unexpected serious adverse reaction)*:
    i. Inform the REC on behalf of the Sponsor as soon as possible, and no later than one calendar day for fatal or life-threatening SAEs.
    ii. Convene a meeting of the Chief Investigator and study investigators as soon as possible, and no later than:
        1. Fifteen calendar days for fatal or life-threatening SAEs
        2. Thirty calendar days for non-fatal and non-life-threatening SAEs

7.6 Pregnancy

Pregnancy is associated with a diverse range of physiological changes, and can therefore be expected to greatly influence both activity and physiological monitoring data. Pregnancy is thus an exclusion criterion for this study.

Where pregnancy in a female participant becomes apparent after the enrolment of the participant to the study, this must be recorded as an adverse event. The participant's referring rheumatologist and GP must be informed, and then the participant must be discharged from the study.

8. DATA ANALYSIS

8.1 Correlation between DAS28 and RADAI-5 measurements

The correlation between paired DAS28 and RADAI-5 measurements taken at each study visit will be assessed by Pearson and Spearman correlation coefficients. DAS28 and RADAI-5 scores will also be dichotomised to binary disease activity values (e.g. high disease activity vs remission/low/moderate disease activity) based on published thresholds, and agreement between categorisation by DAS28 vs RADAI-5 scores assessed by Cohen's kappa statistic.

8.2 Longitudinal RADAI-5 measurements

Longitudinal changes in RADAI-5 will be visualised by Loess regression. The ability of longitudinal RADAI-5 measurements to discern changes in disease activity will be assessed with reference to the published minimal detectable change in DAS28, and the EULAR response criteria.

8.3 Digital biomarkers of disease activity

An exploratory data-driven approach will be used to identify activity, gait and cardiorespiratory signatures that correlate with, and are predictive of, DAS28- and RADAI-5-defined disease activity levels. Continuous activity and heart rate data (evaluated with the monitoring devices) will be segmented per each day and analysed using validated (existing IP) and novel algorithms to identify activity (e.g. measure of volume, pattern and variability of walking), gait (e.g. gait speed) and heart rate (e.g. heart rate variability) digital outcomes [14].

8.4 Participant acceptability

Quantitative feedback from participant acceptability questionnaire Likert scales will be summarised (median/mode and range). Anonymised free text responses will be reproduced verbatim, analysed for common themes and presented in tabular form. Anonymised field notes from the optional focus group meeting will be explored for common themes, and summarised in a tabular form with verbatim quotes as necessary. The focus of these analyses is to gather information around participant acceptability for the purposes of improving the design of our future research studies, rather than to generate generalizable data and results suitable for a qualitative research publication.

9. ETHICAL CONSIDERATIONS

Participants will be required to attend for face-to-face hospital visits on four occasions during study follow-up. To avoid additional study visits beyond standard clinical care, we have incorporated DMARD blood safety tests within the study visit schedule. This will avoid additional trips to hospital, with potential for increased COVID-19 infection risk.

The use of an online ePROMs portal requires a computer or mobile device, internet access, and a modest degree of digital literacy to access the webpage interface. We recognise that these requirements may have an indirect effect of excluding participants of certain socioeconomic backgrounds from participating in the project. However, alternative methods of data capture (such as paper forms) are not feasible owing to the frequency of ePROMs assessments and the need to link these in real time to DAS28 and activity tracker data. Furthermore, a specific aim of this pilot project is to assess the acceptability and feasibility of internet-based ePROMs capture, to guide decisions on use in future larger studies. The screening log for this study will record where participants were unable to participate due to technological barriers, to ascertain if this is likely to be a significant barrier to recruitment to future studies and thus guide the need for future mitigation strategies.

10. DATA HANDLING AND RECORD-KEEPING

10.1 Collection and storage of study data

Personal identifiable data will be stored within Newcastle upon Tyne Hospitals NHS Foundation Trust. Personal identifiable data will be removed before data transfer of link-anonymised data to Newcastle University.

1. Personal data (i.e. participant name and signature) will be recorded on paper consent forms stored within the Trial Master File.
2. Hospital number and name of participant's consultant will be stored along with study participant identification number within a paper record held in the Trial Master File, and in an electronic file on a password-protected server of the Newcastle upon Tyne Hospitals NHS Foundation Trust. This will act as a decoder for the link-anonymised data.
3. Case report forms, participant questionnaires and focus group field notes will be captured in paper format which will be held in the Trial Master File. Case report forms may then be transcribed to an electronic file which will be stored on a password-protected server of Newcastle University. Case report forms transcribed to University servers will have personal

identifiable information except sex and age removed, and be link-anonymised by trial participant number.

10.2 Security arrangements for storage of study data

1. Paper records containing participant-identifiable information will be stored within the Trial Master File and locked within a secure location in Newcastle Hospitals NHS Foundation Trust.
2. Electronic case report forms containing participant-identifiable information will be held in a password protected server of the Newcastle upon Tyne Hospitals NHS Foundation Trust.
3. Data link-anonymised by trial participant number will be stored in a password-protected server of Newcastle University.

10.3 Access to participant-identifiable data

Participant-identifiable data will be accessible to:

1. The Chief Investigator
2. Research investigators named in the delegation log for the purposes of carrying out the procedures listed for the study visits in section 6
3. Monitors and auditors from the R&D services at Newcastle upon Tyne Hospitals NHS Foundation Trust upon valid request

Consent for these parties to access trial data will be included within the informed consent process of the study. All individuals who access participant-identifiable data must have a valid contractual relationship with Newcastle upon Tyne Hospitals NHS Foundation Trust. All other researchers that require access to study data (e.g. for the purposes of data analysis) are not permitted to view participant-identifiable information and are restricted to viewing link-anonymised data.

10.4 Collection and storage of ePROMs data

Remote ePROMs data will be entered by participants directly into the online British Society for Rheumatology (BSR) ePROMs portal. This is a national service provided and maintained by the BSR for use in routine NHS clinical practice, and conforms to all necessary GDPR and Data Protection requirements. The BSR requires that participants complete a separate online consent form within the ePROMs platform before submitting ePROMs data. Submitted ePROMs data will be accessible to the participant's usual clinical team, and to study researchers who have access to the ePROMs portal. Data stored on the BSR ePROMs portal remains available indefinitely, though individual participants can request removal of their data by directly contacting the BSR ePROMs team.

10.5 Collection and storage of digital monitoring device data

Activity data recorded by Axivity AX6 monitors will be stored within the device, which will be posted back to study researchers by the participant. Data will then be downloaded from the device and stored in a password-protected area of the Newcastle University computer servers. Physiological data recorded by VitalPatch monitors is transmitted wirelessly to the study smartphone, where it is stored until downloaded by a study researcher at the next study visit and then stored in a password-protected area of the Newcastle University computer servers.

10.6 Confidentiality

Handling of participant-identifiable data will be in accordance with the Caldicott principles and following Newcastle upon Tyne Hospitals NHS Foundation Trust information governance policies.

11. FINANCE AND INDEMNITY ARRANGEMENTS

11.1 STUDY FINANCE

The study is funded by the NIHR Newcastle Biomedical Research Centre. This funding is administered through Newcastle University.

11.2 STUDY INDEMNITY ARRANGEMENTS

The following arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the following aspects of the study:

1. Study design - Newcastle University indemnity arrangements will apply
2. Study conduct - NHS indemnity arrangements will apply
3. Study management - NHS indemnity arrangements will apply

12. DISSEMINATION OF STUDY RESULTS

Study results will be presented at scientific conferences and/or published in peer-reviewed journals. All personal identifiable information will be removed from the data during analysis to ensure that the results presented are anonymous. Data will be released from the study after a period of time necessary for the protection of any intellectual property rights.

13. QUALITY ASSURANCE

The conduct of this trial must follow the most current approved version of this protocol, and satisfy the requirements of Good Clinical Practice and relevant policies and guidelines issued by Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. Monitors and auditors from Newcastle upon Tyne Hospitals NHS Foundation Trust will be able to request access to all study data for necessary quality assurance purposes.

A serious breach[15] of the project protocol or Good Clinical Practice is deemed to have occurred when a breach is likely to effect to a significant degree:

1. "The safety or physical or mental integrity of the subjects of the study"; or
2. "The scientific value of the study"

Suspected serious breaches should be notified to the Sponsor immediately (within 24 hours). Following consultation with the Chief Investigator the Sponsor should, if it is deemed that a serious breach is suspected, notify the Research Ethics Committee and appropriate regulatory authorities within 7 calendar days of original notification to the Sponsor.

14. REFERENCES

1. Symmons, D., et al., *The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century.* Rheumatology (Oxford), 2002. **41**(7): p. 793-800.
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14. Del Din, S., et al., *Analysis of Free-Living Gait in Older Adults With and Without Parkinson's Disease and With and Without a History of Falls: Identifying Generic and Disease-Specific Characteristics.* J Gerontol A Biol Sci Med Sci, 2019. **74**(4): p. 500-506.
15. Newcastle Joint Research Office, *Notification of serious breaches of Good Clinical Practice or the trial protocol. NJRO-REG-SOP-013. Available online at https://q14784.ideagenqpulse.com/QPulseDocumentService/Documents.svc/documents/active/attachment?number=NJRO-REG-SOP-013 (accessed 03 Feb 2022).*

15. SCHEDULE OF EVENTS

Activity	Visit 1: day 0	Visit 2: Day 28 (+/- 7 days)	Visit 3: Day 56 (+/- 7 days)	Visit 4: Day 84 (+/- 7 days)	Optional Focus Group (<180 days)
Informed consent	X				
Study eligibility assessment	X				
Medical history	X				
Clinical frailty score	X				
Charlson Comorbidity Index	X				
Height and weight	X				
Concomitant medications	X	X	X	X	
Adverse event recording and reporting		X	X	X	
Joint counts / VAS scores	X	X	X	X	
RADAI-5	X	X	X	X	
HAQ-DI	X	X	X	X	
FACIT-F	X	X	X	X	
MFS	X	X	X	X	
PHQ-2	X	X	X	X	
EQ-5D-5L	X	X	X	X	
Register on ePROMs portal	X				
Instruction on use of remote monitoring devices	X				
Provision of study smartphone and charger	X				
Review of ePROMs record		X	X	X	
Provision of monitoring devices and pre-paid envelope	X	X	X	X	
Collection of study smartphone and charger				X	
Bloods (CRP, ESR, FBC, U&Es, LFTs)	X	X	X	X	
Provision of paper questionnaires for next visit	X	X	X		
Experience feedback questionnaire				X	
Optional focus group					X

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, EQ-5D-5L: EuroQol 5D-5L, FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue, FBC: full blood count, HAQ-DI: Health Assessment Questionnaire Disability Index, LFTs: liver function tests, MFS: Mental Fatigue Scale, PHQ-2: Patient Health Questionnaire 2, RADAI-5: Rheumatoid Arthritis Disease Activity Index 5, U&Es: urea and electrolytes.

APPENDIX A: THE DISEASE ACTIVITY IN 28 JOINTS C-REACTIVE PROTEIN (DAS28-CRP) SCORE

The DAS28-CRP score[1] is calculated using the following parameters:

1. Swollen (SJC28) and tender (TJC28) 28 joint counts*
2. C-reactive protein (CRP, mg/L)
3. Patient global health assessment (VAS) (visual analogue scale, 0mm = best, 100mm = worst)

$$DAS28\ (CRP) = 0.56\sqrt{(TJC28)} + 0.28\sqrt{(SJC28)} + 0.36\ln(CRP[mg/l]+1) + 0.014(VAS[mm]) + 0.96$$

* = Where the 28 joints include the bilateral proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, shoulders and knees.

Where CRP is below detectable levels, a value of zero will be used for the DAS28-CRP calculation.

The DAS28-CRP score has validated disease activity thresholds [2,3]:

Disease activity	DAS28-CRP threshold
Remission	< 2.4
Low	2.4 ≤ score ≤ 2.9
Moderate	2.9 < score ≤ 4.6
High	> 4.6

References:

[1] Prevoo ML *et al*. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* (1995); 38: 44–8.

[2] Fleischmann RM *et al*. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? *Ann Rheum Dis* 2015;74:1132-7.

[3] Fleischmann RM *et al*. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. *RMD Open*;3: e000382

APPENDIX B : 1987 ACR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

For those participants diagnosed with rheumatoid arthritis before 2010, a retrospective review of the medical records will be performed to ascertain whether they satisfy the 1987 ACR classification criteria as reproduced below. Individual criteria may be cumulatively satisfied at any time point from onset of symptoms.

"For classification purposes, a participant shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks.

1. **Morning stiffness**
   Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement

2. **Arthritis of 3 or more joint areas**
   At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, knee, ankle, and metatarsophalangeal joints

3. **Arthritis of hand joints**
   At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint

4. **Symmetric arthritis**
   Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)

5. **Rheumatoid nodules**
   Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician

6. **Serum rheumatoid factor**
   Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects

7. **Radiographic changes**
   Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify) "

Reference:

Arnett FC, Edworthy SM, Bloch DA *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* (1988); 31: 315-24.

APPENDIX C : 2010 ACR/EULAR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

For those participants diagnosed with rheumatoid arthritis before 2010, a retrospective review of the medical records will be performed to ascertain whether they satisfy the 1987 ACR classification criteria as reproduced below. Individual criteria may be cumulatively satisfied at any time point from onset of symptoms.

"Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of 6/10 is needed for classification of a participant as having definite RA)"

	Score
A. Joint involvement	
• 1 large joint	0
• 2-10 large joints	1
• 1-3 small joints (with or without large joints)	2
• 4-10 small joints (with or without large joints)	3
• >10 joints (at least one small)	5
B. Serology	
• Negative RhF & negative CCP	0
• RhF between 19-57 IU/ml OR CCP between 3-9 U/ml	2
• RhF>57 IU/ml OR CCP>9 U/ml	3
C. Acute phase reactants	
• Normal CRP AND normal ESR	0
• Abnormal CRP OR abnormal ESR	1
D. Duration of symptoms	
• <6 weeks	0
• ≥6 weeks	1

"'Large joints' refers to shoulders, elbows, hips, knees, and ankles. 'Small joints' refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

Reference:

Aletaha D, Neogi T, Silman AJ *et al*. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* (2010); 62: 2569-81.

APPENDIX D : RHEUMATOID ARTHRITIS DISEASE ACTIVITY INDEX 5 (RADAI-5)

The RADAI-5[1] is a self-completed questionnaire consisting of the following five questions, each scored on a 0-10 integer scale:

1. How active was your arthritis in the last six months? (anchors: 0 = completely inactive, 10 = extremely active)
2. How active is your arthritis today with respect to joint tenderness and swelling? (anchors: 0 = completely inactive, 10 = extremely active)
3. How severe is your arthritis pain today? (anchors: 0 = no pain, 10 = unbearable pain)
4. How would you describe your general health today? (anchors: 0 = excellent, 10 = extremely bad)
5. Did you experience joint (hand) stiffness on awaking yesterday morning? If yes, how long was this stiffness? (anchors: 0 = no stiffness, 10 = stiffness the whole day)

The mean value gives an overall "RADAI-5 score", with validated disease activity thresholds[2]:

Disease activity	RADAI-5 thresholds
Remission	0.0-1.4
Mild	1.6 – 3.0
Moderate	3.2 – 5.4
High	5.6 – 10.0

References:

[1] Leeb BA *et al*. Patient-centered rheumatoid arthritis disease activity assessment by a modified RADAI. *J Rheumatol* 2008;35:1294-9.

[2] Rintelen B *et al*. The rheumatoid arthritis disease activity index-5 in daily use. Proposal for disease activity categories. *J Rheumatol* 2009;36:918-24.