Bio-T-App Protocol

Protocol Title: Driving Improvements in disease outcomes for rheumatoid arthritis patients using digital health remote sensing.

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ISRCTN reference: 79368292
IRAS Number : 236940
ReDA Number: 012369

Protocol Details

Full title:	Driving improvements in disease outcomes for rheumatoid arthritis patients using digital health remote sensing.
Short Title/Acronym:	Bio-T-App
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REC Reference	18/ES/0102
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ReDA Number	012369

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Patient Recruitment Site(s):	Mile End Hospital (Barts Health NHS Trust) Rheumatology Department Bancroft Road London, E1 4DG
Other Collaborators:	Centre for Experimental Medicine & Rheumatology John Vane Science Centre, William Harvey Research Institute Barts and the London School of Medicine & Dentistry Queen Mary University of London, Charterhouse Square London, EC1M 6BQ

1 GLOSSARY of Terms and Abbreviations

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group

2 SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 6.0, dated 7th July 2020)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Signature and Date:

7th July 2020

3 SUMMARY/SYNOPSIS

Short Title	Bio-T-App
Methodology	Prospective, observational pilot study
Research Sites	Mile End Hospital (Barts Health NHS Trust) Rheumatology Department Bancroft Road London, E1 4DG
Objectives/Aims	The aims of the study are to (i) complete the development of the Bio-T-App through a formal testing phase on patients and (ii) to evaluate in a pilot study the health economic impact of the Bio-T-App.
Number of Participants/Patients	60 patients • Active Bio-T-App arm – 30 patients • Control arm – 30 patients
Main Inclusion Criteria	Inclusion Criteria: • Men & Women ≥18 years of age. • Diagnosis of RA • Baseline DAS score < 5.1 • Access to smart phone/tablet/laptop to access the app. • Prescribed a sub-cutaneous biologic drug for rheumatoid arthritis. • Willing and able to provide informed consent • Exclusion Criteria: • Inability to provide consent/comply with study • No access to a smart phone/tablet/laptop • Baseline DAS > 5.1
Statistical Methodology and Analysis (if applicable)	This is a pilot study and no formal power calculation has been performed.
Proposed Start Date	15/11/2018
Proposed End Date	30/11/2019
Study Duration	12 months (6 months recruitment + 6 months follow-up)

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5 INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting 1% of the population and approximately 700,000 patients in the UK. It is characterized by a persistent erosive arthritis that results in significant disability, morbidity and is associated with increased rates of mortality. In recent years the outcome for patients with RA has improved significantly driven largely by the recognition that early diagnosis and tight control of disease equates to better outcomes.

The introduction of biologic drugs has led to dramatic improvements in disease control, although not cure. However, biologic drugs are costly (~£10,000/annum/patient), with the biologic spend for London alone at £250,000,000/annum. Despite this there is also evidence to suggest significant drug waste with a recent audit performed at Barts Health documenting 45% of patients with “spare” drug at home equating to an estimated £100,000/annum in drug waste in this centre alone. Similar figures have been reported from audits of biologic drug amnesties in other trusts. Drug waste is driven by a number of factors including missed injections due to hospital admissions; unreported infections to the prescriber, and or treatment switches.

The situation is further complicated by the supply of biologic drugs, being given to patients in 6 monthly batches by community based companies (e.g healthcare at home/BUPA). These companies provide not only a homecare delivery service, but collect externally held data on biologic administration, adverse events and disease activity that is not accessible/integrated with primary/secondary care.

Rheumatoid arthritis places significant costs on patients, healthcare systems and society. Strategies to help alleviate this are required and must incorporate effective data capture systems to reflect improvements in management and care.

Practical solutions which may address these issues include the down-titration of rheumatic drugs for patients with low disease activity; greater patient participation in disease management, and the increased role of technology to support clinicians and patients in the monitoring and capture of health data.

The European League Against Rheumatism (EULAR) have recommended the tapering of biologic therapies if patients have demonstrated remission. (7) A number of studies have reflected this, and identified early predictive markers for relapse (8) (9). Therefore, recent data supports a role for biologic dose tapering in RA patients with low disease activity.

However, such an approach requires tight monitoring of patients in order to prevent major disease flares that have been demonstrated to have the most significant impact on joint damage. The current standard model of care for RA patients follows patients in routine outpatient appointments at 6 monthly intervals. This results in a disconnect between disease status and hospital appointments, e.g no need for attendance when patients are well and, reciprocally, inability to attend when disease flares or complications arise with treatment. Patients therefore frequently present to primary care during acute disease flare putting additional strains on a system that in general cannot deliver specialist interventions required to control disease.

The validity and usefulness of patient self-administered joint counts have been looked at in previous studies (1, 2, 3). It has been demonstrated that patient joint self-evaluation is a reliable measurement in comparison to physician or nurse assessed DAS28. However, reliability was demonstrated to be lower for patient self-assessed swollen joint count. (3).

Nonetheless this points to the potential of patient self-assessment as an adjunct to current disease management strategies. Self- assessment provides an important perspective and can potentially increase patient engagement with treatment (4). Patients' regular assessment of their own disease activity would allow disease flares to be detected at an earlier stage and improve overall disease management.

The emergence of e-health tools within healthcare has helped to facilitate this process and have been shown to be effective tools in the monitoring and management of patients with arthritis (4, 6) In addition, studies have demonstrated that patients perceive technologies which assist with self management of their disease as useful (5).

Remote monitoring of RA patients to self-assess disease activity via mobile apps is feasible and has been demonstrated to reliably capture disease activity. The use of remote monitoring to trigger hospital appointments and tailor biologics and change or taper medications still requires validation/implementation. This study aims to address this question.

5.1 Risks & Benefits

5.1.1 Risks:

Participants who engage with the Bio-T-App, may encounter technical difficulties. The research team will assist participants to download and set up their app at baseline visit.

Training will be provided, and follow up phone-calls will help identify, support and resolve any technical issues patients may have.

Should users continue to struggle to use the Bio-T-App either through issues with their smartphone/laptop/tablet device or comprehension of the processes involved in reporting their disease activity in the interests of patient safety they will be withdrawn from the study and returned to the standard care provided by the department.

5.1.2 Benefits:

Patients will have regular on-going support through the research team. Access to a clinical research nurse, and increased monitoring and disease management will be included as part of the evaluation of the Bio-T-App. Patients will benefit from an educational element focused on understanding disease activity scores in rheumatoid arthritis.

6 TRIAL OBJECTIVES

6.1 Primary Objective:

The primary objective of the study is to evaluate the integration of a bespoke mobile app (Bio-T-App) for remote monitoring of RA patients by self-assessment as a reliable tool to measure RA disease activity.

6.2 Secondary Objective(s):

The secondary objectives of the study are to evaluate:

1. Effective management of disease activity in patients in Bio-T App versus patients in routine care
2. Health economic impact of the Bio-T-App on patient care versus routine care through the assessment of:
    - Biologic drug expenditure (through tapering medication dosage)
    - Patient access of outpatient resource (face-to-face appointments dependent on need)
3. Patient satisfaction with the Bio-T-App to manage RA symptoms and management of drug treatments. This will be compared against a convenience sample of patients who will be recruited from routine care in NHS clinics.

6.3 Primary Endpoint

1. The proportion of patients who adhere to the study schedule for recording disease activity scores after a six month period from baseline visit.

6.4 Secondary Endpoint

1. The number of patients in low disease activity (defined as (DAS ≤3.2) in Bio-T-App group routine care group at 6 months.
2. The validity of submitted scores when evaluated against other clinical parameters of disease activity and overall clinical picture.
3. Health economic impact
   - Cost of biologic drug in Bio-T-App group versus routine care.
   - Number of outpatient visits in Bio-T-App group versus routine care.
4. Patient satisfaction in Bio-T-App group versus routine care.

7 METHODOLOGY

7.1 Inclusion Criteria

- Men & Women ≥18 years of age.
- Diagnosis of RA
- Baseline DAS score < 5.1
- Access to smart phone/tablet/laptop to access the app.
- Prescribed a sub-cutaneous biologic drug for rheumatoid arthritis.
- Willing and able to provide Informed Consent

7.2 Exclusion Criteria

- Inability to provide consent/comply with study
- No access to a smart phone/tablet/laptop
- Baseline DAS > 5.1

7.3 Study Design / Plan – Study Visits

A cohort of 30 patients will be enrolled to the active arm of the study. These patients will be identified, screened and recruited by delegated members of the Rheumatology research team via routine outpatient clinics in the Rheumatology department of Mile End Hospital. Potential participants will be identified via the Clinical Research Management System (CRMS). This will involve reviewing the patients medical record and history, including personal identifiable information. The study will be discussed with the patient, and they will be provided with a copy of the Participant Information Sheet. The patient will be given sufficient time to decide if they wish to participate. Some patients may be approached once they have exited clinical trials in the department, These trials include STRAP (IRAS ID: 138283) and R4RA (IRAS ID 109361) as the IMP is open label and known to the patients care team.

Following study consent, patients are enrolled onto the Bio-T-App by the clinical research nurse. The clinical research nurse will undertake a training session with the patient incorporating training on swollen and tender joint count assessment and use of the Bio-T-App. A further assessment session 1 week later will assess patient reproducibility of tender and swollen joint assessment and if the clinical research nurse and patient demonstrate concordance in scores then the patient will be activated onto the Bio-T-App and a baseline DAS28 recorded. Baseline routine demographic data and clinical data including disease duration, sero-positivity for rheumatoid factor and ACPA, concomitant medications, comorbidities and treatment duration with biologic drug will also be recorded.

With the agreement of the PI the clinical nurse specialist will select the frequency of biologic medication which will be weekly, fortnightly or monthly. Remote DAS28 scoring will be based on the frequency of prescribed medication. This will be activated on the Bio-T-App. Patients will receive reminders on the Bio-T-App when medication is due and will be prompted to submit a joint count. On a daily basis the clinical nurse specialist will track patients through the Bio-T-App entering CRP values to calculate DAS28 scores. These DAS28 scores will be fed back to the patient via the Bio-T-App. If a patient has been in low disease activity (DAS<3.1) for at least 6 months prior to study start, the PI will determine whether medication tapering is appropriate. The PI will recommend an appropriate dose and the patient will commence the study on this reduced dosing regimen.

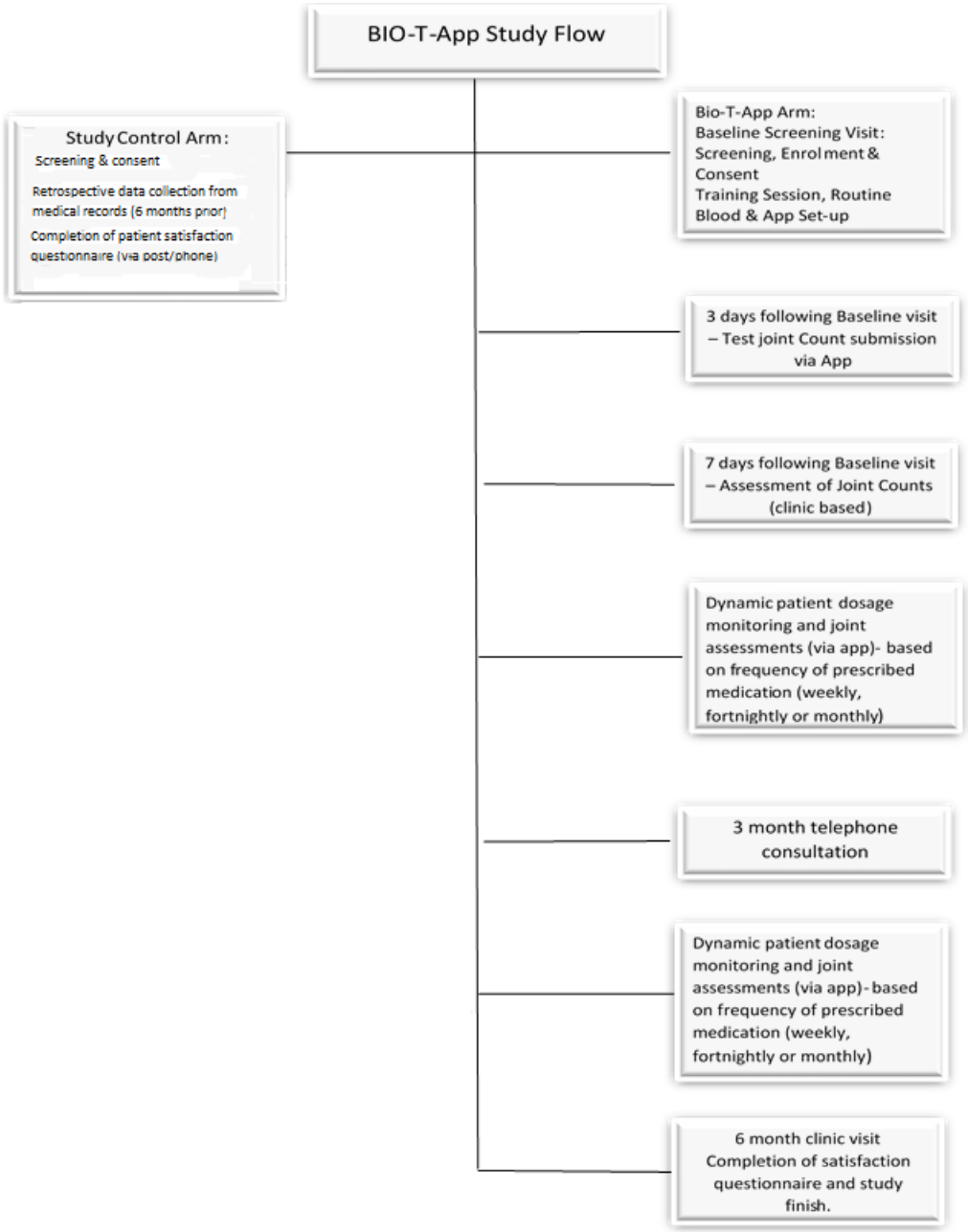
Conversely, if patients are identified within the Bio-T-App that have disease flares (rise in DAS >1.2) or high disease activity (DAS28>5.1) then they will be contacted by the clinical research nurse to discuss and a face-to-face appointment arranged if necessary. All interaction with patients including treatment modifications, biologic dose omission and disease activity will be entered onto the Bio-T-App database.

Patients who have not required a telephone consultation within the first 3 months of the study will receive an automatic scheduled telephone consultation with the clinical research nurse at 3 months time-point. Patients will be followed for a total of 6 months from enrolment and at the end of the 6 month period, patients will be seen for a face-to-face clinic visit with the clinical research nurse to assess DAS28 and complete patient satisfaction questionnaire, system usability score and a validated Mobile Application Rating Scale (MARS).

The comparator arm within the study will be NHS routine care. This will serve as the control arm. A cohort of 30 patients will be recruited from routine care, will be approached and consented for permission to collect data on demographics, out-patient appointments and DAS28 scores. Patients will be sent an ethically approved study invitation letter along with a copy of the Participant Information Sheet prior to their NHS clinic appointment. Information will be collected from the NHS clinical record. Patients will be asked to complete a patient satisfaction questionnaire. These will compare patients experience of treatment and management of disease. Patients will be consented who have a DAS of <5.1 and who are undergoing biologic therapy as part of routine care within the Rheumatology outpatients department of Mile End hospital.

Patient facing documentation such as the participant information sheet, consent form and satisfaction questionnaire have been designed following consultation and feedback with a Rheumatology patient panel.

7.4 Study Scheme Diagram:



8 STUDY PROCEDURES

8.1 Informed Consent:

Signed participant consent will be obtained from all participants. Consent will be sought from a patient once a full explanation of the study has been given by the Research team and a copy of the Participant Information Sheet provided.

The comparator arm within the study will be NHS routine care. A cohort of 30 patients will be recruited from routine NHS care. Control arm participants will be approached and consented for permission to

collect data on demographics, out-patient appointments and DAS28 scores over a 6 month period. This information will be collected retrospectively from their NHS clinical record. All participants will be provided with a participant information sheet and consent form. Patients will be given sufficient time to consider their participation in the study. If eligible patients are unable to attend face-to-face clinic appointments, they may be asked to complete postal consent.

8.2 Study Schedule/Visits

8.2.1 Baseline Screening & Enrolment

Patients will be enrolled in the study once they have consented to take part in the study. The patient will be asked to bring their laptop/smartphone/ tablet device to clinic to complete the baseline study visit

- Patient attends clinic, consents to study.
- Patient is registered on the Bio-T-App and is assigned a study ID
- Baseline demographic and clinical information collected
- Blood results are checked and repeated if not completed within past month (as per routine care)
- Medical history is taken
- Medication history is taken
- Joint count /DAS calculated.
- Patient is taught how to us the Bio-T-App
- Patient is set-up on the app
- Set up notifications and set patient time preference
- Send notification to confirm app settings
- Record biologic drug & joint count schedule
- DAS training session completed with patient and review appointment booked in 1 weeks' time.

As part of the DAS training, and to ensure adequate comprehension by the patient, the patient will be asked to submit a joint count during the week via the app. This will check that notifications are working and that the patient has understood the process to record their joint count correctly and submit it. This will be reviewed by the nurse and followed up at the next clinic review session.

Following informed consent by control arm patients, data will be collected from the NHS clinical record. This will include the patient initials, date of birth and DAS scores. The patient will not need to attend research clinic visits outside routine care.

8.2.2 Clinic based Follow-up Training Session

- Nurse DAS & compare with patient DAS to assess competency with joint count.
- Assess competency with the Bio-T-App.
- Review any questions patient may have.

The Nurse will observe and assess patients' competency at completing a self-directed joint count. If the patient is unable to demonstrate reasonable accuracy, a re-training session will be provided.

8.2.3 Follow-up visits – Virtual

The patient will complete follow up visits using the Bio-T-App. These are linked to the medication schedule and applied either weekly, fortnightly or monthly.

- Patient records drug adherence
- Patient submits joint count
- Nurse enters blood results
- DAS calculated
- Nurse action outcome
- Clinician action outcome
- Follow up action triggered

Following calculation of the patients DAS score based on a patients most recent joint count. Actions by the clinical team will be performed as necessary. A patient management SOP has been developed by the treating physician and patients' progress while being remotely monitored will be reviewed by the PI regularly.

Control arm patients will stay under the care of NHS routine care and will have no alteration to treatment.

Actions based on reported DAS		
DAS score	**Patient notification via App**	**Nurse notification via email.**
DAS ≤ 3.2	Your disease is well controlled	Patient has low DAS, please review on CRMS and implement SOP.
DAS > 3.2 ≤ 5.1	You have moderate disease activity and your rheumatology clinical research nurse has reviewed your DAS score. If there is a relevant change /significant increase we will contact you to discuss.	Patient has moderately high DAS, please review on CRMS and implement SOP.
DAS > 5.1	Your RA disease activity is high, please expect a call from your clinical nurse specialist in the next 48 hours.	Patient has high DAS please review on CRMS and implement SOP.

8.2.4 3 month telephone consultation

- specialist nurse will phone patients assigned to the Bio-T-App.
- Record any con-meds and will discuss any recent changes to RA medications (if applicable).
- determine if there has been any recent illness or hospital admissions.
- the nurse will review recent DAS scores and discuss patient progress with the patient including any further actions that may be required or if the patient needs to be seen in person by the PI.
- document a plan of action for care over the next 3 months.

- Plan for drug titration
- Record if face to face clinic appointment needed.

Control arm patients will not receive any follow up telephone call consultation outside of routine care.

8.2.5 Triggered telephone consultation: DAS > 5.1

- Check on con-meds
- Check recent illness or hospital admission
- Plan for DAS frequency
- Plan for Drug titration
- Record if face to face appointment needed.

8.2.6 Triggered in person consultation with Clinician

- Check con-meds
- Recent illness or hospital admissions
- Physical examination / bloods if required.
- Plan for DAS frequency
- Plan for drug titration or re-escalation if required.

8.2.7 Clinic based 6 month consultation

- patient will complete a face-to-face consultation.
- DAS28 will be measured
- patients current medication administration and dosage reviewed.
- patient asked to complete a satisfaction questionnaire, system usability score and validated MARS questionnaire.
- App deactivated and removed from phone.

Control patients will have DAS scores collected from NHS Clinical Records System retrospectively. The patient will be asked to complete a patient satisfaction questionnaire, but will not be asked to complete the system usability score or validated MARS questionnaire. In circumstances where the patient will not be attending their routine clinic appointment, this questionnaire may be posted to the patients address, along with a cover letter and a pre-stamped and addressed returning envelope. Alternatively, a member of the research team will go through the questionnaire with the patient on the telephone.

8.3 Study App

The Bio-T-App will be accessible on smartphone/ tablet/ laptop devices. Patients assigned to the Bio-T-App study arm will, following enrolment, undergo a short training session and clinical assessment with a clinical nurse specialist. At baseline, patients will receive instructions on how to download the app onto their smartphone/tablet/ laptop devices and how to submit readings to the research team. Readings will be submitted on a weekly, fortnightly or monthly basis depending on current medication treatment schedule.

8.4 Concomitant Medications

Patients will be recruited who have RA with an established treatment regime and low disease activity. As such all medications can be included as part of the treatment package.

8.5 Criteria for Discontinuation

Participants will be discontinued in the study if deemed appropriate by the clinical team.

8.6 Procedure for Collecting Data

The primary measure of disease activity in this study is the DAS28.

The components of the DAS28(CRP) are the number of tender joints (28 joint count), the number of swollen joints (28 joint count), a Patient Global Health index (Visual Analogue Score, VAS), and the CRP (in mg/L). The following 28 joints will be assessed for tenderness in response to pressure or passive motion: finger proximal interphalangeal joints (8), thumb interphalangeal joint (2), metacarpophalangeal (MCP) (10), wrists (2) (includes carpometacarpal, intercarpal, and radiocarpal), elbows (2), shoulders (2), and knees (2).

The formula for determining the DAS28(CRP) is as follows:

$$DAS28(CRP) = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH\ (VAS) + 0.96$$

Low disease activity = DAS28 ≤ 3.2
Moderate disease activity = DAS28 >3.2 but ≤ 5.1
High disease activity = DAS28 >5.1
Disease flare = rise in DAS >1.2

Participant joint counts will be received via the app and entered into the study database. Participant blood results information will be collected in the hospital as per routine care and from this the DAS28 will be calculated by the research nurse.

How regularly a patient needs to submit DAS scores via the app will depend on current treatment schedule which is decided by the PI and clinical team.

8.7 Case Report Forms (CRFs) and storage

A study visit page on the Bio-T-App database will be completed by the research team indicating key assessments and data points collected. All data related to the patients' care will be made available in the NHS care record.

8.8 Follow-up Procedures (if applicable)

Follow up procedures will be performed based on the submitted joint counts of participants via the app. These will be scheduled according to a frequency set by the supervising clinician. Please see schedule below.

8.9 Laboratory Assessments

There are no laboratory assessments performed outside of routine management which will be conducted in line with Barts Health NHS Trust local policies.

8.10 Subject adherence & withdrawal (including data collection / retention for withdrawn participants)

Participants are free to withdraw from the study at any time and are advised as part of the consent and enrolment process. Additional circumstances where it may be inappropriate for a patient to continue in the study include:

- Prolonged difficulty/inability to perform joint counts.
- Non-compliance with study procedures
- Following decision and assessment of supervising clinician.

If a patient, who has previously given informed consent loses capacity to consent during the study, the participant would be withdrawn. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

Adherence within the study shall be defined as the proportion of patients who adhere to the study schedule. Level of adherence will not be classified but simply reported within the trial. Patients who do not adhere or are withdrawn due to the reasons stated above will be included as part of the study analysis.

Schedule of Assessment (in Diagrammatic Format)

Assessment	Screening (Week 0)	Post-screening assessment (+ 1 week)	On-study phase (dynamic scheduling) (d)	3 month follow-up	6 month follow-up
Consent & Enrolment	x				
Clinical Assessment	x			X	X
Physical Assessment / DAS	x				X
App Training session	x				
Joint Counts	X (a)		X (b) (d)	X (b)	X (a)
Joint Count assessment		X (c)			
Follow up phone call				X	

(a) These joint counts will be nurse-led
(b) These joint counts will be patient directed.
(c) Patient joint-count accuracy determined.
(d) Frequency weekly, fortnightly or monthly in line with medication schedule, including a reduced tapered medication schedule as deemed appropriate by the supervising clinician.

In addition to these visits there will be notifications via the Bio-T-App for the patient to record their drug adherence and joint scores. Patients who do not report their DAS scores will be initially reminded via the app and then subsequently followed up by the study research nurse to prompt them to do so.

8.11 End of Study Definition

End of study will be defined as the last 6 month follow-up appointment by the last recruited patient.

9 STATISTICAL CONSIDERATIONS

This is an observational pilot study, and as such no power calculation has been determined. Missing, unused and spurious data will be assessed on an individual basis and may be withdrawn with appropriate justification adjudicated by the Principle Investigator.

10 ETHICS

This study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable, and applicable legal and regulatory requirements.

11 SAFETY CONSIDERATIONS:

Full clinical review and safety assessments will be carried out as per standard practice for subjects under routine clinical care for RA at the clinic visits scheduled for all patients at the 3 month and 6 month follow-up visit.

There will not be any change of biologic therapy without the treating physician first having seen the patient in person to objectively evaluate both their disease activity and the patients own ability to record accurate DAS scores.

There are no other additional interventions in this study so there is no additional risk to any patients participating in this study.

12 DATA HANDLING AND RECORD KEEPING:

12.1 Confidentiality and Data Storage:

A web based electronic will be used to record clinical data from each patient visit. This will be encrypted at the point of the user. The following data points will be recorded and encrypted; initials, date of birth, age at entry, email, addresses and telephone numbers. The electronic database will be held on a secure server within a secure locked room within the Department of Experimental Medicine (key code access to authorised personnel only). Data will be stored in compliance with GDPR & Data Protection Act 2018. All data will be pseudo-anonymised where data of birth and initials will be linked to a unique participant identifier for the patient in an encoded fashion.

12.2 Record Retention and Archiving

During the course of research, all records are the responsibility of the CI and must be kept in secure conditions. When the research study is complete, it is a requirement of Research Governance Framework and Sponsor Policy that the records are maintained for a further 20 years. At the end of the study, the site will be instructed to archive the study documentation for 20 years. At the end of the study, the records will be sent to the repository for long-term storage of Barts Health Trust Modern Records Centre, located in Prescot Street.

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. From the end of the study, it is a requirement of the Research Governance Framework and QMUL Policy that all records are kept for a further 20 years. Electronic data will be stored and archived for 20 years in compliance with QMUL's archiving SOP in encoded password protected format. The data collected and generated as part of this study's objectives will be analysed at the Centre of Experimental Medicine & Rheumatology, Queen Mary University.

12.3 Bio-T Application

The Bio-T-App was built on the Ionic mobile apps framework. The app was built for Android based mobile devices and is also compatible with other iOS mobile devices (i.e. iPhone). The app will be installed on patient's mobile device by the patient and will hold no Patient Identifiable Data. The app will serve as an appointment reminder and data submission tool. The patient will submit Joint Counts and General Health data and upon submission this data will be removed from app immediately. The app will also schedule reminders for patient drug (Biologics) uptake and submit this data to Bio-T-App database. Once the app is closed (i.e. patient logging off) the appointment schedule will not be visible. Reminders will pop-up on patients phone for his/her attention and will trigger action by the patient to submit data. The app can be easily uninstalled by the patient once the study is closed or when the patient decides to withdraw from the study so patient's privacy is even further protected and is decided by patient himself

The Bio-T-App is a mobile/laptop database application which captures real-time disease activity (via patient self-assessment) via a mobile or laptop device. Specifically it will collect RA disease activity scores (joint counts) from patients remotely, to deliver a personalised care plan through integration of remote data (patient self-assessment of disease activity) with the main Bio-T-App maintained centrally by the research team.

12.4 Bio-T-App Database

The Bio-T-App database has a web based interface making it conveniently accessible and it provides a simple and user friendly way of collecting, maintaining, presenting and archiving information from patients.

Patients selected and who consent to participate in the Bio-T-App study will be allocated a unique participant Temp ID number and separate Study ID number once participant confirms Inc/Exc. Criteria are satisfied.

Data uploaded to the Bio-T-App study database will be protected via a number of methods. Two separate databases will exist (although, note, this will not be distinguishable from the 'front end' user interface);

i) Main clinical database for collection of all clinical data via electronic CRF (eCRF)

ii) Database contain initials and date of birth of the participant – this has been risk assessed based on this known study cohort and deemed to be required as a minimum number of data items to accurately link a patient's NHS data for manual entry of data into the Bio-T-App database by the Rheumatology study team and, for direct import of data from NHS records to the Bio-T-App database. Participant information during the study will be pseudo-anonymised where patient initials and date of birth are linked to a unique study identifier. Additionally as patients have previously enrolled in other biopsy driven EMR studies the Initials and DOB will be used to verify the correct patient records are being linked between existing trial databases and Bio-T-App.

Patients selected and who consent to participate in the Bio-T-App study will be allocated a unique participant ID number which will provide a link, with two data items check, between the two databases as described above. All data stored on this separate database will be fully encrypted

No other identifiable data will be collected on the Bio-T-App database and will not be accessible to any individuals outside of the patients' immediate healthcare team, except for authorised reasons for example auditing or monitoring purposes by a member of the central study team, Sponsor or Regulatory body.

12.4.1 Data entry and Data Access to/from Bio-T- app database

The patient source data will be stored electronically within the clinical record. Where patients complete standard assessment questionnaires these will be viewed by the study team co-ordinating the Bio-T-App study but the paper questionnaires will remain in the medical record.

Members of the clinical study team have direct contact with patients as part of provision of care and as such have authorised access to the NHS systems by which they identify patients. The staff members need to have logons for the Clinical systems as well as the NHS Care record service registration with permissions to access Barts Health NHS Trust ICT systems.

The personal data of each patient will be stored in hard copies in a secure locked filling cabinet in a locked room at the local NHS hospital recruiting site. Only the local NHS research team will have access to the physical hard copy of this data and are authorised to do so.

Only study team members, the Principle Investigator, clinical research nurse, project manager and associated clinical staff will have access to the patients' data during the study. Members of the clinical study are responsible for entering date into the Bio-T-App database via a 'frontend' user interface.

12.4.2 Centre for Experimental Medicine & Rheumatology, QMUL

Members of the study team based at QMUL will have view only access rights to the 'front-end' user interface and additional user rights to run reports on the data for data cleaning and other QC and reporting purposes, and for preparing data exports for external collaborators via export functions. Direct access to the personal identifiers database will be restricted to minimum number of senior personnel. For all other staff members, any export or reports of such data will display initials and year of birth and the unique patient ID number.

Data uploaded to the Bio-T-App study database will be protected using the following methods: Additionally as patients have previously enrolled in other biopsy driven EMR studies the Initials and DOB will be used to verify the correct patient records are being linked between existing trial databases and Bio-T-App.

12.4.3 External collaborators

No external collaborators are working with the Bio-T-App study and shall have no direct access to the Bio-T-App database. Patients identified and who consent to participation in Bio-T-App will be allocated a unique study ID number. Data will be collected on electronic CRFs using a specifically designed database. The Bio-T-App database has a modular and role based user account system that is developed to manage rheumatology patients and research studies.

Any sharing of data outside of QMUL, following successful application via the EMR Bio-T-App Oversight Management Committee (OMC) to access Bio-T-App data, will contain only the unique participant ID allocated to each person. As such, personal data has been converted into a pseudo-anonymised form which does not amount to a disclosure of personal data and individuals' identities are fully protected. This is the case even though QMUL, as custodian of all the data, has the ability to link this unique code back to the patients' initials and DOB.

The Bio-T-App database has a web based interface making it conveniently accessible and it provides a simple and user friendly way of collecting, maintaining, presenting and archiving information from patients.

12.5 Data Storage and Security

All data (patient derived remote data via mobile/lap-top device and clinic derived via direct input in the Bio-T-App main database) will be collected and stored on the Bio-T-App database. This has a web based interface making it conveniently accessible and it provides a simple and user friendly way of collecting, maintaining, presenting and archiving information from patients.

Data uploaded to the Bio-T-App database will be protected via a number of methods. Two separate databases will exist although this will not be distinguishable from the 'front end' user interface:

i) Main clinical database for collection of all clinical data via electronic CRF (eCRF);
ii) Database containing identifiable data; full name, initials, date of birth, email address and telephone number of the participant – this is deemed to be required as a minimum number of data items to accurately link the participant and their device for remote data entry to the Bio-T-App and integration with the main Bio-T-App database. Participant information during the study will be pseudo-anonymised where patient details are linked to a unique study identifier.

Patients selected and who consent to participate in the Bio-T-App study will be allocated a unique participant ID number which will provide a link between the two databases as described above. All data stored on both databases will be fully encrypted.

No other identifiable data other than defined above (in section 12.1) will be recorded on the Bio-T-App. Access to patients' medical records will only be for authorised reasons, for example, auditing or monitoring purposes by a member of the central study team, Sponsor, or Regulatory body.

DAS scores and biologic therapy will be assessed by the clinical nurse specialist and any modification to treatment delivered in an appropriate format (telephone consultation, clinical visit).

The Chief Investigator may electively stop the trial prematurely. This can occur in any case where there is a potential compromise of patient information, data from the database or patient safety.

12.6 Data security, data transfer and data back-up

12.6.1 Application Level Security

The Bio-T-App sits on the patients' smartphone device. The patient is provided with log-in details for the app by the clinical team, once registered and set up on the Bio-T-App database. These log-in details will not change. The only patient information stored within the app are the patients initials and gender. In addition the patients schedule of joint counts and medication. This is non-identifiable information. Once the patient is no longer in the study the app will be removed from the patients' phone.

12.6.2 Database level security

The Bio-T-App database has a Dual Factor Authentication (DFA) login system. This is a session access control so user cannot access the database application without a DFA token. This consists of user name plus password, and then a token sent separately to his/her email address or mobile phone number. The database also has page-embedded security and validation measures that make it far more secure than classic Excel, Access or Filemaker (single file databases).

The Bio-T-App database has User Level protection where different levels of access to the application are granted such different user levels can have either no access or read only, or read/write, or a combination of these depending on user's authorisation level.
The Bio-T-App database has a modular and role based user account system that is developed to manage access to the data being collected for this study. Access to personal information that is contained in a separate database to that of the clinical data will be restricted to the minimum number of individuals with the Centre for Experimental Medicine & Rheumatology. This is an additional security layer as re-identification would be unlikely since data will be encrypted inside the database so, even if database was accessed by an unauthorised user, it should not be possible to identify participants.

Wider access to the main clinical database will be granted although user access and user rights will differ depending on the user's role and location i.e. personnel at the Barts Arthritis Centre, who are responsible for data entry into the database versus personnel at Centre for Experimental Medicine & Rheumatology at QMUL who are responsible for quality control checking of the data being received (no data entry rights), and management, maintenance of the database, and sharing data when approved to do so.

The Bio-T-App database also has full audit function (time stamped) so it is possible to know if a database user has made changes, and what and when those changes were made. Furthermore, a robust backup and disaster recovery policy exists in case of sudden data loss or force majeure.

12.6.3 Server level security

The Bio-T-App database is a web-based system which uses HTTPS type of encryption (bidirectional encryption of communications between a client and server) that is commonly used in internet banking or ecommerce systems. Patient data confidentiality is ensured and only patient non-identifiable data is collected within the main clinical database and a full end-user audit trail is in place.

The hosting system where the database is residing is Security Enhanced Linux PHP / MySQL based and very flexible. The database (MySQL type) is entirely separate from the interface. MySQL and PHP are very stable, supported and robust platforms.

If required the database can be also exported for use in more common application based systems like Excel, Access, Filemaker etc. In the same way it is also possible to import data back from other types of databases to MySQL. Data can be stored on the same or a remote server. The Bio-T-App is hosted on the QMUL network and is regularly maintained as per QMUL IT Security policy. Physical access to the server is restricted to individuals by the QMUL security team.

12.6.4 Network Security

Host based firewall are used within the Centre for Experimental Medicine & Rheumatology and also there is an additional external, QMUL firewall. Internal firewall filters the network traffic to server and allows access only to whitelisted services and protocols. External firewall is managed by Central IT Services and protects from any external (WAN related) threats.

12.6.5 Data Transfer

Data exports prepared, and to be shared with an authorised external collaborator, will be transfer via a secure online file pickup service hosted by QMUL which will require a username and password to access and retrieve any such data files.

12.6.6 Data back-up

A two fold back-up system is deployed. This involves a daily synchronisation of the database, ‘like for like’, on separate server / domain. In addition to this, database versioning / backup copies are made so the database can be restored back to a specified date. This provides both an instant ‘live’ copy and, with database versioning, several historical database versions are kept.

Identifiable data will not be collected on the Bio-T-App database and will not be accessible to any individuals outside of the patients' immediate healthcare team, except for authorised reasons for example auditing or monitoring purposes by a member of the central study team, Sponsor or regulatory body.

12.6.7 Tools

At the 6 month final study visit. Participants will be asked to complete a validated patient satisfaction questionnaire.

13 SAFETY REPORTING

13.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities, or independent of study activities.

The reporting period for AEs, and Serious Adverse Events (SAE), begins from the time that the first study specific assessment/procedure is undertaken (Screening visit), and ends after the participant's last visit.

Any reported AE(s) are recorded in the study file and the participant is periodically followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the AE/SAE CRF.

13.2 Serious Adverse Event (SAE)

In research <u>other</u> than Clinical Trials of Investigational Medicinal Products i.e. non-CTIMPs, SAE is defined as an untoward occurrence 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; or
(f) Is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant should be reported to the main REC 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

AND

Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

13.3 Notification & Reporting of SAEs

All AEs discovered by the reporting research centre, whether volunteered by the participants through questioning, or detected through physical examination, laboratory test or any other means will be recorded in the source documents, patient's medical notes, and on the AE/SAE CRF eCRF) and followed as appropriate.

Causality must be assessed and completed by the PI at the local research site or an authorised clinician within the research team who has been delegated this role. The person assessing causality must sign a paper copy of the SAE CRF.
Regardless of suspected causality, all SAEs occurring after the first study specific assessment/procedure is undertaken (screening visit) and until after the participant's last study visit has been completed must be reported to the EMR Clinical Trials Centre, QMUL office immediately, and within 24 hours of the site becoming aware of its occurrence. The SAE will be reviewed at the EMR Clinical Trials Centre for data completeness. The CI will assess the SAE and may send queries back to the reporting local site as applicable. The EMR Clinical Trials Centre will then forward the signed SAE form to JRMO, QMUL as sponsor of the study. Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the coordinating site. The PI or an authorised clinician within the research team who has been delegated this role

shall submit further detailed information relating to the event, as the JRMO shall request within 24 hours of it becoming available.

13.4 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to NRES website and JRMO SOPs.

The Chief Investigator may electively stop the trial prematurely. This can occur in any case where there is a potential compromise of patient information, data from the database or patient safety.

13.5 Annual Progress Reporting

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC “favourable opinion” letter from the MREC) and to the sponsor. Please see NRES website and JRMO SOP for further information

14 MONITORING & AUDITING

Monitoring activities will be commensurate to the risk of the study. As this is a low-risk study “on-site monitoring” will not be required but a triggered visit may occur if warranted, or may be arranged as part of the Centre for Experimental Medicine & Rheumatology on-going quality management system procedures. Such on-site monitoring activities would include verification of patient consent to participate in the study and source data verification checks against patients’ medical notes to monitor the accuracy of the data being collected. For a study of this nature, central monitoring activities will be more appropriate and this will be developed as part of a central data management plan to monitor timely transfer of study data to the study database, review of completeness and accuracy of the data, and to look for any anomalies or unusual patterns in the data that may prompt an “on-site” monitoring visit. The Sponsor retains the right to Audit any study, study site or central facility. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable.

15 TRIAL COMMITTEES

As the study is classified as low-risk, the study will be overseen by a Trial Management Group Committee. This will consist of the Chief Investigator, Co-investigator(s), study manager, research nurse, other clinical team staff, database manager.

The committee will meet to review data collection and will be responsible for the day-to-day running of the study and overseeing implementation of the protocol. The committee will meet monthly at a time and date dictated by the Chief Investigator and a copy of all agendas, papers, and minutes shall be stored in the Trial Master File.

16 FINANCE AND FUNDING

The project is funded through a grant awarded by Barts Charity

The Chief Investigator or any other co-investigators do not have any direct personal involvement in any of the organisations sponsoring or funding the research.

17 INDEMNITY

Queen Mary University of London is sponsor of this study and will provide no-fault compensation to participants recruited to the study.

18 DISSEMINATION OF RESEARCH FINDINGS

The improvements delivered by the Bio-T-App will be disseminated at different levels: i. The results will be presented to local commissioners to implement a risk share agreement for the trust to ensure ongoing funding for Bio-T-App maintenance. In addition the results will be presented to the regional network of rheumatology consultants to support implementation of the Bio-T-App to the network of hospitals within Barts Health and to local trusts.(e.g. BHR and Homerton). ii. Nationally/Internationally. The data analysis will be presented at the regional British Rheumatology Society Meeting and at National Pharmacy conferences (e.g. Clinical Pharmacy Congress) as well as at a future date at International meetings including American-College- Rheumatology-(ACR) and European-League-Against-Rheumatism-(EULAR)

PPI groups. The department of Rheumatology at Barts Health has active links with local patient groups including the local National Rheumatoid Arthritis Society patient group
(http://www.nras.org.uk/groups/east-london-nras-group) and local Joint200 group
(http://www.arthritis- selfhelp.org/newsAndEvents.asp). Disseminating results of the project to patient groups would be vital to disseminate potential benefits of the project.

The Bio-T-App will be submitted to NIHR the Health Services and Delivery Research (HS&DR) to fund future definitive trials and additional funding would be sought through the NHS innovation accelerator to facilitate subsequent adoption nationally. The aim would be to enable to application to be registered as one of the 20 new tech tariffs enabling the application to be rolled out nationally.

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