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Quality of life, sleep and rheumatoid arthritis (QUASAR): A protocol for a prospective mHealth study.

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Abstract

Introduction: People with rheumatoid arthritis (RA) frequently report reduced health-related quality of life (HRQoL), the impact one's health has on physical, emotional and social well-being. There are likely numerous causes for poor HRQol, but people with RA have identified sleep disturbances as a key contributor to their well-being. This study will identify the sleep and circadian rest-activity parameters that predict fluctuations in HRQoL in people with RA.

Methods and analysis: This prospective cohort study will recruit 350 people with RA, aged 18 years or older. Following completion of a paper-based baseline questionnaire, participants will record data on 10 symptoms including pain, fatigue, and mood twice-daily for 30 days using a study-specific mobile application (app). A tri-axial accelerometer will continuously record daytime activity and estimate evening sleep parameters over the 30 days. Every 10 days following study initiation participants will complete a questionnaire that measures disease specific (Arthritis Impact Measurement Scale 2 - Short Form (AIMS2-SF)) and generic (WHOQOL-BREF) quality of life. A final questionnaire will be completed at 60 days after entering the study. The primary outcomes are the AIMS2-SF and WHOQOL-BREF. Structural equation modelling (SEM) and latent trajectory models (LTM) will be used to determine the sleep and rest-activity parameters that predict fluctuations in HRQoL.

Ethics and dissemination: Ethical approval for this study has been obtained from the National Research Ethics Service (REC ref: 17/NW/0217). Results from this study will be disseminated at regional and international conferences, in peer-reviewed journals and Patient and Public Engagement (PPE) events, as appropriate.

Strengths and limitations of this study

1. This study will take advantage of advances in mobile health (mhealth) to embed data collection into the daily lives of participants.

2. Using a patient co-designed smartphone/tablet app it will capture objective and subjective sleep as well as self-reported symptoms.

3. Sophisticated structural equation modelling (SEM) and latent trajectory models (LTM) will enable the study to disentangle the complex relationship between sleep, HRQoL and other symptoms.

Introduction

Quality of life, sleep and rheumatoid arthritis (QUASAR) is a cohort study which will use a patient designed smartphone/tablet app and accelerometer to collect information on sleep and health-related quality of life (HRQoL) in rheumatoid arthritis (RA).

RA is a common chronic inflammatory disease characterised by joint damage, pain and disability [1]. Occurrence between two and four times greater in women a high proportion of people of working age with RA stop work due to the condition[2;3]. People with RA frequently report reduced HRQoL, which can be characterised as the impact one's health has on physical, emotional and social well-being. People with RA have poorer HRQoL when compared to those with other rheumatic diseases[4] or healthy peers[5;6]. Poor HRQoL may even persist when the disease is well controlled[5].

Although there are likely numerous causes for poor HRQol, but people with RA have identified sleep disturbances as a key contributor to their well-being[7-9]. It is well known that people with RA experience sleep disturbances[10;11], with people often reporting less total sleeping time and unrefreshing sleep[8] and greater night time awakenings[7;9]. But sleep is a multifaceted behaviour [12] and it is not clear which, if any, aspects of sleep disturbance impact on HRQoL. Moreover, it has historically been difficult to measure sleep outside of artificial laboratory settings and to disentangle the relationship between sleep, HRQoL and other symptoms, because symptoms change day to day.

Advances in the availability of smartphone apps and wearables for health monitoring provide a hitherto unobtainable mechanism to collect regular self-reported symptoms and objective sleep data, while embedding data collection into participants' everyday lives. This study will use a combination of patient co-designed smartphone/tablet app (provided by uMotif, London, UK) and a tri-axial accelerometer (MotionWatch8, CamNtech, Cambridge, UK) to capture both subjective and objective assessments of sleep quality, continuity and duration, as well as the timing and stability of the periods of time when someone is asleep or active [13]. Furthermore, the uMotif app will be used to collect information about self-reported symptoms which were identified as priorities by patients in a series of focus groups and patient involvement activities. In doing so this study aims to identify which sleep and circadian rest-activity parameters predict reduced HRQoL in people with RA.

Study objectives

1. Describe baseline and period distribution of sleep and circadian rest-activity parameters stratified by age, sex, socioeconomic status and disease characteristics. Determine relative contributions of sleep and circadian rest-activity parameters, pain, fatigue and mood to RA-HRQoL.
2. In an exploratory analysis examine whether the relationship between disease severity, sleep and circadian rest-activity parameters, pain, fatigue and mood and RA-HRQoL are moderated by age and sex.
3. Estimate the potential effect on RA-HRQoL of a successful intervention targeted at the key identified pathway(s).

Experimental design and methods

Methods and analysis:

Study design

We will conduct a prospective cohort study to investigate the relationships between sleep and HRQoL in people with RA.

Identifying and recruiting potential participants

Participants will be recruited via three channels. The primary source for participants will be the National Rheumatoid Arthritis Society (NRAS). NRAS is a national patient organisation with over 7000 members. Emails advertising the study will be sent to NRAS mailing list members and will include a copy of the study information pack comprising:

1. Study poster
2. Participant information sheet
3. Copy of the consent form (for information only)
4. A link to complete an online screening questionnaire

Following approval from the Health Research Authority (HRA) and via arrangements with Clinical Commissioning Groups (CCGs), participants will also be recruited via NHS mailing lists, where such mailing lists are available. NHS mailing lists provide the opportunity to search General Practitioner (GP) records for potentially eligible participants. Local Clinical Research Network (CRN) teams will

search GP records for patients aged 18 or older, with a diagnosis of RA and who are in receipt of a Disease Modifying Anti-rheumatic Drug (DMARD), as recommended by Muller et al[14]. Letters will be sent to the identified patients, provided the GP or clinical team in the practice confirms that approaching the patient is acceptable. Reasons for not approaching patients may include previous refusal for records to be used for research, current hospitalisation, or belief that the participant is not capable of participation. Within the letter, participants will be briefly introduced to the study and persons interested in participating will be asked to email the study team directly for the study information pack, the contents of which are detailed above.

Information about the study will be displayed on the NIHR Clinical Research Network Portfolio to encourage NHS sites to support study recruitment by displaying posters advertising the study in any NHS Rheumatology clinics. NHS sites interested in supporting the study will contact the study team directly for further information and all relevant documentation needed to confirm they have the capacity and capability required to support the study. The displayed posters will provide brief information about the study and will ask persons interested in participating to email the study team directly for the study information pack, the contents of which are detailed above.

Following the receipt of the study information pack, potential participants follow an identical recruitment strategy (Figure 1).

[Figure 1 here]

Figure 1 – Flow of participant entry into the study

Screening questionnaire

Persons who receive the study information pack and are interested in participating in the study are asked to complete the study screening questionnaire. Potential participants are asked to record their sex and date of birth, and to confirm whether they a) have a diagnosis of RA (including date of diagnosis), b) are currently using DMARDs (biologic or conventional synthetic), c) have access to an Android or Apple smartphone or tablet. For the purposes of exclusion criteria interested persons must also indicate whether they are currently employed in shift work. Finally, potential participants are asked to give consent and contact details and preferred contact time (9am and 12 noon, 12 noon and 3pm, 3pm and 6pm or 6pm and 8pm) to enable the study team to contact them to discuss participation in the study.

Eligibility criteria

Screening questionnaire respondents will be considered eligible for the study if they:

- Are aged ≥18 years
- Have a diagnosis of rheumatoid arthritis
- Are currently using DMARDs (biologic or conventional synthetic)
- Have access to an Android or Apple smartphone or tablet

Respondents would be excluded from the study if they:

- Are currently employed in a job that requires shift work

QUASARid

Study participants will be asked to provide data via a three different platforms: paper-based questionnaires, a study app (downloaded onto a smartphone or tablet), and a tri-axial accelerometer that will measure daytime physical activity and sleep. To ensure that the data collected across these platforms can be consistently and accurately linked and matched to each participant, a unique participant identifier will be generated for each participant. The unique identifier, known as a QUASARid, will be automatically generated as the unique survey response which is allocated to the participant when they commence the screening questionnaire.

Telephone call

Potential participants meeting the study inclusion criteria will be telephoned by a member of the study team. To ensure they have had adequate time to review the participant information sheet provided in the study information email, telephone calls will take place no earlier than 24 hours after receipt of a completed screening questionnaire. A total of four attempts to contact the potential participant will be made on consecutive week days. During the phone call a verbal summary of the information sheet will be discussed with the potential participant and they will be given the opportunity to ask as many questions about the study as they wish.

Verbal consent and agreement of study start date

Following the verbal summary of the study information sheet, participants will be given the option to enrol into the study, delay participation, request more time to think about participation or decline to take part in the study. Written consent is subsequently obtained by the completion of two paper copies of the consent form sent to participants within the study pack. The provided consent forms will be signed and dated by the team member responsible for recruitment at the point of obtaining

verbal consent, with participants asked to complete their own signature at the time of completing the baseline questionnaire. One copy of the consent form is to be returned by the participant at the end of their first 30 days in QUASAR, along with the actigraph watch and baseline questionnaire. The second copy is for the patients' personal records.

Once verbal consent has been obtained participants will be asked to agree a study start date, which should be within 14 days of the telephone call taking place. Participants who are unable to commence the study within 14 days will be asked to delay entry into the study. Those who agree a study start date will be asked to confirm their preferred postal address to which the study packs will be sent and a mobile phone number. The mobile phone number will be used to send participants text messages on the agreed study start date and throughout the study to encourage data completion and study compliance.

Study pack

The provision of verbal consent also enables the study pack to be prepared and posted to participants in advance of the agreed study start date. The study pack will include a letter of introduction, two copies of the consent form and a paper copy of the baseline questionnaire. Participants will also be provided with instructions to download and use the study app, as well as an actigraph watch, called a MotionWatch8 (CamNtech, Cambridge, UK) and associated instructions. The study pack will be sent from the University of Manchester using Special Delivery Guaranteed® to arrive no less than one day prior to the study start date.

Document completion – Consent form and baseline questionnaire

Participants are requested to complete paper copies of the consent form and baseline questionnaire (sent within the study pack) on, or before the first day of symptom monitoring. Initially the baseline questionnaire was incorporated into the study app to be completed as part of the on-boarding process. However, due to limits on the number of questions which could be displayed per screen and the associated time required for data completion, app testing with the study team and members of a focus group indicated that this method of delivery would be less acceptable to participants than a paper based document.

The participant's QUASARid will be written onto both the consent form and covering page of the baseline questionnaire to enable data linkage between these documents, the study app and actigraph watch. To encourage completion of the questionnaire is completed in advance of the

monitoring period, participants are asked to indicate the date on which they have completed the questionnaire on the covering page. They will return the baseline questionnaire along with the monitor at the end of the study.

The baseline questionnaire will comprise three sections: Demographic information, information about RA and health status information. The items we will collect are shown in Table 1

Table 1 – Baseline questionnaire domains and scales	
Domain	Scales/measurement
Demographics	
Sex	Tick box – male or female
Date of birth	Day, month, year
Height and Weight	Free text (metric or imperial)
Ethnicity	Free text
Age left education	Free text
Smoking status	Tick box – current, ex-, or never smoker
Occupational status	Tick box – working full time, working part time, student, medically retired, voluntary worker, unemployed but seeking work or retired
Marital status	Tick box – Single, in a relationship, co-habiting, married, civil partnership, separated, divorced or widowed
Alcohol consumption	Tick box –average units per week: 0, 1-5, 6-10, 11-15, 16-20, 21-40, >40
Impact of RA on work	Work productivity question from Work Productivity and Activity Impairment – specific health problem (WPAI-SHP)
Postcode	Free text for first half of postcode
Belief that sleep affects HRQoL	0-10 NRS: 0 “Not at all likely”, 10 “Very likely”
Information about RA	
Date of RA diagnosis	Month and year
Disease activity	Routine Assessment of Patient Index Data 3 (RAPID-3)
Co-morbid rheumatic disease(s) and sleep-related problem(s)	Check list – osteoarthritis, spondyloarthropathy/ankylosing spondylitis, fibromyalgia/chronic widespread pain, gout or other crystal arthritis, Sjogren’s syndrome, restless leg syndrome, obstructive sleep apnea/snoring, thyroid disorder, diabetes, multiple sclerosis, hypertension.
Menopausal status	Tick box – yes/no
Current medication(s) and non-pharmacological intervention use	Check list – parcetamol, non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, weak opiates, strong opiates, drugs for neuropathic pain, glucocorticoids, synthetic disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, sedatives (or hypnotics), mood stabilisers, antidepressants, other sleep medications. Free-text box
Health status information	
Disease specific quality of life	Arthritis Impact Measurement Scale 2 - Short Form (AIMS2-SF)
Generic Quality of life	WHOQOL-BREF
Prioritisation domains for good HRQoL	Participants are asked to use a free text box to indicate top 3 things which are most important to them to ensure they have good quality of life.
Sleep quality	Pittsburgh Sleep Quality Index (PSQI)
Beliefs about sleep	Dysfunctional Beliefs and Attitudes about Sleep questionnaire (DBAS-16)
Insomnia	Sleep Condition Indicator (SCI)

Mood	Hospital Anxiety and Depression Scale (HADS)
Self-efficacy	Arthritis Self-Efficacy Scale-8 item (ASES-8)
Cognitive flexibility	Committed Action Questionnaire (CAQ-8)

Study commences (Day 1)

On the agreed study start date, participants will receive a text message on the mobile phone number the provided during the recruitment process. The reminder text message will ask participants to put on their activity monitor and to download the study app and register for an account. It will also include a study password, which will unlock the app to allow the participant to commence full registration, and a reminder of their QUASARid, which must be entered during the registration process to enable data linkage between the study app, actigraph watch and paper questionnaires.

App installation and account set up

Instructions about how to download the study app, which can be installed onto the participants' Apple or Android smartphone, tablet or both, will be included within the study pack that will be posted to participants. Once the app is installed participants will be asked to:

- complete a standard registration form (including creation of a username and password)
- enter their unique QUASARid, sex and date of birth, to enable linkage between the study's different data collection platforms

Registrations will be monitored via a live database, held by uMotif, of the data collected by the study app, to which the study team is provided secure access. All data provided by participants using the study app are immediately transferred to uMotif server and visible in the database in real-time via 3G/4G/ Wifi. Any participants who have not registered with the app on their agreed start date, or within a 5 day window of that date, will be contacted by the study team to understand what issues may have arisen. If appropriate, participation in the study may be rescheduled for a later date.

Data collection

Following app-installation and the completion of the baseline questionnaire, participants will commence data collection lasting a total of 60 days. The first 30 days of the study comprise the continuous data collection phase of the study during which time participants wear the actigraph watch 24 hours a day and complete a once-daily sleep diary and twice daily symptom reports. During this 30 day monitoring period participants will also complete follow-up questionnaires on days 10, 20 and 30 of the study. No data are recorded between days 31 and 59, but participants are asked to complete a final follow-up questionnaire on day 60 of the study.

During focus groups conducted to inform the design of this study, participants discussed a desire to have options for on-going support from the study team via telephone contact. For that reason we will send personalised messages on days 5, 15 and 25 to encourage participation and give the participant the option to email or telephone the study team if they would like to discuss any issues or concerns. Any emails or requests for telephone calls will be responses to by the study's post-doctoral research associate, or principal investigator, at the earliest possible opportunity, and no later than one working day after the response is received.

A full outline of the data collected is provided below.

Day 1-30 – Actigraph watch and uMotif app

Continuous monitoring of sleep and physical activity.

Participants will wear the MotionWatch 8 (MW8; CamNtech, Cambridge, UK) for 24 hours a day over the 30 days of continuous data collection. The MW8 is a Class I Medical device which conforms to the essential safety and health requirements and provisions of EC Council Directives 93/42.EEC, Annex VII. The MW8 requires a standard watch battery (CR2032) which is replaced each time the watch is used. The configuration of the MW8 for the present study will enable the watch to collect data for up to 45 days, providing an additional two week window for data to be collected in instances where study entry may have been delayed.

The MW8 monitors limb or bodily movements during daily living and sleep at 30 second time points (epochs) using a tri-axial accelerometer. It is waterproof for up to 1 hour at 1 meter and is therefore suitable for use while swimming or showering. As the data are stored on the watch and downloaded via a USB connection by members of the study team after data collection has been completed and

the watches have been returned. There is therefore no real-time data transmission and it will not be possible to assess participant compliance until the actigraph watch is returned.

Daily symptom reporting

During the 30 day continuous data collection, participants will be asked to use the uMotif study app to report their experience of daily symptoms. Within the app, the unique 'motif' interface is used by patients to simply track their daily symptoms. The motif which comprises 10 symptom segments, such as pain severity as highlighted in Figure 2. The uMotif study app has been used in multiple ethics-approved studies, capturing over 64 million data points from patients using their own devices. The uMotif app has been specifically configured to capture the data required for the QUASAR study.

[Figure 2 here]

Figure 2 - Screenshot of uMotif study app

Participants will receive prompts twice daily to complete the symptom ratings, once in the morning and once in the afternoon/evening. Symptom data are scored on an ordinal scale of 1-5 and are recorded by touching and sliding the relevant segment within the motif. The symptoms to be recorded (Table 2) were defined and agreed with consultation of participants in focus groups [15].

Throughout the study participants will receive reminders via the study app to complete the symptom assessments at 8am and 6pm. Participants are able to provide additional symptom reports throughout the day at their discretion.

Table 2- Daily symptoms to be captured by the uMotif study app			
Symptom	Question	Anchor 1 (centre of motif)	Anchor 5 (outside of motif)
Pain	How severe is your pain?	No Pain	Very Severe Pain
Fatigue	How severe is your fatigue?	No Fatigue	Very Severe Fatigue
Mood	How is your mood?	Depressed	Very Happy
Well-being	How well do you feel?	Very Well	Very Unwell
Anxiety	How anxious do you feel?	Very Well	Very Anxious
Illness impact	How much is your illness impacting on your activities?	No Impact	Very Severe Impact
Disease control	How much control do you feel you have over your symptoms?	No Control	Very Good Control
Challenge	How challenging are you finding today?	Not Challenging	Severely Challenging
Sleepiness	How sleepy do you feel?	Not Sleepy	Very Sleepy
Concentration	How would you rate your concentration?	Poor	Excellent

The completion of these symptom data can be continually monitored via a live database, held by uMotif, of the data collected by the study app, to which the study team is provided secure access. As all data provided by participants using the study app are immediately transferred to uMotif server in real-time via 3G/4G/ Wifi, it will be possible for the study team to produce daily reports to monitor whether participants are completing their data in line with the study protocol.

A window of two consecutive days during the 30 day continuous monitoring period will be considered an acceptable period of non-completion for the daily symptom reports, sleep diaries and follow-up questionnaires. After this point, participants will receive a single reminder text message to encourage them to recommence data entry or contact the study team to discuss any concerns or issues, as appropriate.

Day 2-31 – Consensus Sleep Diary

The reminder sent to participants at 8am will also ask them to complete the 9 item Consensus Sleep Diary (CSD). This diary, which is completed in a separate section of the study app ([figure 3 here]

Figure 3), pertains to the previous night's sleep. To ensure coverage of all 30 nights of actigraphy data collection, it will be completed on the morning of days 2-31. Participants will be prompted via

the app to complete the CSD every morning at 8am, though they will be able to complete it earlier if they wish.

[figure 3 here]

Figure 3 – Screenshot of consensus sleep diary within study app

An additional 4 items will ask participants to report the duration of morning stiffness (in minutes), emotional strength, motivation and worry about sleeping the previous evening.

As with the symptom reports, it will be possible to continually monitor sleep diary completion using the live database, held by uMotif. The study team will therefore produce daily reports to monitor whether participants are completing their sleep diaries in line with the study protocol. Any participant who does not complete their sleep diary for more than two days will receive a single reminder text message to encourage them to recommence data entry or contact the study team to discuss any concerns or issues, as appropriate. It will not be possible to retrospectively complete the sleep diaries for missing days.

Day 10, 20 and 30 – HRQoL, disease activity and life events

A number of follow-up questionnaires will be used throughout the study. Prompts to complete the questionnaires will be sent. Requests to complete the follow-up questionnaires will be delivered to participants, via the app to participants, on the day they are to be completed when they open the study app. These reminders are automatically generated and sent from uMotif and cannot be personalised. The questionnaires completed at days 10, 20 and 30 will capture the below items:

- Disease specific quality of life – AIMS2-SF
- Generic quality of life – WHOQOL-BREF
- Disease activity - RAPID-3
- Occurrence of important events

As with all data collected via the study app, the data recorded in each follow-up questionnaire will be immediately transferred to uMotif server in real-time via 3G/4G/ Wifi. Completion of follow-up questionnaires will be monitored within daily reports produced by the study team and any

participant who has not completed their questionnaire within two days of the required date will receive a single reminder text message to request that they complete the questionnaire as soon as possible. Participants will be given instructions to manually access and complete the follow-up questionnaire forms or contact the study team to discuss any concerns or issues, as appropriate.

Following the 30 days of data collection, participants will receive a text message to remind them to stop wearing the activity monitor and to send it back to the study team at the earliest convenient time, using the provided return addressed envelope. The envelopes, to which the relevant postage will be attached to return the package using Royal Mail Signed For® 1st Class must be returned via the local postage to obtain proof of postage; participants will not be required to pay any additional postage to obtain this. In instances where the watch does not appear to have been dropped off at the Post Office within 5 days of the expected end date, the study team will contact the participant.

Participants are not expected to continue tracking their symptoms or using the study app for continuous monitoring after day 30 and at this point participants may wish to uninstall the study app. For that reason, as the completion of the study's final questionnaire will occur 30 days after the continuous data collection phase has ended (day 60), participants may no longer be using the app and may have uninstalled it from their devices. Within the text message sent on day 30 of the study to congratulate participants on completing the continuous monitoring phase, participants are asked to advise the study team if they would like to receive a paper copy of the final follow-up questionnaire.

Day 60 – Final follow-up questionnaire

The study's final follow-up questionnaire will be completed at day 60. It is assumed that those who do not request a paper copy are happy to complete the questionnaire using the app. Participants will be prompted to complete the questionnaire by reminders are automatically generated and sent from uMotif. As before these reminders are generic and cannot be personalised.

The questionnaire will capture:

- Disease specific quality of life – AIMS2-SF
- Generic quality of life – WHOQOL-BREF
- Prioritisation of domains - participants asked to use a free text box to indicate top 3 things which are most important to them to ensure they have good quality of life.

- Disease activity - RAPID-3
- Current medication(s) and non-pharmacological intervention use
- Sleep quality – PSQI
- Occurrence of important events

Table 3– Summary of data collection via study questionnaires.

	Pre-registration	Day ≤1 (paper)	Day 10 (app)	Day 20 (app)	Day 30 (app)	Day 60 (app/paper)
Screening questionnaire	**X**					
Demographics		**X**				
Information about RA		**X**				
RAPID- 3		**X**	**X**	**X**	**X**	**X**
Current medication(s) and non-pharmacological intervention use		**X**				**X**
RAQoL		**X**	**X**	**X**	**X**	**X**
WHOQOL-BREF		**X**	**X**	**X**	**X**	**X**
PSQI		**X**				**X**
DBAS-16		**X**				
SCI		**X**				
HADS		**X**				
ASES-8		**X**				
CAQ-8		**X**				

A complete overview of data collection and participant contact is shown in Figure 4.

[Figure 4 here]

Figure 4 - Data collection and participant contact across 60 days for participants enrolled in QUASAR

Sample size

A sample size calculation has been conducted to determine a minimum sample size required to enable the study to conduct structural equation modelling (SEM). A conservative minimum effect size of 0.2 (rated as small), with 60 daily measurements, 13 observed variables and a significance level of 5% and power of 80%, determined a minimum sample size of 166 participants.

In this study 50 actigraph watches will be obtained. This means that the maximum capacity for concurrent data collection is 50 and that data collection will be conducted in waves. Previous studies have estimated that of all persons who receive the study information pack, 5% will enrol into the study and provide complete useable data. For that reason, a total of 3500 information packs will be sent to participants, to obtain a total sample of 175 participants with full data, in excess of the minimum 166 persons required for the analysis.

Recruitment

In order to manage the flow of participants into the study, given the limited number of actigraph watches available, NRAS have agreed to contact mailing list members in in 7 regionally-stratified recruitment waves in order that actigraph watches can be returned by earlier participants, prepared and sent out to future participants. The dates of each wave are listed below:

Wave 1 – 8 May 2017
Wave 2 – 17 July 2017
Wave 3 – 25 September 2017
Wave 4 – 4 December 2017
Wave 5 – 12 February 2018
Wave 6 – 23 April 2018
Wave 7 – 2 July 2018

The identification of GP practices and NHS Rheumatology clinics able to support recruitment to the QUASAR study will occur throughout the study. Once identified, the letters sent to potential participants identified via the screening of GP records will be sent to coincide with the above mailing waves used by NRAS. Participants who see information about the study in NHS Rheumatology clinics will be free to contact the study team at any point, however their enrolment into the study will be restricted to coincide with the above mailing waves.

Targeted recruitment

The study's third objective is to examine whether the relationships between sleep and HRQoL are moderated by age and sex. It is therefore important to ensure that a representative sample of people with RA are enrolled into the study. Table 4 displays the estimated UK prevalence of RA and demonstrates that women are around three times more likely to be affected than men, and the increased prevalence of RA in older populations[2].

Table 4- **The prevalence of rheumatoid arthritis in the UK**				
Age	Males (%)	UK estimate	Females (%)	UK estimate
16–44	0.02	2,500	0.12	15,100
45–64	0.58	42,900	1.67	126,900
64–74	1.14	27,100	2.56	67,800
75+	2.18	39,100	2.99	85,700
Total adult population	0.44	106,500	1.16	297,600

From previous studies, we know that young men and older people of both sexes are often under-represented populations. They may be less likely to express an interest in taking part in studies, or they may be excluded by the inclusion/exclusion criteria used. In anticipation that some of these 'hard to reach' groups may be under-represented in our sample, we propose to monitor the characteristics of participants who are enrolled in the study and apply stratified recruitment processes in later recruitment waves if required.

Data analysis plan

Analyses techniques used in descriptive epidemiology will address aim 1. Data will be presented as absolute numbers and percentages, presented for the whole group, and stratified by age, sex and level of socioeconomic deprivation.

Using structural equation modelling (SEM) and latent trajectory models (LTM) we will address the studies second aim: to examine if disrupted sleep patterns are associated with poor HRQoL.

SEM will assess whether the sleep and circadian rest-activity parameters measured at baseline mediate the association between RAPID3 score and HRQoL at 60 days (the end of the follow-up period) allowing inter-correlation between the sleep and circadian rest-activity parameters and adjusting for putative confounders. The SEM analysis will be repeated adding to the model pain, fatigue and mood to assess the effect of on HRQoL (for example Figure 5). Finally the analysis will be repeated including the data on mediators collected at day 30. This will allow assessment of whether RAPID3 predicts change in the mediating factors and the subsequent impact on HRQOL at day 60. An exploratory multi-group SEM analysis will assess the moderating effects of age and sex and will thus address the third aim of this study.

[Figure 5 here]

Figure 5 – Hypothetical model of the pathways of relationship between rheumatoid arthritis and quality of life disease severity, sleep, fatigue, mood, and pain– simple model. In this figure rectangles represent observed variables, and circles represent the constructs those variables represent. Solid arrows represent the pathways to be tested. RAPID-3: Routine Assessment of Patient Index Data 3, CSD: Consensus Sleep Diary, PSQI: Pittsburgh Sleep Quality Index, AIMS2-SF: Arthritis Impact Measurement Scale 2 - Short Form.

The SEM analysis assumes that the identified associations are consistent across participants, and uses only selected time points. Latent trajectory models will utilise all of the repeated measures data to fully explore the longitudinal relationships between RAPID3, mediators, and HRQoL, and their variation between participants. First, multilevel growth models, accounting for the clustering of repeated measures (level 1) within participants (level2), will assess the prospective associations of RAPID3 with key observed pathways from the SEM analysis, and the prospective associations with HRQoL. Second, we will assess if distinct clusters of participants can be identified with different longitudinal courses using dual trajectory latent class growth analysis. We will assess how these trajectories are associated with change in HRQoL over 60 days and the socio-demographic and clinical characteristics associated with these different trajectories.

Finally, to estimate how successful treatments that improve sleep might be for people with RA, we will use the information obtained from the above methods to estimate the potential effect on HRQoL of a hypothetical successful intervention targeted at the key identified sleep disturbances, taking into account the proportion of variance in HRQoL explained and how common the sleep disturbance is in the population.

Ethics and dissemination:

This study was underwent a full NHS Research Ethics Committee (REC) review and was allocated to the National Research Ethics Service (NRES) Committee North West – Liverpool Central REC. The study was approved by the NRES Committee North West – Liverpool Central REC on 12 April 2017, reference 17/NW/0217.

Results from this study will be disseminated at regional and international conferences and in peer-reviewed journals. Results will also be disseminated at Patient and Public Engagement (PPE) events where opportunities arise and are appropriate.

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Authors contributions:

JM led the conception and design of the study.

KLD, LC, VS, SM, BH, ML, DSK, WGD and JM made substantial contributions to the conception and design of the study.

JM and ML planned the statistical analysis.

KLD wrote the first draft of the protocol manuscript.

LC, VS, SM, BH, ML, DSK, WGD and JM critically reviewed the protocol manuscript.

KLD, LC, VS, SM, BH, ML, DSK, WGD and JM approved the final version of the document.

Data sharing statement: We intend to make data available for data sharing after the data collection has been completed and the primary aims of the study are met.

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Competing interests statement: The authors have no competing interests to disclose

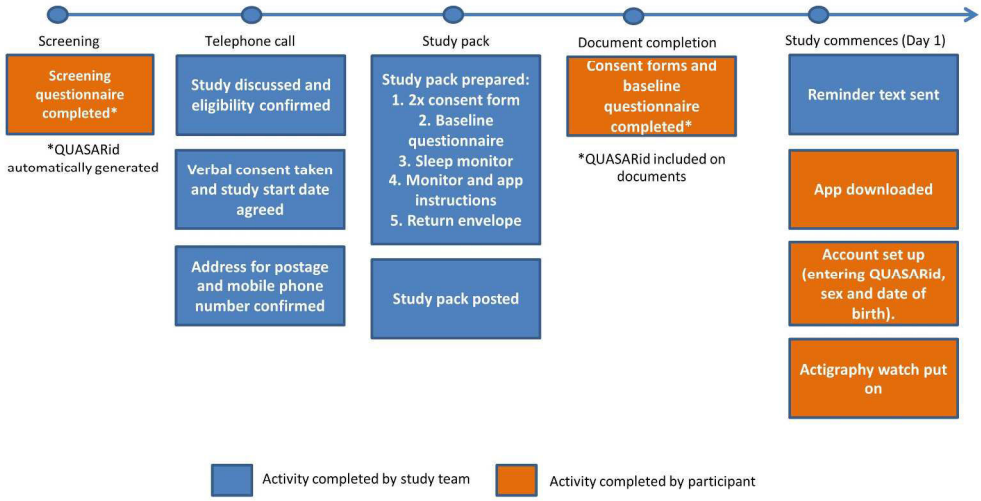

Figure 1 – Flow of participant entry into the study

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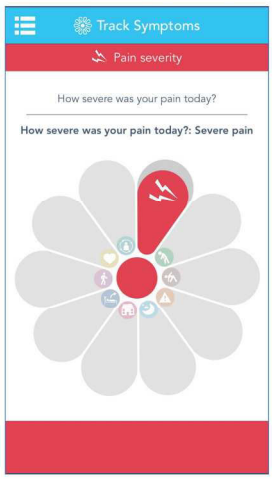

Figure 2 - Screenshot of uMotif study app

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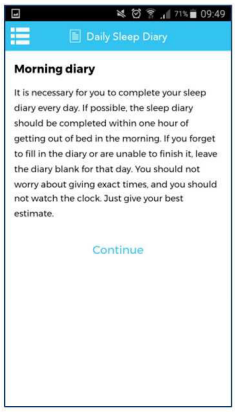

Figure 3 – Screenshot of consensus sleep diary within study app

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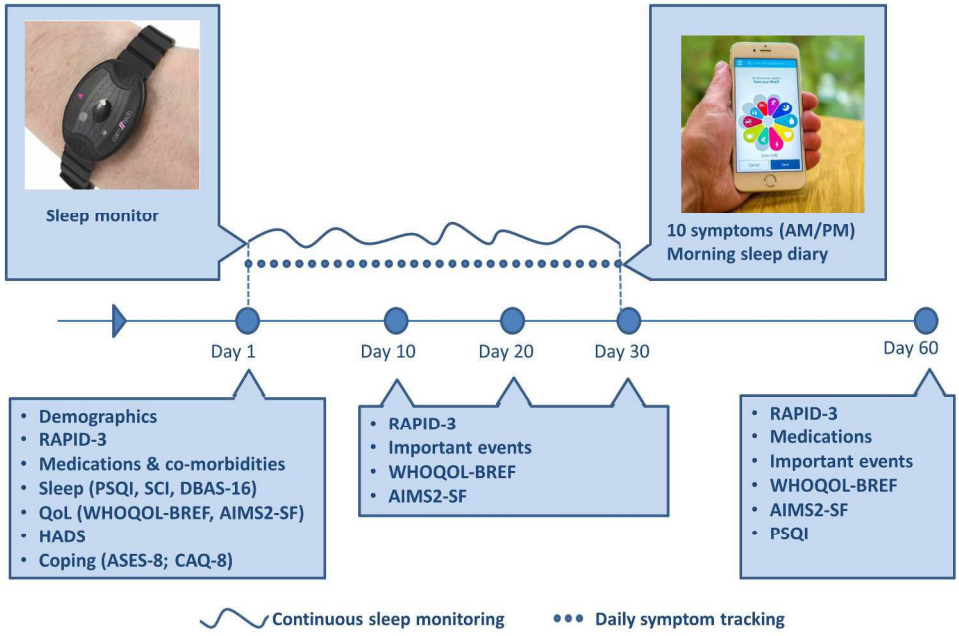

Figure 4 - Data collection and participant contact across 60 days for participants enrolled in QUASAR

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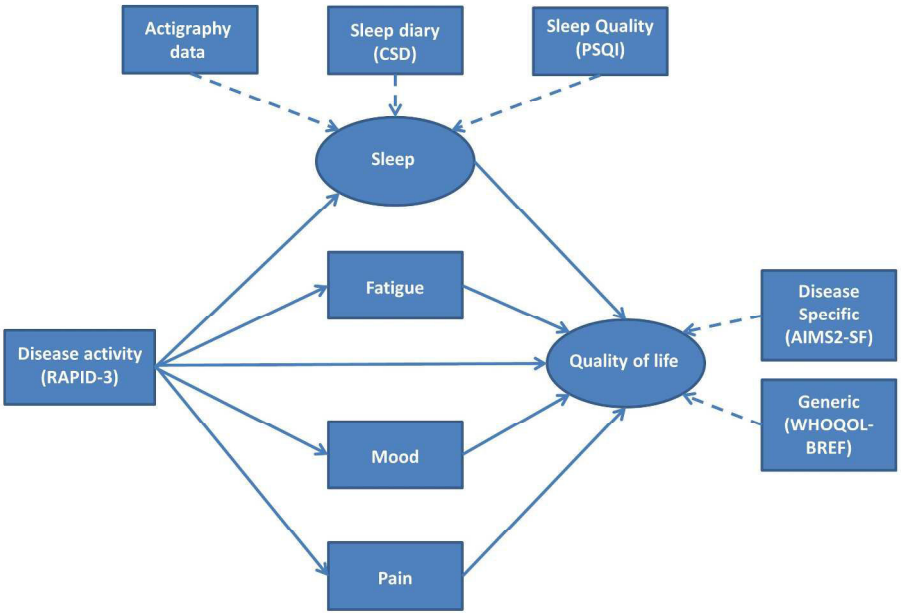

Figure 5 – Hypothetical model of the pathways of relationship between rheumatoid arthritis and quality of life disease severity, sleep, fatigue, mood, and pain– simple model. In this figure rectangles represent observed variables, and circles represent the constructs those variables represent. Solid arrows represent the pathways to be tested. RAPID-3: Routine Assessment of Patient Index Data 3, CSD: Consensus Sleep Diary, PSQI: Pittsburgh Sleep Quality Index, AIMS2-SF: Arthritis Impact Measurement Scale 2 - Short Form.

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Quality of life, sleep and rheumatoid arthritis (QUASAR): A protocol for a prospective UK mHealth study to investigate the relationship between sleep and quality of life in adults with rheumatoid arthritis

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Quality of life, sleep and rheumatoid arthritis (QUASAR): A protocol for a prospective UK mHealth study to investigate the relationship between sleep and quality of life in adults with rheumatoid arthritis

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Abstract

Introduction: People with rheumatoid arthritis (RA) frequently report reduced health-related quality of life (HRQoL), the impact one's health has on physical, emotional and social well-being. There are likely numerous causes for poor HRQol, but people with RA have identified sleep disturbances as a key contributor to their well-being. This study will identify the circadian rest/activity rhythms that predict fluctuations in HRQoL in people with RA.

Methods and analysis: This prospective cohort study will recruit 350 people with RA, aged 18 years or older. Following completion of a paper-based baseline questionnaire, participants will record data on 10 symptoms including pain, fatigue, and mood twice-daily for 30 days using a study-specific mobile application (app). A tri-axial accelerometer will continuously record daytime activity and estimate evening sleep parameters over the 30 days. Every 10 days following study initiation participants will complete a questionnaire that measures disease specific (Arthritis Impact Measurement Scale 2 - Short Form (AIMS2-SF)) and generic (WHOQOL-BREF) quality of life. A final questionnaire will be completed at 60 days after entering the study. The primary outcomes are the AIMS2-SF and WHOQOL-BREF. Structural equation modelling (SEM) and latent trajectory models (LTM) will be used to examine determine the relationship between circadian rest/activity rhythms and HRQoL, over time.

Ethics and dissemination: Ethical approval for this study has been obtained from the National Research Ethics Service (REC ref: 17/NW/0217). Results from this study will be disseminated at regional and international conferences, in peer-reviewed journals and Patient and Public Engagement (PPE) events, as appropriate.

Strengths and limitations of this study

1. This study will take advantage of advances in mobile health (mhealth) to embed data collection into the daily lives of participants.

2. Using a patient co-designed smartphone/tablet app it will capture objective and subjective sleep as well as self-reported symptoms.3. Sophisticated structural equation modelling (SEM) and latent trajectory models (LTM) will enable the study to disentangle the complex relationship between sleep, HRQoL and other symptoms.

4. While the use of actigraphy allows the collection of objective sleep data, it is not able to inform investigation of the relationship between HRQol and sleep architectural parameters or sleep oscillations (e.g., spindles, slow waves).

5. Potential sources of bias include a) sampling bias, if those recruited to this study are only those who experience sleep disturbances and/or are comfortable/familiar with using smartphone apps and activity monitors, and b) loss to follow-up bias if those who do not complete the full data collection protocol are systematically different from those who do.

Introduction

Quality of life, sleep and rheumatoid arthritis (QUASAR) is a prospective cohort study which will use a patient designed smartphone/tablet app and accelerometer to collect information on sleep and health-related quality of life (HRQoL) in rheumatoid arthritis (RA).

RA is a common chronic inflammatory disease characterised by joint damage, pain and disability [1]. The occurrence of RA is between two and four times greater in women and as many as 70% of men and women of working age with RA stop work within 10-15 years of disease duration due to the condition[2;3]. People with RA frequently report reduced HRQoL, which can be characterised as the impact one's health has on physical, emotional and social well-being. People with RA have poorer HRQoL when compared to those with other rheumatic diseases[4] or healthy peers[5;6]. Poor HRQoL may even persist when the disease is well controlled[5].

Although there are likely numerous causes for poor HRQol, people with RA have identified sleep disturbances as a key contributor to their well-being[7-9]. It is well known that people with RA report substantial sleep disturbances[10;11], such as less total sleeping time and unrefreshing sleep[8] and greater night time awakenings[7;9]. The cyclical nature of relationships between sleep disruptions and symptoms such as pain, fatigue and disability is relatively well characterised and likely cyclical[12-14]. However, few studies have determined the relationship between sleep and quality of life among RA populations.

Studies which have investigated the relationship between sleep and HRQoL have tended to suggest that sleep problems are associated with poor HRQoL[15-18]. However, these studies have been of low quality and have been hampered by a number of methodological challenges, which preclude accurate assessment and understanding of the relationship between sleep and HRQoL. First and foremost, sleep is a multifaceted behaviour which comprises objective and subjective components[19]. Despite guidelines endorsing the measurement of both and the potential for discrepancy between subjective and objective reports[20], it is only subjective sleep which has been commonly measured within epidemiological studies because, historically, it has been difficult to objectively measure sleep outside of artificial laboratory settings. Studies have also tended to be cross-sectional in design or to have used low-resolution longitudinal data collection protocols which have not been able to collect data regarding the recurrent and fluctuating day to day changes in sleep and associated symptoms.

Now, advances in the availability of smartphone apps and wearables for health monitoring provide a hitherto unobtainable mechanism to collect regular self-reported symptoms and objective sleep data, while embedding data collection into participants' everyday lives. This study will use a combination of patient co-designed smartphone/tablet app (provided by uMotif, London, UK) and a tri-axial accelerometer (MotionWatch8, CamNtech, Cambridge, UK) to capture both subjective and objective assessments of sleep quality, continuity and duration, as well as the timing and stability of the periods of time when someone is asleep or active [21]. Furthermore, the uMotif app will be used to collect information about self-reported symptoms which were identified as priorities by patients in a series of focus groups and patient involvement activities. In doing so this study aims to identify the relationship between sleep parameters, aspects of the circadian rest/activity rhythms, and HRQoL in people with RA.

Study objectives

1. Describe baseline and period distribution of circadian rest/activity rhythms stratified by age, sex, socioeconomic status and disease characteristics.
2. Determine relative contributions of circadian rest/activity rhythms , pain, fatigue and mood to RA-HRQoL.
3. In an exploratory analysis examine whether the relationship between disease severity, circadian rest/activity rhythms , pain, fatigue, mood and RA-HRQoL are moderated by age and sex.
4. Estimate the potential effect on RA-HRQoL of a successful intervention targeted at the key identified pathway(s).

Experimental design and methods

Methods and analysis:

Study design

We will conduct a prospective cohort study to investigate the relationships between sleep and HRQoL in people with RA.

Identifying and recruiting potential participants

Participants will be recruited via three channels. The primary source for participants will be the National Rheumatoid Arthritis Society (NRAS). NRAS is a national patient organisation with over 7000 members. Emails advertising the study will be sent to NRAS mailing list members and will include a copy of the study information pack comprising:

1. Study poster
2. Participant information sheet
3. Copy of the consent form (for information only)
4. A link to complete an online screening questionnaire

Following approval from the Health Research Authority (HRA) and via arrangements with Clinical Commissioning Groups (CCGs), participants will also be recruited via NHS mailing lists, where such mailing lists are available. NHS mailing lists provide the opportunity to search General Practitioner (GP) records for potentially eligible participants. Local Clinical Research Network (CRN) teams will search GP records for patients aged 18 or older, with a diagnosis of RA and who are in receipt of a Disease Modifying Anti-rheumatic Drug (DMARD), as recommended by Muller et al[22]. Letters will be sent to the identified patients, provided the GP or clinical team in the practice confirms that approaching the patient is acceptable. Reasons for not approaching patients may include previous refusal for records to be used for research, current hospitalisation, or belief that the participant is not capable of participation. Within the letter, participants will be briefly introduced to the study and persons interested in participating will be asked to email the study team directly for the study information pack, the contents of which are detailed above.

Information about the study will be displayed on the NIHR Clinical Research Network Portfolio to encourage NHS sites to support study recruitment by displaying posters advertising the study in any NHS Rheumatology clinics. NHS sites interested in supporting the study will contact the study team directly for further information and all relevant documentation needed to confirm they have the capacity and capability required to support the study. The displayed posters will provide brief information about the study and will ask persons interested in participating to email the study team directly for the study information pack, the contents of which are detailed above.

Following the receipt of the study information pack, potential participants follow an identical recruitment strategy (Figure 1).

[Figure 1 here]

Figure 1 – Flow of participant entry into the study

Screening questionnaire

Persons who receive the study information pack and are interested in participating in the study will be asked to complete the study screening questionnaire. Potential participants are asked to record their sex and date of birth, and to confirm whether they a) have a diagnosis of RA (including date of diagnosis), b) are currently using DMARDs (biologic or conventional synthetic), c) have access to an Android or Apple smartphone or tablet. For the purposes of exclusion criteria, interested persons must also indicate whether they are currently employed in shift work. Finally, potential participants will be asked to give consent and contact details and preferred contact time (9am and 12 noon, 12 noon and 3pm, 3pm and 6pm or 6pm and 8pm) to enable the study team to contact them to discuss participation in the study.

Eligibility criteria

Screening questionnaire respondents will be considered eligible for the study if they:

- Are aged ≥18 years
- Have a diagnosis of rheumatoid arthritis
- Are currently using DMARDs (biologic or conventional synthetic)
- Have access to an Android or Apple smartphone or tablet

Respondents would be excluded from the study if they:

- Are currently employed in a job that requires shift work

QUASARid

Study participants will be asked to provide data via three different platforms: paper-based questionnaires, a study app (downloaded onto a smartphone or tablet), and a tri-axial accelerometer that will measure daytime physical activity and sleep. To ensure that the data collected across these platforms can be consistently and accurately linked and matched to each participant, a unique participant identifier will be generated for each participant. The unique identifier, known as a QUASARid, will be automatically generated as the unique survey response which is allocated to the participant when they commence the screening questionnaire.

Telephone call

Potential participants meeting the study inclusion criteria will be telephoned by a member of the study team. To ensure they have had adequate time to review the participant information sheet provided in the study information email, telephone calls will take place no earlier than 24 hours after receipt of a completed screening questionnaire. A total of four attempts to contact the potential participant will be made on consecutive week days. During the phone call a verbal summary of the information sheet will be discussed with the potential participant and they will be given the opportunity to ask as many questions about the study as they wish.

Verbal consent and agreement of study start date

Following the verbal summary of the study information sheet, participants will be given the option to enrol into the study, delay participation, request more time to think about participation or decline to take part in the study. Written consent will subsequently obtained by the completion of two paper copies of the consent form sent to participants within the study pack. The provided consent forms will be signed and dated by the team member responsible for recruitment at the point of obtaining verbal consent, with participants asked to complete their own signature at the time of completing the baseline questionnaire. One copy of the consent form will be returned by the participant at the end of their first 30 days in QUASAR, along with the actigraph watch and baseline questionnaire. The second copy is for the patients' personal records.

Once verbal consent has been obtained participants will be asked to agree to a study start date, which should be within 14 days of the telephone call taking place. Participants who are unable to commence the study within 14 days will be asked to delay entry into the study. Those who agree a study start date will be asked to confirm their preferred postal address to which the study packs will be sent and a mobile phone number. The mobile phone number will be used to send participants text messages on the agreed study start date and throughout the study to encourage data completion and study compliance.

Study pack

The provision of verbal consent also enables the study pack to be prepared and posted to participants in advance of the agreed study start date. The study pack will include a letter of introduction, two copies of the consent form and a paper copy of the baseline questionnaire. Participants will also be provided with instructions to download and use the study app, as well as an actigraph watch, called a MotionWatch8 (CamNtech, Cambridge, UK) and associated instructions.

The study pack will be sent from the University of Manchester using Special Delivery Guaranteed® to arrive no less than one day prior to the study start date.

Document completion – Consent form and baseline questionnaire

Participants are requested to complete paper copies of the consent form and baseline questionnaire (sent within the study pack) on or before the first day of symptom monitoring. Initially, the baseline questionnaire was incorporated into the study app to be completed as part of the on-boarding process. However, due to limits on the number of questions which could be displayed per screen and the associated time required for data completion, app testing with the study team and members of a focus group indicated that this method of delivery would be less acceptable to participants than a paper based document.

The participant's QUASARid will be written onto both the consent form and covering page of the baseline questionnaire to enable data linkage between these documents, the study app and actigraph watch. To encourage completion of the questionnaire in advance of the monitoring period, participants will be asked to indicate the date on which they have completed the questionnaire on the covering page. They will return the baseline questionnaire along with the monitor at the end of the study.

The baseline questionnaire will comprise three sections: Demographic information, information about RA and health status information.

Demographics

Participants will record a number of demographic variables, including sex, date of birth, weight and height, ethnicity, age left education, average weekly alcohol consumption, smoking status, occupational status, marital status and postcode. Participants will also indicate how likely they believe it is that sleep affects their quality of life and the impact that RA has on their work productivity. A description of the reporting of these items is shown in Table 1.

Information about RA

Disease activity

Participants will record the month and year of their diagnosis. Disease activity will be assessed using the Routine Assessment of Patient Index Data 3 (RAPID-3). The 15 item RAPID-3 is free to use and

has been validated in RA populations. The measure has good validity and acceptable reliability and responsiveness[23].

The RAPID-3 measures 3 domains: physical function (13 discrete response items), pain (1 item 0-10 numerical rating scale (NRS)) and global health (1 item 0-10 NRS)) in the past week. The first 10 items of the physical function domain are scored, transformed into a 0.3-10 scale and summed with the pain and global health domains to produce an overall score of 0-30. These overall scores are then converted into a weighed RAPID 3 score and categorised within the following disease activity score categories: Near remission (0.3-1.0), Low Severity (1.3-2.0), Moderate severity (2.3-4.0), High severity (4.3-10).

Co-morbid rheumatic disease(s) and sleep-related problem(s), and menopausal status

Participants will be asked to record the presence of a variety of other rheumatic diseases, co-morbidities which may affect sleep (e.g. Sjogren's syndrome, diabetes, multiple sclerosis, hypertension (Table 1)) and menopausal status.

For pragmatic reasons it was not possible to embed specific questionnaires about the presence, severity or impact of sleep disorders, as it was necessary to balance the availability of data with minimal participant burden of data completion. Nevertheless, because the presence of such disorders represent important co-variates which should be adjusted for within data analysis, participants will be asked to record whether they experience restless leg syndrome and obstructive sleep apnea/snoring, A full list of co-morbidities collected is shown in Table 1.

Insomnia is recorded using the Sleep Condition Indicator (SCI), an 8 item questionnaire which has good concurrent validity, high internal consistency and is sensitive to change[24]. The SCI performs well to detect possible insomnia disorder and is the only validated and widely used insomnia measure that indexes insomnia disorder against contemporary criteria (e.g. International Classification of Sleep Disorders (ICSD-3); The Diagnostic and Statistical Manual of Mental Disorders (DSM-5))[24].

Medications

Participants will also be asked to record the use of medications including analgesics (e.g. Paracetamol, Nonsteroidal anti-inflammatories (NSAIDs) and opiates and disease modifying anti-rheumatic drugs (DMARDs, e.g. glucocorticoids, biologic DMARDs). The use of sleep medications, including sedatives or hypnotics, mood stabilisers, antidepressants, other sleep medications (e.g.

Chlorpromazine, Haloperidol) will also be collected and participants will be given a free-text box to record other medications or coping strategies they use and the purpose for using the strategy (Table 1).

Quality of life (QoL)

As is recommended[25], participants will complete a generic and disease specific measure of HRQoL. Generic HRQoL will be reported using the WHOQOL-BREF, a 26 item instrument which measures 6 domains in the past 14 days: overall perception of HRQoL (1 discrete response item), health (1 discrete response item), physical (7 discrete response items), psychological (6 discrete response items), social relationships (3 discrete response items) and environment (8 discrete response items). The items from each domain are summed and transformed into a 0-100 score, where higher scores indicate better HRQoL [26]. The WHOQOL-BREF has good internal consistency, discriminant validity (i.e. discriminating ill versus well groups) and sensitivity to change[26].

Disease specific HRQoL will be reported using the 26 item Arthritis Impact Measurement Scale 2 (Short Form) (AIMS-2 SF). The AIMS-2 SF uses discrete response items to capture 5 domains within a 4 week recall period: physical (13 items), symptom (3 items), affect (4 items), social interaction (4 items) and role (2 items). After some items are reverse coded, domain items are summed and converted into a 0-10 scale, where higher scores indicate poorer HRQoL [27]. The AIMS-2 SF shows good internal consistency and acceptable construct validity. The scale also generally demonstrates promising evidence of sensitivity to change, but there is less evidence supporting this for social interaction and role subscales[27].

Participants will also be asked to use a free text box to indicate the top 3 things which are most important to them to ensure they have good quality of life.

Sleep quality and beliefs about sleep

Sleep quality in the past month will be measured using the Pittsburgh Sleep Quality Index (PSQI), the most widely used measure within clinical and research settings[28]. The 18 item instrument comprises 7 domains: sleep quality (1 discrete response item), sleep latency (1 free-text item; 1 discrete response item), sleep duration (1 free-text item), sleep efficiency (2 free-text items), sleep disturbances (9 discrete response items), sleep medications (1 discrete response item), daytime

dysfunction (2 discrete response items). The PSQI has good reliability and validity[28] and demonstrates good sensitivity and specificity to distinguish good and poor sleepers[29].

Participants will also record information regarding their beliefs about sleep using the 16 item Dysfunctional Beliefs and Attitudes about Sleep instrument (DBAS-16). Beliefs about causes, consequences, and treatment of sleep problems are rated on 11-point Likert scales ranging from 0 (strongly disagree) to 10 (strongly agree). Scores are summed and averaged to produce a mean item score where higher scores indicate stronger endorsement of maladaptive beliefs about sleep[30]. The DBAS-16 has good internal consistency and test-retest reliability[30].

Mood, self-efficacy and cognitive flexibility

Finally, mood, self-efficacy and cognitive flexibility will be measured as important co-variates which may affect the relationship between sleep and HRQoL. Mood, specifically anxiety and depression, will be measured using the 14 item Hospital Anxiety and Depression Scale (HADS) [31]. Anxiety (7 items) and depression (7 items) in the preceding week are reported using discreet response questions, scored 0-3). Subscale items are summed to produce a score of 0-21, where higher scores represent poorer mood[31]. Scores rend to be categorised as 0-7 "normal", 8-10 "borderline", >11 "caseness". The HADs is well accepted and has strong internal consistency and high test-retest reliability[31].

Self-efficacy will be assessed using the Arthritis Self-Efficacy Scale-8 item (ASES-8) [32], which will record information about participants' self-efficacy for pain (2 0-10 NRS), preventing pain & fatigue interference(2 0-10 NRS), and for other symptoms(4 0-10 NRS). A self-efficacy score, ranging between 1 and 10, is produced by summing all items and calculating the mean value[32]. Higher scores indicate better self-efficacy. The ASES-8 has been shown to have good reliability, validity and sensitivity to change[32].

Cognitive flexibility will be recorded using the Committed Action Questionnaire (CAQ-8), to assess participants' abilities to persist with or change behaviour in relation to their present situation[33]. The CAQ-8 comprises 4 positive, and 4 negative, commitment to action subscales, which are recorded using 7-point Likert scales. An overall flexibility is scored by reverse coding the negative commitment subscales and summing all items, with higher scores indicating greater flexibility[33]. The CAQ-8 has been shown to have good reliability and internal consistency[33].

Table 1 – Baseline questionnaire domains and scales	
Domain	Scales/measurement
Demographics	
Sex	Tick box – male or female
Date of birth	Day, month, year
Height and Weight	Free text (metric or imperial)
Ethnicity	Free text
Age left education	Free text
Smoking status	Tick box – current, ex-, or never smoker
Occupational status	Tick box – working full time, working part time, student, medically retired, voluntary worker, unemployed but seeking work or retired
Marital status	Tick box – Single, in a relationship, co-habiting, married, civil partnership, separated, divorced or widowed
Alcohol consumption	Tick box –average units per week: 0, 1-5, 6-10, 11-15, 16-20, 21-40, >40
Impact of RA on work	Work productivity question from Work Productivity and Activity Impairment – specific health problem (WPAI-SHP)
Postcode	Free text for first half of postcode
Belief that sleep affects HRQoL	0-10 NRS: 0 “Not at all likely”, 10 “Very likely”
Information about RA	
Date of RA diagnosis	Month and year
Disease activity	Routine Assessment of Patient Index Data 3 (RAPID-3)
Co-morbid rheumatic disease(s) and sleep-related problem(s)	Check list – osteoarthritis, spondyloarthropathy/ankylosing spondylitis, fibromyalgia/chronic widespread pain, gout or other crystal arthritis, Sjogren’s syndrome, restless leg syndrome, obstructive sleep apnea/snoring, thyroid disorder, diabetes, multiple sclerosis, hypertension.
Menopausal status	Tick box – yes/no
Current medication(s) and non-pharmacological intervention use	Check list – parcetamol, non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, weak opiates, strong opiates, drugs for neuropathic pain, glucocorticoids, synthetic disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, sedatives (or hypnotics), mood stabilisers, antidepressants, other sleep medications. Free-text box
Health status information	
Disease specific quality of life	Arthritis Impact Measurement Scale 2 - Short Form (AIMS2-SF)
Generic Quality of life	WHOQOL-BREF
Prioritisation domains for good HRQoL	Participants are asked to use a free text box to indicate top 3 things which are most important to them to ensure they have good quality of life.
Sleep quality	Pittsburgh Sleep Quality Index (PSQI)
Beliefs about sleep	Dysfunctional Beliefs and Attitudes about Sleep questionnaire (DBAS-16)
Insomnia	Sleep Condition Indicator (SCI)

Mood	Hospital Anxiety and Depression Scale (HADS)
Self-efficacy	Arthritis Self-Efficacy Scale-8 item (ASES-8)
Cognitive flexibility	Committed Action Questionnaire (CAQ-8)

Study commences (Day 1)

On the agreed study start date, participants will receive a text message on the mobile phone number provided during the recruitment process. The reminder text message will ask participants to put on their activity monitor and to download the study app and register for an account. It will also include a study password, which will unlock the app to allow the participant to commence full registration, and a reminder of their QUASARid, which must be entered during the registration process to enable data linkage between the study app, actigraph watch and paper questionnaires.

App installation and account set up

Instructions about how to download the study app, which can be installed onto the participants' Apple or Android smartphone, tablet or both, will be included within the study pack that will be posted to participants. Once the app is installed participants will be asked to:

- complete a standard registration form (including creation of a username and password)
- enter their unique QUASARid, sex and date of birth, to enable linkage between the study's different data collection platforms

Registrations will be monitored via a live database, held by uMotif, of the data collected by the study app, to which the study team is provided secure access. All data provided by participants using the study app will be immediately transferred to uMotif server and visible in the database in real-time via 3G/4G/ Wifi. Any participants who have not registered with the app on their agreed start date, or within a 5 day window of that date, will be contacted by the study team to understand what issues may have arisen. If appropriate, participation in the study may be rescheduled for a later date.

Data collection

Following app-installation and the completion of the baseline questionnaire, participants will commence data collection lasting a total of 60 days. The first 30 days of the study comprise the continuous data collection phase of the study during which time participants wear the actigraph watch 24 hours a day and complete a once-daily sleep diary and twice daily symptom reports. During this 30 day monitoring period participants will also complete follow-up questionnaires on days 10, 20 and 30 of the study. No data are recorded between days 31 and 59, but participants are asked to complete a final follow-up questionnaire on day 60 of the study.

During focus groups conducted to inform the design of this study, participants discussed a desire to have options for on-going support from the study team via telephone contact. For that reason we will send personalised messages on days 5, 15 and 25 to encourage participation and give the participant the option to email or telephone the study team if they would like to discuss any issues or concerns. Any emails or requests for telephone calls will be responded to by the study's post-doctoral research associate, or principal investigator, at the earliest possible opportunity, and no later than one working day after the response is received.

A full outline of the data collected is provided below.

Day 1-30 – Actigraph watch and uMotif app

Continuous monitoring of sleep and physical activity.

Participants will wear the MotionWatch 8 (MW8; CamNtech, Cambridge, UK) for 24 hours a day over the 30 days of continuous data collection. The MW8 is a Class I Medical device which conforms to the essential safety and health requirements and provisions of EC Council Directives 93/42.EEC, Annex VII. The MW8 requires a standard watch battery (CR2032) which is replaced each time the watch is used. The configuration of the MW8 for the present study will enable the watch to collect data for up to 45 days, providing an additional two week window for data to be collected in instances where study entry may have been delayed.

The MW8 monitors limb or bodily movements during daily living and sleep at 30 second time points (epochs) using a tri-axial accelerometer. It is waterproof for up to 1 hour at 1 meter and is therefore suitable for use while swimming or showering. Participants are instructed to wear the MW8 on their non-dominant wrist.

Actigraphy has been validated against polysomnography (PSG) data[34]. The MW8 has been shown to provides reliable estimates for both sleep (including sleep latency, duration, efficiency, and fragmentation) and physical activity when worn for at least 14 days[35-37], and has a number of practical features which make it suitable for the purposes of this study, including an event marker and prolonged battery life. Furthermore, the MW8 was specifically selected by participants invited to a research design focus group, who identified the MW8 as their preferred device due to the comfort of wearing it and the lightweight and unobtrusive design.

There is no real-time transmission of actigraphy data because the data are stored on the watches internal memory and can only be downloaded via a USB connection. It will therefore not be possible to assess participant compliance until after data collection has been completed and the actigraph watch is returned.

Following the receipt and download of actigraphy data the following variables will be extracted: total sleep time (the total time spent in sleep according to the epoch-by-epoch wake/sleep categorisation), sleep onset latency (the time which elapsed between the participant getting into bed and the participant falling asleep) and sleep efficiency (the total sleep time, expressed as a proportion of the total times pent in bed). The sleep fragmentation index, a measure of the degree of sleep discontinuity, will be calculated as a percentage of the total time categorised as mobile in the epoch-by-epoch mobile/immobile categorisation and the number of immobile bouts which were less than or equal to one minute in length.

Daily symptom reporting

During the 30 day continuous data collection, participants will be asked to use the uMotif study app to report their experience of daily symptoms. Within the app, the unique 'motif' interface is used by patients to simply track their daily symptoms. The motif which comprises 10 symptom segments, such as pain severity as is highlighted in Figure 2. The uMotif study app has been used in multiple ethics-approved studies, capturing over 64 million data points from patients using their own devices. The uMotif app has been specifically configured to capture the data required for the QUASAR study.

[Figure 2 here]

Figure 2 - Screenshot of uMotif study app

Participants will receive prompts twice daily to complete the symptom ratings, once in the morning and once in the afternoon/evening. Symptom data are scored on an ordinal scale of 1-5 and are recorded by touching and sliding the relevant segment within the motif. The symptoms to be recorded (Table 2) were defined and agreed with consultation of participants in focus groups [38].

Throughout the study participants will receive reminders via the study app to complete the symptom assessments at 8am and 6pm. Participants will be able to provide additional symptom reports throughout the day at their discretion.

Table 2- Daily symptoms to be captured by the uMotif study app			
Symptom	Question	Anchor 1 (centre of motif)	Anchor 5 (outside of motif)
Pain	How severe is your pain?	No Pain	Very Severe Pain
Fatigue	How severe is your fatigue?	No Fatigue	Very Severe Fatigue
Mood	How is your mood?	Depressed	Very Happy
Well-being	How well do you feel?	Very Well	Very Unwell
Anxiety	How anxious do you feel?	Very Well	Very Anxious
Illness impact	How much is your illness impacting on your activities?	No Impact	Very Severe Impact
Disease control	How much control do you feel you have over your symptoms?	No Control	Very Good Control
Challenge	How challenging are you finding today?	Not Challenging	Severely Challenging
Sleepiness	How sleepy do you feel?	Not Sleepy	Very Sleepy
Concentration	How would you rate your concentration?	Poor	Excellent

The completion of these symptom data can be continually monitored via a live database, held by uMotif, of the data collected by the study app, to which the study team is provided secure access. As all data provided by participants using the study app are immediately transferred to uMotif server in real-time via 3G/4G/ Wifi, it will be possible for the study team to produce daily reports to monitor whether participants are completing their data in line with the study protocol.

A window of two consecutive days during the 30 day continuous monitoring period will be considered an acceptable period of non-completion for the daily symptom reports, sleep diaries and follow-up questionnaires. After this point, participants will receive a single reminder text message to encourage them to recommence data entry or contact the study team to discuss any concerns or issues, as appropriate.

Day 2-31 – Consensus Sleep Diary

The reminder sent to participants at 8am will also ask them to complete the 9 item Consensus Sleep Diary (CSD). This diary, which is completed in a separate section of the study app ([figure 3 here]

Figure 3), pertains to the previous night's sleep. To ensure coverage of all 30 nights of actigraphy data collection, it will be completed on the morning of days 2-31. Participants will receive an

automatically generated reminder every morning at 8am to complete the CSD, but are able to complete the diary earlier if they wish.

[figure 3 here]

Figure 3 – Screenshot of consensus sleep diary within study app

The 9 item CSD asks participants to record the time they got into bed, when they tried to sleep, how long it took to fall asleep, number and duration of night time awakenings, the time of final awakening, when they got out of bed, sleep quality, and how refreshed they felt upon awakening. The CSD is widely considered to be a gold-standard sleep diary, having been developed through the collaboration of sleep experts and potential users[39;40].An additional 4 items will ask participants to report the duration of morning stiffness (in minutes), emotional strength, motivation and worry about sleeping the previous evening.

As with the symptom reports, it will be possible to continually monitor sleep diary completion using the live database, held by uMotif. The study team will therefore produce daily reports to monitor whether participants are completing their sleep diaries in line with the study protocol. Any participant who does not complete their sleep diary for more than two days will receive a single reminder text message to encourage them to recommence data entry or contact the study team to discuss any concerns or issues, as appropriate. It will not be possible to retrospectively complete the sleep diaries for missing days.

Day 10, 20 and 30 – HRQoL, disease activity and life events

A number of follow-up questionnaires will be used throughout the study(Table 3). Prompts to complete the questionnaires will be sent. Requests to complete the follow-up questionnaires will be delivered to participants, via the app to participants, on the day they are to be completed when they open the study app. These reminders will be automatically generated and sent from uMotif and cannot be personalised. The questionnaires completed at days 10, 20 and 30 will capture the below items:

- Disease specific quality of life – AIMS2-SF
- Generic quality of life – WHOQOL-BREF

- Disease activity - RAPID-3
- Occurrence of important events

As with all data collected via the study app, the data recorded in each follow-up questionnaire will be immediately transferred to uMotif server in real-time via 3G/4G/ Wifi. Completion of follow-up questionnaires will be monitored within daily reports produced by the study team and any participant who has not completed their questionnaire within two days of the required date will receive a single reminder text message to request that they complete the questionnaire as soon as possible. Participants will be given instructions to manually access and complete the follow-up questionnaire forms or contact the study team to discuss any concerns or issues, as appropriate.

Following the 30 days of data collection, participants will receive a text message to remind them to stop wearing the activity monitor and to send it back to the study team at the earliest convenient time, using the provided return addressed envelope. The envelopes, to which the relevant postage will be attached to return the package using Royal Mail Signed For® 1st Class must be returned via the local postage to obtain proof of postage; participants will not be required to pay any additional postage to obtain this. In instances where the watch does not appear to have been dropped off at the Post Office within 5 days of the expected end date, the study team will contact the participant.

Participants are not expected to continue tracking their symptoms or using the study app for continuous monitoring after day 30 and at this point participants may wish to uninstall the study app. For that reason, as the completion of the study's final questionnaire will occur 30 days after the continuous data collection phase has ended (day 60), participants may no longer be using the app and may have uninstalled it from their devices. Within the text message sent on day 30 of the study to congratulate participants on completing the continuous monitoring phase, participants will be asked to advise the study team if they would like to receive a paper copy of the final follow-up questionnaire.

Day 60 – Final follow-up questionnaire

The study's final follow-up questionnaire will be completed at day 60. It is assumed that those who do not request a paper copy will be happy to complete the questionnaire using the app. Participants will be prompted to complete the questionnaire by reminders automatically generated and sent from uMotif. As before these reminders are generic and cannot be personalised.

The questionnaire will capture:

- Disease specific quality of life – AIMS2-SF
- Generic quality of life – WHOQOL-BREF
- Prioritisation of domains - participants asked to use a free text box to indicate the top 3 things which are most important to them to ensure they have good quality of life.
- Disease activity - RAPID-3
- Current medication(s) and non-pharmacological intervention use
- Sleep quality – PSQI
- Occurrence of important events

Table 3– Summary of data collection via study questionnaires.

	Pre-registration	Day ≤1 (paper)	Day 10 (app)	Day 20 (app)	Day 30 (app)	Day 60 (app/paper)
Screening questionnaire	**X**					
Demographics		**X**				
Information about RA		**X**				
RAPID- 3		**X**	**X**	**X**	**X**	**X**
Current medication(s) and non-pharmacological intervention use		**X**				**X**
AIMS2-SF		**X**	**X**	**X**	**X**	**X**
WHOQOL-BREF		**X**	**X**	**X**	**X**	**X**
PSQI		**X**				**X**
DBAS-16		**X**				
SCI		**X**				
HADS		**X**				
ASES-8		**X**				
CAQ-8		**X**				

A complete overview of data collection and participant contact is shown in Figure 4.

[Figure 4 here]

Figure 4 - Data collection and participant contact across 60 days for participants enrolled in QUASAR

Sample size

Following published guidance[41;42], A sample size calculation has been conducted to determine a minimum sample size required to enable the study to conduct structural equation modelling (SEM). A conservative minimum effect size (defined as correlations between pairs of latent variables) of 0.2 (rated as small). Based on our hypothesized model using baseline and 60 day measurements, containing 13 observed variables and 4 latent variables, with a significance level of 5% and power of 80%, a minimum sample size of 166 participants is required. Recommended sample sizes for latent growth curve analyses are defined in relation to the number of participants and the number of repeated observations and suggest a minimum number of 100 participants should complete at least 3 data points[43]. Our minimum sample size required and data collection protocol are therefore in excess of the requirements for latent growth curve analyses.In this study 50 actigraph watches will be obtained. This means that the maximum capacity for concurrent data collection is 50 and that data collection will be conducted in waves.

Using data from previous studies we conservatively estimate that: a total of 3500 questionnaires mailed will provide 1750 (50%) returned and completed screening questionnaires, 350 (20%) will agree to take part and 175 (50%) will provide complete useable data, in excess of the minimum 166 persons required for the analysis. It is important that a representative sample of people with RA is enrolled into the study. However, Data regarding the characteristics (e.g. age and sex) of persons who receive information about the study will not be available through the proposed recruitment channels. The presence of sampling bias will be examined for by comparing the age and sex distribution of UK population data (Table 4) to a) persons who complete and return screening questionnaires and b) recruited participants to available.

Recruitment

In order to manage the flow of participants into the study and given the limited number of actigraph watches available, NRAS have agreed to contact mailing list members in 7 regionally-stratified recruitment waves in order that actigraph watches can be returned by earlier participants, prepared and sent out to future participants. The dates of each wave are listed below:

Wave 1 – 8 May 2017

Wave 2 – 17 July 2017

Wave 3 – 25 September 2017

Wave 4 – 4 December 2017

Wave 5 – 12 February 2018

Wave 6 – 23 April 2018

Wave 7 – 2 July 2018

The identification of GP practices and NHS Rheumatology clinics able to support recruitment to the QUASAR study will occur throughout the study. Once identified, the letters sent to potential participants identified via the screening of GP records will be sent to coincide with the above mailing waves used by NRAS. Participants who see information about the study in NHS Rheumatology clinics will be free to contact the study team at any point, however their enrolment into the study will be restricted to coincide with the above mailing waves.

Targeted recruitment

The study's third objective is to examine whether the relationships between sleep and HRQoL are moderated by age and sex. It is therefore important to ensure that a representative sample of people with RA are enrolled into the study. Table 4 displays the estimated UK prevalence of RA and demonstrates that women are around three times more likely to be affected than men, and the increased prevalence of RA in older populations[2].

Table 4- **The prevalence of rheumatoid arthritis in the UK**

Age	Males (%)	UK estimate	Females (%)	UK estimate
16–44	0.02	2,500	0.12	15,100
45–64	0.58	42,900	1.67	126,900
65–74	1.14	27,100	2.56	67,800
75+	2.18	39,100	2.99	85,700
Total adult population	0.44	106,500	1.16	297,600

From previous studies, we know that young men [44]and older people of both sexes are often under-represented populations[41,42]. They may be less likely to express an interest in taking part in studies[41], or they may be excluded by the inclusion/exclusion criteria used[42]. In anticipation that some of these 'hard to reach' groups may be under-represented in our sample, we propose to monitor the characteristics of participants who are enrolled in the study and apply stratified recruitment processes in later recruitment waves if required.

Data analysis plan

Analyses techniques used in descriptive epidemiology will address aim 1. Data will be presented as absolute numbers and percentages, presented for the whole group, and stratified by age (18-44; 45-64; 65-74; 75+), sex and level of socioeconomic deprivation (Index of Multiple Deprivation[45], derived using participant postcodes and categorised as quartiles of most deprived, deprived, less deprived and least deprived).

Using structural equation modelling (SEM) and latent trajectory models (LTM) we will address the studies second aim: to examine if disrupted sleep patterns are associated with poor HRQoL.

SEM will assess whether the sleep and circadian rest/activity parameters measured at baseline mediate the association between RAPID3 score and HRQoL at 60 days (the end of the follow-up period) allowing inter-correlation between the sleep and circadian rest/activity parameters and adjusting for putative confounders. The SEM analysis will be repeated adding to the model pain, fatigue and mood to assess the effect of on HRQoL (for example Figure 5). Finally the analysis will be repeated including the data on mediators collected at day 30. This will allow assessment of whether RAPID3 predicts change in the mediating factors and the subsequent impact on HRQOL at day 60. An exploratory multi-group SEM analysis will assess the moderating effects of age and sex and will thus address the third aim of this study.

[Figure 5 here]

Figure 5 – Hypothetical model of the pathways of relationship between rheumatoid arthritis and quality of life disease severity, sleep, fatigue, mood, and pain– simple model. In this figure rectangles represent observed variables, and circles represent the constructs those variables represent. Solid arrows represent the pathways to be tested. RAPID-3: Routine Assessment of Patient Index Data 3, CSD: Consensus Sleep Diary, PSQI: Pittsburgh Sleep Quality Index, AIMS2-SF: Arthritis Impact Measurement Scale 2 - Short Form.

The SEM analysis assumes that the identified associations are consistent across participants, and uses only selected time points. Latent trajectory models will utilise all of the repeated measures data to fully explore the longitudinal relationships between RAPID3, mediators, and HRQoL, and their variation between participants. First, multilevel growth models, accounting for the clustering of repeated measures (level 1) within participants (level2), will assess the prospective associations of RAPID3 with key observed pathways from the SEM analysis, and the prospective associations with HRQoL. Second, we will assess if distinct clusters of participants can be identified with different

longitudinal courses using dual trajectory latent class growth analysis. We will assess how these trajectories are associated with change in HRQoL over 60 days and the socio-demographic and clinical characteristics associated with these different trajectories.

Finally, to estimate how successful treatments that improve sleep might be for people with RA, we will use the information obtained from the above methods to estimate the potential effect on HRQoL of a hypothetical successful intervention targeted at the key identified sleep disturbances, taking into account the proportion of variance in HRQoL explained and how common the sleep disturbance is in the population.

Ethics and dissemination:

This study was underwent a full NHS Research Ethics Committee (REC) review and was allocated to the National Research Ethics Service (NRES) Committee North West – Liverpool Central REC. The study was approved by the NRES Committee North West – Liverpool Central REC on 12 April 2017, reference 17/NW/0217.

Results from this study will be disseminated at regional and international conferences and in peer-reviewed journals. Results will also be disseminated at Patient and Public Engagement (PPE) events where opportunities arise and are appropriate.

Discussion:

People with RA frequently report reduced HRQoL, which may be caused by sleep disturbances. Few studies have determined the relationship between sleep and quality of life among RA populations and those which have are laden with methodological challenges, which preclude accurate assessment and understanding of the relationship between sleep and HRQoL. The QUASAR study is a comprehensive study which has been designed to overcome these challenges. The results of this study will inform future intervention studies by answering key questions regarding the link between sleep and poor HRQoL.

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Authors contributions:

JM led the conception and design of the study.

KLD, LC, VS, SM, BH, BJ, ML, DSK, WGD and JM made substantial contributions to the conception and design of the study.

JM and ML planned the statistical analysis.

KLD wrote the first draft of the protocol manuscript.

LC, VS, SM, BH, BJ, ML, DSK, WGD and JM critically reviewed the protocol manuscript.

KLD, LC, VS, SM, BH, BJ, ML, DSK, WGD and JM approved the final version of the document.

Data sharing statement: We intend to make data available for data sharing after the data collection has been completed and the primary aims of the study are met.

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Competing interests statement: The authors have no competing interests to disclose

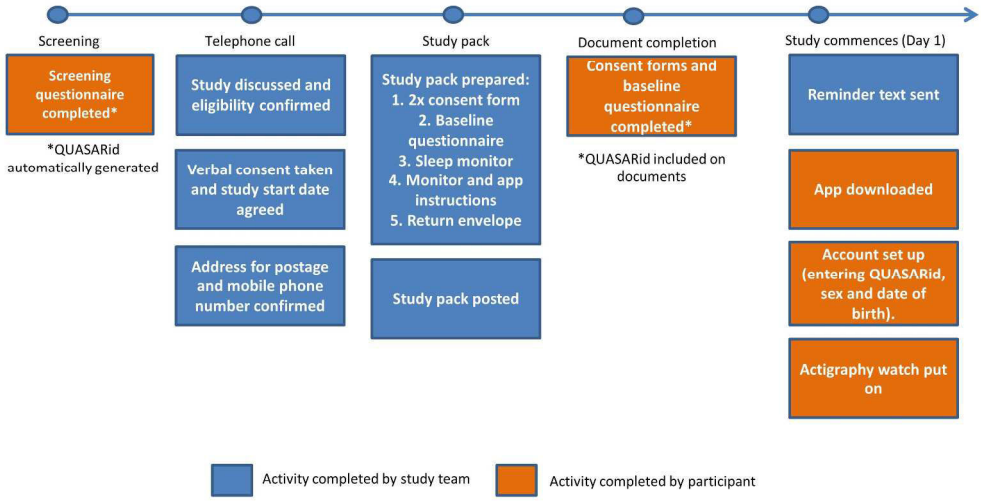

Figure 1 – Flow of participant entry into the study

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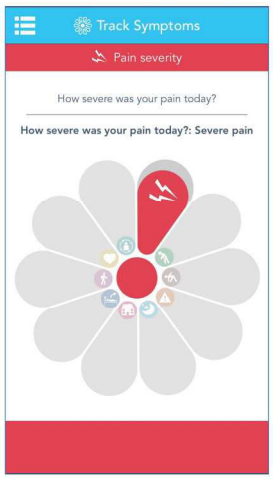

Figure 2 - Screenshot of uMotif study app

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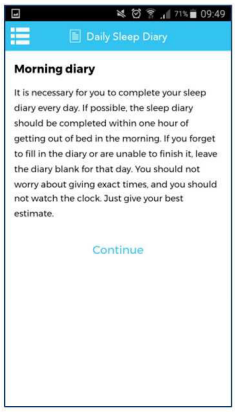

Figure 3 – Screenshot of consensus sleep diary within study app

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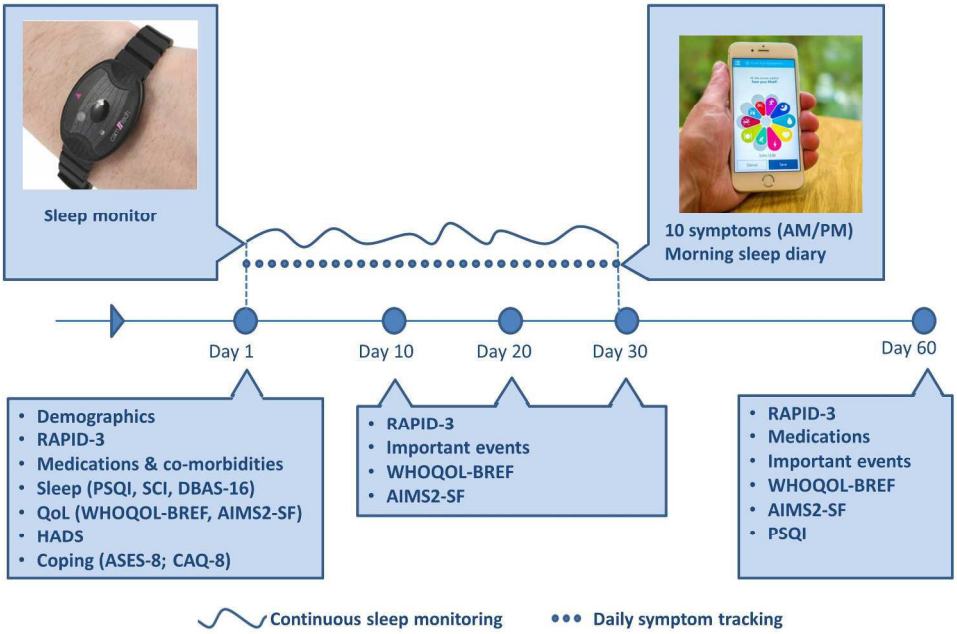

Figure 4 - Data collection and participant contact across 60 days for participants enrolled in QUASAR

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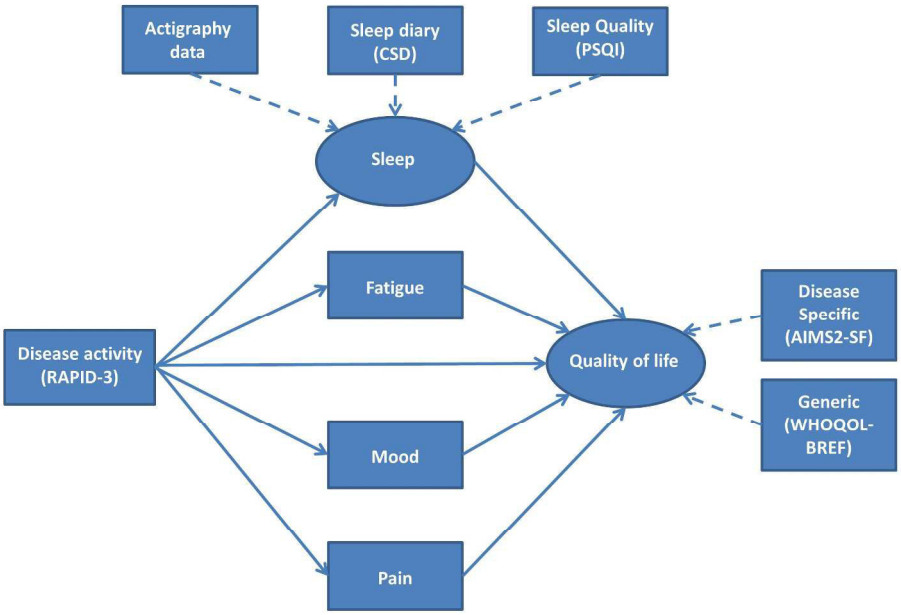

Figure 5 – Hypothetical model of the pathways of relationship between rheumatoid arthritis and quality of life disease severity, sleep, fatigue, mood, and pain– simple model. In this figure rectangles represent observed variables, and circles represent the constructs those variables represent. Solid arrows represent the pathways to be tested. RAPID-3: Routine Assessment of Patient Index Data 3, CSD: Consensus Sleep Diary, PSQI: Pittsburgh Sleep Quality Index, AIMS2-SF: Arthritis Impact Measurement Scale 2 - Short Form.

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BMJ Open

Quality of life, sleep and rheumatoid arthritis (QUASAR): A protocol for a prospective UK mHealth study to investigate the relationship between sleep and quality of life in adults with rheumatoid arthritis

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Quality of life, sleep and rheumatoid arthritis (QUASAR): A protocol for a prospective UK mHealth study to investigate the relationship between sleep and quality of life in adults with rheumatoid arthritis

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Abstract

Introduction: People with rheumatoid arthritis (RA) frequently report reduced health-related quality of life (HRQoL), the impact one's health has on physical, emotional and social well-being. There are likely numerous causes for poor HRQoL, but people with RA have identified sleep disturbances as a key contributor to their well-being. This study will identify sleep/wake rhythm-associated parameters that predict HRQoL in patients with RA.

Methods and analysis: This prospective cohort study will recruit 350 people with RA, aged 18 years or older. Following completion of a paper-based baseline questionnaire, participants will record data on 10 symptoms including pain, fatigue, and mood twice-daily for 30 days using a study-specific mobile application (app). A tri-axial accelerometer will continuously record daytime activity and estimate evening sleep parameters over the 30 days. Every 10 days following study initiation participants will complete a questionnaire that measures disease specific (Arthritis Impact Measurement Scale 2 - Short Form (AIMS2-SF)) and generic (WHOQOL-BREF) quality of life. A final questionnaire will be completed at 60 days after entering the study. The primary outcomes are the AIMS2-SF and WHOQOL-BREF. Structural equation modelling (SEM) and latent trajectory models (LTM) will be used to examine the relationship between sleep/wake rhythm-associated parameters and HRQoL, over time.

Ethics and dissemination: Ethical approval for this study has been obtained from the National Research Ethics Service (REC ref: 17/NW/0217). Results from this study will be disseminated at regional and international conferences, in peer-reviewed journals and Patient and Public Engagement (PPE) events, as appropriate.

Strengths and limitations of this study

1. This study will take advantage of advances in mobile health (mhealth) to embed data collection into the daily lives of participants.

2. Using a patient co-designed smartphone/tablet app it will capture objective and subjective sleep as well as self-reported symptoms.

3. Sophisticated structural equation modelling (SEM) and latent trajectory models (LTM) will enable the study to disentangle the complex relationship between sleep, HRQoL and other symptoms.

4. While the use of actigraphy allows the collection of objective sleep data, it is not able to inform investigation of the relationship between HRQoL and sleep architectural parameters or sleep oscillations (e.g., spindles, slow waves).

5. Potential sources of bias include a) sampling bias, if those recruited to this study are only those who experience sleep disturbances and/or are comfortable/familiar with using smartphone apps and activity monitors, and b) loss to follow-up bias if those who do not complete the full data collection protocol are systematically different from those who do.

Introduction

Quality of life, sleep and rheumatoid arthritis (QUASAR) is a prospective cohort study which will use a patient designed smartphone/tablet app and accelerometer to collect information on sleep and health-related quality of life (HRQoL) in rheumatoid arthritis (RA).

RA is a common chronic inflammatory disease characterised by joint damage, pain and disability. [1] The occurrence of RA is between two and four times greater in women and as many as 70% of men and women of working age with RA stop work within 10-15 years of disease duration due to the condition.[2;3] People with RA frequently report reduced HRQoL, which can be characterised as the impact one's health has on physical, emotional and social well-being. People with RA have poorer HRQoL when compared to those with other rheumatic diseases[4] or healthy peers.[5;6] Poor HRQoL may even persist when the disease is well controlled.[5]

Although there are likely numerous causes for poor HRQoL, people with RA have identified sleep disturbances as a key contributor to their well-being.[7-9] It is well known that people with RA report substantial sleep disturbances,[10;11] such as less total sleeping time and unrefreshing sleep[8] and greater night time awakenings.[7;9] The cyclical nature of relationships between sleep disruptions and symptoms such as pain, fatigue and disability is relatively well characterised and likely cyclical.[12-14]However, few studies have determined the relationship between sleep and quality of life among RA populations.

Studies which have investigated the relationship between sleep and HRQoL have tended to suggest that sleep problems are associated with poor HRQoL.[15-18] However, these studies have been of low quality and have been hampered by a number of methodological challenges, which preclude accurate assessment and understanding of the relationship between sleep and HRQoL. First and foremost, sleep is a multifaceted behaviour which comprises objective and subjective components.[19] Despite guidelines endorsing the measurement of both and the potential for discrepancy between subjective and objective reports,[20] it is only subjective sleep which has been commonly measured within epidemiological studies because, historically, it has been difficult to objectively measure sleep outside of artificial laboratory settings. Studies have also tended to be cross-sectional in design or to have used low-resolution longitudinal data collection protocols which have not been able to collect data regarding the recurrent and fluctuating day to day changes in sleep and associated symptoms.

Now, advances in the availability of smartphone apps and wearables for health monitoring provide a hitherto unobtainable mechanism to collect regular self-reported symptoms and objective sleep data, while embedding data collection into participants' everyday lives. This study will use a combination of patient co-designed smartphone/tablet app (provided by uMotif, London, UK) and a tri-axial accelerometer (MotionWatch8, CamNtech, Cambridge, UK) to capture both subjective and objective assessments of sleep quality, continuity and duration, as well as the timing and stability of the periods of time when someone is asleep or active.[21] Furthermore, the uMotif app will be used to collect information about self-reported symptoms which were identified as priorities by patients in a series of focus groups and patient involvement activities. In doing so this study aims to identify the relationship between sleep parameters, aspects of the sleep/wake rhythm-associated parameters, and HRQoL in people with RA.

Study objectives

1. Describe baseline and period distribution of sleep/wake rhythm-associated parameters stratified by age, sex, socioeconomic status, and disease characteristics.
2. Determine relative contributions of sleep/wake rhythm-associated parameters, pain, fatigue and mood to RA-HRQoL.
3. In an exploratory analysis to examine whether the relationship between disease severity, sleep/wake rhythm-associated parameters, pain, fatigue, mood and RA-HRQoL are moderated by age and sex.
4. Estimate the potential effect on RA-HRQoL of a successful intervention targeted at the key identified pathway(s).

Experimental design and methods

Methods and analysis:

Study design

We will conduct a prospective cohort study to investigate the relationships between sleep and HRQoL in people with RA.

Identifying and recruiting potential participants

Participants will be recruited via three channels. The primary source for participants will be the National Rheumatoid Arthritis Society (NRAS). NRAS is a national patient organisation with over 7000 members. Emails advertising the study will be sent to NRAS mailing list members and will include a copy of the study information pack comprising:

1. Study poster
2. Participant information sheet
3. Copy of the consent form (for information only)
4. A link to complete an online screening questionnaire

Following approval from the Health Research Authority (HRA) and via arrangements with Clinical Commissioning Groups (CCGs), participants will also be recruited via NHS mailing lists, where such mailing lists are available. NHS mailing lists provide the opportunity to search General Practitioner (GP) records for potentially eligible participants. Local Clinical Research Network (CRN) teams will search GP records for patients aged 18 or older, with a diagnosis of RA and who are in receipt of a Disease Modifying Anti-rheumatic Drug (DMARD), as recommended by Muller et al.[22] Letters will be sent to the identified patients, provided the GP or clinical team in the practice confirms that approaching the patient is acceptable. Reasons for not approaching patients may include previous refusal for records to be used for research, current hospitalisation, or belief that the participant is not capable of participation. Within the letter, participants will be briefly introduced to the study and persons interested in participating will be asked to email the study team directly for the study information pack, the contents of which are detailed above.

Information about the study will be displayed on the NIHR Clinical Research Network Portfolio to encourage NHS sites to support study recruitment by displaying posters advertising the study in any NHS Rheumatology clinics. NHS sites interested in supporting the study will contact the study team directly for further information and all relevant documentation needed to confirm they have the capacity and capability required to support the study. The displayed posters will provide brief information about the study and will ask persons interested in participating to email the study team directly for the study information pack, the contents of which are detailed above.

Following the receipt of the study information pack, potential participants follow an identical recruitment strategy (**Error! Reference source not found.**).

[Figure 1 here]

Screening questionnaire

Persons who receive the study information pack and are interested in participating in the study will be asked to complete the study screening questionnaire. Potential participants are asked to record their sex and date of birth, and to confirm whether they a) have a diagnosis of RA (including date of diagnosis), b) are currently using DMARDs (biologic or conventional synthetic), c) have access to an Android or Apple smartphone or tablet. For the purposes of exclusion criteria, interested persons must also indicate whether they are currently employed in shift work. Finally, potential participants will be asked to give consent and contact details and preferred contact time (9am to 12 noon, 12 noon to 3pm, 3pm to 6pm or 6pm to 8pm) to enable the study team to contact them to discuss participation in the study.

Eligibility criteria

Screening questionnaire respondents will be considered eligible for the study if they:

- Are aged ≥18 years
- Have a diagnosis of rheumatoid arthritis
- Are currently using DMARDs (biologic or conventional synthetic)
- Have access to an Android or Apple smartphone or tablet

Respondents would be excluded from the study if they:

- Are currently employed in a job that requires shift work

QUASARid

Study participants will be asked to provide data via three different platforms: paper-based questionnaires, a study app (downloaded onto a smartphone or tablet), and a tri-axial accelerometer that will measure daytime physical activity and sleep. To ensure that the data collected across these platforms can be consistently and accurately linked and matched to each participant, a unique participant identifier will be generated for each participant. The unique identifier, known as a QUASARid, will be automatically generated as the unique survey response which is allocated to the participant when they commence the screening questionnaire.

Telephone call

Potential participants meeting the study inclusion criteria will be telephoned by a member of the study team. To ensure they have had adequate time to review the participant information sheet provided in the study information email, telephone calls will take place no earlier than 24 hours after receipt of a completed screening questionnaire. A total of four attempts to contact the potential participant will be made on consecutive week days. During the phone call a verbal summary of the information sheet will be discussed with the potential participant and they will be given the opportunity to ask as many questions about the study as they wish.

Verbal consent and agreement of study start date

Following the verbal summary of the study information sheet, participants will be given the option to enrol into the study, delay participation, request more time to think about participation or decline to take part in the study. Written consent will subsequently obtained by the completion of two paper copies of the consent form sent to participants within the study pack. The provided consent forms will be signed and dated by the team member responsible for recruitment at the point of obtaining verbal consent, with participants asked to complete their own signature at the time of completing the baseline questionnaire. One copy of the consent form will be returned by the participant at the end of their first 30 days in QUASAR, along with the actigraph watch and baseline questionnaire. The second copy is for the patients' personal records.

Once verbal consent has been obtained participants will be asked to agree to a study start date, which should be within 14 days of the telephone call taking place. Participants who are unable to commence the study within 14 days will be asked to delay entry into the study. Those who agree a study start date will be asked to confirm their preferred postal address to which the study packs will be sent and a mobile phone number. The mobile phone number will be used to send participants text messages on the agreed study start date and throughout the study to encourage data completion and study compliance.

Study pack

The provision of verbal consent also enables the study pack to be prepared and posted to participants in advance of the agreed study start date. The study pack will include a letter of introduction, two copies of the consent form and a paper copy of the baseline questionnaire. Participants will also be provided with instructions to download and use the study app, as well as an actigraph watch, called a MotionWatch8 (CamNtech, Cambridge, UK) and associated instructions.

The study pack will be sent from the University of Manchester using Special Delivery Guaranteed® to arrive no less than one day prior to the study start date.

Document completion – Consent form and baseline questionnaire

Participants are requested to complete paper copies of the consent form and baseline questionnaire (sent within the study pack) on or before the first day of symptom monitoring. Initially, the baseline questionnaire was incorporated into the study app to be completed as part of the on-boarding process. However, due to limits on the number of questions which could be displayed per screen and the associated time required for data completion, app testing with the study team and members of a focus group indicated that this method of delivery would be less acceptable to participants than a paper based document.

The participant's QUASARid will be written onto both the consent form and covering page of the baseline questionnaire to enable data linkage between these documents, the study app and actigraph watch. To encourage completion of the questionnaire in advance of the monitoring period, participants will be asked to indicate the date on which they have completed the questionnaire on the covering page. They will return the baseline questionnaire along with the monitor at the end of the study.

The baseline questionnaire will comprise three sections: Demographic information, information about RA and health status information.

Demographics

Participants will record a number of demographic variables: sex, date of birth, weight and height, ethnicity, age left education, average weekly alcohol consumption, smoking status, occupational status, marital status and postcode. Participants will also indicate how likely they believe it is that sleep affects their quality of life and the impact that RA has on their work productivity. A description of the reporting of these items is shown in Table 1.

Information about RA

Disease activity

Participants will record the month and year of their diagnosis. Disease activity will be assessed using the Routine Assessment of Patient Index Data 3 (RAPID-3). The 15 item RAPID-3 is free to use and

has been validated in RA populations. The measure has good validity and acceptable reliability and responsiveness.[23]

The RAPID-3 measures 3 domains: physical function (13 discrete response items), pain (1 item 0-10 numerical rating scale (NRS)) and global health (1 item 0-10 NRS)) in the past week. The first 10 items of the physical function domain are scored, transformed into a 0.3-10 scale and summed with the pain and global health domains to produce an overall score of 0-30. These overall scores are then converted into a weighed RAPID 3 score and categorised within the following disease activity score categories: Near remission (0.3-1.0), Low Severity (1.3-2.0), Moderate severity (2.3-4.0), High severity (4.3-10).

Co-morbid rheumatic disease(s) and sleep-related problem(s), and menopausal status

Participants will be asked to record the presence of a variety of other rheumatic diseases, co-morbidities which may affect sleep (e.g. Sjögren's syndrome, diabetes, multiple sclerosis, hypertension (Table 1)) and menopausal status.

For pragmatic reasons it was not possible to embed specific questionnaires about the presence, severity or impact of sleep disorders, as it was necessary to balance the availability of data with minimal participant burden of data completion. Nevertheless, because the presence of such disorders represent important co-variates which should be adjusted for within data analysis, participants will be asked to record whether they experience restless leg syndrome and obstructive sleep apnoea/snoring, A full list of co-morbidities collected is shown in Table 1.

Insomnia is recorded using the Sleep Condition Indicator (SCI), an 8 item questionnaire which has good concurrent validity, high internal consistency and is sensitive to change.[24] The SCI performs well to detect possible insomnia disorder and is the only validated and widely used insomnia measure that indexes insomnia disorder against contemporary criteria (e.g. International Classification of Sleep Disorders (ICSD-3); The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)).[24]

Medications

Participants will also be asked to record the use of medications including analgesics (e.g. Paracetamol, Nonsteroidal anti-inflammatories (NSAIDs) and opiates and disease modifying anti-rheumatic drugs (DMARDs, e.g. glucocorticoids, biologic DMARDs). The use of sleep medications, including sedatives or hypnotics, mood stabilisers, antidepressants, other sleep medications (e.g.

Chlorpromazine, Haloperidol) will also be collected and participants will be given a free-text box to record other medications or coping strategies they use and the purpose for using the strategy (Table 1).

Quality of life (QoL)

As is recommended,[25] participants will complete a generic and disease specific measure of HRQoL. Generic HRQoL will be reported using the WHOQOL-BREF, a 26 item instrument which measures 6 domains in the past 14 days: overall perception of HRQoL (1 discrete response item), health (1 discrete response item), physical (7 discrete response items), psychological (6 discrete response items), social relationships (3 discrete response items) and environment (8 discrete response items). The items from each domain are summed and transformed into a 0-100 score, where higher scores indicate better HRQoL.[26] The WHOQOL-BREF has good internal consistency, discriminant validity (i.e. discriminating ill versus well groups) and sensitivity to change.[26]

Disease specific HRQoL will be reported using the 26 item Arthritis Impact Measurement Scale 2 (Short Form) (AIMS-2 SF). The AIMS-2 SF uses discrete response items to capture 5 domains within a 4 week recall period: physical (13 items), symptom (3 items), affect (4 items), social interaction (4 items) and role (2 items). After some items are reverse coded, domain items are summed and converted into a 0-10 scale, where higher scores indicate poorer HRQoL.[27] The AIMS-2 SF shows good internal consistency and acceptable construct validity. The scale also generally demonstrates promising evidence of sensitivity to change, but there is less evidence supporting this for social interaction and role subscales.[27]

Participants will also be asked to use a free text box to indicate the top 3 things which are most important to them to ensure they have good quality of life.

Sleep quality and beliefs about sleep

Sleep quality in the past month will be measured using the Pittsburgh Sleep Quality Index (PSQI), the most widely used measure within clinical and research settings.[28] The 18 item instrument comprises 7 domains: sleep quality (1 discrete response item), sleep latency (1 free-text item; 1 discrete response item), sleep duration (1 free-text item), sleep efficiency (2 free-text items), sleep disturbances (9 discrete response items), sleep medications (1 discrete response item), daytime

dysfunction (2 discrete response items). The PSQI has good reliability and validity[28] and demonstrates good sensitivity and specificity to distinguish good and poor sleepers.[29]

Participants will also record information regarding their beliefs about sleep using the 16 item Dysfunctional Beliefs and Attitudes about Sleep instrument (DBAS-16). Beliefs about causes, consequences, and treatment of sleep problems are rated on 11-point Likert scales ranging from 0 (strongly disagree) to 10 (strongly agree). Scores are summed and averaged to produce a mean item score where higher scores indicate stronger endorsement of maladaptive beliefs about sleep.[30] The DBAS-16 has good internal consistency and test-retest reliability.[30]

Mood, self-efficacy and cognitive flexibility

Finally, mood, self-efficacy and cognitive flexibility will be measured as important co-variates which may affect the relationship between sleep and HRQoL. Mood, specifically anxiety and depression, will be measured using the 14 item Hospital Anxiety and Depression Scale (HADS).[31] Anxiety (7 items) and depression (7 items) in the preceding week are reported using discreet response questions, scored 0-3). Subscale items are summed to produce a score of 0-21, where higher scores represent poorer mood.[31] Scores rend to be categorised as 0-7 “normal”, 8-10 “borderline”, >11 “caseness”. The HADs is well accepted and has strong internal consistency and high test-retest reliability.[31]

Self-efficacy will be assessed using the Arthritis Self-Efficacy Scale-8 item (ASES-8),[32] which will record information about participants’ self-efficacy for pain (2 0-10 NRS), preventing pain & fatigue interference(2 0-10 NRS), and for other symptoms(4 0-10 NRS). A self-efficacy score, ranging between 1 and 10, is produced by summing all items and calculating the mean value.[32] Higher scores indicate better self-efficacy. The ASES-8 has been shown to have good reliability, validity and sensitivity to change.[32]

Cognitive flexibility will be recorded using the Committed Action Questionnaire (CAQ-8), to assess participants’ abilities to persist with or change behaviour in relation to their present situation[33]. The CAQ-8 comprises 4 positive, and 4 negative, commitment to action subscales, which are recorded using 7-point Likert scales. An overall flexibility is scored by reverse coding the negative commitment subscales and summing all items, with higher scores indicating greater flexibility.[33] The CAQ-8 has been shown to have good reliability and internal consistency.[33]

Table 1 – Baseline questionnaire domains and scales	
Domain	Scales/measurement
Demographics	
Sex	Tick box – male or female
Date of birth	Day, month, year
Height and Weight	Free text (metric or imperial)
Ethnicity	Free text
Age left education	Free text
Smoking status	Tick box – current, ex-, or never smoker
Occupational status	Tick box – working full time, working part time, student, medically retired, voluntary worker, unemployed but seeking work or retired
Marital status	Tick box – Single, in a relationship, co-habiting, married, civil partnership, separated, divorced or widowed
Alcohol consumption	Tick box –average units per week: 0, 1-5, 6-10, 11-15, 16-20, 21-40, >40
Impact of RA on work	Work productivity question from Work Productivity and Activity Impairment – specific health problem (WPAI-SHP)
Postcode	Free text for first half of postcode
Belief that sleep affects HRQoL	0-10 NRS: 0 “Not at all likely”, 10 “Very likely”
Information about RA	
Date of RA diagnosis	Month and year
Disease activity	Routine Assessment of Patient Index Data 3 (RAPID-3)
Co-morbid rheumatic disease(s) and sleep-related problem(s)	Check list – osteoarthritis, spondyloarthropathy/ankylosing spondylitis, fibromyalgia/chronic widespread pain, gout or other crystal arthritis, Sjogren’s syndrome, restless leg syndrome, obstructive sleep apnoea/snoring, thyroid disorder, diabetes, multiple sclerosis, hypertension.
Menopausal status	Tick box – yes/no
Current medication(s) and non-pharmacological intervention use	Check list – paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), other analgesics, weak opiates, strong opiates, drugs for neuropathic pain, glucocorticoids, synthetic disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, sedatives (or hypnotics), mood stabilisers, antidepressants, other sleep medications. Free-text box
Health status information	
Disease specific quality of life	Arthritis Impact Measurement Scale 2 - Short Form (AIMS2-SF)
Generic Quality of life	WHOQOL-BREF
Prioritisation domains for good HRQoL	Participants are asked to use a free text box to indicate top 3 things which are most important to them to ensure they have good quality of life.
Sleep quality	Pittsburgh Sleep Quality Index (PSQI)
Beliefs about sleep	Dysfunctional Beliefs and Attitudes about Sleep questionnaire (DBAS-16)
Insomnia	Sleep Condition Indicator (SCI)

Mood	Hospital Anxiety and Depression Scale (HADS)
Self-efficacy	Arthritis Self-Efficacy Scale-8 item (ASES-8)
Cognitive flexibility	Committed Action Questionnaire (CAQ-8)

Study commences (Day 1)

On the agreed study start date, participants will receive a text message on the mobile phone number provided during the recruitment process. The reminder text message will ask participants to put on their activity monitor and to download the study app and register for an account. It will also include a study password, which will unlock the app to allow the participant to commence full registration, and a reminder of their QUASARid, which must be entered during the registration process to enable data linkage between the study app, actigraph watch and paper questionnaires.

App installation and account set up

Instructions about how to download the study app, which can be installed onto the participants' Apple or Android smartphone, tablet or both, will be included within the study pack that will be posted to participants. Once the app is installed participants will be asked to:

- complete a standard registration form (including creation of a username and password)
- enter their unique QUASARid, sex and date of birth, to enable linkage between the study's different data collection platforms

Registrations will be monitored via a live database, held by uMotif, of the data collected by the study app, to which the study team is provided secure access. All data provided by participants using the study app will be immediately transferred to uMotif server and visible in the database in real-time via 3G/4G/ Wifi. Any participants who have not registered with the app on their agreed start date, or within a 5 day window of that date, will be contacted by the study team to understand what issues may have arisen. If appropriate, participation in the study may be rescheduled for a later date.

Data collection

Following app-installation and the completion of the baseline questionnaire, participants will commence data collection lasting a total of 60 days. The first 30 days of the study comprise the continuous data collection phase of the study during which time participants wear the actigraph watch 24 hours a day and complete a once-daily sleep diary and twice daily symptom reports. During this 30 day monitoring period participants will also complete follow-up questionnaires on days 10, 20 and 30 of the study. No data are recorded between days 31 and 59, but participants are asked to complete a final follow-up questionnaire on day 60 of the study.

During focus groups conducted to inform the design of this study, participants discussed a desire to have options for on-going support from the study team via telephone contact. For that reason we will send personalised messages on days 5, 15 and 25 to encourage participation and give the participant the option to email or telephone the study team if they would like to discuss any issues or concerns. Any emails or requests for telephone calls will be responded to by the study's post-doctoral research associate, or principal investigator, at the earliest possible opportunity, and no later than one working day after the response is received.

A full outline of the data collected is provided below.

Day 1-30 – Actigraph watch and uMotif app

Continuous monitoring of sleep and physical activity.

Participants will wear the MotionWatch 8 (MW8; CamNtech, Cambridge, UK) for 24 hours a day over the 30 days of continuous data collection. The MW8 is a Class I Medical device which conforms to the essential safety and health requirements and provisions of EC Council Directives 93/42.EEC, Annex VII. The MW8 requires a standard watch battery (CR2032) which is replaced each time the watch is used. The configuration of the MW8 for the present study will enable the watch to collect data for up to 45 days, providing an additional two week window for data to be collected in instances where study entry may have been delayed.

The MW8 monitors limb or bodily movements during daily living and sleep at 30 second time points (epochs) using a tri-axial accelerometer. It is waterproof for up to 1 hour at 1 meter and is therefore suitable for use while swimming or showering. Participants are instructed to wear the MW8 on their non-dominant wrist.

Actigraphy has been validated against polysomnography (PSG) data.[34] The MW8 has been shown to provides reliable estimates for both sleep (including sleep latency, duration, efficiency, and fragmentation) and physical activity when worn for at least 14 days,[35-37] and has a number of practical features which make it suitable for the purposes of this study, including an event marker and prolonged battery life. Furthermore, the MW8 was specifically selected by participants invited to a research design focus group, who identified the MW8 as their preferred device due to the comfort of wearing it and the lightweight and unobtrusive design.

There is no real-time transmission of actigraphy data because the data are stored on the watches internal memory and can only be downloaded via a USB connection. It will therefore not be possible to assess participant compliance until after data collection has been completed and the actigraph watch is returned.

Following the receipt and download of actigraphy data the following variables will be extracted: total sleep time (the total time spent in sleep according to the epoch-by-epoch wake/sleep categorisation), sleep onset latency (the time which elapsed between the participant getting into bed and the participant falling asleep) and sleep efficiency (the total sleep time, expressed as a proportion of the total times pent in bed). The sleep fragmentation index, a measure of the degree of sleep discontinuity, will be calculated as a percentage of the total time categorised as mobile in the epoch-by-epoch mobile/immobile categorisation and the number of immobile bouts which were less than or equal to one minute in length.

Daily symptom reporting

During the 30 day continuous data collection, participants will be asked to use the uMotif study app to report their experience of daily symptoms. Within the app, the unique 'motif' interface is used by patients to simply track their daily symptoms. The motif which comprises 10 symptom segments, such as pain severity as is highlighted in **Error! Reference source not found.**. The uMotif study app has been used in multiple ethics-approved studies, capturing over 64 million data points from patients using their own devices. The uMotif app has been specifically configured to capture the data required for the QUASAR study.

[Figure 2 here]

Participants will receive prompts twice daily to complete the symptom ratings, once in the morning and once in the afternoon/evening. Symptom data are scored on an ordinal scale of 1-5 and are recorded by touching and sliding the relevant segment within the motif. The symptoms to be recorded (Table 2) were defined and agreed with consultation of participants in focus groups.[38]

Throughout the study participants will receive reminders via the study app to complete the symptom assessments at 8am and 6pm. Participants will be able to provide additional symptom reports throughout the day at their discretion.

Table 2- Daily symptoms to be captured by the uMotif study app			
Symptom	Question	Anchor 1 (centre of motif)	Anchor 5 (outside of motif)
Pain	How severe is your pain?	No Pain	Very Severe Pain
Fatigue	How severe is your fatigue?	No Fatigue	Very Severe Fatigue
Mood	How is your mood?	Depressed	Very Happy
Well-being	How well do you feel?	Very Well	Very Unwell
Anxiety	How anxious do you feel?	Very Well	Very Anxious
Illness impact	How much is your illness impacting on your activities?	No Impact	Very Severe Impact
Disease control	How much control do you feel you have over your symptoms?	No Control	Very Good Control
Challenge	How challenging are you finding today?	Not Challenging	Severely Challenging
Sleepiness	How sleepy do you feel?	Not Sleepy	Very Sleepy
Concentration	How would you rate your concentration?	Poor	Excellent

The completion of these symptom data can be continually monitored via a live database, held by uMotif, of the data collected by the study app, to which the study team is provided secure access. As all data provided by participants using the study app are immediately transferred to uMotif server in real-time via 3G/4G/ Wifi, it will be possible for the study team to produce daily reports to monitor whether participants are completing their data in line with the study protocol.

A window of two consecutive days during the 30 day continuous monitoring period will be considered an acceptable period of non-completion for the daily symptom reports, sleep diaries and follow-up questionnaires. After this point, participants will receive a single reminder text message to encourage them to recommence data entry or contact the study team to discuss any concerns or issues, as appropriate.

Day 2-31 – Consensus Sleep Diary

The reminder sent to participants at 8am will also ask them to complete the 9 item Consensus Sleep Diary (CSD). This diary, which is completed in a separate section of the study app ([figure 3 here]

), pertains to the previous night's sleep. To ensure coverage of all 30 nights of actigraphy data collection, it will be completed on the morning of days 2-31. Participants will receive an

automatically generated reminder every morning at 8am to complete the CSD, but are able to complete the diary earlier if they wish.

[figure 3 here]

The 9 item CSD asks participants to record the time they got into bed, when they tried to sleep, how long it took to fall asleep, number and duration of night time awakenings, the time of final awakening, when they got out of bed, sleep quality, and how refreshed they felt upon awakening. The CSD is widely considered to be a gold-standard sleep diary, having been developed through the collaboration of sleep experts and potential users.[39;40] An additional 4 items will ask participants to report the duration of morning stiffness (in minutes), emotional strength, motivation and worry about sleeping the previous evening.

As with the symptom reports, it will be possible to continually monitor sleep diary completion using the live database, held by uMotif. The study team will therefore produce daily reports to monitor whether participants are completing their sleep diaries in line with the study protocol. Any participant who does not complete their sleep diary for more than two days will receive a single reminder text message to encourage them to recommence data entry or contact the study team to discuss any concerns or issues, as appropriate. It will not be possible to retrospectively complete the sleep diaries for missing days.

Day 10, 20 and 30 – HRQoL, disease activity and life events

A number of follow-up questionnaires will be used throughout the study(Table 3). Prompts to complete the questionnaires will be sent. Requests to complete the follow-up questionnaires will be delivered to participants, via the app to participants, on the day they are to be completed when they open the study app. These reminders will be automatically generated and sent from uMotif and cannot be personalised. The questionnaires completed at days 10, 20 and 30 will capture the below items:

- Disease specific quality of life – AIMS2-SF
- Generic quality of life – WHOQOL-BREF
- Disease activity - RAPID-3

- Occurrence of important events

As with all data collected via the study app, the data recorded in each follow-up questionnaire will be immediately transferred to uMotif server in real-time via 3G/4G/ Wifi. Completion of follow-up questionnaires will be monitored within daily reports produced by the study team and any participant who has not completed their questionnaire within two days of the required date will receive a single reminder text message to request that they complete the questionnaire as soon as possible. Participants will be given instructions to manually access and complete the follow-up questionnaire forms or contact the study team to discuss any concerns or issues, as appropriate.

Following the 30 days of data collection, participants will receive a text message to remind them to stop wearing the activity monitor and to send it back to the study team at the earliest convenient time, using the provided return addressed envelope. The envelopes, to which the relevant postage will be attached to return the package using Royal Mail Signed For® 1st Class must be returned via the local postage to obtain proof of postage; participants will not be required to pay any additional postage to obtain this. In instances where the watch does not appear to have been dropped off at the Post Office within 5 days of the expected end date, the study team will contact the participant.

Participants are not expected to continue tracking their symptoms or using the study app for continuous monitoring after day 30 and at this point participants may wish to uninstall the study app. For that reason, as the completion of the study's final questionnaire will occur 30 days after the continuous data collection phase has ended (day 60), participants may no longer be using the app and may have uninstalled it from their devices. Within the text message sent on day 30 of the study to congratulate participants on completing the continuous monitoring phase, participants will be asked to advise the study team if they would like to receive a paper copy of the final follow-up questionnaire.

Day 60 – Final follow-up questionnaire

The study's final follow-up questionnaire will be completed at day 60. It is assumed that those who do not request a paper copy will be happy to complete the questionnaire using the app. Participants will be prompted to complete the questionnaire by reminders automatically generated and sent from uMotif. As before these reminders are generic and cannot be personalised.

The questionnaire will capture:

- Disease specific quality of life – AIMS2-SF
- Generic quality of life – WHOQOL-BREF
- Prioritisation of domains - participants asked to use a free text box to indicate the top 3 things which are most important to them to ensure they have good quality of life.
- Disease activity - RAPID-3
- Current medication(s) and non-pharmacological intervention use
- Sleep quality – PSQI
- Occurrence of important events

Table 3– Summary of data collection via study questionnaires.

	Pre-registration	Day ≤1 (paper)	Day 10 (app)	Day 20 (app)	Day 30 (app)	Day 60 (app/paper)
Screening questionnaire	**X**					
Demographics		**X**				
Information about RA		**X**				
RAPID- 3		**X**	**X**	**X**	**X**	**X**
Current medication(s) and non-pharmacological intervention use		**X**				**X**
AIMS2-SF		**X**	**X**	**X**	**X**	**X**
WHOQOL-BREF		**X**	**X**	**X**	**X**	**X**
PSQI		**X**				**X**
DBAS-16		**X**				
SCI		**X**				
HADS		**X**				
ASES-8		**X**				
CAQ-8		**X**				

A complete overview of data collection and participant contact is shown in **Error! Reference source not found.**.

[Figure 4 here]

Sample size

Following published guidance,[41;42] A sample size calculation has been conducted to determine a minimum sample size required to enable the study to conduct structural equation modelling (SEM). We have based estimated the sample size to detect a conservative minimum effect size (defined as correlations between pairs of latent variables) of 0.2 (rated as small). Based on our hypothesized model using baseline and 60 day measurements, containing 13 observed variables and 4 latent variables, with a significance level of 5% and power of 80%, a minimum sample size of 166 participants is required. Recommended sample sizes for latent growth curve analyses are defined in relation to the number of participants and the number of repeated observations and suggest a minimum number of 100 participants should complete at least 3 data points.[43] Our minimum sample size required and data collection protocol are therefore in excess of the requirements for latent growth curve analyses. In this study 50 actigraph watches will be obtained. This means that the maximum capacity for concurrent data collection is 50 and that data collection will be conducted in waves.

Using data from previous studies we conservatively estimate that: a total of 3500 questionnaires mailed will provide 1750 (50%) returned and completed screening questionnaires, 350 (20%) will agree to take part and 175 (50%) will provide complete useable data, in excess of the minimum 166 persons required for the analysis. It is important that a representative sample of people with RA is enrolled into the study. However, Data regarding the characteristics (e.g. age and sex) of persons who receive information about the study will not be available through the proposed recruitment channels. The presence of sampling bias will be examined for by comparing the age and sex distribution of UK population data (Table 4) to a) persons who complete and return screening questionnaires and b) recruited participants to available.

Recruitment

In order to manage the flow of participants into the study and given the limited number of actigraph watches available, NRAS have agreed to contact mailing list members in 7 regionally-stratified recruitment waves in order that actigraph watches can be returned by earlier participants, prepared and sent out to future participants. The dates of each wave are listed below:

Wave 1 – 8 May 2017

Wave 2 – 17 July 2017

Wave 3 – 25 September 2017

Wave 4 – 4 December 2017

Wave 5 – 12 February 2018

Wave 6 – 23 April 2018

Wave 7 – 2 July 2018

The identification of GP practices and NHS Rheumatology clinics able to support recruitment to the QUASAR study will occur throughout the study. Once identified, the letters sent to potential participants identified via the screening of GP records will be sent to coincide with the above mailing waves used by NRAS. Participants who see information about the study in NHS Rheumatology clinics will be free to contact the study team at any point, however their enrolment into the study will be restricted to coincide with the above mailing waves.

Targeted recruitment

The study's third objective is to examine whether the relationships between sleep and HRQoL are moderated by age and sex. It is therefore important to ensure that a representative sample of people with RA are enrolled into the study. Table 4 displays the estimated UK prevalence of RA and demonstrates that women are around three times more likely to be affected than men, and the increased prevalence of RA in older populations.[2]

Table 4- **The prevalence of rheumatoid arthritis in the UK**

Age	Males (%)	UK estimate	Females (%)	UK estimate
16–44	0.02	2,500	0.12	15,100
45–64	0.58	42,900	1.67	126,900
65–74	1.14	27,100	2.56	67,800
75+	2.18	39,100	2.99	85,700
Total adult population	0.44	106,500	1.16	297,600

From previous studies, we know that young men[44] and older people of both sexes are often under-represented populations.[41,42] They may be less likely to express an interest in taking part in studies[41], or they may be excluded by the inclusion/exclusion criteria used.[42] In anticipation that some of these 'hard to reach' groups may be under-represented in our sample, we propose to monitor the

characteristics of participants who are enrolled in the study and apply stratified recruitment processes in later recruitment waves if required.

Data analysis plan

Analyses techniques used in descriptive epidemiology will address aim 1. Data will be presented as absolute numbers and percentages, presented for the whole group, and stratified by age (18-44; 45-64; 65-74; 75+), sex and level of socioeconomic deprivation (Index of Multiple Deprivation,[45] derived using participant postcodes and categorised as quartiles of most deprived, deprived, less deprived and least deprived).

Using structural equation modelling (SEM) and latent trajectory models (LTM) we will address the studies second aim: to examine if disrupted sleep patterns are associated with poor HRQoL.

SEM will assess whether the sleep and sleep/wake rhythm-associated parameters measured at baseline mediate the association between RAPID3 score and HRQoL at 60 days (the end of the follow-up period) allowing inter-correlation between the sleep and sleep/wake rhythm-associated parameters and adjusting for putative confounders. The SEM analysis will be repeated adding to the model pain, fatigue and mood to assess the effect of on HRQoL (for example **Error! Reference source not found.**). Finally the analysis will be repeated including the data on mediators collected at day 30. This will allow assessment of whether RAPID3 predicts change in the mediating factors and the subsequent impact on HRQOL at day 60. An exploratory multi-group SEM analysis will assess the moderating effects of age and sex and will thus address the third aim of this study.

[Figure 5 here]

The SEM analysis assumes that the identified associations are consistent across participants, and uses only selected time points. Latent trajectory models will utilise all of the repeated measures data to fully explore the longitudinal relationships between RAPID3, mediators, and HRQoL, and their variation between participants. First, multilevel growth models, accounting for the clustering of repeated measures (level 1) within participants (level2), will assess the prospective associations of RAPID3 with key observed pathways from the SEM analysis, and the prospective associations with HRQoL. Second, we will assess if distinct clusters of participants can be identified with different longitudinal courses using dual trajectory latent class growth analysis. We will assess how these trajectories are associated with change in HRQoL over 60 days and the socio-demographic and clinical characteristics associated with these different trajectories.

Finally, causal mediation analysis methods, specifically the mediational g-formula, will be used to estimate how successful treatments that improve sleep might be for people with RA. G-formula will be applied to the SEM models outlined above. This analysis will estimate the potential effect of a hypothetical intervention targeted at the key causal pathways between the observed variables and HRQoL. The hypothetical interventions which most improve HRQoL will indicate the best treatment targets to be tested in future intervention studies. For example, if disrupted circadian pathways were found to be important drivers of poor QoL, a future study might investigate the impact of advancing or delaying them using phototherapy[46]. However, it is likely that multiple pathways (e.g. sleep-wake cycle; sleep-wake cycle and pain) will impact on HRQoL and an intervention "package" (e.g. phototherapy and behavioural therapy[47]) will need to be developed based on those pathways.

Ethics and dissemination:

This study was underwent a full NHS Research Ethics Committee (REC) review and was allocated to the National Research Ethics Service (NRES) Committee North West – Liverpool Central REC. The study was approved by the NRES Committee North West – Liverpool Central REC on 12 April 2017, reference 17/NW/0217.

Results from this study will be disseminated at regional and international conferences and in peer-reviewed journals. Results will also be disseminated at Patient and Public Engagement (PPE) events where opportunities arise and are appropriate.

Discussion:

People with RA frequently report reduced HRQoL, which may be caused by sleep disturbances. Few studies have determined the relationship between sleep and quality of life among RA populations and those which have are laden with methodological challenges, which preclude accurate assessment and understanding of the relationship between sleep and HRQoL. The QUASAR study is a comprehensive study which has been designed to overcome these challenges. The results of this study will inform future intervention studies by answering key questions regarding the link between sleep and poor HRQoL.

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Authors contributions:

JM led the conception and design of the study.

KLD, LC, VS, SM, BH, BJ, ML, DSK, WGD and JM made substantial contributions to the conception and design of the study.

JM and ML planned the statistical analysis.

KLD wrote the first draft of the protocol manuscript.

LC, VS, SM, BH, BJ, ML, DSK, WGD and JM critically reviewed the protocol manuscript.

KLD, LC, VS, SM, BH, BJ, ML, DSK, WGD and JM approved the final version of the document.

Data sharing statement: We intend to make data available for data sharing after the data collection has been completed and the primary aims of the study are met.

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Competing interests statement: The authors have no competing interests to disclose

Figure legends:

Figure 1 – Flow of participant entry into the study

Figure 2 - Screenshot of uMotif study app

Figure 3 – Screenshot of consensus sleep diary within study app

Figure 4 - Data collection and participant contact across 60 days for participants enrolled in QUASAR

Figure 5 – Hypothetical model of the pathways of relationship between rheumatoid arthritis and quality of life disease severity, sleep, fatigue, mood, and pain– simple model. In this figure rectangles represent observed variables, and circles represent the constructs those variables represent. Solid arrows represent the pathways to be tested. RAPID-3: Routine Assessment of Patient Index Data 3, CSD: Consensus Sleep Diary, PSQI: Pittsburgh Sleep Quality Index, AIMS2-SF: Arthritis Impact Measurement Scale 2 - Short Form.

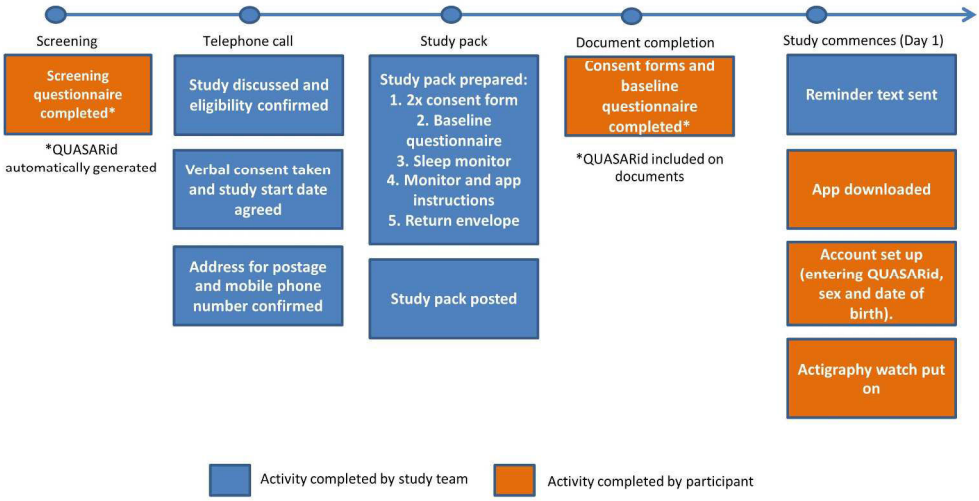


Figure 1 – Flow of participant entry into the study

254x190mm (300 x 300 DPI)

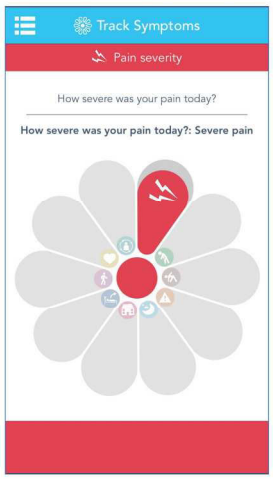


Figure 2 - Screenshot of uMotif study app

254x190mm (300 x 300 DPI)

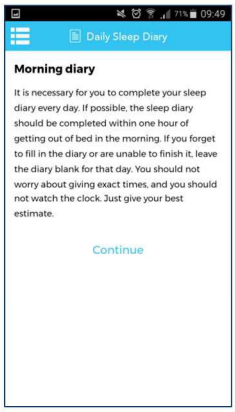


Figure 3 – Screenshot of consensus sleep diary within study app

254x190mm (300 x 300 DPI)

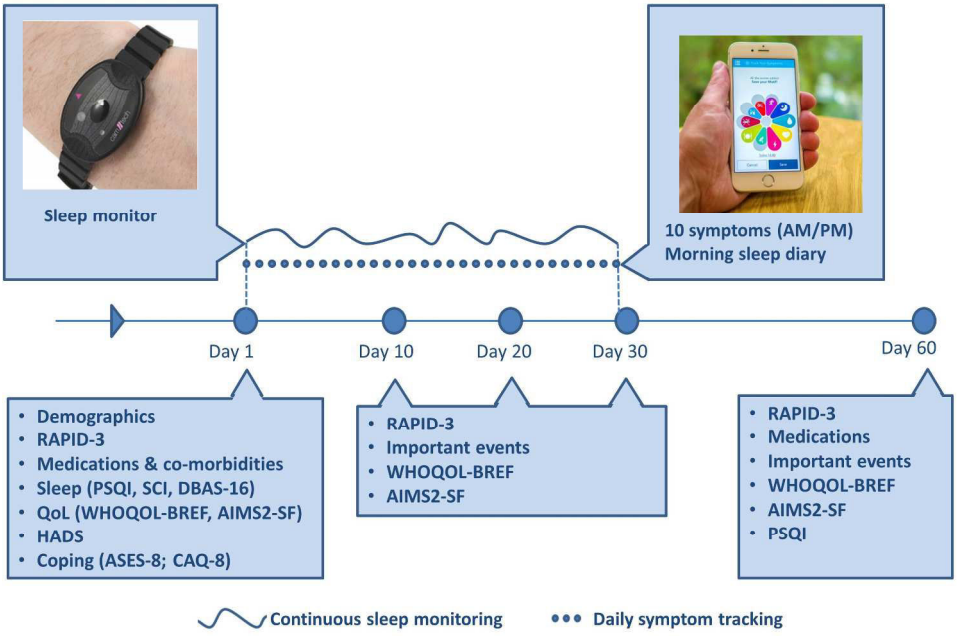
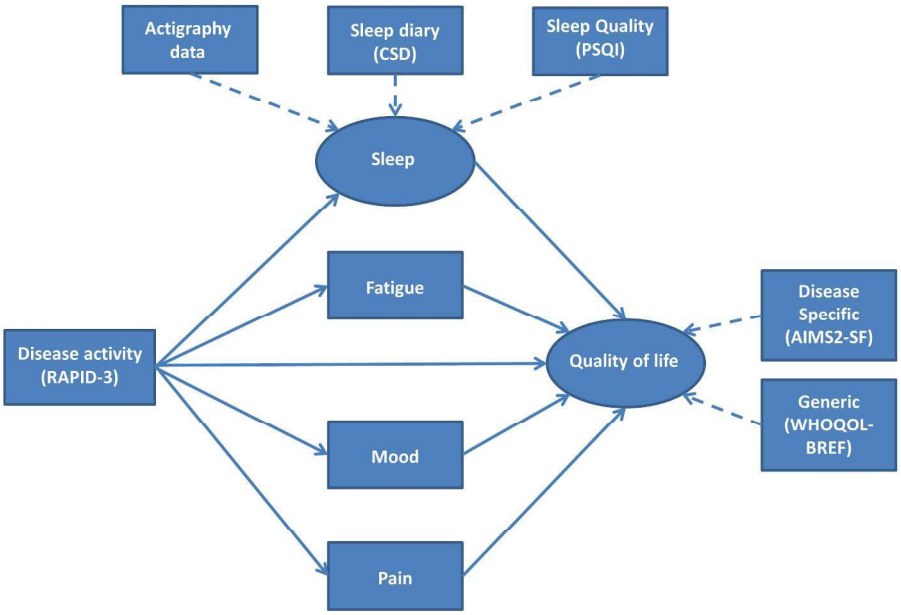


Figure 4 - Data collection and participant contact across 60 days for participants enrolled in QUASAR

254x190mm (300 x 300 DPI)



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254x190mm (300 x 300 DPI)