The use of Digital Patient-Generated Health Data to Support Clinical Care and Research in Musculoskeletal Disease

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

2022

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Word count: 39,136

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Abstract

Mobile health is the application of mobile apps and sensors to obtain data pertinent to wellness and disease diagnosis, prevention, and management. It has the potential to monitor and intervene whenever and wherever as part of managing long-term conditions. With more than 85% of UK adults owning a smartphone and catalysed by the COVID-19 pandemic, there is an opportunity to achieve this in the foreseeable future.

This thesis explores how digital patient-generated health data (PGHD) from mobile apps can advance clinical care and research in long-term conditions, using the example of rheumatoid arthritis (RA) – a chronic, disabling disease of the joints, characterised by fluctuating symptoms and disease severity through time. Infrequent outpatient visits mean that clinicians lack a clear picture of what happens between visits, because patients struggle to recall symptoms. This ultimately results in sub-optimal care. Longitudinal research into patterns of RA disease severity shares the limitation of sporadic data collection. Smartphones offer a unique opportunity to overcome this challenge for both clinical care and research by enabling patients to briefly report their symptoms regularly, integrated into their daily lives.

An initial review of published studies on remote monitoring systems integrated into electronic health records (EHRs) to collect symptoms in long-term conditions found that there were few examples to inform future development of these systems (Chapter 2). Additionally, many of the anticipated benefits of remote monitoring had yet to be realised in practice. This suggests that creating and evaluating such systems is an ambitious achievement.

The Remote Monitoring of Rheumatoid Arthritis (REMORA) programme aims to implement daily symptom monitoring from a smartphone app into the EHR to guide clinical decision-making. The first stage (REMORA1), conducted in 2015-17, was a feasibility study in 20 RA patients over three months. Through qualitative analysis of audio-recorded clinical consultations with REMORA1 patients, where visual summaries of PGHD over time were available for review, I aimed to enhance our understanding of how availability of PGHD influenced clinical care, and identified three distinct ways of using the data depending on when it was introduced (Chapter 3). As part of an essential update of the REMORA technical infrastructure, I set up an observational study to expand on the previous study by: 1) collecting data longer, 2) including a larger cohort of patients, 3) on-boarding without direct assistance, and 4) linking with contextual data collected from the EHR. I reflect on the challenges of setting up a mobile health study and insights gained through the process and from preliminary results (Chapter 4) that informed a current multi-centre trial.

Analysis of daily symptoms allowed characterisation of self-reported RA flares (Chapter 5), where the frequency of flares and relationships with symptom changes were quantified. Building on this, I was able to demonstrate the feasibility of using daily PGHD to predict self-reported flares (Chapter 6), which opens up opportunities for timely interventions to avoid a flare or decrease its impact.

This thesis demonstrates that building a sustainable infrastructure for the collection of daily PGHD on an app and integration into the EHR is complex but achievable. Smartphones make it possible to capture and characterise day-to-day variations in symptoms and occurrence of flares in real time, instead of relying on patient recall at infrequent clinical visits or at the discrete intervals of research - truly harnessing the potential of mobile health for both clinical care and longitudinal research.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Acknowledgements

Completing my PhD would not have been possible without the unwavering support, guidance and input from many fantastic people.

I must start by expressing my deep and sincere gratitude to my supervisory team. **Will**, it has been a pleasure to work closely with you and to be inspired by your always optimistic, supportive and entrepreneurial mind. You provided me an environment to learn and develop myself, and your enthusiasm and big picture vision never failed to motivate me. **Sabine**, thank you for always asking the right, critical questions and for bringing refreshing (and often opposing) viewpoints to my supervisory meetings. We did not get to explore our shared interest in natural wines, but I am certain we will find a time for it in the near future. **John**, your broad expertise in chronic disease epidemiology added richness and depth to my research and academic writing. Thank you for your encouragement and help whenever I needed, and for proving that commuting between London and Manchester indeed is possible.

I am indebted to the **patients** taking part in the different stages of the REMORA study. Without you and your commitment to share your symptoms every day, my research would not have been possible. Your valuable lived experiences of rheumatoid arthritis helped ground my thinking and have made me aware of how crucial it is to involve patients at every step of a digital health study.

I would like to thank the **REMORA1.5 team**. It has been a pleasure to work with all of you, and despite bumps along the way, not to mention a global pandemic, we never failed to keep the eye on that moving go-live star on Mike's timeline. Will once said that it takes a village to raise a mobile health child, and we now know that there is truth to this. The success of the project relied on the expertise that each and every member brought to the team.

Thank you, **Meghna**, for acting as my postgraduate tutor. I thoroughly enjoyed our engaging conversations and your thoughtfulness over the years, and you have always been a great inspiration for my career as a female doctor in science. I am sure we will stay in touch, and I look forward to following your future endeavours.

Although I only stepped foot there during the first six months of my PhD, having been based in the **Centre for Epidemiology Versus Arthritis** has been key in my development and the success of my research. Being surrounded (even virtually) by colleagues with wide-ranging skills, ideas and backgrounds has given me unique experiences, friendships and opportunities for collaborations. A special thanks to **Roze**. You quickly became much more than an office mate. I am grateful that we got to share this wild PhD journey together and I am truly excited for our futures. You go, girl!

And **Lucy**, thank you for always lending an ear and being supportive along the way. Your PhD journey has been inspiring, and I miss the days we had in the office together. To the rest of the **CfE PhD cohort**, thank you for making it all worthwhile - and for supporting the journal club.

I am eternally grateful to **my parents**, **my brother** and **my sister**. Despite being scattered across three continents and 13 time zones deprived from the option to travel, we managed to stay connected as a family and continued to be there for each other through a difficult time. Thank you for always cheering and for celebrating all the small wins with me. Your unwavering support and pep-talks kept me going and I owe you all so much.

And finally, I want to thank my husband, **Mattias**. This PhD journey has been life-changing and rewarding, but it has, at times, also been challenging and hard. You were there to pick me up, offer advice and encouragement when needed and always had a homemade cake to serve to curb my tears. All of this while you were pursuing a PhD yourself. During this time, we also got our puppy, **Harris** - the fluffiest, most barky and affectionate home office mate, I could ever ask for and perhaps the silver lining of the pandemic and working from home. Mattias, you are my solid rock and without you, I would never have made it this far or dared to take advantage of arising opportunities. I therefore dedicate this thesis to you. Thank you for everything you do for me and our little family. Keep chasing your dreams. I love you.

I am experienced enough to do this.
I am knowledgeable enough to do this.
I am prepared enough to do this.
I am mature enough to do this.
I am brave enough to do this.
- Congresswoman AOC

Julie

July 2022

London, UK

About the author

Julie is a clinical academic with broad experience in digital health and patient-generated data. She completed her medical degree in 2019 at the University of Southern Denmark, doing her master's thesis research at the University of California, San Francisco under Profs Jinoos Yazdany and Gabriela Schmajuk after having obtained a prestigious fellowship from the Lundbeck Foundation.

During the final year of her medical degree, she secured full funding for her PhD in digital epidemiology at the University of Manchester directly through the Centre for Epidemiology Versus Arthritis and from a President's Doctoral Scholar Award. Additionally, she obtained continuous funding from various Danish charities and a scholarship from the Anglo-Danish Society. She completed her PhD under excellent supervision from Prof Will Dixon, Dr Sabine van der Veer and Prof John McBeth.

Julie will continue her career in a global pharmaceutical company, pursuing the development, evaluation and integration of innovative, digital solutions to improve the care and lives of people living with long-term conditions.

Publications related to this PhD

Gandrup J, Selby DA, van der Veer SN, Mcbeth J, Dixon WG. Using patient-reported data from a smartphone app to capture and characterize real-time patient-reported flares in rheumatoid arthritis. Rheumatol Adv Pract. 2022;6(1):rkac021. doi:10.1093/rap/rkac021

Gandrup J, Staniland K, Sharp CA, Dixon WG. Better digital health data should be the foundation to transform outpatient consultations for people living with long-term conditions. J R Soc Med. 2022;115(6):208-212. doi:10.1177/01410768221089020

Laverty L*, **Gandrup J***, Sharp CA, et al. Using patient-generated health data in clinical practice: How timing influences its function in rheumatology outpatient consultations. Patient Educ Couns. 2022;105(3):625-631. doi:10.1016/j.pec.2021.06.027 *Equally contributing first authors

Gandrup J, Ali SM, McBeth J, van der Veer SN, Dixon WG. Remote symptom monitoring integrated into electronic health records: A systematic review. J Am Med Inform Assoc. 2020;27(11):1752-1763. doi:10.1093/jamia/ocaa177

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Awards and achievements

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2021	American College for Rheumatology 2021 meeting, online (poster)
2021	British Society for Rheumatology annual meeting 2021, online (oral)
2021	Health Service Research UK annual conference, online (oral)
2021	UK-RiME spring showcase, online (oral)
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1

Introduction

On a balmy June morning in 1878, photographer Eadweard Muybridge was finally ready to settle an age-old public controversy about equine gait: is a running horse ever completely aloft? To unravel this, Muybridge had lined up a dozen state-of-the-art cameras along one side of a horse racetrack. When the horse galloped down the track, it broke twelve trip-wires each connected to a different camera, resulting in the camera shutters firing rapidly one after another to capture the horse in different stages of motion. The series made a brief filmstrip of the horse's progress along the track - capturing, for the very first time, ephemeral details the eye could not pick out at such speeds, such as the position of the legs and the angle of the tail. It was clear: a running horse indeed lifts all four hooves off the ground at the same time.

Developing methods to expand how and how often we observe a phenomenon can greatly improve our understanding of that phenomenon and increase the likelihood of finding new patterns and insights. Just as technological innovation allowed Muybridge to reveal the secrets of equine gait by increasing the frequency of his observations, there are long-standing questions in clinical care and longitudinal research that are poised to be answered with the advent of more frequent data collection using new technology. These are the topics of this thesis.

1.1 The burden and challenges of long-term conditions

One in four people in the United Kingdom (UK) are living with a long-term condition (LTC) such as asthma, inflammatory bowel disease, diabetes or arthritis.(1) LTCs are

conditions that at present cannot be cured but are controlled by medications or other treatment or therapies.

In addition to imposing a considerable burden on patients and their families, LTCs also have a substantial financial impact on society and the health system. Collectively, they account for up to 70% of the National Health Service (NHS) budget, posing a significant challenge to public and societal resources at large due to increasing demand for services and financial pressures.(2) Costs come from frequent contacts with general practitioners and shared care with hospital specialists at ongoing outpatient visits as well as from treatments and therapies. At the same time, life expectancy of the UK population has been steadily increasing and this trend is projected to continue in the future,(3) contributing to an increasing prevalence of people suffering from one or more LTCs.

Rheumatoid arthritis (RA) exemplifies challenges with LTCs and will serve as the disease focus for this thesis. RA is a systemic, inflammatory, autoimmune disease primarily affecting synovial joints, especially those of the hands and feet. Chronic inflammation results in joint pain, stiffness, and swelling, which over time can lead to cartilage damage and joint destruction. With its prevalence estimated to around 0.5-1% in western countries, it is the most common inflammatory arthritis.(4) Symptoms of RA can vary considerably through time with periods of relative normalcy followed by "flares": periods of unrelenting symptoms, such as pain or fatigue. Due to its chronic and fluctuating nature, RA requires continuous management of care and often life-long medication use, resulting in a myriad of clinical follow-up visits and frequent contacts with multiple health services. Timely management of worsening disease activity is key for improving patient outcomes, further emphasising the need for repeated and accurate clinical assessments.

1.2 Patterns of disease in rheumatoid arthritis

Before going into further detail with fluctuations and flares, I will briefly outline the most common symptoms, other subjective experiences and related consequences experienced by people living with RA.

1.2.1 Joint swelling and stiffness

Joint swelling - or synovitis - is inflammation of the synovial membrane that lines the joints. Synovitis results in swollen, tender and warm joints that can limit joint movement. Joint stiffness can be caused by inflammation of structures in and around the joint, which leads to an increased amount of synovial fluid within the joint. Morning stiffness is a cardinal symptom of RA that can last for more than an hour every day.(5) Measuring inflammation in the clinic relies on assessment of tenderness, swelling, warmth and redness using observation and palpation by a skilled clinician, which are part of established measurement of disease activity. In the wake of the COVID-19 pandemic and the rapid shift towards remote models of care, efforts into teaching patients to do joint assessments themselves have emerged as a useful addition to traditional clinical assessment.(6)

1.2.2 Pain

People living with RA frequently identify pain as their main struggle, one that often persists despite optimal control of inflammatory disease.(7) RA pain may be constant or intermittent, localized or widespread, and can be associated with psychological distress, can impair physical and social functioning, and can increase health-care utilization.(8) RA pain is complex, but inflammation, peripheral and central pain processing and structural change within the joint itself each play a contributing role as do psychosocial and social processes.

1.2.3 Fatigue

RA fatigue is often as disabling as pain. Qualitative studies have showed that fatigue is experienced by patients as a multidimensional, unpredictable, bothersome symptom with far-reaching consequences for everyday life.(9) Patients make a clear distinction between their systemic RA fatigue and "normal" everyday tiredness as fatigue is not necessarily preceded by physical activity and it does not always resolve with rest.(10) Professional support for fatigue is rare and patients who choose to discuss fatigue with their clinician tend to feel it is dismissed.(10) Despite the perceived importance of fatigue, the symptom's prognosis remains poorly understood and poorly managed, although telephone-delivered cognitive behavioural approaches and personalised exercise programmes recently proved promising in reducing severity and impact of fatigue.(11,12)

1.2.4 Sleep disturbances

Sleep disturbance is another important and well-documented concern for people living with RA. Patients report difficulty falling asleep, poor sleep quality, and feelings of non-restorative sleep. Like fatigue, treatment of this specific symptom remains a challenge. Consequences of impaired sleep are many, including exacerbated inflammation and inflammation-related symptoms such as pain, mental and physical fatigue, mood disorders and poor quality of life.(13,14)

1.2.5 Functional disability

Functional disability refers to acquired difficulties with performing everyday activities, such as dressing, eating, and walking. Specifically for RA patients, difficult tasks might include doing buttons, opening jars, reaching above the head, or getting up from a chair. Some patients will require support from aids or devices (such as a cane or crutches) and few will physically depend on help from others. It remains a common problem among RA patients, although it appears that under current more aggressive treatment strategies the disability prognosis may be better than it was previously.(15)

1.2.6 Quality of life

Partly as a result of the high symptom burden, RA has a profound impact on health-related quality of life. People suffering from RA report a lower quality of life than those with type 2 diabetes, myocardial infarction and hypertension on both physical and mental components (measured using the Medical Outcomes Study 36-item Short-Form Health Survey).(16) Data from longitudinal, observational studies have shown that health-related quality of life increases with improved disease control, yet it remains lower among those with well-controlled RA compared to the general population.(17)

1.2.7 Work capacity

Despite much improved treatment strategies, many patients with RA still have to take sick leave or stop working because of their RA. If remaining in paid work, patients may experience problems due to their RA resulting in productivity loss while at work.(18) Boonen et al. described that work productivity can be seen as a spectrum *"starting with*

normal productivity and progressing through presenteeism (reduced productivity at work) and temporary absence (short- and long-term sick leave) to permanent absence from work (official work disability, early retirement, and voluntary stopping of work)".(19) The disease's impact on work productivity is costly to both patient and society.

1.2.8 Flares

Like other inflammatory conditions, RA is characterised by a pattern of fluctuating symptoms. This section considers in more detail how the above symptoms and experiences of disease change through time. Despite the therapeutic advances that have been made in treating RA and more ambitious treatment targets, patients still experience debilitating episodes of worsening symptoms - even for those who at other times may be in clinical remission (i.e. low disease activity). This worsening is generally referred to as a flare.

Flares from the patient-perspective

Flares generally represent a significant burden on patients. One qualitative study described the experience of living with RA from the patient perspective as moving back and forth along a continuum (see Figure 1.1); from living with RA in the background to living with RA in the foreground of their lives.(20) When RA is in the background, patients are aware of their continuous daily symptoms, which they aim to micromanage themselves. With RA moving into the foreground, patients experience unpredictable, fluctuating, exacerbating symptoms that may lead to a flare. Finally, dealing with RA in the foreground shows how patients attempt to regain control and manage their flare as it takes hold, seeking medical help only when their self-management and coping strategies can no longer contain the increasing symptoms and they feel that they are losing control. From this description, it is clear that flares matter to patients, and thinking about flares as one end of a continuum of living with RA serves as a helpful framework for better understanding flares and symptom fluctuations.

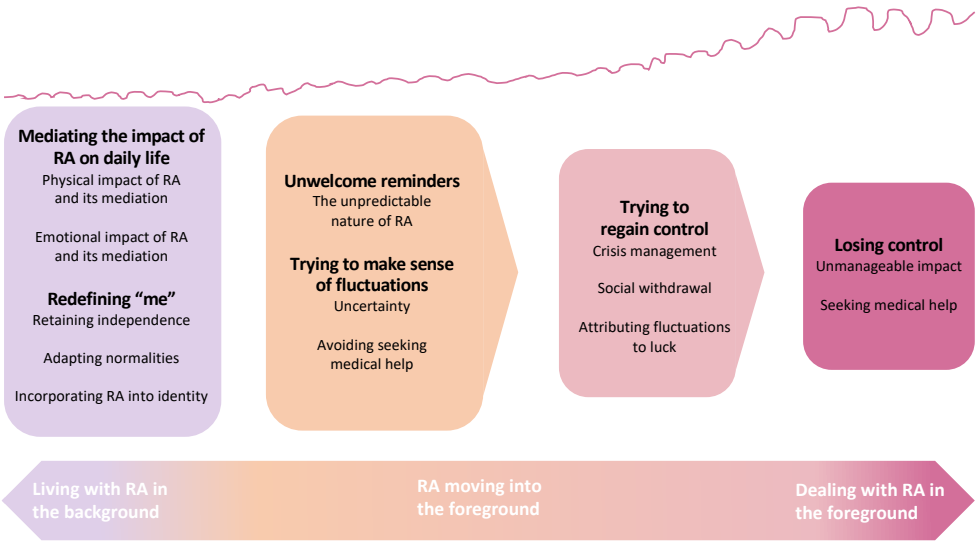

Figure 1.1. *Patients' experience of living with RA. Trying to maintain a balance while dealing with fluctuating RA symptoms and flares. Reproduced from Flurey et al. (2014) with permission from Oxford University Press and the author.*

Relation between flares and clinical and patient-reported outcomes

In addition to being burdensome for the patient while present, flares have been shown to worsen long-term clinical outcomes such as radiographic progression, functional deterioration, and worsening cardiovascular comorbidity. Due to the lack of a standardized definition of flares, these studies have used a range of different flare definitions described in Table 1.1.

Using three different disease activity score (DAS)-based flare definitions measured every three months for 10 years, Markusse et al. found that during a flare, functional ability decreased and patients reported higher scores for disease activity, pain and morning stiffness. Joint damage progression (measured yearly) occurred more often when a patient experienced a flare during that year. (21) Additionally, they found a dose-response effect between the number of flares and the degree of long-term functional disability and joint damage.

Kuettel et al. found a higher incidence of radiographic progression and functional impairment in flaring RA patients with low disease activity at baseline, confirming earlier findings.(22,23) They used a patient-reported flare definition, and asked patients to recall flares retrospectively once a year over two years of follow-up.

Flares have also been linked to an increased risk of cardiovascular disease. Using a less common clinician-focused flare definition, Myasoedova et al. reported a 7% increase in risk of cardiovascular events with the exposure to each acute flare.(24)

Despite diverse flare definitions and measurement intervals, these findings indicate an association between flares and worse outcomes. This, in turn, suggest important clinical outcome benefits of keeping patients free from flares, by identifying flares early and offering timely management and tight control of disease activity.

Early identification of flares

People suffering from migraines often describe that symptoms such as fatigue, visual and sensory aura and changed mood precede the headache phase. These symptoms can, with experience, act as a warning that an attack is imminent. RA does not have a similar recognised, well-described early "warning" sign or prodromal phase prior to a flare. That said, a qualitative study in 67 RA patients described that some participants noticed early warning signs of an impending flare, particularly flu-like symptoms, fatigue, and pain in specific joints.(25) Further longitudinal research needs to capture RA symptoms and flares prospectively to better quantify and characterise both the period of time leading up to a flare and the flare itself. Early identification, even prediction, of a flare or identification of a pre-flare period based on patient-reported symptoms might provide an opportunity for a timely intervention to either prevent or reduce the impact of a larger flare (see next section). Because of the apparent impact on clinical outcomes described in previous sections, identifying and predicting flares is of direct relevance to clinical practice.

Flare management strategies

There are differences in patients' needs along the spectrum of disease activity and flare, as shown in Figure 1. People with RA use a range of individual strategies to manage their intensifying symptoms and reduce their impact on their daily lives. These might include self-management with rest, pacing activities, avoiding known triggers, applying heat/cold, use of assistive devices (brace, canes), and escalating medications such as non-steroidal anti-inflammatory drugs (NSAIDs).(25,26) Patients also seek assistance for daily activities from relatives. Seeking medical help from a clinician, on the other hand, is often described as a last resort when self-management and coping strategies can no longer contain the worsening symptoms.(20) Effective pharmacological strategies for rapidly managing a flare and reducing their impact largely rely on steroids. Steroids are often used to try to quickly

bring a flare under control. If only one or few joints are involved, a steroid can be given by injection (such as depomedrone), otherwise it can be taken orally (such as prednisone). However, steroids can have significant side effects in the longer term, so it should generally be used with care to balance benefits and harm. If flares are significant or continue to occur, it indicates that the patient's regimen of maintenance medication is not adequate. This may lead to addition of a medication, switching one drug for another or increasing the dose of medication that the patient is currently taking.(27)

Defining flares in clinical practice

In order to identify a flare early and intervene, it is crucial to measure a flare accurately. Various definitions have been adopted to try to measure flares in clinical practice. These definitions consists of different components such as inflammatory biomarkers, joint counts, patient-reported symptoms and treatment modifications. Overall, four broad categories of definitions emerge: composite disease activity score-based flare, patient-reported flares, clinician-reported flares, and combined flare definitions - see Table 1.1 for an overview of various flare definitions and examples, adapted from Bozzalla-Cassione in (28). This suggests that patients and clinicians define flares differently: patients may focus on changes in subjective aspects, such as pain, mood disturbance and the need to seek help.(25) Clinicians are more likely to (also) consider changes in more objective aspects of RA, such as blood tests and formal disease activity measurements, to inform treatment decisions.(29) Additionally, flares are mainly assessed through questions asking about recall of symptoms over a longer period or since the last visit or assessed in the moment of the clinical encounter. Despite the substantial interest in RA flares, there is at present no standardized definition available, so being clear about which components of flare one wishes to explore is essential. For this thesis, I am interested in the symptom component, and I will therefore employ a pragmatic patient-based flare definition in the following chapters.

Table 1.1*. Rheumatoid arthritis flare definitions adapted from Bozzalla-Cassione et al. in (28)*

Flare definition	Components	Examples
Patient-based flare	- Symptoms - Patient judgment	- "Has your disease flared up since the last assessment?" (30) - "During the past 6 months, have you had a flare in your RA?" (26) - "Are you experiencing a flare of your RA at this time?" (31) - "Over the last 3 months, did you experience symptoms suggestive of disease exacerbation?" (32)
Clinician-reported flare	- Clinician judgement - The necessity of treatment modification	- Worsening of signs and symptoms of sufficient intensity and duration to lead to a change in therapy (33) - Clinician's intention to treat (34)
Composite disease activity score-based flare	- Joint counts - Patient-reported outcomes (e.g. a patient global assessment) - Biomarkers of inflammation (CRP or ESR)	- ΔDAS28 > 1.2 (35) - ΔDAS28 > 1.2 or >0.6 if the final DAS28 ≥ 3.2 (36) - ΔDAS28 > 0.6 and DAS28 > 2.6 (32)
Combined flare definition	- Combination of the above	- RA Flare Questionnaire (OMERACT) (37) - FLARE-RA Questionnaire (38) - ΔDAS28 ≥ 1.2 or ≥ 0.6 if final DAS28>3.2 OR Investigator's judgment of flare (39)

DAS28, disease activity score on 28 joints; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OMERACT, Outcome Measures in Rheumatology; TJC, tender joint count; SJC, swollen joint count.

Section summary

RA is characterised by a myriad of unpredictable and debilitating symptoms and frequent flares that interfere with daily living, quality of life and working capacity. Recurring flares can increase the risk of radiographic progression, disability and cardiovascular disease. Because of the apparent impact of flares on both clinical and patient-reported outcomes, timely identification, and possibly prediction, of flares is of direct relevance to clinical practice, allowing for early management, better disease control and avoidance of poor long-term outcomes. The current assessment of flares, however, relies on a range of different definitions, many of which rely on recall and none of which include real-time assessment of the time-varying symptoms that are a direct consequence of the flare.

1.3 How rheumatoid arthritis outpatient care currently works

In this section, I will review the clinical management strategies of RA and explain some pitfalls of the current model of outpatient care.

1.3.1 Diagnosing RA and treating to target

Diagnosing RA is a highly specialised and individualized process led by the rheumatologist, in part because it is a clinical diagnosis rather than a condition that has a definitive diagnostic test as seen with other diseases like diabetes or cancer. At present, there are no diagnostic criteria for RA. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have proposed classification criteria, meant to identify patients for clinical studies and trials rather than supporting clinical diagnosis.(40) The classification criteria include symptom duration, number and distribution of affected joints, serological parameters such as presence of autoantibodies (rheumatoid factor and anti-citrullinated protein antibodies) and acute phase reactants (C-reactive protein and erythrocyte sedimentation rate). These classification criteria – nonetheless – do give a clear sense of factors involved in the clinical diagnosis of disease.

Rapid referral to specialist care of patients with suspected RA is important to avoid delay in diagnosis and treatment initiation. In the UK, following National Institute for Health and Care Excellence (NICE) quality standards, adults with suspected RA should be referred to specialist early inflammatory arthritis clinics within three working days of presenting in primary care.(41) Following a rheumatologist's diagnosis of RA, the current management strategy follows a quickly initialised treat-to-target approach based on tight monitoring of disease activity and change of treatment if the treatment target is not reached.(27,42) The treatment goal is remission or at the very least low disease activity if remission cannot be attained. An effective treat-to-target approach relies on frequent monitoring of disease activity and prompt treatment adaptations, as discussed below.

1.3.2 Measuring disease activity

Other LTCs benefit from having readily measurable markers that reflect disease activity. However, RA does not (yet) have a single, specific marker that can be used to monitor disease activity. Instead, there are several composite scores available to measure clinical disease activity, some of which I have touched upon already when discussing flares (see

1.2.8). For my thesis, I will focus on the Disease Activity Score modified for 28 joints (DAS28 score), acknowledging that other well-validated measures exist such as the Clinical Disease Activity Index (CDAI). The DAS28 is the most widely accepted outcome measure in Europe in both observational studies and trials and it is widely used in UK practices since it defines the threshold for access to biologic therapies. The DAS28 score is calculated from a formula that includes tender joint counts (out of 28 joints), swollen joint counts, ESR or CRP and a patient global assessment of health measured on a 0-10 cm scale (very good to very bad). The component variables are transformed and weighted, resulting in relatively high importance of tender joints and acute phase reactants.(43) A DAS28 of greater than 5.1 implies high disease activity, less than 3.2 low disease activity, and less than 2.6 remission.

1.3.3 Outpatient consultations

RA is managed through clinical outpatient consultations. Generally, outpatient consultations follow a model that has been largely unchanged for centuries.(44) Prior to the consultation, a clinician reviews the referral letter or past visit notes. The consultation proceeds with history taking, examination and investigations. This sequence is repeated at subsequent follow-up appointments. The clinician's primary goals are to gather sufficient information to assess disease severity and treatment response to guide management. At the same time, patients hope that consultations allow them to explain their concerns, so clinicians can guide them towards better health and wellbeing. The consultation should answer questions and support shared decision-making, treating patients with respect and dignity, while paying attention to their emotions. Figure 1.2 presents the structure of a typical RA outpatient consultation.

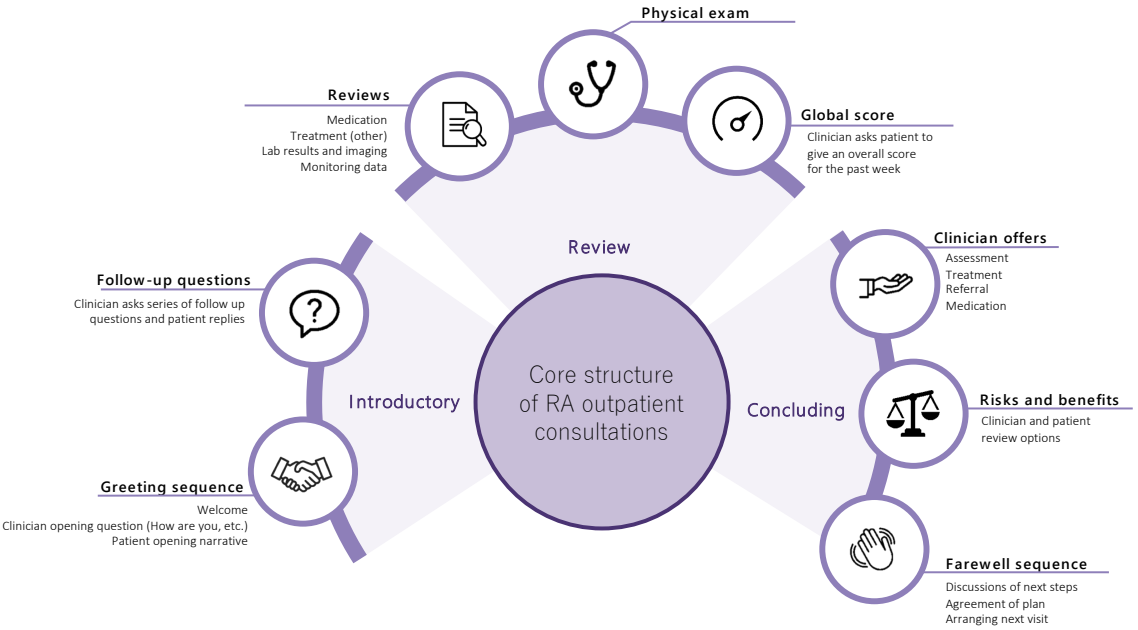

Figure 1.2. *Structure and steps in a typical rheumatoid arthritis follow-up outpatient consultation. Outpatient consultations are normally scheduled every 6-12 month and last 15-20 minutes.*

In patients with active RA, disease activity should be assessed every 1–3 months at a clinical outpatient consultation. Once the desired treatment target is achieved, less frequent follow-up (usually every 6–12 months) is recommended.(45)

The clinician's initial assessment of disease activity relies on the patient's report of current, recent and not-so-recent symptoms and flares. However, the fleeting nature of the disease means that it is not unusual for symptoms to be absent when the patient sees their clinician. Answering the rheumatologist's question "*How have you been since your last visit?*" is challenging for patients, because it asks them to recall flares and accurately describe symptom fluctuations over a long period, typically 6 to 12 months. Additionally, consultations are often short and time-pressured. An accurate picture can further be obscured by patients' willingness to discuss symptoms, eloquence, recall, stoicism, the influence of recent disease severity, and much more. Therefore, the data collected from the patient during these visits provides only a few isolated snapshots that may not be representative of patients' health as experienced in the routine course of daily life. The objective measures of disease severity like DAS28 only measure what is happening that day, thereby missing any disease states between visits. Clinician-related factors, such as tight schedules and running late, can also influence the consultation, making efficient elicitation and collation of pertinent patient information challenging. This means that clinical

management decisions often are made using information that is incomplete or incorrect; in turn, this may lead to missed opportunities to optimise disease management. Finally, disease activity assessments can only be carried out at the time of (often infrequent) appointments, risking late identification of worsening and hence late initiation of relevant interventions and treatments. As we saw in the previous section, there is evidence that flares impact on clinical outcomes. This suggests the need for a better way of monitoring disease activity with higher data collection frequency in between sporadic visits to ensure optimal adherence to the treat-to-target approach and hence better outcomes.

Section summary

> Infrequent RA outpatient consultations may hamper optimal disease management. Shared decision-making by clinicians and patients is often based on an incomplete and potentially incorrect picture of how a patient's disease has changed since they were last seen, which may lead to inaccurate assessments and suboptimal management of disease activity. A clearer picture of how disease activity changes through time through higher frequency data collection (e.g. daily or weekly) could improve accuracy of assessments, but current models of clinical care do not support this.

1.4 Understanding symptom fluctuations and flares through research

In the previous section, I described how clinical management of RA aims to control disease activity, avoid flares and sustain remission. Suboptimal management of flares remains a hurdle in optimizing outcomes despite the availability of more effective treatments and treat-to-target approaches. Flares are often both unpredictable and debilitating and a better understanding of flares and characterisation of the natural history is therefore important to both patients suffering from RA and their clinicians.

Our current knowledge of symptom fluctuations and flares is primarily based on research studies asking people living with RA to recall a history or prior experience of flares or fluctuating symptoms. Most of this research is done in traditional longitudinal cohorts and registers, which was the case with many of the clinical outcome studies described in the previous section. In terms of understanding disease fluctuations, these types of studies have

some important limitations. As in clinical practice, data collection for research is often equally sporadic, mostly ranging in frequency from once every three months to once every year, usually asking patients to recall past flares. As I have highlighted before, this retrospective characterization of flares is subject to recall error and may not provide an accurate picture of the lived day-to-day reality.(46,47) This limits our ability to detect short-term, e.g. day-to-day, variations in disease severity, resulting in potentially underestimating the true prevalence of flares, in particular short-lived ones. Additionally, it hampers further quantitative research into the characteristics, underlying mechanisms, and impact of RA flares, which leads to important research gaps. These include questions around frequency and duration of flares, exploring flares as the exposure (e.g. do more flares lead to worse outcomes?) and exploring flare as the outcome (e.g. what causes flares, does a certain treatment lead to fewer flares?). Predicting flares reliably relies on being able to accurately measure both the onset of flare and the time-varying things preceding the flare (the predictors) e.g. patient-reported symptoms. This is also not possible using traditional methods, which measure these variables sporadically.

One example is trying to estimate the frequency of self-reported flares: a cohort of Danish RA patients in remission or low disease activity at baseline reported a prevalence of self-reported flares of 36% when asked '*Are you experiencing a flare of your RA at this time*?' at 3-month intervals.(48) This was slightly lower than an observational study in established RA in a US cohort, where the frequency of self-reported flares ('*During the past 6 months, have you had a flare in your rheumatoid arthritis?*') ranged from 54 to 74% when asked at 6-month intervals.(49) In the UK, 90% of 612 RA patients not on advanced therapies reported to have had a flare in the last 12 months, and 23% indicated having experienced six or more flares.(50) Even with heterogeneity in anchor questions to detect flares, periods of recall and in the patient populations, previous work suggests that self-reported flares are common, but the assessments are far from ideal and hampered by the limitations outlined above.

Section summary

> The current model of research into patterns of symptom fluctuations and flares in RA is, like clinical care, hampered by infrequent data collection. This limits our understanding of three vital areas in relation to fluctuating symptoms and flares: 1) The ability to describe day-to-day changes and better characterise the natural history of disease including

frequency of flares, 2) the ability to examine associations, and ultimately causal relationships, between time-varying variables and flares, and 3) the ability to predict a flare.

1.5 Smartphones, patient-generated health data and remote monitoring

We have now laid out the shared problem of clinical management and longitudinal research in RA relating to symptom fluctuations and flares: both are hampered by sporadic data collection. It is plausible that availability of a patient-friendly solution that allows for much more frequent data collection as part of day-to-day life could enhance both clinical care and research. This section highlights such a common solution, which harnesses consumer technologies and patient-generated health data.

1.5.1 Opportunities from smartphones

Digital consumer technologies such as smartphones and wearables are becoming increasingly pervasive. In 2021, smartphone penetration reached nearly 90% among UK adults (16+).(51) While this number has been increasing steadily over the past ten years in all age groups, smartphone ownership among people aged 55 and above jumped from 51% in 2018 to 83% in 2021, indicating that smartphones are becoming ubiquitous among older age groups as well.

As such, smartphones may offer a unique opportunity to overcome some of the challenges raised above by enabling patients to briefly report their symptoms regularly, integrated into their daily lives. This will be explored in more detail in the following sub-sections: first for clinical care and then for research.

1.5.2 Patient-generated health data

With smartphones becoming ubiquitous, unique opportunities to collect digital health data directly from patients have emerged. Key features of such digital 'patient-generated health data' (PGHD) are that the patient, not the healthcare provider, captures the data, and that the data are obtained outside of clinical settings. Therefore, there is an opportunity for the data to be collected longitudinally and, importantly, with high frequency. The US Office of the National Coordinator for Health Information Technology (ONC) more specifically

defines PGHD as "health-related data - including health history, symptoms, biometric data, treatment history, lifestyle choices, and other information - created, recorded, or gathered by or from patients (…) to help address a health concern."(52) This includes patient-reported data gathered through questionnaires and data generated from remote monitoring devices, such as mobile health apps and wearable devices. From the ONC definition, it is clear that PGHD constitutes a plethora of data categories, but for the purpose of my thesis, I will focus on the use of patient-reported outcomes (PROs), primarily patient-reported symptoms. The US Food and Drug Administration defines PROs as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."(53)

1.5.3 Potential benefits of PGHD for clinical care

Patients spend over 99% of their time outside of the clinical environment. Smartphones allow PGHD to be collected in real-time from patients in their daily environments. They are small, carried everywhere, and used intensively. To quantify this, the UK adult internet users spent more than three and a half hours online a day in 2020.(54) This opens up opportunities for remote monitoring of RA symptoms in the time in between clinic visits.

If collected frequently between visits and displayed as trends over time during the consultation, benefits of remotely collected PGHD for clinical care are many: having longitudinal PGHD available can support the patient's recall of past symptom fluctuations (or even tell the story for them) rather than requiring them to summarise a large part of their life in the few minutes available. Upon inspection, the data might reveal changes in disease experience not currently considered or show patterns of symptoms or flares that otherwise would have remained hidden and therefore missed.(55) When interpreted and used as a foundation for the conversation, it can help to improve patient and clinician communication,(56) thereby potentially improving shared clinical decision-making. All of these things contribute to a clearer, more holistic and complete picture of disease through time compared to traditional consultations. Because clinical decisions are based on assessment of disease severity and prior treatment response, having more accurate PGHD available from remote monitoring is envisioned to lead to more optimal disease management decisions, thereby leading to better disease control and potentially improved outcomes.(57) Appendix 9.1.1 provides a simplified logic model for how a remote symptom-monitoring intervention using a smartphone app might change patient outcomes.

The transition from collecting discrete episodes of data in a clinical setting where patients spend little time, to a model where patients collect digital PGHD more continuously in the context of their everyday lives could ultimately guide future models of care. These models could embrace patient-initiated follow-ups,(58) clinical prioritisation (patients who may require a review versus possibly reduced appointment frequency for stable patients), or prediction and more timely management of imminent flares through just-in-time interventions. Many of these models, however, rely on data being (automatically) monitored between visits rather than only supporting the conversation during the visit, and developing the algorithm to do this may be challenging.

1.5.4 Greater impact by integrating PGHD into electronic health records

In order to have the greatest impact on patient care, PGHD need to be presented and be actionable at the time of the clinical decision.(59,60) The clinician's go-to tool during outpatient consultations is increasingly the electronic health record (EHR). In there, all vital information about diagnoses, treatments, investigations and previous visits is stored. The most optimal way of ensuring impact, is integrating PGHD directly into the EHR.(59) This gives clinicians access to the right information at the right time without the hassle of logging into and switching between external systems (such integration is also known as 'single sign-on'). Technically, integration means that the PGHD is added to a patient's health record manually or transmitted automatically into the EHR, often via a third-party vendor. Depending on the data type and EHR capabilities, the data is stored either in structured data fields or as free (or unstructured) text. PGHD stored in structured data fields can be used as the basis for a visual longitudinal dashboard ideally allowing tracking over time in relation to other clinical information available in the EHR (e.g., laboratory tests and medication). A published opinion piece that I wrote (see Appendix 9.1.2) describes a vision for this in more detail.

While using smartphones to collect PGHD outside of clinics is promising, the ability to successfully transfer the data to EHRs, and use it effectively in clinical settings poses many challenges. According to the ONC, technical challenges include concerns about managing and making sense of the continuous stream of large quantities of data, questions about the accuracy of PGHD measurements, user authentication risks, undeveloped interoperability standards, data provenance issues, and gaps in privacy and security protections.(61) For patients, challenges remain in lack of access to technology in some age groups, high drop-

off rate in app usage, perceived lack of value, and digital literacy. Clinicians may encounter several challenges in using PGHD, such as the impact on already complicated and overstretched clinical workflows, the management of patient expectations, the potential for increased liability, and the limited body of evidence for the clinical value of PGHD.(60) Progress in all (or at least in the vast majority) of these areas is essential to achieving the envisioned future benefits of PGHD.

Finally, successful integration of PGHD into clinical care would mean that large datasets of routinely collected data were available for secondary research uses. The next section describes the benefits of PGHD for longitudinal research.

1.5.5 Benefits of PGHD for longitudinal research

Smartphones enable PGHD collection in everyday settings, rather than in the context of a clinical or research visit. They eliminate the need to fill out paper-based or internet-based questionnaires at inconvenient times or carry around research loan devices. Apps for data collection can be developed by researchers, downloaded remotely by participants and data transfer can happen automatically. This results in a relatively low burden on the participant in the study and hence may allow for longer data collection periods and easier recruitment of larger cohorts. Moreover, smartphones can facilitate a higher sampling frequency, e.g. hourly, daily or weekly, thus allowing novel timescales to be studied such as between and within-day changes in disease fluctuations. This was recently done in axial spondyloarthritis, another chronic inflammatory disease, which like RA is characterised by fluctuating periods of flare and remission.(62) The authors explored daily self-reported experiences of axial spondyloarthritis flares using a smartphone app and identified two clusters of participants with distinct flare profiles. Similar work was recently published in myositis.(63) In addition to patients actively entering self-reported data, embedded sensors can be used to passively collect data on behaviour and/or environment. Sensors can further help alleviate the patient from having to enter data into an app manually and eliminate recall bias. For example, Gossec and colleagues predicted weekly patient-reported flares based on passively collected step counts from fitness trackers worn by 155 patients with RA and axial spondyloarthritis. Using machine learning processing, they found that patient-reported flares were strongly linked to physical activity in both patient groups and that patient-level physical activity data can be used to detect self-reported flares with great accuracy.(64)

Overall, smartphones enable larger-scale, longer studies that collect more granular data about exposures and outcomes on the individual level, usually also incurring lower costs than traditional studies through their easy scalability. Examples worth highlighting are the *Cloudy with a Chance of Pain* study(65) and the more recent COVID Zoe app. *Cloudy* was a national smartphone study in 2016 that aimed to collect a large dataset to examine the relationship between local weather and daily pain in people living with long-term pain conditions. The study recruited over 10.000 participants and analysed daily data and GPS data collected over a 15-month period, delivering on the promise of how consumer technology can support health research at scale. More recently during the pandemic, the COVID Zoe app recruited over 4 million participants in the UK, providing novel and timely insights into the distribution and symptoms of disease, convincingly identifying anosmia as a characteristic symptom of COVID and changing government advice.(66)

1.5.6 Collect once, use twice (or multiple times)

The Cloudy study described above collected data just for research purposes in patients with RA and other long-term pain conditions. As the self-reported data required for RA care and research overlap, it is plausible that we might collect this data once and use it to support both purposes. While I will focus on data for clinical care and longitudinal research, additional purposes might also benefit from collection and aggregation of PGHD, including but not limited to quality/service improvement, audit, benchmarking and commissioning.(67) To generate a sustainable pipeline of data for multiple purposes we need to "*consider ways to reduce inefficiencies in data acquisition: a harmonised approach to the selection, collection, analysis, and reporting of PROMs, integration into the electronic health record, and guidance on the optimal presentation and use of data*."(67) The challenges of fragmented data collection are surmountable, but examples are still limited.

Section summary

Patients can contribute digital health data (PGHD) from their smartphones with frequent data collection integrated into daily lives. Insights into day-to-day health can feed into their clinical care and management (especially if integrated into the EHR) and be used for longitudinal research, solving the problems with infrequent data collection for both purposes. Smartphones therefore make it possible to capture and characterise day-to-day

variations in symptoms and occurrence of flares in real time, instead of relying on patient recall at the discrete intervals of traditional research or at infrequent clinical appointments. Collecting PGHD once and using it for both purposes is challenging, but nonetheless possible, as we will see in the forthcoming section.

1.6 REMORA as the case study

My PhD builds on the results and continued work on the Remote Monitoring of Rheumatoid Arthritis (REMORA) programme.(55) The programme has several stages, which I will briefly outline below (see Figure 1.3). The REMORA programme enables people living with RA to report eight daily symptoms (such as pain, fatigue and emotional well-being) using a bespoke smartphone app with data integrated into the EHR. Ultimately, REMORA aims to solve the issues mentioned until now, materialising the ideas that were put forward in the previous section.

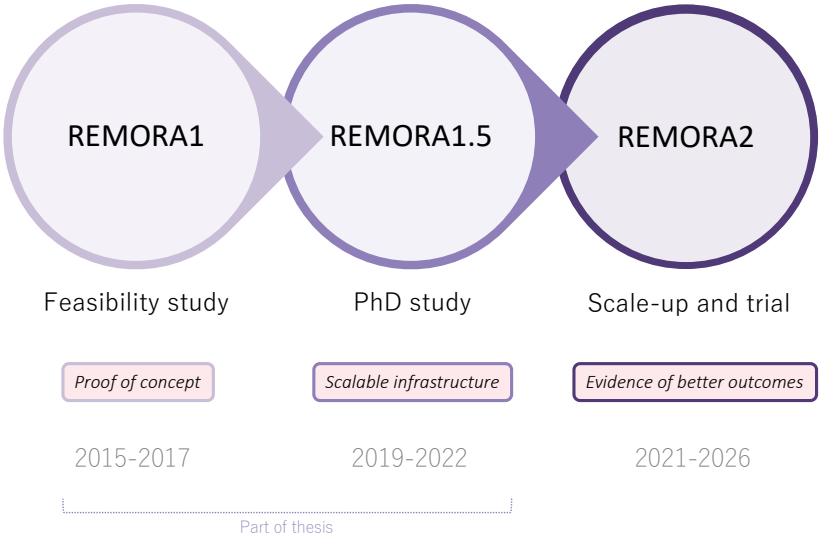

Figure 1.3. *The three stages of the Remote Monitoring of Rheumatoid Arthritis (REMORA) programme, including overall aims, time periods and which stages contributed to this thesis.*

1.6.1 REMORA1 - Proof of concept

The objective of the proof of concept study was to evaluate the system's acceptability and feasibility including exploration of participants' views and experiences of remote monitoring, with specific focus on how integration of smartphone data into the EHR in graphical format influenced consultations.(55) Following co-design of the REMORA app, it was tested in a small, selected group of 20 patients and two rheumatologists at Salford Royal NHS Foundation Trust (SRFT) over a three-month study period. The results showed, impressively, that participants tracked daily symptoms on >90% of all days. Participants viewed the intervention positively, with regular symptom reporting identifying changes in condition that would otherwise have been missed, and promoting shared conversations about disease management. Overall, REMORA showed a strong proof of transformative potential of integrating PGHD into clinical practice. At the same time, it generated a rich quantitative dataset of daily symptoms as well as qualitative data from interviews with stakeholders and audio-recordings of clinic visits. This data is the foundation for Chapters 2, 3, 5 and 6.

1.6.2 REMORA1.5 - Scalable infrastructure

An integrated remote monitoring system is more than just an app. To develop the programme further, it was necessary to develop a scalable end-to-end technical infrastructure to allow the system to be implemented more widely at a later stage, rather than having a bespoke solution for a single clinic. As part of the scalability effort, patients needed to be better supported to download, log in and start using the app independently, so it was essential to develop robust patient supporting materials. Similarly, clinicians needed to be supported in finding and using the patient-reported data, and a new and much improved interactive EHR dashboard displaying the data was designed. The new infrastructure was developed then tested in an observational study aiming to recruit 50-100 patients, which formed a large part of this PhD. The aims, setup and insights from the study will be described in Chapter 4.

1.6.3 REMORA2 - Scale-up and robust trial

As explained in this chapter, remote symptom monitoring integrated into clinical care has substantial potential. However, the expected benefits are currently only supported by a

limited body of evidence that rarely involves rigorous evaluations.(68) Therefore, the next phase of the REMORA programme aims to robustly evaluate the benefits of remote monitoring on outcomes such as disease activity scores through a cluster stepped wedge trial involving multiple rheumatology outpatient departments across Greater Manchester and North London. The trial focuses on assessing improvements in clinical outcomes, a health economic evaluation, learnings about implementing at scale and a better understanding of barriers to digital inclusion. REMORA2 is not a part of my thesis, but learnings from REMORA1.5 informed the design and many aspects of REMORA2.

1.7 Aims and objectives

The overarching aim of my PhD is to examine how digital PGHD can advance clinical care and research in long-term conditions, through the example of RA. More specifically the scientific objectives are to:

1. Describe the current state of the art of EHR-integrated remote symptom monitoring systems in the field of long-term conditions by systematically reviewing the literature;

2. Understand how PGHD can be used in RA clinical consultations and how it may affect interactions between patients and clinicians,

3. Examine patterns of RA symptoms, including flares, over time using PGHD;

4. Investigate the feasibility of predicting self-reported RA flares based on daily PGHD and consider how this can inform new models of care

I will explore objective 2-4 using stage 1 of the REMORA programme. In parallel, the thesis considers some of the practical challenges in setting up a mobile health research study to which I significantly contributed through the course of my PhD (REMORA1.5).

1.8 Note on journal format of thesis and thesis structure

My thesis is presented in journal format, allowing for the inclusion of chapters that are suitable for submission for publication in a peer-reviewed journal. I believe that the results from my thesis are relevant and of interest to the wider academic community as well as for clinicians and patients, and dissemination through publications seemed like a natural choice. Additionally, this has enabled me to develop further my academic writing skills.

In order to meet the research objectives, the thesis is divided into seven chapters. The majority of the chapters follow the journal format. They start with a brief introduction that describes how the chapter fits into the thesis and corresponds to the research objectives, followed by a contribution statement, which briefly outlines my contribution to the work. The published papers have separate reference lists. Chapter 2 and 3 are about using PGHD to support clinical care. They are followed by Chapter 4, which describes the setup of a new phase of the REMORA study (not in journal format to allow more flexibility). Chapter 5 and 6 then concern the use of PGHD for longitudinal research about symptom patterns in RA. The thesis ends with a discussion, which draws conclusions and makes recommendations for clinical care and future research.

Chapter 2, 3 and 5 have already been published in peer-reviewed journals and Chapter 6 is in review. The first-author Commentary in Appendix 9.1.2 is also published.

2

Review of EHR-integrated symptom monitoring systems in long-term conditions

2.1 Introduction

Before designing and setting up REMORA1.5, it was useful to systematically review which systems already existed that collected self-reported symptoms remotely and described the use as part of clinical care. I was not aware of other comprehensive reviews that addressed this, so it would provide an opportunity to assimilate lessons learned, which could inform the future development of the next phase of the REMORA programme. Collection and use of patient-reported symptoms in clinical care have many benefits, as outlined in the introduction, but most of the evidence supporting this comes from non-EHR integrated systems, so I was also interested in exploring what the level of evidence was to support EHR-integrated symptom monitoring.

I did not limit the search to systems in rheumatology only, as I quickly recognised that there were close to no published examples. Instead, I searched across LTCs more broadly, as learnings from one LTC most likely would be applicable to other LTCs, given their similarities in care paths and disease course.

The aim of this chapter was therefore to map the landscape of EHR-integrated remote symptom monitoring systems in the field of LTCs. Objectives were to:

1. Characterize state of the art systems,
2. describe their use in clinical settings, and

3. outline the anticipated and realized benefits.

2.2 Contribution statement

I developed the research objectives for the systematic review with input from my co-authors. Guided by an experienced research librarian within the Centre, I developed the search strategy and ran it in three electronic databases. A colleague acted as second reviewer and together we screened titles, abstract, and full-text articles and eventually included 12 studies for review. I extracted data, synthesised it, and assessed the quality of included studies following frequent discussions with my co-authors. I finally drafted the manuscript, iterated it based on extensive feedback and submitted it for publication. The manuscript was published in Journal of the American Medical Informatics Association (*JAMIA)* in 2020.

2.3 Article 1: Remote symptom monitoring integrated into electronic health records: A systematic review

Journal of the American Medical Informatics Association, 0(0), 2020, 1–12
doi: 10.1093/jamia/ocaa177
Review

Review

Remote symptom monitoring integrated into electronic health records: A systematic review

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Received 7 May 2020; Editorial Decision 9 July 2020; ; Editorial Decision 9 July 2020; Accepted 22 July 2020

ABSTRACT

Objective: People with long-term conditions require serial clinical assessments. Digital patient-reported symptoms collected between visits can inform these, especially if integrated into electronic health records (EHRs) and clinical workflows. This systematic review identified and summarized EHR-integrated systems to remotely collect patient-reported symptoms and examined their anticipated and realized benefits in long-term conditions.

Materials and Methods: We searched Medline, Web of Science, and Embase. Inclusion criteria were symptom reporting systems in adults with long-term conditions; data integrated into the EHR; data collection outside of clinic; data used in clinical care. We synthesized data thematically. Benefits were assessed against a list of outcome indicators. We critically appraised studies using the Mixed Methods Appraisal Tool.

Results: We included 12 studies representing 10 systems. Seven were in oncology. Systems were technically and functionally heterogeneous, with the majority being fully integrated (data viewable in the EHR). Half of the systems enabled regular symptom tracking between visits. We identified 3 symptom report-guided clinical workflows: Consultation-only (data used during consultation, n = 5), alert-based (real-time alerts for providers, n = 4) and patient-initiated visits (n = 1). Few author-described anticipated benefits, primarily to improve communication and resultant health outcomes, were realized based on the study results, and were only supported by evidence from early-stage qualitative studies. Studies were primarily feasibility and pilot studies of acceptable quality.

Discussion and Conclusions: EHR-integrated remote symptom monitoring is possible, but there are few published efforts to inform development of these systems. Currently there is limited evidence that this improves care and outcomes, warranting future robust, quantitative studies of efficacy and effectiveness.

Key words: remote monitoring, electronic health record, long-term conditions, digital health, mobile health, patient-generated health data

INTRODUCTION

Nearly 1 in 4 adults across Europe and almost 1 out of 2 adults in the US are living with a long-term condition (LTC), and globally, LTCs are among the leading causes of years lived with disability.[1–3] LTCs often require continuous management of care and life-long medication use, and the majority of health care spending in the developed world is in LTCs.[4] As health care systems experience an increasing demand for services, there is a growing need to find innovative approaches to the provision and delivery of care to aid clinical and self-management of people living with an LTC.

At the same time, digital technologies are becoming increasingly pervasive, providing unique opportunities to collect health data directly from patients that can aid clinical decision-making and make care more patient-centric. Key features of patient-generated health data (PGHD) are: 1) the patient, not the health care provider, captures the data; 2) the data are obtained outside of clinical settings; and, therefore, 3) the data can be collected longitudinally and with high frequency.[5] PGHD may include not only clinical data (such as home-based blood glucose measurements), but also other patient-reported aspects of health, such as symptoms, medical history, physical activity, and more. Some of these would be considered patient-reported outcomes (PROs). For the purpose of this review, we will focus exclusively on patient-reported symptom data, acknowledging that there is an overlap with certain PROs.

Collecting patient-reported symptom data remotely prior to a consultation might change clinical workflows, making them more efficient by not requiring patients to fill out assessments in the waiting room or reporting symptoms within the limited time patients have with their clinician during the clinic consultation. PGHD could also give a much clearer and complete picture of life outside of the clinic with more continuous, longitudinal monitoring. Longitudinal data could be used to inform ongoing care management and provide important insights into a patient's health and well-being.[6] Integrating this important information real-time with the electronic health record (EHR) would facilitate a more systematic symptom review at the point of care and allow tracking of symptom severity over time alongside other clinical information.[7–9] Logging onto separate systems is a recognized barrier for clinicians to adopting a new health IT system, highlighting the importance of better integration.[10,11] Integration into EHRs have been an aspiration for more than a decade, but despite the suggested benefits and opportunities of integrating patient-reported symptom data from remote monitoring into EHRs and clinical practice in LTCs, the supporting evidence for this remains unclear.[10]

OBJECTIVE

No comprehensive systematic reviews exist of published EHR-integrated systems that remotely collect self-reported symptoms for clinical decision-making. Our aim was therefore to map the landscape of EHR-integrated remote symptom monitoring systems in the field of LTCs. Specifically, the objectives were to 1) characterize state of the art systems, 2) describe their use in clinical settings, and 3) outline the anticipated and realized benefits.

MATERIALS AND METHODS

We designed and reported the systematic review according to (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) PRISMA guidance.[12]

Search strategy

We searched 3 electronic literature databases—Embase, MEDLINE, and Web of Science—until November 11, 2019. We were not interested in purely technical or system development papers, so we did not search computer science databases. The search strategy, which was developed in consultation with an experienced research librarian, consisted of a combination of Medical Subject Headings (MeSH) and free-text keyword terms related to the following 3 concepts: 1) long-term conditions including cancer,[13] 2) patient-generated health data, and 3) data capture systems.[14] We initially developed the search strategy in MEDLINE (see Supplementary Material Table 1) and then adapted to other databases.

Selecting relevant studies

Studies were considered relevant if they met all of the following criteria:

- Evaluated symptom reporting systems, using a definition adapted from Vegesna et al:[15] "An ambulatory, noninvasive digital technology used to capture patient data in real time and transmit health information for assessment by a health professional." This evaluation excluded studies focusing on systems exclusively for sensor, wearable, implant, or biometric data, as they have been reviewed elsewhere.[15–17]
- Included adult patients living with an LTC as the study population, following the World Health Organization's definition.[13]
- Facilitated a direct integration of digital patient-reported symptoms into the EHR on a single sign-on basis for the clinician.[18]
- Collected the symptom data remotely (ie, outside of conventional clinical settings). This excluded data collected on a tablet or computer in the waiting room before a clinic visit.
- Reported on systems that were used to communicate symptoms between patient and health care provider in a clinical consultation, thereby potentially influencing clinical decision-making. This excluded self–management-only systems.

Studies on video consultations were excluded, as we believe they represent a separate, distinct branch of telehealth. As we wanted a comprehensive overview of relevant systems, we did not exclude studies based on study design, quality, or sample size.

Retrieved records were imported into Endnote and deduplicated. Two reviewers, JG and SMA, independently screened titles and abstracts against the predefined inclusion criteria. For studies considered potentially relevant, we retrieved the full papers and 1 reviewer (JG) identified those meeting the criteria for inclusion. As a quality audit, a second person (SMA) reviewed a 10% random sample of full text references to check for agreement. The review team met regularly to align interpretations, and at each stage of the review process, discrepancies were solved through consensus discussion. Reference lists of included studies were additionally screened manually, as were reference list of recent important work in the field known to the authors.

Data extraction and synthesis

We developed a data extraction form on the basis of the Office of the National Coordinator (ONC) for Health Information Technology PGHD white paper which presents a framework for describing the context and use of PGHD.[5] It includes 3 steps in data flow: Capture (creation and storage of health data by the patient); transfer (communication of captured data to health care designees); and re-

Table 1. Overview of studies included in the systematic review

Reference, (year)	Country	Type of study	Disease subtype	Number of patients	Setting	**Patient demographics: Age[a] Gender Ethnicity**	Commercial tool, (name)
Cancer							
Graetz et al (2018)	USA	Randomized controlled feasibility trial	Breast	44	Medical breast cancer center	59.9 [34; 77] 100% female 25% non-white	Not reported
Snyder et al (2013)	USA	Single-arm prospective pilot study	Breast, prostate	52	Academic cancer center	58 [28–81] 72% female 18% non-white	No (PatientViewPoint)
Warrington et al (2019)	UK	Observational clinical field testing	Breast	12	Medical oncology breast service in a cancer center.	47.5 (10.3) [33; 73] 100% female Not reported	No (eRAPID)
Zylla et al (2019)	USA	Prospective feasibility study	Non-hematologic	80	Large, urban community cancer center	62 [26; 85] (median) 66% female 4% non-white	Yes (EPIC MyChart)
Garcia et al (2019)	USA	Clinical quality improvement initiative	Various subtypes	3521	Medical oncology clinic	57.2 (13.4) 68.1% female 16.7% non-white	Yes (EPIC MyChart)
Wagner et al (2015)	USA	Implementation study	Gynecologic	636	Gynecologic oncology clinic	55.1 (12.8) [21; 90] 100% female 12.9% non-white	Yes (EPIC MyChart)
Girgis et al (2017)	Australia	Mixed methods feasibility study	Most subtypes	35	Two public hospital cancer centers	62.2 (11.2) [39; 85] 69% female Not reported	No (PROMPT-Care)
Van Egdom et al (2019)	The Netherlands	Overview of development and implementation	Breast	239	Academic Breast Cancer Centre	Not reported Not reported Not reported	Not reported
Rheumatology							
Austin et al (2019)	UK	Feasibility and acceptability study	Rheumatoid arthritis	20	Rheumatology clinic at a large, academic hospital	[32; 84] 75% female Not reported	No (REMORA)
Neurology							
Schougaard et al (2019)	Denmark	Parallel 2-arm pragmatic randomized controlled trial	Epilepsy	593	Academic neurology department	45.8 (17.1) 45% female Not reported	No (AmbuFlex)
Multiple disease areas							
Biber et al (2018)	USA	Overview of implementation experiences	All ambulatory clinics. From primary care to sub-specialty surgical practices	200.000	Large academic health care system	Not reported Not reported Not reported	No (mEVAL)
Schougaard et al (2016)	Denmark	Overview of implementation experiences	9 groups (Heart disease, epilepsy, narcolepsy, RA, sleep apnoea, prostate + colorectal cancer, asthma, renal failure)	Not reported	15 outpatient clinics in 1 region	Not reported Not reported Not reported	No (AmbuFlex)

[a]Mean age in years (standard deviation) [range].

Table 2. Specifications of the 10 systems for integrated remote patient-reported symptom monitoring

System	Data capture tool	EHR integration status for data[a]	Patient authentication	Data flow described?	Well described data security measures[b]	Option for patient to provide additional information	Feedback of own data to patient
Cancer							
Graetz et al	Website	Full integration	Not reported	Yes	Not reported	Not reported	Not reported
Snyder et al	Website	Full integration	Unique system log-in	Not reported	Yes	Yes	Yes Graphics of symptoms over time
Warrington et al	Website	Full integration	Unique system log-in	Yes	Yes	Yes	Yes Graphics of symptoms over time or written format
Zylla et al	Patient portal	Full integration	Personal patient portal log-in	Not reported	Not reported	Not reported	Not reported
Garcia et al Wagner et al	Patient portal	Full integration	Personal patient portal log-in	Yes	No	Not reported	Not reported
Girgis et al	Website	Full integration	Personal health identification or medical record number + password	Yes	No	Not reported	Not reported
Van Egdom et al	Website	Full integration	Not reported	Not reported	No	Not reported	Not reported
Rheumatology							
Austin et al	Smartphone app	Full integration	Unique system log-in	Yes	No	Yes	Yes Graphics of symptoms over time
Neurology							
Schougaard et al	Website	Partial integration	Personal health identification or Medical record number + password	Not reported	Yes	Not reported	Yes Graphics of symptoms over time
Multiple diseases							
Biber et al	Website	Full integration	Personal link. No need for log-in.	Not reported	No	Not reported	No

[a]"Full" integration allows data to be viewed from within the EHR. "Partial" has data available for review via a link inside the EHR that transfers the viewer to a secure website.

[b]Described in further detail than simply stating "firewall."

view (health care designee receiving the data and using it for decision-making).

We pilot-tested the extraction forms among the authors. The final list included items on study characteristics, technical and functional system specifications, response rate (defined as the author-reported percent completed questionnaires from the total eligible), clinical use, and anticipated and reported benefits of integrated symptom monitoring. JG reviewed and extracted data from eligible studies. Additional information on the systems was sought for the studies that had been described in detail elsewhere, such as in technical system architecture publications or protocols.

For objective 3, we were interested in seeing what kinds of anticipated benefits the authors thought were most important and if they succeeded in realizing any of them by looking at which benefits they evaluated. We adopted the 10 outcome indicators proposed by Chen et al to guide our evaluation of anticipated and realized benefits of remote symptom monitoring.[6] The indicators aimed to evaluate the impact of routinely collected PROs on patients, service providers, and organizations (Supplementary Material Table 2). They were initially developed for an oncologic setting, but as the frameworks upon which the 10 indicators rely are not disease-specific, it makes them useful for evaluating impacts beyond oncology.

We mapped each stated benefit against this list of indicators to be able to count and compare anticipated and realized benefits. Here, a benefit was defined as a positive result or consequence of integrated symptom monitoring stated by the authors. We classified benefits either as "anticipated" (what the authors stated as possible benefits in the introduction of their publication) or "realized" (supported by the study findings). Evidence for realized benefits was further categorized as quantitative, qualitative (eg, through interviews)

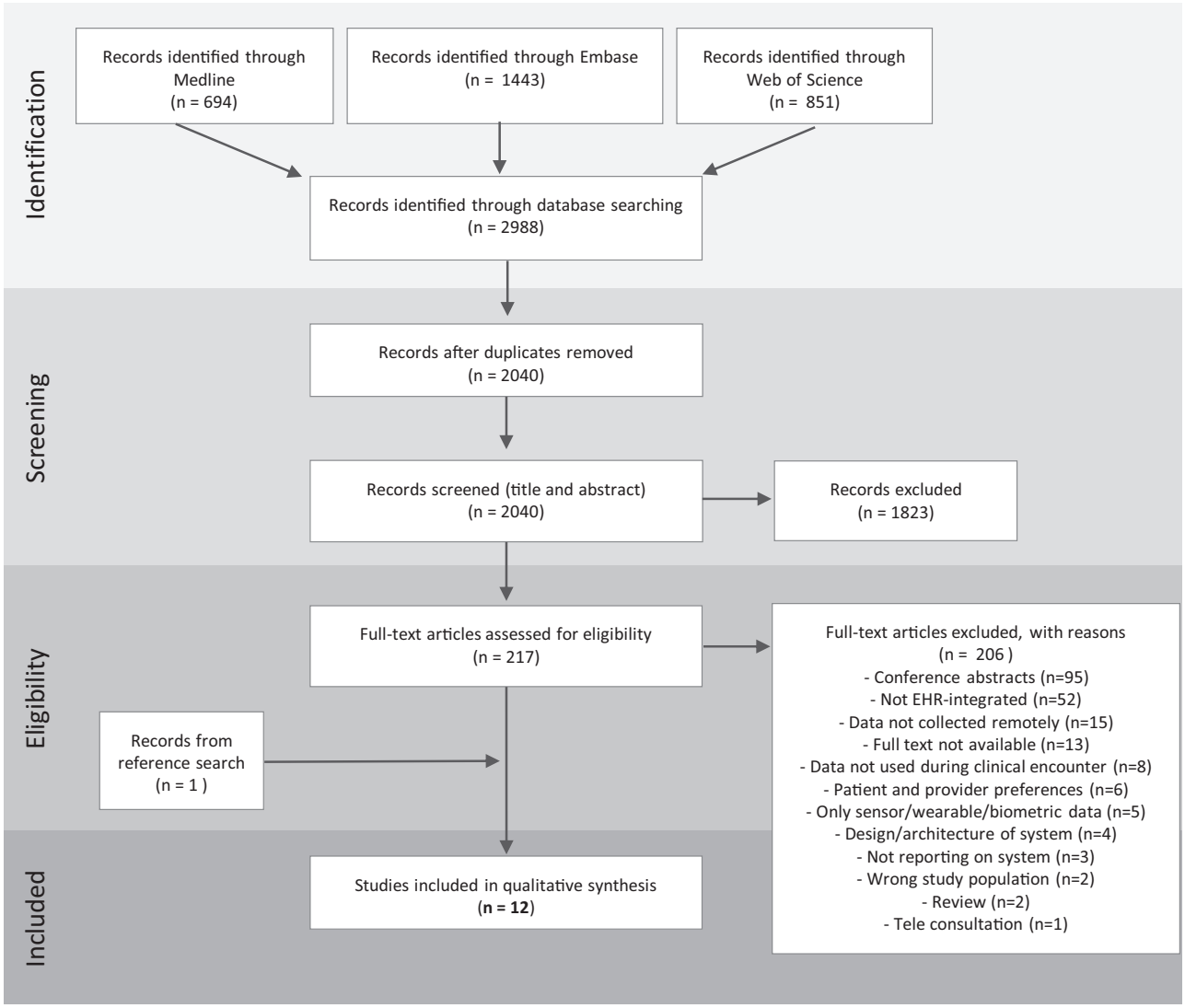

Figure 1. PRISMA flow diagram illustrating the systematic review process from electronic searching through to study inclusion.

or both; in the latter case, we counted an outcome twice for that study.

No attempt was made to quantitatively synthesize the results.

Methodological quality assessment

Two reviewers (JG and SMA) independently evaluated the quality of each study reporting on realized benefits with the Mixed Methods Appraisal Tool (MMAT), which allows concomitant appraisal of quantitative, qualitative, and mixed-methods studies.[19] Where discrepancies appeared, consensus was reached through discussion.

RESULTS

Of 2040 articles identified through the search, 12 were selected for final inclusion, representing 10 unique systems. Figure 1 shows the PRISMA flow diagram depicting the review process.

All but 3 systems were used in oncology (Table 1).[20–22] Half of the systems were in the United States, and only 3 systems were commercially available. Half of the systems were utilized for more than 1 disease subtype, such as tracking both breast and prostate cancer symptoms using PatientViewpoint[23] or for 9 different diagnostic groups using AmbuFlex.[24] The majority of studies were conducted in a single location.[20,21,23,25–30]

System specifications

Data capture technologies

Table 2 shows that patient data capture technologies included 1 smartphone application available for Android phones[20] and 2 online patient portals tethered to the EHR,[25,27,30] but the majority of systems used websites that could be accessed from the patient's home computer or any web-based device.[21–23,26,28,29,31]

EHR integration status

EHR integration was split into 2 categories based on where the data was viewed from: "full integration" and "partial integration." Full EHR integration allowed data to be viewed and manipulated alongside other clinical data elements within the EHR. Nine out of 10 systems were fully integrated.[20,22,23,25,26,28–31] The two online patient portals represented one type of fully integrated systems, and they were both EPIC MyChart portals. Registered patients could view

portions of their medical record, add data to it, and exchange messages with physicians through a secure member website. One system represented partial integration, where data was available for review via a link inside the EHR that transferred the viewer to a secure website.[21]

There were different methods for displaying the data to the provider in the EHR. Garcia et al developed a system that displayed data as if they were lab results within the EHR.[25] Austin et al's smartphone app likewise had resultant PGHD immediately available in the EHR results section.[20] Another way of displaying the data included a separate interface displaying symptoms graphs embedded in the EHR such as Warrington et al's.[29]

Data flow and security

The flow of data from patient-facing technology to provider interface was described by half of the systems.[20,25,28,29,31] Security measures were rarely described in detail. An example of well-described security measures came from Schougaard et al. They described how all data activities in the study were documented and stored in the WestChronic web system, where the system was located physically, and the specifications of the firewall. They described how backup was performed weekly and that all data transactions fulfilled conditions established by the Danish Data Protection Agency.[21] In contrast, 5 systems only reported a "firewall," and some did not describe security measures at all.[20,22,25,26,28,30,31]

Additional features

Graphical or written feedback of self-reported symptom data over time was available to patients in 4 systems.[20,21,23,29] Three systems allowed patients to capture additional or contextual information in free text outside of the questions asked.[20,23,29] Two systems provided self-management resources, including recommendations to manage milder symptoms,[29] and e-mails with links to websites for managing symptoms exceeding predefined severity scores.[31]

System usage

Frequency and purpose

As per Table 3, data collection frequency varied significantly, but overall fell into 2 groups: 1) longitudinal data collection at predefined intervals between visits, and 2) a single request before a scheduled clinic visit. For the longitudinal data group, patients were asked to report items with frequencies varying from daily to monthly.[20,23,28–30] Additionally, 2 systems had the option for patients to report more frequently if desired. For systems with high reporting frequency, the duration of data collection per individual participant did not exceed 6 months, and, mostly it was less than 3 months. For some—and especially in cancer—the purpose was surveillance of patients undergoing toxic treatments; for others, it was to track fluctuating symptoms between follow-ups. Three systems also used the data as a basis for referrals to supportive care specialists, such as psychologists and nutritionists.[25,27,31] The single request group reported symptoms just once in the lead-up to a scheduled outpatient visit, primarily with the purpose of replacing the typical waiting room or in-consultation assessments.[22,24–26,31]

Type and number of items collected

We identified 5 groups of collected patient-reported data: physical symptoms, psychological symptoms, quality of life, supportive care needs, and medication adherence.[32] All systems included physical symptoms. Seven out of 12 references described reporting in 3 or more groups, most commonly a combination of physical and psychological symptoms and quality of life.[21–26,31] Two systems used Patient-Reported Outcomes Measurement Information System computer adaptive tests.[22,25]

The maximum number of items requested per session ranged from 9 to 48 across systems. Generally, the systems that reported less often requested the highest number of items (> 40 items per reporting). However, the number of items requested was not available for 5 of the included systems.[22–24,26,28]

Response rate

Austin et al's smartphone app had the highest response rate of 91% (range 78%–95%), despite asking patients to report on a daily basis.[20] Similar rates were found across disciplines for Schougaard et al's AmbuFlex system that asked to report before a visit (81%–98%).[24] The lowest rates were found among the systems using patient portals (35%–52%), but, in contrast to the other systems, these were tested in naturalistic rather than more controlled settings.[25,27,30] All 10 systems provided prompts to the patient when they were due to report.

Clinical use

Workflow

We observed similarities in how the symptom data was integrated into clinic workflows, and synthesized them into 3 categories (Table 4). Five systems described a "consultation-only" workflow, which meant that the clinician viewed symptom data in the EHR just before or during the clinic consultation and inspected it with or without the patient to inform discussions and decision-making.[20,22,23,26,31] An "alert-based" workflow included alerts to the clinical team when symptoms exceeded a predefined score (see below), but was otherwise similar to the "simple" workflow; this was described by 3 systems.[23,25,28,29] Finally, 1 "on-demand" workflow meant that patients were sent questionnaires every 3, 6, or 12 months to guide their visit scheduling.[24] Responses were given a green, yellow, or red color by a predefined automated algorithm. Green responses were handled automatically by the software. Yellow and red responses were shown on an alert list, where clinicians decided whether the patient needed a visit. A moderation to the "on-demand" workflow allowed the patients to indicate a need for contact by filling in questionnaires only when they felt they needed a visit.[21]

Alerts

After patients completed their questionnaires, 5 systems sent real-time alerts triggered by patient responses exceeding predefined thresholds primarily directed to staff.[21,25,28–30] Alerts were either automated e-mails or EHR in-basket messages, and were most commonly set up to prompt follow-up by the treating clinician, nurse, or research coordinator. One oncology system additionally generated automatic referrals to nutritionists, social workers, and other supportive staff.[25,27]

Anticipated and realized benefits

From Figure 2, it is evident that there were several anticipated benefits to routine symptom reporting, but that few were actually realized. Improved health outcomes were particularly anticipated, but no study provided evidence for achieving these benefits. Evidence for the benefits that were realized was primarily of a qualitative nature. They involved better patient-provider communication, detec-

Table 3. Type, duration, frequency and completeness of data collection by included systems for integrated remote patient-reported symptom monitoring

System	PGHD collected outcome instruments used	Number of items	Reporting frequency	Duration of data collection/study	Response rate, %[a]	Maximum data points per patient throughout study
Cancer						
Graetz et al	Physical symptoms Medication adherence	Not reported	Weekly + ad hoc	Individual: 6–8 weeks Study: 6 months	Not reported[b]	Unable to calculate
Snyder et al	Physical symptoms Psychological symptoms Quality of life Instrument: PROMIS	Not reported	Every 2 weeks	Individual: up to 6 months Study: 6 months	85% (190/224) overall. 71% by individual patient	Unable to calculate
Warrington et al	Physical symptoms Instrument: CTCAE	12 items	Weekly + ad hoc	Individual: app. 12 weeks Study: 3 months	63% (range 33%–92%)	144 items
Zylla et al	Physical symptoms Quality of life	23 items	Every 2 weeks	Individual: 12 weeks Study: app. 8 months	46% (125/271) were completed electronically. 66% (183/271) overall (range 58%–83%)	138 items
Garcia et al	Physical symptoms Psychological symptoms	App. 40 items	Before clinic visit	Individual: unknown Study: 2,5 years	51,6% (3521/6825) for any assessment	98 items
Wagner et al	Supportive care needs Instrument: PROMIS CATs			Individual: unknown Study: 2 years, 3 months	36,8% for first assessment 34,5% for all assessments	104 items
Girgis et al	Physical symptoms Psychological symptoms Supportive care needs	47 items	Before clinic visit or Monthly	Individual: unknown Study: 3 months	77% (67/87) of assessments were completed[c]	141 items
Van Egdom et al	Physical symptoms Psychological symptoms Quality of life	Not reported	Before clinic visit	2 years evaluation (ongoing)	83.3% at baseline, 55.1% after 12 months overall	Unable to calculate
Rheumatology						
Austin et al	Physical symptoms Psychological symptoms	Daily: 9 Weekly: 11 Monthly: 23	Daily, weekly, monthly	Individual: 3 months Study: unknown	91% (range 78–95%)	1011 items
Neurology						
Schougaard et al	Physical symptoms Psychological symptoms Medication adherence Quality of life	48 items	Needs-based or Before clinic visit	Individual: 18 months Study: 24 months	Not applicable (Needs-based)	Unable to calculate
Multiple disease areas						
Biber et al	Physical symptoms Psychological symptoms Quality of life Instrument: PROMIS CATs	Not reported	Before clinic visit	Individual: unknown Study: 15 months (but ongoing effort)	47% overall. 17 %/47% at home	Unable to calculate
Schougaard et al	Physical symptoms Psychological symptoms Quality of life	Not reported	Before clinic visit	Unknown (ongoing)	81–98% across disciplines for initial assessment. 90–98% for follow-up	Unable to calculate

Abbreviations: CATs, computerized axial tomography scan; patient-generated health data; PROMIS, CTCAE, common terminology criteria for adverse events; PGHD,Patient-Reported Outcomes Measurement Information System.

[a]Response rate defined as percent completed questionnaires from total eligible. For highest frequency of reporting option within each system (eg, daily for Austin et al.).

[b]Used mean app use rate instead [Mean app use rate was 55%, defined as (number of reports/number of weeks enrolled)].

[c]Only shown overall including in-clinic completion and not specifically for home assessments.

Table 4. Clinical use of integrated remote patient-reported symptom monitoring systems

System	Workflow	Alerts to care team	Results guide the frequency or format of consultations	Format of provider feedback	Provider training in use and interpretation
Cancer					
Longitudinal monitoring between visits					
Graetz et al	Alert-based	Yes to clinical team	Depends on action by medical team	Graphical depiction over time	Not reported
Snyder et al	Consultation-only	No	No	Graphical depiction over time	Yes
Warrington et al	Alert-based	Yes to clinical team	Depends on action by medical team	Plain-text table, highlighting with an asterisk	Yes
Zylla et al	Alert-based	Yes to clinical team	Depends on action by medical team	Graphical depiction over time	Not reported
Single request before visits					
Garcia et al and Wagner et al	Alert-based	Yes to clinical team + supportive care providers	No	Not reported	Not reported
Girgis et al	Consultation-only	No	No	Graphical depiction over time	Yes
Van Egdom et al	Consultation-only	No	No	Graphical depiction over time	Not reported
Rheumatology					
Longitudinal monitoring between visits					
Austin et al	Consultation-only	No	No	Graphical depiction of over time	Not reported
Neurology					
Needs-based follow-up visits					
Schougaard et al	On demand	Yes to clinical team	Yes	Graphical depiction over time	Not reported
Multiple diseases					
Single request before visits					
Biber et al	Consultation-only	No	No	Graphical depiction over time	Yes

Definitions: Alert-based, real-time alerts for providers when reporting severe symptoms; Consultation-only, data only used during consultation; On-demand, patient-initiated visits.

tion of unrecognized or hidden problems, changes to patient management, such as clinical management and decision-making, and changes to patient health behavior, including patient self-management and patient empowerment.

Two randomized controlled studies were the only studies that sought to provide quantitative evidence. However, neither of the studies compared integrated remote symptom monitoring to usual care without monitoring or to other types of symptom monitoring approaches; Schougaard et al compared patient-initiated to fixed interval PGHD-based follow-up,[21] while Graetz et al compared symptom and medication adherence reporting with reminders to reporting without reminders.[28] Therefore, no studies reported on the quantitative evidence of benefits that we were interested in for the purpose of this review.

Quality assessment

Ten out of 12 studies were pilot, implementation, acceptability, or feasibility studies. Six studies reported on both qualitative and quantitative methods and were therefore classified as mixed methods. Results from the MMAT quality appraisal showed that most studies were of acceptable quality (see Supplementary Material Table 3), though the qualitative domains generally showed higher quality than the quantitative. Most quantitative descriptive studies lacked a representative sample, while the two randomized trials both lacked blinding and suffered from high dropout rates, which lowered their quality. The mixed method studies appropriately used the design and integrated the data well, but none considered divergent qualitative and quantitative findings, which could indicate some outcome reporting bias.

Four studies were not appraised, as they did not report on realized benefits. These studies reported on experiences with implementation in larger health systems. Overall, they discussed challenges with system-wide implementation, what is essential for a successful process, and summarized metrics supporting the feasibility of such an approach.

DISCUSSION

This systematic literature review of EHR-integrated remote symptom monitoring systems to support LTC management resulted in a heterogeneous list of 10 systems of which 7 were developed in oncology settings. Half of the systems requested a single symptom report ahead of a scheduled appointment while the other half allowed regular symptom tracking between visits. Systems moderated clinical workflows in 3 different ways: using data only during consultations, generating real-time alerts to providers, and scheduling outpatient visits. Of the anticipated key benefits, only a few benefits

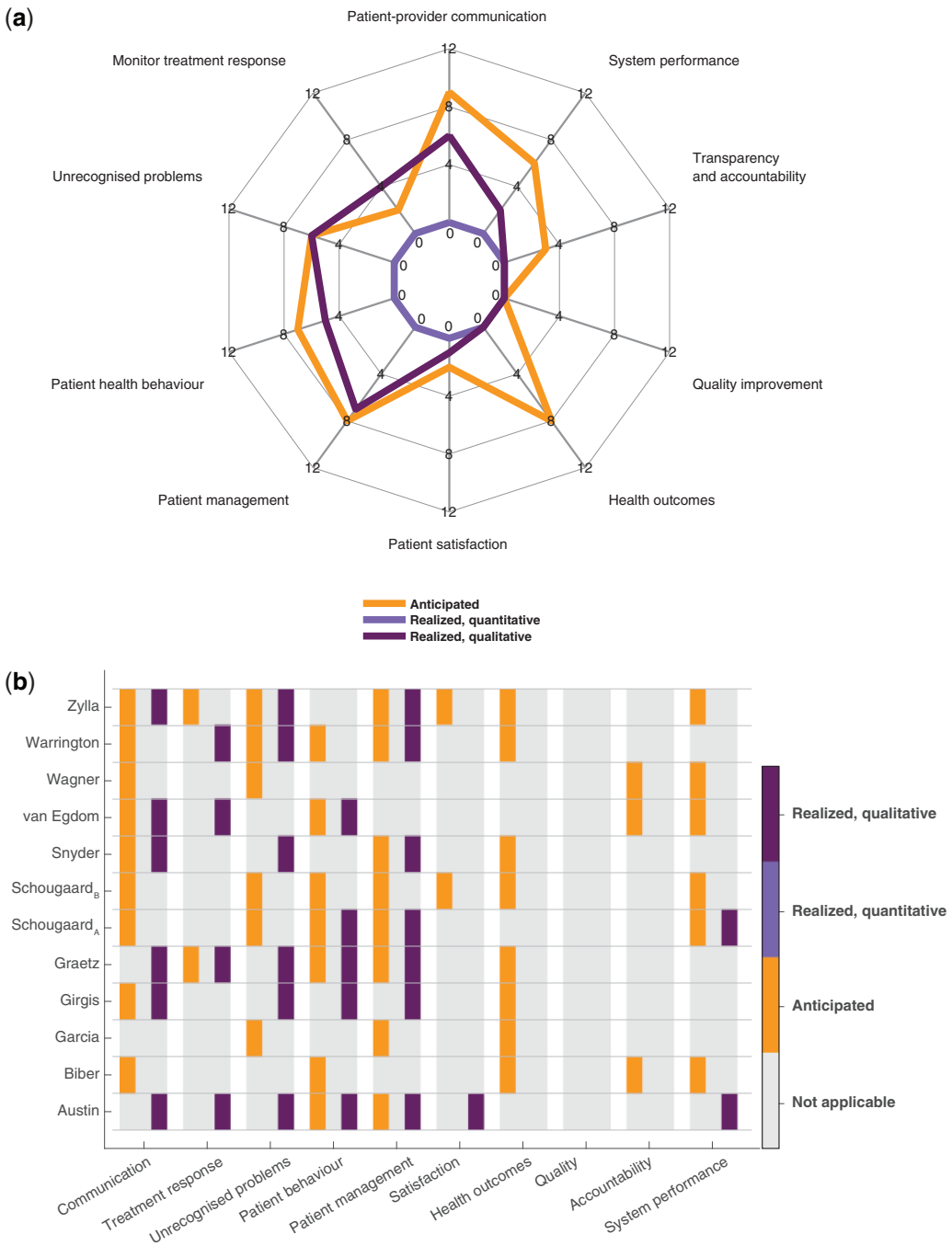

Figure 2. Summarized counts of anticipated and realized benefits showing that anticipated benefits outweigh realized benefits and that the latter are solely qualitative. (a) Spider plot illustrating summarized counts of benefits categorized after Chen et al's 10 outcome indicators. Divided into anticipated (orange), realized quantitative (light purple), and realized qualitative (dark purple) benefits. (b) Heat map showing individual included references and their benefits in each of the categories: anticipated, realized quantitative, and realized qualitative benefits. Color convention as in (a).

were realized and solely supported by qualitative evidence. Realized benefits included better patient–provider communication, detection of unrecognized or hidden problems, and changes to patient management.

The reported benefits should be viewed cautiously in light of aspects of study design. The majority of studies were early stage research, such as feasibility, pilot, and acceptability studies, and drawing conclusions on effectiveness should generally be avoided. Potential selection biases were present in a subgroup of studies where patients were identified by clinical staff or self-selected.[20,29,31] The acceptability of these systems to other, perhaps less enthusiastic, participants, early and late adopters of technology, and different levels of digital literacy, is unknown. Most systems were implemented in a single setting, thereby limiting the generalizability of their results. Despite being 1 of the bigger concerns ,[33] security measures were infrequently described. For the

purpose of replication and providing blueprints for EHR integration moving forward, technical aspects need to be reported in more detail.

Limitations

Although our search was comprehensive, it is possible we missed some systems. In particular, unpublished initiatives, remote symptom monitoring modules integrated into larger EHR systems, and systems that were used to collect data in the waiting room but may have had the capability to support symptom reporting from home.

The anticipated benefits summarized in this article included only those that the authors stated within the introduction section. It is possible that authors considered the anticipated benefits of remote monitoring to be wider but were not comprehensive in describing them.

Other PGHD systems

Although out of scope for our review, PGHD systems focusing on aspects other than symptoms have been integrated in EHRs. Examples include diabetes and glucose measurements,[34] hypertension and blood pressure measurements,[35] and asthma and peak flow monitoring.[36] Limitations shared among these efforts include low numbers of included patients, few engaged providers, and difficulties in displaying patient-reported data in a useful way within the EHR. Nonetheless, developing efficient ways to incorporate multiple types of PGHD in the EHR opens up a platform for capturing additional data types that further support the shift in clinical care models. However, problems of data integration are compounded by problems of visualization and making sense of large amounts of PGHD. At the moment, it is unclear how best to present PGHD to patients and clinicians in order to make the data meaningful in the clinical context. One solution to unlocking the value of PGHD while simultaneously avoiding information overload is visual analytics.[37] Visualizing health data in a smarter and more interactive manner by leveraging visual analytics might aid the interpretation of complex health data, but more user-centered research is needed to better understand how this works in LTCs. There is, however, the necessary challenge of graph literacy in the general population if graphical data are to be used as a tool to support shared decision-making.[38]

Noah et al evaluated randomized controlled trials that assessed the effects of using noninvasive wearable biosensors for remote patient monitoring on clinical outcomes.[17] They found that, while some remote monitoring interventions proved promising in changing clinical outcomes, there are still large gaps in the evidence base. Like us, they were limited by high heterogeneity and scarcity of high-quality studies, indicating that high-quality evaluations are warranted across the broader field of remote patient monitoring.

Calls to action

Based on the findings presented in this review, we suggest 3 calls to action for harnessing the potential of integrated remote symptom monitoring: i) strengthening the quantitative evidence base, ii) accelerating work beyond oncology, and iii) improving interoperability. Below we outline each of these.

Strengthening the quantitative evidence base

The large number of pilot, implementation, and feasibility studies in our review demonstrate an emerging field. The next stride will be to quantitatively evaluate the effect of these systems in larger, more diverse populations. The National Institute for Health and Care Excellence has defined what good levels of evidence for digital health care technologies look like in the United Kingdom.[39] Based on functions and potential user risks, technologies are stratified into evidence tiers. Symptom tracking functions that connect with a health care professional require Tier 3a evidence, the minimum standard being evidence from a high-quality observational or quasi-experimental study demonstrating impact on relevant outcomes, and should present comparative data. None of our included studies reached this level of evidence. Future studies should deliver this high-quality knowledge base.[40]

Accelerating work beyond oncology

Collecting PGHD remotely provides an opportunity for making consultations more efficient and patient-centric, while repeated collection could give a more complete picture of the patient and allows for continuous monitoring. The majority of our included studies were used within oncology, and 4 out of 5 systems that examined longitudinal monitoring between visits were used in cancer patients. Extrapolating these findings to other LTCs warrants caution, since oncology treatment regimens tend to be short-term instead of long-term, focus on monitoring side effects rather than symptoms related to the underlying condition, and patients might have different motivators to monitor symptoms during serious illness or end-of-life care. Recently, a randomized trial showed that monitoring chemotherapy side effects improved quality of life, acute hospital admissions, and survival.[41] Despite not being integrated with the EHR, similar evidence from remote symptom monitoring on patient outcomes are rare across other LTC. Whether and how these results generalize from cancer to other LTCs is unknown, and accelerating work in fields outside of oncology is therefore highly encouraged.

Improving interoperability

Undeveloped interoperability standards were one of the challenges of PGHD integration laid out in the Office of the National Coordinator for Health Information Technology (ONC) report.[33] Although not specifically addressed in any of the included papers, we found that each system developed their own technical infrastructure for integration. The emerging data exchange standard called Fast Healthcare Interoperability Resources (FHIR)[42] and its latest extensions, SMART-on-FHIR and SMART Markers,[43,44] are approaches developed to streamline and simplify EHR integration. Leveraging standards-based data exchange through interoperability could potentially both solve the interoperability challenge proposed by the ONC as well as ease EHR integration, making it an achievable goal for more health care systems.

CONCLUSION

This systematic review shows that despite having been an aspiration for decades, there are few published studies to inform future development of EHR-integrated remote symptom monitoring systems for LTC care, but that integration is achievable. We found early indications from qualitative studies in support of integrated remote symptom reporting being beneficial, but these findings must be interpreted with caution. This implies we are still in the era of promise rather than realization when it comes to integrating patient-reported symptom data into the EHR. The next step will be for robust, quantitative studies to provide evidence of benefits—particularly beyond oncology.

FUNDING

This work was supported by the Centre for Epidemiology Versus Arthritis (grant number 21755). The funder did not contribute to the concept, design, data collection and interpretation, or drafting of this manuscript.

AUTHOR CONTRIBUTIONS

JG and SMA conducted the literature search and systematic review, and JG abstracted the data. JM, SNV, and WGD assisted in developing the research question and synthesizing the results. JG drafted the manuscript. All authors were involved in revising the manuscript critically, and all authors approved the final version to be submitted for publication.

The first and senior author (JG) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

ACKNOWLEDGMENTS

We would like to thank Mary Ingram, university research librarian, for her kind help and support in developing the search strategy.

CONFLICT OF INTEREST STATEMENT

WGD has received consultancy fees from Abbvie, Bayer, and Google unrelated to this work.

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3

Using patient-generated health data in rheumatoid arthritis outpatient consultations

3.1 Introduction

To maximise the benefits of PGHD for clinical care, clinicians need to be supported in integrating the data into their consultation and clinical decision-making. Limited evidence exists about how patients and clinicians interact with PGHD when presented during a consultation. This interaction is essential to understand and decipher, to enable development of useful and evidence-based support materials. I had a unique opportunity to start filling this research gap with information from transcribed REMORA1 research consultations between two study clinicians and their patients who had used the REMORA1 app daily for three months and now came back to the clinic for a clinical visit. It was left to the discretion of the clinician to decide when and how to discuss and use the data. The consultations resembled normal follow-up outpatient consultations, with the necessary clinical decisions and treatment changes made as usual.

Through qualitative analysis of the transcripts, this chapter aimed to gain insights into how daily PGHD displayed as symptom graphs in the EHR informed discussions between clinicians and patients with RA in a consultation. Specific objectives were to investigate:

1) when the PGHD was introduced and by whom during the consultation, and
2) how the PGHD was discussed between the clinician and patient.

3.2 Contribution statement

A multidisciplinary team with experience in digital health technologies was gathered to conduct the study. The team consisted of clinicians, health informaticians, qualitative researchers, and health service researchers specialising in clinical decision-making. The qualitative analysis was led by Dr Louise Laverty, a medical sociologist. She did the initial close coding and developed initial suggestions for themes, which were then discussed extensively and agreed among the team members. I coded 25% of the 17 transcripts focusing on how the data was used in the consultation and attended, and occasionally led, all analysis meeting to discuss themes, results and interpretations. Using my medical background, I provided a clinical angle to the discussions and context for the broader study.

I created all tables and figures, wrote the initial draft of the introduction and discussion and critically reviewed and revised subsequent drafts. Additionally, I assisted in replying to reviewers' comments when it came back from peer review. Being a true team effort, this has given me experiences in working closely as a team from study conceptualisation, formulation of research question, deciding on analysis approach to coding, interpretation of results and finally writing up and editing. The article was published in Patient Education and Counseling (PEC) in 2021 (https://doi.org/10.1016/j.pec.2021.06.027) with myself and Dr Louise Laverty as equally contributing first authors.

3.3 Article 2: Using patient-generated health data in clinical practice: How timing influences its function in rheumatology outpatient consultation

Patient Education and Counseling 105 (xxxx) 625–631

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pec

Using patient-generated health data in clinical practice: How timing influences its function in rheumatology outpatient consultations

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ARTICLE INFO

Article history:
Received 7 December 2020
Received in revised form 22 June 2021
Accepted 24 June 2021
Available online xxxx

Keywords:
Patient-generated health data
Remote monitoring
Shared decision-making
Rheumatoid arthritis

ABSTRACT

Objective: Utilizing patient-generated health data (PGHD) in clinical consultations and informing clinical and shared decision-making processes has the potential to improve clinical practice but has proven challenging to implement. Looking at consultations between people with rheumatoid arthritis (RA) and rheumatologists, this study examines when and how daily PGHD was discussed in outpatient consultations.
Methods: We conducted a secondary qualitative analysis of 17 audio-recorded research outpatient consultations using thematic and interactional approaches.
Results: Clinicians decided when to look at the PGHD and what symptoms to prioritise during the consultation. When PGHD was introduced early in consultations, it was usually used to invite patients to collaborate (elicit new information). When introduced later, PGHD was used to corroborate patient accounts and to convince the patient about proposed actions and treatments. Clinicians occasionally disregarded PGHD if it did not fit into their clinical assessment.
Conclusion: The time that PGHD is introduced may influence how PGHD is used in consultations. Further research is needed to understand how best to empower patients to discuss PGHD.
Practice implications: Educating patients and clinicians about the importance of timing and strategies when using PGHD in consultations may help promote shared decision-making.

1. Introduction

Medicine and healthcare are placing growing importance on the use of information and technology to improve care and efficiencies in resource-scarce times [1,2]. Patients are encouraged by health professionals to use technology to measure, monitor and record data on their health remotely [3]. One such example is patient-generated health data (PGHD) where the patient collects health-related data (such as symptoms, history, assessments) outside the clinic, as directed by their physician, to help address a health concern (also known as 'pushed' self-tracking, or in this case, remote monitoring) [4–6]. For policy-makers, digital health can provide benefits to patients, professionals and the wider healthcare system [3,7,8]. Others, however, have expressed concerns about the use of technology in healthcare, such as how it may blur the boundaries between the medical clinic and the private space of the home [7,9]. What is clear from the evidence, however, is that digital health technologies are rarely introduced or adopted into healthcare without some problems. Even if they are successfully integrated into electronic health record (EHR) systems [10–13], it remains unclear how the data are used in clinical practice and what impact this may have on decision-making and clinical outcomes [14–17].

Remote monitoring is seen as having particular utility for populations with long-term conditions (LTCs) that often require continuous management of care and life-long medication use [8].

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https://doi.org/10.1016/j.pec.2021.06.027
0738-3991/

Rheumatoid arthritis (RA) exemplifies challenges in the management of LTCs. Assessment of RA disease activity relies on patient reports of symptoms and can be challenging for patients because it asks them to summarise fluctuating symptoms typically over 6–12 months [18,19]. Therefore, the assessment that takes place during outpatient clinic visits provides only a snapshot of the patient's health. This may hamper optimal disease control, which in turn may lead to pain, disability, lower quality of life, and higher mortality [20,21]. This paper examines how new PGHD recorded daily in an app and presented within the EHR during consultations informs discussions between clinicians and patients with RA. The next section will review the existing literature on healthcare technologies that generate PGHD for remote monitoring.

1.1. Previous research on PGHD in healthcare

Digital health interventions that require patients to record information remotely can take many forms depending on the health condition, context, and technology. What they have in common is that patients have to become active participants and perform new tasks and practices outside of the medical clinic. These may range from simple administrative tasks to more complex clinical activities that would have typically been carried out by healthcare professionals [5]. To perform these roles, patients have to become disciplined and careful observers of their bodies [3]. For patients, the benefits of engaging in these new tasks and roles include an increased knowledge of their condition and feelings of control and reassurance that are at a distance from the clinic [10,22]. The drawbacks, however, are that participating can be time-consuming and the constant surveillance may reinforce a patient's experiences of an ill body causing distress or anxiety [3,7]. Furthermore, what is discussed and considered clinically relevant is still controlled by healthcare professionals [6,11].

The integration of PGHD into clinical practice also requires additional roles for healthcare professionals. As well as clerical and managerial tasks, professionals often have to undertake 'inclusion work' with patients [23]. This may include encouraging patients to participate in PGHD collection, giving them relevant information, and providing comfort and reassurance to support them as users. Professionals also have to learn to interpret new forms of data and integrate this with existing clinical knowledge [8,9,12] whilst keeping their service running smoothly and on time [22,24]. Medical professionals might see the utility of remote monitoring technology in general, but some may not consider it valuable or relevant to their everyday practice [13]. The insights provided by PGHD could be used to promote a shared decision-making approach to patient consultations [25,26]. However, to date, it is unclear how this may work in practice.

Previous work in this area shows that technology does not always work as intended as it becomes adapted to fit into patients' lives and existing clinical practice [14]. This reflects the challenge of patients, healthcare professionals, and technology interacting within clinical settings [26]. The focus of these studies, however, rarely examines what happens when these technologies and the data they may generate are used in clinical settings. A review of thirty digital health interventions found that only one study included observations of its use in practice [8]. There is a gap, therefore, in understanding what happens when patients and healthcare professionals interact with these technologies and the data that comes from them in healthcare settings.

This study aimed to gain insight into how daily PGHD, collected on a smartphone app and displayed as symptom graphs in the EHR, informed discussions between clinicians and patients with RA in a consultation. Specific objectives were to investigate 1) when the PGHD was introduced and by whom during the consultation, and 2) how the PGHD was discussed between clinicians and patients.

2. Methods

2.1. Study setting and source of the data

We conducted a secondary analysis of transcribed clinic consultations obtained for the REMORA feasibility study [27]. The primary aim of the study was to test the feasibility of collecting daily self-reported symptoms (i.e. the items we refer to as PGHD which included: pain, function, fatigue, sleep, physical well-being, emotional well-being, coping, morning stiffness; for the full list see Appendix 1) from RA patients over three months using a smartphone app with data integrated into the EHR [27]. PGHD from the app provided longitudinal information in consultations that had not been previously available to clinicians. Under usual circumstances, clinicians would ask patients to verbally summarise their symptoms since their last visit.

Participants were asked to attend an ancillary research consultation to discuss the PGHD following a three-month data collection period; this paper analyses these consultations. These consultations were conducted by practising rheumatologists who made clinical decisions and treatment changes as needed. They were scheduled for 30 min, with the mean actual appointment time being 19 min (range 10–32). Typical clinical appointments are 15–20 min. During research appointments, the PGHD were displayed as graphs over time in the EHR (see Fig. 1) to support discussions around symptoms and symptom management decisions. The clinicians were not given explicit instructions about how to introduce or discuss the PGHD with patients given the exploratory stage of the research. Instead, they used their own clinical experience and discretion to fit the discussion of PGHD into the appointments. The PGHD were available for patients to see continuously on the app, although were not reviewed by clinicians between clinical appointments. Using PGHD for self-management was left to the patients' discretion.

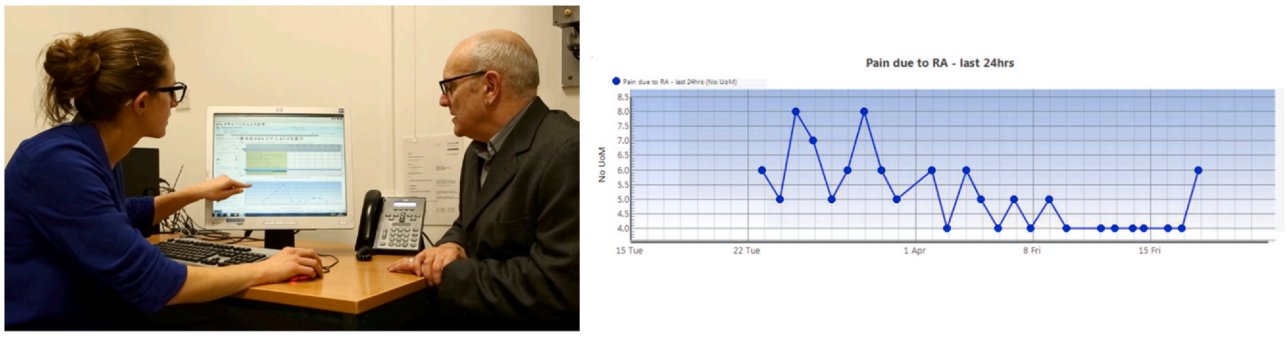

Fig. 1. Symptom graph as displayed within the electronic health record in the REMORA study (in this example: daily pain scores).
With permission from the authors.

2.2. Participants

Twenty patients participated in the study, with seventeen patients giving consent to audio-record their research consultation. Fourteen patients were female (in keeping with the female preponderance of RA); all but one were white British; they had a mean age of 56.9 (standard deviation 11.1) years. Two rheumatologists took part in the study; one male consultant rheumatologist (WD) and one female rheumatology specialty trainee (CS). They are both members of the research team. A professional transcription service transcribed the audio-recordings verbatim.

2.3. Analysis

The analysis aimed to understand when and how PGHD was used by clinicians and patients in clinical appointments. A reflexive thematic approach to analysis was taken to ensure that the themes were representative of the data [28,29]**.** Transcripts were closely read to ensure familiarity before line-by-line coding. One author (LL, medical sociologist) did the initial close coding of the transcripts and developed an initial draft of the themes. This was shared with the research team who reviewed the coding of the transcripts (AE, SV: qualitative researchers) and provided context for the broader study (CS, WD, JG: clinicians). The research team then reviewed and refined the three final inductive themes which aimed to reflect how the PGHD was being used in the interaction (see Table 1 for a summary).

The analysis also explored the structure of the appointments, building on existing interactional approaches used in the analysis of medical encounters. Medical appointments are activities that follow a particular structure (for example introduction, problem presentation, exam, offer, closing) that sets out what can and cannot be done by participants (patients' role in reporting symptoms and answering questions, doctors' role to listen and to decide on diagnosis) [15,16,30]. During analysis, conversational segments were sorted into categories that illustrated the typical structure and order of the appointments. We used this to develop Fig. 2. In the following extracts, C refers to Clinician and P refers to Patient.

3. Results

3.1. When and by whom is PGHD introduced?

The structure of the RA appointments is organised into three sections: the introductory section, the review section, and the concluding section (see Fig. 2). In the majority of appointments (12 out of 17), clinicians introduced and discussed the PGHD during the review section of the appointment when they review evidence and information related to the patients' condition. In five appointments, the clinician integrated the PGHD into the introductory section as the patient was asked to report on their condition, and in four appointments the PGHD was also discussed in the concluding section. The implications of the PGHD being raised in different sections of the appointments will be discussed in the following themes.

It is important to note that four patients referred to their PGHD during their opening narrative in the introductory section but were told by the clinician that they would revisit the PGHD later. As such, it was clinicians who controlled when PGHD was going to fit into the clinical appointment. Additionally, it was clinicians who decided which of the PGHD symptom graphs produced in the EHR (i.e., pain, function, fatigue, sleep, physical well-being, emotional well-being, coping, or morning stiffness) were discussed.

3.2. How is PGHD used?

Our analysis showed that there were three main ways in which clinicians used the PGHD from the app with patients: To invite patients to *collaborate (*during the Introductory phase), to *corroborate* patients' verbal accounts (during the Review phase), and to *convince* patients that further action was needed (during the Concluding phase).

3.2.1. Collaborating

When clinicians used PGHD early in the appointment it was to invite patients to collaborate. The clinician would discuss the graph trends with the patient during the introductory section: asking them to offer context to explain the PGHD and expand on their symptoms and to engage in an active collaborative process to identify triggers and important events. This approach used the PGHD to elicit new information about their condition. Example 1 shows the patient and clinician discussing a flare highlighted in the PGHD to try and understand what had led to the event and understand triggers:

C: Yep. It's interesting to us to see, because what you described fitted…all this part fitted with what you describe, but then…well, that's one of the reasons why the app's really interesting, to see what we can capture that people aren't necessarily able to recall every time. So fatigue has also rose up as the flare went on. Feet difficulties. Similar picture in again. Same time in August.

P: Yeah, there was something must have happened then. Erm…I was on holiday, obviously doing a lot of walking, and then I was really struggling and in a lot of pain with it.

C: Have you noticed that doing extra…doing lots of walking and stuff like that, has that triggered a flare

P: Yeah, it does trigger it, yeah.

C: And then the same thing again, so your ability to cope, and your morning stiffness has improved.

Example 1. *(Clinician 2, Patient: Female, 50–60 years).*

In Example 2, the clinician uses the PGHD to invite the patient to recall their symptoms at a particular time, which leads to a discussion about what further support could be in place:

C: Tender joints. Looks like your joints weren't so good towards the end of November [looking at graph].

P: No, they weren't.

C: And what happened then, can you remember?

Table 1
Summary of themes and codes.

Themes	Collaborating	Corroborating	Convincing
Codes	Clinician refers to PGHD at start of appointment to initiate discussion Clinician reports reviewing PGHD prior to appointment Clinician uses PGHD graphs to look at patterns over time Patient volunteers PGHD to give context to symptoms Clinician asks for context to PGHD Clinician uses PGHD to review treatment response	Clinician uses PGHD to confirm what has been stated verbally Clinician passively refers to PGHD Clinician does not follow up patient-initiated PGHD Clinician moves PGHD to topic for later in appointment	Clinician refers to PGHD when giving assessment of condition Clinician uses PGHD as evidence to offer change to treatment plan

Fig. 2. Illustration of the clinical appointment structure of the rheumatoid arthritis outpatient consultation. The orange semi-circles depict when the patient-generated health data (PGHD) was introduced into consultations, and for what purpose. The steps within the three different sections (Introductory, Review, and Concluding) do not happen in a particular order, and some steps may not occur in all consultations.

P: Well, it will be the knee and the hand.
C: Okay. And which knee, the…?
P: The right knee, with all that's been done, yeah.
C: Yeah. And which bits of your hand?
P: Just there.
C: Over there, okay.
P: This hand, they replaced the wrist, so it's been ideal ever since.
C: Okay. And have you got splints and gloves and things like that at home? Have you seen occupational therapy recently?

Example 2. *(Clinician 2, Patient: Male, 70–80 years).*

Clinicians used PGHD to engage with the patient to look at particular events and flares to help understand triggers of RA, opening up avenues for further support and treatment. It allows the patient to give context to the PGHD and contribute their interpretation and understanding of their condition, and highlight aspects of their symptoms that clinicians might not otherwise prioritise.

3.2.2. Corroborating

Clinicians most frequently used PGHD to corroborate the patient's verbal account during the review section in the consultation. The PGHD became a tool to confirm, verify or even challenge what the patient had already reported earlier in the appointment. In Example 3, the clinician refers to the PGHD in their opening question but asks the patient to report generally on how they have been. The clinician then returns to the PGHD with more focussed questioning during the review section of the appointment. The PGHD is used to confirm the patient's verbal account and focus on the patient-reported problem (sleep) which leads to a recommendation for medication towards the end of the appointment.

C: You've been entering the data for the last three months or so now, but how have things been in that time?
P: I've been okay. My knees still like to play up, and my sleep patterns are still very bad. I can go to sleep for about two hours and then I'm wide awake, or I can be wide awake and then not falling asleep till the early hours.
….
C: Okay. I've looked back through the scores from what you were reporting, and it seems as though everything's pretty much in the middle. Your pain score's kind of between four and six out of ten, and the same for your ability to do physical activities, and your timers. The one thing that does stand out, is the.
P: sleep.
C:.sleep, which kind of matches what you've just said, where you're kind of scoring out of.usually around seven, but kind of up to nine on some days.
….
C: So the plan will be, to increase the Amitriptyline to 75 mg in the first instance, and if you don't get a refreshing night's sleep with that, and I suspect you may not, just because of how you've sort of haven't done so with 50 mg, then I'd go back and see your GP after, you know, a few weeks or a month or so, and then…and bump it up to a hundred.

Example 3. *(Clinician 1, Patient: Female, 30–40 years).*

Clinicians would sometimes corroborate patients' verbal accounts with PGHD to get a more accurate picture of a patient's

condition. The use of PGHD, in these examples, functions as an additional 'checking' task for clinicians. Some examples raised the possibility that such corroboration could be interpreted by patients as verifying or checking up. In Example 4, the patient reports that one of their treatments is wearing off after two weeks. Later in the appointment when the PGHD graphs are reviewed, the clinician suggests that the patient's account may not be accurate.

C: So if we go back a two week period I guess that would be beginning of November. So I'm not sure I'd have been able to pick out that two weekly pattern.

P: No. I think I have a problem with pacing, and I think the more I do the more my pain levels are. Probably the days that it's spiked is when I've been working and….

C: Okay. So you can pick out that most recently it's been at its worst hasn't it over the three months?

P: Yeah, because I feel the steroid's worn off. That's interesting, that, because it's just gone slightly up again hasn't it?

C: It looks almost like there are monthly cycles doesn't it, rather than fortnightly?

P: Yeah. How weird.

Example 4. *(Clinician 2, Patient: Female, 40–50 years).*

3.2.3. Convincing

In the concluding section of the clinical appointments, clinicians would infrequently draw on the PGHD as additional evidence to convince the patient about proposed actions and treatment. In Example 5, the clinician summarises their assessment of the patient's condition and refers to PGHD to make their case:

C: Okay. So I guess the things to consider are the impact on your quality of life, which perhaps the [PGHD] might have helped you to see is perhaps bigger than…because you're somebody that's very resilient and you just manage to get on regardless really, but it sounds like it does have a significant impact on you, even though you manage to do everything, most of the things that you want to. So there's that kind of point of view. […] Do you see what I mean?

P: Yeah, sure.

C: So it's always your decision. It's difficult for me because we've just met for the first time, but from what X has said on his previous letter he was really keen to get you back on [the medication] if possible.

Example 5. *(Clinician 2, Patient: Female, 50–60 years).*

The PGHD was sometimes treated as an objective measure, comparable to other numerical data reviewed in the appointment (such as blood test results, and counts of swollen and tender joints), albeit one that needed further explanation to allow for interpretation. However, at times, when the PGHD did not support the clinicians' assessment of disease activity based on their examination findings, it was used as a subjective self-reported figure that should be treated with caution. In Example 6, the clinician chooses to downplay both the patient's account and the PGHD to try to convince the patient that their RA is perhaps worse than they are letting on and that perhaps additional therapy is needed:

C: Now, looking at the scores that you've provided over the last three months, you know, from that it sounds as though there's almost nothing going on because the pain scores have been minimal. Talking to you as well, it doesn't sound as though there's very much active inflammation, but I think that you're quite stoical and the fact that wrist is a little bit swollen rings quite an alarm bell in my mind, despite all of those other reassuring things that, actually, maybe the rheumatoid isn't as perfectly controlled as it might be.

Example 6. *(Clinician 2, Patient: Male, 60–70 years).*

The three uses of the PGHD as discussed above were not mutually exclusive and were often used in combination throughout the appointment. For example, corroborating a patient's verbal account and then inviting the patient to collaborate on interpreting their condition further.

4. Discussion and conclusion

4.1. Discussion

This work aimed to better understand how engagement with PGHD informed discussions between clinicians and patients during the consultation. Our findings suggest that PGHD is used differently by clinicians depending on when they introduce it in the appointment and has different functions accordingly. When the PGHD is discussed in the introductory section, it can provide new information to the clinician who can then explore the pertinent issues in more depth throughout the appointment. As such, collaboration can encourage an active approach to interaction in contrast to using PGHD to corroborate what is already known. As with previous literature, the PGHD on its own tells the clinician very little other than the frequency and severity of symptoms and flares, and benefits from context from the patient to make sense of it [2].

The ambiguity of the PGHD can result in several possible outcomes. The use of PGHD can provide an opportunity for clinicians to collaborate more with patients by interpreting the data together to elicit additional insights into a patient's condition. Alternatively, the clinician may ignore or reject PGHD if it does not fit into their clinical formulation, raising the question about how clinicians' value PGHD [23]. The introduction of PGHD may require clinicians to be open to having a new approach and to be convinced of the potential for the data to benefit patient outcomes.

The challenge, then, is that the introduction of PGHD into medical appointments requires the clinician to engage in new tasks (interpretation of data, encouraging patients to give context) whilst trying to integrate this data into existing clinical work that has to be completed through the (brief) encounter [31]. Introducing PGHD early into the appointment requires the clinician to change their existing way of running their appointment, a fixed format and structure they were taught at medical school. It may feel more natural for a clinician to integrate PGHD as an additional 'score' to check-in review sections of an appointment, rather than using it as a starting point for the consultation, but this limits the interpretation of PGHD into supporting evidence to corroborate patient accounts**.** Furthermore, this study has shown that, in contrast to previous concerns [24,32], integrating PGHD into appointments does not lead to a significant increase in the length of appointments.

The use of PGHD in these examples illustrate asymmetry in the medical appointment – clinicians were in control of when, what, and how PGHD was used in appointments. Previous work with patients [26] found that they believed PGHD legitimised their experiences in the consultations. Also, the graphs offered the opportunity to discuss important non-clinical symptoms, such as sleep, that might be difficult for patients to raise spontaneously. Training programs on how to effectively utilize PGHD in clinical encounters with patients should be developed and evaluated, informed by existing guidance and previous studies [23,32,33]. This is paramount to capitalise on the potential for the implementation of PGHD into the standard medical interview structure to lead to more shared conversations, and to enhance patient care.

4.2. Limitations

Our patient and clinician samples were highly selective as part of a pilot study investigating the feasibility of collecting daily symptom reports from RA patients using a smartphone app and integrating it into the EHR [11]. The research consultations were intended to involve the PGHD and the data was referred to in every consultation.

They were conducted by two clinicians who were part of the research team and therefore had a particular interest in using the PGHD. These limitations warrant caution in extrapolating the way PGHD was used to routine outpatient consultations. Our approach might be perceived as a best-case scenario, and further research around the use of PGHD in more naturalistic settings is needed. There is also a need for better ways of evaluating the influence of PGHD on treatment decisions.

4.3. Conclusion

We found that the time at which PGHD was reviewed during the consultation appeared to impact how the data were used by clinicians. Patients in this study did not get the opportunity to decide when, and what was discussed in the appointments. Educating patients and clinicians about the effect that the timing and different uses of PGHD might have upon the consultation may help to maximise its benefits, especially in improving shared decision-making in clinical outpatient consultations.

4.4. Practice implications

PGHD, integrated into the EHR, has the potential to move patient-clinician consultations one step closer towards genuine shared and patient-centred decision making. However, PGHD alone is not enough to achieve this. To harness these opportunities, there is a need first, to better understand how PGHD might best be used to support patients and clinicians to have more collaborative, shared discussions, during consultations. Once this is better established, the focus moves to train patients and clinicians in using PGHD effectively throughout the consultation.

Funding

This study was funded by Versus Arthritis (REMORA and CfE grant numbers 21226). This research was supported by the National Institute for Health Research Applied Research Collaboration Greater Manchester (NIHR ARC-GM). The views expressed in this publication are those of the authors and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

CRediT authorship contribution statement

Louise Laverty: Conceptualisation, Formal analysis, Writing - original draft. **Julie Gandrup:** Conceptualisation, Formal analysis, Writing - review & editing. **Caroline Sanders:** Funding acquisition, Methodology, Writing - review & editing. **Dawn Dowding:** Funding acquisition, Methodology, Writing - review & editing, Supervision. **William G Dixon:** Conceptualisation, Funding acquisition, Methodology, Writing - review & editing, Supervision. **Sabine N van der Veer:** Conceptualisation, Funding acquisition, Methodology, Writing - review & editing, Supervision.

Declaration of interest

None

Acknowledgements

We thank Bridget Weston and Lynn Austin for their generous contributions in the early phases of this research and in the original pilot study.

Appendix 1

Patient-generated health data items collected on the REMORA smartphone app. Only the daily items were available as graphs in the patient's electronic health record for discussion during the consultation.

Daily
- Pain
- Function
- Fatigue
- Sleep
- Physical wellbeing
- Emotional wellbeing
- Coping
- Morning stiffness

Weekly
- Tender joint count
- Swollen joint count
- Patient global assessment
- Employment status
- Hours missed at work due to health problems
- Hours missed at work due to other reasons
- Hours actually worked
- Degree health affected work productivity
- Degree health affected daily activities
- Occurrence of flare in the last week
- Flare description

Monthly
- Health Assessment Questionnaire (Validated questionnaire consisting of 23 items to assess physical function)

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4

Setting up a mobile health study: REMORA1.5

4.1 Why we needed REMORA1.5

The REMORA1 feasibility study provided proof of potential transformative value of integrated remote symptom monitoring for patients, clinicians and researchers.(55) However, the technical infrastructure was bespoke and integrated with one specific site only. Thus, the next challenge in the REMORA programme was to make it scalable. This included an essential update of the technical infrastructure so it could be deployed at multiple sites without the need for the research team's presence in clinic to assist participants with setup.

The testing of this new infrastructure was carried out at one site, and it provided an opportunity to expand on the REMORA1 research on four important parameters: 1) Longer data collection, 2) more participants that were more representative of "real-life" patients, 3) on-boarding without assistance from a researcher, and 4) linking with contextual data collected from the EHR (e.g. disease activity scores and medication data). The new observational study that harnessed these advances made up REMORA1.5. I led or was deeply involved in all phases of the study: conceptualization, writing the protocol, applying for and receiving NHS Research Ethics Committee approval, maintaining approvals through several amendments (both minor and major), setting up the study and overseeing its daily running.

Unfortunately, delays during the technical development led to time constraints to complete the study as planned. The study start date was pushed back substantially (~10 months),

which in turn meant that I had less time to recruit participants, and the data collection period was shortened. For my PhD, this meant I did not have time to complete follow-up or do the analyses as initially intended.

This chapter illustrates the complexity of setting up the study, reasons why delays happened, and my learnings gained through supporting the establishment of the REMORA1.5 study. It also presents preliminary, descriptive results from the observational study.

4.2 Setting up the study

The original aims of the REMORA1.5 study were to examine the patterns of RA symptoms and flares on a day-to-day basis as well as investigate patterns of treatment response through time. I also wished to explore the feasibility of collecting daily data over a longer time period by looking at attrition and completion rates. I was not interested in evaluating feasibility and acceptability using qualitative methods, as this would be covered in the future REMORA2 study.

The full protocol for the study, which I wrote, can be found in Appendix 9.3.1, but I will briefly cover the most central things about the methods below before presenting preliminary results from an interim analysis.

4.2.1 Funding and stakeholder involvement

The REMORA1.5 project was funded through a Health System Led Investment scheme from NHS England focussed on healthcare provider digitisation.

The funding supported a broad team consisting of multiple stakeholders necessary to develop the technical infrastructure and set up the research study: the research team at the University (including a data manager, information governance officer, and myself, amongst others), a University app development team, a project manager, and multiple external system developers. The funding also covered activities relating to the PPIE group, who met regularly throughout the set-up phase. The PPIE group was involved in many critical study decisions and they assisted in identifying potential barriers and helped to find possible solutions.

The study was eligible for support by the regional clinical research nurse network, who carried out all tasks relating to participant recruitment.

4.2.2 Methods

Study design, patient population and recruitment strategies

The study design was a prospective cohort study. We aimed to recruit 50-100 patients with RA from Salford Royal NHS Foundation Trust's rheumatology outpatient clinic. People were eligible if they 1) were a Salford rheumatology outpatient, 2) were >18 years of age, 3) owned and could use an Android smartphone ("bring you own device"), and 4) were able to understand verbal and written instructions in English.

Due to the COVID-19 pandemic, we had to plan for both in-person and remote recruitment, as many follow-up outpatient consultations were being carried out virtually. The recruitment period spanned six months from October 2021 to April 2022. The clinic's research nurses were responsible for identifying, recruiting and consenting participants, but clinicians could also refer patients directly. If an eligible participant came for an in-person clinic appointment, a research nurse took consent in clinic. If an eligible participant had a virtual consultation, the consent form was emailed or posted (depending on patient preference) and had to be signed and returned electronically. Following consent, the participants received written download and user instructions for the REMORA app and completing NHS Login. NHS login makes it easier and quicker for patients to access multiple digital health and care services with just one email address and password. It is a trusted, safe, and secure login developed by the NHS, so patients know their health and care data is protected to the highest standards. This allowed the participants to download the app by themselves and start tracking their symptoms. Besides regular clinical appointments, there were no additional study visits required.

We later submitted an amendment for approval to contact participants who had provided consent but had not started using the app (approved 22/02/22). In such cases, I rang to ask if they needed any further support to start engaging with the app. If no response or data had been received after three days from the first call, I called again on a maximum of two additional occasions, after which I stopped following up.

Data collection

For this study, data was collected both from the app and from the EHR. The technical infrastructure that was necessary for any data to be collected is outlined below in more detail, followed by a description of the two data collection methods (for patient and clinician-reported data).

1) Technical data collection infrastructure

Figure 4.1 provides a visual overview of the technical infrastructure that faciliated a secure dataflow between the app, the EHR and a research database. Once a research nurse had recruited and consented a participant, the patient logged into the REMORA app using their NHS Login (if they did not have one, guidance were provided for how to set one up). The first time they logged in, they were asked to provide eConsent to share their data with the University of Manchester for research purposes. This only acted as a digital statement to confirm people's willingness to share their data, with the purpose of demonstrating that such a digital consent "token" could be moved through the system. Formal consent was included in the main consent process. Following eConsent, the participant was ready to start entering their daily symptoms (i.e. the PGHD). The PGHD was transferred to a central repository within a secure NHS environment using Fast Healthcare Interoperability Resources (FHIR) standards. The repository was part of the Greater Manchester Digital Platform (GMDP), an existing regional data repository managed separate from the University. Graphical summaries of symptom data held in this repository were made available via Tableau, a data visualisation tool. The graphical summary was integrated seamlessly into the Trust's EHR system. This meant that clinicians –once they had selected the right patient in the EHR– could securely view the graphical summary for that patient within the EHR without having to log in again (i.e. single sign-on).

Three times a day, PGHD was automatically pulled down from the central repository into a research database at the University of Manchester.

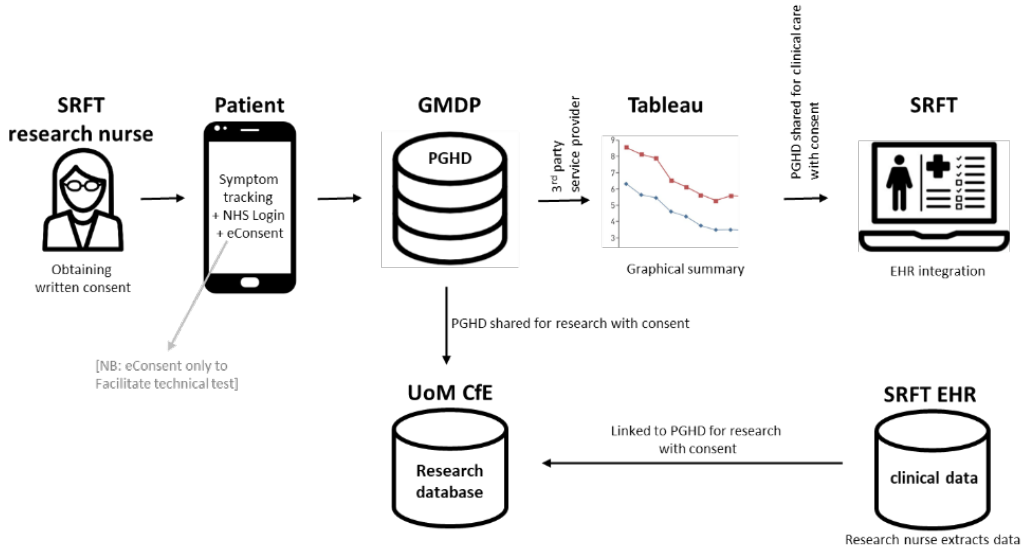

Figure 4.1*. Visual depiction of the REMORA1.5 technical infrastructure. GMDP: Greater Manchester Digital Platform, SRFT: Salford Royal NHS Foundation Trust, EHR: electronic health record, PGHD: Patient-generated health data, UoM: University of Manchester*

2) Patient-reported data from the REMORA app

Included participants tracked their symptoms on the REMORA app for a period of six months as part of their daily life. The app prompted daily, weekly, and monthly question sets with a single notification or alert each evening. See Figure 4.2 for screenshots of the app.

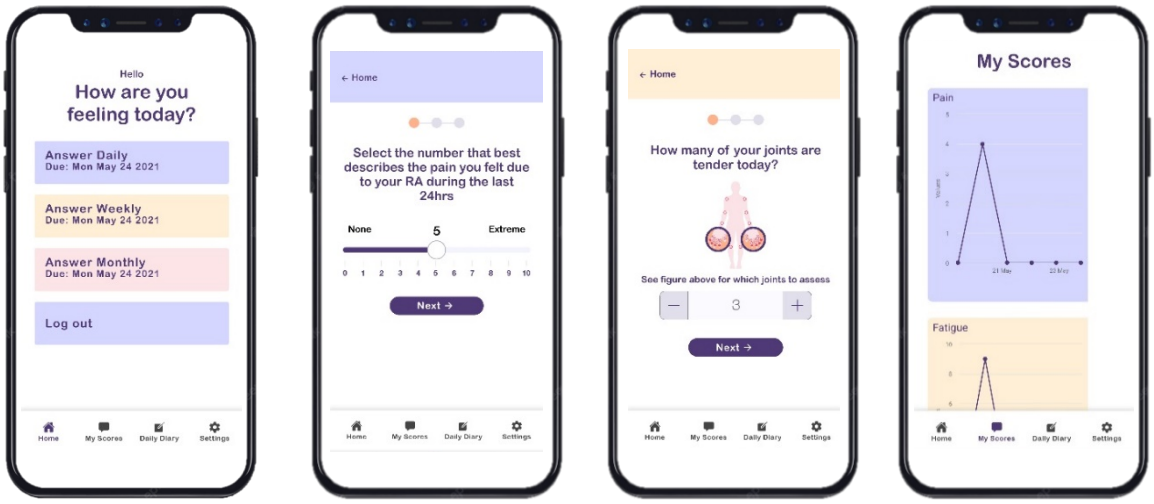

Figure 4.2*: Screenshots from the REMORA app*

Daily questions included seven common symptoms (pain, fatigue, function, sleep, coping, and emotional and physical wellbeing) rated on a 0-10 numerical rating scale, and duration of morning stiffness using ordinal scales, while weekly and monthly questions were longer questionnaires about flares, tender and swollen joint counts (out of 28 joints), employment status, work participation and the health assessment questionnaire (HAQ).(69) Completion of the daily question set took around 1 minute, while a monthly question set could take up to 5 minutes. Besides the pre-defined question sets, participants had two different options to provide further contextual information within the app. If a participant reported that they had a flare within the last week, they had the option to note down factors they believed caused the flare. Additionally, there was a free-text diary function. Information written here was private, and would not be shared. Graphed summaries of three specific symptoms (pain, fatigue and sleep) were available to review within the app (screenshot furthest to the right in Figure 4.2). Importantly, data was not monitored in between scheduled consultations, and this was made explicit to the participants at multiple occasions before providing consent to take part.

To collect data, participants had to download the app and start using it by themselves without support at hand beyond a written set of instructions and written guidance within the app. In order for this to be successful, the written instructions needed to be easily comprehensible. I lead on the development of the app download and user instructions in close collaboration with our REMORA patient and public involvement and engagement (PPIE) group. It began as a long, text-heavy document but evolved into a two-page visual cartoon (see Appendix 9.3.2) inspired by an NHS App poster that was displayed at restaurants and other hospitality venues at the time. In addition to the patient materials, I monitored the REMORA email inbox daily, where participants were instructed to direct any questions or concerns.

3) Clinician-reported data from the electronic health record

Clinician-reported contextual information was extracted from the EHR and entered into a REDCap database. The collected data items were informed by the EULAR core dataset recommendations for observational research and the data I needed to address my research questions.(70) Extracted data included duration of disease, disease activity scores, baseline medication and any recorded changes, comorbidities and various other typical baseline characteristics. Design challenges emerged around how to best capture key elements about the anti-rheumatic drugs a participant was taking at baseline and record any changes

(stopping and/or starting a drug) at subsequent visits. Steroids posed additional challenges since administration route, dose and treatment duration vary to a great degree. Other important design considerations included reducing the amount of free-text fields to a minimum, to set rules for data entry in specific fields to avoid odd entries and to structure the forms in a format that later could be easily merged with the smartphone dataset. The data items were extracted manually by the research nurses from the patient's EHR at baseline and all subsequent visits during the 6-months follow-up (starting from the participant's first app entry) and entered into the database. I designed the REDCap database with input from the REMORA data manager and trialled it among research nurses. The REDCap data was later moved to the research database and linked with the PGHD for a complete dataset (lower part of Figure 4.1). The data quality of the REDCap data was not monitored frequently due to limited resources.

Monitoring data completeness and quality

Completeness of the daily symptom data from the app was monitored via an online dashboard developed by the centre's data manager that showed days since last symptom report for each participant (Figure 4.3). The dashboard was colour-coded from green (<5 days since last report) to orange (5-8 days since last report) to red (>8 days since last report), so upon manual inspection it was easy to identify which participants to follow up with. Subsequently, after cross-referencing with an electronic participant list, I manually sent reminder emails to participants on day 5, day 8 and day 15 of not reporting any symptoms in the app. The standardized emails offered participants two ways of contacting the research team (email and telephone) if they needed assistance or had any concerns.

Participant ID (arbitrary)	First Day Report	Last Day Report	Days Since Last Report
1	01/04/2022 16:30:22	14/06/2022 00:54:23	0
2	21/09/2021 12:44:41	13/06/2022 21:16:32	1
3	26/10/2021 12:20:20	13/06/2022 18:43:21	1
4	01/11/2021 15:16:39	13/06/2022 21:16:19	1
5	26/11/2021 23:17:32	13/06/2022 21:02:19	1
6	05/12/2021 08:33:23	13/06/2022 21:40:07	1
7	24/12/2021 12:08:48	13/06/2022 15:38:28	1
8	08/01/2022 11:19:06	13/06/2022 22:12:31	1
9	16/01/2022 17:24:07	13/06/2022 22:57:42	1
10	29/01/2022 19:08:54	13/06/2022 10:32:45	1
11	01/02/2022 09:12:24	13/06/2022 22:58:55	1
12	02/02/2022 12:36:30	13/06/2022 18:58:28	1
13	12/02/2022 18:32:23	13/06/2022 19:22:20	1
14	13/02/2022 19:50:01	13/06/2022 22:46:35	1
15	02/03/2022 20:28:50	13/06/2022 21:04:31	1
16	16/11/2021 11:55:07	12/06/2022 22:44:42	2
17	16/02/2022 19:22:08	12/06/2022 19:20:48	2
18	05/02/2022 13:03:37	11/06/2022 17:19:04	3
19	19/01/2022 12:17:27	06/06/2022 19:07:48	8
20	04/01/2022 12:02:41	05/06/2022 07:25:07	9
21	23/03/2022 00:32:03	30/05/2022 23:08:09	15

Figure 4.3*. REMORA1.5 dashboard to monitor participants' completion of daily questions in the app.*

Data visualisation and clinician training

The graphical summary in the EHR was developed in collaboration with a Tableau data visualisation expert and iterated in a joint 2-hour, online workshop with the PPIE group and clinicians, which I co-developed and moderated. The result was an interactive and intuitive visualisation, which gave a quick overview of the participant's PGHD since the last visit. For clinicians wishing to explore the data in more depth, different symptoms could be highlighted or combined, time intervals changed and free-text entries added or removed. Figure 4.4 shows the EHR visualisation for a simulated patient with three months of data.

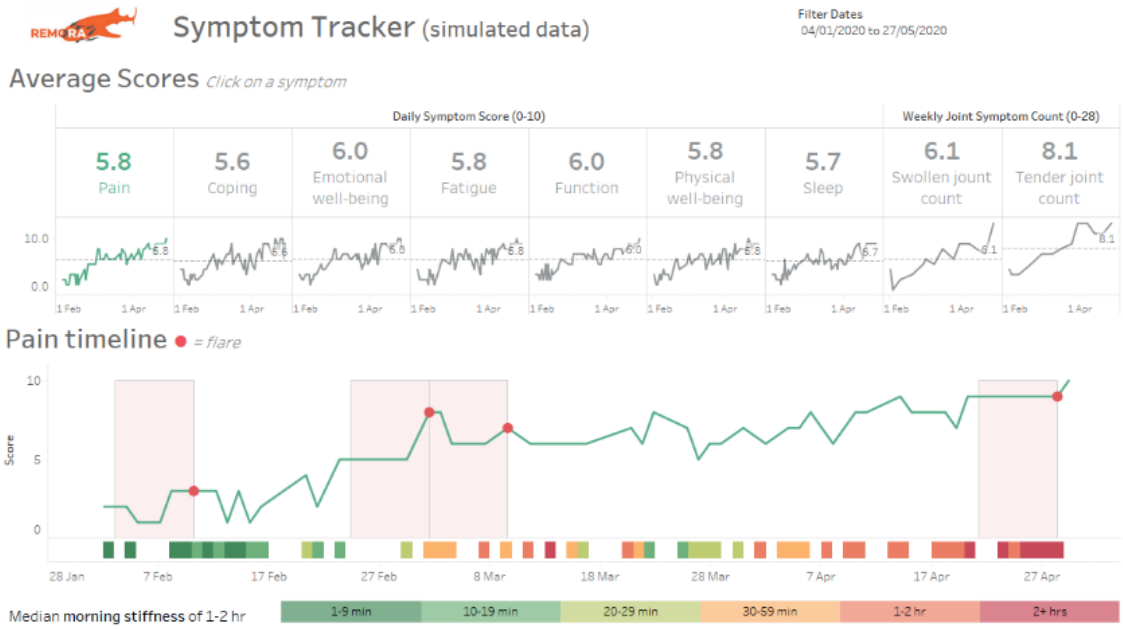

Figure 4.4. *The REMORA data visualisation available from within the electronic health record. Data from a simulated patient.*

As the PGHD represented a whole new source of data for clinicians, they required training in where to find it in the EHR and incorporate it into their consultation. Based on a literature search, I developed a clinician training program that consisted of three core elements: a 1-hour information and hands-on training session, an FAQ document (see Appendix 9.3.3), and a printed reminder note to remind clinicians to check the REMORA data in the EHR. Following development and feedback from members of the clinic's multidisciplinary team, I conducted the training with clinicians in the clinic prior to go-live.

4.3 Reasons for delays

Most bumps along the way were attributed to setting up the technical infrastructure and the integration with NHS Login. Other bumps were attributed to the project management. It was a large, complex digital health study with many internal and external stakeholders.

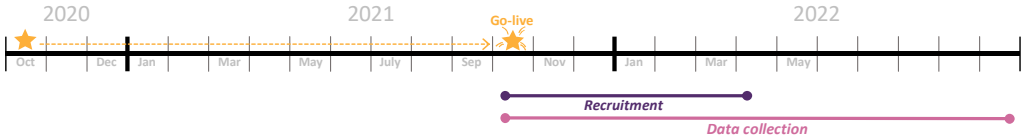

Figure 4.5. *Timeline of the REMORA1.5 study. Stars represent planned go-live and the delay until the actual go-live.*

Despite good intentions and careful planning, issues emerged around communication between teams and 3rd parties, documentation of key elements, responsibilities and insufficient resources, which meant that delivery of the infrastructure was delayed. To add to this, the project was launched right at the peak of the first COVID-19 wave in 2020 and ran through the entire pandemic. Some stakeholders were forced to shift focus and resources to COVID-related projects, and the REMORA project could therefore not always be prioritised. Nonetheless, these things were all upstream from the research study itself, and the challenges of setting it all up notwithstanding, the study took off and is generating valuable data already (see timeline in Figure 4.5).

4.4 Preliminary results

Recruitment for the study ended April 12th 2022. At the time of writing, data collection is still ongoing for the majority of participants, so the following results arise from an interim dataset (data lock date 25/05/22) with varying follow-up times.

4.4.1 Baseline characteristics

At the end of the recruitment period, 74 participants had consented to participate. Of the 74 participants, 32 participants downloaded the app and contributed at least one day of symptom data. Figure 4.6 gives a visual overview of cumulative recruitment over time, showing how recruitment (the darker line) was relatively steady throughout the recruitment period with a plateau in March. It is also evident that the number of participant starting

tracking and contributing at least one day of symptom data (= active participants) is lower than the amount of recruited participants (the lighter line).

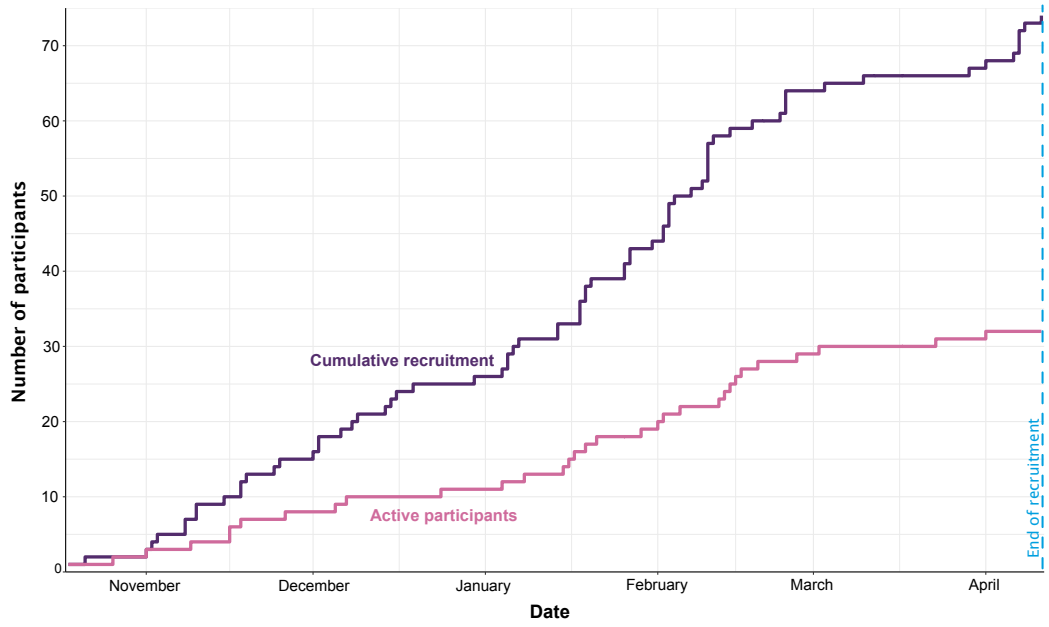

***Figure 4.6**. Cumulative recruitment over the 6 months recruitment period (dark line). Pink line denotes the cumulative sum of participants who started using the app and entered at least one symptom (active participants).*

The baseline characteristics of all participants are presented in Table 4.1, stratified by those who downloaded and used the app at least once (tracking, n=32) and those who did not use the app at all (non-tracking, n=42). The non-tracking group was older and had more active disease (according to the DAS28 recorded in the EHR), but were otherwise similar to the tracking group. Data on comorbidities and baseline medication use will be explored at a later stage. Comparing these two groups is essential for learning about the generalisability of future results and to identify groups of participants who would benefit from more support in using the app in upcoming studies.

Table 4.1. Participant characteristics at baseline in the REMORA1.5 study. n(%) if not otherwise stated. Stratified on tracking participants (participants who entered at least one symptom on the app) and non-tracking (participants who consented to the study but never entered any symptom data).

	Total (N=74)	**Tracking (N=32)**	**Non-tracking (N=42)**
Age			
Median [IQR]	56.0 [46.5 65.0]	52.0 [42.0 64.0]	60.5 [50.3 65.8]
Gender			
Male	20 (27.0%)	10 (31.3%)	10 (23.8%)
Female	54 (73.0%)	22 (68.8%)	32 (76.2%)

	Total (N=74)	Tracking (N=32)	Non-tracking (N=42)
Ethnicity			
White	65 (87.8%)	29 (90.6%)	36 (85.7%)
Non-white	9 (12.2%)	3 (9.4%)	6 (14.3%)
Years since diagnosis			
Median [IQR]	5.00 [2.00 8.00]	4.50 [2.75 11.0]	5.00 [2.00 7.00]
Missing	1 (1.4%)	0 (0%)	1 (2.4%)
BMI			
Median [IQR]	29.0 [25.0 32.5]	30.0 [25.0 31.0]	29.0 [24.5 33.8]
Missing	27 (36.5%)	15 (46.9%)	12 (28.6%)
Smoking status			
Current	9 (12.2%)	4 (12.5%)	5 (11.9%)
Former	17 (23.0%)	7 (21.9%)	10 (23.8%)
Never	28 (37.8%)	9 (28.1%)	19 (45.2%)
Not stated	20 (27.0%)	12 (37.5%)	8 (19.0%)
RhF status			
Positive	49 (66.2%)	23 (71.9%)	26 (61.9%)
Negative	18 (24.3%)	7 (21.9%)	11 (26.2%)
Not stated	7 (9.5%)	2 (6.3%)	5 (11.9%)
CCP antibody status			
Positive	39 (52.7%)	16 (50.0%)	23 (54.8%)
Negative	18 (24.3%)	9 (28.1%)	9 (21.4%)
Not stated	17 (23.0%)	7 (21.9%)	10 (23.8%)
<u>DAS28 and its components</u>			
DAS28 (recorded in EHR)			
Median [IQR]	3.45 [2.24 5.30]	3.09 [2.17 4.97]	4.95 [2.32 5.64]
Missing	32 (43.2%)	12 (37.5%)	20 (47.6%)
DAS28-CRP (calculated)			
Median [IQR]	4.49 [3.38 5.10]	4.49 [3.38 5.50]	4.48 [3.33 5.07]
Missing	21 (28.4%)	11 (34.4%)	10 (23.8%)
DAS28-ESR (calculated)			
Median [IQR]	4.98 [3.41 5.75]	5.09 [3.35 5.56]	4.79 [3.53 5.80]
Missing	22 (29.7%)	12 (37.5%)	10 (23.8%)
Patient global assessment (0-100)			
Median [IQR]	61.0 [30.0 75.0]	60.0 [20.0 70.0]	60.0 [40.0 80.0]
Missing	16 (21.6%)	7 (21.9%)	9 (21.4%)
Tender joints (0-28)			
Median [IQR]	5 [2 9]	5 [0 9]	5.00 [2 8]
Missing	12 (16.2%)	5 (15.6%)	7 (16.7%)
Swollen joints (0-28)			
Median [IQR]	2 [0 5]	2 [0 6]	2 [0 5]
Missing	13 (17.6%)	6 (18.8%)	7 (16.7%)
CRP (mg/L)			
Median [IQR]	4.00 [4.00 14.5]	4.40 [4.00 15.0]	4.00 [4.00 10.5]
Missing	3 (4.1%)	3 (9.4%)	0 (0%)
ESR (mm/hr)			
Median [IQR]	23.5 [11.0 41.3]	23.0 [14.0 38.0]	24.0 [10.0 43.0]
Missing	4 (5.4%)	3 (9.4%)	1 (2.4%)

IQR: Inter-quartile range, RhF: Rheumatoid factor, CCP: Cyclic Citrullinated Peptide, DAS28: Disease activity score using 28 joints, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, mg: Microgram, L: Liter, mm: Millimetre, hr: Hour

4.4.2 Reporting patterns

At the time of extracting the dataset for my analyses, the median number of days in the study was 107 (IQR 49, 138). Each participant contributed daily scores on a median of 67 (IQR 17, 97) days and completed a median of 9 (IQR 7, 14) weekly questionnaires. This resulted in a total of 2152 daily questionnaires and 290 weekly questionnaires.

Figure 4.7 shows the patterns of daily entries through time. Each row reflects an individual participant, with participants sorted based on their engagement level (i.e. total number of daily entries). Weeks are coloured according to the answer to the weekly flare question "Did you experience a flare in the last week?".

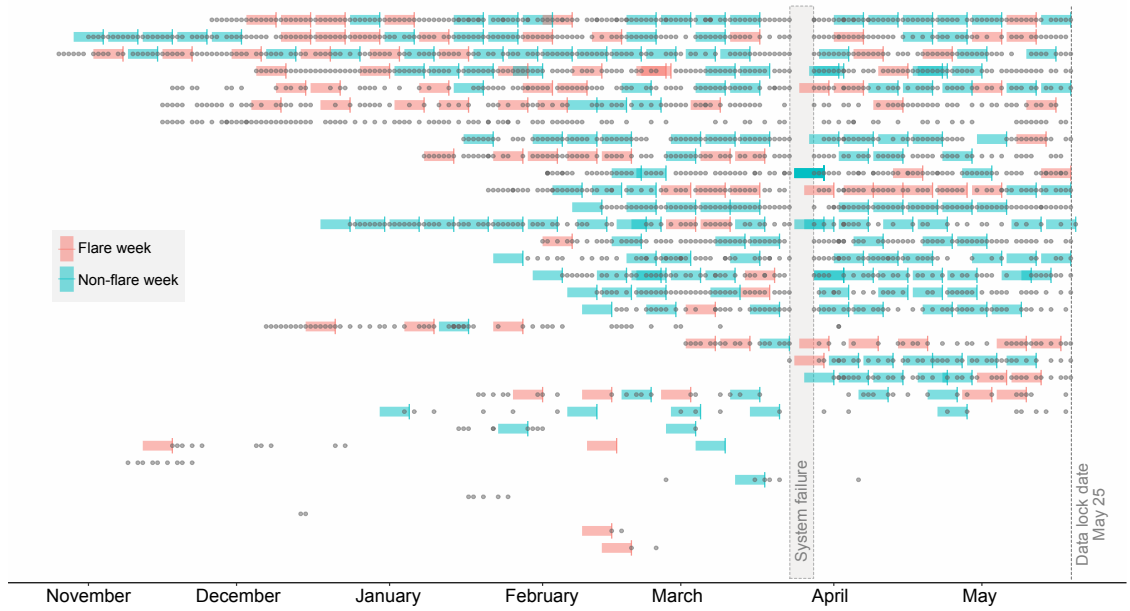

Figure 4.7 *Patterns of daily and weekly data entry. Sorted on number of daily entries (highest to lowest from top to bottom). Each row is a different participant. Vertical lines denote weekly responses, point daily responses. The shaded bands represents the week preceding each weekly response and the two colours denote whether patients reported a flare or no flare in that week. (The platform for receiving symptom data was down over a week end of March).*

4.4.3 Flares

Twenty-eight out of 32 (88%) participants reported at least one flare week, with 95 patient-reported flares in total out of 289 answered flare questions (33%). They reported a median

of two flares each (IQR 1 to 7) with a range of 0-10 flares. These results are similar to the flare findings in REMORA1 which are presented in the next chapter.

4.4.4 Email reminders

I sent 111 email reminders from 20th of December-25th of May 2022 to 25 unique participants to nudge them to recommence using the app. The split was 67 Day 5 emails, 30 Day 8 emails and 14 Day 15 emails. Of the participants receiving reminders, they received a median of two reminders each (IQR 1 to 5). The maximum number of reminders sent to one participant was 20. Four participants accounted for 50% (56/111) of the reminders sent.

Figure 4.8 provides an overview of daily entries and email reminders and three examples of different patterns of responsiveness (no reminders necessary, responsive to reminders and not responsive to reminders). The dots with a vertical line on the same day represents days where a reminder was sent and the patient picked up tracking again immediately after. Of the reminders sent, 46% (51/111) were followed by a data entry within two days of receiving the email.

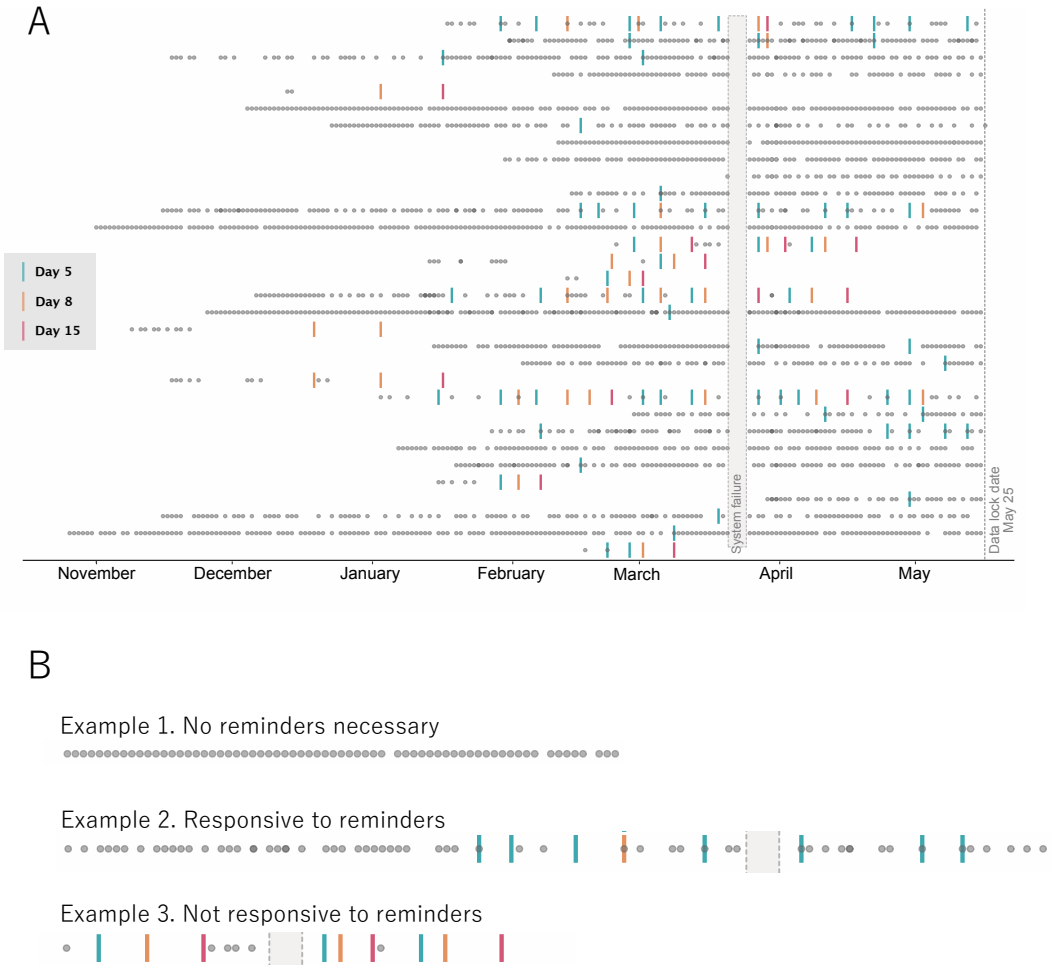

Figure 4.8*. Daily data entries and email reminders overt time. A. Overview of whole cohort. Each row represents a participant and the dots a daily data entry. Vertical lines represent an email reminder, coloured according to email type (approximately day 5, day 8, and day 15). Participants were not contacted again, if they did not recommence data entry. B. Three examples highlighting different response patterns.*

4.4.5 Follow-up phone calls

During follow up with consented participants who did not start using the app, I called 25 participants. Due to the delay in getting ethical approval, calls were made five months after recruitment had started, so for most participants, their original consent was many months ago. Around a third (8/25) did not pick up at all. Another third (9/25) asked to be withdrawn from the study. When asked about reasons for withdrawing, participants explained that it was "*too much information*", that they did not know what they were signing up for, that they had "*a lot on the plate at the moment*" or were "*too sick to think about it*". Some also reported lacking the tech skills with no one around to offer assistance. Only 3 participants started using the app after the follow-up call. The main reasons for not starting

to use the app, despite wanting to take part, were being busy or snowed under with other things (caring for others, bereavements, personal issues). They just had not found the time. Some had lost the download and user instructions (which were re-sent via email immediately after the call). One participant explained that he had been ill with a fractured foot and *"didn't want to ruin your research study and give you poor results*".

4.5 Discussion of preliminary insights

Below I will draw together some of the main insights from setting up REMORA1.5 and the preliminary results and describe where these have informed the future REMORA2 trial. Although much could be learned from the development of the technical infrastructure in itself, I will focus on the things related to the observational research study that I was responsible for during my PhD: initial recruitment, initiating tracking and sustaining engagement. The information that informed the insights came from various sources, some of which have been presented already, such as the data monitoring system. Other sources included emails and phone calls with patients (both patients participating in the study and patients from the PPIE group), notes and emails from research nurses, and meeting minutes from project management meetings.

4.5.1 Optimising recruitment

The study recruited to target (n=74) within the allotted recruitment period thanks to the research nurse team at Salford Royal. The research nurses noted that it was an easy study to recruit to, with many patients immediately understanding the concept and direct benefits to them.

The recruitment relied on the patient materials that I developed in collaboration with the PPIE group and the centre's information governance officer: posters, information leaflets, the participant information sheet and the app download and user instructions. Despite every effort to keep it simple, the complex study setup resulted in a lengthy participant information sheet (~10 pages) with details about data flow, data security and data sharing agreements. To make up for the long information sheet, we provided the research nurses with eight "key messages" that they could cover with the participants before taking consent. However, it was unclear if these were used, as multiple participants later explained they did not know what they signed up for and asked to be withdrawn from the study on

this basis. The patient materials need to balance the requirement for details with the need to be brief and understandable. A brief, predominantly visual summary could be attached, which does not require participants to read the full document in detail, but still provides a good understanding of what the study requires. This was successfully done in another mobile health study within the Centre and will be done in REMORA2.(71) Additionally, the people responsible for recruiting should be trained thoroughly to ensure agreement and consistency. Because of the pandemic, we had to perform all site training online, but based on my experiences, I would recommend to do it in-person.

For REMORA1.5, the app was only available on Android phones. Due to time and resource constraints on app development, the original plan to make it available on both iPhones and Android phones could not be honoured. During recruitment, the research nurses made us aware that nearly half of approached patients were ineligible because they owned an iPhone, despite showing interest and wanting to participate. So, catering to only one operating system possibly slows down or extends recruitment. Making the app available on both operating systems is therefore a priority in REMORA2, where timelines are tight and therefore leave little room for delays. Alternatively, loan devices could be offered to participants. We decided against this, as it adds to the burden of daily data entry to carry an extra, non-familiar device, risked disengagement and importantly could not be done while conducting remote on-boarding.

4.5.2 Initiating symptom tracking

Less than half of the consented participants started using the app, but of those, many kept using it consistently. During recruitment, I had limited options to take action against the poor conversion rate from consented participants to those who submitted at least one symptom report. It is possible, however, that conversion of these participants had been better if follow-up had happened nearer to their expected start of using the app, e.g. one week after having provided consent.

For the future REMORA2 study, it will be essential to have a well-tested strategy in place to follow up with participants in a timely manner and offer additional support throughout the course of recruitment, consenting and on-boarding. At the same time – and in line with the previous section - patient materials need to be short and comprehensible to not act as a barrier for conversion. The PPIE group, for example, suggested a short video explaining how to do it, including setting up the NHS Login. Alternatively, participants could receive

technical assistance in person in the clinic from a research nurse, dedicated member of staff or volunteers. While this might increase conversion, it would hinder future scalability and increase costs. It would be useful to more systematically understand what keeps participants from downloading and starting to use the app and get a better idea of what support they might need. This was not in the scope for REMORA1.5, but based on the low conversion rate, a more detailed mixed methods and economic evaluation will be addressed by dedicated work packages in REMORA2.

4.5.3 Sustaining engagement

The preliminary data showed that many participants stayed engaged with the app for long period of times, but completion rates and patterns of engagement over time will have to be explored in more detail when follow-up is complete. As there is no standard way of defining completion rate, different definitions could be examined, e.g. from first to last symptom tracked, out of 180 possible days or censor after x number of days of not tracking.

A fundamental challenge of mobile health studies is sustaining engagement.(72) Loss of engagement can have substantial impacts on data integrity, creating issues such as bias (if those who disengage are different from those who remain engaged), reduced data quality, and high rates of data missingness.(73) In REMORA1, patients demonstrated 80–90% adherence with the app over 12 weeks with a significant one-on-one on-boarding effort. Similarly, an American study of an app collecting daily patient-reported outcomes in 78 people with RA over six months demonstrated a median adherence to daily questionnaires of 80% (though with significant decrease in adherence on a month-to-month basis, declining to 60% by month six).(74) In contrast to these high engagement figures, Seppen et al. demonstrated challenges with engaging RA participants weekly for just four weeks. In their two pilot studies, the completion rates declined from 100% (28/28) and 78% (21/27) in week 1 to 61% (17/28) and 37% (10/27) in week 4, respectively.(75) On a larger scale, in Cloudy with a Chance of Pain, a mobile health research study collecting daily symptom data in patients with chronic pain and not integrated with clinical care, around 35% of participants were lost after the first seven days and more than 55% after the first months. Still, 14% (865/6370) of participants provided data on most days in the first six months and around 30% of participants were in the high-engagement or moderate-engagement cluster, entering data on at least half of days throughout the 6 months.(76) In comparison,

fewer than 20% of participants in the first five Apple ResearchKit studies collecting some kind of self-reported data were active by 10 weeks as measured by daily use.(77) These studies suggest that sustaining engagement over longer periods of time remains a challenge that needs to be considered in future studies. Broadly speaking, studies integrated into clinical care appear better at sustaining engagement than those purely for research.

An important factor for sustained engagement in a study with high data sampling frequency is convenience.(73) In REMORA1.5, participants had to log in with their NHS login every time they were prompted to enter data into the app. A lengthy log-in procedure that needed completing every day was expected to cause frustration and potentially increase attrition. In an email, one highly engaged participant wrote "*I find having to log in through the NHS everyday a bit of a pain. Some older people may find this off-putting.*" Some participants reported it challenging to set up an NHS Login in the first place if they did not already have one. To increase convenience, face or touch ID could be enabled as a way of logging securely into the app, which is planned for REMORA2, where the required resources will be balanced against the risk of losing participants at the onset. At the very least, the app should support auto-fill of information, which the current version did not. Again, this requires balancing available resources against the risk of losing participants. Despite the millions of people in the UK (28 millions by October 2021(78)), who set up an NHS Login during the pandemic, which was necessary to access the official NHS COVID vaccine passport, some participants in our study still needed to be better supported in order to set it up. As this is a crucial step for linking smartphone data to the correct health record, these participants should be identified early in future studies to increase engagement.

Another way of ensuring high engagement is to continuously screen for data missingness. Monitoring completion of daily data entries provided an opportunity to intervene, when participants had disengaged with the REMORA app for >5 days. The manual process of checking, cross-referencing and sending emails was labour-intensive, error prone and dependent on one person, but it was the only feasible way of configuring the system at the time. The results showed that the reminders served a purpose: 45% of email nudges were followed by a data entry within 2 days of receiving it. It is, however important to weigh the manual effort likely to be expended on the task against the achievable benefits (e.g. the increase in amount of completed data), but this could be solved by automating data monitoring and reminder creation.(73) Setting up a fully automated data monitoring system is a key priority for REMORA2. Additionally, the mode (email vs. SMS for example), frequency and amount of reminders need to be carefully considered to not bother

participants too often or unnecessarily, which risks having the unintended opposite effect. Work with PPIE groups, qualitative research with participants and quantitative evaluation of the success of different modes/frequencies within a study would help identify the optimal strategy.

4.5 Conclusion

Despite the challenges and delays in setting up REMORA1.5, the study is running and we are collecting original data from a larger group of people in a more naturalistic setting, expanding on the learnings from REMORA1. Delays were mainly attributed to developing the technical infrastructure, converting consented participants into tracking participants and ensuring efficient follow-up with disengaged participants over time. Insights from REMORA1.5 have already informed key decisions in REMORA2. The original aims of REMORA1.5 relating to patterns of symptoms and flares over time and treatment response will be answered once data collection finishes.

5

Characterising patient-reported rheumatoid arthritis flares using daily symptom data

5.1 Introduction

A better and more detailed characterisation of patient-reported flares could potentially provide clinically useful insights into symptom variation and trajectories as well as help to untangle which symptoms (or combination of symptoms) and their patterns drive a flare. The daily data collected as part of the REMORA1 study, although limited in size, was well suited to provide some preliminary answers to questions about the temporal relationship between RA symptoms and flares. Therefore, I set out to understand the frequency and duration of weekly patient-reported flares in this cohort and to explore their associations with various summary features of daily symptoms reported during the preceding week.

5.2 Contribution statement

I developed the research questions, analysed the daily symptom data collected during the REMORA1 study and prepared the manuscript with input from my co-authors. It was submitted and ultimately published in Rheumatology Advances in Practice in 2022 (https://doi.org/10.1093/rap/rkac021). Supplementary figures and tables belonging to this publication can be found in Appendix 9.4.

5.3 Article 3: Using patient-reported data from a smartphone app to capture and characterize real-time patient-reported flares in rheumatoid arthritis

RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2022;00:1–9
https://doi.org/10.1093/rap/rkac021
Advance Access Publication 16 March 2022

Original article

Using patient-reported data from a smartphone app to capture and characterize real-time patient-reported flares in rheumatoid arthritis

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Abstract

Objective. We aimed to explore the frequency of self-reported flares and their association with preceding symptoms collected through a smartphone app by people with RA.

Methods. We used data from the Remote Monitoring of RA study, in which patients tracked their daily symptoms and weekly flares on an app. We summarized the number of self-reported flare weeks. For each week preceding a flare question, we calculated three summary features for daily symptoms: mean, variability and slope. Mixed effects logistic regression models quantified associations between flare weeks and symptom summary features. Pain was used as an example symptom for multivariate modelling.

Results. Twenty patients tracked their symptoms for a median of 81 days (interquartile range 80, 82). Fifteen of 20 participants reported at least one flare week, adding up to 54 flare weeks out of 198 participant weeks in total. Univariate mixed effects models showed that higher mean and steeper upward slopes in symptom scores in the week preceding the flare increased the likelihood of flare occurrence, but the association with variability was less strong. Multivariate modelling showed that for pain, mean scores and variability were associated with higher odds of flare, with odds ratios 1.83 (95% CI, 1.15, 2.97) and 3.12 (95% CI, 1.07, 9.13), respectively.

Conclusion. Our study suggests that patient-reported flares are common and are associated with higher daily RA symptom scores in the preceding week. Enabling patients to collect daily symptom data on their smartphones might, ultimately, facilitate prediction and more timely management of imminent flares.

Key words: RA, flare, patient-generated health data, mHealth, smartphone

CLINICAL SCIENCE

Key messages

- Patient-reported flares were common, occurring at least once in 75% of RA patients over 3 months.
- Patient-reported flares were associated with higher mean scores in daily RA symptoms in the preceding week.
- Frequent patient-reported data might, ultimately, facilitate prediction and more timely management of RA flares.

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Submitted 7 February 2022; accepted 10 March 2022

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Introduction

Treatment of patients with RA aims to control disease activity and sustain remission [1]. Although major advancements in the treatment of RA have made these realistic goals for many patients [2], RA patients (even those in remission) still experience transient episodes of worsening disease activity called flares [3, 4]. These fluctuations in disease activity are associated with poor

clinical outcomes, can lead to progression of radiographic joint damage and impaired function, and accelerate cardiovascular co-morbidity [5–8]. Suboptimal management of flares remains a hurdle in optimizing outcomes, including quality of life and activities of daily living, for people living with RA, despite the availability of more effective treatments and treat-to-target approaches.

To date, most studies of RA flares have defined flares using patient recall at infrequent intervals, usually 3–12 months apart [9, 10]. These methods can result in missing flares owing to recall error and therefore lead to an underestimation of the real prevalence of flares in RA. In routine clinical care, flares occurring between scheduled consultations might also not be captured by commonly used disease activity measures, such as the DAS28. This incomplete information about flares leads to delayed and missed treatment opportunities, which, in turn, can have a negative effect on patient outcomes. This implies an unmet need to capture and explore transient flares with greater accuracy. The same is true for RA symptoms more broadly, and capturing these alongside self-reported flares might provide new insights into the temporal relationship between them.

With the increasing adoption of smartphones and use of digital technology in clinical care and research, we now have an opportunity to collect health data directly from patients and at higher frequency. These technologies make it possible to capture and characterize day-to-day variations in disease severity and occurrence of flares in real time, instead of relying on patient recall at the discrete intervals of traditional research in cohorts and registers or at infrequent clinical appointments. This opportunity of better characterizing day-to-day changes and acute deterioration in disease expands way beyond RA into other rheumatic and long-term disease areas, such as mental health and oncology [11, 12].

In this study, we aimed to characterize patient-reported flares using daily symptom data collected through a smartphone app in people living with RA. Specific objectives were to understand the frequency and duration of patient-reported flares and to explore associations between symptom summary features and patient-reported flares.

Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for reporting this study [13].

Setting and participants

We conducted a secondary analysis of patient-reported symptom data obtained for the REmote MOnitoring of RA (REMORA) study [14]. The primary aim of the REMORA study was to test the feasibility of collecting daily patient-reported symptoms from 20 RA patients over 85 days using a smartphone app, with data integrated into the electronic health record. Patients were recruited from the rheumatology outpatient clinic at a single hospital site (Salford Royal NHS Foundation Trust, UK) in 2016. Patients were eligible if they had clinician-verified RA and were willing to participate and able to provide written consent. They could have either active or inactive disease. After consenting, members of the research team set up patients' phones, provided user instructions verbally and supported them throughout the study.

All patients were prompted to enter seven daily symptoms on a 0–10 numerical rating scale (NRS), where 10 represented the highest symptom severity. Items were adapted from the RA Impact of Disease questionnaire for daily use [15] (see Table 1 for a list of data items relevant to this analysis). Once a week, patients were asked if they had experienced a flare in the preceding week. Patients could view their own data as graphs over time in the app, but data were not reviewed by the clinical team in between clinical appointments, and patients were advised to take the usual action in case of health problems. During a subsequent clinical research consultation that mimicked a typical consultation, patients and clinicians reviewed the data in the electronic health record together. All 20 patients and their daily and weekly patient-reported data were included in this analysis. An illustration of a single patient's tracked symptoms and self-reported flares is shown in Fig. 1.

Definition of flares and explanatory variables

Patient-reported flares

The occurrence of patient-reported flares was used as the outcome, which was derived from the weekly question prompted via the app every seventh day. The question 'Have you experienced a flare in the last week?' could be answered 'yes' or 'no'. What classified as a flare was left to the discretion of the patient answering the question. The 7 days before the weekly flare question were deemed to be a flare week if the patient answered 'yes'. Conversely, if the patient answered 'no' the week was deemed a non-flare week. Weeks with missing flare data (i.e. an unanswered flare question) were not included in the analysis.

Owing to the way in which the app was configured, it was possible for patients to answer the weekly flare question at their own instigation outside of the prompted weekly schedule. To deal with answers to non-scheduled flare questions, we set up the following two rules: if patients answered the flare question more than once on the same day, we kept the entry with a flare if the multiple responses differed; and if patients answered the flare question on consecutive days or days closer than 5 days of each other, we kept the entry that was closest to the original 7-day scheduled questions or the earliest entry in that week if none fitted the weekly pattern.

Symptom summary features

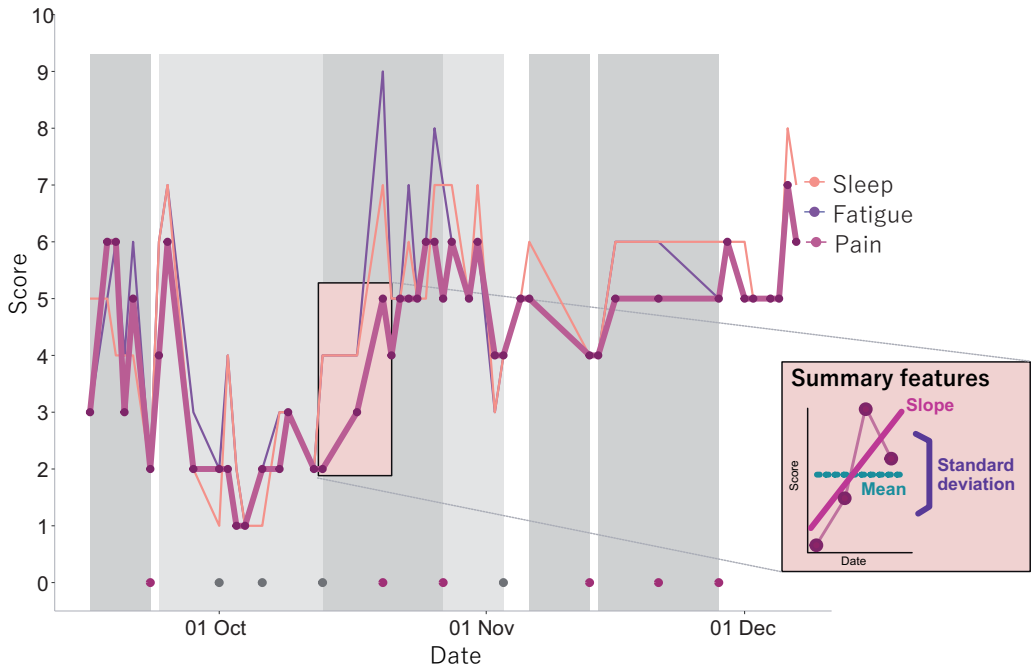
For each week before the flare question, we calculated the following symptom summary features across the

Table 1 Daily and weekly data items collected on the REMORA app included in this analysis

Item	Prompt	Scale	Range
Daily			
Pain	Select the number that best describes the pain you felt due to your RA during the last 24 h	NRS	None, 0; extreme (10)
Function	Select the number that best describes the difficulty you had in doing daily physical activities due to your RA during the last 24 h	NRS	No difficulty, 0; extreme difficulty (10)
Fatigue	Select the number that best describes how much fatigue you felt due to your RA during the last 24 h	NRS	No fatigue, 0; totally exhausted (10)
Sleep	Select the number that best describes the sleep difficulties (i.e. resting at night) you felt due to your RA during the last 24 h	NRS	No difficulty, 0; extreme difficulty (10)
Physical well-being	Considering your arthritis overall, how would you rate your level of physical well-being during the last 24 h?	NRS	Very good, 0; very bad (10)
Emotional well-being	Considering your arthritis overall, how would you rate your level of emotional well-being during the last 24 h	NRS	Very good, 0; very bad (10)
Coping	Considering your arthritis overall, how well did you cope (manage, deal, make do) with your RA during the last 24 h?	NRS	Very well, 0; very poorly (10)
Weekly			
Occurrence of flare	Have you experienced a flare in the last week?	Dichotomous	Yes; No

NRS: Numerical rating scale.

Fig. 1 Example of raw daily and weekly data



Example patient illustrating symptom tracking for three (of seven) selected daily symptoms and weekly flares. The red dots towards the bottom indicate that the patient answered 'yes' to the weekly flare question, the grey dots when the patient answered 'no'. Missing flare reports are not represented here. The 7 days leading up to the flare question are highlighted as either a flare week (darker grey) or a non-flare week (lighter grey). The inset in the lower right corner explains the three summary features for pain as a symptom: mean, standard deviation (variability) and slope.

daily symptoms in that week as our explanatory variables: mean score, S.D. and slope (see Fig. 1). The mean score represented symptom severity. The S.D. was chosen as a measure of variability of the symptoms in the preceding week. It is the most common measure of variability, which averages the absolute deviation of the symptom score (e.g. pain) of each day from the mean over the 7-day period, thus capturing symptom volatility. The slope was equal to the beta coefficient from fitting a linear model through the daily data points of the preceding week, thus capturing both the extent of change and the change direction (i.e. positive or negative). The patient-reported symptom scores were ordinal variables, but for the purpose of this analysis they were treated as continuous variables.

In preparation for modelling (see below under "Associations between patient-reported symptoms and flares"), we explored correlations between the summary features of symptoms with a correlation plot calculating Pearson's correlation coefficients for combinations of symptom summary features.

Statistical analysis

We used descriptive statistics to summarize patient age, gender and ethnicity [categorical variables as count (percentage) and continuous variables as median (interquartile range, IQR)].

Each patient's time in the study was calculated as the number of days between first and last active symptom reporting, with a maximum of 85 days. We calculated completion rates for daily and weekly questions. For daily entries, the numerator was the number of days on which at least one symptom score was completed, with the denominator as the patient's time in the study. For weekly entries, the numerator was the number of completed weekly responses, and the denominator was the number of weeks in which a weekly question set was triggered.

Frequency and duration of flares

For flare frequency, we calculated the proportion of patients reporting at least one flare over the course of the study. For flare duration, we counted the number of consecutive weeks patients reported flares.

Descriptive comparison of symptom summary features between flare and non-flare weeks

We calculated summary means of the symptom summary features in flare and non-flare weeks. We looked at the mean symptom scores in a patient's flare weeks and compared that with the mean symptom score in the patient's non-flare weeks, and then averaged across the population. The same comparison was made for the other two symptom summary features: S.D. and slope.

Associations between patient-reported symptoms and flares

For modelling purposes, we only included participant weeks that had $\geq$5 days of daily symptom data before a completed flare question (answering either 'yes' or 'no'). This was to ensure a balance between excluding too many participant weeks and the possibility of daily data missing not at random. To assess the impact of different definitions of a participant week on our findings, we performed two sensitivity analyses including participant weeks having 7 days of daily symptom data (i.e. complete weeks) and participant weeks with $\geq$1 day of daily entries (i.e. all weeks).

To quantify the associations between patient-reported flares and the seven daily symptoms, we used mixed effect logistic regression analyses, with patients as the random effect, which took into account the hierarchical structure of the data with multiple measurements within patients. The analyses were performed with flare week yes/no as a binary dependent variable. The three symptom summary features were used as explanatory variables. The modelling followed a two-step approach: first, univariate modelling looked at the derived summary features of one symptom at a time in its own model, resulting in 21 distinctive models (three symptom summary features across each of the seven daily symptoms), followed by multivariate modelling wherein we included all three summary features for a specific symptom (resulting in seven models: one for each symptom). We initially considered one model that included the three summary features and all seven symptoms simultaneously, but this was not possible owing to strong collinearity between individual symptoms (see Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online). For all models, we reported unadjusted odds ratio (OR) estimates with 95% CI. All analyses were performed in R v.4.0.5 (R Core Team, 2021) [16].

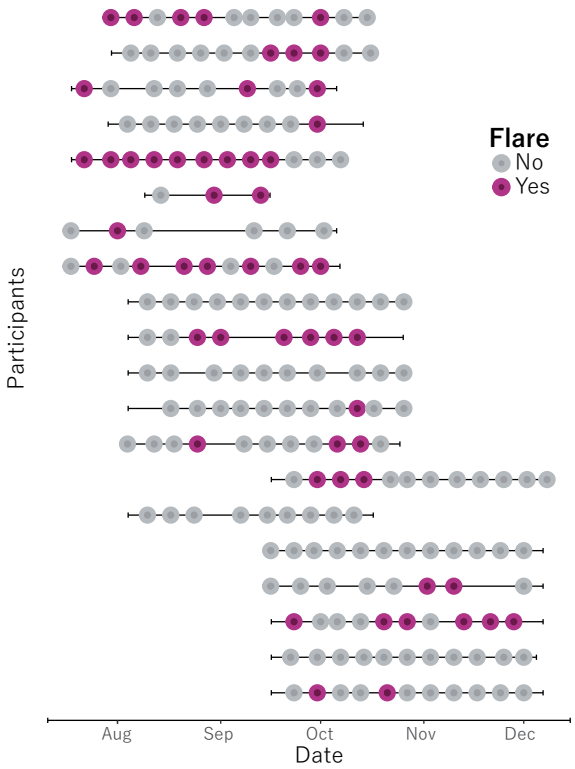
Results

Twenty RA patients took part in the study, of whom 14 were female (70%). The median age was 58.5 (IQR 48, 64) years, and all except one (95%) were of white British ethnicity. The median number of days in the study was 81 (IQR 80, 82). A total of 9177 daily symptom scores were submitted through the app out of 11 011 possible entries (i.e. an 83% completion rate). A total of 198 weekly flare questions were answered throughout the study period out of a possible 225 weeks, resulting in a completion rate of 88%. Fig. 1 shows an example of raw daily and weekly symptom tracking data for one patient in the cohort.

Frequency and duration of patient-reported flares

Fifteen of 20 patients (75%) reported at least one flare week over the 3-month study period, with 54 patient-reported flares in total out of 198 answered flare questions. Patients reported a median of two flare weeks (IQR 0.5–4). Fig. 2 shows that, of the patients reporting a flare, two-thirds (10 of 15) reported flares for two or

Fig. 2 Overview of flare distribution for each patient in the REMORA study



A pink dot indicates that the patient answered 'yes' to the weekly flare question in the REMORA app. A grey dot indicates a 'no' answer. Horizontal lines represent the time from first tracked symptom to last (i.e. time in study for each patient).

more consecutive weeks, and one-third (5 of 15) reported flares for three or more consecutive weeks.

Descriptive comparison of symptom summary features between flare and non-flare weeks

All mean symptom scores were higher [difference on average 0.67 (S.E. 0.24)] in flare weeks compared with non-flare weeks (Table 2). The S.D., a measure of variability, was marginally higher in flare weeks. For slope, there was a small but consistently positive increase for all symptoms in flare weeks.

Associations between daily symptoms and flares

Daily symptoms were reported on ≥5 days for 168 of 198 weeks in which a flare question was answered. Univariate modelling of data from these 168 participant weeks revealed that flare occurrence was significantly associated with higher mean scores across all seven symptoms (Fig. 3A). For instance, a single unit increase in mean pain score over the week was associated with a twofold increased likelihood of a flare [OR 2.23 (95% CI 1.28, 3.90)]. Likewise, higher S.D. of all symptoms except fatigue and sleep was significantly associated with flare occurrence, but the 95% CIs were wide. Larger slopes (i.e. more steeply increasing scores) of all symptoms were also significantly associated with occurrence of flares, although also here the confidence intervals were wide.

Fig. 3B shows that, in the multivariate model for pain using each of its three derived symptom summary features, mean pain scores appeared to be more clearly associated with a flare [OR 1.83 (95% CI 1.15, 2.97)] than the change in scores in the preceding week [OR 3.26 (95% CI 0.57, 18.74) for slope]. Variability was also significantly associated with higher odds of flares [OR 3.12 (95% CI 1.07, 9.13) for S.D.], but with a wider CI. Multivariate models for the remaining six symptoms showed comparable significant results for mean scores, with ORs ranging between 1.64 and 2.13. Likewise, associations with S.D. and slope were less convincing, with wide CIs (Supplementary Fig. S2, available at *Rheumatology Advances in Practice* online).

Sensitivity analyses

Sensitivity analyses for univariate models with two different definitions of a participant week showed similar results: when running the models using the complete weeks ($n = 88$ participant weeks) definition and the all weeks definition ($n = 198$ participant weeks), we found that higher scores of the majority of symptoms were still significantly associated with an increased likelihood of flare occurrence (Supplementary Fig. S3, available at *Rheumatology Advances in Practice* online).

When running the multivariate pain model, mean pain remained significantly associated with higher odds of flare occurrence for both definitions. When looking at the broadest definition of a participant week (all weeks), the association with S.D. was no longer as clear (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Discussion

This study demonstrated the ability to use real-time daily patient-reported symptom data to characterize patient-reported flares in RA. We showed that self-reported flares were frequent, occurring in 75% of patients over 3 months. The majority of patients experienced more than one flare. Patients had higher scores (for mean, variability and slope) across a range of daily symptoms in the week preceding a flare. When looking at the relative importance of daily symptom summary features on the occurrence of flares, higher mean scores in the week preceding the flare seemed more important for the likelihood of a flare occurring compared with symptom variability and slope; it matters more to have higher symptom scores rather than varying or increasing scores.

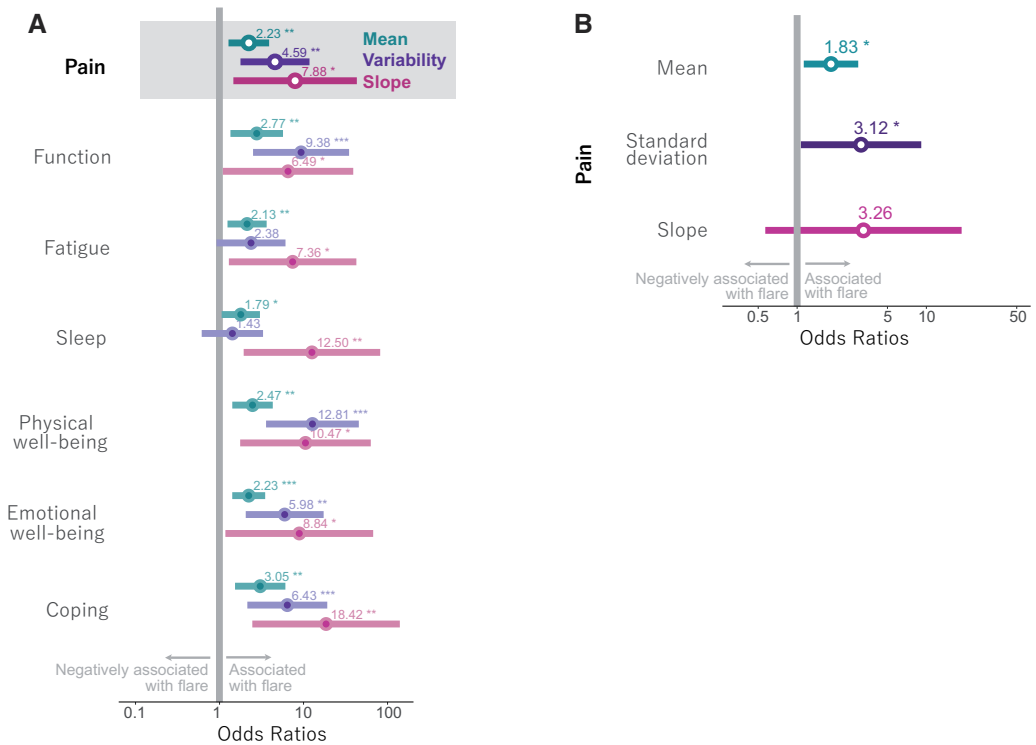
We found that 75% of patients reported to have experienced a flare over the 3-month study period, and the majority reported more than one flare. In a cohort of

Table 2 Differences in mean symptom summary features (mean, s.d. and slope) across seven daily symptoms in flare and non-flare weeks

Symptom summary feature	Symptom	Flare weeks (n^a = 15)	Non-flare weeks (n^a = 15)
Mean (s.d.) symptom score in the week before flare reporting	Pain	4.4 (1.8)	3.6 (1.9)
	Function	4.2 (1.7)	3.4 (2.0)
	Fatigue	4.4 (2.0)	3.8 (1.8)
	Sleep	4.1 (2.5)	3.9 (2.4)
	Emotional well-being	3.9 (1.6)	3.3 (1.5)
	Physical well-being	4.2 (1.5)	3.3 (1.6)
	Coping	3.9 (1.4)	3.1 (1.5)
Standard deviation (s.d.) of symptom scores in the week before flare reporting	Pain	1.0 (0.4)	0.7 (0.4)
	Function	0.9 (0.4)	0.8 (0.4)
	Fatigue	1.0 (0.5)	0.8 (0.4)
	Sleep	0.8 (0.5)	0.9 (0.5)
	Emotional well-being	0.9 (0.5)	0.7 (0.3)
	Physical well-being	1.0 (0.4)	0.7 (0.3)
	Coping	0.9 (0.4)	0.7 (0.5)
Slope (s.d.) of symptom scores in the week before flare reporting	Pain	0.12 (0.19)	−0.01 (0.14)
	Function	0.09 (0.17)	−0.02 (0.13)
	Fatigue	0.08 (0.23)	−0.04 (0.12)
	Sleep	0.10 (0.17)	−0.01 (0.18)
	Emotional well-being	0.06 (0.19)	−0.05 (0.14)
	Physical well-being	0.13 (0.17)	0.02 (0.14)
	Coping	0.10 (0.15)	−0.06 (0.15)

[a]*n* refers to the number of participants contributing data to the analysis.

Fig. 3 Associations between summary features and flare state



(**A**) Univariate mixed effect logistic regression modelling showing, for each symptom, the associations between three symptom summary features (mean, s.d./ variability and slope) and flare state. (**B**) Multivariate modelling of pain using each of the three symptom summary features.

Danish RA patients in remission or low disease activity at baseline, Kuettel *et al.* [17] found a prevalence of self-reported flares of 36% when asked 'Are you experiencing a flare of your RA at this time?' at 3-month intervals. These proportions were slightly lower than an observational study in established RA, where the frequency of self-reported flares ('During the past 6 months, have you had a flare in your rheumatoid arthritis?') ranged from 54 to 74% when asked at 6-month intervals [18]. Despite different anchor questions to detect flares, various periods of recall and differences in RA patient populations (unselected disease *vs* remission/low disease activity *vs* established RA), previous work and our study underline that self-reported flares are common in RA patients.

We defined a flare from the patient's perspective. The weekly flare question used here was developed for the REMORA study and has not been validated externally. Currently available and validated flare measurement tools (such as the OMERACT Flare Questionnaire and the FLARE-RA questionnaires [10, 19]) do not allow for simple, one-item weekly sampling, hence our flare question was intentionally pragmatic. With this simple question, the term flare was left open to interpretation by patients. This approach is likely to have yielded a range of flare experiences and intensities. The concept of flares and its definition usually differ according to patient and clinician views: patients can focus on subjective changes, such as pain, general signs, mood disturbance and the need to seek help [3], whereas clinicians are more likely to consider objective changes, such as tender and swollen joint counts or increased inflammatory markers, on which they can base treatment decision-making [9]. However, patient-generated health data are increasingly acknowledged as an important aspect of managing patients with RA, especially given an acceleration of virtual care during the COVID-19 pandemic, justifying a patient-centric approach [20].

We chose mean (S.D.) and slope as our symptom summary features because they capture different aspects of the symptom data in the week preceding a flare and have been reported in other studies in different musculoskeletal conditions [21, 22]. They are intuitive and interpretable; higher/lower scores, higher/lower variability in scores and steep/gradual increase or decrease in scores. In our analyses, the mean showed the clearest association with the occurrence of flare across all models. A cautious interpretation would be that, in our cohort, flares seem to be particularly driven by higher mean scores. For pain, we also found that even a modest change in mean score increased the likelihood of a flare [OR 2.23 (95% CI 1.28, 3.90) for the univariate model]. To contextualize this number, a 15% change in pain is considered to be a clinically important difference in RA [23], highlighting the clinical utility of using daily symptoms to identify meaningful deteriorations. Owing to our small sample size, we were limited in how detailed the exploration of the associations with flares could be. Larger datasets would allow for more sophisticated methods for summarizing daily data and could shed more light on these associations. This would, however, need to be balanced against easy interpretability.

In the future, frequent self-monitoring of common symptoms using digital devices could aid in the early detection, even prediction, of flares and deteriorations in clinical settings. These data could be used to alert a clinician or clinical team, opening up opportunities to intervene and prevent, even in patients in otherwise stable remission. Such just-in-time interventions might include self-management advice, treatment adaptations or triggering a clinical contact. One early-stage study, so far reported as an abstract, explored classification of patient-reported flares using patient-reported outcomes collected on a smartphone app [24]. They found that daily pain scores and specific individual items from the OMERACT FLARE Instrument appeared effective in classifying new-onset flares, confirming the early feasibility demonstrated by our study of using frequently collected patient-reported measures to predict flares. Some qualitative studies have raised concerns about patients feeling reminded about their disease when doing frequent symptom tracking, resulting in either making patients too preoccupied with their disease or an internal resistance to use the app [25, 26]. Additionally, mHealth studies are inherently vulnerable to high attrition rates. Although the REMORA study saw high engagement throughout the study period (for more details, see Austin *et al.* [14]), approaches for maximizing engagement with symptom tracking need to be considered actively [27]. Exploring the use of passive sensor data as a proxy for patient-reported flares is another interesting development that would alleviate the patient burden of manually entering data with high frequency [28]. Translating such results into clinical care models, however, requires careful implementation including validation and clinical acceptability.

Limitations

There are a number of limitations to our study. First of all, this was a pilot study, with few participants from a selected group of patients in one clinic, potentially limiting the generalizability of our results. Laboratory data, such as CRP, or disease activity measures, such as the DAS28 or the Clinical Disease Activity Index (CDAI), were not collected, preventing us from examining the relationship between patient-reported flares and established composite measures of disease activity. A prospective study linking patient-reported symptoms and flares with frequent clinically reported disease activity measurements would address this shortcoming. Additionally, we did not have access to information about treatment, medications and self-management strategies, which would have contextualized our results further.

Finally, the high correlation between the daily symptoms in combination with the limited sample size hampered the development of a full, multivariate model to

quantify which symptom or summary feature (or combination within and across these) had the strongest association with flares. A future study with a larger sample size would allow us to start developing flare prediction models, in which dimensionality reduction techniques could be applied to account for the high correlation.

Conclusion

In our RA cohort, self-reported flares were frequent. Flare weeks were broadly associated with higher scores (for mean, variability and slope) across a range of daily symptoms in the preceding week. When looking at associations between symptom summary features and patient-reported flares, the mean score showed the clearest association with the occurrence of flare across all seven common symptoms examined. For variability and slope, the association was less conclusive, largely owing to the limited sample size.

Our study is an early example of what daily changes in RA symptoms and prospectively collected self-reported flares might look like. Future analysis of daily symptoms might allow us to predict imminent flares, opening the opportunity for just-in-time interventions.

Acknowledgements

All authors contributed to the conception of the idea for the study and research questions. J.G. performed the analyses and drafted the manuscript. All authors were involved in interpreting the findings and revising the manuscript critically. All authors approved the final version to be submitted for publication. All authors had full access to all the data in the study.

Funding: This work was supported by the Centre for Epidemiology Versus Arthritis (grant number 21755). The funder did not contribute to the concept, design, data collection and interpretation, or drafting of this manuscript.

Disclosure statement: W.G.D. has received consultancy fees from Google and Abbvie, unrelated to this work. The remaining authors have declared no conflicts of interest.

Data availability statement

The data underlying this article cannot be shared publicly due to them containing infomation that could compromise research participant consent. The data will be shared on reasonable request to the corresponding author (J.G.).

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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6

Predicting patient-reported flares based on daily patient-generated health data

6.1 Introduction

In the previous chapter I explored how daily PGHD can be used to provide us important insight into the associations between RA symptoms and patient-reported flares. Ultimately, the goal is to be able to identify the flare early or even *before* it unfolds. This would make it possible to intervene in a timely manner, thereby reducing the burden of a flare for the patient and hopefully reduce the negative impact on longer-term clinical outcomes. Machine learning, a subfield of artificial intelligence, is capable of detecting complex, inherent patterns hidden in large datasets. In larger datasets with high dimensionality and/or multiple variables, machine learning may provide an advantage over more traditional statistical methods such as logistic regression in generating efficient and precise prediction models.(79) As I was interested in prediction of the class, or category, that the daily PGHD belongs to (i.e. flare or non-flare), this was a task well-suited for classification. There are a number of candidate algorithms to do this, but based on methods used in previous research into flare prediction, I chose random forest, naïve Bayes and logistic regression with regularisation (elastic net) here.

This chapter therefore aimed to examine the feasibility of using daily symptom data from the REMORA1 study to classify self-reported flares using different supervised machine

learning methods. The objectives were 1) to fit three binary classifiers and consider their performance, and 2) to explore the implications of different cut off values for the best performing model for predicting a flare.

6.2 Contribution statement

This piece of work followed naturally from the previous chapter about characterising flares in the same dataset. I conceptualised the idea together with a colleague statistician, and we frequently met to discuss implications and next steps. He led on the machine learning analyses, while I contributed descriptive analyses, exploration of different cut-offs for the best performing model and finalised all figures and tables. Ultimately, I drafted the entire manuscript and it is currently in review at RMD Open. I also presented this work as part of an oral poster tour at EULAR 2022 in Copenhagen in June 2022.

6.3 Manuscript 4: Classifying self-reported rheumatoid arthritis flares using daily patient-generated data collected on a smartphone app

Classifying self-reported rheumatoid arthritis flares using daily patient-generated collected on a smartphone app

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ABSTRACT

Objectives: The ability to predict rheumatoid arthritis (RA) flares between clinic visits based on real-time, longitudinal patient-generated data could potentially allow for timely interventions to avoid disease worsening. We aimed to investigate the feasibility of using machine learning methods to classify self-reported RA flares based on a dataset of daily symptom data collected on an app.

Methods: We used daily symptoms and weekly flares reported on the REMORA smartphone app from 20 RA patients over 3 months. Predictors were several summary features of the daily symptom scores collected in the week leading up to the flare question. We fitted three binary classifiers: logistic regression +/- elastic net regularization, a random forest and naïve Bayes. Performance was evaluated according to the area under the curve (AUC) of the receiver operating characteristic curve.

Results: The data comprised an average of 60.6 daily reports and 10.5 weekly reports per participant. AUCs were broadly similar between models, but logistic regression with elastic net had the highest AUC of 0.82. At a cut-off requiring specificity to be 0.80, the corresponding sensitivity to detect flares was 0.60 for this model. The positive predictive value in this population was 53%, and negative predictive value 85%.

Conclusion: Predicting self-reported flares based on daily symptom scorings in the preceding week using machine learning methods was feasible. The observed predictive accuracy might improve as we obtain more data. Analysis of frequently collected patient-generated data may allow us to predict flares before they unfold, opening up opportunities for just-in-time interventions.

KEYWORDS

Flare, patient-generated health data, smartphone, machine learning

KEY MESSAGES

- **What is already known on this topic**
    - There is an unmet need to be able to identify - or even predict – RA flares between clinic visits in order to optimise disease management
- **What this study adds**
    - Through application of machine learning we were able to predict self-reported RA flares based on longitudinal, daily patient-generated health data with decent accuracy
    - At a cut-off requiring specificity to be 0.80, the sensitivity to detect flares was 0.60 for the best performing model. The positive predictive value was 53%, and negative predictive value 85%.
- **How this study might affect research, practice or policy**
    - As we begin to understand how we can use regular symptom tracking data to predict imminent flares in RA before they unfold, we in turn open opportunities for just-in-time interventions that can improve RA disease management.

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by fluctuations in disease severity over time, with periods of worsening referred to as "flares". Flares represent a significant burden on patients, including uncontrollable symptoms and compromised ability to perform everyday tasks [1], and are associated with negative outcomes such as loss of functional ability and structural damage [2,3]. To minimise the impact of significant flares on the patient, it is important that a flare is identified early, so necessary interventions can be initiated. However, changes in disease severity often occur between scheduled visits to a clinician (usually every 6–12 months) which might hamper optimal disease management. In the early stages of a flare, patients self-manage, then progress to seeking medical help when they feel they are losing control [4]. Understanding when a flare is happening—or about to happen—could remove some of the barriers to seeking help.

Patient-generated health data, including patient-reported symptoms, could play an increasingly important role in clinical decision-making [5]. Smartphones, tablets and wearable devices can facilitate collection of self-reported symptom data between scheduled clinical appointments and at a much higher frequency, e.g. daily or weekly. This would allow us to "listen in" on the short-term patterns of RA disease severity and identify flares earlier or even predict flares before they unfold. The ability to identify or predict flares between clinical appointments based on patient-generated data would potentially allow for timely interventions. These might include self-management advice, medication adjustment, triggering a remote consultation or bringing forward a planned visit. Just-in-time adaptive interventions are an emerging area of research which, until now, have primarily been deployed in mental health and behaviour-change treatments [6,7].

Due to the potentially high-dimensional and non-linear nature of intensively-collected patient-generated data, modern machine learning methods could offer benefits over traditional tools, such as logistic regression, for accurate prediction. Machine learning is increasingly being employed in rheumatology: see for example Hügle et al. (2020) [8]. However, the literature on predicting distant outcomes such as flares through longitudinal patient-generated health data is still in its infancy and currently limited by heterogeneity in predictors, flare definitions, frequency of data collection and classification methods [9,10].

The purpose of this analysis was to investigate the feasibility of using machine learning methods to classify self-reported RA flares based on a small dataset of daily symptom data collected via a smartphone app. Specifically, the objectives were 1) to fit three binary

classifiers and consider their performance, and 2) to explore the implications of different cutoff values for predicting a flare.

METHODS

Data

This study was a post-hoc analysis of data from the first phase of the Remote Monitoring of Rheumatoid Arthritis (REMORA) study [11], which involved 20 RA patients using a smartphone application to track their daily symptoms over three months.

Participants received prompts every evening to report several symptoms on a 0–10 numerical rating scale based on the RAID scale adapted for daily use [12]: pain, function ('difficulty in doing daily activities'), fatigue (attributed to RA), sleep quality, overall physical and emotional wellbeing and 'ability to cope'. Users reported the duration of morning stiffness daily using one of seven time intervals. Weekly questionnaires asked patients about self-assessed tender and swollen joint counts and the binary flare question: 'Have you experienced a flare in the last week?'. These questions were prompted by a notification every seven days to complete the weekly question set. Patients were eligible to participate in the study if they had clinician-verified RA, were treated at a specific outpatient clinic at a single hospital site, were willing to participate and able to provide written consent. For further details of the REMORA study, see Austin et al. (2019) [11].

Definition of outcomes and explanatory variables

We treated each weekly flare report as a binary outcome. What classified as a flare was left to the discretion of the patient answering the question. Weeks with missing flare data (i.e. an unanswered flare question) were not included in the analysis.

To fit a binary classification model, it is necessary to extract a 'feature vector' or list of predictors from the sequence of daily symptom data that are mapped to each weekly flare report. The seven days up to and including each flare report were treated as the exposure period. For each exposure period, we calculated the following five symptom summary features for each of the eight daily symptoms: Minimum, maximum, mean score, standard deviation (SD) and slope. Isolated daily reports (those not followed by a flare report in the next 6 days) were discarded, so every remaining exposure period contained at least two

daily data points. Although not prompted, participants were able to answer the weekly flare question at any time during the week outside of the 7-day schedule, resulting in some partially overlapping exposure periods. In that case, we allowed the intersecting daily symptom reports to correspond to multiple outcomes. Where the same participant responded more than once on the same date, we assumed later-recorded responses superseded earlier ones.

The patient-reported symptom scores were collected using integer numerical rating scales from 0-10 (morning stiffness on a 7-point ordinal scale). For the purpose of this analysis, we treated all symptoms as continuous variables.

Statistical analysis

Machine learning classification concerns the task of recognizing objects and being able to separate them into categories. The aim of our analysis was to classify each week as a flare week or non-flare week based on the symptom summary features. While the most popular binary classification models are simpler ones, like logistic regression and naïve Bayes, the seemingly high-dimensional and nonlinear nature of disease activity motivates more complex 'black box' machine learning approaches, including random forest classifiers. We fitted three distinct classes of binary classification models to the data: logistic regression with and without elastic net regularization, a random forest and naïve Bayes.

When evaluating the performance of classifiers, a training dataset is required for fitting the classifiers and another distinct dataset is needed for the evaluation and test of those classifiers. We trained our models using the R package mlr3 [13]. 10-fold cross-validation was performed, with 18 (90%) participants comprising the training sets and the remaining two (10%) the test sets. The validation was repeated ten times, each time reserving two different participants for testing. In the case of longitudinal data collected from individuals, the training–test data splits should fall between participants, so that data associated with a particular patient fall entirely in a training set or a test set, so we are not testing and training within the same patient timeline. In other words, the models were tested on different patients to those on which they were trained [14]. The performance of each of the models was then evaluated against patient-reported flares as gold standard according to the area under the curve (AUC) of the receiver operating characteristics (ROC) curve. The model with the highest AUC in the test dataset was considered as the best final model.

We considered sensitivity and specificity for ten different thresholds in order to illustrate different ways in which the predictive model could behave in a clinical setting. Sensitivity is the proportion of those with a flare who have a positive prediction, while the specificity is the proportion of those without a flare that have correctly been predicted to have no flare. We did this by setting the sensitivity from 0.5 up to 0.9 in 0.1 unit increments, then doing the same for specificity (see Table 1). Corresponding positive predictive values, i.e. the probability that those with a predicted flare indeed go on to have a flare, and negative predictive values, i.e. the probability that those with a predicted non-flare indeed do not experience a flare, were also considered for these different thresholds to illustrate their potential impact and clinical utility.

RESULTS

The collected dataset comprised 20 unique participants completing a total of 1325 daily and 213 weekly questionnaires. Each participant reported an average of 61 daily reports and 11 weekly reports over an average follow-up time of 81 days (IQR 79–82). Of the participants, 60% were female, all but one were of white British ethnicity, and mean age was 57±11. years. Patterns of daily and weekly responses for each app user are shown in Figure 1.

Participants reported a median of two flares (IQR 0.75-4.25) each over the course of the study resulting in 57 flares in total. The largest number of flares reported by a single participant was nine, while five participants reported no flares at all.

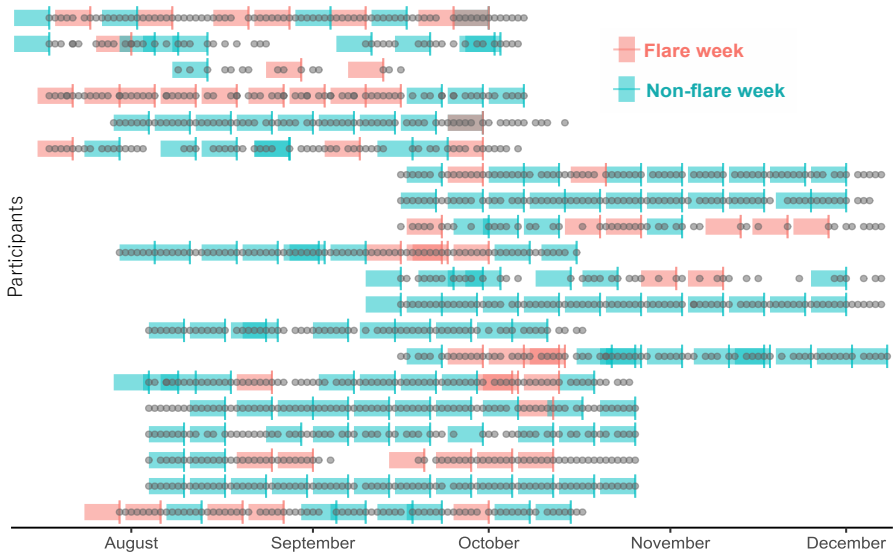

Figure 1. Patterns of daily and weekly data entry. Each row is a different participant. Vertical lines denote weekly responses, point daily responses. The shaded bands represents the week preceding each weekly response and the two colours denote whether patients reported a flare or no flare in that week.

Classifier performances are visualized in Figure 2. AUCs were broadly similar for all models, but the model with the highest AUC was the logistic regression with elastic net regularization with an AUC of 0.82. This was followed by naïve Bayes and random forest with AUCs of 0.77 and 0.75, respectively. Un-regularized logistic regression, as expected, had the lowest AUC of 0.71.

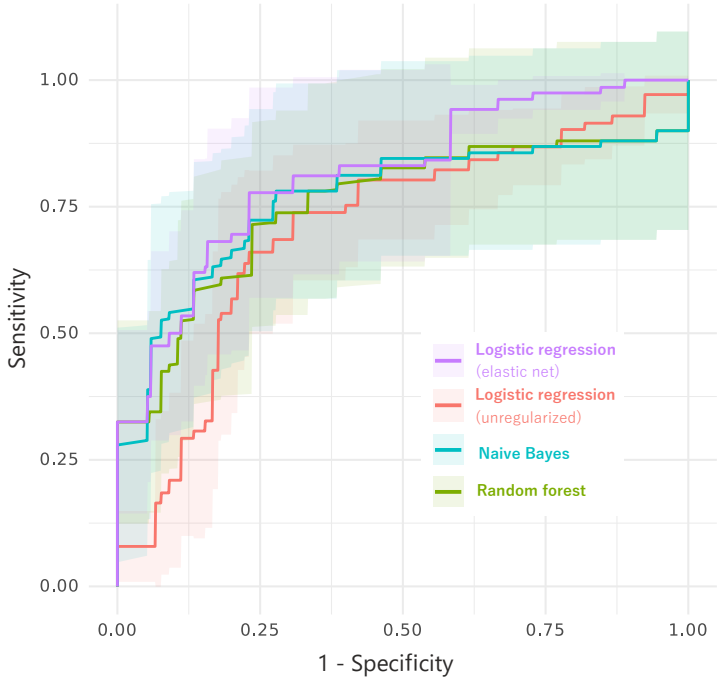

Figure 2 Classifier performance for each of the four models.

Table 1 shows the sensitivity, specificity and positive and negative predictive values for a range of different thresholds for the model with the highest AUC. At a cutoff requiring specificity to be 0.80, the corresponding sensitivity to detect flares was 0.60 for the regularized logistic regression model, meaning that the prediction model correctly identified three in every five self-reported flares, and four in every five non-flares. At this cutoff, and given the prevalence of flares within our dataset, the positive predictive value was 0.53 and the negative predictive value was 0.85, meaning there was (only) a 53% chance that the patient actually had a flare after the algorithm predicted a flare, but an 85% chance the patient did not have a flare, if the algorithm predicted a non-flare.

For that same model, we also considered a different threshold that favored identifying true positives, i.e. ability to correctly identify those reporting a flare. At a cutoff requiring sensitivity to be 0.80, the corresponding specificity was 0.72. The positive predictive value was 0.51 and negative predictive value 0.90 for this threshold. Of all the sensitivity and specificity options, ranging from 0.5-0.9, the greatest positive predictive value was 0.65 (with an associated negative predictive value of 0.83) and the highest negative predictive value was 0.92 (where the best corresponding positive predictive value was 0.51).

Table 1 *Sensitivity, specificity, positive and negative predictive values and implications at different cut-offs. Shown for logistic regression with elastic net regularization*

	Psychometric properties			
	Sensitivity	**Specificity**	**Positive predictive value**	**Negative predictive value**
Cut-off 1	0.50	0.90	0.65	0.83
Cut-off 2	0.60	0.80	0.53	0.85
Cut-off 3	0.70	0.74	0.49	0.87
Cut-off 4	0.80	0.72	0.51	0.90
Cut-off 5	0.90	0.43	0.37	0.92
Cut-off 6	0.88	0.50	0.39	0.92
Cut-off 7	0.87	0.60	0.44	0.92
Cut-off 8	0.83	0.70	0.51	0.92
Cut-off 9	0.60	0.80	0.53	0.85
Cut-off 10	0.50	0.90	0.65	0.83

DISCUSSION

With this study, we showed that it is feasible to use robust machine learning methods to predict patient-reported flares based on daily symptom scorings in the preceding week with decent accuracy. Of the three classifiers fitted, logistic regression with elastic net regularization had the highest overall AUC of 0.82, but across the different models AUCs were broadly similar. For the model with the highest AUC, at a cut point requiring specificity to be 0.80, sensitivity to detect flare was 0.60 resulting in accurate prediction of three out of five flares from the prior week's daily symptom data. Given the prevalence of flares in this cohort, the best PPV we could achieve meant only around two of every three positive predictions were correct (PPV 0.65). If we instead prioritised a higher NPV, we

were able to correctly predict over nine in every ten non-flare weeks, although this meant the accuracy of predicted flare weeks fell to only one in two being correct (NPV and PPV 0.92 and 0.51, respectively). Models were fitted to a relatively small dataset of 20 highly selected RA patients with three months of daily symptoms, so interpretations should be cautious. Nonetheless, our study serves as an early indicative example of how prediction of flares based on daily patient-generated data is possible and feasible.

Other examples of predicting RA flares using longitudinal patient-generated health data are sparse. Haynes et al. attempted to classify weekly-reported flares from a combination of daily RA symptom scorings and weekly flare questionnaires collected on a smartphone. Similar to our results, their best performing logistic regression classification model had an AUC of 0.81 and, at a cutoff requiring specificity to be ≥0.80, sensitivity to detect flare was 0.62 [9]. As an alternative to patients actively entering the data, Gossec et al. predicted weekly patient-reported flares based on passively-collected step counts from fitness trackers in 155 patients with RA and axial spondyloarthritis. Using a naïve Bayes classification model, they found that patient-reported flares were strongly linked to physical activity and that machine-learning processing of patient-level physical activity data can be used to detect flares with great accuracy [10]. Their results raise the possibility for passive surveillance that might, in the future, lead to just-in-time interventions without the need for continuous active symptom tracking.

The methodology of our study has several limitations. First, as already mentioned, the dataset is limited in size, which makes interpretation of results more challenging and additionally limits the possibility of understanding the importance of different predictors for classifying a flare. For modelling purposes, we treated the original ordinal features as continuous. This preserves the information in the ordering but requires the assumption that the numerical distance between each category is approximately equal. We assumed that this was reasonable for our analysis, but other more complex methods could be utilized to account for ordinal data. The feature vectors also do not account for temporal dependence (or autocorrelation) within or between patient-weeks, i.e. the fact that pain today may depend on pain yesterday, or that likelihood of reporting a flare this week is affected by reports in previous weeks. Isolated daily scores —those not within seven days of a subsequent flare report—were discarded. However, in a different analysis approach, these could be treated as censored observations. We fitted several different models, but the lack of an external validation dataset limits the generalisability of our results. Finally, our

definition of flare was a non-validated pragmatic patient-centred one, which left it to the patient to decide when a flare occurred, and therefore it could be interpreted differently by different patients. Multiple definitions of RA flares have been suggested [15,16], but to date no reference standard has been agreed. This might consequently make it harder to predict a 'flare' if each patient's interpretation of a flare is different.

While sensitivity and specificity of a test are stable, positive and negative predictive values are influenced by the prevalence of the disease in the population. When prevalence decreases, the positive predictive value decreases too. In contrast, the negative predictive value will increase. The prevalence of patient-reported flares in our cohort therefore influences predictive values, and its broader usability is dependent on our cohort's representativeness of the broader RA population.

Our results point to a future where real-time analysis of frequently collected patient-generated data from symptom tracking may allow us to predict imminent flares before they unfold. This in turn opens opportunities for just-in-time adaptive interventions (JITAIs). JITAIs "leverage mobile technology to deliver the right type of support, at the right time based on ongoing information about the individual's internal state and context" [17]. Until now, they have primarily been deployed in supporting health behaviour change [7,18], but they hold enormous potential for fluctuating diseases like RA where timely intervention for increase in disease activity is beneficial. Depending on the nature and implication of a JITAI, different cut-off values for an intervention decision need to be considered. Because of cost and other implications, different interventions will require different levels of predictive certainty before an action is triggered. In RA, we could imagine, say, two different scenarios in response to a predicted flare: One where a self-management advice is newly offered or promoted via a notification within the app, and a second where a scheduled clinical consultation is brought forward based on the data entered by the patient. Striking the right balance between missing true flares and flagging up false positives is crucial. We might tolerate to serve up a written self-management advice for more false positives, because the implications are relatively few. This would also mean we rarely miss the opportunity of providing the advice to someone with a true flare that the predictive test has failed to identify. On the other hand, we need more caution when offering a clinical consultation. Here, tolerance for false positives should be low because of the high implications – scheduling an expensive consultation because a flare is predicted, but where that consultation is wasted as there is no true flare. In this instance, a high positive predictive value of the algorithm is essential. If we apply these considerations to our results,

we could foresee that self-management could be usefully delivered in response to the predicted flares. Whether incorrectly promoting self-management advice to one in every two people who might have a flare (PPV 0.51, NPV 0.92) would need formal evaluation to see if this is indeed acceptable. Conversely, given the current model performance and prevalence of flares, we would be unlikely to use the predictive model to trigger a time- and resource-intensive clinical intervention because, at best, only two in three of these predicted flares would be correct (PPV 0.65, NPV 0.83).

Conclusion

Predicting self-reported flares based on daily symptom scorings in the preceding week using machine learning methods was feasible, with regularized logistic regression seeming to outperform the other machine learning methods in this small dataset. It is possible that the observed predictive accuracy will improve as we obtain more data. As we begin to understand how we can use regular symptom tracking data to predict imminent flares in RA before they unfold, we in turn open opportunities for just-in-time adaptive interventions. This is now a tangible future, but more data and more research is needed to realise the ultimate aim of using machine learning to offer a fully personalised care approach to improve patient outcomes.

COMPETING INTERESTS

WGD has received consultancy fees from Google, unrelated to this work. All other authors declare no conflicts of interest.

FUNDING

This work was supported by the Centre for Epidemiology Versus Arthritis (grant number 21755).

CONTRIBUTIONS

All authors contributed to the conception of the idea for the study and research questions. DAS and JG performed the analyses and drafted the manuscript. All authors were involved in interpreting the findings and revising the manuscript critically. All authors approved the final version to be submitted for publication. All authors had full access to all the data in the study.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author (JG). The data are not publicly available due to them containing information that could compromise research participant consent.

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7

Discussion

This thesis examined how digital patient-generated health data can advance clinical care and research in musculoskeletal and other long-term conditions, through the example of RA. In this chapter, I first assimilate the learnings from each chapter under subheadings reflecting the objectives set out in the introduction. I then exploring implications for future clinical care and research based on my findings before discuss strengths and limitations.

7.1 Current state of EHR-integrated remote symptom monitoring

I addressed this objective in Chapter 2 through a systematic review of the literature across long-term conditions.(80) Besides REMORA, I found no other published smartphone-based systems that integrated daily symptom monitoring into the EHR and only a subset of systems collected data continuously between clinical visits. Systems were technically heterogeneous, and information about dataflow and security measures were rarely reported, making it challenging to learn from their findings on this crucial aspect. Additionally, there was limited evidence that integrated symptom monitoring improved care and outcomes, largely owing to the research being still in its early stages.

Overall, the review established that EHR-integrated remote symptom monitoring is possible, but there were few published efforts to inform future development of these systems, highlighting that it is a challenging and ambitious achievement. The experiences reported in Chapter 4 about setting up REMORA1.5 underpin this. Developing the

scalable, technical infrastructure that allows for frequent collection of PGHD and direct integration into the EHR is complex and reaching the significant potential of the wider use of PGHD requires numerous challenges to be addressed by a broad range of stakeholders, as described in the introduction.(61) Technical challenges include managing and making sense of large quantities of data, accuracy of PGHD measurements, user authentication risks, undeveloped interoperability standards, and gaps in privacy and security protections. For patients, challenges remain in lack of access to technology in some groups, high drop-off rates and digital literacy. Clinicians may encounter challenges in using PGHD, such as the impact on already overstretched clinical workflows, the management of patient expectations, the potential for increased liability and the limited body of evidence for the clinical value for use of PGHD. Progress in all of these areas is essential to achieving the envisioned future benefits of integrated PGHD. The learnings from REMORA shows that these barriers can be successfully addressed, resulting in improved insights for clinicians and researchers and improved care for patients.

Following this systematic review, the COVID-19 pandemic led to a rapid increase in the use of technology in healthcare. The benefits of remote monitoring quickly became apparent, both for the monitoring of COVID itself and for supporting regular care that suddenly had to be performed remotely. This urgent need for innovative approaches has acted as a catalyst for the digital transformation in healthcare more broadly. In rheumatology, many remote monitoring clinics emerged in response to the pandemic, particularly focussed around telehealth and remote consultations. Much has happened over a short period of time and the speed of innovation does rarely match the speed of academic evaluation and publication. However, by updating my systematic review in June 2022 focusing on rheumatoid arthritis only, I found that only one additional paper had been published since I ran the original search in 2019. Seppen et al. reported on their MijnReuma Reade app, which collects patient-reported outcomes from patients with RA on a weekly basis. Their system is integrated into the local EHR at a hospital in Amsterdam, Netherlands. The aim of the app is to reduce the frequency of clinic visits if the self-monitored disease activity is low. Their feasibility studies showed acceptable patient satisfaction and usability, but app usage rates declined significantly over the four week study period.(75) The group is currently running a 12-month randomized controlled trial assessing the safety and efficacy of patient-initiated follow up assisted by the app versus usual care, with results due to be published soon. The primary outcomes are health care utilization and disease activity at 12 months.(58) Another relevant daily symptom

monitoring system – though it is outside the inclusion criteria of the original review, because it is not EHR-integrated – is a system from Brigham and Women's in Boston, US. In a randomised controlled trial, the group reported positive experiences with an app to collect daily PGHD from 191 patients with RA over six months. They compared daily symptom tracking and care coordination (flagging up of flares using an algorithm based on worsening symptoms and follow-up) versus care coordination alone (phone calls to assess for flares), but found no significant improvement in patient satisfaction or disease activity (CDAI).(81). Median adherence to the daily questions was 79% (interquartile range 48-90%).(74) Work is underway to integrate this system with the local EHR. All in all, the updated search suggests that the majority of systems in RA continue to be stand-alone solutions not integrated into EHRs, most likely owing to the technical challenges of doing this at pace. The field of continuous symptom monitoring for use in clinical care in RA continues to be in the era of promise rather than realization when it comes to integrating PGHD into the EHR, but there is progress.

7.2 Using PGHD in clinical practice

Chapter 3 addressed this objective through qualitative analysis of audio-recorded consultations from REMORA1.(82) Clinicians were in control of when, what, and how PGHD was used in appointments. However, the PGHD had different functions depending on when the clinician introduced it during the consultation: To collaborate (early), corroborate (middle) or convince (end). Without any prior instructions on how to utilize the PGHD into the standard outpatient consultation, the two clinicians mainly used the data to corroborate patients' verbal accounts, by either confirming, verifying or challenging what was already reported during the review phase. It may feel more comfortable for a clinician to integrate PGHD as an additional 'score' to check alongside lab results, imaging or treatment response in the review section, but this seems to limit the interpretation of PGHD into supporting evidence to simply verify patient accounts. Instead, introducing it early in the appointment may provide the clinician an opportunity to interpret the data in collaboration with the patient to elicit additional insights and to explore the pertinent issues in more depth throughout the appointment, supporting better shared decision-making.

As such, in addition to the challenges for clinicians laid out in the previous section, an important remaining challenge that limits successful implementation of PGHD into routine

practice is a lack of knowledge on how clinicians can effectively utilize this new data source in their encounters with patients. Further research is needed into which strategy, if any, gives the best outcomes and improves consultations the most.(83,84) The introduction of PGHD requires that clinicians are open to having a new approach to the way they conduct their consultation and to be convinced of the potential for the data to benefit patient outcomes.(60) The insights into how clinicians used the PGHD in REMORA1 informed parts of the clinician training program I developed for REMORA1.5, as described in Chapter 4. Specifically, findings were presented as part of the initial 1-hour training session, but it was still left to clinicians' discretion to decide how to use the PGHD in their consultations during the study. Effectively incorporating PGHD into clinical conversations also demonstrates clinicians' positive attitude and perceived usefulness of the data towards the patient, which might have a further beneficial effect on patients' engagement with the app – this is key for sustained engagement.(55,85)

In addition to using the data during the consultation, clinicians can review the data in preparation for the consultation before the patient arrives. Clinicians might also want to check up on patients who they know are struggling in between appointments by reviewing their data or even look over the data if a patient gets in touch with the clinic because they are not feeling well. These are all potential uses of PGHD, which the audio-recordings in this study did not pick up and which warrants further studies.

Educating patients and clinicians about the effect that timing and different uses of PGHD might have upon the consultation could help maximise its benefits, thereby increasing its potential to move outpatient consultations closer to the goal of facilitating better and shared decision-making.

7.3 Associations between daily symptoms and self-reported flares

I addressed this objective in Chapter 5 using daily symptoms and weekly flares collected in the REMORA1 study. I found that self-reported flares occurred frequently and were broadly associated with higher symptom scores across the range of daily symptoms in the preceding week, all of which were collected prospectively in real time.(86) When looking at the relative importance of daily symptom summary features on the occurrence of flares, higher mean scores in the week preceding the flare seemed more important for the

likelihood of a flare occurring compared with symptom variability and slope; it mattered more to have higher symptom scores rather than varying or increasing scores. The high correlation between daily symptoms in our dataset impeded disentangling the contribution of individual symptoms to the flare experience. This raises the question of whether it is necessary to collect eight daily symptoms or whether a subset would be sufficient.

I had planned to address this objective using the larger dataset collected in REMORA1.5, but this was not possible due to the reasons outlined in Chapter 4. The dataset resulting from REMORA1.5 will instead be used to validate the associations found using the REMORA1 data. In regards to flare frequency, the preliminary data presented in Chapter 4 in REMORA1.5 was comparable to that of REMORA1, which is promising for future validations: 88% of participants in REMORA1.5 reported at least one flare over 16 weeks vs. 75% in REMORA1 over 12 weeks and 33% of answered flare questions in REMORA1.5 confirmed a flare vs. 27% in REMORA1. The larger number of patients and longer data collection period will hopefully result in smaller confidence intervals, thus increasing confidence in the observed associations, allowing us to draw more robust conclusions on the relationship between daily symptoms and flares. It is unclear if we will experience the same problem of high correlation between the daily symptoms, but if not it might be possible to explore which individual symptom (or combination or patterns of symptoms) drive a flare. Finally, by having contextual data from the EHR available, it will be possible to look for associations with, for instance, disease activity or a specific treatment.

My study with the REMORA1 data demonstrated the ability to use real-time daily patient-reported symptom data to characterize patient-reported RA flares without the need to resort to recall in questionnaires, highlighting how frequently collected PGHD can advance longitudinal epidemiological research. Enabling patients to collect daily symptom data on their smartphones may ultimately facilitate prediction and more timely management of imminent flares, which was the topic of Chapter 6.

7.4 Predicting self-reported flares using daily PGHD

The purpose of the analysis in Chapter 6 was to investigate the feasibility of using supervised machine learning methods to predict self-reported RA flares based on daily symptoms. Performance of the three fitted classifiers was broadly similar, but the best

performing model had an area under the curve (AUC) of 0.82. I explored different cut-offs for flare detection for this particular model. With specificity set to 0.80, the corresponding sensitivity to detect flares was 0.60. At this threshold, there was a 53% chance that the patient actually had a flare after the algorithm predicted a flare, but an 85% chance the patient did not have a flare if the algorithm predicted a non-flare. Of all options considered for this model, the greatest positive predictive value was, perhaps rather disappointingly, 0.65. One could expect a prevalent outcome like self-reported flare to be easier to predict than a rarer outcome and thus have a higher positive predictive value. However, it is reasonable to assume that the observed predictive accuracy will improve with more data from a larger dataset, as more data reduces potential overfitting to a few outliers and makes it easier to pick up subtle changes. The similarly structured data resulting from the REMORA1.5 study will serve as an excellent dataset for external validation and optimisation of the model presented in Chapter 6.

As we begin to understand how we can use regular symptom tracking data to predict imminent flares in RA before they unfold, we open opportunities for just-in-time interventions to avoid the worsening in disease severity. This new model of care will be discussed in more detail below under future clinical implications.

7.5 Future clinical implications

Adding to the findings of this thesis described in previous sections, a range of additional clinical benefits could be realised following successful integration of remote symptom monitoring systems, such as REMORA, into routine clinical practice. These will be outlined below, from supporting new models of care to monitoring treatment response and expanding into other disease areas.

7.5.1 Supporting new models of care

Firstly, in addition to supporting conversations during the clinical consultation as described in Chapter 3, remote symptom monitoring could inform new, improved models of care, solving some of the pitfalls of the traditional outpatient care model outlined in the introduction. Using PGHD to remotely predict flares between clinical appointments, work I initiated in this thesis, may allow for timely interventions that harnesses mobile devices to prevent a flare from occurring or reduce its impacts. Such interventions might be referred

to as just-in-time adaptive interventions (JITAIs). JITAIs "leverage mobile technology to deliver the right type of support, at the right time based on ongoing information about the individual's internal state and context".(87) It is an emerging approach that until now, has been primarily deployed in supporting health behaviour,(88,89) but I envision it holds great potential for fluctuating diseases such as RA where timely intervention to manage increases in disease activity is beneficial. In RA, JITAIs could include digital self-management advice, for example instructions on how to deal with acute increases in pain, medication adjustments, triggering a remote consultation or bringing forward a planned clinic visit.

PGHD can also support patient-initiated follow-ups (PIFU), which gives patients the responsibility for booking follow-up appointments when they require them, allowing them to be seen quickly when they need to, while avoiding the inconvenience of appointments that are of low clinical value as described in the introduction.(58) PIFU has gained significant national interest in the wake of the pandemic and is currently being rolled out widely. It is imagined to be a key part of the solution for long-term sustainability of NHS outpatient services and is supposed to help reach the goal of reducing outpatient follow ups by 25% by 2023.(90) Although there is limited evidence that PIFU improves outcomes, such as disease activity or patient satisfaction, most studies find it to be comparable to standard care models and it might therefore be possible to achieve similar disease control with fewer outpatient visit.(91–94) Frequently collected PGHD can support PIFU by acting like a safety net if monitored between requested visits: PGHD allows the clinician to check up on PIFU-managed patients in the community, and lets them spot if a patient needs to come in, who has not made an appointment by themselves. Additionally, it is a way for patients to monitor their condition and to support them in deciding when action is needed. PIFU is not only a change in how outpatient care is delivered – it requires that the patient becomes an active participant in their own care, and to do this they must have the abilities to self-monitor and self-manage their disease.(95)

7.5.2 Monitoring treatment response

Monitoring treatment response is especially relevant in RA, as a substantial number of patients fail to show a response on their disease modifying anti-rheumatic drug and could benefit from a quicker switch to another drug.(96) More personalised treatment could possibly be facilitated through better and more frequent assessment of treatment response and longitudinal PGHD could support this. Monitoring symptoms continuously would

allow quicker identification of non-response to a treatment, could pick up treatment-related side effects or could show that a certain treatment works well.(97) Subsequent adjustments to medications based on a patient's symptoms could then be made, such as switching or discontinuing medications, adding a new treatment or dose reduction/tapering. Discontinuing expensive biologic treatments sooner might additionally result in significant cost savings. Patients with early RA who are most likely to benefit from a tight treat-to-target strategy or patients starting a new medication may benefit particularly from monitoring treatment response.(98,99)

7.5.4 Other long-term conditions and multi-morbidity

Finally, clinical care of other or multiple LTCs could potentially benefit from continuous remote symptom monitoring in the same way as described in REMORA. Most LTCs are, like RA, managed in outpatient-based specialties and successful outpatient care requires a clear understanding of how patients' symptoms and management evolve through time. As evidenced in Chapter 2, systems have already been implemented in for example inflammatory bowel disease, heart failure, epilepsy, and oncology settings, but none of these studies looked at daily symptoms tracked longitudinally. An estimated 15 million people in the UK have at least one LTC and the number of people with multiple conditions ("multi-morbidity") is rising.(2) Treating multi-morbidity is complicated by the need to see multiple specialists. There is a potential to enhance the care and management of people living with multi-morbidity by having symptom tracking systems that allow patient-centred ways of collecting any symptom data without replicating across multiple apps.

7.6 Future research implications

A number of areas for future research follow from the findings of my thesis and the clinical implications. They cover a range of different types of research including observational research, methods development and interventional research.

7.6.1 Defining clinically meaningful disease worsening and flares

For the new models of care suggested above, identifying patients who are struggling is crucial. Questions remain around how best to use PGHD to do so. There is a need to be able to identify within-person changes that are clinically meaningful, but there is currently no consensus on how to define this for frequently collected symptoms in RA (i.e. patient-reported pain, fatigue, sleep etc.). Similarly, rather than relying on self-reported flares, developing consensus definitions of remission, pre-flare and flare based on daily patient-generated symptom data is important. A qualitative study involving patients, clinicians and researchers would be suitable to start exploring these symptom-based flares. Focus groups could ask participants to annotate symptom trajectories to identify periods of 'remission', 'pre-flare' and 'flare', and to identify features of interest like duration and severity. Using these new definitions, an algorithm could be developed using artificial intelligence to provide automated early detection and prediction of flares.

In addition to being able to accurately predict a flare, there is a need for a parallel research agenda to start exploring which interventions to deliver, when and how. These interventions need to balance benefits of more tight disease management against potential harms such as overtreatment and costs of the interventions.(100) This will require careful design then robust evaluation to increase their likelihood of being adopted in clinical practice.

7.6.2 Evaluating treatment response

Having treatment data available alongside frequently collected PGHD would allow for improved evaluation of treatment response and could enhance pharmaco-epidemiological research.(101) Examples might include comparative effectiveness of different treatments including trajectories of change (e.g. faster response with drug A vs. drug B). However, analysis challenges arise in looking at treatment response using time-series data (i.e. longitudinal PGHD) as opposed to using data from just two distant data points many months apart. Latent classes can consider general trends in treatment trajectories (e.g. getting better quickly/slowly, going down then up, stable).(102) Any selected (or developed) method needs to account for time-series data that might include a number of flares – hence the need to be able to define a flare, as described in the previous section. Comparative effectiveness research using observational data must acknowledge and

consider confounding by indication, where the reason for receiving a particular drug might also be associated with the treatment response, be it a change over six months or the shape of a response trajectory.(103) Additionally, missing data poses a challenge for the analysis. In case of missing data, researchers typically do analysis of complete cases or impute missing data points. Restricting analysis to participants with complete data would reduce the sample size to near zero. Imputing missing data may therefore be a better solution, but this requires that data is missing at random, which is questionable in the case of daily PGHD. Still, patterns of missing data should be explored, as missing data can be informative in itself: a missing data point may add to our ability to predict an outcome such as a flare. Qualitative research would, for instance, allow us to interview participants who had periods of missingness and gain an understanding of whether their data was missing because they were particularly well, were particularly unwell, or whether it was indeed random.

REMORA1.5 collected treatment information with the goal of being able to assess treatment response for participants and to identify different patterns of response (e.g. good, moderate and poor responders, or perhaps now rapid or slow responders). Future analysis of the data will show if this is feasible.

7.6.3 From active to passive monitoring

Finally, it is questionable whether continuous active data collection is feasible in the longer term for chronic disease monitoring. In REMORA1.5 we found that the participants who initiated tracking generally sustained engagement with the app for up to six months. However, this is far from the reality for most mobile health studies that often suffer from high attrition.(72) Instead, an adaptive sampling frequency might allow the daily symptom collection to be reduced to a more optimal frequency based on the patient's own data, while not losing important information. This will, however, have to be balanced against making the data entry a natural part of everyday life, as more frequent intended usage may lead to better adherence to monitoring rather than less frequent entries. Alternatively, sensor data offers an opportunity to measure user behaviour and environment without requiring active input from the participant beyond installing a data collection app on their smartphone.(104) In the future, development of "passive" digital biomarkers that has been thoroughly validated and correlate well with disease activity, patient-reported outcomes or

flare occurrence could be a viable alternative to long-term active patient monitoring and could be used as novel endpoints in clinical trials.(105–107)

7.7 Strengths and limitations

Research within this thesis has a number of strengths and limitations, which should be taken into account when considering the above findings and conclusions.

7.7.1 Limitations

It is important to acknowledge some limitations of this thesis, particularly in relation to the REMORA1 dataset.

Much of the analysis was performed on data coming from the REMORA1 study. As discussed in multiple chapters, REMORA1 had the inherent characteristic of being a small, selected cohort (n=20) of highly motivated and engaged RA patients from a single clinic, which may limit the generalisability of the findings. The external validity is affected primarily by selection bias, i.e. the recruited cohort is likely not representative of the wider RA population. For my quantitative results in Chapter 5 and 6 this is mainly an issue if the relationship between symptoms and flares is significantly different in those who did and did not take part, which is a possibility but not necessarily true. For example, if participants are more or less likely to participate in the study if they have many flares or worse disease activity. However, even if the study cohort has more flares, results are still valid if the symptoms associated with a flare are the same as those who have fewer flares. On the other hand, when using the PGHD in clinical care, the clinician is interested in using the data to understand what has changed within an individual, so the selection bias is perhaps less important in this situation. Still, highly motivated patients may have higher completion rates and therefore provide their clinician with more useful data to discuss during a consultation and vice versa. Patients who are well-controlled may want to stop monitoring their symptoms and not be reminded that they are sick, which also limits the amount of data the clinician has available.(75,108)

Laboratory data, disease activity measures and treatment information were not collected as part of REMORA1, preventing me from examining the relationship between patient-reported flares and established measures of disease activity in this dataset. A prospective

study linking patient-reported symptoms and flares with frequently collected clinically reported disease activity would address this shortcoming, although this would be practically challenging with flares happening relatively often. Another limitation is the self-reported flare question, which was developed for REMORA and not psychometrically or externally validated. Currently, there is no gold standard for measuring flares and available flare measurement instruments do not include simple questions that can be used on a daily basis, so the self-report was a pragmatic solution.

It is worth noting, however, that the original scope of REMORA1 was to design and pilot test a novel data collection method, and consequently was limited in terms of investigated research questions, population, exposures and outcomes. REMORA1.5 was designed to address most of the above-mentioned limitations by having a larger and more representative cohort of patients with RA, despite being carried out in the same clinic. It also collected all the contextual information from the clinical team (disease activity, medications) that was lacking in REMORA1.

In REMORA1.5, the low conversion rate from consented to tracking participants was an important drawback. Although it did not seem like there were many obvious differences between the two groups in terms of their baseline characteristics, it is possible that they differed in other unmeasured aspects such as education, digital literacy or beliefs about symptom tracking or digital health. This will be picked up as a separate work stream in REMORA2.

Finally, REMORA1.5 did not go live in time for me to complete follow-up for all participants. Nonetheless, I have contributed to successfully implementing an integrated symptom monitoring system on a scalable infrastructure, and have started to show that it is useful for improving clinical care and opens up several research opportunities.

7.7.2 Strengths

One key strength is the robust approach for the development of REMORA: Starting with a smaller proof of concept study (REMORA1) and, based on the learnings, incrementally scaling up through subsequent stages (REMORA1.5 and in the future REMORA2). Although a lengthy process, starting small and ensuring everything is right before moving ahead provides an opportunity to reflect, take key learnings forward and optimise decisions

based on mistakes made in earlier stages. Intervention refinement is one of the core elements for developing and evaluating complex interventions.(109)

Figure 7.1. *Phases in the lifecycle of a mobile health research study*

Another benefit is the real-world experience of establishing a technical infrastructure and data collection process for a mobile health study in a general RA population. I have gained a broad perspective on the challenges and opportunities of collecting PGHD once and re-using it for multiple purposes, especially compared to analysing readily available data, e.g., from a disease registry. Consequently, this thesis covers nearly all phases of the lifecycle of a mobile health research study as shown in Figure 7.1. By having been exposed to these different phases, I was able to demonstrate the utility of frequently collected PGHD for both clinical care and research.

Finally, there are some strengths in relation to the individual methods used. Throughout my thesis I have combined multiple methods from a range of disciplines: systemic literature review, qualitative analysis, epidemiology, and machine learning. The combination of these

allowed me to study different aspects of the problem, thereby leading to more in-depth insights. It underpinned how research in digital health requires the whole spectrum of methods to be successful, of which I learned and practiced a few. Combining different methods effectively also requires interdisciplinary work with experts in each field. In agreement with the findings from the systematic literature review, this thesis has showed that in order for a mobile health study to be successful from conceptualisation to analysis and dissemination, it indeed requires input and expertise from various disciplines. At the centre of this work is the patient. I have tried to ensure that the research in my thesis has been patient-centred by frequently interacting with the REMORA PPI group and I have a patient co-author on two of the resulting publications.

7.8 Final remarks

We are moving from a time when disease could be measured only at sparse intervals, to a situation where many aspects and correlates of disease can be tracked frequently or for the first time using digital devices. This thesis demonstrated that building a sustainable technical infrastructure for the collection of daily digital PGHD on a smartphone app and integration into the EHR is complex but nonetheless achievable. The benefits of integrated symptom tracking for clinical care are vast, and although many have yet to be realised in real-world rheumatology practice, realisation is within reach and has been accelerated by the COVID pandemic. This thesis also highlighted some of the opportunities for using frequently collected PGHD for longitudinal epidemiological research in RA: better characterising patterns of disease through time and predicting disease flares, which can ultimately support new models of outpatient care.

Just as technological innovation allowed Eadweard Muybridge to reveal the secrets of equine gait by increasing the frequency of his observations, this thesis has established that frequent, longitudinal collection of patient-generated health data from smartphones indeed holds an enormous potential for advancing clinical care and research in RA.

8

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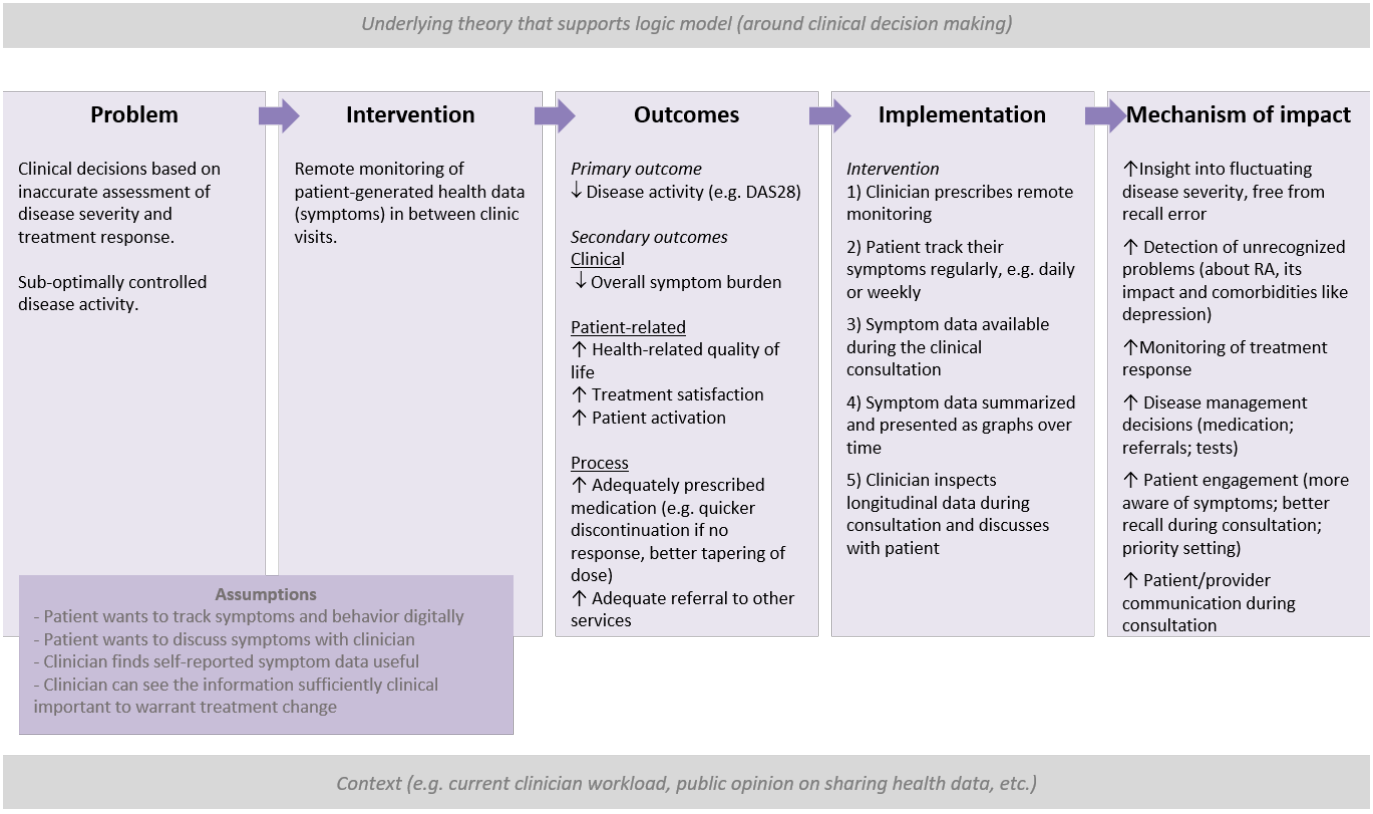
9

Appendices

9.1 Appendices to Chapter 1

9.1.1 Logic model for a remote monitoring system, such as REMORA



9.1.2 Transforming outpatient's opinion piece

Published in Journal of the Royal Society of Medicine in 2022.
https://doi.org/10.1177%2F01410768221089020

The Royal Society of Medicine

Commentary

Journal of the Royal Society of Medicine; 0(0) 1–5
DOI: 10.1177/01410768221089020

Better digital health data should be the foundation to transform outpatient consultations for people living with long-term conditions

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Outpatient departments support disease management for people living with long-term conditions (LTCs) like cardiovascular disease, diabetes and arthritis. The demand for outpatient care is increasing: around one in four people in the UK now live with one or more LTCs,[1] with outpatient appointment numbers increasing by more than 50% in the decade to 2018–19.[2]

The pandemic led to a rapid increase in the use of technology for consultations. In July 2020, remote consultations accounted for >70% of interactions in primary care, up from 25% the previous year.[3] This digital transformation is heralded as an opportunity for future care, acknowledging benefits such as reducing travel, reducing the spread of infections and reducing non-attendance. Nonetheless, these opportunities come balanced by challenges. Successful outpatient care requires a clear understanding of how patients' symptoms and management evolve through time. Through the pandemic, the reduction in good-quality information to inform shared decision making became apparent: virtual care misses the richness of face-to-face consultations, and removes the ability to perform physical examinations.

The National Health Service (NHS) now seeks to 'build back better', expanding on its pre-existing vision,[4] informed by the rapid changes forced by the pandemic.[5] Outpatient clinics are unlikely to revert to the same pre-pandemic operating model, not least because accelerated digital transformation has delivered many of the above benefits. During this period of change, it is vital that we think carefully about how digitisation can support the collection, collation and presentation of clinical data for excellent care, as well as for other secondary uses.[6] A strong data foundation for outpatients is particularly important if we are to offset some of the challenges of fewer face-to-face consultations.

This article considers the purpose of a consultation, then explores opportunities for advancing the collection and use of digital health data to transform outpatients. It considers how such data might also be used for other purposes such as planning and research. The article focuses on the collection and presentation of data from structured data entry into the electronic health record (EHR) and the use of integrated electronic patient-generated health data to improve shared decision making[7] and provide more patient-centred care.

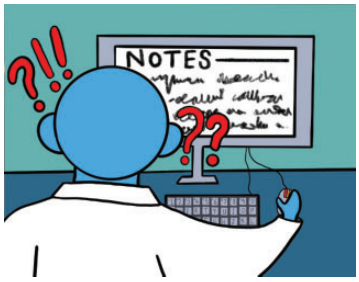
The model for outpatient consultations

Outpatient visits follow a model unchanged for centuries.[8] Prior to the consultation, a clinician reviews the referral letter or past visit notes. The consultation proceeds with history taking, examination and investigations, a sequence repeated at follow-up appointments. The clinician's goals are to gather sufficient information to reach a differential diagnosis and assess disease severity and treatment response to guide management. Patients hope that consultations allow them to explain their concerns, so clinicians can guide them towards better health and wellbeing.[9] Unfortunately, steps in this process can be imperfect, especially when time is constrained. Efficient elicitation and collation of pertinent information is often

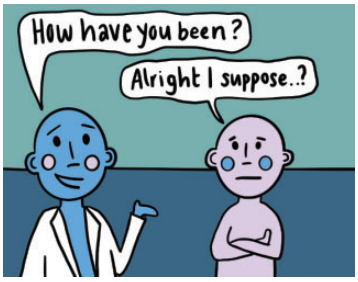
Figure 1. Current and future outpatient consultations. (a) Example of pitfalls in the current outpatient process due to data gaps, illustrated through the story of a 20-min rheumatology consultation. (b) Examples of opportunities from structured, integrated digital health data collected by both patients and clinicians, illustrated through the same 20-min rheumatology consultation. EHR: electronic health record; PGHD: patient-generated health data.

(a)

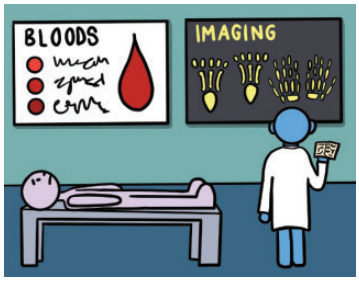
Current state



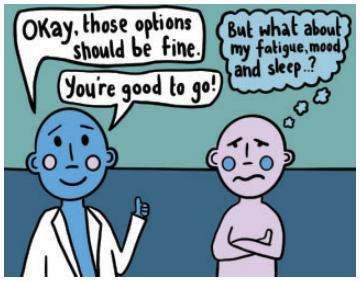
Prior to the consultation, the clinician is digging through notes to find diagnosis, disease severity, medication. Trying to reconstruct a timeline to understand progression and treatment response.



Consultation begins. The patient struggles to summarise symptoms since the last visit 12 months ago. History is limited by recall.



The clinician pulls up lab results, imaging, data from other sources from external systems that are slow and not cooperating. Performs physical examination.



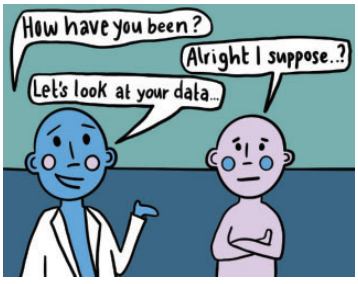
Past clinical data and recent patient info lead to shared informed decisions abouttreatment and referrals. The ending is rushed. The patient's concerns are not aired.

The clinician dictates or types outpatient letter. Already behind schedule...

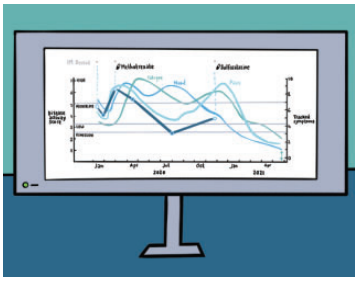
(b)

Future with technology

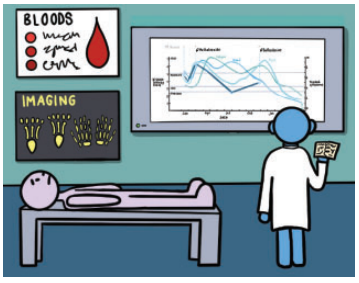
Prior to the consultation, the clinician accesses the automated clinical summary and longitudinal record to understand progression of disease and treatment response up until last visit.



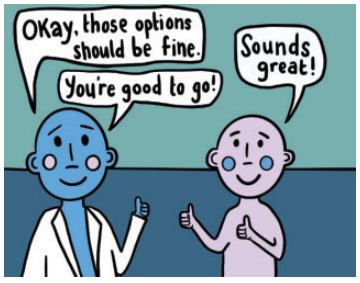
Consultation begins. Patient struggles to summarise symptoms since last visit, butthe clinician quickly turns to the PGHD to aid the patient's memory by reviewing the data together.



PGHD in the EHR dashboard facilitates a patient-centred discussion around the patient's fluctuating disease severity, providing a clearer picture of treatment response through time.



The clinician pulls up lab results, imaging and other data from the intuitive, integrated EHR and performs a physical examination.



Past clinical data and longitudinal patient-generated data lead to a shared, informed decision about treatment and referrals. The patient's concerns are aired and addressed.

The clinician enters data from the consultation in structured fields, which generates an automated letter to the patient about the findings and agreed decisions. It also adds new information to the automated clinical summary.

challenging, with knock-on consequences for the rest of the consultation (Figure 1(a)). We propose that technology can help improve this.

Unlocking the potential of electronic health records and structured data capture

Piecing together information by scanning scores of outpatient letters can be time-consuming and frustrating. This is further complicated if records are inaccurate, incomplete or inaccessible. Paper records (still used in around one in four hospital Trusts[10]) may be filed in the wrong order, fallen out or otherwise missing. Digital health records provide easier access but are still a series of free-text documents requiring time to review manually.

While the primary purpose of health data is to guide individual care, such data are also used to understand the healthcare system through planning and research. The lack of structured and coded outpatient data means, amazingly, there is no detailed overview of outpatient services in the UK. For example, we do not know about outpatient case mix or prescribing because diagnosis and medication data are locked away within unstructured letters. National clinical audits mostly rely on manual data entry into an online audit database. These audits provide important insights about which service improvements are required and the impact of interventions, but data collection is highly inefficient and often incomplete.

Structured data collection using EHRs seems an obvious solution for direct care and secondary uses (Figure 1(b)). But the challenges are significant. Clinicians may be reluctant to enter coded information – understandably, investing time to enter data will not be acceptable without direct benefits. Hospital EHR departments equally do not have the capacity to develop multiple bespoke data entry systems for the varied outpatient-based specialties.

Could there be a common solution across outpatient-based specialties? It is theoretically possible to design a generic outpatient data collection system for all departments caring for patients with LTCs. All share a need to collect the same core information: demographics, environmental exposures, vital signs, diagnoses, results, medications and – for each disease – the disease-specific outcome measures. By focussing efforts on a common system, data can be standardised using accepted coding terminologies (e.g. Snomed for diagnoses and d + md for medications). Data quality would increase, further supporting interoperability and enabling national statistics. More importantly, it could support better, safer care by reducing inaccurate or incomplete information, and data can follow patients as they move between providers. This structured data could be used as the basis for a visual longitudinal record (Figure 2(a)), providing an accessible summary of, say, disease severity against medication use through time. This can act as a visual aid during consultations, allowing patients and clinicians to jointly understand treatment response and make shared informed decisions, thereby providing a return on investment to the clinicians who enter structured data.

The NHS X Tech Plan for health and care states, '*we will know we have succeeded when clinicians find technology makes their working lives much easier [and] adding to clinical records, and looking things up from the whole of a patient's record, become straightforward and intuitive*'.[11] This is a laudable aim.

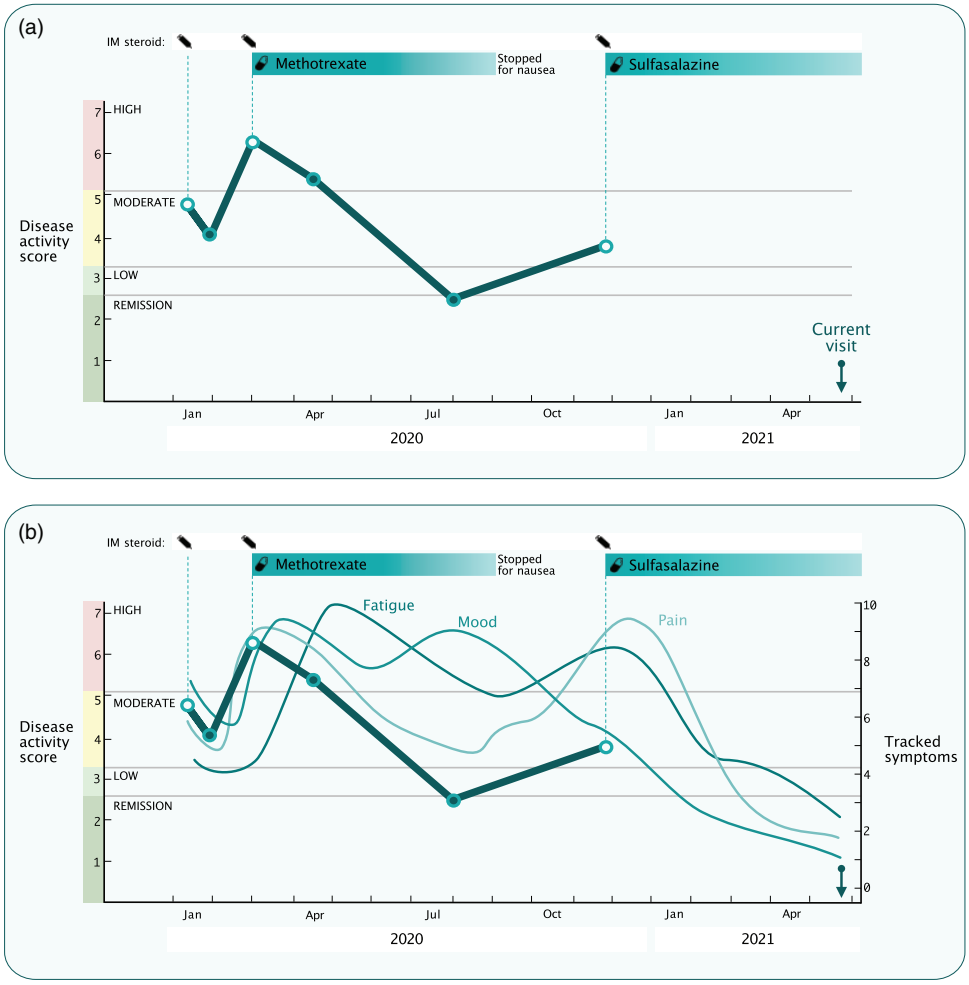
A clearer picture of health through time: patient-generated data

Even if clinicians have a perfect view of what has happened until the last visit, we need patients to describe what has happened since then (Figure 2). It is well known that patients have difficulty recalling events from preceding months, and succinctly summarising day-to-day variations in symptoms (Figure 1(a)).

Integration of patient-generated data from consumer technologies into clinical care systems could be transformative by providing a more comprehensive picture of how patients live with their medical conditions, complementing provider-led capture of health-related data. Additionally, it is a way to capture and augment the patient voice and strengthen the patient–provider relationship. Collecting patient questionnaire data electronically from home prior to a visit could save time and resources in clinic, even more so if that was done longitudinally between clinics (Figures 1(b) and 2(b)). Passive monitoring using sensing technology is imagined to offer a viable, future alternative to long-term symptom tracking, though there are still hurdles to overcome before such 'digital biomarkers' are adopted in clinical care.[12] Digital inclusion should be considered during development, implementation and evaluation to ensure that patients, even those with fewer digital skills, have the digital access, skills and confidence they need to contribute and benefit from digital health data.

Healthcare systems have been slow to formally integrate patient-generated data into EHRs. Efforts to date have predominantly been small-scale pilots in highly selected groups of participants (although non-integrated solutions are available and on the rise).[13] This is due to the myriad of technical challenges, including data security and privacy, data standardisation, data analytics and visualisation, workflow integration and device interoperability, as well as patient

Figure 2. (a) Longitudinal visual record of a hypothetical patient with rheumatoid arthritis. The visualisation starts with a presentation in January 2020 with moderate disease severity. Following initial treatment with intramuscular (IM) steroid, there was initial improvement but then there was a recurrence with worsening disease severity. Methotrexate was commenced at the end of February, after which disease activity improved. Treatment was discontinued in August due to intolerable nausea. The most recent visit found moderate disease activity and the clinician commenced a second disease-modifying anti-rheumatic drug, sulfasalazine, alongside administration of IM steroid injection. The vertical arrow indicates the visit that the patient is currently coming to clinic for. (b) The same longitudinal visual record with real-time patient-generated health data (here symptom tracking of fatigue, mood and pain) added, illustrating good patient benefit from the new treatment.



and provider concerns.[14] Nonetheless, it is achievable: in the UK, our Remote Monitoring of Rheumatoid Arthritis study uniquely integrated daily patient-reported symptoms from smartphones into the EHR, delivering proof that integrated systems are feasible and can transform consultations for clinician and patient benefit.[15]

A strong data foundation for future outpatient care

Outpatient-based specialties share a common goal when collecting information: gather the necessary, accurate information to understand diagnoses, disease severity and treatment response, to inform decision making and effective communication. So, collect the right information, in the right way, and present it usefully. From clinicians, this means collecting coded, structured information while providing a 'return on time investment' by presenting a longitudinal view of disease severity and treatment response. From patients, a new infrastructure is needed to securely connect and present data collected between visits in the NHS. Together, this could underpin some of the national digital ambition, such as patient-initiated follow-up and 'just in time' interventions. It could

also support a learning healthcare system that continually improves by collecting and processing data to inform better decision-making.

Realisation of this vision is within reach. It requires a change in how EHRs can best support collection of the right data from outpatients with useful real-time feedback. Uncoupling care organisations from the constrained functionality of their EHR providers would help. We are starting to learn how patient-generated data can be technically integrated into the NHS, how integrated patient data may lead to better health outcomes, the cost-effectiveness of remote patient monitoring, and what supporting materials are needed for both clinicians and patients. Despite its many challenges, we must strive to provide a solid data foundation for the inevitable changes in outpatient care in coming years to ensure we deliver safer, more efficient and more person-centred care.

Declarations

Competing Interests: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: WGD has received consultancy fees from Abbvie and Google unrelated to this work. All other authors have nothing to declare.

Funding: The author(s) disclosed receipt of the following financial support for the research, authorship, and publication of this article: This work was funded by the Centre for Epidemiology Versus Arthritis (grant number 21755).

Ethics approval: Not applicable.

Guarantor: WGD.

Contributorship: JG and WGD conceived the idea for the Commentary. All authors drafted the sections and approved the final version.

Acknowledgements: None.

Provenance: Not commissioned; peer-reviewed by Peter Aspinall.

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9.2 Appendices to Chapter 2

9.2.1 **Supplementary table 1**. Final search query from MEDLINE via Ovid

Long-term conditions	Patient-generated health data	Data capture systems
1. Chronic Disease/ 2. ((chronic* or persistent or long* term or ongoing) adj (disease* or disab* or ill* or condition* or health condition* or medical condition*)).mp. 3. Cardiovascular Diseases/ 4. ("heart disease*" or "heart failure" or "myocardial ischemia" or "coronary disease *" or "coronary artery disease*" or "myocardial infarct*" or hypertension or "high blood pressure").mp. 5. Heart Failure/ 6. Lung Diseases, Obstructive/ 7. Pulmonary Disease, Chronic Obstructive/ 8. ("obstructive lung disease*" or "obstructive pulmonary disease*" or copd or asthma or bronchitis).mp. 9. Cystic fibrosis/ 10. cystic fibrosis.mp. 11. Stroke/ 12. Stroke.mp. 13. (cerebrovascular or "brain isch?emia" or "cerebral infarc*" or "carotid artery disease*" or stroke or epilep* or seizure*).mp. 14. (Huntington* or Parkinson* or "amyotrophic lateral sclerosis" or "multiple sclerosis" or "motor neuron disease").mp. 15. Colonic Diseases, Functional/ 16. Irritable Bowel Syndrome/ 17. Irritable bowel syndrome.mp. 18. Musculoskeletal Diseases/ 19. (arthritis or RA or osteoarthritis or rheumati* or fibromyalgia).mp. 20. Renal Insufficiency, Chronic/ 21. ((renal or kidney) adj (failure* or insufficienc*)).mp. 22. Diabetes Mellitus/ 23. Diabetes Mellitus, Type 1/ 24. Diabetes Mellitus, Type 2/ 25. (diabetes or diabetic*).mp. 26. Neoplasms/ 27. (cancer* or oncolog* or neoplasm* or carcinom* or tumo?r* or malignan* or leuk?emia).mp. 28. Bipolar Disorder/ 29. bipolar disorder.mp. 30. Schizophrenia/ 31. schizophrenia.mp. 32. ((mental* or psychiatr* or psychological* or behavio*) adj (ill* or disorder* or disease* or distress* or disab* or problem* or health* or patient* or treatment)).mp.	33. Patient Generated Health Data/ 34. (patient-generated health data or PGHD).mp. 35. patient-generated health information.mp. 36. patient-generated data.mp. 37. (patient-generated or person-generated or caregiver-generated or consumer-generated).mp. 38. Patient Reported Outcome Measures/ 39. patient reported outcome*.mp. 40. patient reported outcome measure*.mp.	41. Remote patient monitoring.mp. 42. (digital adj2 (monitor* or track* or report* or record*)).mp. 43. (remote adj2 (monitor* or track* or report* or record*)).mp. 44. (electronic adj2 (monitor* or track* or report* or record*)).mp. 45. (tele adj2 (monitor* or track* or report* or record*)).mp. 46. (computer-based adj2 (monitor* or track* or report* or record*)).mp. 47. (smartphone adj2 (monitor* or track* or report* or record*)).mp. 48. (symptom adj2 (monitor* or track* or report* or record*)).mp. 49. Cell Phone/ 50. Smartphone/ 51. Smartphone.mp. 52. iPad.mp. 53. Mobile Applications/ 54. Mobile application*.mp. 55. (mhealth or mobile health).mp. 56. Telemedicine/ 57. telemedicine.mp. 58. digital health.mp. 59. Electronic Health Records/ 60. (electronic health record* or electronic medical record* or electronic patient record*).mp. 61. Patient Portals/ 62. Patient portal*.mp. 63. Health Records, Personal/ 64. Personal health record.mp. 65. self track*.mp. 66. Health IT.mp. 67. Medical Informatics/ 68. health information technology.mp.
69. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 31 or 32 70. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 71. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 72. 69 and 70 and 71		

9.2.2 **Supplementary table 2.** Outcome indicators adapted from Chen et al., against which anticipated and realized benefits from the included studies were assessed.

Number	Outcome
1	Patient-provider communication
2	Monitor treatment response
3	Detect unrecognised problems
4	Changes to patient health behaviour
5	Changes to patient management
6	Improved patient satisfaction
7	Improved health outcomes
8	Strong and effective quality improvement
9	Increased transparency, accountability, public reporting
10	Better system performance (monitoring, planning, financing, evaluating, responding)

Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res 2013;13:211. doi:10.1186/1472-6963-13-211

9.2.3 **Supplementary table 3.** Risk of bias for studies reporting on realized benefits based on criteria from the Mixed Methods Appraisal Tool

Domain	**Criterion**	Austin et al.	Biber et al.*	Garcia et al.*	Girgis et al.	Graetz et al.	Schou-gaard et al.*	Schou-gaard et al.	Snyder et al.	Van Egdom et al.*	Wagner et al.	Warring-ton et al.	Zylla et al.
Screening question	Clear research question	✓	X	✓	✓	✓	X	✓	✓	X	✓	✓	✓
	Data adequate to address research questions	✓	?	X	✓	✓	?	✓	✓	?	✓	✓	✓
Qualitative	Appropriate qualitative approach	✓			✓	✓			✓			✓	
	Adequate data collection methods	✓			✓	✓			✓			✓	
	Findings adequately derived from data	✓			✓	?			?			✓	
	Interpretation substantiated by data	✓			✓	?			✓			✓	
	Coherence: data sources, collection, analysis and interpretation	✓			✓	X			✓			✓	
Quantitative descriptive	Relevance of sampling strategy	✓			?				✓		✓	✓	✓
	Representative sample	X			X				?		X	X	X
	Appropriate measures	✓			✓				✓		✓	✓	✓
	Low risk of non-response bias	?			?				?		?	?	?
	Appropriate statistical analysis	✓			✓				✓		✓	✓	✓
Randomized controlled trial	Appropriate randomization					✓		✓					
	Comparable groups at baseline					✓		✓					
	Complete outcome data					?		✓					
	Blinding					X		X					
	Low drop-out rate					X		X					
Mixed methods	Appropriateness of mixed-methods design	✓			✓	✓			✓			✓	
	Effective integration of quant. and qual. data	✓			✓	✓			✓			✓	
	Adequate outcome interpretation	✓			?	✓			✓			✓	
	Considerations of divergent quantitative and qualitative findings	?			?	?			?			?	
	Adherence to quality criteria of methods	✓			X	X			X			✓	
	Total scores	**14/17**			**11/17**	**8/17**		**5/7**	**12/17**		**4/6**	**14/17**	**5/7**
	Percentages	**82%**			**65%**	**47%**		**71%**	**71%**		**67%**	**82%**	**71%**

9.3 Appendices to Chapter 4

9.3.1 REMORA1.5 protocol

RESEARCH PROTOCOL

Remote monitoring of rheumatoid arthritis

Investigating patterns of disease and treatment response in rheumatoid arthritis patients using the REMORA smartphone app for daily symptom tracking

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2) Introduction

What is the problem being addresses?

Rheumatoid arthritis (RA) is a common long-term condition that causes painful, swollen joints and disability. Symptoms vary from day to day and the progression of the disease is unpredictable. People living with RA frequently experience flares - a temporary worsening in symptoms. Evidence suggests that early detection and treatment of flares seem essential to improve long-term outcomes. Until recently, we have not been able to capture these short-term variations in disease severity and occurrence of flares outside of asking the patient to recall them at infrequent clinic visits – usually every 6-12 months. But with the widespread use of digital technologies, opportunities for collecting patient-reported data digitally with increased frequency has emerged. This has potential to give us an understanding of what happens with RA symptoms, signs and experiences outside of clinic allowing researchers to answer questions that have previously been impossible to address.

What we aim to do

This study asks adult RA patients to keep track of their daily symptoms using the Remote Monitoring in RA (REMORA) app on their smartphone. The results are automatically sent to their electronic patient record for discussion at their next clinical appointment. Additionally, we will use the data from the app and the patient record to answer research questions with the aims of:

1) Understanding the patterns of RA symptoms and flares on a day-to-day basis
2) Investigating patterns of treatment response

We will recruit 50-100 RA patients from Salford Royal NHS Foundation Trust to track their symptoms on their own smartphone for up to 12 months. The study is funded by the Greater Manchester Digital Fund.

What we hope to achieve

We will learn valuable insights that can lead us to better management of people living with RA in the future. Our results will provide better answers to the important questions "*what does to the future hold?*" and "*will this drug work*?".

2) BACKGROUND

Rheumatoid arthritis (RA) is a long-term condition that requires continuous management of care and life-long medication use. Knowing "what the future holds for me" is central to people suffering from RA, as they go about and manage their disease outside of clinic. Clinical experience is invaluable in providing some answers to this. Scientific evidence of long-term change and disease patterns over time traditionally comes from research in longitudinal cohorts and registers. These important data sources also provide some evidence about response to different RA treatments addressing another important question of "will this drug work for me?".

However, research in cohorts and registers is typically limited to understanding what happens to the patient at discrete intervals, usually every 3, 6, or 12 months. People living with RA frequently experience flares, which area transient increases in joint pain, swelling, and other symptoms such as stiffness and fatigue that indicate increased inflammation and worsening of their RA. These episodes vary widely in frequency, duration, and intensity.(1) There is a growing body of evidence which suggests that early identification and treatment of flares improve long-term outcomes.(2) Until recently, we have not been able to capture short-term variations in disease severity and occurrence of flares outside of patient recall at the discrete intervals of traditional research in cohorts and registers or when the patient sees their clinician at infrequent clinic visits– usually every 6-12 month.

As digital technologies are becoming increasingly pervasive, unique opportunities to collect health data directly from patients have emerged. Key features of such patient-generated health data (PGHD) are: 1. the patient, not the healthcare provider, captures the data; 2. the data are obtained outside of clinical settings; and, therefore, 3. the data can be collected longitudinally and with high frequency.(3) Collecting PGHD with increased frequency has potential to give us an understanding of what happens with RA symptoms, signs and experiences outside of clinic allowing researchers to answer questions that have previously been impossible to address.(4)

We ran the novel REmote MOnitoring of RA (REMORA) pilot study, where we integrated daily patient-generated data from a smartphone app into the electronic health record (EHR) system of a single hospital and tested its acceptability with 20 RA patients and two clinicians for three months.(5) The results showed that participants tracked daily symptoms on >90% of all days. Participants viewed the intervention positively, with regular symptom reporting identifying changes in condition that would otherwise have been missed, and promoting shared conversations about disease management. Overall REMORA showed a strong proof of transformative potential of integrating patient-generated health data into clinical care and research.

For this research study we will re-implement the REMORA system back in the clinic with the aim of exploring the patterns of RA symptoms and flares on a day-to-day basis as well as investigating patterns of treatment response.

3) STUDY OBJECTIVES

4.1 Primary Question/Objective:

The primary aim of this study is to examine the natural history of day-to-day RA disease severity and treatment response by tracking patient-reported symptoms using the REMORA app. The primary aim will be addressed through the following objectives:

Natural history:

- Describe changes in self-reported symptoms over time
    - In individual patients
    - Summarized across the population

- Describe the correlation between self-reported symptoms (e.g. pain and fatigue) over time
- Examine the frequency and extent of patient-reported RA flares

Treatment response:

- Describe changes in self-reported symptoms after treatment initiation, and compare between different treatments

4.2 Secondary Question/Objective:

We will inspect clusters of trajectories of self-reported symptoms in the whole cohort, then stratified on treatment: Can we differentiate groups who have different response to treatment (e.g. good, moderate, non-responders) and identify variables that are associated with that response?

Additionally, we wish to test how valid patient-reported measures are compared to clinicians'. We will validate patient-reported tender and swollen joint counts against a clinician's assessment after patients have received online education of how to do their joint counts.

4) OUTCOME MEASURES

The primary outcome measures will be results that give us insights into the natural history of RA disease severity and disease flares as well as trajectories of treatment response to different medications, measured using the self-reported symptoms within the smartphone app.

The secondary outcome measures are the answers to the secondary questions raised earlier.

5) STUDY DESIGN & PROTOCOL

6.1 Participants

Study participants will be adult patients diagnosed with RA attending the Rheumatology Outpatient department at Salford Royal NHS Foundation Trust (SRFT).

Study participants for our secondary objectives will additionally include clinicians seeing patients enrolled in the study.

6.2 Study Intervention and/or Procedures

The study is a prospective cohort study.

App data

After completing consent, patients will download and install the app onto their own smartphone (Android phones) following user instructions and log in with their NHS login (instructions will be provided for setting up an NHS login and downloading and using the app). Upon downloading the app, patients will be asked for an activation code provided in the download instructions (this is only required once). Similarly, they will be asked one time to confirm that they agree to share their data for research purposes (see under eConsent). All patients will then track their symptom

data on the app for a period of up to 12 months as part of their daily life. The app will prompt daily, weekly, and monthly question sets with a single notification or alert each evening. See Figure 1 for screenshots of the app. Daily questions include visual analogue scales for symptom severity, while weekly and monthly questions are longer questionnaires (see appendix A for a list of items). The prior REMORA study showed that this burden of data entry was both acceptable and feasible to collect, with data entered on >90% of possible days over a three month period. The data will become available within the EHR as symptom graphs for the clinician to access, interpret and discuss with the patient during the routine clinical consultation. Hence, there are no extra study visits to the clinic. Besides the pre-defined question sets, patients have two different options to provide further contextual information within the app. If the patient reports that they had a flare within the last week, they will be provided the option to note down factors they believed caused the flare. This information will be shared with the clinician as part of the data coming from the app. Additionally, there is a free-text diary function. Information written here is private, and will not be shared. The level of data sharing will be clear to the participant within the app.

EHR data

Participants will give consent to allow researchers to access their EHR. Specific data items (see box 1) will be extracted from the doctor's notes and added to a research database (see under Data Collection below). This data will be used to adjust statistical analyses and investigate treatment response.

Box 1: Items to extract from the EHR

- Diagnosis and duration of disease
- Disease activity scores (CDAI, DAS28)
- Medication, administration, and dosage
- Comorbidities
- Age
- Gender
- Ethnicity
- Smoking
- BMI

Patient-reported joint counts

To help patients to understand how to assess whether their joints are 'swollen' or 'tender', online education in the form of videos will be provided to patients. These videos will be available through a direct link in the REMORA app and through a web address which they may enter manually into a browser.

6) STUDY PARTICIPANTS

7.1 Inclusion Criteria:

Patients

Inclusion criteria

- Adult (> 18 years of age) RA patients attending the outpatient clinic at SRFT (in person or remote consultation)
- There is no upper age limit. Both males and females will be included
- Own an Android smartphone

7.2 Exclusion Criteria:

Exclusion criteria

- Patients who feel too unwell to take part or who are unable to understand the project information will be excluded

- The study does not have the capacity to translate materials into other languages. Therefore potential participants who are unable to speak English and understand English verbal explanations will be excluded

Clinicians

Clinicians are eligible if they see RA patients in the outpatient clinic at SRFT (both in person and remotely).

7.3 Recruitment:

Patient recruitment and consenting

We will recruit our participants from Salford Royal NHS Foundation Trust's rheumatology department for up to 6 months. There are different strategies for recruitment and on-boarding depending on the current Covid-19 circumstances: In clinic and remote. Both strategies are likely to be used simultaneously. Additionally, clinicians can refer patients directly to the research nurses for possible recruitment. The department's research nurse team will assist in recruitment and running of the study. Please see Appendix B for a flowchart containing information about recruitment. For both scenarios, the research nurses screen clinic lists for eligible patients one month ahead, call the patient to ask for contact method preference (notes down email address if this is not already known) and sends out an information leaflet and patient information sheet via post or email. The research nurses keep track of who has responded and declined and will nudge patients after 2 and 3 weeks if a patient has not responded, by making a phone call to the patient.

We will also hang posters in the waiting room and leave information flyers for patients to read. The material will include contact information, so interested patients that have not already been approached can get in touch with the research nurse team.

In clinic recruitment and consenting: If face to face consultations proceed as normal, we will recruit and on-board patients directly in the clinic. After having identified eligible patients and sent them information leaflets and the patient information sheet, the research nurses will take consent in clinic at the time of the face-to-face visit of the patient. Because the patient information sheet is rather lengthy, we will provide the research nurses with "key messages" (Appendix C) to go through with the patient, before signing the consent form. When consent is given, the participant will receive instructions for downloading and using the app.

Remote recruitment and consenting: If consultations continue to be carried out over telephone/video, we will proceed with a remote strategy. The research nurse team will email or post consent forms and download instructions to patients who have expressed interest in participating. After at least 24 hours after the forms have been received by the patient, a research nurse will call the patient to answer any questions about the study and will also provide "key messages" from the PIS. Following the conversation the patient signs and returns the consent form via email to the research nurse team. This can be done by:

1. Signing the consent form received via post using wet ink, take a photo of the signed form, and attach this photo to an email to the research nurse team.
2. Pasting an electronic signature on the form received via email, attach the signed form to an email to the research nurse team. If the patient has a printer, they can also print out the consent form and follow the steps above.

Following the return of the consent form, the download and user instructions can then be opened and read (these were received with the consent forms).

We aim to recruit 50-100 patients from the clinic over the 6-month period.

What will consent forms include?

Due to the two different ways of consenting, participants can complete either a paper or a digital consent form. See submitted consent forms for details. In broad terms these will include:

- Providing consent, informed by the patient information sheet and opportunity to ask questions
- Understanding that the study will collect self-reported symptoms via the app
- Willingness to share symptom data from the app and app usage data with the research team and the clinician seeing the patient during clinic consultation
- Willingness to share app data with other bone fide researchers beyond the study team, where access has been agreed by the lead investigator
- Ability to withdraw at any time. However, it will not be possible to remove data from the project once it has been anonymised as we will not be able to identify the specific data
- Understanding that their GP or other NHS providers will not be informed of participation and data will not be shared
- Understanding that data is stored for 10 years at the University of Manchester
- Agreeing to take part in the study on the basis that researchers will access their electronic health records (EHRs) (secondary care) to allow for collection of clinician-derived data e.g. presence of comorbidities, medication prescriptions, and medication changes.
- Understanding that the NHS number will be securely used as the linkage key throughout the study
- Understanding that health information collected will <u>not</u> routinely be viewed by the medical team until next clinical consultation and that the participant should communicate with their clinical team as usual.

If the consent form is signed and returned electronically via email, a copy will be printed and stored in the clinic with the paper consent forms.

Following up with participants during on-boarding

The university research team will follow up with participants who have not submitted their first symptom report within one week after signing the consent form and receiving the on-boarding materials. In this case, a member of the research team will call the study participant on their contact number to check if s/he needs any further support to start engaging with the app. If no response or data has been received after 72 hours of the first call, we will call the study

participant on a maximum of two occasions in 72 hours, after which we will stop following up with the participant.

Trialling eConsent module

Additionally, when patients first download and log into the app they will be asked (once) to agree to their data being collected by the remora app for research. Agreement, by patients, to the collection of their app data for research is a requirement for taking part in the study (it is covered in the paper consent form, statement 5. The inclusion on the app of this consent question '*I agree to my data being collected by the REMORA app for research*' is for the purpose of trialling the embedding of an eConsent module into the technology. This work to embed an eConsent module into the app is necessary to inform the development of a future digital system that automatically directs data flow according to patient preference for using data in clinic and/or for research purposes.

Clinician involvement

We aim to involve up to 10 rheumatologists seeing RA patients, both consultants and registrars. Additionally, other members of the care team such as specialist nurses, physiotherapists, and pharmacists will have access to the data in the EHR. Prior to study start, we will arrange online meetings to inform about the purpose of our study and for answering questions. For the interested clinicians, we will provide a training program. This will include instructions for where to find the patient-reported data in the EHR, suggestions for how to use the data visualisation in clinic based on previous research within our group, and encourage to measure DAS-28 scores for all patients during every visit. One clinician from the clinic participated in the pilot study and will act as "super user" and assist in recruiting additional clinicians. Additionally, the Clinical Lead from the outpatient clinic has endorsed the study and will contribute as much as possible.

7.4 Participants who withdraw consent [or lose capacity to consent]:

Participants can withdraw consent at any time without giving any reason, as participation in the research is voluntary, without their care or legal rights being affected. Individuals will not be able to withdraw any data already collected.

7) DATA COLLECTION AND DATA SECURITY

8.1 Data collection

App data

Data collection and flow after having obtained consent is depicted visually in Figure 2. Briefly, participants download the app, enter the activation code provided in the instructions (to avoid unauthorised use by non-participants), indicate that they agree to share the data collected on the REMORA app for research on the eConsent module and log in with their NHS login credentials. After these few steps, the patient is ready to start tracking their symptoms. PGHD

from the smartphone flows into a database on the Greater Manchester Digital Platform (GMDP CIS REMORA database) hosted by Greater Manchester Combined Authority (GM CA). Data transfer is via an encrypted line. There will be a data processing contract in place between UoM (as data controller) and GM CA (as data processor).
The patient logs into the app using their NHS login, and the NHS number follows the patient's PGHD through the data flow as identifier and will be used for linkage throughout the study. A hashed version of the NHS number will be recorded in the CIS REMORA database in the GM Digital Platform. This hashed NHS number will be: (i) used to enable the visualisation of the PGHD in the EHR; (ii) associated with the PGHD pulled down from the GM Digital Platform to the UoM (described below); (iii) as the linkage key between PGHD and EHR data in a research database. It is not possible to allocate a unique participant ID along with the NHS number as the technical infrastructure does not allow for this.

Once a day, the CfE data manager will securely remote into the GMDP CIS REMORA database via a secure portal and pull down PGHD with the hashed NHS number into a research database within the University's Research Data Storage (RDS). The data transfer process is over an encrypted line.

In addition to a copy of the PGHD being transferred to UoM, the PGHD will be available as a graphical summary for the participants' clinician to review, when they view their EHR during a clinical consultation. A 3rd party service provider (GM Health and Social Care Partnership, GMHSCP) has set up the technical system for enabling the visualisation of PGHD to be viewed in the EHR. The way in which the technical system has been configured means that the GMHSCP will not be processing data rather it has enabled the use of a data visualisation tool, Tableau, to display the PGHD. The Tableau visualisation will query the GMDP database directly and render the results in a web page form which will be embedded within the Salford Royal EHR. Of note, data will not be stored on either the Tableau Server or the SRFT Systems – they will query the data held in the GMDP database 'on demand'.

<u>EHR data</u>
Participants' EHR data will be extracted manually by the research nurse team and inputted to a database called 'clinical database' at SRFT. The 'clinical database' will be built in REDCap, an online tool for building and managing databases trailed at UoM. The University has granted permission to collect identifiable data in REDcap from January 2021.The research nurse team will receive REDCap login information from the UoM research team. They will use participants' NHS numbers as identifier in the database. This 'clinical database' will be exported from REDCap to RDS at the UoM, the data checked and then deleted from the study team's REDCap account when the study concludes. Using the patient's NHS number as identifier, the research team will link the PGHD from the app with the 'clinical database' to create one merged database stored within the RDS at the University. During recruitment, the research nurses will draw up an electronic Participant Data List. This lists NHS number, name and contact details for each participant. The list will be password-protected and stored on a Trust computer and shared with the UoM research team using encrypted transfer.

<u>Meta data</u>

We will collect meta data about the clinician's use of the REMORA visualisation in clinic; how often did they open the visualisation and for how long per patient. This will be tracked anonymously through the Tableau visualisation, and data will be stored in RDS.

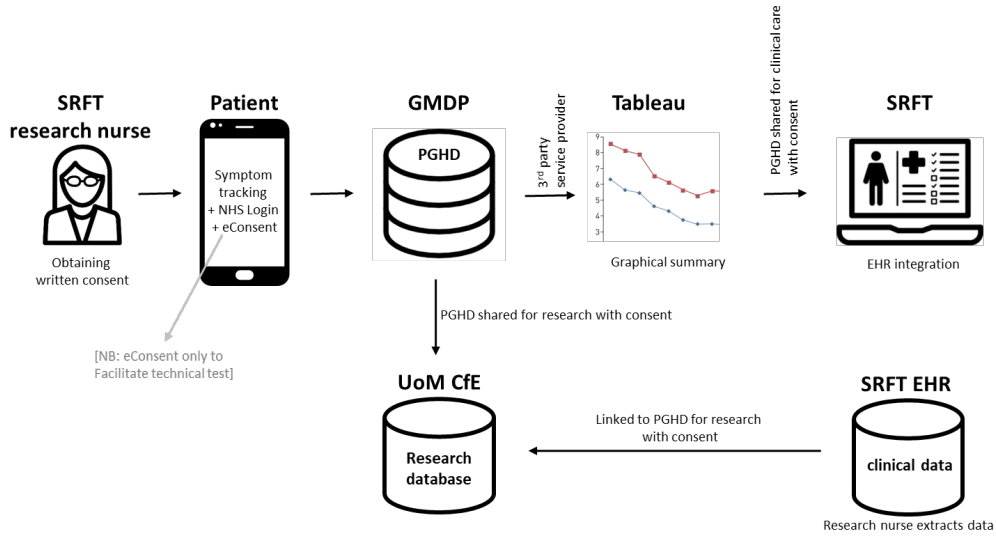

***Figure 0.1: Data collection**. After having consented to participate, the patient starts tracking their symptoms (=PGHD). PGHD from the smartphone is transferred to a secure database within the Greater Manchester Digital Platform infrastructure. From here, a copy of the PGHD is moved to a research database in UoM's RDS. Manually extracted data from the EHR is linked to the research database using the NHS number as linkage key. Additionally, clinicians are able to get a view onto the repository through the EHR, so they can see their patient's data as graphs over time. This is facilitated by the 3rd party data processor, Tableau.*

8.2 Confidentiality

We will collect the following direct identifiers:

- *Electronic and paper consent form*: capturing participant's name and signature.
- *Electronic participants data listing form*: NHS number (for linkage) name, postal address, email address, telephone number

Consent forms will be kept for 5 years after study completion in accordance with the University's record retention schedule and thereafter destroyed using the University's confidential paper shredding and disposal service Restore Data shred, https://www.staffnet.manchester.ac.uk/igo/records-information-management/disposal-of-confidential-material/. All personal data captured and transferred by the research nurse team will be stored securely in a locked cabinet at the University and moved to RDS at the earliest opportunity. This data will only be accessible to the UoM study team and only those within the team that need to have access to it will be granted access.

8.3 Physical security arrangements for data storage

For the data held in the app

Patients will log in using their NHS login credentials. NHS login makes it easier and quicker for patients to access multiple digital health and care services, with just one email address and password. This is a trusted, safe, and secure login developed by the NHS, so patients know their health and care data is protected. For security reasons, NHS login information will not be stored within the app. The authentication of the patient through the NHS login is valid for 3 hours. This means that the patient will have to log in to the app every day to answer their questionnaires. The patient can also decide to actively log out of the app, but can always log back in with their NHS login.

The raw symptom scores inputted by the patient are not stored within the app, but immediately pushed into the GMDP. Only the graphical summaries and the personal diary entries are retained on the phone. These will be deleted when the app is deleted from the phone and cannot be restored.

For the data held at University of Manchester

For remote recruitment and consenting, directly identifying personal data will be captured and stored electronically in Research Data Storage Service (RDS). Two separate RDS drives will be set up: RDS 1 will hold the (pseudonymised) attribute data. RDS 2 will hold all the directly identifying personal data (i.e. electronic consent forms and the participant data listing form). Access to RDS 2 will be limited only to those on the research team that needs access to this information. Any directly identifying personal data on paper will be stored in a locked cabinet at SRFT and later at UoM with restricted access. To save space, these documents will be scanned and uploaded to RDS at the earliest opportunity.

RDS is the recommended storage solution for research data at the University and underpins the Research Data Management Service. It is a dual-sited, petabyte-level SAN-based storage architecture, hosted and maintained by University of Manchester IT Services. The storage is mirrored and snapped to support the requirement around backup. The University's storage infrastructure is hosted and replicated across two data centres (approx. 4KM apart) for resilience and disaster recovery purposes. RDS is replicated across both data centres.

For PGHD held at GMDP

The PGHD held within the databases at GMDP will be stored in the FHIR Server using Amazon Web Services (AWS). All AWS resources will utilise Identity and Access Management (IAM) for access control and authentication to control who is signed in and has permissions to use the resources. AWS Platform as a Service (PaaS) resources will utilise Service Endpoints to increase security and reduce data flow through the Hub. All PaaS services are to have encryption at rest and in flight enabled and enforced; no data is to be stored or transmitted in plain text.

Meta data

Meta data about the clinicians' use of the visualisation will be stored in RDS with the attribute research data as described above.

8.4 Data retention

The research data (along with associated documents) will be stored in accordance to the UoM Record Retention Schedule for 10 years after the end of the study. At the end of the 10 year time period, a review of the data will be made as to whether it is appropriate to retain an anonymised version of the data for research purposes or whether to permanently delete the data in accordance with the University of Manchester data destruction policy.

Retention of directly identifying personal data after the end of the study is as follows:

- Informed Consent Form - this will be stored in-line with the University's Record Retention Schedule and SOP for taking recordings of participants (end of study + 5 years for high risk non-interventional studies) and thereafter destroyed following the UoM data destruction policy.
- Electronic participant list file – capturing names and email address for those participants that have consented to receive communications and or wish to be contacted in the future about research. It will be stored for 10 years (participants can ask to be removed from the list at any time) and then destroyed in accordance with the University's data destruction policy.

8) STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis

Patterns of symptoms and treatment response

All statistical analysis will be performed in the program R in consultation with a senior statistician within the Centre for Epidemiology at the University of Manchester, who has experience with longitudinal data collected from smartphones. The aim of the analysis is to identify distinct patterns of symptom reporting over time.

Statistical analysis includes:

1) Cluster analysis will be used to identify subgroups of subjects with distinct patterns of symptoms over time. The TraMineR package in R will be used to calculate a number of variables that summarize the sequence of symptom records for each individual. These variables can be combined with simple descriptive statistics and used in the cluster analysis to identify distinct subgroups. In addition, TraMineR can also calculate the distance between any two sequences of distinct symptom data using sequence analysis, and use this distance to perform cluster analysis.

2) We will investigate if the subsequent symptom reporting differs between subjects taking different treatments. The variables derived for the cluster analysis will be used as predictors in a multinomial logistic regression model.

9.2 Sample Size:

We aim to recruit 50-100 patients for the study. No sample size calculations will be needed for this observational, descriptive study. However, previous statistical experience with this kind of

data within our centre, suggests that this sample size is enough for clinically meaningful exploratory analysis.(5)

9) DATA MONITORING AND QUALITY ASSURANCE

The study will be subject to the audit and monitoring regime of the University of Manchester.

Data quality will be automatically monitored throughout the study. When the smartphone data is downloaded from the GMDP to RDS (as described in the data flow), a script will be run on the data to capture any missing data points. If data is missing for the same patient 5 days in a row, an automated email will be sent to the patient encouraging the patient to get in touch with the research team via email. If the same patient has still not entered any data by day 8, another automated email will be sent, providing a phone number for the patient to get in touch with the research team. See Appendix D for example text. By day 15, if the patient continues to not enter data on the app, we will consider the patient as dropped out. We will let the patient know that we will not try to reach them any further.

10) PEER REVIEW

This REMORA study was one of six projects which was submitted for the Health System Led Investment (HSLI) in Provider Digitisation competition at Salford Royal NHS Foundation Trust with funds being provided by the Greater Manchester Digital Fund. These projects were all peer-reviewed and REMORA was one of three that was funded following the external peer-review process. University of Manchester was awarded £131,139 from Salford Royal NHS Foundation Trust after the peer-review.

Review has been carried out in parallel with writing the protocol by multiple members of the research team and advice and feedback have been sought from relevant persons in the affiliated institutions (SRFT and LHCRE).

Our named patient partner has also reviewed all written material and provided feedback from the patient's perspective. This has been further supported by the REMORA Patient and Public Involvement group that has reconvened multiple times throughout the planning phase (for more detail about PPI work see below).

Finally, two independent experts from other institutions have reviewed the protocol and provided feedback.

11) ETHICAL and REGULATORY CONSIDERATIONS

12.1 Approvals

NHS Research Ethics Committee and HRA approval will be obtained before commencing research. The study will be conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

12.2 Risks

From the REMORA pilot study we know that patients do not find it too onerous to track their symptoms daily for three months, with completion rates exceeding 90%. Given that the burden on participants is proven to be acceptable, we have identified 3 particular issues that has the potential to present a risk and/or burden to participants:

1. Participants may over focus on their symptoms through the regular tracking, which might negatively impact their mood.
   To address these issues participants will be given contact details for the research team at the UoM with whom they will be able to discuss any concerns. In addition, the PIS provides information on how participants can withdraw from the study if they wish.
2. Participants may not know how to use the technology, or do not have capacity to solve problems themselves.
   To mitigate these issues we have set up a user support system, where participants can email the study team at any time with questions or technical issues. The email inbox is monitored Monday-Friday, and the research team will get back to the patient as soon as possible to solve the query. As this is a smartphone study that requires some level of digital literacy, we expect participants to be able to use email for support.
3. Participants believing that their health i.e. symptoms are monitored in real time by either the research team or their clinical team.
   To address this there are explicit statements in both the PIS and consent that tells participants that the app data is viewed only at their routine clinic visit, is not monitored throughout the study period, and that their data is only shared with their rheumatologist, and hence not their GP or other specialty providers. They will be reminded that they need to get in touch with their clinical team as normal if they have any clinical concerns.

We do not envision any risks for the researchers themselves. Researchers are not in direct physical contact with research participants.

12) STATEMENT OF INDEMNITY

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

13) PATIENT AND PUBLIC INVOLVEMENT

We have gathered a REMORA PPI group that will assist with different aspects of the study. Amongst others, these include deciding on the best recruitment strategy, developing and revising all patient-facing material, developing the app, and our dissemination strategy. We have 8 members in the group of various age and with different disease duration. We have planned 6 PPI group meetings in total: 5 in the planning phase (some of which have already taken place) and 1 after the study. See table below for an overview of planned PPI meetings.

Meeting date	Topic
June 8th 2020	Introductions, overview of research, future meetings
June 29th 2020	Review 1st version of all patient-facing material
July 8th 2020	Data visualisation workshop together with clinicians
September 25th 2020	App demonstration and review of download instructions
November 2020	Patient-reported joint counts and demonstration videos
Early 2022	End-of-study meeting: Results and plans for dissemination

14) FUNDING and RESOURCES

The study is funded by NHS England via the Greater Manchester Digital Fund through the Digital Department at SRFT and supported by Centre for Epidemiology Versus Arthritis. Additional funding comes from the NIHR ARC Greater Manchester.

15) PUBLICATION POLICY

We intend to submit research findings to national and international scientific meetings and for publication. Our PPI/E group will assist in developing strategies for dissemination beyond scientific publications. Additionally, the research will form part of Dr Gandrup's PhD thesis.

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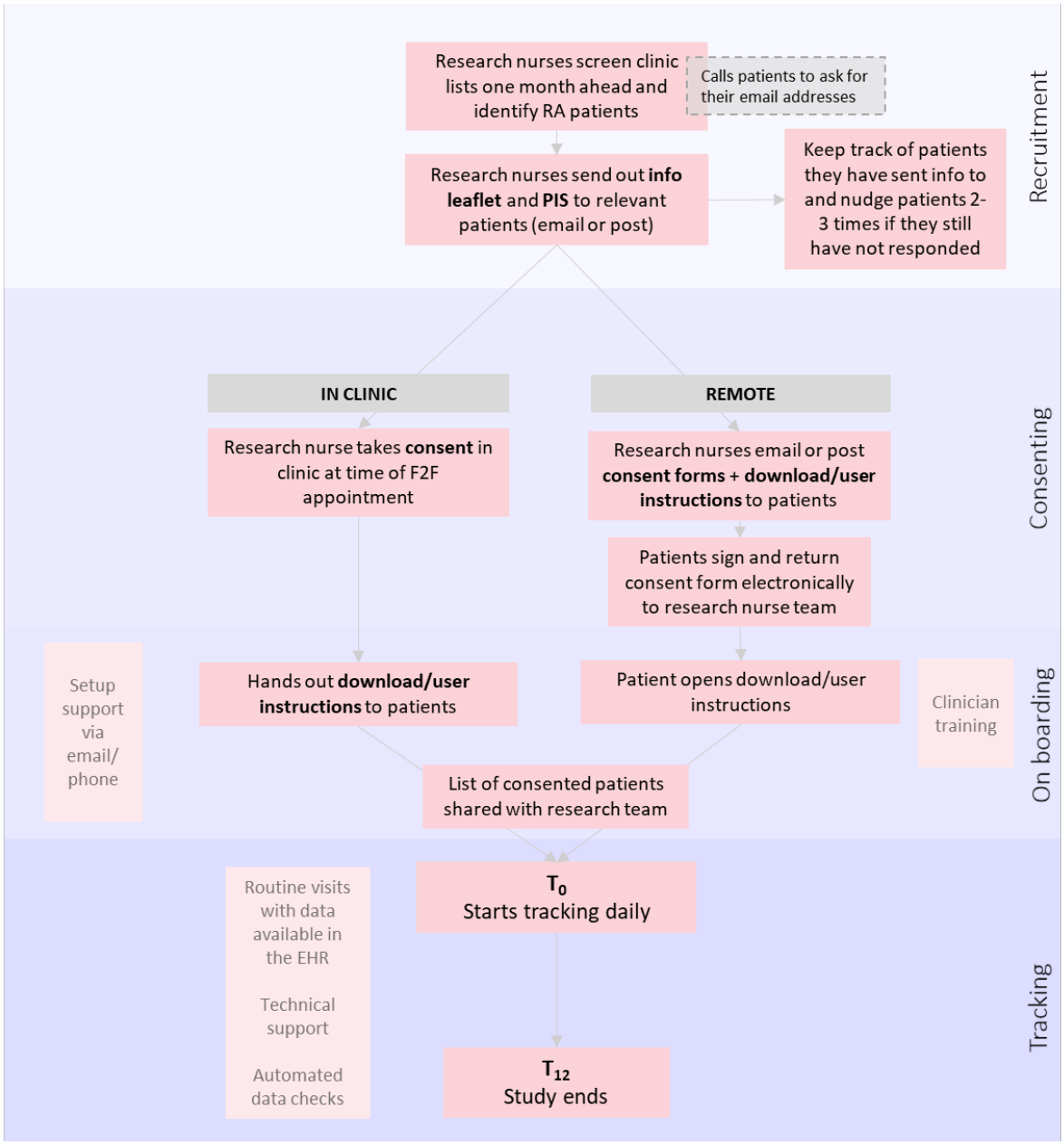
Appendix A. Question sets related to disease activity and impact, and their frequencies collected via the REMORA smartphone app

Data item	Question stem	Scale	Anchors
Daily data collection			
Pain	Select the number that best describes the pain you felt due to your RA during the last 24 h	VAS	None (0); extreme (10)
Function	Select the number that best describes the difficulty you had in doing daily physical activities due to your RA during the last 24 h	VAS	No difficulty (0); extreme difficulty (10)
Fatigue	Select the number that best describes how much fatigue you felt due to your RA during the last 24 h	VAS	No fatigue (0); totally exhausted (10)
Sleep	Select the number that best describes the sleep difficulties (i.e. resting at night) you felt due to your RA during the last 24 h	VAS	No difficulty (0); extreme difficulty (10)
Physical well-being	Considering your arthritis overall, how would you rate your level of physical well-being during the last 24 h?	VAS	Very good (0); very bad (10)
Emotional well-being	Considering your arthritis overall, how would you rate your level of emotional well-being during the last 24 h	VAS	Very good (0); very bad (10)
Coping	Considering your arthritis overall, how well did you cope (manage, deal, make do) with your RA during the last 24 h?	VAS	Very well (0); very poorly (10)
Morning stiffness	How long did your morning stiffness last today? (please enter '0' if you did not experience any stiffness)	7-point Likert scale	0 min; 0–9 min; 10–19 min; 20–29 min; 30–59 min; 1–2 h; >2 h
Weekly data collection			
Tender joint count	How many of your joints are tender today?	NRS	0 to 28
Swollen joint count	How many of your joints are swollen today?	NRS	0 to 28
Patient global assessment	Considering all of the ways your arthritis has affected you, how do you feel your arthritis has been in the last week?	VAS	Very well (0); very poor (100)
Employment status	Are you currently employed (working for pay)?	Dichotomous	Yes; no
Hours missed due to health problems	During the past seven days, how many hours did you miss from work because of problems associated with your RA?	n.a.	0 to [no upper limit]
Hours missed due to other reasons	During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?	n.a.	0 to [no upper limit]
Hours actually worked	During the past seven days, how many hours did you actually work?	n.a.	0 to [no upper limit]

Data item	Question stem	Scale	Anchors
Degree health affected work productivity	During the past seven days, how much did your RA affect your productivity while you were working?	VAS	RA had no effect on work (0); RA completely prevented me from working (10)
Degree health affected daily activities	During the past seven days, how much did your RA affect your ability to do your regular daily activities, other than work at a job?	VAS	RA had no effect on my daily activities (0); RA completely prevented me from doing my daily activities (10)
Occurrence of flare	Have you experienced a flare in the last week?	Dichotomous	Yes; no
Flare description	Please describe how your flare has affected you	Free-text[a]	n.a.
Monthly data collection			
Health Assessment Questionnaire (HAQ)	Validated questionnaire consisting of 23 items to assess physical function in RA,	n.a. (score 0-3)	n.a.

[a] For people reporting a flare, there is a free text field to enter information on its impact and potential causes that is shared with clinicians. The app also has a diary function for patients to record symptoms, feelings and thoughts in free text to support self-management. n.a.: not applicable; NRS: numerical rating scale; VAS: visual analogue scale.

Appendix B. Flow diagram: What happens at what point during the study



Appendix C. Key messages from PIS provided by CRN team to patients before signing consent forms

- The purpose of the REMORA research study is to understand the patterns of rheumatoid arthritis (RA) symptoms and flares on a day-to-day basis and to examine the response to the treatment you are on through time.
- You will be tracking your RA symptoms daily, weekly, and monthly on the free REMORA smartphone app for up to 12 months. You will need to have your own smartphone.
- The data you provide will link up securely to your hospital record and will be available to you and your rheumatologist as graphs at your next clinic visit.
- The symptom data from the app will also be available to researchers at the University of Manchester. Besides the symptom data, they will need permission to access your hospital records to extract information on disease duration, other diseases you might have, your medication and the changes made to them, measures of disease activity, and demographic items (such as age, ethnicity, gender, smoking status, weight).
- You will not be compensated for taking part
- Your symptom data will not be routinely viewed or monitored by the medical team until your next clinic consultation. You should communicate with your clinical team as usual and seek help if you need it.
- The University of Manchester is responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. Your data will be kept confidential and secure on its journey from your phone and in the research and clinical databases at the University of Manchester and Salford Royal NHS Foundation Trust respectively. This is in accordance with Good Clinical Practice and national standards for data security.
- Your research data will be stored securely at the University for 10 years

Appendix D. Automated reminder emails to participants in response to non-completion of symptom data entry on the REMORA smartphone app

1. After **three** days of not completing any questionnaires

Hello_____,

We have noticed that you have not completed your daily questionnaires on the REMORA app for the last few days and we wanted to check that everything is okay. If there are any issues, you want to talk about please email remora@manchester.ac.uk and we will get back to you ASAP.

Please include your name so that we know who you are.

Thanks for all your effort so far.

The REMORA research team

2. After **eight** days of not completing any questionnaires

Hello_____,

We have noticed that you have not completed your daily questionnaires on the REMORA app. We wanted to check that everything is okay. If you have just forgotten to do it, please could you complete it within the next 24 hours?

If there are any issues, you want to talk about please email remora@manchester.ac.uk or leave a voice message at [number] and we will get back to you ASAP. Please include your name so that we know who you are.

Thanks for all your effort so far.

The REMORA research team

3. After **15** days of not completing any questionnaires

Hello_____,

We have noticed that you have not completed your daily questionnaires on the REMORA app for a longer period.

If there are any issues, you want to talk about please email remora@manchester.ac.uk or leave a voice message at [number] and we will get back to you ASAP. Please include your name so that we know who you are.

The study team will not try to contact you again. We will consider you as dropped out of the study.

Thanks for all your effort. We have appreciated your participation in the REMORA study greatly.

The REMORA research team

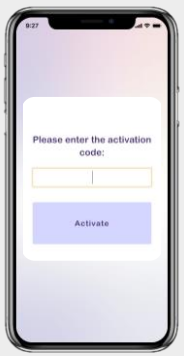
9.3.2 REMORA1.5 app download and user guide

How to download and set up the REMORA app on your phone

1

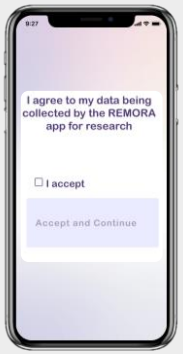
Download the REMORA app from Google Play by searching for "REMORA". The REMORA app icon is shown above. The app is free to download.*

2



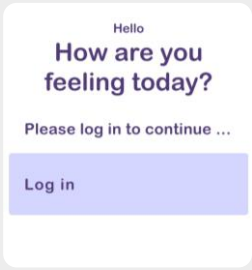
Open the REMORA app - you will be asked to enter an activation code. Please enter **748298**. You only need to enter this <u>once</u>. Please don't share the activation code.

3



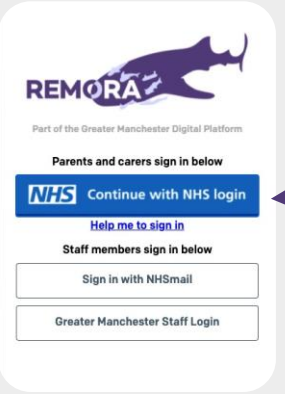
After successfully entering the activation code, you will be asked to confirm that you would like to share your data for research. You will only be asked this <u>once</u>.

4



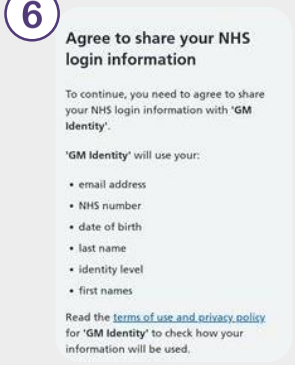
You will now reach the REMORA login page. Press "Log in" to continue.

5



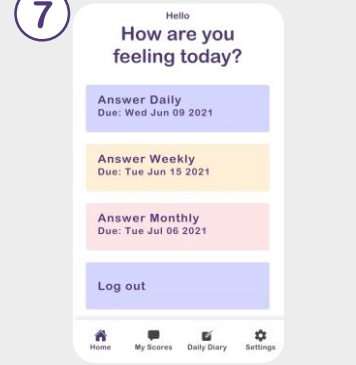
You will then be prompted to 'Continue with NHS Login'. Sign in using your NHS Login. If you do not have an NHS login, see the info box below. You will receive a code by text to "remember my device".

6



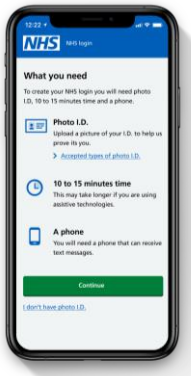
You will be asked to agree to share your NHS login information with "*GM Identity*". This is necessary to link your data to the right patient record.

7



You are now ready to start tracking your symptoms!

NHS login



If you do **not** have an NHS Login account, visit https://www.nhsapp.service.nhs.uk/login to create one.

An instruction video and more information for the setup process can be found at: https://digital.nhs.uk/services/nhs-login/nhs-login-for-health-and-care/getting-started-with-nhs-login-the-patient-journey#top

You will need:

- A phone with a camera for taking pictures and recording a short video of yourself (you might need assistance)
- Photo ID - passport or driving license
- Your NHS number
- Your email address and telephone number
- 15 minutes – and a few hours, possibly overnight, for your account to be authorised by NHS

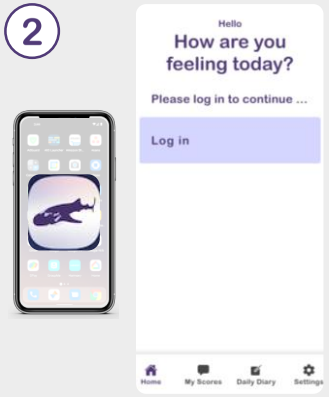
** If you do **not** have a Google Play account , please ask for separate instructions*

How to use the REMORA app

1

Your phone will alarm (sound and/or vibrate) when it is time to answer questions – daily, weekly or monthly.

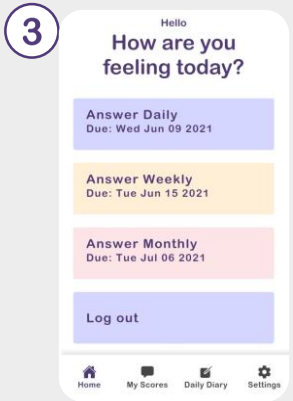
2



Press the app icon and log in with your NHS login – you will need to log in <u>every time</u> you want to use the app.

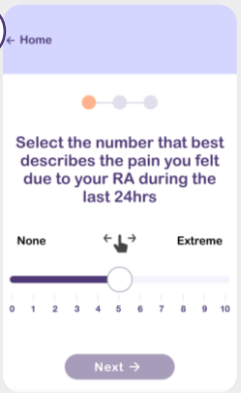
Hint: you can save your email in your personal dictionary so that you only have to type in the first few characters

3



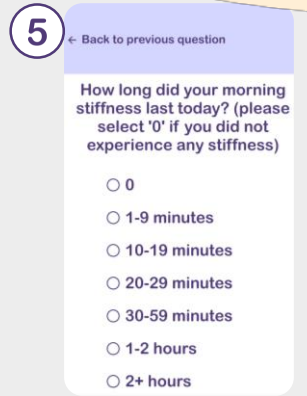
You will reach the homepage shown above. The question set that is due to be completed will be highlighted.

4



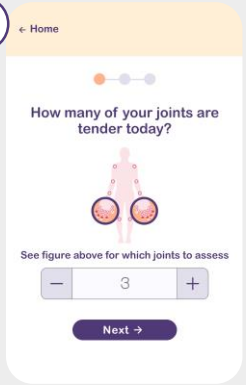
Answer questions like this by touching the circle and sliding from left to right until you reach your answer.

5



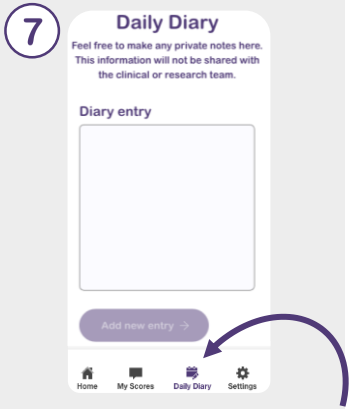
Answer questions like this by touching the circle next to your answer.

6



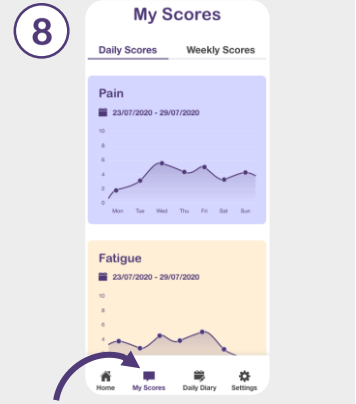
Answer questions like this by typing the number into the empty box or use the + or – signs to increase or decrease the number.

7



The 'Daily Diary' function allows you to note additional information relating to your RA - this will remain private to you.

8



Under 'My Scores' you can see some of your symptoms graphed over time.

9

Press the 'Settings' icon to see instructions for using the REMORA app. You might find answers to many of your questions here.

If you need assistance or have questions about the use of the app, please email ***remora@manchester.ac.uk***
We answer Monday-Friday and will get back as quickly as possible.

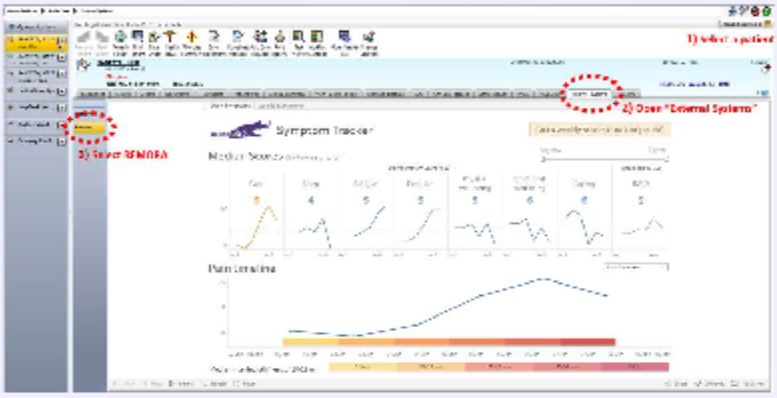
9.3.3 Clinician FAQ document

What is REMORA?

The REmote MOnitoring of Rheumatoid Arthritis study is a smartphone study that asks people living with RA to track their symptoms daily, weekly, and monthly on the REMORA app. The data will be available to you directly in the EPR to support conversations and to help you gain a clearer picture of the patient's disease severity through time. The data will also allow researchers at UoM to learn more about RA symptom patterns, flares, and treatment response.

Where can you find the REMORA data in the EPR?

1. Select a patient in the EPR
2. Open the "External Systems" tab in EPR
3. Select REMORA from the tab on the left side to see the interactive symptom graphs



How to document REMORA in the EPR?

- If it informs your decision-making, describe in the outpatient letter (like examination findings)
- Examples: "Based on the review of REMORA data…", "REMORA data showed persistent pain…"

How can you use the data in your consultation?

- It's up to you when to introduce REMORA in your consultation. Previous research in using REMORA indicated that when REMORA was introduced early in consultations, it was usually used to invite patients to elicit new information. When introduced later, it was used to validate patient accounts and to assure unconvinced patient about actions and treatments.

- **What if there is a flare? Is there a threshold for actions?**
For this study, REMORA is simply a tool to collect data from patients. It is not a decision-support tool and the data is not monitored in between visits to the clinic. You decide how to use the data.

- Will REMORA increase my consultation time? No, our previous research did not show an increase in consultation time, but this will be explored further.

Get in touch!

Email **remora@manchester.ac.uk** if you have any questions, concerns or experience technical issues. We monitor the email Mon-Fri within normal working hours and will get back to you as quickly as possible.

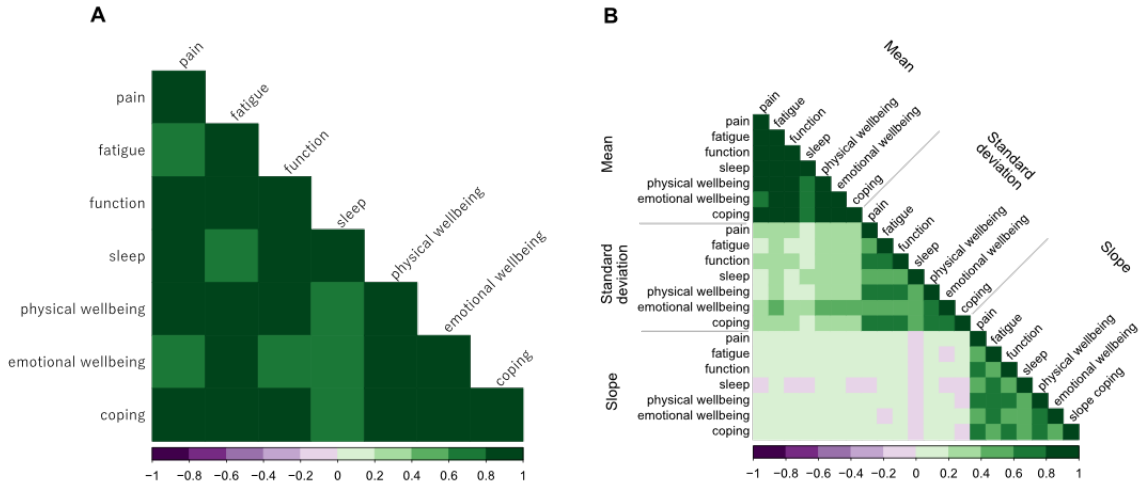
v1.0 | 26/08/2021

Answers to the most common patient questions

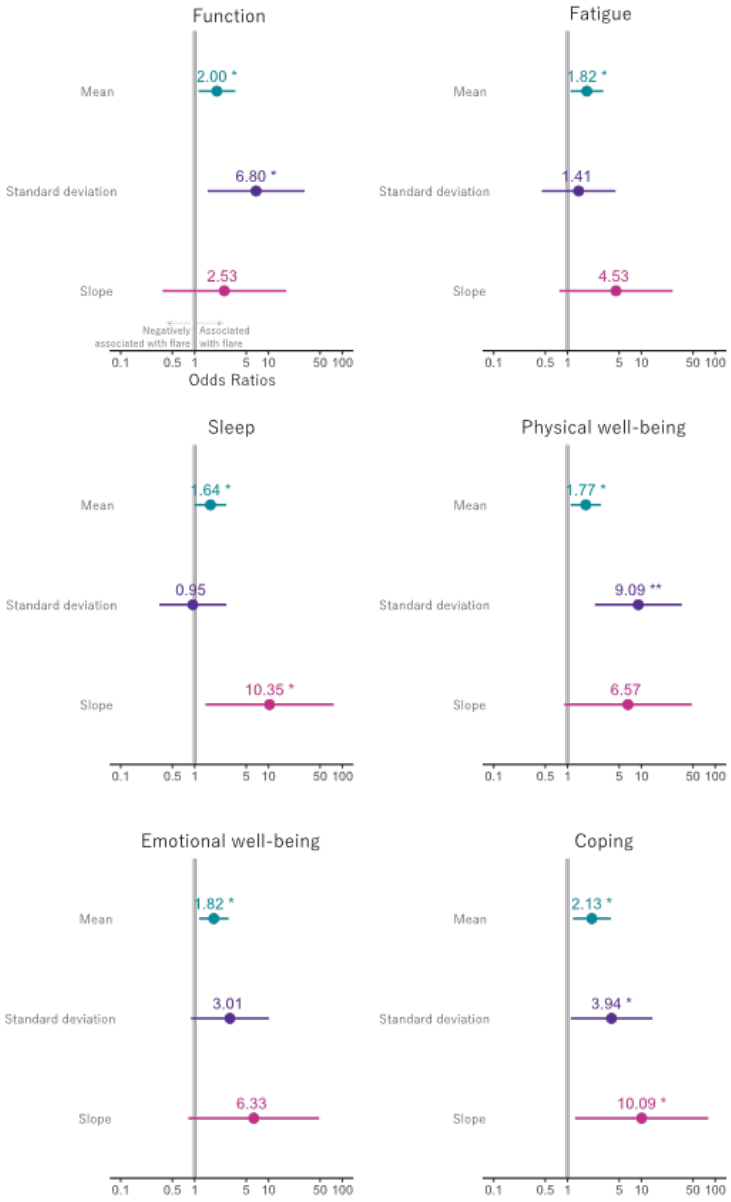
How do I track my symptoms?	You download the REMORA app onto your smartphone and answer the questionnaires daily.
Why should I track my symptoms?	Remembering accurately what has happened with your symptoms between scheduled clinic visits can be challenging. By tracking your symptoms daily, you provide your rheumatologist with the best possible data.
Do I have to enter my data daily even if I'm feeling well?	Yes, it is really important that you record your symptoms even when you are feeling well. This provides the clinician with the best picture of you disease severity.
How long will it take me to track my symptoms daily?	It should take you less than 2 minutes daily to complete the questionnaire. We will ask you a few extra questions once a week and once a month that might take a little longer.
My app is not working. Whom should I contact?	You should reach out to the REMORA team at **remora@manchester.ac.uk**
Can I take notes on the app and share with my clinician?	Yes, there is a private diary function, where you can take notes. These will **not** be shared. However, if you experience a flare, you have the option to note down additional information in context to the flare, and this will be shared with your clinician like the symptom scores.
If I lose my phone will someone be able to access my information on the app or my medical records?	No! You will have to log in to the app every time you use it, and it automatically logs you out when leaving the app. If you lose your phone, please contact the research team.
If I do not answer questionnaires at the exact time and date can I do it later?	The daily questionnaire for a specific day will be "open" for 24 hours. You can answer it any time in that time window.
When I complete my daily input in the app, is it linked to and registered on my notes at the hospital?	Yes, your symptom scores entered on the app are linked to your hospital record. The data flows automatically, so you don't have to do anything to "move" it.
Is my data and personal information safe?	Yes! Your data is being kept safe and secure at all times. The app is adhering to all data protection regulations.
Will the Rheumatology nurses have access to my data if I need to contact them?	Yes, the rheumatology nurses have access to your symptom data entered on the app.
If I experience a flare will you be informed as I enter my data in the app and call me to a clinic earlier?	No. The data you enter is **not monitored** between your scheduled clinic visits. Please seek medical attention as you would normally do in case of worsening/emergencies.
What should I do if I want to stop using the app?	Please get in touch with the research team at remora@manchester.ac.uk or call the research nurses at 0161 206 6077.

9.4 Appendices to Chapter 5

9.4.1 **Supplementary Figure S1**: Correlation plot (Pearson's correlation coefficients) of A**.** Daily symptoms scores and **B.** Symptom summary features



9.4.2 **Supplementary Figure S2:** Multivariate mixed effect logistic regression models for six daily symptoms and each of their three symptom summary features exploring the effects on patient-reported flares.



9.4.3 **Supplementary Figure S3:** Sensitivity analyses of different definitions of a participant week for univariate modelling. A: All weeks (no restrictions on days of daily data in a participant week, n=198). **B**: Complete weeks (only 7 days of daily data in a participant week, n=88).

9.4.4 **Supplementary Table S1:** Results from sensitivity analyses of different definitions of a participant week for multivariate analyses looking at associations between symptom summary features of pain and the occurrence of patient-reported flare. "All weeks" is the broadest definition, including all participant weeks no matter the number of daily reporting in that week. "Complete weeks" is the most restrictive definition, only including participant weeks with seven days of daily data.

	OR (95% CI)	P value*
5-7 days (n=168)		
Mean pain	1.83 (1.15-2.97)	**< 0.05**
SD pain	3.12 (1.07-9.13)	**< 0.05**
Slope pain	3.26 (0.57-18.74)	0.19
All weeks (n=198)		
Mean pain	1.94 (1.25-2.30)	**<0.01**
SD pain	1.99 (0.83-4.76)	0.12
Slope pain	3.71 (0.82-16.85)	0.09
Complete weeks (n=88)		
Mean pain	1.89 (1.03-3.48)	**<0.05**
SD pain	4.50 (0.88-28.44)	0.07
Slope pain	30.36 (0.80-1146.58)	0.07

OR = odds ratio, CI = confidence interval

* Modelling results calculated via multi-level mixed effects logistic regression modelling