Utilising Smartphone-Based Apps and Wearable Accelerometer Sensors in Idiopathic Inflammatory Myopathies to Improve Treatment and Research

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SCHOOL OF BIOLOGICAL SCIENCES

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Abstract

Clinical management and longitudinal research of chronic diseases are hampered by infrequency of data collection. For example, a clinician may assess a patient with a chronic condition at six-monthly intervals, thus basing their management plan on "data" collected on two days out of 365, equating to only 0.5% of days. It is plausible that increasing the frequency of data collection may enhance clinical care and the accuracy of longitudinal research.

The idiopathic inflammatory myopathies (IIMs) are a group of chronic multi-system inflammatory conditions that exemplify the limitation of infrequent data collection. Recent technological advances have made the prospect of the "digital healthcare revolution" a possible reality. Digital healthcare technology includes smartphone-based apps and wearable sensors. Combined, these two technologies offer two key opportunities over "traditional" approaches of data collection: 1) the ability to measure novel parameters, and 2) the ability to collect frequent longitudinal "free-living" data outside the confines of a clinical/research facility.

During my PhD I carried out the Myositis Physical Activity Device (MyoPAD) study, which aimed to 1) investigate the need for more frequent monitoring in the IIMs and 2) to carry out a "mobile-health" (mHealth) study investigating engagement with and utility of daily symptom collection via a smartphone-based app and continuous remote gait pattern measurement via a thigh-worn accelerometer sensor.

An initial review of accelerometer data collection in IIM study populations was carried out (Chapter 2). This review indicated that accelerometer data collection in IIM populations was in its infancy. Further, no previous study has used such data to quantify gait patterns, rather accelerometer data was used to quantify physical activity levels instead.

Qualitative interviews were carried out with MyoPAD participants (Chapter 3). Themes identified include 1) pain and fatigue as predominant symptoms, 2) day-to-day symptom variation, 3) IIM flare characterisation, and 4) limitations of disease activity methods.

A 91 day trial of the MyoPAD app and sensor in 20 adult IIM participants revealed high engagement. Qualitative interviews facilitated identification of enablers/barriers to engagement (Chapter 4).

Analysis of daily symptom data allowed characterisation of IIM flares, which have not been previously defined or investigated (Chapter 5). The frequency of flares and their relationships with symptom changes were quantified.

Finally, a method of processing accelerometer data for individual participant gait parameter assessment was developed (Chapter 6). The relationships between gait pattern and IIM disease activity were quantified, providing preliminary insights useful for focusing future research.

Overall, this thesis has demonstrated that collection of daily symptom data and continuous accelerometer data is feasible and practical. Daily symptom and gait pattern data can provide novel insights, potentially useful for both IIM clinical and research applications. These results pave the way for completion of future steps necessary for translation into clinical/research settings, which include economic analysis and regulatory approval.

It is possible that, in the not too distant future, remote daily/continuous data collection will become the norm, thus relegating infrequent data collection to the past and revolutionising clinical management and research for the IIMs and other diseases.

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.

Copyright statement

Acknowledgements

Dedication

I dedicate this thesis to my wife, Jennifer, my daughter, Georgina, and my dog, Betty. Thank you for support, tips and inspiration, which frequently occurred on long walks in the park.

Acknowledgements

Completion of my PhD would not have been possible without the support, guidance and input of many people and organisations.

I am greatly indebted to the participants who took part in the MyoPAD study, without whom my research would not have been possible. The continual participation required throughout each participant's 91 day study period required a great deal of commitment for which I am truly grateful.

I would like to express my deepest gratitude to my supervisor, Professor Hector Chinoy, who introduced me to myositis research in 2014 when I was an Academic Clinical Fellow. His considered guidance and democratic supervisory style has allowed me to take advantage of arising opportunities that have progressed my skill set, experiences and future opportunities. His commitment to the patient population, particularly those with myositis, has inspired me to always keep the patient at the heart of my research.

Professor William Dixon's expert input has been invaluable throughout my PhD. His expertise in the burgeoning area of digital epidemiology has made my PhD exciting and rewarding. His focus on details has taught me a great deal about its importance in research, something I will take with me in future projects. I feel that my experiences in digital epidemiology has provided me with an advantageous skill set that I can utilise in future to answer further clinically relevant questions.

I had very little experience of qualitative research prior to my PhD. I am therefore enormously grateful to Dr Kelly Howells in providing such careful and patient advice and guidance throughout my PhD. I now truly see the unique utility and importance that qualitative research possesses, especially when combined with quantitative methods. I will certainly utilise qualitative methods in future studies and encourage other colleagues to do so.

I am grateful to Dr Max Little for introducing me to the world of signal processing, an area that I knew very little about prior to my PhD. I found this complex area of statistics to be pleasingly challenging, thus enhancing my statistical and computational skills immeasurably. The input and unique viewpoints that Dr Little and the rest of his team (particularly Reham Badawy) have provided have shaped my PhD for the better.

I would like to thank my PhD Advisor, Professor Sandra Bucci. Although, thankfully, I have not required frequent input from Professor Bucci, it has been reassuring to know that someone impartial and constructive is available when needed. I would particularly like to thank Professor Bucci for enquiring about me wellbeing just before I started re-

deployment to general medicine in April 2020 in response to the COVID-19 pandemic. It reminded me of the importance of taking time to enquire about the wellbeing of other colleagues, friends and family throughout the pandemic.

My PhD would not have happened without the support of The Manchester National Institute for Health Research Biomedical Research Centre (BRC). They awarded me with funds for the three years of my PhD after I had unsuccessfully applied to other funding bodies. I only utilised the first year of funding after I was subsequently awarded a Clinical Research Fellowship from Versus Arthritis. The training and support provided by the BRC were invaluable throughout my PhD.

I am truly grateful to Versus Arthritis for awarding me with a Clinical Research Fellowship, which funded the second and third years of my PhD. The acknowledgement that my project was worth funding provided a boost to my confidence and productivity. Versus Arthritis and the fellows community has provided invaluable support and input throughout my PhD.

I am greatly indebted to the industry partners to the MyoPAD study, ZiteLab and SENS Innovation. The expert input of Mikkel Kramme Abildtoft and Niels Steen Krogh from ZiteLab, and Kasper Lykkegaard and Morten Kjægaard from SENS Innovation has been invaluable. My interactions with each company has made me realise the utility of industry involvement and collaboration, which I will take with me into future projects.

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My time within the Myositis Research Team has been invaluable to by development as a researcher. The frequent team meetings with such a range of researchers (Dr Janine Lamb, Paul New, Professor William Ollier, Dr James Lilleker, Dr Andrew Snedden, Professor Robert Cooper, Professor Hector Chinoy) provided the perfect forum in which to develop well-rounded ideas and achievable plans.

Being based in the Centre for Epidemiology Versus Arthritis and the wider Centre for Musculoskeletal Research has been key in my development and the success of my research. Being surrounded by researchers with such wide ranging skill sets, ideas and complementary personalities has given me unique experiences, friendships and collaboration opportunities. Attending seminars within the Centre has been invaluable for idea stimulation and skill development. I have had the opportunity to present on a number of occasions at various departmental seminars; the fair, constructive and collaborative feedback received certainly enhanced my research.

I would also like to thank Dr Sabine Van Der Veer and Dr James Galloway for expertly examining my viva, which was an intellectually stimulating and formative experience.

I am, however, perhaps most indebted to Dr Marwan Bukhari who initially introduced me to the world of clinical research when I was a second year medical student. His encouragement, infectious energy and mentorship inspired me to pursue research.

Without this initial encouragement so early on in my career, I am certain that I would not have been able to take advantage of arising opportunities, which have directly lead to completion of my PhD.

About the author

Alexander Oldroyd is a clinical academic with skills in epidemiology, statistics, longitudinal modelling and qualitative research. He is driven by the desire to improve people's lives through innovative research and patient-centred clinical care.

He completed his medical degree at the University of Lancaster and also obtained an MSc in medical statistics as an intercalated degree. Following his medical degree he undertook integrated clinical and research training as an Academic Foundation Doctor and subsequently as a National Institute for Health (NIHR) Academic Clinical Fellow. He completed examinations for Membership of the Royal College of Physicians (MRCP) in 2015. He began rheumatology specialist training in 2017.

In 2017 he secured PhD funding from the Manchester NIHR Biomedical Research Centre. He then additionally was awarded a Clinical Research Fellowship by Versus Arthritis in 2018 for the second and third years of his PhD. Alexander was supervised by Professor Hector Chinoy, Professor William Dixon, Dr Kelly Howells and Dr Max Little throughout his PhD.

Alexander plans to continue both rheumatology specialist training and research as an NIHR Academic Clinical Lecturer, pursuing the development and testing of innovative methods with the aim on improving patient care.

Publications related to this PhD

Oldroyd, A., Little, M., Dixon, W., Chinoy, H. A review of accelerometer-derived physical activity in the idiopathic inflammatory myopathies. BMC Rheumatol. 2019 Oct. 21;3:41.

Oldroyd, A., Dixon, W., Chinoy, H., Howells, K. Patient insights on living with idiopathic inflammatory myopathy and the limitations of disease activity measurement methods – a qualitative study. BMC Rheumatol. 2020 Sept. **4,** 47.

Alexander's full publication record is available at ORCID (ID 0000-0001-5701-6490).

Awards

2019 Eric Bywaters Prize – Royal Society of Medicine
2019 Travel bursary – Global Conference on Myositis
2018 Winner of the registrar research presentation – Manchester Medical Society research meeting
2018, 2019 and 2020 Best research oral presentation prize – Manchester Rheumatology Afternoon research meetings

Conference presentations

Oral presentations
Global Conference on Myositis 2019
British Society of Rheumatology annual conference 2018
American College of Rheumatology annual scientific meeting 2017
Poster presentations
British Society of Rheumatology annual conference 2019
British Society of Rheumatology annual conference 2018

Committee membership

2020 – present
International Myositis Assessment and Clinic Studies Group (IMACS) – Scientific Committee trainee member

2019 – present
Steering Committee for development of IMACS myositis cancer screening guidelines

2019 – present
Steering Committee for development of British Society of Rheumatology Myositis Treatment Guidelines

2018 – 2020
Member of Versus Arthritis Fellow's Steering Committee

2017 – 2020
Coordinator of Manchester Rheumatology Afternoon meetings – monthly educational meetings with case presentations and external speaker presentations – attended by regional consultants and speciality trainees

Chapter 1

1 Introduction

"I had," he said, "come to an entirely erroneous conclusion, my dear Watson, how dangerous it always is to reason from insufficient data."

Sherlock Holmes

The Adventure of the Speckled Band[1]

The availability of data is central to assessing a situation. This statement is true whether you are a doctor wanting to assess the patient in front of you, an epidemiologist wanting to identify the risk factors for a certain disease, or indeed if you are a 19th century fictional detective investigating a person's murder by a supposed giant moor-stalking hound.

Firstly, in the introduction I will explain the overall unmet need that this thesis will aim to address - namely how infrequent data collection limits clinical care and research. Secondly, I will introduce the idiopathic inflammatory myopathies (IIMs), a condition where clinical care and research are victim to limitations of infrequent data collection. Thirdly and finally, I will explore two digital solutions that may solve the unmet need of infrequent data collection, namely daily patient-reported outcome measurements (PROMs) collected via smartphone-based apps and continuous gait pattern assessment using accelerometer-sensor collected data.

It is intended that the introduction will provide the reader with necessary background information to understand and appreciate the rationale of my PhD research and the implications of the results. The relevant background covers many topics due to the wide variety of methodologies employed in my research. To maintain the focus within the introduction, exhaustive detailed explanation of basic concepts will be avoided, thus

allowing for more detailed description of important or novel concepts/methodologies. Further, prior understanding of basic epidemiology and statistics are assumed.

1.1 Data use in clinical and research settings

1.1.1 How is data used in clinical consultations?

Clinicians use available data to form an assessment of the patient in front of them. Such an assessment can take many forms. For example, a clinician in an emergency department may want to diagnose what condition may be causing a patient's chest pain, or they may want to form an assessment on how "active" a patient's previously diagnosed condition is. This diagnosis or assessment can then be used to form an appropriate management plan.

It is therefore of utmost importance that the assessment is accurate. An inaccurate assessment risks the clinician forming an inappropriate management plan and the patient's condition being treated unsatisfactorily. The accuracy of a clinician's assessment rests predominantly on the availability of data. A clinician will likely be interested in a wide variety of data, which will vary greatly between consultations, specialities and individual patients and clinicians. Data may comprise patient reported symptoms, physical examination features or investigation results. Such data can then be used to confirm /refute their hypothesised diagnosis and form a subsequent management plan.

1.1.2 How is data used in scientific research?

In general, scientists use available data to investigate the order of the natural world. For example, an epidemiologist may desire to elicit the relationship between a certain risk factor, such as smoking, and the development of a certain disease, such as lung cancer. Findings can then inform any subsequent research or appropriate intervention. For example, research findings may facilitate the formation of public health campaigns that aim to curtail smoking levels, and reduce the incidence of lung cancer.

Assessment of the studied relationship(s) and any subsequent interventions rely on the availability of data. Insufficient data risks non-identification of the relationship(s) or the formation of erroneous conclusions.

1.1.3 Impact of volume of available data

The volume of data available is integral to the strength of the corresponding conclusion made. A large volume of data that is representative of the studied subject (e.g. UK population or individual patient) maximises the likelihood of an accurate conclusion being formed[2]. In contrast, a small volume of data that is unrepresentative of the studied subject can result in formation of an erroneous conclusion.

1.1.3.1 How frequency of data collection impacts clinical decision making

In a typical clinical setting, a clinician may review a patient with a chronic condition in an out-patient clinic. The clinician will collect relevant data, such as patient reported symptoms or investigation results. The clinician will then form an assessment and corresponding management plan, and then organise to review the patient again after a certain interval. These intervals can be long in duration, such as six or 12 months.

These long intervals limit the scope of "data sampling" that a clinician is able to carry out. For example, a clinician that reviews a patient every six months relies on data, such as the presence or severity of certain symptoms, sampled on only two individual days. Data on the remaining 363 days of that year are not available to the clinician. Of course, a clinician could ask the patient questions about certain aspects of their disease, such as the severity of symptoms over the last six months, but this will typically only provide a general patient-reported summary, which will be subject to other limiting factors, such as recall bias[3,4]. The symptoms or examination features that a patient conveys on the two days that they attend the out-patient clinic may not be necessarily representative of the remaining 363 days of the year.

Therefore, limiting data collection to individual days separated by long durations could potentially lead to inaccurate clinical assessment and result in formation of inappropriate management plans.

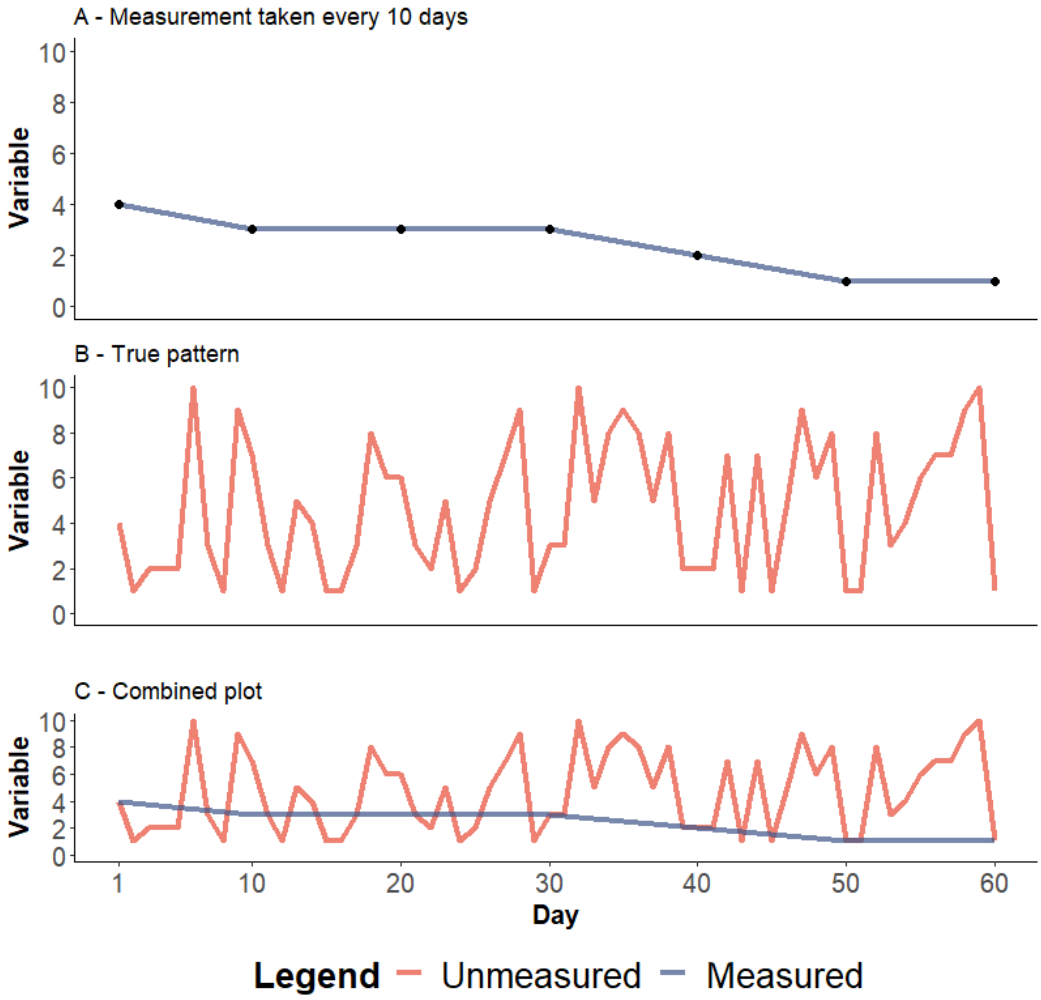
1.1.3.2 How infrequent data collection limits research

The volume of data collected in a research study affects how representative it is of the wider population and the strength of the conclusions made. Longitudinal studies aim to investigate how a parameter changes over time in a population. They therefore rely on the days upon which data is sampled being representative of the days that are not sampled. For example, a participant may enter an observational longitudinal study that lasts three years. They attend the research centre for data collection (e.g. questionnaire

completion, blood sampling) every three months. Therefore, for each participant, data is sampled on a total of 13 study visit days. Data on the remaining 1,092 days is not available to the research team. It is plausible that data on the sampled 13 days may not necessarily be representative of the other 1,092 days. Data variation within the unmeasured time frames may also not be detected (see Figure 1 for graphical illustration). This limitation can lead to erroneous conclusions being made.

Figure 1 - Graphical illustration of how infrequent data collection throughout a longitudinal study may not detect true underlying data patterns

Panel A displays the perceived pattern of the data when measured every 10 days of a 60 day study. Panel B displays the "true", more variable, data pattern. Panel C displays the incongruity of the measured and true data pattern.



1.1.3.3 How could these limitations be solved?

Increasing the availability of data to clinicians and researchers could improve the accuracy of patient assessment and longitudinal studies. One possible way of increasing data availability in clinical settings would be ask the patient to attend the out-patient clinic more frequently. This is, however, not necessarily feasible. Clinician time limitations, financial restrictions on healthcare services, and the impact upon the patient's daily life render this solution impractical[5,6].

Similarly, for longitudinal research studies, sampling data from study participants could be carried out on a larger proportion of days of the study duration. However, the increased cost and participant burden of additional study visits also limits the feasibility of this approach[7].

The availability of a user-friendly and practical method that allows for more frequent data collection (e.g. daily/continuous) could potentially enhance the accuracy of clinical assessments and conclusions drawn from longitudinal research studies.

Section summary

In summary, it is evident that clinical care and research of chronic medical conditions may be limited by infrequent data collection. It is plausible that increasing the frequency of data collection may improve clinical care and research by enabling more accurate detection of underlying longitudinal patterns. However, the current model of clinical assessment and research data collection do not enable data collection at a high frequency (i.e. daily).

Many chronic disease are managed via out-patient hospital appointments and are subject to the clinical and research limitations described above. One such chronic disease, and the focus of this thesis, are the IIMs.

1.2 The idiopathic inflammatory myopathies

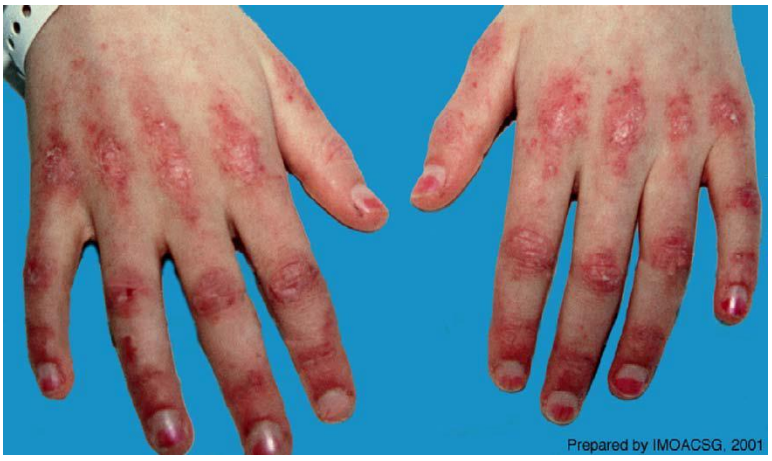
The IIMs are a group of chronic autoimmune conditions characterised by muscle inflammation (myositis) and internal organ involvement[8], resulting in widespread organ dysfunction[9–13], increased lifelong morbidity[14–16], and early mortality[17–19]. As with many other chronic conditions, IIM clinical care and longitudinal research are potentially affected by limitations associated with infrequent data collection.

In this section I will introduce pertinent aspects of the IIMs. I will particularly focus upon common symptoms and the impact of IIM-induced weakness upon walking pattern. I will also describe the "gold-standard" methods of disease activity and damage assessment. Finally, I will summarise how the IIMs are potentially particularly affected by previously described infrequent data collection.

1.2.1 IIM subtypes

A number of distinct IIM sub-types are recognised, including polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), anti-synthetase syndrome (ASS), immune-mediated necrotising myopathy (IMNM), and juvenile DM (JDM). The spectrum of clinical phenotype differs between each sub-type, however muscle inflammation (myositis) is a common feature. Distinct features include skin manifestations in DM, such as Gottron's papules (Figure 2), interstitial lung disease (ILD) in ASS[20], and severe myositis in IMNM[21].

Figure 2- Gottron's papules over metacarpal and interphalangeal joints in a patient with dermatomyositis



Reproduced with kind permission of Drs Miller, Schiffenbauer and Rider[22]

All adult IIM subtypes apart from IBM will be further explored. IBM has not been included due to the distinct pathophysiology (e.g. irreversible and marked muscle wasting), symptomatology (e.g. predominance of falls), prognosis and methods of disease activity assessment[23]. IBM is typically considered as a separate entity to other IIM subtypes, with clinical trials and other research studies tending not to include IBM patients alongside other IIM subtypes. IBM itself may well benefit from digital technology innovations, however this will best be considered separately to ensure that methods and results are tailored to this distinct condition.

1.2.2 Symptoms associated with the IIMs

Myositis affecting skeletal muscles is the most common manifestation of the IIMs. Skeletal muscles are most commonly affected in a proximal arm and leg distribution[24,25]. Myositis of the proximal arm and leg musculature leads to a number of symptoms, particularly weakness, fatigue and pain.

1.2.2.1 Weakness

Muscle strength can be reduced in IIM due to either active myositis, fat replacement or by reduced muscle mass due to previous inflammation ("muscle atrophy"). Weakness of movements carried out by affected proximal arm and leg muscles are commonly affected. The deltoid muscle, which is responsible for shoulder abduction, is the most commonly affected arm muscle. Myositis of the deltoid muscle therefore typically results in weakness of shoulder abduction, making activities such as hair combing and reaching for objects on a shelf difficult. Leg muscles most commonly affected are those responsible for hip flexion, such as the rectus femoris muscle. Weak hip flexion can result in difficulty walking or standing from a seated position, a common initial reporting symptom. It is therefore understandable that IIM-related weakness is associated with disability[26] and reduced quality of life[27].

1.2.2.2 Fatigue

Fatigue is commonly reported by people with IIM[28–30]. Fatigue was in fact reported to be one of the most common and troublesome symptoms reported within a German IIM cohort[31]. As in many other chronic conditions, there is a likely complex multifactorial relationship between fatigue, myositis, muscle atrophy and many other aspects of the disease, such as anaemia of chronic disease, ILD, depression and medication side

effects. Fatigue can lead to marked disability in many patients and is unfortunately commonly intractable to medical interventions.

1.2.2.3 Pain

IIM-associated pain is commonly reported by patients[28–30]. The relationships between pain, myositis, muscle damage, other disease manifestations and comorbidities is complex and yet to be unravelled via research. Muscle specific pain ("myalgia") can occur in active disease due to myositis. Pain can also occur in disease remission due to muscle atrophy; the reduced skeletal mass available to carry out limb movements can result in premature muscle fatigue, resulting in pain. Additionally, some patients with an IIM develop a chronic widespread pain syndrome similar to fibromyalgia[32].

Other symptoms that can affect people with an IIM include shortness of breath due to ILD[33,34], skin manifestations[35], reduced exercise tolerance due to heart muscle involvement[36] and anaemia of chronic disease. Psychological symptoms, such as depression, are also common in people with an IIM and these are typically due to multiple factors, such as functional impairment, effect on employment and personal relationships[26,37,38].

1.2.2.4 IIM flares

Patients with an IIM typically report symptom "flares". To date, no consensus definition of an IIM flare has been formed. Anecdotally, individual patients, clinicians, and researchers tend to have differing definitions of an IIM flare. Patients tend to report a flare when their symptoms suddenly worsen, whereas clinicians tend to diagnose a flare only when increased doses of immunosuppressive medication is needed. The small number of previous studies that investigated IIM flares have used definitions based on the need for increased immunosuppressive medication[39–41]. The common reporting of IIM flares and stark lack of related research makes this an area worthy of future research, with the aim of developing a consensus definition for use in clinical and research settings.

1.2.2.5 Qualitative insights into IIM symptoms

A number of qualitative studies have carried out research to capture patient perspectives on IIM-related symptoms[28–30,42]. A number of insights into symptom patterns and experiences of living with an IIM have been identified, including: 1) the predominance of pain as a symptom; 2) frequent symptom variation; 3) disparity of symptom perceptions by healthcare professionals and patients.

Specific participant quotations provided further detail about specific experiences of IIM-associated pain[42]:

> "…the pain is one my body would feel like someone just either scalded you with red-hot water, just constant burning…"

> "…a board with a million needles on it and someone's just stuck it, just brutal pain."

These studies also highlight the ability of qualitative research to provide detailed insights into aspects of living with an IIM across the study population and on an individual participant basis.

Qualitative research into the IIMs is, however, overall limited. Two particularly important research questions that could be answered via qualitative approaches persist.

Firstly, the question over whether or not patients perceive that their symptoms vary on a day-to-day basis is one of the most relevant to this thesis. If patients do indeed perceive that their symptoms vary frequently, then this will illustrate an important limitation of the current model of IIM clinical care and research, namely that clinicians may be unable to identify such day-to-day variations due to infrequent clinical assessment on individual days. Qualitative research could provide detailed descriptions of which symptoms vary on a day-to-day basis, factors that trigger or influence day-to-day variation, and the impact of such variation upon quality of life.

Secondly, qualitative research may be able to provide further information of patient definitions of an IIM flare, thus informing future quantitative analysis. This may form the basis for developing an evidence-based consensus definition of an IIM flare, which may be potentially useful in both clinical and research settings.

Section summary

In summary, it is known that the IIMs can result in a number of symptoms, such as pain, fatigue and weakness, and that these symptoms can vary on a day-to-day basis. Research on day-to-day symptom variation and characterisation of IIM-flares is however overall limited. Further qualitative research in this area may more clearly identify predominant IIM symptoms, delineate day-to-day variation, and provide initial evidence around IIM-flares. Evidence in this area may provide rationale for more frequent (i.e. daily) symptom monitoring.

1.2.3 Impact of the IIMs upon walking pattern

IIM-induced myositis can result in limb weakness, as described above. Weakness of leg muscles can therefore affect walking pattern. In this section I will summarise the fundamentals of the walking (gait) cycle and how it can be affected by IIM-induced weakness.

1.2.3.1 The gait cycle

An individual's walking pattern is referred to as their "gait". A single complete gait cycle comprises a number of discrete phases and movements[43,44]. Firstly, gait can be divided into two phases:

- Stance phase – the phase during which the foot is in contact with the ground
- Swing phase – the phase during which the foot is not in contact with the ground

Each phase can be further divided into the following consecutive stages (Figure 3):

Stance phase –

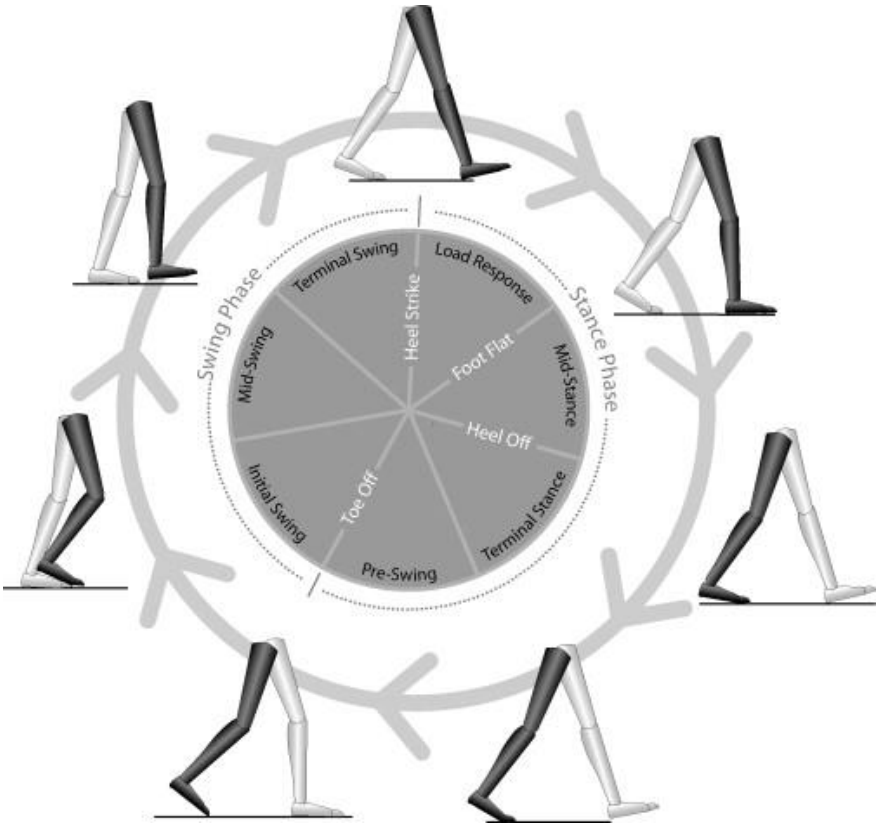
1. Heel strike: when the foot makes initial contact with the floor. The heel is the first part of the foot to make contact.
2. Load response: following heel strike, the plantar aspect of the foot makes full contact with the floor.
3. Mid stance: the plantar aspect of the foot remains in full contact with the floor whilst the leg advances over the foot. Corresponding ankle dorsiflexion, knee extension and hip extension occur. The hip flexors also contract to counter the hip extensors, thus preventing over-extension.

4. Terminal stance: the heel begins to rise from the floor whilst the forefoot and toes remain in contact with the floor.
5. Pre-swing: the point at which the toe ends contact with the floor marks the end of the stance phase and the beginning of the swing phase. This positions the limb for the swing phase.

Swing phase -

1. Initial swing: the foot lifts from the floor due to hip and knee flexion. This moves the leg and foot anteriorly.
2. Mid-swing: this stage begins when the moving foot is directly under the body's centre of gravity (i.e. opposite the foot in stance phase) and ends when the swinging limb's tibia is vertical and is anterior to the foot in stance phase. Subsequently, the knee extends and the ankle dorsiflexes.
3. Terminal swing: knee extension, hip flexion and ankle dorsiflexion completes the swing phase, with the beginning of the initial contact stage (heel strike).

Figure 3 - Diagrammatic representation of gait cycle phases



Adapted from Rueterbories et al. Med Eng Phys 2010;32:545–52.[45]

It can be challenging to identify quantifiable measurements as the gait cycle is a continuous process without easily definable boundaries. Measurement of the following aspects of gait have been used to characterise the pattern[46–49]:

- Step length – the distance between successive heel strikes of opposite feet
- Stride length – the distance between successive points of heel strike of the same foot
- Walking base – the distance between the direction of movement of each foot
- Step time – the time spent during a single step i.e. time between the heel strike of one foot and the heel strike of the other foot
- Stride time – the time taken to complete a single stride (two single successive steps of each foot)
- Stance time – time spent in the stance phase of the gait cycle
- Swing time – time spent in the swing phase of the gait cycle
- Single limb time – the amount of time spent when only a single leg is in contact with the floor i.e. the other limb is in the swing phase
- Double limb time – the amount of time spent when both legs are in contact with the floor i.e. both legs are in the stance phase
- Cadence – the number of steps during a unit of time e.g. 20 steps per minute
- Speed – the distance covered during a unit of time e.g. 1.2 metres per second

1.2.3.2 Potentially detectable IIM gait abnormalities

Activity of the muscles that cause hip flexion, are integral to the gait cycle. Contraction of the following muscles result in hip flexion: psoas major, iliacus, rectus femoris, sartorius, tensor fasciae latae and the muscles of the medial compartment (pectineus, adductor longus, adductor brevis and gracilis)[50,51]. IIM-induced myositis can markedly affect the hip flexors[24,25] and therefore can affect the gait stages that depend on hip flexion. For example, prolonged swing time can result from insufficient muscle strength required to flex the hip joint and forwardly displace the leg.

Objective research into gait pattern variation in the IIMs is limited, thus rationale regarding the potential role of gait pattern measurement is based on logical extrapolations related to typical muscle pattern weakness.

A small study by Siegel *et al* characterised the gait of three female IIM (PM or DM) cases and a single healthy control[52]. All IIM cases demonstrated weakness of hip flexors and

hip extensors. A number of gait pattern abnormalities were demonstrated in comparison to the healthy control:

1. Reduced stride length
2. Prolonged step time
3. Increased double limb time

Section summary

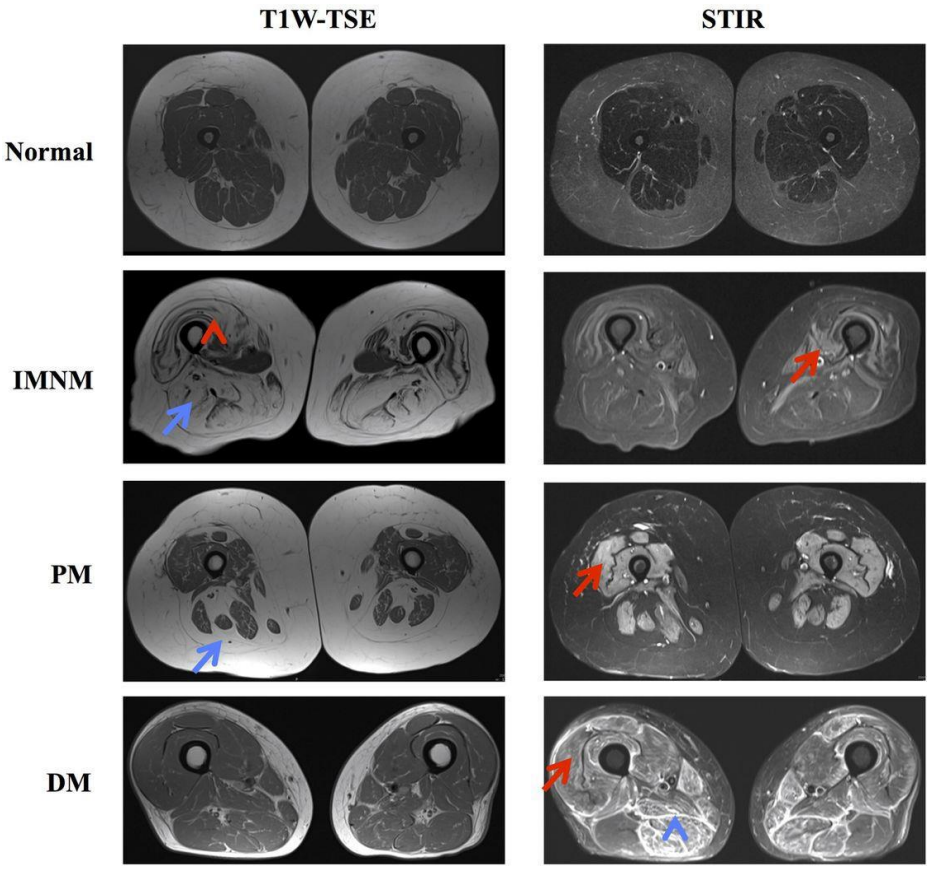
In summary, characteristic muscle weakness patterns and existing evidence suggests that IIM-induced weakness may affect gait pattern. It is important to note, however, that evidence in this area is limited. Together with symptom assessment, objective gait pattern measurement may represent useful methods of IIM "disease activity" assessment. In the subsequent section I will explore the concept of disease activity and outline the current "gold-standard" assessment method.

1.2.4 IIM disease activity and disease damage

The above symptoms and other clinical manifestations of the IIMs can be due to either "disease activity", "disease damage", or a combination of both. The inflammatory component of IIM, which leads to myositis and systemic inflammation, is potentially reversible and therefore represents "disease activity". In contrast, "disease damage" is represented by the largely irreversible damage caused by cumulative IIM disease activity. Disease damage may take the form of muscle atrophy, fibrosis and scarring[53]. Figure 4 illustrates myositis and muscle atrophy detected via an MRI scan.

Figure 4 - Magnetic resonance imaging scan of IIM manifestations

T1-weighted turbo spin echo (T1W-TSE) and short tau inversion recovery (STIR) magnetic resonance imaging scans displaying myositis (red arrows), muscle atrophy (red arrow heads), fat replacement (blue arrows), and fascia oedema (blue arrow heads) in healthy patients (normal), immune-mediated necrotising myopathy (IMNM), polymyositis (PM), and dermatomyositis (DM)



Reproduced with kind permission from Pinal-Fernandez *et al* [54]

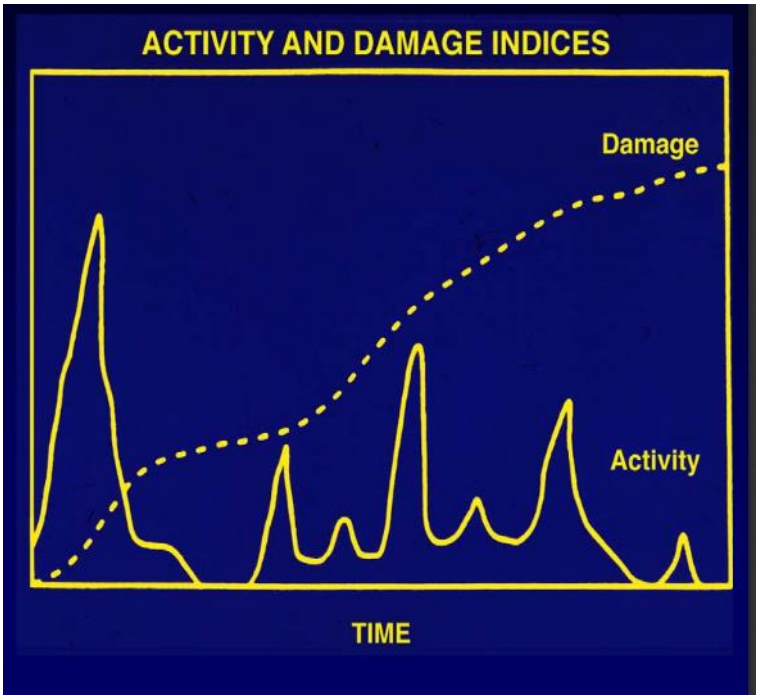
IIM disease activity trajectories are traditionally described as taking the following patterns:

1. Chronic persistent disease activity
2. Relapsing-remitting disease activity (Figure 5)
3. Single episode of disease activity

It is important to note, however, that the volume of research to support existence of these distinct patterns is limited[17,55]. Regardless of pattern, each episode of active

disease can occur rapidly and unpredictably[17,53]. Therefore, being able to identify active IIM disease is imperative in appropriately instigating treatments, with the aim of preventing damage.

Figure 5 - Diagrammatic representation of relapsing-remitting IIM disease activity and cumulative damage development



Adapted from Rider et al, Myositis Core Set Measures of Activity, including MMT8 and the Preliminary Definitions of Improvement, https://www.niehs.nih.gov/research/resources/assets/docs/myositis_core_set_measures_of_activity_including_the_mmt8_and_preliminary_definitions_of_improvement_508.pdf , accessed 20th July, 2020

1.2.4.1 How is IIM disease activity measured?

The ability to measure IIM disease activity is vitally important for a number of reasons, for example it informs a clinician about what treatments are required for an individual patient, also it allows researchers to objectively assess efficacy of a new drug.

The most accurate approach to objective IIM disease activity measurement that currently exists is the International Myositis Assessment and Clinical Studies Group (IMACS) "Disease Activity Core Set Measures"[56].

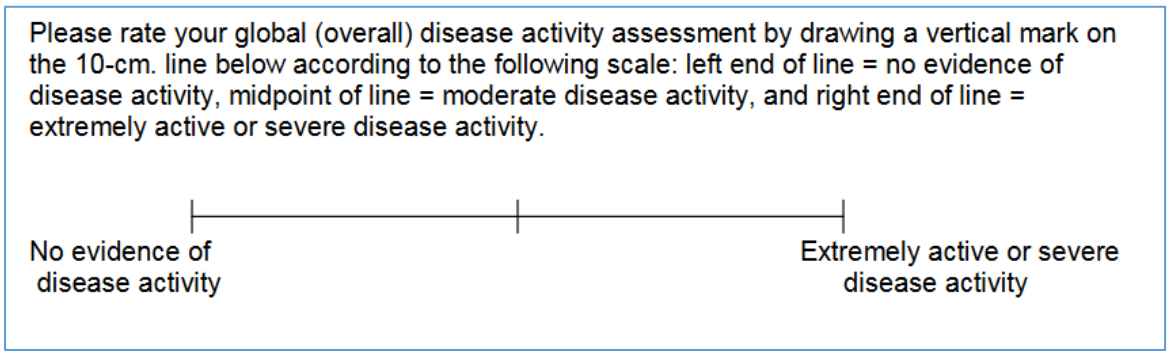
Proformas for each Core Set Measure are included in the Appendices. The IMACS Disease Activity Core Set Measures comprises the following six items:

1. Physician global activity assessment[56]

Format – visual analogue scale (VAS) or Likert scale

This is the physician's overall assessment of a patient's IIM disease activity. A 10cm VAS (Figure 6) or five-point ordinal scale (0 = no evidence of disease activity, 1 = mild disease activity, 2 = moderate disease activity, 3 = severe disease activity, and 4 = extremely severe disease activity) is used.

Figure 6 - Example of a visual analogue scale, as used in the IMACS Core Set Measures



Adapted from Rider et al, Disease Activity Core Set Measures, https://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm, accessed 20th July, 2020

2. Patient global assessment (PGA) of disease activity[56]

Format – VAS or Likert scale

The PGA is the patient's overall measurement of how active their IIM is at that time. A 10cm VAS or five-point ordinal scale is used.

3. Manual muscle testing (MMT)[25,57,58]

Format – clinical examination

This allows quantifiable assessment of the strength of a patient's muscle groups at the time of clinical examination. A complete assessment comprises measurement of 26

muscle groups (Table 1) or an abbreviated assessment 8 groups. The strength of each muscle is recorded on a 0-10 scale (Kendall MMT scale)[59], with 10 representing maximal strength and 0 representing no muscle contraction at all (Table 2).

Table 1 – The 26 muscle groups assessed during manual muscle testing

Muscle group	**Individual muscle**
Axial	Neck flexors
	Neck extensors
Proximal muscles	Trapezius
	Deltoid
	Biceps brachii
	Gluteus maximus
	Gluteus medius
	Iliopsoas
	Hamstrings
	Quadriceps
Distal muscles	Wrist extensors
	Wrist flexors
	Ankle dorsiflexors
	Ankle plantar flexors

Table 2 – Kendall manual muscle testing scale

	Function of the muscle	**Grade**
No movement	No contractions felt in the muscle	0
	Tendon becomes prominent or feeble contraction felt in the muscle, but no visible movement of the part	Trace
Test movement	**Movement in horizontal plane**	
	Moves through partial range of motion	1
	Moves through complete range of motion	2
	Antigravity Position	
	Moves through partial range of motion	3
Test position	Gradual release from test position	4
	Holds test position (no added pressure)	5
	Holds test position against slight pressure	6
	Holds test position against slight to moderate pressure	7
	Holds test position against moderate pressure	8
	Holds test position against moderate to strong pressure	9
	Holds test position against strong pressure	10

4. Functional assessment[60,61]

Format – paper-based questionnaire

The Health Assessment Questionnaire Disability Index (HAQ) is used to assess a patient's physical function and disability.

5. Muscle enzyme concentrations[53,57]

Format – laboratory blood test

The serum concentration of at least two of the four muscle-associated enzymes: creatine phosphokinase (CK), aspartate transaminase, alanine transaminase, lactate dehydrogenase.

6. Extramuscular assessment[62,63]

Format – questionnaire tailored and validated to the IIMs

This component aims to measure the degree of disease activity associated with extra-muscular IIM manifestations. The Myositis Disease Activity Assessment Tool (MDAAT) comprises a physician's assessment of disease activity over the previous four weeks in the following organ systems: systemic symptoms, skin, joints, gastrointestinal tract, lungs, heart and skeletal muscles. A 10cm VAS and a 0-4 scale are assigned to each domain.

1.2.4.2 Limitations of the IMACS Core Set Measures

The IMACS Core Set Measures are limited in a number of ways. Neither common symptoms, such as pain and fatigue, nor gait pattern are assessed in the IMACS Core Set Measures. Non-measurement of relevant symptoms and gait pattern may limit the ability of the IMACS Core Set Measures to comprehensively assess the disease activity of a patient or study participant. The MMT also has a number of particular limitations, which include a "ceiling effect" (i.e. maximum score of 260 on the MMT26 limiting range of strength assessment), high inter and intra-rater variability and low sensitivity to detect change[25,56]. Further, specialist skills and knowledge are required to use and interpret the IMACS Core Set Measures, thus limiting uptake and utilisation in non-specialist clinical and research settings. Collection of all information required typically takes around 10 minutes in duration; a typical "follow up" consultation may only last 20 minutes in total, therefore clinicians may be disincentivised to collect all fields of the IMACS Core Set Measures, thus limiting comprehensive assessment. Finally, the design of the IMACS Core Set Measures restricts data collection to face-to-face settings, making collection outside these time points infeasible.

1.2.4.3 How is IIM disease damage measured?

IMACS have also developed and validated a set of "Disease Damage Core Set Measures"[56]. These are not intended to aid identification of muscle damage, which would typically be identified via MRI scanning (Figure 4), but can rather quantify degree of damage, which could therefore be compared on separate time points. Overlapping components of the disease activity and damage Core Set Measures include functional assessment via validated questionnaire (e.g. HAQ) and MMT. The Disease Damage Core

Set Measures also comprise a Myositis Disease Damage Index[64], and both physician and patient global assessments of disease damage[56].

Section summary

IIM disease activity assessment is important in enabling a clinician to form an appropriate management plan and allowing researchers to quantify disease activity for a multitude of reasons, such as efficacy detection of a new drug. The current gold-standard method allows quantification of a number of relevant aspects of disease activity, however is overall limited through restriction of use to infrequent study assessments and time pressured face-to-face clinical appointments.

1.2.5 Limitations of infrequent data collection upon IIM clinical care and research

Infrequent data collection limits IIM clinical care and research in a number of ways.

Firstly, patients with an IIM are typically reviewed in out-patient hospital clinic appointments, which may be typically separated by 6-12 month intervals. Due to the design of the IMACS Core Set Measures disease activity assessment can only be carried out at the time of these infrequent appointments. This risks late identification of worsening disease activity and late instigation of treatment, thus increasing the risk of irreversible muscle damage and disability. Empirical evidence confirming this is, however, not available due, in part, to the inability to collect frequent disease activity data that could identify the beginning of a flare. Future dedicated research in this area is required to investigate the hypothesis that late flare identification negatively impacts prognosis.

Secondly, it may be challenging for a patient to accurately convey complex patterns of symptom variations and day-to-day variation in the short time (typically 20 minutes) available in a consultation. This risks inaccurate assessment and formation of an inappropriate management plan.

Thirdly, longitudinal IIM research is potentially limited by infrequent assessment and reliance upon the IMACS Core Set Measures, thus limiting ability to detect day-to-day disease activity variations, for example.

Fourthly, the infrequent nature of data collection in clinical and research settings limits the detection of IIM flares and prohibits vital further quantitative research into their characteristics (i.e. frequency, duration, associated symptoms).

Finally, reliance upon MMT during a consultation or research visit as the key method of IIM-related muscle weakness assessment limits detection of its impact upon gait pattern and function.

It is plausible that availability of a method that allows more frequent (i.e. daily) data collection may enhance clinical care and research. Such a method may allow 1) more detailed assessment of important IIM symptoms (e.g. pain and fatigue), 2) quantification of day-to-day symptom variation, and 3) identification of flares. Further, a method that allows frequent identification of gait pattern abnormalities may provide a method capable of more accurate delineation of the impact of IIM-related muscle weakness, compared to infrequent MMT measurements.

As mentioned earlier, two potential user-friendly solutions that could facilitate frequent data collection are 1) daily symptom PROM/symptom collection via smartphone-based apps, and 2) continuous gait pattern measurement collected via wearable accelerometer sensors.

1.3 The potential solutions

Recent technological advances have made the prospect of the "digital healthcare revolution" a possible reality[65,66]. Digital healthcare technology includes, but is not limited to, smartphone-based apps, wearable sensors, algorithm-based decision support tools, telemedicine (i.e. consultation via video-link), and electronic health records. Two key opportunities that digital technologies offer are 1) the ability to measure novel parameters, and 2) the ability to collect frequent longitudinal "free-living" data outside the confines of a clinical facility.

In this section I will firstly describe the opportunities provided by daily PROM/symptom data collection via smartphone-based apps. I will then explore methods of continuous gait pattern assessment, including via wearable accelerometer devices.

1.3.1 Daily symptom collection

Daily collection of IIM-specific PROM/symptom data is now possible via apps on ubiquitous smartphones.

1.3.1.1 What are patient reported outcome measurements?

The US Food and Drug Administration define a PROM 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"[67]. PROMs typically consist of standardised questionnaires that allow a patient to directly report on the impact of their disease or treatment upon their health. PROMs can be used to allow a patient to report on how their disease or treatment impacts upon a multitude of aspects of their health, such as limitations on activities of daily living (ADLs), pain, mood and quality of life (QOL).

An important facet of PROMs is that the response comes directly from the patient i.e. without interpretation or amendment by a health professional. This allows a patient to report on aspects of their disease or treatment that is best assessed by themselves, as opposed to a clinician.

In clinical settings, PROMs allow a patient to communicate to their health care professional how their disease or treatment impacts upon multiple aspects of their health, thus guiding a health care professional's treatment decisions. It is important to note, however, that PROMs are not necessarily commonly used across routine clinical practice, despite the evident opportunities provided. One clinical area where PROMs are routinely used is in the assessment of patients who are being considered for or have undergone total knee or hip replacements. The Oxford Knee Score is a validated PROM that assesses a patient's pain and function and can therefore be used to assess "success" of a knee or hip replacement[68]. PROMs have utility in research settings, including screening to identify potential study participants, investigating natural disease course in long term epidemiological studies, and as endpoints in clinical trials. For example, recent rheumatoid arthritis clinical trials of baricitinib[69] and tofacitinib[70] have included PROMs that assess domains such as quality of life using the EQ-5D-5L[71] and work productivity using the Work Productivity and Activity Impairment questionnaire[72].

Advantages of PROMs include short completion time, standardisation across patients and patient groups, and low cost. PROMs can be used as a proxy measurement to quantify the activity of a patient's disease. Therefore, PROMs can complement other "traditional" measurements of disease activity, such as validated blood tests and radiographic imaging.

1.3.1.2 Patient reported outcome measurement use in the IIMs

PROMs have been developed and utilised in clinical and research settings to improve assessment of the IIMs. PROMs are particularly useful in assessing patients with an IIM as the condition lacks clear and distinct endpoints, which may exist in other conditions. Further, PROMs are ideally placed to assess the impacts upon a patient's health as other outcomes for the IIMs are based on pathophysiological manifestations of the disease, such as muscle weakness and elevated muscle enzymes.

The ability of a number of PROMs to measure IIM disease activity have been investigated (Table 3). Investigated PROMs assess the following domains – health related quality of life (HRQOL), PGA of disease activity, physical function, pain and fatigue. PROMs developed specifically for the IIMs are scarce and the majority of PROMs validated in IIM populations were initially developed in populations with other conditions.

Table 3 – PROMs that have been utilised in IIM research populations

Domain	Patient reported outcome measurement
Health related quality of life	36 Item Short Form Survey[73] Nottingham Health Profile[74] Individual Neuromuscular Quality of Life Questionnaire[75]
Patient global assessment of disease activity	Visual analogue scale (10cm)[56]
Physical function/disability	Health Assessment Questionnaire Disability Index[60] Myositis Activities Profile[61] Activities of Daily Living Barthel Index[76] Human Activity Profile[77] Neuromuscular Symptom and Disability Functional Score [78] Amyotrophic Lateral Sclerosis Functional Rating Scale [79] Convery Assessment Scale[80] Arthritis Impact Measurement Scales-2[81]
Pain	Visual analogue scale (10cm)[82] Visual analogue scale (numeric)[83] Short form McGill Pain questionnaire[84]
Fatigue	Multidimensional Assessment of Fatigue[85] Profile of Mood States Fatigue Scale[86]

1.3.1.3 Patient reported outcome measurement submission via electronic devices

PROMs are traditionally entered and recorded on paper forms. This is indeed the case for the previously discussed PROMs. Over recent decades, electronic devices, such as personal computers, electronic tablet devices and smartphones, have become widely available and access is expected to further increase[87]. The potential for PROMs to be entered via mobile electronic devices has become more realistic. Potential advantages of PROM submission via a mobile device include reduced time entry, reduced secondary data entry errors, possibility for remote submission, and increased frequency of submission[88]. Additional features of electronic mobile devices that improve their utility for PROM collection include the ability to send automated completion reminders at pre-specified times, possibility of direct patient feedback, and avoidance of extraneous, illegible or contradictory responses. A number of studies utilising this technology have been carried out and this section will discuss them in further detail.

A number of PROMs validated for the IIMs have been translated into electronic device format in other conditions[89–98], demonstrating equivalence of validity. For example, touchscreen visual analogue scales have been used for patients to report global activity[90,95,98–105] and pain levels, each demonstrating improved user-friendliness compared to paper-based versions in osteoarthritis, rheumatoid arthritis and psoriatic arthritis populations. A variety of electronic devices have been utilised, including personal computers, personal digital assistants, smartphones, and tablet/touch screens.

Therefore, collection of PROMs related to IIM symptoms via electronic devices, such as smartphone-based apps, may be feasible.

1.3.1.4 Mobile health studies and collection of PROMs via smartphone-based apps

In this section I will introduce the concept of "mobile health" (mHealth) studies, explore beneficial aspects of mHealth studies, and then briefly outline the small number of smartphone apps developed for PROM collection in IIM cohorts.

The World Health Organisation Global Observatory for eHealth defines "mobile health" as[106]:

> "Medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices. mHealth involves the use and capitalization on a mobile phone's core utility of voice and short messaging service as well as more complex functionalities and applications including general packet radio service, third and fourth generation mobile

telecommunications (3G and 4G systems), global positioning system, and Bluetooth technology."

Therefore, mHealth studies cover a variety of methodologies that utilise the wide-ranging functionality of smartphones. Widespread ownership of smartphones (78% of UK population) makes data collection via apps feasible and provides a novel method of PROM collection[107].

mHealth study methodology has the ability to complement "traditional" research approaches. Specific benefits/facets of mHealth studies that utilise smartphone-based apps include:

- **Rapid collection of data across large international populations.** For example, the COVID Symptom Study App enabled rapid collection of longitudinal data on 2,035,395 individuals (UK and USA) over a total of 34,435,272 person-days. This data has enabled identification of important risk factors for reporting a positive COVID-19 test among front-line health-care workers[108]. Traditional epidemiological methods would be unlikely to rapidly collect such volumes data.
- **Facilitation of large cohorts via remote recruitment.** For example, the "Cloudy With a Chance of Pain" study remotely recruited 10,584 participants, thus allowing detailed analysis of the relationship between weather and pain[109].
- **Utilisation of "co-design"**, which refers to protocol formulation by the study team alongside other relevant stakeholders, such as potential participants, and future data users, such as researchers or clinicians[110]. For example, Cai *et al* reported utilisation of co-design in the development of an app to improve self-management for young people with juvenile idiopathic arthritis[111].
- **Implementation into clinical trials**, thus providing an additional method of efficacy assessment. For example, the RA-BUILD and RA-BEAM studies collected daily symptom data from participants taking part in a trial investigating the efficacy of baricitinib for treatment of rheumatoid arthritis[112]. Daily symptom data provided further evidence of efficacy.
- **The utilisation of frequent (i.e. daily/weekly) data to allow identification of changes of disease pattern.** For example, Eisner *et al* described data collection via a smartphone-based app with the aim of schizophrenia flare detection[113,114].

- **The ability to remotely collect longitudinal patient registry data**, as demonstrated by the ArthritisPower study, which collects longitudinal PROM data from participants enrolled in a patient register[115].

1.3.1.5 PROM collection via smartphone-based apps in IIM studies

Very few IIM-specific smartphone apps that allow symptom recording have been developed, despite the potential utility of smartphone app-based symptom collection.

The NuMe app, developed by Portable Genomics, contains "modules" designed to allow patients to enter data about many different health conditions, including IIM, cystic fibrosis and ovarian cancer[116]. The IIM specific module allows entry of a number of PROMs related to a wide variety of symptoms, including pain levels, swallowing difficulty and rashes. According to the Portable Genomics website, entered data will be shared with industry partners with the aim of advancing IIM research. Analysis of data collected via the app has not been published. The app was launched in 2018 but is no longer available for download.

The My Pacer app was developed as part of a study coordinated by the University of Pittsburgh[117]. The primary aim of the study is to develop new "telemedicine" methods for treating patients with IIM. The secondary aim of the study is to delineate the utility of Fitbit-collected data in quantifying physical function. The study enrolled adult IIM patients for six month periods. Every month, participants answer a set of PROMs and carry out specific physical function tests (e.g. standing from a chair). Participants are also asked to wear a Fitbit (wrist worn device that provides activity measures, including step count, heart rate) for one week periods every month. The study began in 2019 and data collection is still underway. Results have not yet been published.

Section summary

In summary, it is known that PROMs can assess certain aspects relevant to the IIMs, such as pain, fatigue and HRQOL. Also, recent studies have demonstrated the opportunity of PROM collection via smartphone-based apps. Research on the utility of smartphone app-based PROM/symptom data collection in IIM populations is limited. Further research in this area is required to delineate the potential utility of daily PROM/symptom data collection via a smartphone-based app in an IIM cohort. Further,

daily PROM/symptom data may provide novel insights into predominant-symptoms, degree of day-to-day variation, and flares.

1.3.2 Continuous gait pattern assessment

As described earlier, hip flexor weakness due to IIM-related myositis can result in gait pattern abnormalities. Remote gait monitoring via wearable accelerometer devices may provide a novel method of continuous data useful for clinical and research settings. In this section I will explore how accelerometer devices can allow continuous gait pattern measurement, which may be useful in detecting IIM-specific gait pattern abnormalities.

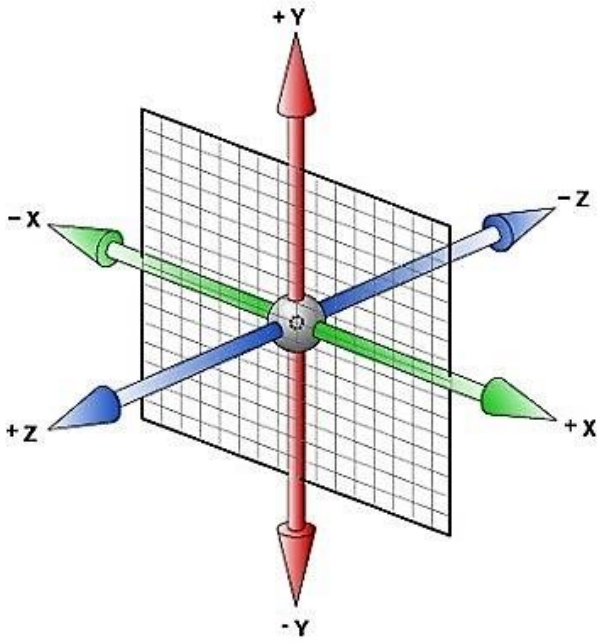
Gait can be measured and quantified by a number of methods. Laboratory-based methods can accurately characterise the components of an individual's gait through detection from sensitive walkways or the tracking of sensors placed on a number of body locations[118–122]. Although accurate, the technique is time-consuming, expensive and can only measure gait whilst in the laboratory. The need for gait analysis in "real-world" settings (i.e. when the study participant is going about their daily activity) has given rise to a number of other methods. One such technique is the use of accelerometer devices.

1.3.2.1 What are accelerometer devices?

Accelerometers are small, non-invasive, light weight, portable devices that can measure acceleration in one or more plane. Modern "capacitive" accelerometers comprise a small micro electro mechanical system (MEMS) with a proof mass attached to the end of a cantilever beam, which is surrounded by a set of fixed beams. External acceleration deflects the proof mass and generates a variation of capacitance between the fixed beams. This capacitance variation generates an electrical signal, which is then converted into a digital or analog output. This output can be used to quantify acceleration in a particular directional plane[123–126].

Accelerometers typically measure acceleration in a single plane (uniaxial) or three planes (triaxial) (Figure 7). The three planes are referred to as anteroposterior (AP), mediolateral (ML) and vertical (V). Acceleration is typically measured multiple times each second (i.e. 10-100 Hz).

Figure 7 - Graphical representation of triaxial acceleration measurement

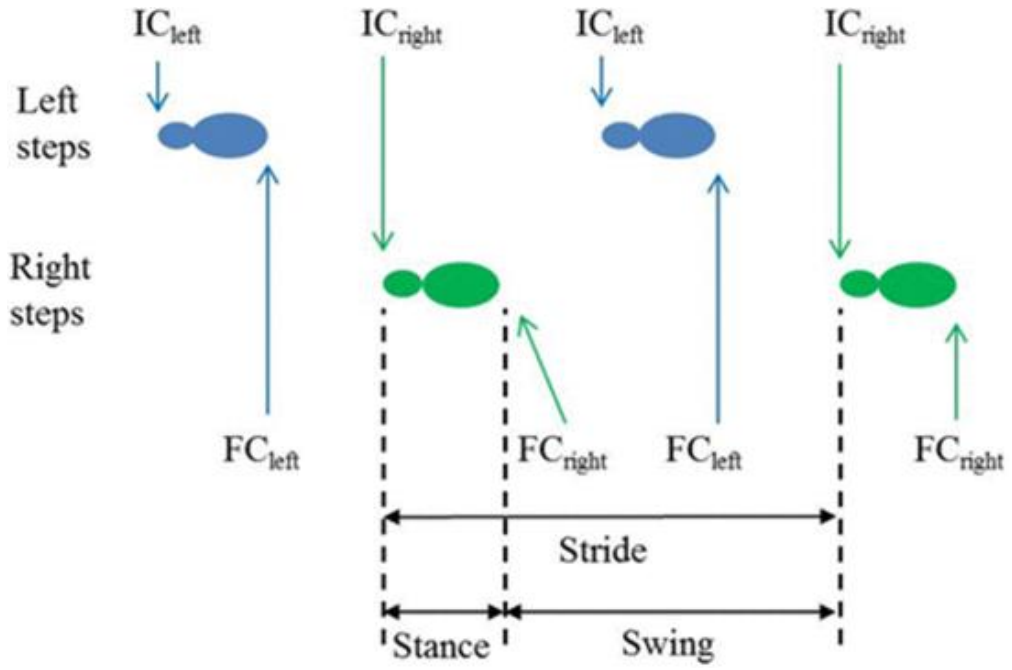


Adapted from Rotate 3d, https://www.w3.org/Talks/2012/0416-CSS-WWW2012/Demos/transforms/demo-rotate3d.html, accessed 20th July, 2020

1.3.2.2 Accelerometer-derived data use in gait characterisation

A number of previous studies have developed systems through which gait parameters can be measured via collection of tri-axial data acceleration data from wearable accelerometer devices. Del Din *et al* described an algorithm developed to identify initial foot contact and final foot contact from accelerometer-derived data; they were then subsequently able to measure the stance time, stride time and swing time (Figure 8)[127]. Godfrey *et al* also employed an algorithm to identify gait parameters, including step velocity and step length from accelerometer-derived data[128]. They were able to identify asymmetry of gait characteristics between each leg. Roy *et al* identified that "correlated jerks on all three axes" indicated heel-strike, from which other gait phases could be identified, thus using of the heel strike as a point of reference[129].

Figure 8 - Identification of stride, stance, and swing times from the double support phase of the initial foot contact and final foot contact algorithm



IC = initial foot contact, FC = final foot contact

Adapted from Del Din et al, IEEE J Biomed Heal Informatics 2016;20:838–47.[127]

Other gait parameters, such as step count and cadence have been calculated through commercially available devices with pre-installed algorithms, such as the ActiGraph device; such devices are also able to calculate non-gait related variables, such as time spent sitting and intensity of physical activity[130–134]. Commercially available accelerometer-containing devices, although useful for certain applications, limit the analysis and generalisability of results, as the algorithm to identify gait parameters cannot be tailored to the particular situation and study population.

The small size and user-friendliness of accelerometer devices make them ideal at measuring "real-world" gait pattern – i.e. an individual's gait pattern whilst going about their ADLs. In clinical applications, real-world measurement and variation of gait parameters have been demonstrated following a stroke[135], Parkinson's Disease[136], OA[137] and following total hip replacement[138].

1.3.2.3 What previous accelerometer-based studies have been carried out in IIM cohorts?

Accelerometer data has been collected in IIM cohorts, not for the purpose of gait pattern characterisation, but for the continuous quantification of level of "physical activity" (i.e. low, moderate or vigorous). Only 9 papers have reported accelerometer-derived data in IIM research[139–147]. These papers, their findings and limitations are described in the review paper entitled "A Review of Accelerometer-Derived Physical Activity in the Idiopathic Inflammatory Myopathies", which is included in Chapter 2 of this thesis.

In summary, 9 papers describing accelerometer use in 162 individual IIM cases were identified (four papers analysed data from two individual studies). Eight out of the 9 studies investigated juvenile dermatomyositis (JDM) populations and only one reported on an adult-onset population. Critically, all studies used accelerometer data to estimate levels of physical activity and none aimed to measure gait pattern. A number of useful lessons can, however, be learned from these studies. Firstly, continuous wearing of accelerometer devices (timeframes varied between studies) was well tolerated by study participants. Secondly, the location of accelerometer placement (e.g. wrist-worn, hip-worn, thigh-worn) must be carefully considered when analysing data and interpreting results. Thirdly, only weak and inconsistent associations between IIM disease activity and physical activity were identified. This indicates that perhaps a more detailed approach, such as gait parameter assessment, is required to capture the impact of IIM-related muscle weakness. Finally, and perhaps most importantly, these studies indicate an appetite for novel remote methods of IIM disease activity monitoring. This is also illustrated by an expert report by the European Neuromuscular Centre, which called for "a new study to re-examine the core set outcome measures of IMACS and to develop the use of accelerometry (and other mobile-health applications)"[148].

Section summary

In summary, it is known that wearable accelerometer devices can allow remote quantification of gait pattern. However, no study has used accelerometer data to quantify gait pattern in the IIMs. Research into the utility of remote gait pattern measurement in the IIMs is warranted, with the aim of developing a disease activity assessment method to complement the IMACS Core Set Measures.

1.4 Fundamentals of epidemiology and mHealth methods

mHealth approaches represent a novel method of data collection that can be employed in epidemiological studies. Epidemiology is defined as follows:

> "Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems."[149]

A number of core aspects of design, conduct, analysis and interpretation are central to ensuring accurate and rigorous epidemiological studies. Factors related to study design include, but are not limited to, population selection, validity assessment, bias (selection and information), engagement, and confounding.

mHealth methods, such as data collection via a smartphone-based app or accelerometer sensor are still subject to such study design factors. Researchers employing mHealth methods must therefore ensure adherence to the fundamentals of epidemiology, or otherwise risk rendering their results inaccurate or irrelevant.

In this section I will briefly review three key principle components of epidemiology study design (selection bias, measurement accuracy/precision, and engagement) and explore how they are pertinent to mHealth studies.

1.4.1 Selection bias

Epidemiological studies strive to ensure that the population they are studying and collecting data from are representative of the population that the results/findings may be applied to. Selection bias occurs when the studied population is not representative of the intended population. This can lead to production of results and findings that can not be accurately extrapolated to the intended wider population (i.e. diminished external validity). Selection bias can occur due to a wide number of aspects of study design, which include inclusion/exclusion criteria, participant burden, and provision of participant remuneration. The "healthy worker effect" is an example of selection bias, which refers to study participants who are employed tending to be healthier than those who are not employed[149]. Recruitment of a predominantly unemployed study cohort may therefore provide results that may not be relevant to the wider population, which will include employed people.

Selection bias can affect recruitment in mHealth studies. For example, many mHealth studies may include personal ownership of a smartphone or other personal electronic

device as a prerequisite to study inclusion. This automatically excludes the estimated 22% (14.7 million) of UK population who do not own a smartphone. Further, "digital literacy" refers to an individual's ability and confidence to use an electronic device, such as a smartphone[150]. A low level of digital literacy may deter a person from volunteering for an mHealth study, thus causing selection bias and affecting the external validity of results.

1.4.2 Measurement bias

Epidemiological studies measure certain variables of interest. It is imperative that the method used to measure such a variable is accurate (i.e. measures the true value), precise (i.e. provides a sufficiently detailed measurement), valid (i.e. measures what it purports to measure) and reliable (i.e. repeated measurements are sufficiently similar).

Measurement bias is an important aspect to consider when designing an mHealth study. A study team must ensure that the mHealth technique they are using to measure a certain variable is accurate, precise, valid and reliable. Use of previously validated question sets can go some way to mitigate introduction of measurement bias.

1.4.3 Participant engagement

Epidemiological studies are greatly affected by the degree to which participants engage. High engagement can ensure validity of study results, whereas low engagement risks attrition bias (i.e. disengagement of a particular "non-random" subsection of a cohort), subsequently resulting in reduced external validity and inhibiting translation into clinical practice. Engagement with "traditional" research studies is a well explored area. Factors associated with disengagement and methods available to mitigate this have been developed, for example in interventional clinical trials where fewer face to face appointments and the need for uncomfortable procedures (e.g. blood sampling) may reduce engagement[151–153].

The majority of mHealth studies report high attrition rates, for example, Bot *et al* reported that only 898 (11%) of the 8,320 initially recruited to a Parkinson's Disease mHealth study contributed the intended minimum of five days of data throughout the study period[154]. High attrition rates have wide ranging impacts, including volume of data available (i.e. large degree of missing data), analysis (e.g. need to account for selection bias), strength of results (e.g. smaller than expected population may weaken study power) and future translation into healthcare (e.g. high attrition rates may indicate

future weak uptake). Therefore, research into factors associated with engagement particular to mHealth studies is important to ensure efficient study design and maximal validity.

A number of frameworks addressing factors related to engagement with mHealth systems have been developed. Each framework was developed to address specific situations and implementations of mHealth solutions. Frameworks can be grouped into 1) theory informed integrative reviews[155,156], 2) frameworks based on a logic model for developing and implementing a technology[157,158], 3) frameworks presented as a list of criteria[159,160], 4) frameworks based on static models of systems[161,162], 5) frameworks based on individual adoption/engagement[163,164], and 6) frameworks based on dynamic/developmental models of systems[165,166].

In 2005 Eysenbach introduced the concept of "science of attrition" and proposed a number of factors that influence engagement and attrition[164]. This framework usefully facilitates consideration of a wide variety of practical aspects integral to the success of newly designed and implemented mHealth solutions. These include:

- Quantity and appropriateness of information given before the trial and expectation management
- Ease of enrolment, recruiting the "right" users and degree of pre-enrolment screening
- Ease of drop out/discontinuation
- Usability and interface issues
- Push factors (i.e. reminders)
- Personal contact via face-to-face or telephone, as opposed to virtual contact
- Positive feedback, buy-in and encouragement from change agents and from health professionals/care providers
- Tangible and intangible observable advantages in completing the trial or continuing to use it
- Intervention has been fully paid for
- Workload and time required
- Competing interventions
- External events
- Networking effects/peer pressure, peer-to-peer communication, and community building
- Experience of the user

Some of these factors are amenable and under the control of the researcher (e.g. quantity of information given before the enrolment), whereas others are clearly not (e.g. occurrence of external events). Recognition of these factors provides a framework upon which researchers can amend their mHealth study, thus facilitating engagement and quality of results. mHealth engagement will be considered within the Eysenbach framework throughout the thesis, where appropriate.

Section summary

In summary, it is imperative that mHealth studies consider the fundamental principles of epidemiology. As described, engagement with mHealth studies can vary widely. No study has, however, investigated engagement in an IIM-specific mHealth study. Identification of "enablers" and "barriers" to engagement in an IIM mHealth study may provide valuable information that can inform the design of future studies.

1.5 Introduction summary and aims

It is my vision that technological innovations as part of the digital healthcare revolution will enhance IIM clinical care and research through enabling more frequent data collection. Such opportunities have been exploited and realised in other conditions, however advances in the IIMs is markedly limited.

A number of specific steps are required before digital solutions can be implemented into clinical care. Such steps include, but are not limited to:

1. Delineation of clinical need/unmet need
2. Technology hardware development
3. Technology software development
4. Development of code capable to processing collected data
5. Demonstration of clinical/research utility
6. Economic analysis
7. Embedding within healthcare

These are outlined in the American Medical Association's "Digital Health Implementation Playbook"[167]. Personal smartphone ownership is widespread and many wearable accelerometer sensors are already commercially available, thus fulfilling step 2. This thesis will therefore aim to address steps 1, 3, 4 and 5.

During my PhD I designed and carried out the Myositis Physical Activity Device (MyoPAD) study. The MyoPAD study recruited a cohort of participants with an IIM. Recruited participants answered PROM questions each day of the 91 day study period via a specially designed smartphone-based app. They also continuously wore a thigh-worn accelerometer sensor, which collected gait pattern data. Additionally, participants took part in one-on-one qualitative interviews on the first study day and just after the final study day. A total of 21,709 PROM answers, 40,145 hours of accelerometer data, and data from 29 qualitative interviews were collected from the MyoPAD study.

Using data from the MyoPAD study, I aim to complete the following specific objectives:

1. Use qualitative data to explore participants' perspectives on IIM-related symptoms, degree of day-to-day symptom variation, flare characterisation, and perceptions surrounding ability of current methods to capture disease activity, thus delineating the unmet need and potential role(s) of frequent data collection (Chapter 3)
2. Investigate engagement with daily PROM submission via a smartphone-based app and wearing of a thigh-worn accelerometer sensor for continuous gait pattern characterisation (Chapter 4)
3. Investigate how daily PROM data can provide novel insights into IIM flares (Chapter 5)
4. Develop a reproducible method of processing raw accelerometer data into gait parameter data, ready for research purposes (Chapter 6)
5. Investigate if IIM disease activity (represented by the IMACS Core Set Measures) is associated with remotely collected gait pattern data (Chapter 6)

Additionally, I aim to complete the following objective, which took place outside the MyoPAD study:

6. Systematically review previous studies that collected accelerometer data in IIM populations, with the aim of delineating the extent of research in this area, informing data collection and analysis within the MyoPAD study (Chapter 2)

Fulfilling these objectives will provide evidence on how frequent PROM/symptom and continuous gait pattern data collection may potentially complement IIM clinical care and research, thus bringing us closer to the benefits promised by the digital healthcare revolution.

1.6 Note on journal format of thesis

I chose to present my thesis in "journal format". The main reason I chose this format is to facilitate subsequent publication in academic journals. I feel that the results of my thesis may be of interest to the wider academic, clinician and patient population. Preparation of each chapter in journal style will therefore facilitate publication and dissemination. Chapters 2 and 3 have already been published in peer-reviewed journals and chapters 4, 5 and 6 are in preparation for submission.

Each chapter will begin with a brief introduction of its specific rationale and aims. This will be followed by a prepared manuscript. Each results chapter will address the above overall aims. Due to the journal format of this thesis, it is unfortunately inevitable that information or concepts described in the introduction will be repeated in the background section of the results chapters.

Chapter 7 includes a summary of the overall findings followed by a description of their clinical and research relevance. Future research directions will also be outlined.

Chapter 2

2 Review of accelerometer data collection in IIM research

"Never trust to general impressions, my boy, but concentrate yourself upon details."

Sherlock Holmes

The Adventure of the Blue Carbuncle[168]

2.1 Introduction

Collection of accelerometer data has provided useful insights in a number of disease areas. I recognised early on in my PhD that very few studies had collected accelerometer data for IIM research, despite the evident potential opportunities as described in the introduction. I therefore realised that it would be useful to systematically review existing evidence, with the aim of synthesising findings and assimilating learned lessons, thus enhancing my subsequent research.

Accelerometer data collection is a useful method that can complement "traditionally" collected data, however such utility introduces distinct complexities that must be considered and addressed. Specific consideration must be given to choice of accelerometer device, location of device placement, duration of data collection, analysis and interpretation. These considerations and others are reviewed in this chapter.

This chapter therefore aims to answer the following questions:

- How many studies have collected accelerometer data in IIM populations/cohorts?
- What methodology did each study employ (e.g. device used, study duration, analysis)?
- Are any accelerometer-derived variables, such as physical activity, associated with IIM disease activity measurements, such as muscle strength?
- What lessons can be learned from these studies?

2.2 Description of contribution

I carried out the literature review, synthesis of findings across studies and manuscript preparation. My supervisory team (Prof Chinoy, Prof Dixon, Dr Little) provided detailed input and guidance on data extraction and manuscript preparation. The manuscript was published in BMC Rheumatology in 2019[169]:

Alexander Oldroyd, Max A Little, William Dixon, Hector Chinoy. A review of accelerometer-derived physical activity in the idiopathic inflammatory myopathies. BMC Rheumatol. 2019 Oct 21;3:41. doi: 10.1186/s41927-019-0088-1.

2.3 Additional papers published since completion of systematic review

Eight published papers were identified at the time of manuscript preparation[139–146]. One further eligible paper was subsequently published in May 2020[147]. This study by Berntsen *et al* utilised data from a JDM cohort, data of which had previously been utilised in another study already included in the review[145]. Accelerometer data collected in this additional study was processed into levels of physical activity - i.e. sedentary, light or moderate-to-vigorous. It is noteworthy that this study reported that peak torque (i.e. strength) of knee extension was positively associated with time spent in moderate-to-vigorous physical activity. This study did not use accelerometer data to quantify gait pattern.

2.4 Manuscript 1

A review of accelerometer-derived physical activity in the idiopathic inflammatory myopathies

BMC Rheumatology

RESEARCH ARTICLE Open Access

A review of accelerometer-derived physical activity in the idiopathic inflammatory myopathies

Alexander Oldroyd[1,2,3,4*], Max A. Little[5,6], William Dixon[1,2,3,4] and Hector Chinoy[1,2,3]

Abstract

Background: The idiopathic inflammatory myopathies (IIMs) are a group of rare conditions characterised by muscle inflammation (myositis). Accurate disease activity assessment is vital in both clinical and research settings, however, current available methods lack ability to quantify associated variation of physical activity, an important consequence of myositis.
This study aims to review studies that have collected accelerometer-derived physical activity data in IIM populations, and to investigate if these studies identified associations between physical and myositis disease activity.

Methods: A narrative review was conducted to identify original articles that have collected accelerometer-derived physical activity data in IIM populations. The following databases were searched from February 2000 until February 2019: Medline via PubMed, Embase via OVID and Scopus.

Results: Of the 297 publications screened, eight studies describing accelerometer use in 181 IIM cases were identified. Seven out of the eight studies investigated juvenile dermatomyositis (JDM) populations and only one reported on an adult-onset population. Population sizes, disease duration, accelerometer devices used, body placement sites, and study duration varied between each study.
Accelerometer-derived physical activity levels were reduced in IIM cohorts, compared to healthy controls, and studies reported improvement of physical activity levels following exercise programme interventions, thus demonstrating efficacy.
Higher levels of accelerometer-derived physical activity measurements were associated with shorter JDM disease duration, current glucocorticoid use and lower serum creatine kinase. However, no clear association between muscle strength and accelerometer-derived physical activity measures was identified.

Conclusions: The use of accelerometer-derived physical activity in IIM research is in its infancy. Whilst knowledge is currently limited to small studies, the opportunities are promising and future research in this area has the potential to improve disease activity assessment for clinical and research applications.

Keywords: Myositis, Muscle, Outcome measures, Human activities, Review, Accelerometry

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Background

The idiopathic inflammatory myopathies (IIMs) are a group of rare (annual incidence of 1.5–10 per million person-years [1], prevalence of 14 per 100,000 [2]) autoimmune conditions that can cause widespread inflammation and damage [3, 4]. A number of IIM subtypes are recognised, including dermatomyositis (DM), juvenile DM (JDM), polymyositis (PM) and inclusion body myositis. The most common manifestation of the IIMs is muscle inflammation, termed "myositis". Each episode of myositis, if left untreated, results in irreversible muscle breakdown, disability and early mortality [5, 6]. Therefore, in clinical settings, the ability to identify and quantify the severity of active myositis is imperative, to allow appropriate treatment with the aim of preventing damage. Further, the availability of valid measurements of myositis disease activity is essential in research settings, e.g. to evaluate the efficacy of interventions.

A number of measurements of myositis disease activity currently exist and include manual muscle testing via the MMT-8, serum creatine kinase (CK) levels and validated questionnaires, such as the Health Assessment Questionnaire Disability Index (HAQ-DI). JDM-specific disease activity can also be assessed by measures such as the Childhood Myositis Assessment Scale (CMAS), Childhood Health Assessment Questionnaire (CHAQ) and the Paediatric Quality of Life Inventory (PEDS-QL). A number of valid measurements of myositis disease activity have been assimilated into the International Myositis Assessment and Clinical Studies Group (IMACS) "Disease Activity Core Set Measures" [7], which is currently used as the gold-standard of myositis disease activity assessment in both clinical and research settings.

These measurements of myositis disease activity, although accurate, only capture specific aspects of disease activity, and do not necessarily objectively assess the patient-experienced consequence of myositis – namely reduced ability to carry out physical activities due to active muscle disease or irreversible muscle damage [8]. A qualitative study by Alemo Munters et al. identified that ability to carry out physical activities, including walking, participating in social activities and cycling were particularly affected in a myositis population [9]. Importantly, this study also identified that limitations of these physical activities are not wholly assessed in the HAQ-DI and Myositis Activities Profile (MAP) [10], two leading methods of patient-reported disease activity assessment - only 21% of reported disabilities were covered by the HAQ-DI and only 32% were covered by the MAP.

Objective assessment of physical activity may provide a novel method for myositis disease activity assessment. Here, we take the World Health organisation definition of physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure" [11]. Worsening myositis leads to reduced force generation capability predominantly of proximal limb muscles [12, 13]. Subsequent slower walking speed and reduced stride length, as reported by Siegel et al. [14], result in patient-reported walking difficulty, particularly whilst climbing stairs. A number of studies have confirmed the impact of myositis upon physical activity, along with the association between myositis disease activity and physical activity [15–17]. Alexanderson et al. showed that in a myositis cohort, within the first year after diagnosis and treatment initiation, improvement of the Functional Index of myositis test, a measure of physical activity, was associated with improvement of the MMT-8 and reduction of CK [15].

A number of methods of assessing physical activity are available. The gold-standard measurement of energy expenditure, and therefore physical activity, is the "doubly labelled water" (DLW) method [18]. DLW is water with hydrogen and oxygen molecules replaced by traceable isotopes. Following ingestion and attainment of equilibrium within the body, serial blood or urine measurements of the concentration of the isotopes can be used to estimate the body's metabolic rate. Although accurate, this technique is time-consuming, expensive, and not suited to measuring physical activity over prolonged continuous periods in a "real-world" setting (i.e. when the study participant is going about their daily activity).

The need for physical activity measurement in real-world settings has given rise to a number of more practical methods. One such technique is the use of accelerometer devices. Accelerometers are small, non-invasive, lightweight, portable devices that can measure acceleration in one or more geometric plane (Fig. 1). Modern "capacitive" accelerometers comprise a small micro electro-mechanical system with a proof mass attached to the end of a cantilever beam, which is surrounded by a set of fixed beams. External acceleration deflects the proof mass and generates a variation of capacitance between the fixed beams. This capacitance variation generates an electrical signal, which

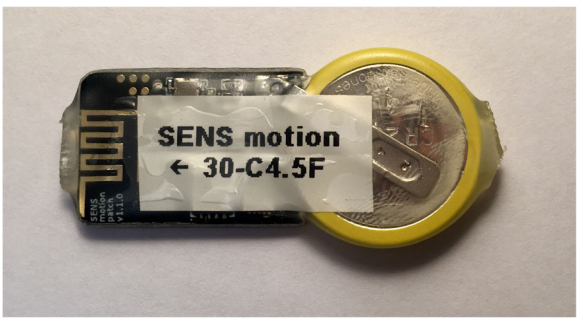

Fig. 1 Image of internal components of an accelerometer device – thigh worn SENS Motion Plus device, which measures 20 mm × 50 mm × 3.5 mm. Reproduced with kind permission of SENS Innovation

is then converted into a digital or analog output. This output can be used to quantify acceleration in a particular directional plane [19, 20].

Accelerometers typically measure acceleration in a single plane (uniaxial) or three orthogonal planes (triaxial). Accelerometers are capable of measuring tri-axial acceleration at high sampling rates, typically 50–100 Hz. Sampling at such a high rate over prolonged periods of time provides a temporal characterisation of physical activity, thus enabling detection of frequent (i.e. daily) changes. The acceleration data can either be analysed in its "raw" format or processed into a number of "composite" measures, such as number of steps in a time period, distance travelled or intensity of physical activity (typically categorised as sedentary, light, moderate or vigorous). Therefore, composite outputs from accelerometer-containing devices can be used to objectively summarise physical activity and identify temporal changes, for example differentiating periods of physical activity from sedentary behaviour, or identifying changes in levels of activity following an intervention. The interpretation of accelerometer-derived measurement in medical research is dependent on a number of important factors, such as body site placement (e.g. wrist, thigh, lower back), duration of use, and device used. Further, study population factors, such as disease of study interest, disease duration, presence of comorbidities, control group use, and behavioural factors such as lifestyle and living environment, also greatly influence the interpretation of collected data.

Therefore, with the need for more accurate myositis disease activity assessment and the opportunity of physical activity assessment using accelerometers, a review of studies to date on this topic will provide a useful summary of current knowledge. It will also provide an understanding of future research needs in this area.

This review aims to identify studies that have used accelerometer-derived physical activity data in studies of myositis populations, collate and compare reported physical activity data and lastly, investigate if these studies identified associations between physical activity and measures of myositis disease activity.

Methods

A narrative review was conducted to identify original articles that have used accelerometer devices in the myositis populations/cohorts. The following databases were searched from February 2000 until February 2019: Medline via PubMed, Embase via OVID and Scopus. The following medical subject headings (MeSH) terms were used to identify appropriate studies: "myositis", "accelerometry", "exercise test" and "exercise". The "myositis" MeSH term encompasses the DM, PM, and inclusion body myositis subtypes. Each identified study's references were also examined for further appropriate studies. Studies were included if they were written in English, studied physician-confirmed human myositis cases, and measured physical activity using accelerometer-containing devices. Case reports were excluded.

The abstract of each identified study was reviewed for eligibility and excluded where appropriate. Full text review of all potentially eligible studies was subsequently carried out. Only studies that fulfilled the inclusion criteria were included in the review.

Conference abstracts were not included in the search due to the likely insufficient methodology and results details required to fully compare studies and identified relationships between accelerometer-derived physical activity and measures of myositis disease activity.

Ethical approval was not required for this study.

Results

The initial search returned 297 studies. Following removal of 12 duplicates, 28 animal studies and a further 249 that did not meet the inclusion criteria, eight distinct articles, which utilised accelerometer-derived data to represent physical activity in a total of 181 myositis cases, were identified (Fig. 2), details in Tables 1 and 2. The studies varied with respect to populations investigated, devices used, site of device placement and duration of study, each of which will be considered in turn, before we compare findings and address the reported associations between physical activity and myositis disease activity.

Populations investigated

Seven out of the eight studies used accelerometers in JDM populations [21–27] and only one, Bachasson et al. [28], reported on an adult-onset population. Both Mathiesen et al. and Berntsen et al. reported the findings from populations comprising participants both younger than and older than 18 years of age – however all study participants had experienced myositis onset aged younger than 18 years. Population sizes ranged from five to 45 study participants. Disease duration prior to study commencement varied between each study, from newly diagnosed cases to 36 years after disease onset. Bachasson et al. was the only study to report accelerometer data that was collected from the time of first treatment following diagnosis [28].

Devices

Actical, ActiGraph, Sense Wear and GENEActiv (Fig. 3) devices were used. Each accelerometer-containing device collects acceleration magnitude multiple times each second and/or provides a summarized measure of physical activity. Measures of physical activity included the "Euclidean Norm Minus One" (GENEActiv device) [28], time spent in light, moderate or vigorous states (Actical, ActiGraph GT3X devices) [21, 23, 24, 26, 27], "counts" per minute (CPM, ActiGraph GT1M device) [22, 27]

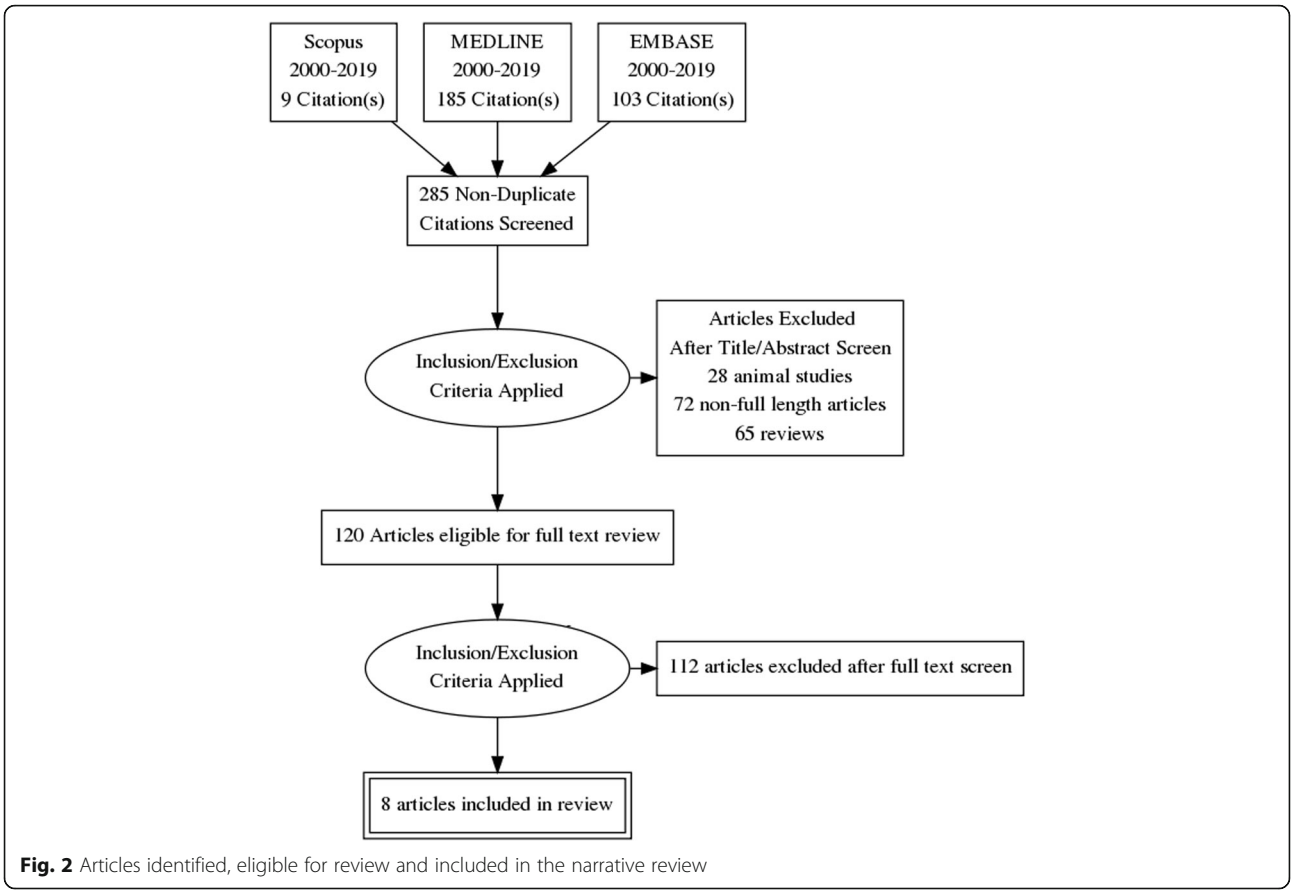

Fig. 2 Articles identified, eligible for review and included in the narrative review

and number of steps recorded in 48 h (Sense Wear device) [25].

The study by Bachasson et al. was the only one not to report a summary measure of physical activity, such as step count [28]. They reported the mean daily "vector magnitude"; the vector magnitude was calculated as the "Euclidean Norm Minus One" (ENMO). ENMO is calculated by summing the squared acceleration of each of the three accelerometer axes at each time point (i.e. Euclidean Norm) and then subtracting the gravitational component, which is 1 g (1 g = 9.81 m/s^2). The assumption is that increases of the mean daily vector magnitude indicates increasing levels of physical activity. Vector magnitude, being a simple mathematical operation, may preserve the relevant complexity and variation of physical activity; this contrasts to complex, composite measures such as step count which may lose important variation because in practice, these algorithms are confounded by unknown factors and developed for different populations than the one under study.

Six studies reported summary variables related to intensity of physical activity, measured in "counts", as collected by ActiGraph GT3X and Actical devices [21–24, 26, 27]. The number of counts in a minute can be used as a proxy representation of intensity of physical activity. A single count represents an acceleration measurement exceeding a pre-specified threshold. Subsequently, each time period is assigned as corresponding to sedentary (< 100 cpm), light (> 100 and < 2295 cpm), and moderate-to-vigorous (> 2295 cpm) activity, depending on the number of counts detected in a minute. Mathiesen et al. was the only study to report CPM, without subsequently ascribing inactive, light, moderate or vigorous intensity [22].

Riisager et al. used a Sense Wear body monitoring system [25], which detects steps based on accelerometer data using a data-driven machine learning algorithm – i.e. steps are detected when the pattern of collected accelerometer data correspond to step-associated signals; however, details of the algorithm used to detect steps is not available as it is proprietary information. The number of steps per 48 h period was reported as their surrogate measurement of physical activity.

Site of device placement

A wide variety of body sites for accelerometer placement were used in the reviewed studies, including wrist [28], upper arm [25], waist [23] and hip [21, 27]. Studies by Mathiesen et al. [22] and Habers et al. [26] did not explicitly state what site was used, however the manufacturers of the employed accelerometer devices advise them to be

Table 1 Summary of studies that met inclusion criteria – studied populations and accelerometer-specific characteristics of each study

Authors	Population	Number of participants	Duration of disease	Control group	Accelerometer device used	Duration of accelerometer data collection	Body site of accelerometer placement	Physical activity measurement	Identified associations between accelerometer-assessed physical activity and disease activity
Bachasson et al. [28]	Adult IIM cases	5 (DM = 1, IMNM = 3, ASS = 1)	Newly diagnosed		GENEActiv	14 days each month for 6 months	Wrist-worn	ENMO	Increasing ENMO followed decreasing CK and increasing SF-36 (no formal statistical test reported)
Stephens et al. [21]	JDM	15	Not reported		Actical accelerometer	7 days	Right hip	Time spent light, moderate or vigorous physical activity	Not reported
Mathiesen et al. [22]	JDM	31	Range 2–36 years		ActiGraph GT1M accelerometer	7 days	Not explicitly described[a]	Counts per minute	Not reported
Pinto et al. [23]	JDM	19	Mean 7.6 years (SD 3.2)	Healthy controls (n = 19)	ActiGraph GT3X	7 days	Elastic belt at the waistline	Time spent light, moderate or vigorous physical activity	Longer disease duration was associated with more time spent in a sedentary state (p-value = 0.026) Current glucocorticoid use was associated with more time spent in a moderate to vigorous physical activity state (p-value = < 0.001)
Pinto et al. [24]	JDM	19	Mean 7.6 years (SD 3.2)	JSLE (n = 20)	ActiGraph GT3X	7 days	Elastic belt at the waistline	Time spent light, moderate or vigorous physical activity	Not reported
Riisager et al. [25]	JDM	21	Median 3.4 years (range 1.4–10.3)		Sense Wear accelerometer	Two 3 day periods of data collection, 12 weeks apart	Armband on upper arm	Number of steps in 48 h period	Accelerometer-assessed physical activity improved from 16,412 to 21,079 steps per 48 h period following a 12 week exercise programme (p-value = 0.015)
Habers et al. [26]	JDM	26	Median 4.4 years (0.8–11.4)	Intervention (home-based exercise programme) group vs control group	Actical	7 days – carried out three or four times throughout the study	Not explicitly described[a]	Time spent in inactive, light, moderate or vigorous physical activity	No change in accelerometer-assessed physical activity between intervention (treadmill and strength exercise programme) and control groups (p-values = > 0.05)
Berntsen et al. [27]	JDM	45	Mean 20.8 years (SD 11.9)	Healthy controls (n = 45)	Actigraph GT3X	8 days	Dominant hip	Time spent in inactive, light, moderate or vigorous physical activity. Counts per minute	Shorter mean daily time spent in moderate to vigorous physical activity in inactive JDM group, compared to active JDM group (p-value = < 0.01)

[a]Manufacturer recommends the device to be worn on the waist at the mid-axillary line

IIM Idiopathic inflammatory myopathy, *JDM* Juvenile dermatomyositis, *DM* Dermatomyositis, *IMNM* Immune-mediated necrotising myopathy, *ASS* Anti-synthetase syndrome, *SD* Standard deviation, *JSLE* Juvenile systemic lupus erythematosus, *CK* Creatine kinase, *SF-36* 36 Item Short Form Survey, *MMT-8* Manual muscle testing, *ENMO* Euclidean norm minus one

Table 2 Reported accelerometer-derived physical activity levels in myositis cohorts

Authors		Counts per minute	Mean no. steps in 48 h	Sedentary % of day	Light % of day	Moderate % of day	Vigorous % of day	MVPA % of day
Riisager et al. [25]	Pre-training *N* = 21		16,412					
	Post-training		21,079					
Habers et al. [26] [a]	Pre-training *N* = 26			83.0	14.0	2.8	0.1	2.9
	Post-training			80.0	15.0	4.6	0.1	4.7
Stephens et al. [21] [b]	*N* = 15			37.7	12.3	1.4	0.6	2.2
Pinto et al. [23] [b]	JDM cohort *N* = 19			69.4	28.0			3.7 [c]
	Control cohort *N* = 19			66.1	29.3			4.6 [c]
Berntsen et al. [27] [b]	"Active" disease *N* = 16	351 [d]		38.0	11.9			3.5 [e]
	"Inactive" disease *N* = 29	321 [d]		40.6	11.8			3.0 [e]
	Control group *N* = 45	423 [d]		39.4	11.3			4.2 [e]
Mathiesen et al. [22] [b]	< 18 years of age N = 19	513						
	> = 18 years of age *N* = 12	322						

[a]Accelerometer device was worn throughout 24 h periods for 7 days
[b]Accelerometer data from non-sleeping hours was analysed
[c]*P*-value > 0.05 derived from Mann-Whitney U-test
[d]*P*-value < 0.01 derived from Wilcoxon signed rank test
[e]*P*-value < 0.01 derived from t-test
JDM Juvenile dermatomyositis, *MVPA* Moderate to vigorous physical activity

worn on the hip at the mid-axillary line. The site of accelerometer placement has an important impact upon study methodology, data interpretation and analysis. For example, walking speed estimation may vary between arm and thigh-worn accelerometers, as arm swing may limit accurate estimation. Studies have attempted to identify the most appropriate site of body placement in healthy states and certain disease areas [29–32], however each research question necessitates careful consideration of body site placement to ensure the provision of appropriate data. With myositis predominantly affecting proximal limb muscles and subsequently affecting gait, as described previously, it is plausible that lower limb placement would be most appropriate.

Duration of data collection

The duration of accelerometer data collection varied between each study. Duration of accelerometer data collection periods ranged from seven to 84 days. Most studies collected accelerometer-derived data continuously throughout 7 day periods. However, studies by Riisager et al. [25] and Habers et al. [26] recorded two separate periods of accelerometer data, prior to and following 12 week exercise intervention programmes, with the aim of assessing for the effect of the intervention upon physical activity. A data collection period long enough to detect changes of disease activity is required; short 7 day periods may limit the ability to detect substantial change. The use of two separate data collection periods by Riisager et al. and Habers et al. may improve the ability to detect changes in disease activity without the need for prolonged, continuous periods.

Accelerometer-derived physical activity levels in myositis populations

Quantifiable levels of accelerometer-derived physical activity were reported by a number of the identified studies (Table 2) and comparison across studies revealed a number of relationships.

Time Spent in MVPA was the most commonly reported accelerometer-derived physical activity measurement [21, 23, 26, 27]. Across all studies, where reported, myositis populations spent similar proportions of time in MVPA, ranging from 2.2–3.7% (prior to intervention, where applicable), thus indicating consistency, despite variations in devices employed and populations studied.

When compared to control cohorts, physical activity levels appeared to be lower in myositis cohorts; however study limitations, such as small populations, limit

Fig. 3 Wrist worn GENEActiv accelerometer device. Reproduced with kind permission of Activinsights

identification of definitive differences. Both Pinto et al. [23] and Berntsen et al. [27] demonstrated that their JDM populations spent less time in MVPA, compared to healthy controls: Pinto et al. reported that their JDM cohort spent 3.7% of each day in MVPA, compared to 4.6% in the control cohort, although this difference did not reach statistical significance (Mann-Whitney U-test p-value > 0.05), possibly in part due to the small ($n = 19$) cohort size. Berntsen et al. [27] demonstrated that their JDM group spent 3.5% of each day in MVPA, compared to 4.2% in the control group (t-test p-value < 0.01). Berntsen et al. also demonstrated a significantly lower CPM level in their JDM group, compared to the control group: 351 vs 423 CPM, respectively (Wilcoxon signed rank test p-value < 0.01). Mathiesen et al. [22] reported mean counts per minute from a JDM cohort – 513 in those younger than 18 years. Although they did not directly compare these findings with a healthy control population within the same study, they did compare against reference values from a study of healthy 9 and 15 year old children by Andersen et al. [33], who reported similar physical activity levels ranging 412–789 CPM. These comparisons suggested no statistically significant difference to the age and sex-matched healthy controls.

Associations between accelerometer-derived physical activity data and myositis disease activity

Five out of the eight studies investigated associations between accelerometer-derived physical activity data and myositis disease activity variables/states. Only one of these studies (Bachasson et al. [28]) primarily aimed to investigate this association whilst the other studies reported associations whilst investigating other relationships [23, 25–27].

Bachasson et al. [28] and Riisager et al. [25] each investigated the association between accelerometer-derived physical activity and a number of myositis disease activity measurements including muscle strength via MMT-8 scores, which, as discussed previously, is a valid measurement of disease activity. Bachasson et al. reported a positive association, whereas Riisager et al. did not. Bachasson et al. found that improvement of accelerometer-derived data (ENMO), using GENEActiv devices, followed longitudinal improvements in MMT-8 scores, CK levels and Short Form Health Survey (SF-36) questionnaire scores over the first 6 months after diagnosis and treatment initiation. No formal statistical analysis was carried out due to the small study population size ($n = 5$). The ENMO ranged from 12 to 22 mili g (a unit of acceleration) at baseline and 22 to 45 mili g after 6 months of treatment. This increase, however, may not represent a meaningful change, with a study by Bakrania et al. demonstrating GENEActiv-derived mean ENMO values of 8 mili g for standing still and 65 mili g for "self-paced free living walking" [34]. Although increased ENMO was associated with stronger (higher) MMT-8 scores, the relatively high baseline values (range 105–140, maximum value = 150) precluded detection of substantial increases after 6 months of treatment (range 145–150), due to ceiling effect. The observed increase of ENMO also corresponded with reductions of CK (baseline range 1375–6366 IU/L, 6 months after treatment initiation range 50–300 IU/L), which indicates reducing disease activity, and increase in SF-36 scores (baseline range 20–40, 6 months after treatment initiation range 48–90), which indicate improving quality of life. The authors therefore concluded that associations exist between myositis disease activity and ENMO-derived physical activity.

Pinto et al. [23] investigated associations between physical activity intensity (represented by number of counts per minute recorded via Actigraph GTX accelerometers: < 100 cpm = sedentary, > 100 and < 2295 cpm = light and > 2295 cpm = moderate-to-vigorous) and a number of myositis disease activity measures including the CMAS, the CHAQ,

disease activity score (DAS), manual muscle testing, CK levels, current and cumulative dose of glucocorticoids and disease duration [23]. Analysis was performed via calculation of Pearson's correlation coefficients; no adjustment for potential confounding variables, such as age or gender, was performed. They identified that increased time spent in a sedentary state ($r = 0.65$, p-value = < 0.01) and shorter time in moderate to vigorous physical activity state ($r = -0.51$, p-value = 0.03) was associated with longer JDM disease duration. Further, they identified that more time spent in a moderate to vigorous physical activity state was associated with current glucocorticoid use ($r = 0.75$, p-value = < 0.01). They reported no association between physical activity and the CHAQ ($r = -0.27$, p-value = 0.27) and a number of other myositis disease activity assessment methods, including the PEDS-QL ($r = 0.07$, p-value = 0.78).

Riisager et al. [25] measured physical activity (via the number of steps detected in a 48 h period using an accelerometer-containing Sense Wear armband) along with the MMT-8 and the CMAS, prior to and following a 12 week exercise bike programme. Although the number of steps in a 48 h period increased following the training programme (16,412 to 21,079, p-value 0.02), no corresponding change in MMT-8 or CMAS were identified (no raw figures or statistical comparison results were supplied).

Habers et al. [26] also investigated the change in accelerometer-derived physical activity (represented by percentage of time spent in inactive, light, moderate and vigorous activity states, as measured by an Actical device over a 7 day period) in a JDM population following a 12 week treadmill and strength exercise programme [26]. In contrast to the associations identified by Riisager et al. [26], Habers et al. [26] reported no change in accelerometer-derived physical activity following the exercise intervention. This is despite improvement of the median parental disability score (0.22 vs 0.18), as part of the CHAQ, which, as discussed previously, is a valid measurement of JDM myositis disease activity [26]. Statistical comparison of the pre and post-intervention values was not reported. Therefore, although direct associations between accelerometer-derived physical activity and myositis disease activity measurements were not investigated by Habers et al. [26], the absence of improvement in physical activity despite improvement of the CHAQ indicates that an association between the two may not exist.

The study by Berntsen et al. was the only one to compare physical activity levels between those with "active" and "inactive" disease activity, according to the PRINTO criteria for clinically inactive disease [35]. Disease duration, gender distribution and disease duration were similar between the two groups. The inactive group ($n = 29$) demonstrated similar, but significantly lower, physical activity levels to the active group ($n = 16$), according to duration in MVPA (3% vs 3.5% of day, respectively) and CPM (321 vs 351, respectively, Wilcoxon signed rank test p-value < 0.01). Although significant, the differences between the "active" and "inactive" groups are likely not substantial enough to constitute clinically meaningful differences. Associations with disease activity measurements were not investigated for, however both CPM and MVPA duration were found to be significantly associated with maximal oxygen uptake (VO_{2max}).

Discussion

The purpose of this narrative review was to 1) identify studies that have collected accelerometer-derived physical activity data in studies of myositis populations, 2) collate and compare reported physical activity data and 3) investigate if these studies identified associations between physical activity and measures of myositis disease activity.

Firstly, we have identified that the use of accelerometer-derived physical activity data in myositis research is limited. The cause is likely multifactorial, with limited awareness of the potential benefits of accelerometer use, additional cost incurred and limited analysis expertise, each contributing. Additionally, the small number ($n = 8$) of studies that have collected such data do so under incompatible protocols, which makes direct comparison challenging and may account for some of the conflicting findings across these studies. No study included more than 45 participants, thus potentially limiting the ability to form clear conclusions. Forming a study cohort large enough for sufficient statistical power is limited by the rarity of the IIMs (incidence of 11/million person-years, prevalence of 14/100,000).

Accelerometer use in myositis is still in its infancy, and so it is useful to reflect on how such devices are furthering knowledge in other disease areas. Studies have been able to differentiate the severity of stroke by comparing morning peak of accelerometer-derived physical activity [36, 37]. In multiple sclerosis, disease-specific "count cut-points" were developed, thus allowing intensity of physical activity to be measured [38, 39]. However, in musculoskeletal disease, where there is a direct link between disease and locomotion, research has to date been less extensive but is beginning to provide important insights. For example, it has been demonstrated that accelerometer-derived data can detect improvement of physical activity following treatment initiation in patients with rheumatoid arthritis [40].

Quantification of physical activity using proportion of time spent in MVPA appeared consistent across studies of myositis populations and, where available, comparison of MVPA and CPM against healthy controls indicated lower physical activity levels. It is likely that the observed reduced MVPA and CPM are due to diminished muscle

strength capability and exercise tolerance as a result of active myositis or myositis-induced muscle damage. Therefore, accelerometer-derived physical activity measurements may provide a useful method of quantification of differences of exercise tolerance between myositis and control populations, however further dedicated research in larger longitudinal cohorts will be required to fully clarify this capability.

A subset of the reviewed studies ($n = 5$ [23, 25–28]) have revealed insights into associations between accelerometer-derived physical activity data and myositis disease activity. Higher levels of physical activity were associated with lower CK (indicating diminished myositis) and improved SF-36 in an adult cohort [28] and shorter disease duration and current glucocorticoid use (mean dose 4.2 mg/day) in a juvenile population [23]. Further, the utility of accelerometer-derived physical activity data to detect changes following a 12 week exercise programme in a JDM cohort was illustrated by Riisager et al. where step count per 48 h increased [25]. This is in contrast to a study by Habers et al. which reported no detection of change in accelerometer-derived physical activity following a 12 week exercise intervention, despite changes in muscle function tests [26]. These studies' findings also indicate that a relationship between accelerometer-derived physical activity and a number of disease activity measures (including the CHAQ, CMAS and MMT-8) may not exist, as no significant associations were identified. Detection of associations between accelerometer-derived physical activity and changes in the MMT-8 may have been limited by a ceiling effect, as demonstrated by Bachasson et al. [28]. Only one study compared accelerometer-derived physical activity between myositis cases with "active" and "inactive" disease. Interestingly, significantly lower levels of physical activity (CPM and mean daily MVPA duration) were reported in the "inactive" group. Unmeasured factors, such as degree of muscle damage, current treatment and involvement in previous exercise programmes was not reported. Therefore, unfortunately, the limited number of studies and their sample sizes preclude firm conclusions, but it remains plausible that physical activity may be a useful future surrogate measure for myositis disease activity with some early, promising observed associations.

Further research to investigate the utility of accelerometer-derived physical activity data in the IIMs and identify associations with myositis disease activity is warranted. Quantification of myositis disease activity would ideally be carried out longitudinally alongside continuous collection of accelerometer-derived physical activity data. In addition to disease activity, the IMACS Core Set Measures can quantify cumulative damage and differentiate between the two [7]. Therefore, a study to investigate the relationship between serial changes of accelerometer-derived physical activity data and the IMACS Core Set Measures may be the most appropriate approach. This approach could be complemented by additional frequent (i.e. daily) collection of disease activity proxy-measurements, such as patient reported outcome measurements; this approach has shown promise in a recent study in a population with rheumatoid arthritis [41]. None of the identified studies used the high sampling rate of accelerometers to identify changes of physical activity across short time periods, such as day-to-day. This approach has provided important insights in other disease areas, such as Parkinson's disease [42]. Investigation into the association between short term (e.g. daily) temporal changes of physical activity in IIM cases could identify previously unrecognised variation of disease activity and potentially response to treatments in a clinical trial setting. Further, no identified study collected accelerometer data over periods longer than 6 months. Measurement of long term changes of accelerometer-derived physical activity may aid IIM disease course characterisation and identify factors predictive of relapse and remission, such as demographics, clinical features or the presence of myositis specific autoantibodies [43].

Identification of the appropriate method of collection of accelerometer data in IIM populations is required. Standardisation will improve comparison between studies and should allow replication of significant findings. Aspects of standardisation to be investigated include type of device, bodily site of placement, duration of data collection and reporting data format (i.e. raw data vs. derived physical activity measures). However, important disease manifestation differences within the IIMs must be considered, for example predominantly proximal muscle weakness in DM, compared to distal weakness in inclusion body myositis; investigation into each IIM subtype should therefore be considered, allowing focused standardisation.

The most appropriate method of processing and analysing accelerometer-derived data for the IIMs may be distinct from other musculoskeletal conditions and should be identified. For example, particular gait variations in the IIMs, as discussed previously may impact identification of steps and calculation of step count. A full description of the wide variety of algorithms for processing and analysing accelerometer-derived data is outside the scope of this review, however the implementation of "machine learning" techniques for data segmentation and detailed physical activity characterisation, which have proven fruitful in other rheumatological disease areas [44, 45], is promising.

Conclusions

In summary, this narrative review has identified and summarised the small number of studies that have used accelerometer-derived physical activity measures in IIM populations and investigated for associations with myositis

disease activity. Promisingly, a subset of these studies identified that a number of validated measures of myositis disease activity are associated with accelerometer-derived physical activity, including CK level, disease duration and glucocorticoid use. However, limited or no association was found with a number of other disease activity measures, including the CHAQ, CMAS and MMT-8. Further research into this potentially worthwhile area is warranted, with the aim of developing the most appropriate method of collection of accelerometer-derived physical activity data in IIM populations and clearly delineating relationships with disease activity measures.

Abbreviations

CHAQ: Childhood Health Assessment Questionnaire; CK: Creatine kinase; CMAS: Childhood Myositis Assessment Score; DAS: Disease activity score; DLW: Doubly labelled water; DM: Dermatomyositis; ENMO: Euclidean norm minus one; FI-2: Functional Index-2; HAQ-DI: Health Assessment Questionnaire - Disability Index; IMACS: International Myositis Assessment and Clinical Studies Group; JDM: Juvenile dermatomyositis; MAP: Myositis Activity Profile; MeSH: Medical subject headings; MMT: Manual muscle testing; MVPA: Moderate to vigorous physical activity; PEDS-QL: Paediatric Quality of Life Inventory; PM: Polymyositis

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Authors' contributions

AO lead the review process and extracted relevant data. ML and WD provided expert guidance and perspectives on interpretation of accelerometer-derived physical activity results. HC provided overall supervision. All authors (AO, ML, WD, HC) had input to the study design, interpretation of results and read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Chapter 3

3 Qualitative insights into IIM symptom patterns and limitations of the current model of IIM clinical care

"There is nothing more deceptive than an obvious fact."

Sherlock Holmes
The Boscombe Valley Mystery[170]

3.1 Introduction and rationale

The current model of IIM clinical care risks inaccurate patient assessment, which can adversely affect formation of patient management, as described in the introduction. I realised early on that patients who have first-hand experience of the current model of IIM clinical care could provide invaluable insights into this area. I therefore decided to carry out in depth qualitative interviews with patient participants recruited to my PhD research study - the Myositis Physical Activity Device (MyoPAD) study.

I was also struck by the discordance between patient and clinician priority of manifestations of IIMs reported by Mecoli *et al*, where symptoms such as fatigue were ranked highly by patients, whereas clinicians prioritised lung involvement and dysphagia[29].

I particularly wanted to explore patient experiences on pain and the relationship with disease activity; this is in part due to the general acceptance among clinicians that the

IIMs manifest with "painless weakness", which previous qualitative research indicates is not true.

Finally, I wanted to particularly explore to what extent participants felt that their symptoms vary. This is in part to explore the utility of daily symptom monitoring.

This chapter therefore aims to answer the following questions:

- How do patients view the current model of IIM clinical care?
- What symptoms are most important to them?
- Do symptoms remain constant or vary?
- Do patients perceive currently available methods, such as CK level or MMT, to be accurate measurements of IIM disease activity?

3.2 Description of contribution

I designed the MyoPAD study protocol along with my supervisory team. I lead the application for ethical approval and funding. I recruited and enrolled each participant and carried out the one-on-one interviews prior to and after each participant's 91 day study period. I analysed collected qualitative data under the supervision of Dr Kelly Howells (Co-Supervisor). I prepared the manuscript and assimilated amendments from my supervisory team.

Results from interviews before and after each participant's 91 day study period form the basis of this Chapter and also contribute to exploration of engagement barriers/enablers in Chapter 4.

I used "grounded theory" as a method to identify underlying themes[171]. Grounded theory involves using collected qualitative data to identify themes without pre-existing conceptualisations. "Open-coding" is used to assign concepts to key phrases. These codes are then subsequently grouped into over-arching themes. This approach was used to ensure that pre-existing assumptions regarding IIM-related symptoms were not instrumental in theme formation. Other approaches, such as phenomenology and ethnography may have risked introduction of pre-existing conceptualisations.

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3.3 Manuscript 2

Patient insights on living with idiopathic inflammatory myopathy and the limitations of disease activity measurement methods – a qualitative study

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Patient insights on living with idiopathic inflammatory myopathy and the limitations of disease activity measurement methods – a qualitative study

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Abstract

Background: The idiopathic inflammatory myopathies (IIMs) are chronic autoimmune conditions, typically resulting in proximal muscle weakness and impacting upon quality of life. Accurate measurement of IIM disease activity is imperative for appropriate medical management and carrying out valid clinical trials. The International Myositis Assessment and Clinical Studies Group (IMACS) "Disease Activity Core Set Measures" are the current gold-standard of IIM disease activity assessment. Anecdotally, patients with an IIM report that the IMACS Core Set Measures and other available methods do not necessarily capture their perceived disease activity. Investigating the patient experiences of living with an IIM and their views on the accuracy of the IMACS Core Set Measures will provide valuable insights for both clinical and research purposes.

Methods: Eighteen interviews with patients with an IIM were carried out and analysed thematically, using a grounded theory approach. Experiences on living with an IIM and perceptions on the accuracy of disease activity measurement methods were explored.

Results: Interview analysis revealed four themes: 1) fatigue, 2) pain, 3) day-to-day symptom variation, 4) limitations of creatine kinase levels and manual muscle testing.

Conclusions: This study has provided valuable insights into patient experiences of living with an IIM. Aspects of IIM disease activity perceived not to be wholly measured by the IMACS Core Set Measures have also been identified. These findings have implications for future IIM clinical care and research, in particular providing justification for research into pain, fatigue and symptom variation.

Keywords: Myositis, Qualitative, Outcome assessment, Pain, Fatigue

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Background

The idiopathic inflammatory myopathies (IIMs) are a group of chronic autoimmune conditions that can lead to widespread inflammation and damage [1, 2]. A number of clinical IIM subtypes are recognised, including dermatomyositis (DM), juvenile DM (JDM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), anti-synthetase syndrome (ASS), and sporadic inclusion body myositis. A wide variety of IIM manifestations can occur, including muscle inflammation (myositis) of proximal limb muscles leading to weakness [3–6], skin inflammation, interstitial lung disease and an increased malignancy risk. The disease course is variable, with many patients reporting unpredictable episodic exacerbations of symptoms and disability [7].

Living with IIMs can impact significantly on quality of life [7–9]; this impact on quality of life being a combination of disease manifestations, requirement of repeated medical interactions and treatment complications.

Extensive qualitative research by OMERACT has investigated the impact of living with IIM [10–13]. Focus groups, one-on-one interviews and a Delphi survey identified a number of themes, which included 1) predominance of pain and fatigue, 2) the emotional consequence of the disease, 3) symptom variability, 4) limitations in participation in society, 5) impact of relationships with healthcare providers, 6) insomnia and 7) cognitive dysfunction. Identification of these themes has informed subsequent research and development of IIM-specific outcome measurements, such as the Myositis Activities Profile [14] and the Functional Index [15].

"Disease activity" is defined as the features of a disease that are potentially reversible with treatment, such as active myositis, whereas "disease damage" refers to permanent and irreversible features that are a consequence of disease activity, such as muscle fibrosis [16]. Accurate assessment of disease activity is imperative to allow for appropriate medical management. A number of valid measurements of myositis disease activity have been combined into the International Myositis Assessment and Clinical Studies Group (IMACS) "Disease Activity Core Set Measures" [17], which is currently used as the gold-standard of IIM disease activity assessment. The IMACS Disease Activity Core Set Measures include manual muscle strength testing (MMT), blood tests for creatine kinase (CK) levels, the Health Assessment Questionnaire (HAQ) (a validated measure of functional ability), and both patient and physician "global assessment" of disease activity. These measurements can be used in both clinical and research settings when disease activity quantification is required.

Anecdotally, many people with an IIM report that the IMACS Disease Activity Core Set Measures, and other clinical methods, such as MRI scanning, do not necessarily capture their own perception of disease activity. This discrepancy between clinical measurement and patient-perceived disease activity may result in an incomplete quantification of disease activity, thus limiting and misfocusing clinical interventions otherwise aimed to improve symptoms, quality of life and function.

Investigation of the patient-perceived accuracy of IIM disease activity assessment methods may provide insights that will inform future development of new outcome measurements or the tailoring of existing methods. Also, further understanding of the patient-experience can assist health care professionals to better comprehend the impact of living with IIM.

In this study, we conducted qualitative interviews to understand the patient experience of living with IIM and their perceptions of the ability of currently available methods to measure IIM disease activity accurately.

Methods

Recruitment and qualitative interviews were carried out as part of the Myositis Physical Activity Device (MyoPAD) study. The study aimed to design and trial the MyoPAD system, which entails a smartphone-based app, allowing entry of daily PROMs, and a thigh worn accelerometer sensor, which allows for remote and continuous characterisation of gait parameters. Results of quantitative analysis of data collected through the MyoPAD study will be published separately. This paper will report the results of analysis of qualitative interview data, collected at the time of recruitment.

Participants were recruited from the specialist neuromuscular clinic at Salford Royal Hospital, Salford, UK. Participants were invited to join the MyoPAD study if they were aged 18 years or over, had a physician-verified IIM diagnosis (International Myositis Classification Criteria Project [18] or European Neuromuscular Centre [19] criteria) of PM, DM, IMNM or ASS, owned their own smartphone (Apple or Android; to allow daily app data entry) and had regular access to their own Wi-Fi connection (to allow frequent data transfer). Participants unable to enter data via an app or walk independently were excluded from recruitment. Participants unable to converse in English were also excluded as the study did not have capacity to conduct interviews in another language.

All participants were invited to interviews (maximum 1 hour in duration) at their time of recruitment to the MyoPAD Study. Participants received an information sheet prior to the interview with a list of possible areas of discussion. A.O. conducted all interviews, which took place in Salford Royal Hospital's Clinical Research Facility. Participants were given the option to attend the interview with a partner or friend who were also invited to contribute to the discussion where appropriate

following verbal consent from the participant. Interviews followed a semi-structured format with pre-prepared interview guides (see Supplementary Material for interview topic guide). Interviews were audio-recorded and transcribed.

During the interview, participants were invited to discuss the following: their experiences of living with an IIM, symptoms, symptom variability, perceived ability to convey symptoms during a clinical consultation, and views on current methods of IIM disease activity measurement. Participants were also invited to discuss aspects of living with an IIM that they perceived to be under-recognised or not fully assessed in clinical consultations.

Interview transcript data was analysed thematically, using a grounded theory approach [20]. Coding was carried out by A.O. and K.H. using NVivo qualitative data analysis software (QSR International Pty Ltd., Version 11, 2015). Initial coding formed the basis for long descriptive accounts of the coded data that were circulated, discussed and refined during analysis meetings between A.O. and K.H. Initial codes were grouped to form core thematic categories based on multiple sources of interview data.

The Greater Manchester Central Research Ethics Committee approved the study (ref. 18/NW/0676). Informed written consent was provided by all study participants prior to interviews. Consent included permission to record interviews and reproduce anonymised quotations.

Results

Eighteen (61% female) participants with a verified IIM diagnosis took part in the interviews. Four participants were accompanied by a friend or partner; only one partner quotation contributed to theme formation. The median age of the cohort was 52 years (IQR 44, 56) with a median IIM disease duration of 5 years (IQR 2, 6). Analysis of baseline interview data revealed four main themes. Each theme will be discussed in turn, with accompanying quotations (Table 1).

Fatigue

Fatigue, as a manifestation of reduced physical endurance, was the most common and prominent symptom, and was reported by all participants (Textbox quotations 1 and 2). Activities of daily living (ADLs) were frequently reported to be affected by fatigue. In particular, ADLs that require sustained shoulder abduction, such as hair drying/styling and telephone use, were frequently reported to be affected (Textbox quotation 3). In contrast, participants reported less impact upon shorter duration tasks, such as dressing; some also reported tailoring their ADLs to purposefully include such short duration needs of exertion (Textbox quotation 4). The impact of fatigue upon their ability to wash, dress or care for children was a source of great concern for a number of participants (Textbox quotation 5).

A number of participants reported instigating strategies to help cope with or ameliorate their fatigue, which include planning "rest days" (Textbox quotations 6 and 7).

Fatigue was reported to be a more important symptom compared to perceived muscle weakness, which was not associated with perceived variations of disease activity or a factor that directly impacts upon quality of life (Textbox quotations 2 and 8). Multiple participants explained that fatigue is not commonly assessed or addressed during clinical consultations. A reduced awareness amongst clinicians of fatigue as an IIM-related symptom was suggested as a possible reason for this omission (Textbox quotation 9).

Travel was reported to be a particularly fatigue-inducing activity, with a number of participants reporting limiting their travel to only the essential. Also, the need to plan all aspects of travel details, such as the presence of steps or slopes, the location of rest facilities and the assurance that an emergency contact be available, was a source of concern and sense of limitation to a number of participants, their partners and families (Textbox quotation 10). This need to meticulously plan all travel, even short distances, appeared to add to a sense of loss of independence and their condition dominating many aspects of their life.

Pain

Second to fatigue, pain was a key symptom. The character of pain was reported in a number of different ways, including "spasm", "muscle burning", "feeling like you've run a marathon", and so severe that "it does bring you to tears", however it was generally reported that conveying the nature of the pain was difficult (Textbox quotation 11).

Pain was noted to be linked to carrying out physical activities, even of low intensity. The occurrence of pain whilst carrying out daily activities was a particularly troublesome symptom (Textbox quotation 12). A number of participants acknowledged that pain may only be experienced when they exceed a certain level of duration of physical exertion, typically associated with certain ADLs. Participants reported needing to therefore be more purposeful and deliberate in planning and executing ADLs, choosing which were essential and which can be postponed until they felt capable.

Day-to-day symptom variation – characterisation of good and bad days

Symptom variation was reported by the majority of participants. Many participants reported that symptoms, particularly fatigue and pain, varied on a day-to-day or even hour-to-hour basis (Textbox quotations 14 and 15). Many participants recognised the occurrence of "good"

Table 1 Quotations from participants

Quotation number	Quotation
Fatigue	
1	*"I would say that the fatigue has more of an effect than the pain. Sort of, I get aches but that's not the worst but, it's just the sort of real exhaustion that is the worst."*
2	*"Fatigue is my main component. I think for me rather than muscle weakness and rather than pain it's fatigue, concentration and focus."*
3	"So washing my hair is not too bad and then when I'm coming to dry my hair, that can be difficult, holding my hands up."
4	*"What I've been able to maintain is like, short, sharp things. So if I have to do something quite quick, it doesn't bother me."*
5	*"My daughter likes her in plaits, and trying to plait her hair, that can get quite tiring, I have to rest my arms."*
6	*"Then you start to do daily chores like having a shower or, in my case because I've got a little girl; making breakfast for her, helping her to get dressed, ironing her uniform for school. All of those day to day things that you used to do without thinking about it; adjusting the shower head, washing your hair."*
7	*"I know tomorrow is going to be a rest day because of the drive today."*
8	*"Profound weakness with my myositis seems to be much more background."*
9	*"I think the fatigue side seems to be missed quite a bit, that's never sort of talked about too much, it's more just "what's your strength" and "are you breathing okay"."*
10	*P12's partner: "The logistics. Where is the toilet going to be? You know, where are the steps? You know, we have to plan everything. Everything [PARTICIPANT] does needs careful planning, because it could be detrimental to her wellbeing."*
Pain	
11	*"It's not pain, it's a really hard one to describe and I know other people will have said the same thing to you, it's not pain for me it's a muscle burning that I get. And I wouldn't describe it as painful, I'd describe it as uncomfortable but yeah you can feel something going on but it's really hard to explain and burning is the nearest I can get to it."*
12	*"I get, what I call proper pain and then, in my legs and arms if I lift them or try to lift anything or try to hold them up for a length of time, washing my hair, that kind of thing, then I'll feel like a burn like you get with extreme exercise."*
13	*"I don't feel that anyone [CLINICIANS] I've spoken to recognise pain as part of it."*
Day-to-day symptom variation – characterisation of good and bad days	
14	"*I will be fine one day, the next day I can feel absolutely terrible."*
15	*"I could be tired for an hour and be fine the next hour, particularly in the early days."*
16	*"There's a hill that leads up home, and if I'm having what I call a good day I can charge up it, and then a day where I know is a flare, I'll stop two or three times."*
17	*"But I just feel like I've been hit by a bus. And you just ache. But the next day everything's okay."*
18	*"I suffer greatly in the mornings, first thing. I can tell by the way I am first thing in the morning, I tend to get a grasp of how the day is going to go."*
19	*"You do tend to do far too much on the good days, and then you pay for it a couple of days later."*
20	*"There's definitely a finite resource with the fatigue effect and I know that's very difficult to quantify."*
21	*"My condition is up and down all over the place so it can almost change day on day, which is ridiculous. Family and friends, that's the hardest thing they struggle to get their heads around. I will be fine one day, the next day I can feel absolutely terrible."*
22	*"I think doctors can't understand either, that some days you can be quite well and other days you can be really, really bad."*
23	"*On the outside we look normal, we look well, you know, everybody says, "oh you look really well" … actually if they knew what a struggle it was for me to actually get to be somewhere … people don't recognise the exhaustion and the tiredness that can go with it and the effort you have to put into doing the simplest tasks."*
24	*"Myositis isn't a common condition, so people don't really understand what it is about so, therefore they're probably more reluctant to ask what that is… So, it's unknown isn't it. Therefore, people tend to respond to unknown things with oh yeah, yeah, you're looking okay, that's fine it must be difficult, but I don't think they quite know."*
25	*"A lot of people have said that they've come out of the doctor's office feeling quite frustrated because they haven't been able to convey to the doctor that they feel the way they do."*
26	*"Because I could have a really bad week in the first month after seeing the rheumatologist and then, by the time I've got there, I'm quite dapper and, you know, you walk in but, there's been them days where you are crying in pain or you just feel so fatigued and brain fogged that…so, yeah because it's so variable you can look totally different than you have been."*
27	*"Your brain tends to remember good days...unfortunately, your brain goes back to a healthy state quite quickly."*
28	*"So, I actually wrote it down in the book, sort of, what it was that started and when and how that had gone. So, I could go in and say this is what's happened because I knew I wouldn't remember what to say, this is how it was."*

Table 1 Quotations from participants *(Continued)*

Quotation number	Quotation
29	*"I get the CK checked once every few months, but that never correlates to having a flare."*
Limitations of CK levels and MMT as measurements of disease activity	
30	*"My own feelings are that I quite often feel worse than the results that come back from any of the tests [CK level] really."*
31	*"Although there is a three hundred limit for normal, when my CK score goes from about one-sixty, one-seventy to two-forty, two-fifty, it is still within the normal range but I am in full flare."*
32	*"I feel that because my CK levels have come down that I just feel that's what people are happy with and because it's all judged on that."*
33	*"I find medical professionals and different people interpret it [CK levels] in different ways."*
34	*"I could walk a short distance, but if I had to keep walking then I would really struggle and probably need to go to sleep afterwards. Like lifting an arm up, I can do it once but if I had to hold the arm up for any length of time, I wouldn't be able to do it."*
35	*"I don't think it gives a very accurate representation of strength because I think people try really hard to resist and showing how strong they can be, because that's your nature isn't it, you want to try and do well in it, but actually the effort that's involved can really exhaust you, and as much as anything it's repeating those movements."*
36	*"I think the fatigue side seems to be missed quite a bit, that's never sort of talked about too much, it's more just is what's your strength and off you go."*

CK creatine kinase, *MMT* manual muscle testing, *IIM* idiopathic inflammatory myopathy

and "bad" days, however these varied between participants and impacted upon their function in individual ways, depending on their lifestyle. Good days were characterised by increased physical stamina, thus allowing increased fulfilment of activities of daily living (ADLs), improved walking ability, a perception of higher energy levels and diminished or absent pain (Textbox quotation 16). In contrast, "bad days" were characterised by higher levels of pain and fatigue and the presence of malaise, resulting in difficulty carrying out ADLs (Textbox quotation 17). Participants commonly noted an ability to identify if they were going to experience a bad day according to their symptoms at the time of waking (Textbox quotation 18). A number of participants described more severe symptoms, such as pain and fatigue, in the days following a "good day" and suggested that this may be due to over-exertion (Textbox quotation 19).

Energy rationing, i.e. conserving one's own energy by carrying out only certain physical activities, was commonly reported, especially by participants with longer IIM disease durations, as a coping strategy to prevent debilitating fatigue associated with over-exertion. A number of participants expressed that only a certain amount of energy was available to them each day, which, if exceeded, would result in subsequent "bad" days characterised by worsening of symptoms including fatigue and pain. Further, the difficulty in quantifying this amount of energy was acknowledged (Textbox quotation 20). The finite amount of energy perceived to be available for a certain day was described as a "sugar cube" by one participant (P4), with them "constantly trying to offset" against physical exertion.

Symptom fluctuation was reported to be under-recognised by both family members/friends and clinicians (Textbox quotations 21 and 22). A number of participants explained that this non-recognition of symptoms and symptom variation may be due to the absence of clear visual indicators of illness or symptoms. This lead to a perception of IIM being an "invisible disease" (Textbox quotation 23). Participants explained the ensuing underlying frustration that non-recognition of IIM can cause, in part due to low levels of public awareness and rarity of the condition (Textbox quotation 24).

The combination of symptom variation, infrequent clinical review and perception of difficulty conveying the wide variety of symptoms was a source of concern reported by many participants (Textbox quotation 25). In particular, a number of participants recognised that the assessment at a clinic appointment may not capture fluctuations of disease activity since the previous assessment (Textbox quotation 26). A further reported limitation of infrequent clinical reviews is the difficulty to recollect, perhaps multiple symptom fluctuations that may have occurred months previously, with "good days" and improved symptoms being preferentially recollected, therefore potentially limiting the clinician's understanding of the patient experience (Textbox quotation 27). A small number of participants reported keeping a diary of symptoms, flare occurrence and perceived causes, thus improving symptom variation recollection at the time of appointment (Textbox quotation 28).

Limitations of CK levels and MMT as measurements of disease activity

Many participants provided detailed views on their perception of the ability of CK levels and MMT to assess IIM disease activity. The majority of participants explained their experiences of changes of CK levels not

corresponding to symptom fluctuations (Textbox quotation 29). Even the small number of participants who felt that the CK was associated with their disease activity felt that it underestimated the extent of their symptoms (Textbox quotation 30). The comparison of an individual CK level against the normal laboratory range was criticised, with participants perceiving the comparison to their own baseline perhaps being more appropriate (Textbox quotation 31). Further, a number of participants perceived that clinicians may base their assessment of IIM disease activity solely on the CK level, without taking extra-muscular manifestations into account (Textbox quotation 32). A number of participants also suggested that changes of the CK level is interpreted differently by various clinicians (Textbox quotation 33).

Drawbacks of MMT, as a measure of disease activity, were also reported by many participants, these included differing results between clinicians, the inability of MMT to assess fatigue on sustained muscle use and inability to capture day-to-day strength variation (Textbox quotation 34). Participants also noted the inability of MMT to assess endurance, which, as described earlier, is a major source of functional limitation. It was also reported that the MMT assessment may vary greatly depending on other factors, in particular patient motivation and a clinician's prior knowledge of weakness (Textbox quotation 35). A perception of clinicians relying predominantly on the MMT to assess disease activity was conveyed, with participants feeling that hidden symptoms, such as fatigue, would be missed, as described earlier (Textbox quotation 36).

Discussion

Our study aimed to understand the patient-reported experience of living with IIM and to explore patient perceptions of the ability of currently available methods to accurately measure disease activity. This qualitative study has provided a number of valuable insights.

Fatigue and pain were reported to be predominant symptoms, resulting in reduced function and impacting upon quality of life. Our findings replicate findings reported in a number of OMERACT studies, which, as mentioned earlier, investigated patient experiences of living with IIM and identified that both pain and fatigue were predominant symptoms. Of the small number of studies that have quantitatively measured fatigue and myalgia (muscle-related pain) in IIM populations, scores were typically high (mean 7/10 for fatigue and 4/10 for pain in DM) [21].

In combination with infrequent clinical reviews and perceived drawbacks of MMT and CK levels, participants felt that disease activity could not be wholly quantified by their clinicians. A number of studies have investigated the validity of MMT assessment and interpretation of CK levels. Both MMT and CK levels have been deemed to accurately represent IIM disease activity and therefore appropriately form two of the six IMACS Disease Activity Core Set Measures [17]. Rider et al reported high levels of convergent construct validity, internal reliability and inter-rater reliability [22]. In this study, disease activity was represented by physician global activity score, function (HAQ) and MRI changes, however fatigue and pain were not included. Development and validation of quantitative IIM-specific measurements of fatigue, pain and other symptom qualities, such as day-to-day variation, in the form of patient reported outcome measures could potentially enhance IIM disease activity assessment. OMERACT have recently recommended inclusion of pain and fatigue in the core set for IIM clinical trial outcome measures ("life impact area") and measurement instrument selection will be carried out in the near future [23]. This recognition of the importance of patient symptoms follows changes in 2014 for rheumatoid arthritis clinical trials when OMERACT added in fatigue to the Core Domain Set following patient participant focus group input [24, 25]. Participants reported that fatigue results in difficulty carrying out particular ADLs, such as combing hair or sustained telephone use. However participants perceived that such difficulties are not clearly captured or quantified in routine clinical practice. Although validated measurements of function, such as the HAQ [26] or SF-36 [27], assess such activities (e.g. ability to "wash and dry your body" – HAQ), these responses are assimilated into an overall conglomerated score, thus potentially falsely missing a patient's limited ability to complete such a task. Perhaps IIM-specific outcome tools, such as the Adult Myopathy Assessment Tool [28] or Functional Index [15], that measure task endurance could more accurately quantify functional limitation of ADLs.

Day-to-day symptom variation was reported by the majority of participants; this being in contrast to the traditional understanding of IIM-related symptoms being less variable. Regardt et al reported that symptom variation is an important facet of the IIMs [29]. This was in association with cognitive dysfunction, limitations in daily activities and participation in society. To our knowledge, no other study has investigated the detailed variations of IIM-related symptoms in either a qualitative or quantitative manner. It is imperative that, during a consultation, clinicians caring for people with IIM are able to understand variations of symptoms and their impact on quality of life. Further, infrequent clinical assessment, alongside frequent symptom variation, may risk inaccurate quantification of disease activity assessment. Inaccurate or selective recall may also impact consultations and comprehensive conveyance of symptoms, as described by our participants and reported in previous studies [30, 31]. Novel methods, such as collection of daily patient-

reported outcome measures, may provide a solution and allow quantification of symptom variation, for use in both clinical and research settings. Recent development of a smartphone-based method of daily symptom tracking in rheumatoid arthritis has demonstrated added patient benefit, enhancing clinical consultations and improving symptom variability recognition [32]; development of a similar method, tailored to the IIMs, could potentially remedy a number of limitations described by the participants of our study.

Finally, IIMs were felt to be an "invisible" set of diseases, with limited understanding from friends, colleagues and clinicians being a source of concern and social isolation. The concept of a hidden disease is present in other chronic conditions, such as rheumatoid arthritis [33], systemic lupus erythematosus [34] and fibromyalgia [35]. Difficulty in communicating symptoms to clinicians, friends, family members and colleagues is common in other chronic diseases that lack outward visibility [36, 37]. Both the hidden component of IIM and low awareness amongst the general and healthcare populations may further add to communication difficulties in social, professional and medical conversations. Again, novel continuous remote monitoring methods may facilitate reporting of hidden disease aspects and enhance clinicians' understanding. Impact of IIM upon "participation in society" was also reported from focus group work carried out by Regardt et al. [29] and Chung et al reported higher levels of social isolation, compared to rheumatoid arthritis, spinal osteoporosis and knee osteoarthritis [38]. Social isolation and a perception of lack of understanding from others is commonly reported in other disabling chronic conditions, such as rheumatoid arthritis [39, 40], Parkinson's Disease [41] and multiple sclerosis [42].

Strengths include the novelty of carrying out a detailed qualitative study in an IIM population with a particular focus upon participant-perceived accuracy of disease activity assessment methods. Another strength includes the fact that the demographics of the population mirror that of the general adult IIM population, thus potentially aiding generalisability, however this may be mitigated by recruitment bias, which is the most important potential limitation of this study. Although appropriate for the MyoPAD study, the exclusion criteria will have precluded certain sub-groups, such as those with more profound walking disability, whose experiences of living with an IIM may differ from our recruited cohort. Self-selection may also have occurred, with only particularly motivated patients agreeing to take part in one-to-one interviews, thus potentially excluding certain sub-groups. This potential recruitment bias may affect generalisability of findings, therefore validation of results in other IIM populations is warranted. Future qualitative research that includes a cohort with varying disease activity, disease duration and additional IIM subgroups broader cultural backgrounds is warranted and will provide a wider perspective on this topic.

Our findings have the potential to influence clinical practice in a number of ways. Clinicians should be mindful to assess regularly and quantify, where possible, pain and fatigue levels when reviewing IIM patients. Regular assessment of such symptoms with a focus on resolution as a treatment aim may influence self-management and positively impact patient quality of life. Clinicians should also be aware of frequent symptom variability and ensure enquiry into variation since the last assessment.

The predominance of pain and fatigue as major perceived symptoms of IIM are an important and key finding. Reporting of frequent symptom variability is also illustrated within our study. The model of conventional pre-planned and infrequent clinic appointments may impact on accurate disease activity assessment, and thus may not be helpful for our patients. A future research agenda into novel methods to address these issues could greatly enhance patient care. Other suggested research includes identifying if reported symptoms, including pain and fatigue, are due to IIM disease activity and/or damage; such distinction will allow for focused development of corresponding outcome measures.

Conclusions

In conclusion, our study has provided in depth qualitative insights into the patient-experience of living with IIM, highlighting that pain and fatigue are predominant symptoms, alongside frequent symptom variation and the impact of current methods of IIM disease activity assessment. Consideration should now be given to capturing pain and fatigue along with other routine clinical assessments in a more frequent manner for IIM patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s41927-020-00146-3.

Additional file 1.

Abbreviations

ASS: Anti-synthetase syndrome; ADL: Activities of daily living; DM: Dermatomyositis; HAQ: Health Assessment Questionnaire; IIM: Idiopathic inflammatory myopathy; IMACS: International Myositis Assessment and Clinical Studies Group; IMNM: Immune-mediated necrotizing myopathy; JDM: Juvenile dermatomyositis; MMT: Manual muscle testing; MyoPAD Study: Myositis Physical Activity Device Study; OMERACT: Outcome Measures in Rheumatology; PM: Polymyositis; SF-36: 36 Item Short Form Survey

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Authors' contributions
AO carried out participant interviews. KH and AO jointly analysed interview transcripts and identification of themes. HC, WD and KH provided study supervision. All authors (AO, HC, WD, KH) had input to the study design, interpretation of results and read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The Greater Manchester Central Research Ethics Committee approved the study (ref. 18/NW/0676). Informed written consent was provided by all study participants prior to interviews. Consent included permission to record interviews and reproduce anonymised quotations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Chapter 4

4 Participant engagement with daily PROM and continuous accelerometer data collection

"Data! Data! Data!" he cried impatiently. "I can't make bricks without clay."

Sherlock Holmes

The Adventure of the Copper Beeches[173]

4.1 Introduction

As described previously, the MyoPAD study aimed to design and test an mHealth system that allows for daily PROM collection and continuous accelerometer data collection, which can be used for gait pattern quantification. The MyoPAD study recruited 20 patient participants with an IIM and ran from August 2019 to January 2020.

I realised that it would be beneficial to explore the extent to which participants engaged with the MyoPAD system, in particular for potential future translation into clinical practice or research studies. Further, identification of enablers and barriers to engagement would help inform future iterations of the MyoPAD study and other similar mHealth studies.

This chapter therefore aims to answer the following questions:

- How well do participants engage with 91 days of daily PROM and continuous accelerometer data collection, as part of the MyoPAD study?
- What are the participants' views on taking part in the MyoPAD study?
- What enablers/barriers to engagement exist?

4.2 Description of contribution

I lead all stages of the MyoPAD Study from inception through to delivery under guidance by my supervisory team. I wrote the initial funding application for my fellowship, which secured required study funds. I also prepared the ethical application for the MyoPAD Study. The ethical application constituted a large piece of work that required coordination of involvement of a number of organisations (University of Manchester, Salford Royal Hospital, industry partners, Medicines and Healthcare products Regulatory Agency). Further, the atypical approaches used in the MyoPAD Study, particularly app and sensor use, required preparation of detailed data security, information governance and intellectual property evidence. Therefore, a large amount of time was dedicated to securing ethical application, which was granted in April 2019.

I worked alongside our two industry partners, ZiteLab and SENS Innovation, to design and tailor the smartphone-based app and accelerometer sensors used in the MyoPAD study. I recruited and enrolled all participants into the MyoPAD study and provided technical assistance, where required, throughout each participant's 91 day data collection period. I analysed all relevant data collected from the MyoPAD study under the supervision of my entire supervisory team.

This chapter's manuscript is currently in preparation for journal submission.

4.3 Manuscript 3

Engagement and participant experiences with smartphone-based daily patient reported outcomes and continuous gait pattern measurement - Findings from the Myositis Physical Activity Device Study

Background

The idiopathic inflammatory myopathies (IIMs) are a group of chronic diseases characterised by proximal muscle inflammation (myositis), weakness, and impaired walking pattern (gait) [24,25,52,174,175]. Patients with an IIM are typically cared for by a multi-disciplinary clinical team and are assessed at infrequent outpatient appointments, which are typically separated by long durations (typically 3-6 months). Relevant clinical information, such as objective disease activity assessment, the presence of symptoms, effect upon employment, flare occurrence and function, can only be collected at these individual time points. Such infrequent assessment potentially limits the quality of care provided, for example through non or late identification of worsening disease activity. IIM longitudinal research studies, including interventional clinical trials, are also potentially limited by infrequent data collection. Increased frequency of data collection could therefore potentially enhance IIM clinical care and longitudinal research.

The "digital healthcare revolution" and recent advances in frequent remote monitoring via increasingly ubiquitous personal devices (e.g. smartphones) have the potential to enhance the traditional model of treatment efficacy assessment in both research and clinical settings[88,115,176]. REMORA, a recent mobile-health (mHealth) study, demonstrated the feasibility and benefits of collection of daily patient-reported outcome measurements (PROMs) via a smartphone-based application (app) integrated into clinical care, with data also made available for research[177].

Other mHealth studies have demonstrated the feasibility and accuracy of continuous remote gait pattern assessment via wearable accelerometer devices in a number of disease areas[135–137,178]. Accelerometers are small, non-invasive, lightweight, portable devices that can measure acceleration in one or more geometric plane, multiple times per second[123–126]. The resulting acceleration pattern can then be used to accurately identify important components of the gait cycle, thus characterising gait. Such methodology may provide novel insights of treatment efficacy in diseases, such as IIM, that impact walking pattern.

Therefore, daily PROMs, in combination with objective and continuous measurement of gait pattern, could form the basis of novel and accurate outcome measurements for use in IIM research trials and clinical settings. The Myositis Physical Activity Device (MyoPAD) Study designed and tested a smartphone and accelerometer-based system to improve IIM disease activity measurement via remotely collected PROMs and gait pattern. Assessment of engagement (i.e. degree of participant involvement) with the MyoPAD system and identification of enablers/barriers to engagement will inform future studies and delineate feasible clinical/research applications. In summary, this study aimed to:

- Quantify participant engagement with the MyoPAD system throughout a 91 day study period
- Investigate participant experiences of taking part in the study, thus identifying engagement enablers and barriers

Methods

The MyoPAD system comprises a smartphone-based app, which allows entry of daily PROMs, and a thigh worn accelerometer sensor, which allows for remote and continuous characterisation of gait parameters.

A draft study protocol, outlining potential study duration, app functionality, frequency of PROMs, and use of accelerometer sensors, was drawn up by the study team. A list of potential PROM questions, divided into daily, weekly and monthly sets, was also prepared. A focus group with IIM patient participants (N = 5) was hosted. Topics discussed included app functionality (interface, question frequency and content, answer format), acceptable use of a wearable accelerometer sensor and study duration. The study protocol was subsequently amended to include suggestions made during the focus group. A final set of PROM questions was decided by the study team, incorporating feedback from the focus group.

Domains of IIM disease activity to be assessed via PROMs included patient global assessment, pain (global and myositis-related), fatigue, sleep, weakness, mood, function, flare occurrence and impact upon employment. PROMs were compiled (Table 4) from the Health Assessment Questionnaire (HAQ) [60], the Consensus Sleep Diary[179], IMACS Disease Activity Core Set Measures[56], and Work Productivity and Activity Impairment Questionnaire[180]. Daily function was assessed using three individual

questions taken from the HAQ; these three PROMs were chosen due to these abilities (washing and dressing, walking outdoors, walking up steps) having been prioritised by focus group participants. Also, weekly function was assessed using two PROMs taken from the HAQ (ability to carry shopping, ability to pick up clothes from the floor) as these abilities were deemed to change on an, at most, weekly basis by the focus group participants. Three participants subsequently tested the app prototype over 10 day periods; suggested functionality amendments were implemented where possible, thus resulting in the final protocol.

Table 4 - Question sets related to disease activity and impact, and their frequencies

Domain	Question stem	Answer scale	Answer anchors
Daily data collection			
Global activity	Considering all of the ways it affects you, how active do you feel your myositis is today?	VAS	"Not active" (0); "Very active" (100)
Pain	What is your overall level of pain today?	VAS	"No pain" (0); "Extreme pain" (100)
Pain	What is your level of pain due to myositis today?	VAS	"No pain" (0); "Extreme pain" (100)
Fatigue	How much fatigue do you feel today?	VAS	"No fatigue" (0); "Very severe fatigue" (100)
Sleep	How refreshed did you feel when you woke up for the day?	5 point Likert scale	"Not at all rested" "Slightly rested" "Somewhat rested" "Well-rested" "Very well-rested"
Sleep	How would you rate the quality of your sleep last night?	5 point Likert scale	"Very poor" "Poor" "Fair" "Good" "Very good"
Weakness	How weak do you feel today?	VAS	

Mood	How would you rate your mood today?	5 point Likert scale	"Poor" to "Excellent"
Function	Are you able to wash and dress yourself today?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Are you able to walk outdoors on flat ground today?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Are you able to walk up five steps today?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Weekly data collection			
Flare occurrence	Have you experienced a flare of myositis in the last seven days?	Dichotomous	Yes; no
Function	Have you been able to carry shopping bags in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Exercise	Have you been able to exercise in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Social interaction	Have you been able to socialise in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Function	Have you been able to reach and get down a 5 pound object (such as a bag of sugar) from just above your head in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"

Function	Have you been able to bend down to pick up clothing from the floor in the last seven days?	Ordinal with checkbox	"Unable to do" "With some difficulty" "With much difficulty" "Without any difficulty"
Employment status	Are you currently employed (working for pay)?	Dichotomous	Yes; no
Effect of myositis on employment	Has your ability to work been affected by myositis in the last seven days?	Dichotomous	Yes; no
Hours of employment missed due to myositis	During the past seven days, how many hours did you miss from work because of problems associated with your myositis?	Numerical	
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?	Numerical	
Hours worked	During the past seven days, how many hours did you actually work?	Numerical	
Degree myositis affected work productivity	During the past seven days, how much did your myositis affect your productivity while you were working?	VAS	"Myositis had no effect on work" (0); "Myositis completely prevented me from working" (100)
Monthly data collection			
Function	Health Assessment Questionnaire. Validated questionnaire comprising 23 item assessing physical function	Overall score of 0-3	

VAS = visual analogue scale

The app software was developed by a collaborating industry partner, ZiteLab ApS. The MyoPAD app was available to study participants for download from the Apple App Store and Google Play (see supplementary material for screenshot examples). SENS Motion Plus (manufactured by SENS Innovation Aps) accelerometer sensors were used to remotely monitor gait parameters (see supplementary material for images of sensors within adhesive patches). The accelerometer sensor (dimensions 3cm x 6cm x 0.5cm) is contained within an adhesive patch and attached to the lateral aspect of a participant's thigh, just above the knee. The accelerometer system measures acceleration in three perpendicular axes up to 100Hz; acceleration signals are then sent via Bluetooth to the participant's smartphone and then transferred to a secure cloud-based storage system, which is then available for download, processing and analysis by the research team. The accelerometer system is capable of storing up to two weeks' of data if Bluetooth connectivity does not occur.

Participant recruitment

Participants were recruited from the specialist neuromuscular clinic at Salford Royal Hospital, UK. Participants were invited to join the MyoPAD study if they were over 18 years of age, had a physician-verified IIM diagnosis via the International Myositis Classification Criteria Project[181] or European Neuromuscular Centre criteria[182], owned their own smartphone and had regular access to their own Wi-Fi connection. Included IIM subtypes were polymyositis (PM), dermatomyositis (DM), immune-mediated necrotising myopathy (IMNM) and anti-synthetase syndrome (ASS). Participants unable to walk or enter information via a smartphone touchscreen were excluded from the study. The study did not have the capacity to translate materials into other languages. Therefore potential participants who were unable to speak English and understand English verbal explanations were ineligible for recruitment.

Study period

Recruited participants were invited to take part in a 91 day study period. Participants attended the Clinical Research Facility at Salford Royal Hospital on the first day and after completion of their study period. Disease activity was assessed using IMACS Disease Activity Core Set Measures[56] at each visit.

Each participant was invited to a total of two interviews (maximum one hour in duration), which occurred at baseline and follow up visits. Interviews were carried out to identify qualitative reasons for observed quantitative findings. Participants received an information sheet prior to the interview with a list of possible areas of discussion. A.O.

conducted all interviews, which took place in Salford Royal Hospital's Clinical Research Facility. Participants were given the option to attend the interview with a partner or friend who were also invited to contribute to the discussion where appropriate. Interviews followed a semi-structured format with pre-prepared interview guides (see Supplementary Material). Interviews were audio-recorded and transcribed.

During the initial (baseline) interview, participants were invited to discuss their prior experiences of using mobile health devices, perceived enablers/barriers to engagement and perceived benefits/drawbacks of the availability of daily PROM and continuous gait pattern data. These topics were chosen to identify reasons for observed quantitative engagement patterns. During the second (follow up) interview, participants were invited to discuss their experiences of using the MyoPAD system, identified enablers/barriers to engagement and suggested alterations to the system.

Participants were invited to download the two required study apps onto their smartphone: 1) the "MyoPAD app" that allowed completion of daily PROM questions, and 2) the SENS Motion Plus app that facilitated transmission of accelerometer data.

Verbal and paper-based instructions for completing the PROM questions were provided to each participant. Participants were asked to complete PROM question sets every day of the 91 day study period. Each participant therefore had the potential to complete a maximum of 91 daily, 13 weekly and four monthly PROM sets. All individual PROMs in each set had to be completed for a PROM set to be submitted; therefore omission of even a single PROM would result in the whole set not being submitted. Participants did not receive automated reminders or "push factors" for PROM completion.

Participants were also provided with a single SENS Motion Plus accelerometer sensor and replacement adhesive patches. The method of fixing the accelerometer sensor into the adhesive patch and placement onto the lateral aspect of the thigh was demonstrated to each participant, along with written instructions, to allow for self-replacement of the adhesive patch when required. Each participant had the potential to continuously wear a sensor for a maximum of 91 days equating to 2,184 hours throughout the 91 day study period (total potential wear time varied per participant due to varying study initiation times on the first study day).

A member of the MyoPAD Study team was available for technical support throughout the study period, when required.

See Appendix 9.4 for app screenshots, images of accelerometer sensors and participant instructions.

Analysis

App

App engagement was assessed via the completeness of available PROM sets each day. Analysis of PROM engagement only considered PROM sets and not individual PROMs. A participant's status could change from one day to the next. The proportion of the total available number of individual PROM sets completed per participant was calculated for each study day. Subsequently, the percentage of the cohort that completed available PROM sets for each study day was calculated. This was carried out for daily, weekly and monthly PROM sets separately.

Sensor

Participant engagement with wearing their accelerometer sensor was also investigated. The percentage of total potential sensor hours collected on each study day (maximum 24 hours per day) per participant was calculated. Each participant began wearing a sensor at different times on the first day ("day one") of the study; the total possible wear time on day one was calculated for each participant (i.e. 14 hours for a participant that began to wear a sensor at 10am on day one); subsequently the percentage sensor wear time during day one was calculated for each participant. The total percentage of sensor hours collected across all participants on each study day was subsequently calculated.

Active participant definition

An "active day" was defined as one where a participant completed all available PROM sets and submitted 16 hours or more (i.e. >67%) of sensor data. Day one of the study was deemed to be "active" if all available PROM sets were completed and >67% of possible sensor data was recorded (i.e. a participant that began wearing a sensor at 10am on day one had a total of 14 hours of possible sensor data, day one was therefore deemed to be an "active day" if all PROM sets were completed and more than 9 hours and 23 minutes (67%) of sensor data was submitted). This binary status of each participant could change day-to-day. The proportion of the cohort deemed to have had active days was calculated for each study day.

All quantitative analysis was carried out using the statistical programme "R"[183].

Interview analysis

Interview transcript data was analysed thematically, using a grounded theory approach[171]. Grounded theory was selected to limit the influence of pre-existing

conceptualisations upon theme formation. Coding was initially carried out by A.O. and K.H. using NVivo qualitative data analysis software (QSR International Pty Ltd, Version 11, 2015). Initial coding formed the basis for long descriptive accounts of the coded data that were circulated, discussed and refined during analysis meetings with K.H. Initial codes were grouped to form core thematic categories based on multiple sources of interview data.

Ethical approval

The Greater Manchester Central Research Ethics Committee approved the study (ref. 18/NW/0676).

Results

Cohort description

Twenty participants took part in the study, of whom 13 (65%) were female. The median age of the cohort was 50 years (IQR 43, 56) with a median IIM disease duration of three years (IQR 2, 5; range 1-26 years). Eleven (55%) had DM, five (25%) PM, three (15%) IMNM and one (5%) ASS.

App

A total of 1,888 PROM sets (21,709 individual PROMs), 87% of a potential total 2,160, were completed throughout the 91 day study period.

Daily PROMs

A total of 1,563, 86% of a potential total of 1,820, daily PROM sets were completed throughout the study period. Five (25%) participants completed PROM set entry every day throughout the 91 day study period, with a further three (15%) completing 90 days and 8 (40%) completing more than 70 days.

Weekly PROMs

A total of 248, 95% of a potential total of 260, weekly PROM sets were completed throughout the study period. Fourteen (70%) participants completed all 13 weekly PROM sets. The remaining six (30%) completed at least 10 weekly PROM sets.

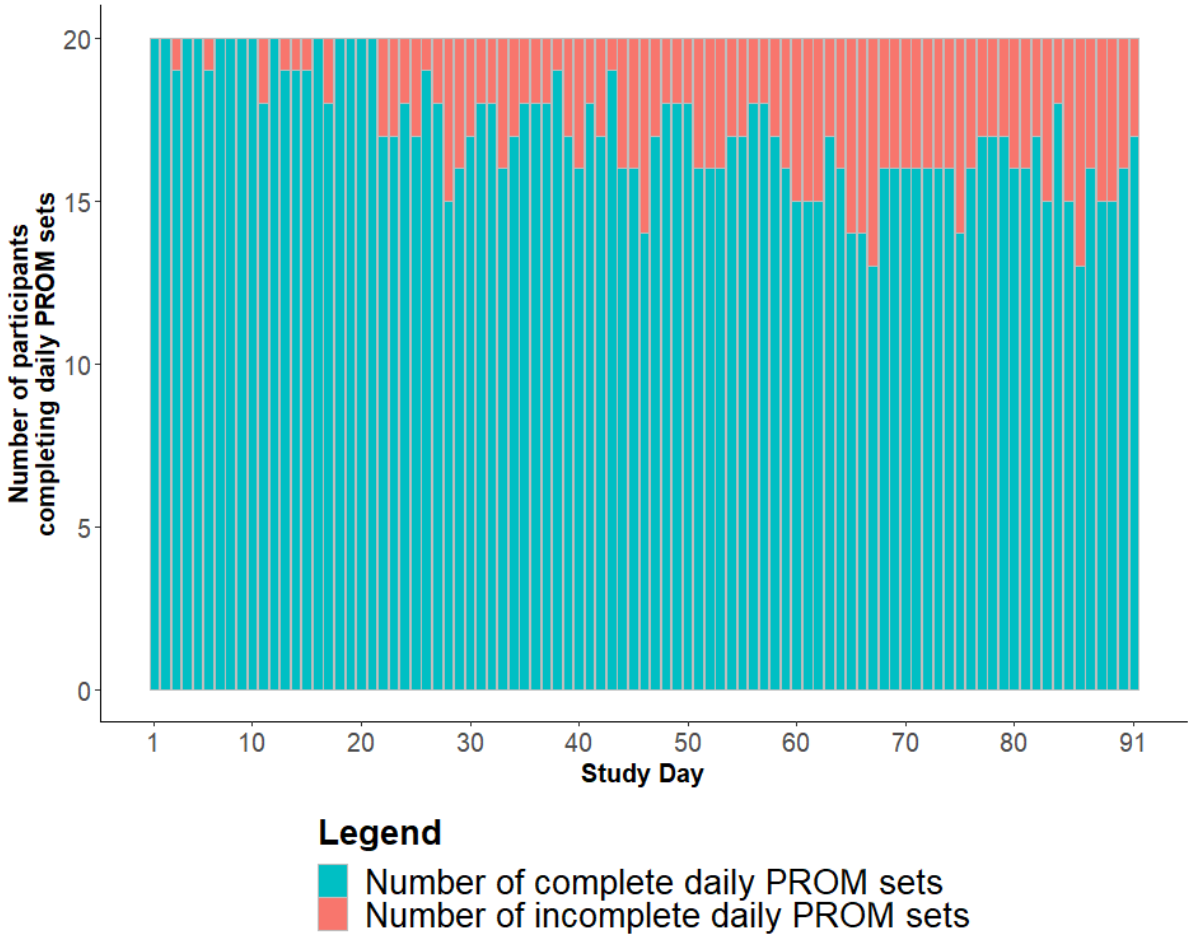
Monthly PROMs

A total of 77 monthly PROM sets, 96% of a potential total of 80, monthly PROM sets were completed throughout the study period. Further, 17 (85%) participants completed all four monthly PROM question sets. The remaining three (15%) completed three monthly PROM question sets.

App completion over time

The median percentage completion across the entire study period was 85% (IQR 80, 90). The minimum completion percentage was 65%, which occurred on two study days - days 67 and 86. All available PROM sets were completed on 14 (15%) study days, 90-99% on 24 (26%) study days, 80-89% on 39 (43%) study days, and <80% on 14 (15%) study days. Although overall high, daily PROM set completion reduced gradually throughout the 91 day study period (Figure 9).

Figure 9 - Number of participants completing daily PROM sets across the cohort on each study day

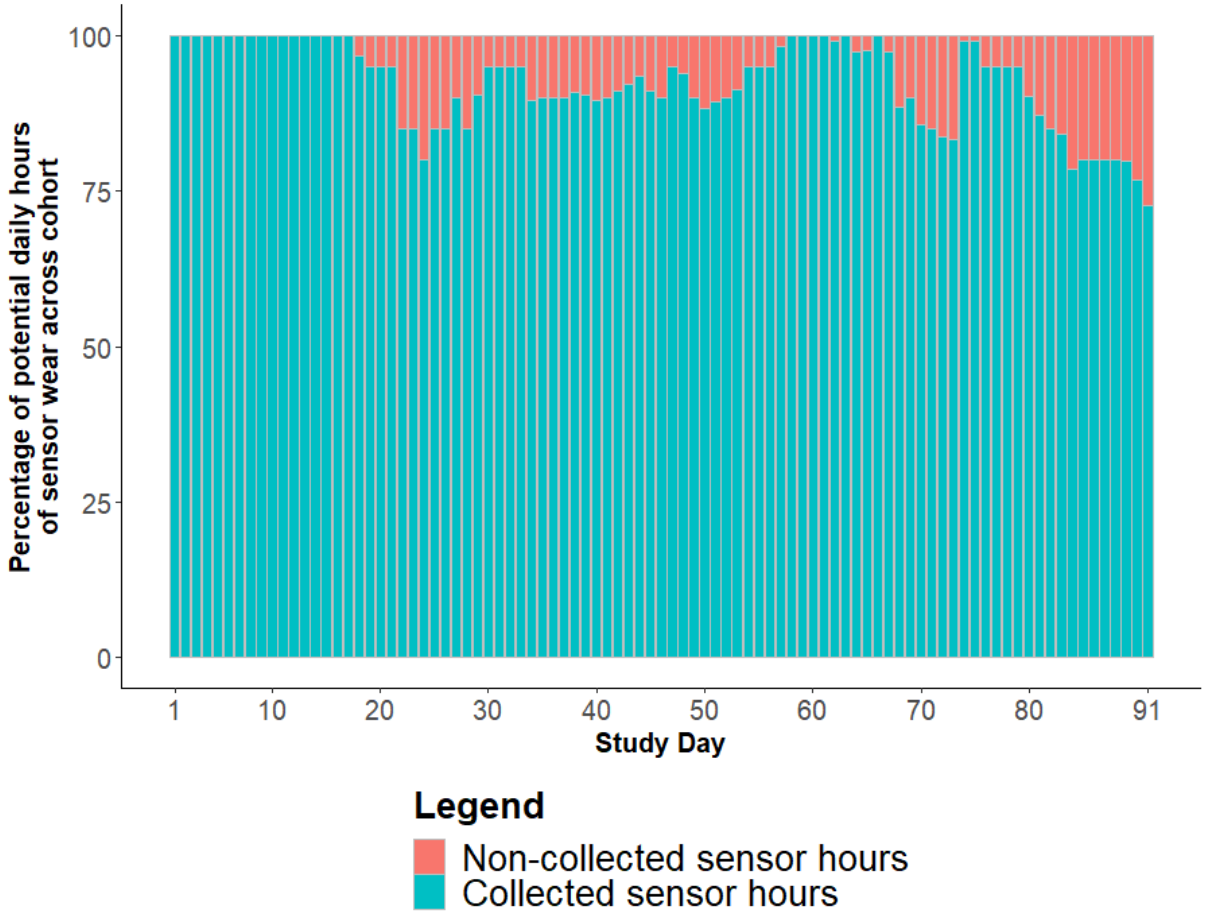


PROM = patient-reported outcome measurements

Sensor

A total of 40,145 hours of sensor data was collected throughout the 91 day study period; this was 92% of the potential total wear time of 43,439 hours (varying wear time between participants on the first study day resulted in total potential wear time not being divisible by 24). The median daily wear time for participants was 23 hours (IQR 21, 24, range 16, 24). Eight (40%) participants completed 100% of potential sensor wear time throughout the 91 day study period, with a further six (30%) completing more than 90%, and five (25%) completing more than 75%. The single remaining participant completed 66% of potential sensor wear time. The percentage of potential sensor wear time remained high throughout the total study period across the cohort (median 95% [IQR 89, 100]), but reduced towards the end (Figure 10).

Figure 10 - Proportion of potential daily hours of sensor wear time across cohort on each study day



Active participants description

Figure 11, which plots the proportion of the cohort engaging as defined by "active days" (see earlier definition), indicates reducing engagement throughout the study period. Engagement was, however, overall high with 80% of all participant days being deemed as "active". Figure 11 also indicates that engagement with the sensor was typically higher compared to the app. Indeed, of the 338 participant-days that were "non-active", the majority were due to disengagement with the app (190 [56%]), compared to only 80 (24%) due to sensor disengagement; the remaining 68 "non-active" days (20%) were due to disengagement with both the app and sensor.

Figure 12, which plots engagement throughout the study period for each participant, indicates that, again, disengagement with the app was more common than for the

sensor. Further, participants typically would re-engage following short periods of disengagement.

Figure 11 - Proportion of active participant days throughout study period - divided by app, sensor and both app and sensor

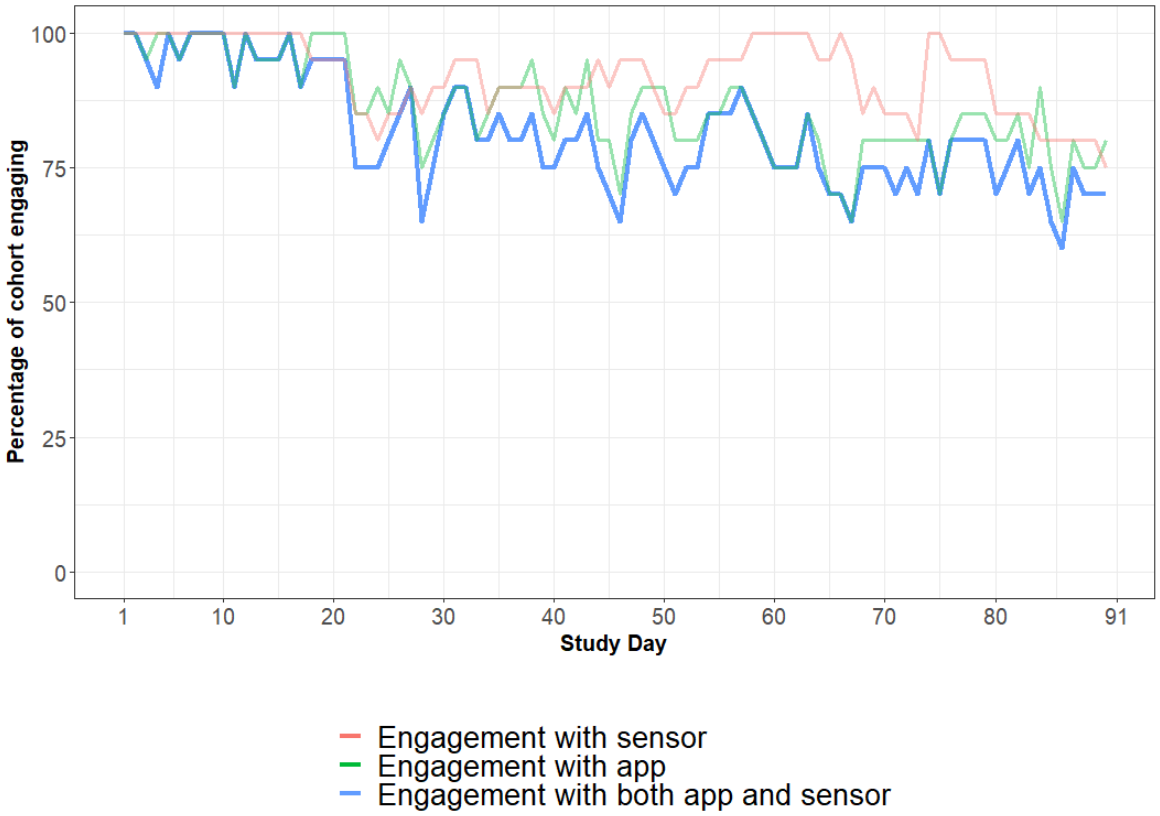
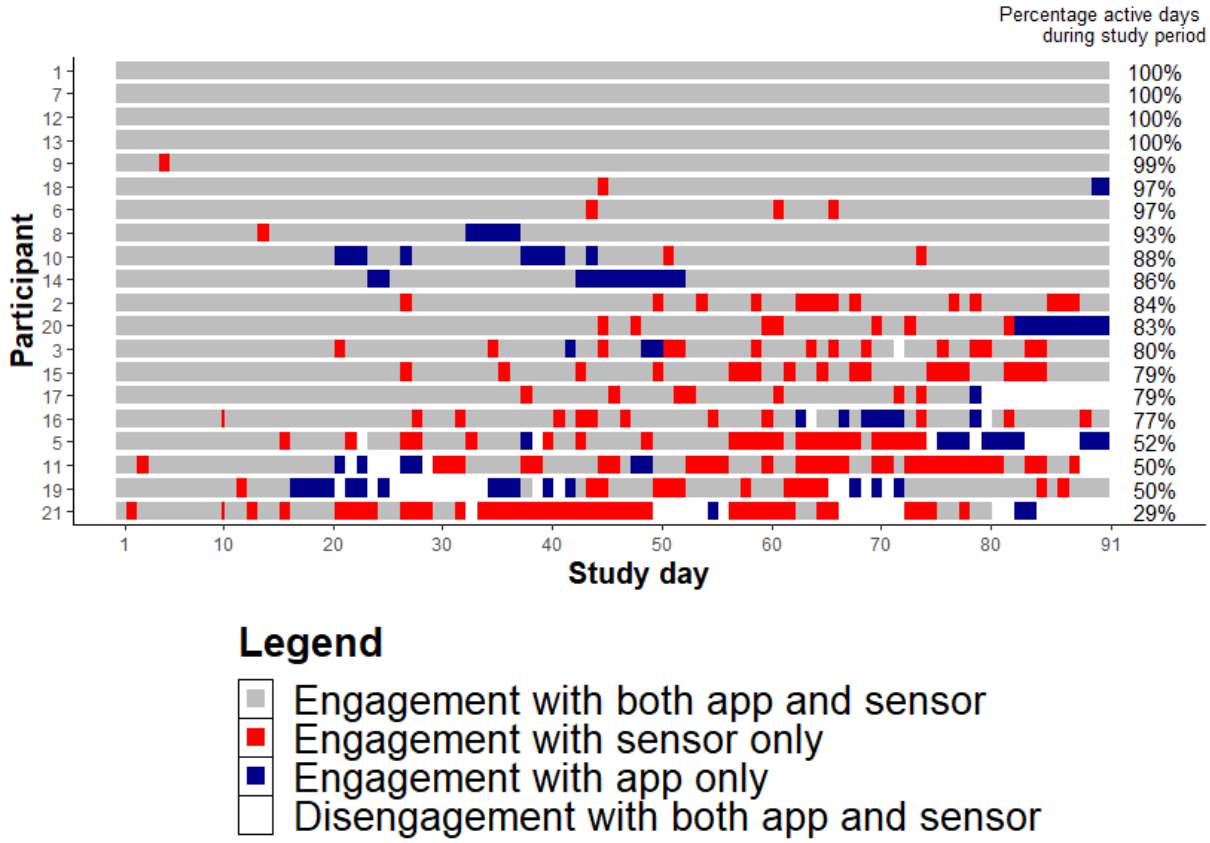


Figure 12 - "Active day" status of each individual participant across the study period



Qualitative component

Eighteen participants attended baseline interviews and 11 attended follow up interviews. Fewer participants attended follow up interviews due to time/practicality issues (N=5) and non-IIM related illness (N=2). Transcript analysis revealed three app-focused themes: 1) app engagement enablers, 2) app use leading to beneficial alteration of disease perception and 3) app engagement barriers. Three further sensor-focused themes were identified: 1) sensor engagement enablers, 2) sensor wearing acting as a positive visible marker of disease and 3) sensor engagement barriers.

App-focused themes

1) **App engagement enablers**

During baseline interviews, the majority of participants anticipated that answering PROM questions on a daily basis would be acceptable (Textbox 5.1) and this view was maintained after the end of the study, especially as many recognised that their symptoms can change on a day-to-day basis (Textbox 5.2). The 91 day study duration was also anticipated to be acceptable (Textbox 5.3). Some participants acknowledged the long study duration, however as they frequently used their smartphones, they suggested that using the MyoPAD app would most likely not impact their pre-existing routine (Textbox 5.4). This observation was validated in the follow up interviews, with participants confirming that the study duration was acceptable, indeed a minority of participants were keen to continue using the app due to the perceived benefit of increased data provision (Textbox 5.5).

Participants were overall positive about their experiences with the app throughout the study period. Clear and simple PROM wording and format, daily completion, sense of routine, and small number of answer formats (VAS, Likert, binary) were deemed to be factors associated with improved app engagement (Textbox 5.6 and 5.7).

Highly engaged participants, e.g. participants 1 and 7 (see Figure 12 for graphical representation of engagement levels throughout study period), reported particular features of the app that they attributed to high engagement levels: the daily routine of answering PROM questions (Textbox 5.8), the short duration of time required to answer all questions (Textbox 5.9) and the recognition that questions addressed symptoms highly relevant to them (Textbox 5.10).

2) **App use leading to beneficial alteration of disease perception**

A number of participants reported that participation in the study has unexpectedly altered the perception of their condition. For example, answering daily PROMs provided time and structure to consider their IIM disease activity and how it impacted them on a certain day (Textbox 5.11 and 5.12), thus enhancing engagement. A minority of participants also reported that this "gave permission" to adjust their ADLs accordingly, for example resting if they felt fatigue or amending analgesia if pain levels were heightened (Textbox 5.13 and 5.14).

3) App engagement barriers

A number of barriers to app engagement were identified. In particular, engagement barriers reported by participants 5 and 19, who had lower engagement levels (see Figure 12 for graphical representation of engagement levels throughout study period), included the need to answer the same questions each day (Textbox 5.15), a perceived simplicity of questions (Textbox 5.16), forgetting to answer questions (Textbox 5.17), and the occurrence of other higher priority personal commitments (Textbox 5.18).

Suggested amendments to the app included availability of a "free text" box to allow justification of answers and numeric display of selected VAS answer (Textbox 5.19). One participant highlighted the potential detrimental impact of negative questions, such as "how weak do you feel today?", and suggested converting to a more positive form, i.e. "how strong do you feel today?" Another participant suggested the possibility of randomly altering the order of questions each day, with the aim of avoiding learning a regular order and consequently submitting invalid answers (Textbox 5.20).

Table 5 - Quotations from interviews related to app engagement

	1) App engagement enablers
5.1	I think every day is about right.
5.2	(Daily PROM questions were) acceptable and also seemed necessary because of, I suppose, the daily fluctuation in the disease.
5.3	I think it's probably long enough. The length of it, doesn't make me sort of think "oh three months of this!" it doesn't put me off.
5.4	It does seem like a long time but I'll just get into the habit of it. We spend most of the time fiddling with our phones anyway don't we?
5.5	It wouldn't have bothered me if it had been a longer study, because if it's going to provide something useful ultimately then, I think you know, it's not a chore is it, if you know something helpful is going to come from it.
5.6	Yeah, I thought they were good. The slider was quite good, yeah. I thought they were all good really. It was quite simple and easy to answer really, and that's what you want, don't you? If you are going to be having that all the time, you don't want a big long load of questions.
5.7	Well, you've got daily, weekly and monthly, so once you get into the routine of it, it's not an issue, it's something you do.

5.8	It's like playing a game on your app. You just get into a routine.
5.9	It's just a couple of minutes, it's no time at all. It's not a daily chore, I think it's something you sort of look forward to, it's part of a cycle of knowledge.
5.10	I know that my weakness is up and down each day, so I liked being able to answer the questions about that.
2)	**App use leading to beneficial alteration of disease perception**
5.11	I think it's made me think about it more, rather than just trying to put it out of my mind, which is what I did a lot of the time, I have had to think about how I'm being affected by it.
5.12	So, it made me actually realise that although there are times when I have quite negative and bad days, it actually made me think actually, you know, this is actually better than I thought it was.
5.13	I think it's a positive thing, I am actually considering how it affects me and what I can do about how it affects me. I think I've got a bit complacent about it because its five years since I was diagnosed and I would say I had a year getting better and now I seem to be declining again. So it has made me think about it and think, maybe I should be a bit more proactive and actually try to do something about improving things.
5.14	I actually felt that I was trying to improve my sleep because it was quite clear that the poor sleep was having a correlation between that and how bad I felt. So yeah, I thought it was quite useful.
3)	**App engagement barriers**
5.15	I found the questions a little bit repetitive. It gets to the point where you almost just clicking automatically. Occasionally I found myself having to think a little bit harder about just to make sure I was answering them correctly. I'm sure it affected quality of my answers.
5.16	Clarity (of the questions) wasn't a problem, but I think yes, they could be a little bit too simplistic so I kind of switched off for a few days. I suppose I would have liked more complicated questions…so I could provide more detail.
5.17	Every now and again I would forget.
5.18	I actually gave myself a break (from answering PROM questions) over Christmas. I thought I would be too busy to answer them properly.

5.19	I wasn't altogether keen on the sliding scale thing, I found that a bit…it's a bit crude, it's a bit difficult to actually work it out. I wonder whether a numeric score would be better or whether you could have that as a numeric that then converted to where it was on the scale.
5.20	It gets to the point where you are, kind of, you are almost automatically answering things. So, probably maybe the middle stages of the work that I was doing, I probably got a little bit blasé with it. I wonder if you could vary them perhaps, I don't know whether there is any way you could sort of randomise the questions.

Sensor-focused themes

1) **Sensor engagement enablers**

All participants, prior to the study, anticipated that wearing a sensor would not be intrusive on their everyday life. Indeed, after the study, the majority reported that they quickly became unaware of wearing the sensor (Textbox 6.1 and 6.2). Only cosmetic amendments were suggested, with one participant comparing the sensor to a previously seen wearable blood glucose monitor used for diabetes mellitus (Textbox 6.3). Changing the sensor's adhesive patch was reported to be straightforward and did not impact engagement (Textbox 6.4).

Participants 1 and 7 (highly engaged participants) each explained that knowing they were wearing the sensor to allow for remote monitoring made them feel reassured and "connected" to clinicians (Textboxes 6.5 and 6.6). Also, a strong interest in technology and the perceived benefit of additional information provided by the sensor were additional factors contributing to engagement (Textbox 6.7).

2) **Sensor wearing acting as a positive visible marker of disease**

A minority of participants reported that wearing a sensor provided a positive visible marker of an otherwise invisible disease, thus increasing commitment to continued wearing. Two participants explained that the visibility of the sensor provided "an interesting talking point" that allowed further discussion about their IIM with friends, family and colleagues (Textbox 6.8 and 6.9).

3) Sensor engagement barriers

Very few participants reported barriers to sensor engagement. Participants 5 and 19 (lower engagement levels) explained that practical factors were the main reasons for periods of sensor disengagement. For example, needing to remove the sensor prior to an MRI scan (Textbox 6.10) or for special occasions (Textbox 6.11).

Table 6 - Quotations from interviews related to sensor engagement

	1) Sensor engagement enablers
6.1	I didn't feel conscious about it. Actually, it was weirdly quite nice to have something on your leg to touch when your legs are aching, you know, it felt like you were doing something positive about it.
6.2	Once I got used to it, I just didn't even really notice it was there.
6.3	Somebody at work has a diabetes sensor, which obviously has been around for quite a while and been through a lot of trials and things, and that looks a bit prettier. It (the sensor) was fine, it could have been prettier.
6.4	I didn't have any problems (changing the adhesive patch), it was fine. Once you actually put it on your leg you didn't have to keep pushing it, it stuck very quickly, and it feels fine. Only took five minutes every two weeks.
6.5	Having it there knowing somebody was reading something made you not feel quite as abandoned in between your consultations, it felt like you were connected to something.
6.6	I think it's (wearing a sensor) all connected to feeling part of a team, if you like, something constructive going on, I don't think it doesn't…it's not a chore that you want to get rid of. I think it just becomes part of a cycle you have to be in.
6.7	I really do hope this works because as I said before I'm a great believer in technology, and I can see the benefits to this. Real time information, rather than a blood test that you take every 12 weeks.
	2) Sensor wearing acting as a positive visible marker of disease
6.8	I was quite proud to be part of the trial as well. I was showing people "look at my leg".
6.9	When I went into the hydrotherapy pool it wasn't an issue to me for people to see it (the sensor). The physio said "what's that" and I explained what it was and it was, kind of, a nice way to talk about my condition.

	3) Sensor engagement barriers
6.10	I think I took it off one day I went for an MRI scan and I had a break (from wearing the sensor) for a few days.
6.11	I knew it was going to be Christmas just after it (the adhesive patch) needed changing, so I thought I would just give myself a break for a few days over Christmas.

Discussion

This study has explored participant engagement patterns and experiences over three months in the MyoPAD study using a smartphone app and thigh-worn accelerometer. Engagement was high throughout the study for the majority of the cohort. Identified enablers of engagement included app design (e.g. simple interface, clear questions), sensor design (e.g. discrete appearance), perceived benefit of gait pattern monitoring, and interest in technology. Engagement barriers included development of apathy with repetitive question sets, perceived negative phrasing of questions and occurrence of other high priority personal commitments. Engagement was higher with the sensor compared to the app throughout the study period, in part due to the requirement of active app completion versus passive sensor wearing. The high engagement suggests the methodology is both feasible and acceptable to participants, and could support the vision of enhanced and more frequent IIM disease activity assessment.

Comparison to previous research

Engagement levels in mHealth studies vary widely between studies. For example, a study designed to track daily asthma symptoms initially recruited 7,593 participants, however after 6 months only 175 (2%) participants remained engaged[184]. In contrast, the REMORA study, which collected daily symptom data from participants with rheumatoid arthritis over a three month period, reported high engagement with daily symptom scores submitted on a median of 91% of days[177].

The level of engagement with mHealth solutions has wide ranging implications, including for analysis (e.g. needing to account for selection bias), precision of results (e.g. a smaller than expected population may weaken study power) and future translation into healthcare. The literature suggests that participant engagement in mHealth studies is impacted by many motivational and practical factors, as assimilated and described by Eysenbach[164]. Engagement with the MyoPAD study was high in comparison to many other mHealth studies, which is likely due to multiple factors. Factors described by

Eysenbach which recognisably influenced engagement in the MyoPAD study include 1) the low "workload and time required" (i.e. short time duration to complete app questions), 2) comprehensive "quantity and appropriateness of information given before the trial" and 3) "personal contact" during enrolment.

Very few studies have collected both PROM and accelerometer data using smartphone-based apps or wearable devices, however, high engagement has been reported. Beukenhorst *et al* recently reported high engagement with the KOALAP study - participants wore a smartwatch on 73% of all available days over a 90 day study period and answered on average 66% of daily PROM questions [185]. Druce *et al* also reported high engagement (91% over a 30 day study period) with twice daily PROM collection and continuous accelerometer data collection from a wrist-worn device [186]. A number of factors related to engagement patterns were reported, including a self-selected highly motivated cohort, use of automated reminders and availability of technical support.

Co-design of the MyoPAD study alongside participants via a focus group may have contributed to the observed high engagement. Study "co-design" refers to protocol formulation by the study team alongside other relevant stakeholders, such as potential participants, and future data users, such as researchers or clinicians[110]. A number of specific aspects of the MyoPAD study were influenced by study participants. Firstly, participants highlighted the importance of including pain and fatigue as PROM domains, which were not initially deemed essential by the study team. Secondly, participants recommended the daily frequency of PROM completion; the study team had formerly considered twice-daily PROM completion. Thirdly, participants deemed the 91 day study period to be feasible and highlighted that a longer duration may be acceptable; the study team had previously considered shorter study durations.

Study strengths and limitations

The combination of quantitative and qualitative methods has provided a comprehensive assessment of engagement in the MyoPAD study, allowing us to understand not just the level of engagement, but why that happened within individual participants. Further, the focus upon individual high and low engagers has identified enablers and barriers that will inform future mHealth studies.

There are, however, a number of limitations to this study. Firstly, the small size of the study cohort may limit external validity. Secondly, the cohort is a self-selected, highly motivated and "digital literate" population; this is possibly a major factor responsible for the observed high engagement levels. These factors and important qualities of the

recruited IIM cohort should be taken into account when extrapolating our findings into other populations, especially with other conditions. Future recruitment of larger populations with broader levels of digital or health literacy may result in lower engagement patterns and proportionally lower levels of data collection[150].

Implications for future research

Lessons learnt about engagement in the MyoPAD study can be implemented in future mHealth studies in a number of ways. Potential app/sensor modifications suggested by participants include: 1) increased complexity of PROM questions, thus allowing participants to convey symptoms in a more detailed way; 2) varying order of daily questions, thus mitigating a perceived sense of repetition; 3) inclusion of a "free text" box that allows participants to qualify and explain provided answers; 4) cosmetic amendments to sensor (dedicated qualitative research will be required to fully investigate desired amendments). Potential study design amendments include: 1) inclusion of functionality that allows participants to review their own submitted data; 2) remote enrolment (i.e. not required to attend a hospital/university to enrol); 3) use of "push factors" (i.e. automated reminders via the app to completed PROM questions); 4) ensuring that the study period does not coincide with important public holidays, such as Christmas. Future research studies could subsequently investigate the impact upon engagement of these suggested amendments.

Conclusion

The MyoPAD study has demonstrated that smartphone app-based collection of daily PROM data and accelerometer-based gait pattern data is feasible, acceptable to participants and generates comprehensive quantitative data potentially useful for IIM clinical care and research. This approach to data collection has the potential to revolutionise IIM-specific data collection, thus ushering in the era of truly patient-centred clinical care and research as part of the digital healthcare revolution.

Chapter 5

5 Characterising idiopathic inflammatory myopathy flares using daily symptom data

"It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts."

Sherlock Holmes

A Scandal in Bohemia[187]

5.1 Introduction

Many of the patient participants that I interviewed in the MyoPAD study (Chapter 3) reported "flares", "good and bad days" and frequent symptom variation. I quickly realised that very little previous research has been carried out on characterising flares in IIM patients.

I suspected that constraints related to the frequency of data collection in IIM patients was a major reason that flares have not previously been characterised. Detailed characterisation of flares in IIM patients could potentially provide clinically useful insights into symptom variation and trajectories. Further, the development of a method to accurately identify symptom flares could potentially provide a useful future outcome measure.

I realised that analysis of daily symptom data that I collected during the MyoPAD study could form an initial evidence base for characterisation of IIM flares and demonstrate the utility of such collected data to the broader research community, thus hopefully engendering a wider uptake.

Therefore, this chapter aims to answer the following questions:

- Can daily symptom data provide useful insights into flares in IIM patients?
- What are the characteristics of IIM symptom flares (e.g. frequency duration, severity)?

5.2 Description of contribution

I analysed daily symptom data collected from the MyoPAD study and prepared the manuscript along with Professor Chinoy and Professor Dixon. The manuscript is in preparation for journal submission.

I feel that is important to recognise that the analysis in this chapter was inspired by a paper by Parry *et al*[188], where daily symptom data (collected via paper-based diaries) was used to characterise osteoarthritis symptom flares.

5.3 Manuscript 4

Characterising idiopathic inflammatory myopathy symptom flares using daily symptom data collected via a smartphone-based app - results from the myositis physical activity device study

Background

The idiopathic inflammatory myopathies (IIMs) are chronic multisystem inflammatory conditions[24,174]. Muscle inflammation, termed "myositis", is the most common clinical manifestation of the IIMs. Typical symptoms associated with myositis include weakness, fatigue, and muscle pain ("myalgia"). The concept of an IIM flare is widely used but interpretation of the term varies between patients, clinicians and researchers. No consensus definition of an IIM flare exists.

Recent qualitative research has identified that patients typically characterise flares as a marked increase of any symptom, typically of very short (typically 1-2 days) duration[172]. Clinicians typically consider an IIM flare to be characterised by a sudden increase of symptoms above baseline. The level of baseline may vary greatly between patients. The identification of such sudden and short-lived symptom increases has been previously challenging to identify for a multitude of reasons, including recall bias, and inability to quantify symptom severity and/or delineate the onset/resolution.

The "digital healthcare revolution" has lead to the prospect of increasing use of digital technologies in clinical care and research[66,176]. Combined with increasing personal smartphone ownership in recent years[107,189], collection of daily symptom information using patient-reported outcome measurements (PROMs) via tailor-made smartphone apps is possible. This has been demonstrated in a number of conditions, including rheumatoid arthritis[177], schizophrenia[113], and Parkinson's Disease[190]. It is plausible that daily symptom scores, collected via a smartphone-based app, could, for the first time, help characterisation of IIM patient-reported flares. Detailed characterisation of patient-reported flares using smartphone app-based data may also provide novel insights into IIM symptom patterns. Further, the subsequent development of a remote method of flare identification using smartphone-based apps may improve recognition of a flare, thus allowing for early treatment initiation and potential prevention of irreversible damage. The overall aim of this study was to explore the relationships between symptom severity and the occurrence/absence of a patient-

reported IIM flare. Further, this study aimed to use patient-reported daily symptom data to characterise the occurrence and characteristics of IIM flares.

Methods

The Myositis Physical Activity Device (MyoPAD) Study designed and tested a smartphone and accelerometer-based system with the aim of developing a method of daily/continuous data collection applicable for use in IIM research and clinical care.

Symptoms that the app questions should address were identified through a focus group (number of participants = 5). Identified flare-associated symptoms included weakness, fatigue, myalgia (muscle-specific pain) and overall pain (i.e. non-muscle specific pain). A final panel of daily symptom questions were subsequently created by the study team (a daily question addressing "global activity" was also included) (Table 7). Each symptom score could be answered on a 0-100 horizontal visual analogue scale (VAS). A weekly question relating to flare occurrence (binary) was also included. The questions and functionality of the app was "beta-tested" and approved by a further three IIM patient participants.

Table 7 - Questions available via the MyoPAD app

Domain	Question stem	Answer scale	Answer anchors
Daily questions			
Global activity	Considering all of the ways it affects you, how active do you feel your myositis is today?	VAS	"Not active" (0); "Very active" (100)
Fatigue	How much fatigue do you feel today?	VAS	"No fatigue" (0); "Very severe fatigue" (100)
Weakness	How weak do you feel today?	VAS	"No weakness" (0); "Very severe weakness" (100)
Myalgia	What is your level of pain due to myositis today?	VAS	"No pain" (0); "Extreme pain" (100)
Pain	What is your overall level of pain today?	VAS	"No pain" (0); "Extreme pain" (100)
Weekly question			
Flare occurrence	Have you experienced a flare of myositis in the last seven days?	Dichotomous	"Yes"; "no"

VAS = visual analogue scale

The MyoPAD app allows users to answer daily questions, the answers of which are remotely transferred to a secure cloud-based sever. The app software was developed by a collaborating industry partner, ZiteLab ApS. The MyoPAD app was available to study participants for download from the Apple App Store and Google Play.

Participants were recruited from the specialist neuromuscular clinic at Salford Royal Hospital, UK. Participants were invited to join the MyoPAD study if they were over 18 years of age, had a physician-verified IIM diagnosis via the International Myositis Classification Criteria Project[181] or European Neuromuscular Centre criteria[182], owned their own smartphone and had regular access to their own Wi-Fi connection. Included IIM subtypes included polymyositis (PM), dermatomyositis (DM), immune-mediated necrotising myopathy (IMNM) and anti-synthetase syndrome (ASS). Participants unable to walk or enter information via a smartphone touchscreen were excluded from the study. Further, participants with inclusion body myositis or connective tissue disease-related IIM were

excluded. The study did not have the capacity to translate materials into other languages. Therefore potential participants who were unable to speak English and understand English verbal explanations were ineligible for recruitment.

Recruited participants were invited to take part in a 91 day study period. Participants attended the Clinical Research Facility at Salford Royal Hospital on the first day and after completion of their study period. Participants were invited to download the MyoPAD app onto their smartphone. Verbal and paper-based instructions for completing the symptom questions were provided to each participant. A member of the MyoPAD Study team was available for technical support, when required.

Participants were asked to complete symptom questions every day of the 91 day study period. All individual questions had to be completed to allow submission; therefore omission of even a single question would result in non-submission. Participants did not receive automated reminders or "push factor" notifications for question completion.

Two definitions of flare occurrence were used in analysis: 1) patient-reported and 2) symptom-based.

Description of patient-reported flare

The patient-reported flare occurrence data was derived from the weekly question asked via the app (Table 7). Only responses that were actively answered were included in analysis, i.e. an omitted weekly flare question was not counted as absence of a patient-reported flare. The week (seven days) prior to the weekly flare question was deemed to be a "flare week" if a flare was reported. Conversely, the week prior to the weekly question was deemed to be a "non-flare week" if a flare was denied. The number of patient-reported flares was calculated and summarised across the cohort. The following were calculated for each week prior to each flare question:

- Mean score of each daily symptom
- Mean magnitude of day-to-day change of each daily symptom (i.e. negative differences were multiplied by -1)

Variables were compared between flare and non-flare weeks using the independent 2 group t-test.

Description of symptom-based flare

The "symptom-based" flare definition is based on identifying acute increases of symptoms compared to a participant's recent trend, which is a common patient and

clinician characterisation of IIM flares. The four day trailing mean was calculated for each symptom score for each individual participant. An a priori definition of a symptom flare was formed - a symptom flare was defined as occurring on a day where the symptom score was 10 points higher than the four day trailing mean. No definitions of "minimal clinically important difference" for each daily symptom in IIM have been made. The 10 point threshold was therefore based on minimal clinically important differences identified in studies of other rheumatological conditions, including rheumatoid arthritis, ankylosing spondylitis and systemic lupus erythematosus [191–195]. The following parameters were calculated across the cohort to provide comprehensive characterisation of each symptom-based flare (i.e. global activity, fatigue, weakness, myalgia and overall pain):

- The number of symptom-based flares and corresponding incidence rate per 100 person-days across the cohort
- The magnitude of the symptom score increase on the first day of each symptom-based flare.
- The score of the "peak" (highest score before flare resolution) for each flare
- The time taken for the symptom-based flare to "resolve", which was defined as the time taken for the score to return to the pre-flare 4 day trailing mean
- Flare recurrence within the 10 days after flare occurrence was identified and the median interval time was calculated

Subsequently, the synchronicity of patient-reported and symptom-based flares was ascertained by calculating the proportion of patient-reported flares that coincided with a symptom-based flare.

All analysis was carried out using the statistical programme "R"[183].

Ethical approval

The Greater Manchester Central Research Ethics Committee approved the study (ref. 18/NW/0676).

Results

Twenty participants took part in the study, of whom 13 (65%) were female. The median age of the cohort was 50 years (IQR 43, 56) with a median IIM disease duration of three

years (IQR 2, 5; range 1-26 years). Eleven (55%) had DM, five (25%) PM, three (15%) IMNM and one (5%) ASS.

A total of 7,810 daily symptom scores were submitted throughout the 91 day study period, 86% of potential total of 9,100. A total of 248 weekly flare questions were submitted throughout the 91 day study period, 95% of a potential total of 260. Data was collected on a total of 1,562 individual participant days.

Patient-reported flare analysis

A total of 80 (32%) patient-reported flares weeks were reported across the cohort. Participants reported flares on a median of three weeks (IQR 2, 5) per participant, out of a potential maximum of 13. The mean of each symptom score and the mean magnitude of day-to-day change is displayed in Table 8. The mean of each symptom score was significantly higher in flare weeks, compared to non-flare weeks. The magnitude of day-to-day change was also higher flare weeks, compared to non-flare weeks, however this difference was only significant for global activity and weakness.

Table 8 - Mean score and magnitude of day-to-day variation for each symptom score, separated by patient-reported flare weeks and non-flare weeks

	Variable	Whole cohort	Flare weeks	Non-flare weeks	p-value†
Mean (SD) symptom score 7 days prior to flare reporting	**Global activity**	32.4 (21.4)	38.8 (19.7)	29.3 (21.6)	<0.01
	Fatigue	36.8 (21.9)	43.0 (19.4)	33.8 (22.5)	<0.01
	Weakness	33.0 (23.1)	38.4 (20.1)	30.4 (24.1)	<0.01
	Myalgia	25.6 (18.7)	34.2 (21.9)	21.5 (15.5)	<0.01
	Overall pain	28.3 (19.6)	35.7 (21.0)	24.7 (18.0)	<0.01
Mean (SD) magnitude of day to day change 7 days prior to flare reporting	**Global activity**	8.0 (5.9)	9.3 (5.5)	6.0 (7.4)	0.01
	Fatigue	10.8 (7.2)	11.7 (6.8)	10.3 (7.4)	0.15
	Weakness	8.6 (6.0)	10.1 (5.8)	7.9 (6.0)	<0.01
	Myalgia	7.5 (5.8)	8.6 (6.2)	7.0 (5.5)	0.05
	Overall pain	8.4 (6.1)	9.2 (6.4)	8.0 (5.9)	0.15

† Variables were compared between flare and non-flare weeks using the independent 2 group t-test

SD = standard deviation

Symptom-based flare analysis

A total of 606 symptom-based flares were identified. Tables 9, 10 and 11 display the characteristics of each symptom-based flare, including mean scores, number of identified flares, median score of flare "peak" and duration until flare resolution. Figure 13 displays an example of a single weakness symptom-based flare for a single participant and Figure 14 displays the characteristics of each symptom-based flare.

As an example, 119 weakness flares were identified with a median six per participant throughout the 91 study period. This corresponds to an incidence rate of 8.2 per 100 person-days. The median difference between symptom score and four day trailing mean on the first day of the flare was 18 and the median peak score was 59. Weakness flares typically resolved after three days. Sixty seven (56%) of weakness flares saw another within 10 days and the median time to a repeat flare was five days.

The most commonly occurring flare was due to fatigue, which also had the highest score increase on the first day of a flare and the highest peak score. Myalgia flares were least common and had the lowest peak score. Flares typically resolved after three days, however fatigue flares were typically shorter in duration and lasted two days. Another flare occurred within 10 days after over 40% of all flares.

Table 9 - Profiles of symptom-based flares, including mean symptom score, median number of flare events per participant and corresponding incidence rate

	Median number of flare events per participant (IQR)	**Total number of flare events across cohort (%)**	**Incidence rate / 100 person-days (95% CI)**
Global activity	6 (3, 8)	123 (6.8)	8.5 (7.1, 10.2)
Fatigue	7 (4, 10)	148 (8.1)	10.5 (8.8, 12.3)
Weakness	6 (2, 8)	119 (6.5)	8.2 (6.8, 9.9)
Myalgia	4 (2, 7)	98 (5.4)	6.7 (5.4, 8.2)
Overall pain	5 (2, 9)	118 (6.5)	8.2 (6.8, 9.8)

IQR = interquartile range, CI = confidence interval

Table 10 - Profile of symptom-based flares, including magnitude of symptom score increase on first day of flare and score of "peak of flare", median duration of flare and proportion with repeated flares within 10 days

	Median (IQR) symptom 4 day trailing mean on first day of flare	**Median (IQR) magnitude of score increase on first day of flare**	**Median (IQR) score of "peak" of flare**
Global activity	31.8 (23.0, 44.5)	15.3 (11.9, 21.4)	52.0 (37.3, 65.8)
Fatigue	36.5 (26.1, 51.4)	18.9 (12.9, 26.5)	63.0 (46.0, 76.0)
Weakness	36.8 (25.8, 46.6)	17.5 (12.1, 29.1)	59.0 (43.0, 72.5)
Myalgia	27.0 (20.8, 41.3)	17.1 (13.3, 24.0)	44.0 (35.5, 64.0)
Overall pain	32.0 (21.3 46.3)	17.5 (13.1, 24.8)	52.5 (37.0, 70.0)

IQR = interquartile range

Table 11 - Profile of symptom-based flares, including duration of flare and proportion with repeated flares within 10 days

	Median (IQR) duration before symptom score return to pre-flare level / days	**Number (%) with repeated flares within 10 days**	**Median (IQR) time to repeated flare**
Global activity	3 (2, 4)	63 (51)	5 (3, 6)
Fatigue	2 (2, 4)	95 (64)	4 (3, 7)
Weakness	3 (2, 4)	67 (56)	5 (3, 7)
Myalgia	3 (2, 4)	49 (50)	5 (3, 6)
Overall pain	3 (2, 4)	52 (44)	5 (3, 6)

IQR = interquartile range

Figure 13 - Example of single weakness symptom-based flare for one participant

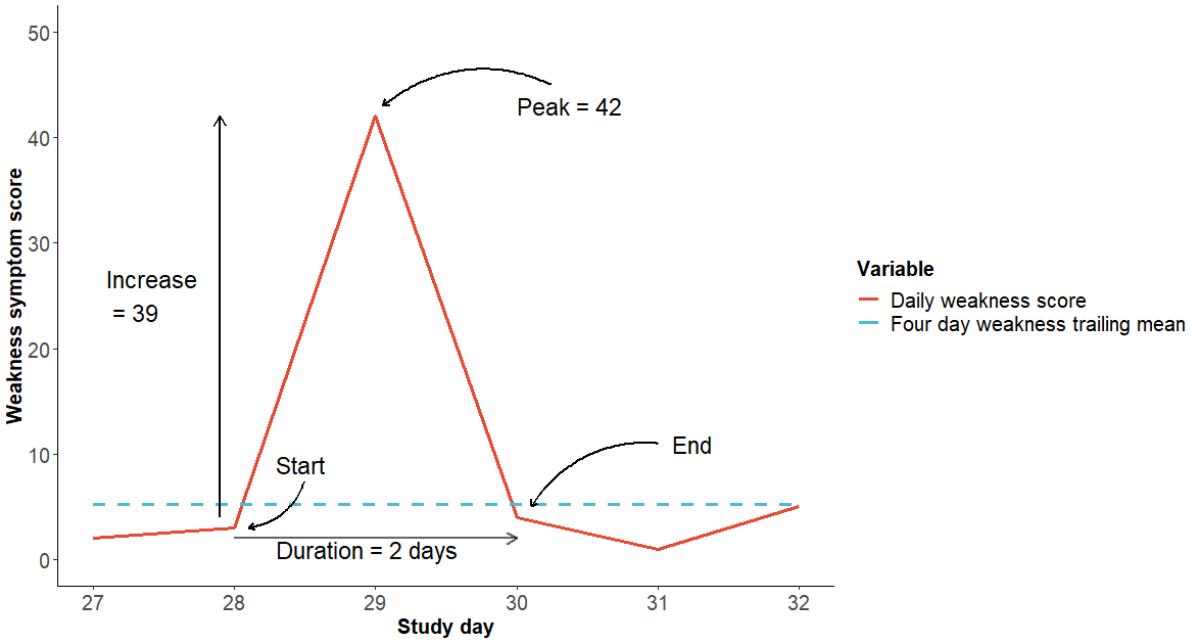
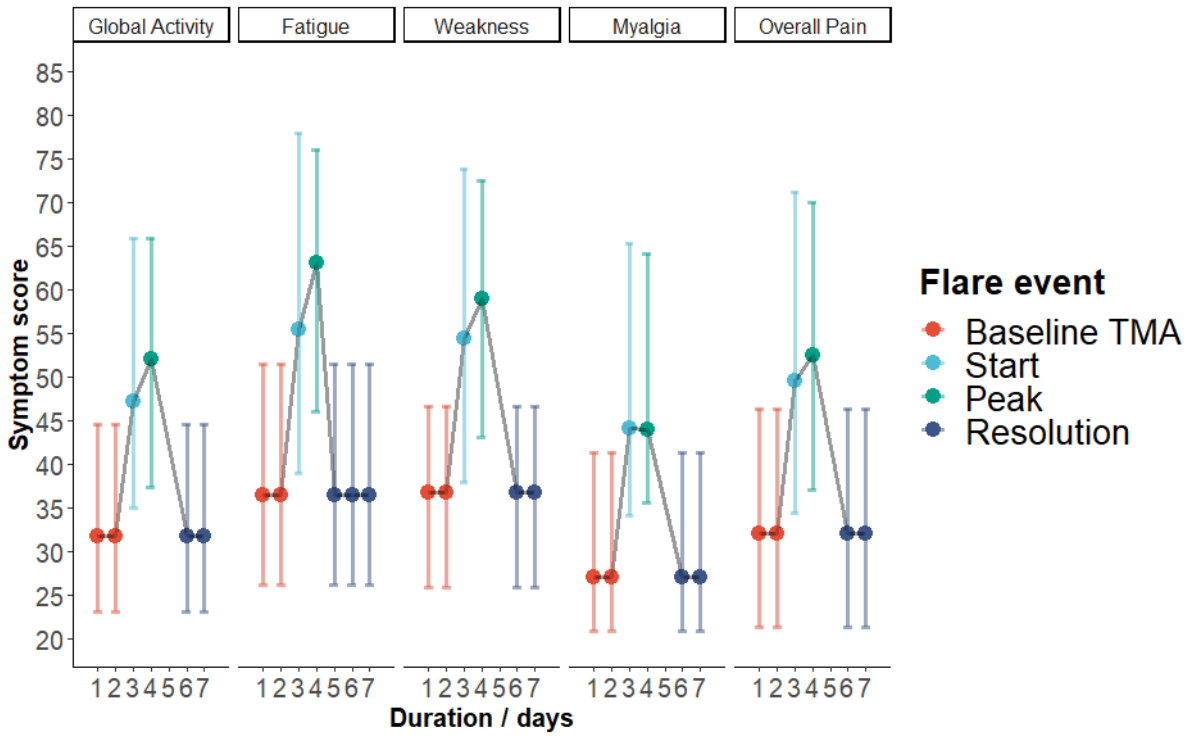


Figure 14 - Summary of temporal features of each symptom-based flare and corresponding events



TMA = four day trailing mean

Error bars refer to upper and lower quartiles

Synchronicity of patient and symptom-based flares

Table 12 displays the number of patient-reported flares that did and did not occur alongside symptom-based flares. Out of the 80 patient-reported flare weeks, 56 (70%) coincided with at least one symptom-based flare and 24 (30%) did not. Of the 168 patient reported non-flare weeks, 97 (58%) coincided with at least one symptom-based flare and 71 (42%) did not.

This corresponds to a sensitivity of 70% for the occurrence of a symptom-based flare to "predict" a patient-reported flare. Corresponding specificity, positive predictive value and negative predictive values are 46%, 37% and 78%, respectively.

Out of all symptom-based flares, fatigue saw the highest proportion of flares occur during a patient-reported flare week (15%) and myalgia saw the fewest (10%).

Table 12 - Number of symptom-based flares that did and did not occur during a patient-reported flare week

Symptom-based flare		Patient-reported flare		Row total
		Reported	Not reported	
Total	**Occurred**	56 (22)	97 (37)	153 (59)
	Did not occur	24 (9)	83 (32)	107(41)
Global	**Occurred**	37 (14)	66 (25)	103 (40)
	Did not occur	43 (17)	114 (44)	157 (60)
Fatigue	**Occurred**	39 (15)	80 (31)	119 (46)
	Did not occur	41 (16)	100 (38)	141 (54)
Weakness	**Occurred**	35 (13)	65 (25)	100 (38)
	Did not occur	45 (17)	115 (44)	160 (62)
Myalgia	**Occurred**	26 (10)	55 (21)	81 (31)
	Did not occur	54 (21)	125 (48)	179 (69)
Overall pain	**Occurred**	33 (13)	61 (23)	94 (36)
	Did not occur	47 (18)	119 (46)	166 (64)
Column total		80 (31)	180 (69)	

Numbers are expressed as whole numbers (percentage)

The denominator of percentages reported within the table is 260, which is the total number of weeks where patient-reported flare questions were available

Discussion

This study has utilised remotely collected daily symptom and weekly flare data to characterise patient-reported IIM flares. This study has identified a number of findings, which will be summarised in turn.

Patient-reported flares were generally associated with increased symptom scores and increased day-to-day variation of global activity and weakness. This finding is not unexpected and provides evidence of the role that symptoms play in patient-reported flares. Day-to-day symptom variation has been reported in a number of previous qualitative studies[28–30,42]. Therefore results from the MyoPAD Study corroborate this phenomenon and indicate the potential importance of measurement of symptom variation alongside absolute scores.

The frequency of patient-reported and symptom-based flares have been quantified. On average, three patient-reported flares per participant occurred throughout the 3 month study period, thus indicating a high frequency. Symptom-based flares were also frequent, occurring 7-11 times every 100 days on average. Interestingly, these symptom-based flares were typically of very short duration (2-3 days). Myalgia flares occurred least frequently and fatigue flares occurred most frequently. Previous research has highlighted the prominent role that fatigue plays as a prominent manifestation of the IIMs[28–31]. In particular, qualitative analysis of interviews carried out as part of the MyoPAD Study highlighted the predominance of fatigue as a symptom and the short duration of IIM flares[172]. The interplay between the IIMs, disease activity and fatigue is complex and research into this area is challenging. Daily symptom monitoring, however, may provide an opportunity to further delineate underlying relationships, as demonstrated in this study.

Finally, although the majority of patient-reported flares coincided with at least one symptom-based flare, as expected, around one third of patient-reported flares did not coincide with a symptom-based flare. This indicates that patient-reported IIM flares are possibly not wholly characterised by sudden increases of symptoms and likely are far more complex than clinicians or researchers may have previously appreciated. Other factors, such as functional limitation, inability to perform specific tasks or the occurrence of other unmeasured symptoms may account for these patient-reported flares.

As described earlier, no previous study has investigated the characteristics or frequency of IIM flares based on patient-reported occurrence or symptom data. The small number of previous studies that have considered IIM flares have defined them on the basis of escalation of immunosuppression[39–41]. This treatment-based definition of a flare likely represents a clinician-centric approach. Development of a consensus definition of IIM flare, taking account of both patient and clinician perspectives, could enable detection in both clinical and research settings. It may be appropriate to follow a similar approach taken by OMERACT, who has developed consensus definitions of flares in a number of conditions. Qualitative and quantitative data were utilised in the recent development of a definition of rheumatoid arthritis flare, which involved clinicians, patients and researchers[196–198].

Development of a definition of IIM flare could potentially take the following steps. Firstly, detailed and dedicated qualitative exploration of the views of patients, clinicians and researchers on the characteristics of IIM flares is required. Such qualitative research could outline the spectrum of patient-reported symptoms associated with flares, identify

potential flare "triggers", and highlight accurate/inaccurate methods of flare detection. Qualitative insights from clinicians and researchers, which may corroborate or contrast these findings, will likely provide valuable insights. Secondly, collection of longitudinal quantitative data, including daily symptom data, from an IIM cohort could provide detailed characterisation of the relationships between symptoms, validated measures of disease activity (e.g. International Myositis Assessment and Clinic Studies Group [IMACS] Core Set Measures), and treatment changes, such as escalation of immunosuppression. Similar methods used in the MyoPAD study could be used in this step. Finally, a consensus definition of IIM flares could be formed by patients, clinicians and researchers. It is likely that a single overarching definition of IIM flares could be formed, however, it is plausible that qualitative and quantitative data will suggest that IIM flares represent multiple distinct underlying processes, thus requiring multiple definitions of each "flare type". Such flare types may include 1) "single organ disease flare" (i.e. escalation of symptoms due to active disease in single organ, such as muscle), 2) "multi-organ disease flare" (i.e. escalation of symptoms due to active disease in multiple organs, such as lungs, skin and muscle), 3) "damage-related flare" (i.e. temporary escalation of symptoms due to energy requirement demand above that which is possible due to accrual of organ damage), and 4) "treatment withdrawal flare" (i.e. escalation of symptoms due to recent planned reduction of steroid dose). These flare types are of course hypothetical and many others may be identified through the outlined research approach. Carrying out these described steps would likely require the combined efforts of the international IIM research community. Bodies such as IMACS and MyoNet (a global IIM network) are well placed to facilitate and coordinate such research collaboration.

Remote daily monitoring methods, as demonstrated to be feasible in this study, could potentially play a role in detection of such defined IIM flares types in clinical settings. For example, remote detection of particular symptom patterns associated with specific flare types may be used to alert a clinician or researcher, thus allowing the opportunity to instigate appropriate treatment. It must be acknowledged, however, that comprehensive validation and careful tailoring of remote flare detection must be carried out prior to implementation into clinical practice. Steps required prior to implementation into clinical practice are outline in the American Medical Association's "Digital Health Implementation Playbook"[167]. Further, the potential introduction of unintended consequences must be kept in mind during clinical translation[199–201].

The use of remotely collected symptom data in research is in its infancy, however the feasibility and potential distinct benefits are beginning to be realised. For example, two recent large interventional trials investigating the efficacy of baricitinib in rheumatoid arthritis collected remote daily symptom data on almost 2,000 study participants[112]. Daily data on rheumatoid arthritis-related symptoms, including joint stiffness and fatigue, provided a further method of treatment efficacy assessment. Remote daily data collection could complement "traditional" methods of research data collection. For example, detection of frequently varying underlying trends, undetectable by infrequent data collection, could potentially be detected using remote daily data collection.

There are a number of limitations to this study that must be highlighted. Firstly, this study analysed data from a small cohort, thus potentially limiting external validity. Secondly, participants were not asked to provide details on why they reported a flare. Availability of such details may have allowed further characterisation of flares where no symptom-based flare coincided. Thirdly, the threshold of an increase of at least 10 symptom points used in the definition of symptom-based flares may have been too "lenient" and resulted in false identification of irrelevant symptom variations. Future research on IIM flare definition, as described above, could include identification of the minimum clinically important difference specific to IIM-related symptoms.

Conclusion

In conclusion, remote daily symptom data collection via a smartphone-based app has allowed preliminary characterisation of patient-reported and symptom-based IIM flares. These findings highlight the potential complexity of IIM flares and the importance of future research to develop a consensus definition. The opportunities posed by the digital healthcare revolution and smartphone app-based daily symptom data collection make remote flare detection a plausible future capability, thus potentially liberating IIM clinical management and research from the confines of the clinic room and research facility.

Chapter 6

6 Using accelerometer data to investigate the relationship between gait pattern and idiopathic inflammatory myopathy disease activity

"Try to learn the features of a disease or injury as precisely as you know the features, the gait, the tricks of manner of your most intimate friend. Him even in a crowd, you can recognize at once; it may be a crowd of men dressed alike . . . and yet, by knowing these trifles well, you make your diagnosis or recognition with ease."

Dr Joseph Bell, a professor of Sir Arthur Conan Doyle whilst the University of Edinburgh Medical School, upon whom Sherlock Holmes is based

Foreword to A Study in Scarlet[202]

6.1 Introduction

New methods of IIM disease activity are needed. Measurement using the IMACS Core Set Measures restricts assessment to infrequent face-to-face clinical appointments or study visits. Further, participants frequently convey the inability of the IMACS Core Set Measures to comprehensively assess their disease activity, as illustrated in Chapter 3. In particular, patients frequently communicate the inability of MMT to capture the consequence of IIM-induced hip flexor weakness.

I therefore wanted to develop a new method of IIM disease activity that could ideally provide continuous assessment and capture the impact of hip flexor weakness. Continuous gait pattern assessment using accelerometer data collected from a thigh-worn sensor may provide such a new method. I therefore aimed to investigate if gait pattern is indeed associated with IIM disease activity using data collected from the

MyoPAD Study (i.e. IMACS Core Set Measures and remotely collected accelerometer data).

As described in the introduction and demonstrated in the review paper (Chapter 2), no previous study has used remotely collected accelerometer data to characterise IIM-specific gait patterns either between or within individuals. The methods and analysis in this chapter therefore represent preliminary steps into this area. It is important to convey reproducible methods so that other researchers can, if desired, employ such methods in other cohorts. Open source publication of computational scripts used for data processing and analysis is now encouraged. My use of the statistical programme "R" lends itself to open-source sharing[183]; indeed, an R package entirely dedicated to sharing of reproducible code has even been developed[203].

As mentioned at the start of Chapter 4, a large proportion of research time was spent on setting up the MyoPAD Study (i.e. ethical application, app development, participant recruitment). A large proportion of time was also dedicated to preparing and processing the large volume of collected raw accelerometer data (43,356,600,000 data points). The remaining available time was therefore dedicated to identifying preliminary relationships between IIM disease activity and gait parameters, thus focusing and informing future research, which I will carry out after my PhD.

In summary, the specific question that Chapter 6 aims to answer is:

- Is gait pattern associated with IIM disease activity, as represented by the IMACS Core Set Measures?

In this chapter I will present the findings in manuscript format.

6.2 Description of contribution

I analysed all accelerometer data collected in the MyoPAD Study under the supervision of Dr Little (Co-Supervisor). I also led manuscript preparation with input from my supervisory team (Professor Dixon and Professor Chinoy). The manuscript is currently in preparation for journal submission.

6.3 Manuscript 5

Using wearable accelerometer sensor data to investigate the relationship between gait pattern and idiopathic inflammatory myopathy disease activity

Background

Wearable technologies represent a key component of the "digital healthcare revolution"[178]. Wearable technology solutions have been developed for a wide range of medical conditions, including diabetes[204], fertility[205], cardiac arrhythmias[206], and Parkinson's Disease[207]. One key opportunity that wearable technology offers is the ability to collect relevant longitudinal "free-living" data outside the confines of a clinical facility.

The idiopathic inflammatory myopathies (IIMs) are a group of chronic multisystem inflammatory conditions[24,174] typically characterised by autoimmune muscle inflammation ("myositis"). The current model of IIM clinical care is based on infrequent clinician assessment at specialist clinics. Data collection on IIM-specific parameters, including disease activity, are limited to such infrequent assessment, which may be separated by 3-6 month intervals. The current gold standard of IIM disease activity measurement is the International Myositis Assessment and Clinic Studies Group (IMACS) Core Set Measures[56]. Recent qualitative research has illustrated the patient-reported perception that current methods of disease activity assessment, specifically manual muscle testing (MMT), do not comprehensively capture the day-to-day impacts of myositis[172]. Further, limitations of MMT, such as the "ceiling effect" and low sensitivity to detect change[56], warrants the need for more accurate methods of quantifying the impact of IIM-related muscle weakness.

Measurement of walking (gait) pattern may provide a solution. A single gait cycle can be divided into stance time (time foot is in contact with ground) and swing time (time foot is not in contact with ground). Stance time invariably constitutes 60-62% of a gait cycle and swing time 38-40%[44,208–211]. Stance:swing time ratio therefore typically ranges 1.5 to 1.6. IIM-related myositis commonly affects the hip flexor muscles[25] and resulting weakness can adversely affect gait pattern. IIM-related hip flexor weakness can therefore potentially lead to detectable prolonged stance and swing phases and an overall slower gait pattern[25,52].

Accelerometers are small, non-invasive, lightweight, portable devices that can remotely and continuously measure acceleration in one or more geometric plane, multiple times per second[123–126]. The small size and low mass of accelerometers makes embedding within wearable sensors possible. Research in other disease areas has demonstrated the ability to extract gait parameters from accelerometer data[127–129,135–137,212–215].

Data collected from wearable accelerometer sensors therefore provide a potential opportunity to identify gait pattern abnormalities relevant to IIM disease activity on a frequent or continuous basis outside the confines of the timing of clinical assessment. Such opportunities were recognised by the European Neuromuscular Centre, which called for "a new study to re-examine the core set outcome measures of IMACS and to develop the use of accelerometry (and other mobile-health applications)"[148].

A number of previous studies have collected data from wearable accelerometers in IIM populations[139–147]. All studies processed accelerometer data to measure "physical activity", which includes average step count per minute and time spent in differing physical activity intensity states (i.e. sedentary, light, moderate or vigorous). Although potentially useful in a number of settings, physical activity parameters are generic and may not provide IIM-specific data. Indeed, only weak associations between physical activity parameters and IIM disease activity have been identified across previous studies[169].

A number of particular steps are required to allow development and clinical translation of wearable digital technologies. Such steps include, but are not limited to 1) technology hardware/software development, 2) demonstration of clinical utility, 3) economic analysis, and 4) embedding within healthcare. These are outlined in the American Medical Association's "Digital Health Implementation Playbook"[167]. The commercial accelerometer sensor market is plentiful, providing multiple hardware options that also allow for continuous remote data transmission[178]. Initial development of reproducible code that allows conversion of raw accelerometer data into IIM-relevant gait parameter data is therefore required. Such code can be developed in freely available open-source statistical programmes, such as "R"[183]; indeed, an R package wholly dedicated to developing reproducible code is available[203]. Unrestricted sharing of code facilitates wider uptake of novel data science methods, improves clarity of methods, enables assessment of reproducibility of findings, and allows improvements to be made by external researchers[216–218]. Further, preliminary exploration of the relationships between accelerometer-based gait parameter data and IIM disease activity is warranted. Fulfilment of these two steps (i.e. code development and relationship exploration) may

provide a foundation upon which subsequent necessary steps can be completed, resulting in eventual clinical implementation.

In summary, wearable accelerometer-based remote gait pattern measurement in IIM patients may provide a novel method of remote continuous disease activity assessment, which may be useful in clinical and research settings. This study will describe a reproducible method of accelerometer-based remote gait pattern assessment. This study will also aim to investigate the associations between gait pattern and IIM disease activity, as represented by the IMACS Core Set Measures.

Methods

In 2019, the Myositis Physical Activity Device (MyoPAD) study recruited a cohort of adult participants with an IIM. The study was designed to facilitate investigation into the potential utility of collection of continuous accelerometer data via a thigh-worn sensor.

Participants were recruited via the specialist neuromuscular clinic at Salford Royal Hospital, UK. Participants were invited to join the MyoPAD study if they were over 18 years of age, had a physician-verified IIM diagnosis via the International Myositis Classification Criteria Project[181] or European Neuromuscular Centre criteria[182], owned their own smartphone and had regular access to their own Wi-Fi connection. IIM subtypes included were polymyositis (PM), dermatomyositis (DM), immune-mediated necrotising myopathy (IMNM) and anti-synthetase syndrome (ASS). Participants unable to walk or enter information via a smartphone touchscreen were excluded from the study. The study did not have the capacity to translate materials into other languages. Therefore potential participants who were unable to speak English and understand English verbal explanations were ineligible for recruitment.

Recruited participants were invited to take part in a 91 day study period. Participants were invited to attend the Clinical Research Facility at Salford Royal Hospital twice: 1) on the first day and 2) after completion of their study period. Disease activity was assessed on the first study day (baseline) using the IMACS Disease Activity Core Set Measures, which comprise 1) physician global assessment (visual analogue score [VAS] 0-10), 2) patient global assessment (VAS 0-10), 3) manual muscle testing (MMT), 4) functional assessment, such as the Health Assessment Questionnaire (HAQ), 5) extra-muscular activity assessment using the Myositis Disease Activity Assessment Tool (MDAAT), and 6) serum muscle enzyme level, such as creatine kinase (CK). Each of the IMACS Core Set Measures, apart from CK, were collected. MMT was assessed using the MMT26 score,

which assesses the strength (0-10 Kendall Scale) of 26 muscle groups, giving an overall score up to 260.

Participants were provided with a single SENS Motion Plus accelerometer sensor and replacement adhesive patches. SENS Motion Plus (manufactured by SENS Innovation Aps) accelerometer sensors were used to collect continuous accelerometer data. The accelerometer sensor (dimensions 3cm x 6cm x 0.5cm) is contained within an adhesive patch and attached to the lateral aspect of a participant's thigh, just above the knee. The accelerometer system measures acceleration in three perpendicular axes up to 100Hz; acceleration signals are sent via Bluetooth to the participant's smartphone and then transferred to a secure cloud-based storage system, which is available for download by the research team. The accelerometer system is capable of storing up to two weeks' of data if Bluetooth connectivity does not occur. The method of fixing the accelerometer sensor into the adhesive patch and placement onto the lateral aspect of the thigh was demonstrated to each participant, along with provision of written instructions, to allow self-replacement of the adhesive patch when required. Each participant was asked to walk for 10 metres along a corridor with a flat surface just after initial sensor placement. Each participant had the potential to continuously wear a sensor for a maximum of 91 days.

Accelerometer data was prepared using the following approach: 1) initial data processing, 2) activity status identification, 3) event detection, and 4) gait parameter calculation. The approach used in this study is based on methods used in other similar studies[127–129,212–215]. Reproducible code for steps 1-4 are included as supplementary material.

1 - Initial data processing

The gravitational component was removed from each of the three perpendicular X, Y and Z signals using L1-trend filtering, which produces piecewise linear outputs and is a variation on the Hodrick-Prescott filtering method[219,220]. L1-trend filtering was carried out using the "l1tf" package[221] in the statistical programme "R"[183].

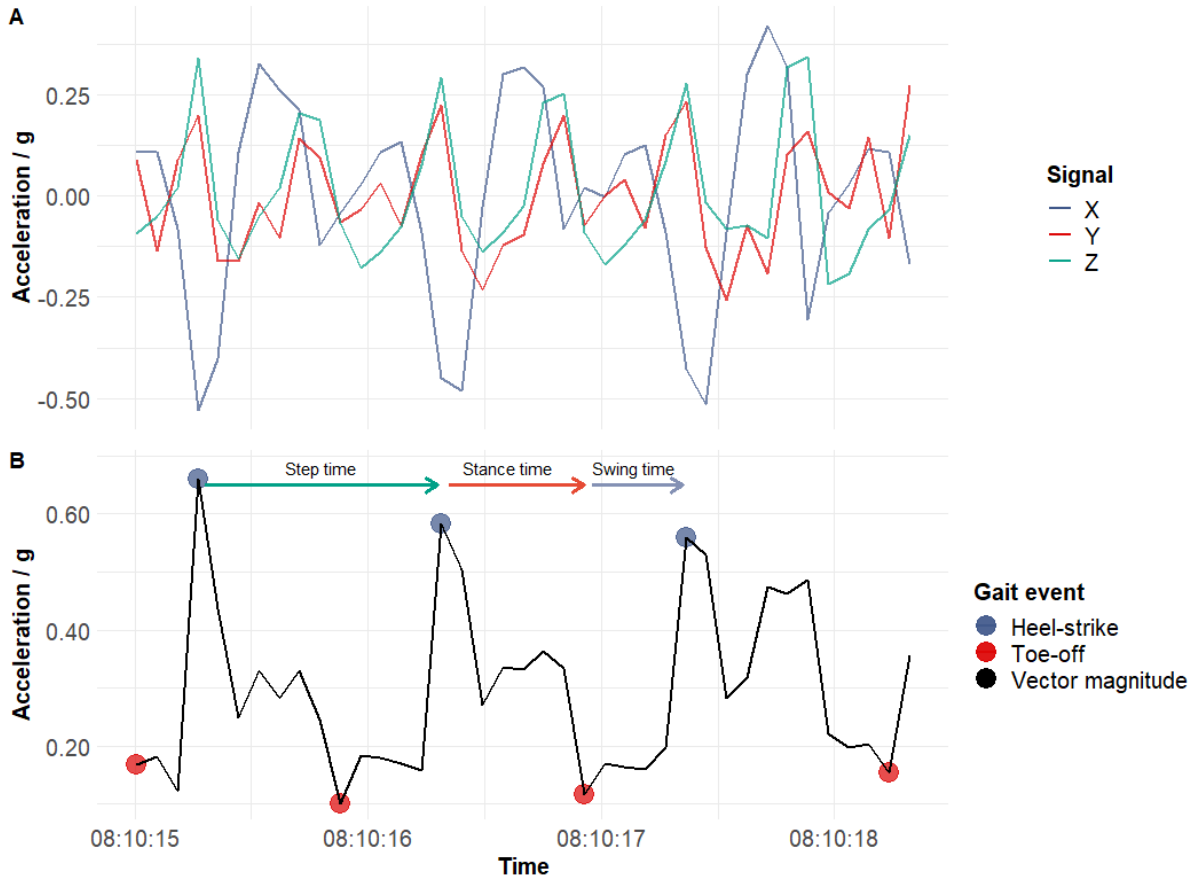
2 - Activity status identification

A Hidden Markov Model (HMM) was then applied to each participant's data. Two "states" throughout the entire study 91 day study period were predicted - walking and non-walking. Walking state identification was "trained" using accelerometer data from the 10 metre walking period just after sensor placement. Only accelerometer data throughout the 91 day study period that corresponded to the walking state was retained.

3 - Event detection

The X, Y and Z signals were combined into a single vector magnitude signal[222–224]. Heel-strike and toe-off events were identified via signal "peaks" (local signal maxima) and "troughs" (local signal minima), respectively, using the "findpeaks" function of the "pracma" R package [225]. Stance time was calculated as the time between each heel-strike and toe-off event. Swing time was calculated as the time between each toe-off and heel-strike event. The step time (time between two heel-strike events) was calculated. The stance:swing time ratio was also calculated. See Figure 15 for graphical illustration of calculation of gait parameters from raw accelerometer data.

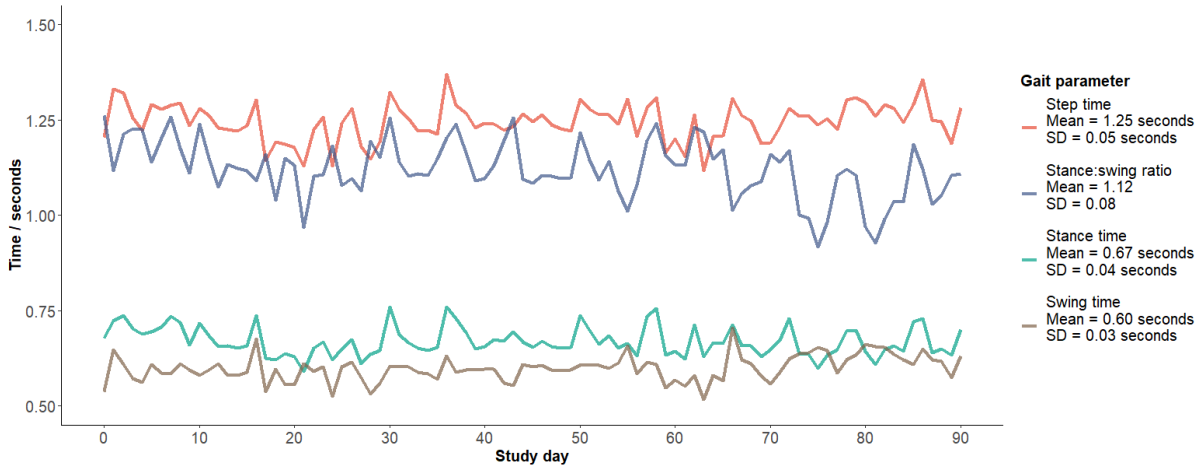
Figure 15 - Plots demonstrating a 3.5 second sample of accelerometer X, Y, Z (A) and vector magnitude signals with identification of heel-strike and toe-off events, and duration of gait phases (B)



4 - Gait parameter calculation

The mean step time, stance time, swing time and stance:swing time ratio for each participant on each day of the study period was calculated. The mean of each gait parameter for each participant across the entire 91 day study period was subsequently calculated. Also, the longitudinal variation of each gait parameter throughout the study duration was assessed via calculation of the standard deviation (SD) for each participant. See Figure 16 for graphical representation of calculated gait parameters for a single participant.

Figure 16 - Example of calculated gait parameters for single participant throughout study period



SD = standard deviation

Analysis

Summary variables of the cohort demographics and baseline IMACS Core Set Measures were calculated.

Simple linear modelling was used to investigate the relationships between each IMACS Core Set Measure and each gait parameter - step time, stance time, swing time and stance:swing ratio. The mean and SD (representing day-to-day variation) of each gait parameter were included as candidate variables. Gait parameters were modelled as number of tenths of a second to aid interpretation (i.e. stance time of 0.71 seconds was converted to 7.1 tenths of a second).

Results were interpreted in the context of meaningful differences of each IMACS Core Set Measure. Determination of minimal clinically important differences (MCIDs) for the IMACS Core Set Measures in the IIMs is lacking. A change of 5% of absolute values of MMT26 and VAS scores (physician global, patient global MDAAT) has been determined as meaningful, according to the 2016 ACR/EULAR Response Criteria[226,227]. Therefore, a change of 0.5 or more of patient global, physician global or MDAAT VAS scores and a change of 13 (5% of 260) or more of MMT26 score was employed as the MCID in this study. The MCID for HAQ has been reported as 0.25 in other rheumatic diseases[228–230].

Results

Twenty participants took part in the MyoPAD study. Data of two participants were excluded from analysis due to incomplete availability of baseline IMACS Core Set Measures. Therefore, data of the remaining 18 participants was analysed. Eleven (61%) participants were female. The median age of the cohort was 52 years (IQR 44, 57) with a median IIM disease duration of three years (IQR 2, 5; range 1-26 years). Nine (50%) had DM, five (28%) PM, three (17%) IMNM and one (6%) ASS. A total of 36,365 hours of sensor data was collected throughout the 91 day study period, with a median of 2,128 hours (97% of potential total) collected per participant.

The profile of baseline disease activity of the cohort is displayed in Table 13. Overall, the cohort displayed moderate to low disease activity, as evidenced by physician and patient global VAS scores. The functional impairment of the cohort was also low, as evidenced by HAQ scores and high MMT26 scores. Summary gait parameters across the cohort are also displayed in Table 13. Of note, the mean stance:swing time ratio (1.25) was reduced compared to the expected value of 1.5 to 1.6. This indicates that swing time constitutes a larger than expected proportion of the overall gait cycle in the study cohort.

Table 13 - Summary of IMACS Core Set Measures and gait parameters across the study cohort

	Variable	Median/mean	IQR/SD	Range
IMACS Core Set Measure	**Physician global VAS (range 0-10)**	4.0	2.6, 5.9	0.0, 8.5
	Patient global VAS (range 0-10)	3.0	2.0, 5.0	0.0, 9.0
	MMT26 (range 0-260)	254	244, 256	237, 260
	HAQ (range 0-3)	0.9	0.5, 1.1	0.0, 1.88
	MDAAT VAS (range 0-10)	2.5	2.1, 4.3	0.0, 6.5
Gait parameter	**Step time / seconds**	1.23	0.04	1.14, 1.25
	Stance time / seconds	0.71	0.04	0.64, 0.96
	Swing time / seconds	0.58	0.06	0.49, 0.69
	Stance:swing time ratio	1.25	0.12	1.02, 1.51

IMACS Core Set Measures are displayed as median and IQR

Gait parameters are displayed as mean and SD

IMACS = International Myositis Assessment and Clinical Studies Group, IQR = interquartile range, SD = standard deviation, VAS = visual analogue score, MMT = manual muscle testing, HAQ = Health Assessment Questionnaire, MDAAT = Myositis Disease Activity Assessment Tool

Simple linear modelling was used to investigate preliminary associations between each IMACS Core Set Measure and each calculated gait parameter, which were modelled as tenths of seconds (i.e. stance time of 0.71 seconds was converted to 7.1 tenths of a second). Modelling results are displayed in Table 14 and are graphically summarised in Figure 17. Clearly consistent associations between gait parameters and IMACS Core Set Measures were not observed, however a number of potentially important relationships were observed, which will be outlined in turn.

Prolonged step time was associated with higher physician global VAS. This magnitude of association corresponds to a 1.5 increase of physician global VAS score (range 0-10) for every 0.1 second increase in step time. Therefore, an increase of step time of only 0.03 second is associated with an increase of physician global VAS score of 0.5, which is the minimum meaningful difference.

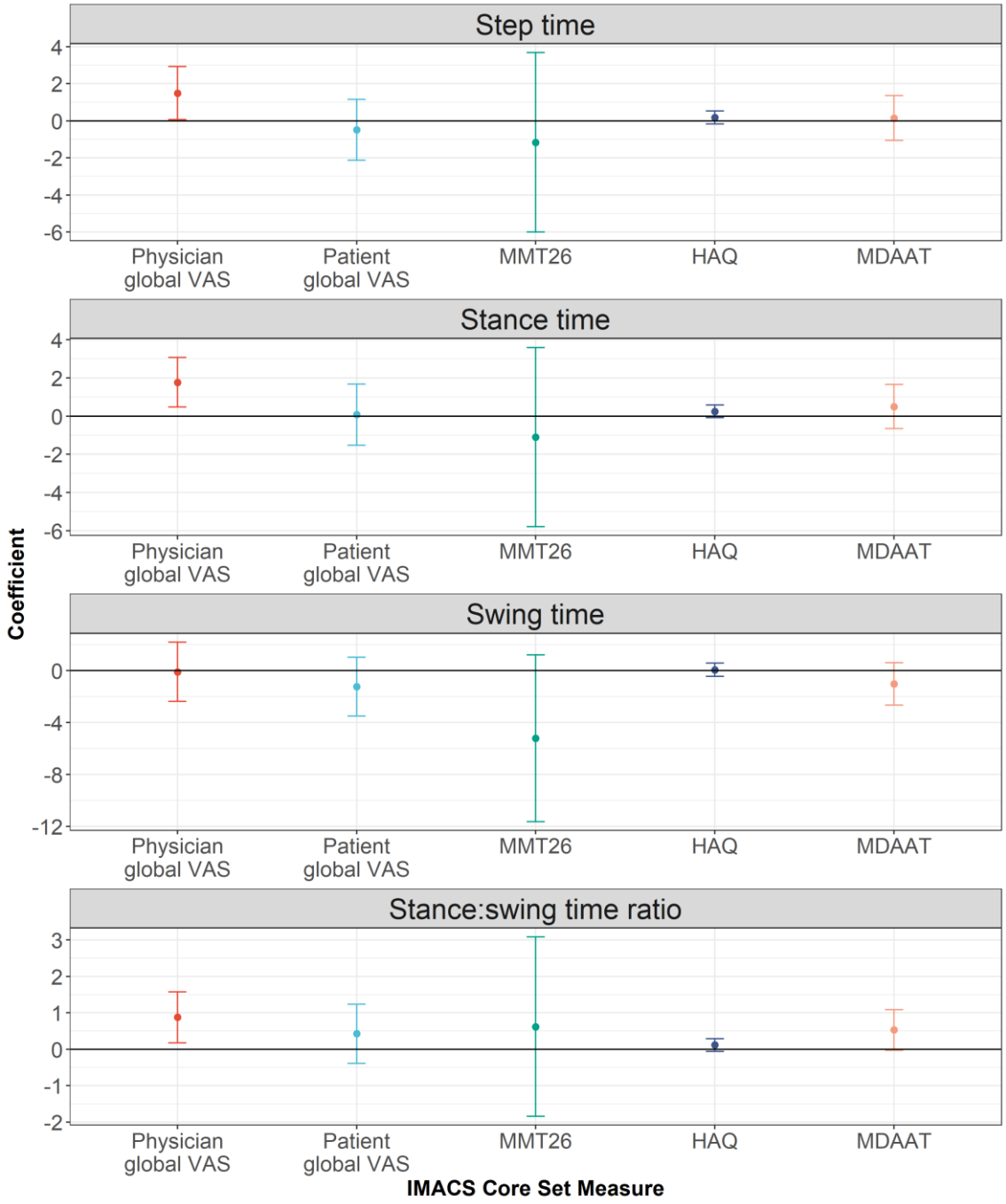
Prolonged stance time was associated with higher physician global VAS. This relationship corresponded to a 1.8 increase of physician global VAS score (range 0-10) for every 0.1 second increase in stance time. Therefore, an increase of stance time of only 0.03 seconds corresponds to an increase of physician global VAS of 0.5, which is the previously identified minimum meaningful difference.

Analysis indicated that prolonged swing time was potentially associated with lower MMT26 score. This corresponds to a 0.1 second prolongation of swing time with every 5.2 point reduction on the MMT26 scale (range 0-260). Therefore, a reduction of 13 points on the MMT26 scale (identified clinically meaningful difference) could potentially be associated with a 0.25 second prolongation of swing time.

Higher stance:swing time ratio was associated with higher physician VAS. This corresponds to an increase of 0.88 of physician global VAS score for every 0.1 increment of stance:swing time ratio. Analysis indicated that higher stance:swing time ratio was also potentially associated with higher MDAAT VAS (range 0-10). This corresponds to an increase of 0.5 for every 0.1 increment of stance:swing time ratio.

Higher physician global VAS was associated with higher step time SD, stance time SD and stance:swing time SD. Swing time SD was not associated with physician global VAS.

Figure 17 - Graphical summaries of simple linear regression of each gait parameter and each IMACS Core Set Measure (modelling results of gait parameter standard deviations are not displayed)



VAS = visual analogue scale, MMT = manual muscle testing, HAQ = Health Assessment Questionnaire, MDAAT = Myositis Disease Activity Assessment Tool, IMACS = International Myositis Assessment and Clinical Studies Group

Error bars refer to upper and lower boundaries of 95% confidence intervals

Table 14 - Simple linear modelling of each IMACS Core Set Measure against each gait parameter

Gait parameter†	IMACS Core Set Measure	Coef	95% CI
Step time	**Physician global VAS**	1.49	0.06, 2.93
	Patient global VAS	-0.49	-2.12, 1.15
	MMT26	-1.16	-5.99, 3.68
	HAQ	0.18	-0.17, 0.53
	MDAAT VAS	0.14	-1.06, 1.35
Stance time	**Physician global VAS**	1.77	0.47, 3.07
	Patient global VAS	0.08	-1.52, 1.68
	MMT26	-1.10	-5.79, 3.60
	HAQ	0.25	-0.08, 0.58
	MDAAT VAS	0.50	-0.65, 1.65
Swing time	**Physician global VAS**	-0.10	-2.37, 2.18
	Patient global VAS	-1.23	-3.50, 1.03
	MMT26	-5.21	-11.61, 1.20
	HAQ	0.06	-0.45, 0.57
	MDAAT VAS	-1.02	-2.66, 0.61
Stance:swing time ratio	**Physician global VAS**	0.88	0.18, 1.57
	Patient global VAS	0.43	-0.39, 1.24
	MMT26	0.62	-1.84, 3.08
	HAQ	0.12	-0.06, 0.29
	MDAAT VAS	0.53	-0.03, 1.09
Step time SD	**Physician global VAS**	0.78	-0.02, 1.58
	Patient global VAS	-0.04	-0.95, 0.87
	MMT26	-1.37	-3.96, 1.23
	HAQ	0.01	-0.19, 0.21
	MDAAT VAS	0.03	-0.64, 0.69
Stance time SD	**Physician global VAS**	0.79	0.32, 1.25
	Patient global VAS	0.20	-0.41, 0.82
	MMT26	-0.72	-2.51, 1.08
	HAQ	0.08	-0.06, 0.21
	MDAAT VAS	0.17	-0.28, 0.61
Swing time SD	**Physician global VAS**	0.05	-0.27, 0.37
	Patient global VAS	0.12	-0.20, 0.45
	MMT26	-0.62	-1.55, 0.30
	HAQ	0.02	-0.06, 0.09
	MDAAT VAS	-0.06	-0.30, 0.18
Stance:swing time ratio SD	**Physician global VAS**	1.62	0.05, 3.2
	Patient global VAS	0.35	-1.45, 2.16
	MMT26	-3.52	-8.57, 1.53
	HAQ	0.26	-0.12, 0.63
	MDAAT VAS	0.14	-1.19, 1.46

IMACS = International Myositis Assessment and Clinical Studies Group, coef = coefficient, CI = confidence interval, VAS = visual analogue score, MMT = manual muscle testing, HAQ = Health Assessment Questionnaire, MDAAT = Myositis Disease Activity Assessment Tool, SD = standard deviation

† All gait parameters are reported as tenths of seconds to aid interpretation

Discussion

This study has detailed a reproducible method of remote gait pattern assessment using a single thigh-worn accelerometer device. This study has also investigated associations between IIM disease activity and gait pattern parameters.

The methods described and computational code (see Appendices) developed for this study is fully reproducible and can be executed in the open source statistics programme R[183]. As described earlier, code sharing facilitates uptake and provides a framework into which future innovations can be integrated[216–218]. Future directions for such accelerometer data collection and processing include 1) improvement of precision of activity status identification (i.e. walking/non-walking) through use HMMs with a higher number of states or other statistical methods, such as support vector machine binary classifier[213], 2) integration of gyroscope data, and 3) exploration of the utility of collection of data from multiple sensors. The particular benefit of data collection from multiple accelerometer sensors includes the opportunity to measure further gait parameters (e.g. double-limb support time) from bilaterally thigh-placed sensors[231,232].

Analysis investigating relationships between gait parameters and IIM disease activity, as represented by the IMACS Core Set Measures, revealed a number of potential relationships that can inform future research directions. Before discussing these relationships, is it important to note that the small study cohort size limits precision and results should therefore be considered as information useful to inform future confirmatory analysis in larger cohorts.

Higher disease activity, represented by physician global VAS, was associated with prolonged stance time and higher stance:swing time ratio. Additionally, a potential relationship between step time and physician global VAS was observed. The observed prolonged step and stance times may be explained by hip flexor weakness due to underlying IIM-induced myositis[25]. Higher IIM disease activity may result in weaker hip flexion leading to reduced ability to support body-weight during single limb support phases of the gait cycle. Such weakness may be compensated by increasing time spent in "double-limb support" phases, resulting in prolonged stance time. Prolonged step time and increased double-limb support time has previously been observed in a small study by Siegel *et al*, which compared gait patterns between three IIM cases and a single healthy control[52]. Weak hip flexion can result in increased stance time and increased double-limb support time in other conditions, such as multiple sclerosis[233–235]. Further, previous research has indicated that even mild weakness of hip flexors is

particularly associated with detectable abnormal gait[236]. Although plausible, this mechanism is hypothetical and requires corroboration via detailed gait laboratory analysis. Serial gait laboratory data from an IIM patient cohort with a wide spectrum of disease activity may allow identification of the relationship between the IMACS Core Set Measures and additional gait parameters, including double-limb support time. Such evidence may clearly delineate any underlying relationships, thus paving the way for translation into clinical practice.

Associations between gait parameters and MMT26 score were not observed. Identification of associations between MMT26 and gait parameters were possibly limited due to the small range of MMT26 values across the cohort and the previously mentioned "ceiling effect". Recent research has demonstrated utility of hand held dynamometry (HHD) as a method of quantitative muscle strength measurement in IIM cohorts[237,238]. HHD provides quantitative strength values (in contrast to the subjective values elicited from MMT), which are not subject to a ceiling effect. A further benefit of HHD over MMT is low inter and intra-rater variation[237,238]. Future studies investigating the role of remote gait monitoring in the IIMs could therefore perhaps employ HHD as an objective method of muscle strength assessment.

Finally, analysis indicates that higher stance time SD, representing day-to-day variation, may be associated with higher IIM disease activity. This may potentially be a manifestation of the "boom and bust" pattern of energy availability/expenditure; i.e. patients with high IIM disease activity may be able to compensate for weak hip flexor muscles on one day, but then be unable to compensate the next due to fatigue, thus resulting in detectable day-to-day variation. Corroborating quantitative research in this area is lacking, however previous qualitative research from the MyoPAD study cohort illustrates the patient experience of the need for "energy-rationing" and of "good" and "bad" days[172]. The potential need to detect such day-to-day variation illustrates the utility of continuous remote monitoring as measurement of such variables in gait laboratories would be impractical and prohibitively costly.

Clinical/research implications

It is our hope that this study's methods and results trigger the wider uptake of remote gait analysis in the IIMs and possibly other related diseases, thus benefitting both research and clinical care. IIM research could benefit from remote gait analysis in a number of ways. Firstly, longitudinal gait parameter assessment could form a novel outcome measure in IIM interventional trials, which have been limited by the scope of available outcome measures. For example, MMT has formed primary or secondary

outcomes in many IIM trials[239–243], but is limited, as described earlier, by a ceiling effect, poor sensitivity to change, and marked inter and intra-rater variability[25,56]. Remotely collected gait parameter data, which provides objective quantitative data not subject to a ceiling effect, may provide further insights into IIM-induced muscle weakness and the impact upon gait and function.

Remote collection of longitudinal gait parameter data may enhance clinical care by providing an objective measure of the day-to-day impact of IIM-induced muscle weakness. Objective measures of IIM disease activity (e.g. serum CK level) available for use in clinical practice are few in number. The availability of an objective measure in the form of gait pattern data may allow clinicians to better distinguish between symptoms due to active disease and irreversible muscle damage, thus guiding treatment. Potential future integration of this study's method of gait parameter measurement into electronic health records may confer wide ranging benefits, including enhanced patient-doctor communication and improved patient satisfaction[244]. Effective implementation of digital technology solutions, such as wearable accelerometer sensors, into routine healthcare requires the execution of a specific number of steps, thus ensuring utility, safety and effectiveness. Such steps were described earlier and are detailed in the American Medical Association's "Digital Health Implementation Playbook"[167].

The economic impact of routine use of wearable technologies in healthcare is also noteworthy. It has been estimated that, in the USA, replacing just one in five outpatient appointments with "digital consultations" (i.e. remote consultation using data collected from wearable technology) could save $40 billion each year[245]. Remodelling of the current model of IIM patient care is required, in part due to associated costs and access to IIM specialists. Routine use of wearable technology, such as accelerometer sensors, and the introduction of digital consultations may contribute to a more dynamic and cost-effective system.

Limitations

There are a number of limitations to this study that should be acknowledged. Firstly, the small cohort size limits the strength of detection of relationships between gait parameters and the IMACS Core Set Measures. Secondly, study participant selection bias may impact external validity of results. An important source of study participant selection is "digital literacy" [150]; lower ability or confidence in using mHealth devices, such as an accelerometer sensor, may have deterred participant involvement. Thirdly, the described method of gait parameter assessment has not been fully validated in a

gold-standard gait lab. Such validation is warranted as part of a future research agenda. Fourthly, IIM disease activity was assessed using individual components of the IMACS Core Set Measures, apart from CK level. Further, no single summary or composite measure of IIM disease activity using the IMACS Core Set Measures is available. Availability of such a composite measure may allow further identification of relationships between gait pattern and IIM disease activity. Finally, a number of potentially important gait parameters were not included in this analysis. These gait parameters include cadence (number of steps in 60 second period), stride length, gait asymmetry and, as discussed, double-limb support time.

Conclusions

This study has demonstrated a reproducible method of remotely collecting and processing accelerometer data, thus allowing IIM-specific gait pattern characterisation and identification of particular abnormalities associated with disease activity. This study may therefore represent a small but important part of the digital healthcare revolution, thus potentially allowing the first steps to be taken towards transformation of the current model of IIM clinical care and research outcome measurement.

Chapter 7

7 Discussion and conclusions

Throughout my thesis I have aimed to explore the role that frequent remote monitoring can potentially play in IIM research and clinical care. In this section I will: 1) assimilate the major findings, 2) outline strengths and limitations, 3) suggest a future research agenda to allow translation into clinical/research settings, and 4) explore the eventual future clinical and research implications.

7.1 Major findings

Overall, research within this thesis has demonstrated three major findings: 1) need for and feasibility of remote monitoring to facilitate increased frequency of data collection, 2) preliminary characterisation of IIM flares, and 3) early exploration of whether gait pattern data can provide a novel method of remote IIM disease activity assessment.

7.1.1 Need for and feasibility of increased frequency of data collection

Results from qualitative interviews in Chapter 3 illustrated a number of specific limitations of the current model of IIM clinical care and disease activity assessment. Patients perceived that certain measures, particularly the MMT and CK, were unable to comprehensively quantify their IIM disease activity, thus potentially limiting treatment decisions. Frequent day-to-day variation of symptoms, which cannot be detected via currently available methods, was also commonly reported. Finally, pain and fatigue were identified as being absent from routine assessment in clinical care, despite these symptoms being identified as the most likely to frequently change on "good" and "bad" days. An objective of the MyoPAD Study was to develop a system that could detect day-to-day symptom variation and quantify predominant symptoms, such as pain and fatigue. The observed high engagement during the MyoPAD Study indicates that daily symptom assessment is feasible (Chapter 4).

7.1.2 Preliminary characterisation of IIM flares

As discussed in the introduction, very little research has been carried out into IIM flares. Indeed, the only studies to define IIM flares used clinician-centred definitions dependent on immunosuppressive treatment escalation. Flare research is complex and challenging and needs to be tailored to the specific disease being considered. For example, recent flare definition for rheumatoid arthritis by OMERACT involved multiple qualitative and quantitative studies involving patients, clinicians and researchers[196–198]. This thesis aimed to provide initial explorations into characterising IIM flares, with the aim of informing future research into this important area.

Qualitative results from Chapter 3 provide patient insights on the characteristics of IIM flares. Reduced physical endurance and escalation of symptoms were commonly associated. Participants also reported that they perceived flares to happen frequently and were typically of short (2-3 days) duration. Further, a number of participants perceived that serum CK levels were not always raised when experiencing heightened symptoms or a flare. In Chapter 5 I used daily collected symptom data to investigate the link between symptoms and patient-reported flares. I identified that symptom flares are frequent and typically of short duration, prospectively quantifying the patterns described during the qualitative interviews. I also identified that patient-reported flares were usually associated with a symptom-flare (based on sudden increase of symptom score compared to underlying trend). These results indicate that IIM flares are likely characterised by short duration increases in symptoms, predominantly fatigue and pain. Flare definitions employed in previous studies that rely on the need for treatment escalation would likely miss these frequent short duration symptom increases. Interestingly, a significant minority (31%) of patient-reported flares were not associated with any symptom-based flare. This indicates that patients may consider a flare to be characterised by manifestations other than sudden symptom increases, such as functional limitation and effect upon other factors, such as employment ability, mood and sleep.

Results also illustrated the utility of collecting daily symptom data, as the relationships between patient-reported and symptom-based flares could not have been investigated using infrequently collected data. It is plausible and probable that IIM flares comprise multiple pathological processes, resulting in distinct symptom patterns and varying detectability via investigations. Further understanding of these underlying pathological processes and resulting symptom manifestations may allow for detailed and accurate

characterisation of multiple "types" of IIM flares, as described in the discussion section of Chapter 5.

7.1.3 Potential ability of gait pattern data to provide a novel method of remote IIM disease activity assessment

In the introduction I outlined how gait pattern data could potentially provide a novel method of IIM disease activity measurement. Assimilated literature in Chapter 2 and engagement results in Chapter 4 indicate that accelerometer data collection in IIM cohorts is practical and feasible. The weak associations between disease activity and accelerometer data-based physical activity parameters identified in Chapter 2 indicated the need for more detailed data that assesses the consequence of hip flexor muscle weakness, such as gait pattern data. Quantitative analysis of gait data in Chapter 6 identified that gait pattern may be associated with IIM disease activity (e.g. prolonged stance time and physician/patient global VAS), however the strength of identified associations is limited due to the small study cohort. As described in Chapter 6, these preliminary insights can inform future research into this area, which will be described later.

7.2 Strengths and limitations

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

7.2.1 Strengths

Throughout my thesis I have combined multiple disciplines to investigate the unmet need - qualitative interviews and analysis, systematic review, "traditional" epidemiology, mHealth techniques, statistics and signal processing. Each approach is of equal importance and the combination enhances the overall impact of the findings. Future investigation of particular research topics, such as characterising IIM flares, will require comprehensive using such "mixed methods". Use of each discipline has greatly enhanced my skill set and appreciation for the utility of mixed methods research.

I have tried to ensure that the research throughout my thesis is patient-centred. I considered the "patient impact" throughout design of use of the MyoPAD app and accelerometer sensor, participant involvement, analysis and identification of conclusions.

I believe that eventual clinical translation will be facilitated through the focus on patient benefit that I maintained.

The methods employed in my research generated large volumes of data (21,709 individual PROMs and 40,145 hours of sensor data), which allowed for identification of the above findings and conclusions. In particular, it was the high frequency of data, facilitated by mHealth methods, which allowed for characterisation of IIM flares and detailed gait pattern measurement. Collection of such data would not have been feasible using "traditional" epidemiological approaches.

7.2.2 Limitations

A number of limitations of my research throughout this thesis are evident; outlining these may inform the design of future studies.

The MyoPAD Study recruited only a small cohort (N = 20). Although the small cohort size did not limit the ability to characterise flares or measure gait patterns, the external validity and strength of the findings are limited. External validity is affected primarily by probable selection bias, i.e. the recruited cohort is likely not representative of the wider IIM population. As discussed in Chapter 4, the recruited cohort were highly motivated and "digitally literate", thus ensuring high engagement. It is therefore plausible that future wider use of smartphone apps and thigh-worn sensors in a representative cohort may see lower levels of engagement and thus statistical power.

Repeated measurements of IIM disease activity were not taken throughout the MyoPAD Study. This was, in part, due to participant preference expressed during the co-design phase. I, along with the rest of the study team, prioritised engagement and frequent data collection above repeated disease activity measurement. Repeated IIM disease activity measurements may have allowed for more detailed investigation, for example, into the validity of continuous gait pattern data as a "digital biomarker". However, I feel that the strength of my thesis lies in demonstrating how frequent data collection can complement, not necessarily replace, infrequent disease activity measurement.

The small range and spread of disease activity data (IMACS Core Set Measures) within the cohort may have impaired identification of relationships with gait parameters. This was particularly evident with MMT26 scores, which only ranged 237-260. Future studies could potentially endeavour to recruit an IIM cohort with wide ranging disease activity parameters, thus enhancing the ability to detect underlying relationships.

Another drawback was the limited extent of quantitative analysis into relationships between IMACS Core Set Measures and gait parameters carried out. Only simple linear modelling was utilised and no investigation into detailed longitudinal patterns was carried out.

Finally, the same participants provided input and data across multiple aspects of the thesis. This is due to the design of the MyoPAD Study. This may have limited the breadth of qualitative, PROM and gait pattern data available for analysis, thus, again, limiting external validity.

7.3 Future research agenda to allow translation into clinical and research settings

Delineation of the overall findings of this thesis and acknowledgment of limitations can aid the development of a focused and effective future research agenda. This research agenda's overall aim could be to make remote monitoring of continuous PROM/symptom and gait data a reality in future clinical and research settings.

In the introduction I outlined the steps necessary for the development and eventual clinical implementation of digital health solutions. These include:

1. Delineation of clinical need/unmet need
2. Technology hardware development
3. Technology software development
4. Development of code capable to processing collected data
5. Demonstration of clinical/research utility
6. Economic analysis
7. Embedding within healthcare

Considerable further demonstration of clinical/research utility (step 5) is required as this thesis has only provided preliminary relevant evidence. Further research should therefore aim to address steps 5, 6 and 7. This section will discuss specific research that can address steps 5 and 7. Economic analysis (step 6) is a highly complex area that requires explanation of a number of unique concepts and is therefore outside the scope of discussion within this thesis.

7.3.1 Demonstration of clinical utility

A programme of research to outline the clinical utility in the IIMs is warranted.

Firstly, the potential ability of gait parameter data to provide clinically useful IIM-specific information is required. Longitudinal data could be collected in a larger cohort in a manner similar to the MyoPAD study, with the addition of extra collection of IMACS Core Set Measures on a monthly basis. The finding in Chapter 6 that prolonged stance time, indicative of prolonged double limb support time, is potentially associated with IIM disease activity provides evidence that data collection from bilateral thigh accelerometer sensors is warranted. Bilateral thigh sensors will allow double limb support time to be measured. Developed code and other identified potential relationships from Chapter 6 could form the basis of analysis into this area. Analysis could focus on identifying changes of gait parameters associated with changes of disease activity. Results could thus delineate how remote gait monitoring could form a proxy measurement for disease activity in clinical settings.

Secondly, the impact of availability of daily PROM/symptom data upon clinicians' decision making should be assessed. Qualitative approaches are potentially best-placed to precisely identify the impact made. Focus groups and one-on-one interviews with clinicians (e.g. general rheumatologists, IIM specialists, physiotherapists, specialist nurses) may provide a comprehensive picture of potential clinical impact. Participants could be provided with a hypothetical patient vignette, firstly without and then with daily PROM/symptom data. Comparison of the management decisions made could therefore delineate the precise impact that daily PROM/symptom data could pose. Further, direct comparison of the clinical outcomes of patients treated with and without remotely collected data could identify the specific clinical impact that this approach confers. This approach is currently being planned as part of the REMORA2 study, which is a subsequent step of the previously mentioned REMORA study, which investigated the utility of daily smartphone-collected PROM/symptom data in patients with rheumatoid arthritis. The REMORA2 study will recruit patients with rheumatoid arthritis and randomise them to either the intervention or control group. The intervention group will submit daily PROM/symptom data via a smartphone-based app and this data will be available to clinicians during clinical consultations. The control group will receive standard care. The added clinical benefit that provision of PROM/symptom data to clinicians confers will be quantified through comparison of disease-specific outcome measures between the two groups. The approach used in the REMORA2 can be tailored to a future IIM-focused study. Raw symptom data and the identification of flares,

symptom-based and patient reported as defined in Chapter 5, could be included. Further, lessons learned in the REMORA2 study, regarding recruitment, engagement (participant and clinician), and analysis can inform a future IIM-specific study.

7.3.2 Demonstration of research utility

Remote symptom and gait pattern monitoring could provide many benefits to IIM research (observational and interventional). However, the role that this methodology could play as novel outcome measures is particularly worthy of further investigation.

As mentioned a number of times throughout this thesis, certain qualities of the IMACS Core Set Measures reduces their accuracy as outcome measures, thus potentially limiting the accuracy of efficacy of new treatments in clinical trials. A dedicated programme of research will be necessary to assess pertinent accuracy parameters to delineate the role of remote symptom and gait pattern monitoring as outcome measures; these include, but are not limited to acceptability, reliability, validity and ability to detect change[56,246,247]. It would be appropriate to follow the OMERACT approach for development and validation of remote symptom and gait pattern monitoring as outcomes in IIM research[248]. OMERACT require a measure to be able to measure truth (e.g. construct validity), be capable of discriminating changes in underlying state (i.e. identify meaningful changes of disease activity), and to be feasible (i.e. practical in research/clinical settings). Preliminary insights and evidence could be generated via daily symptom monitoring and gait pattern measurement in upcoming IIM interventional trials, such as the MyoJAK study, which aims to assess the efficacy of baricitinib (a Janus Kinase inhibitor) in IIMs. Identification of associations with disease activity changes related to baricitinib administration will provide proof of concept that daily symptom/gait parameter data could provide complementary insights for interventional drug trials, similar to that in the RA-BEAM and RA-BUILD studies[112].

Recent research has highlighted the utility of using hand held dynamometry (HHD) as a method of quantitative muscle strength measurement in IIM cohorts[237,238]. Benefits of HHD over MMT include 1) the provision of a quantitative strength value (as opposed to subjective strength assessment), 2) absence of ceiling effect, and 3) low inter and intra-rater variability. It may therefore perhaps be appropriate for future development/validation research to investigate associations between gait parameters and muscle strength assessed used HHD, as opposed to MMT.

7.3.3 Embedding within healthcare

Embedding of remote PROM/symptom and gait data collection within healthcare systems will be essential to ensure widespread clinical translation. This could be achieved in a number of ways, however integration into increasingly ubiquitous "electronic health record" (EHR) systems is potentially the most impactful. The format of data collected (PROM and accelerometer data) in the MyoPAD Study could feasibly allow integration into EHRs. In recent years EHRs have superseded paper-based records in many health care settings, with 77% of UK NHS hospitals reporting use of an EHR in 2019[249]. Indeed, "paperless" patient data systems in all UK hospitals is part NHS Long Term Plan[250]. Integration of data collected from mHealth devices, such as smartphone-based apps and wearable sensors, is feasible and offers a number of potential benefits[251,252] Potential benefits include 1) improved patient-clinician communication, 2) availability for additional objective outcome assessment, 3) personalisation of management, 4) identification of previously unrecognised problems, and 5) improved patient satisfaction[244]. A number of barriers to EHR/mHealth integration do exist, however, and may explain the reason for the lack of widespread uptake. Barriers include 1) technical capability, 2) information governance/security, 3) potential for increased workload (i.e. increased volume of results for clinicians to review), 4) need for demonstration of utility, and 5) lack of awareness of opportunities in clinician community[253]. Increased awareness of potential opportunities provided by use of such remotely collected data among patient and clinician populations will be required to ensure adequate uptake following EHR integration. Dissemination via professional bodies (e.g. British Society of Rheumatology), patient charities (e.g. Versus Arthritis) and social media may facilitate uptake.

Two particular steps are required to achieve EHR integration.

Firstly, software integration, thus allowing a seamless flow of data from smartphone/sensor into the EHR, is vital. Recent advances in interoperability include the development of the Fast Healthcare Interoperability Resources (FHIR) framework, which standardises the design of mHealth systems, thus allowing for easier EHR integration[254]. Software of the MyoPAD app and accelerometer sensor is FHIR "compliant" so integration is feasible, though will require further funding and close collaboration between the developer industry partner and candidate hospital's EHR team.

Secondly, collaboration with existing UK regulation frameworks and approval processes is essential. Close collaboration with NHSX, the organisation tasked with "driving forward the digital transformation of health and social care", could ensure safe and effective

clinical integration. In particular, the newly developed Digital Technology Assessment Criteria by NHSX set out the baseline criteria that must be met prior to clinical use in NHS settings[255]. Further, a clear evidence standards framework for digital technologies has been set out by the National Institute for Health and Care Excellence (NICE)[256]. Following NHSX and NICE criteria/frameworks during clinical integration can ensure regulatory compliance and safety.

It is important to consider factors that may affect uptake of use of frequent remotely generated patient data in clinical settings. A useful framework that considers these aspects was developed by Greenhalgh et al in 2017[257]. The "non-adoption, abandonment, and challenges to the scale-up, spread and sustainability" (NASSS) framework could be applied to the widespread adoption of patient generated data in healthcare settings. The NASSS framework encourages the consideration of 1) the medical condition (i.e. is the technology suited to addressing the clinical need?), 2) the technology (i.e. practical aspects of the technology, such as ease of use), 3) the "value proposition" (i.e. will the new technology confer adequate added value?), 4) the adopters (i.e. enablers and barriers relating to the intended individual users), 5) the organisation (i.e. is the organisation ready to commit to and adopt a novel way of data collection?), 6) the wider context (i.e. can the novel technology be expanded outside the early adopters and "champions"), and 7) interaction between domains and adaptation over time (i.e. factors affecting uptake will continuously change over time and thus requires continual review).

7.4 Future clinical implications

A range of clinical benefits could be realised following integration of remote PROM/symptom and gait data collection into routine clinical practice.

Firstly, the ability for clinicians and patients to be able to discuss symptom data, including the occurrence of flares and other associated information, such as potential flare "triggers", may enhance communication, focus clinical consultations and personalise treatment, as demonstrated in rheumatoid arthritis in the previously mentioned REMORA study[177]. Further, the ability to remotely detect the occurrence of flares or symptom patterns associated with increased disease activity may allow a clinician to proactively instigate appropriate treatment and possibly prevent irreversible muscle damage and disability.

Secondly, remotely collected gait pattern data may provide a novel method of passive continuous IIM disease activity measurement. Detection of gait pattern abnormalities associated with disease activity, such as stance time, may allow clinicians to identify patients with improving/worsening IIM. Again, such ability may allow clinicians to proactively instigate muscle damage preventing/limiting treatment.

Thirdly, daily PROM/symptom data and continuous accelerometer data could potentially facilitate individual patient treatment effectiveness assessment. A clinician could potentially assess the effectiveness of new treatment in an individual patient using remotely collected PROM/symptom and gait pattern data. For example, longitudinal reductions in fatigue and shortening of stance time coinciding with initiation of methotrexate (a commonly used medication used for IIM treatment) could provide evidence that this treatment may be conferring benefit. Conversely, persistence of symptom-based flares and prolongation of stance time may provide evidence that a new treatment is not conferring benefit.

It is, however, important to consider the possibility of unintended consequences and "e-iatrogenic" harm that could occur with routine use of remotely collected PROM/symptom and gait pattern data[199–201]. These include 1) data security breaches, 2) increased clinician workload, 3) increased medical intervention (e.g. false identification of flare and inappropriate immunosuppression), 4) formation of "treatment hierarchy" based on patient digital literacy (e.g. potential of lower quality care for those without smartphone access), and 5) overdependence on technology[258]. These unintended consequences, and others, must be considered during the process of implementation into clinical care.

Clinical care of other or multiple chronic conditions could potentially be enhanced via remote PROM/symptom and/or gait pattern data collection. An estimated 15 million people in the UK have at least one chronic health condition[259] and the prevalence of "multi-morbidity" (i.e. living with more than one chronic health condition) is increasing[260]. The current model of out-patient assessment by individual clinicians of separate specialities may not enable the provision of best care for patients living with multi-morbidity. Recommendations from NICE in 2016 included: "improving quality of life by reducing treatment burden, adverse events, and unplanned care" and "improving coordination of care across services". Integration of continuous remote monitoring into the routine assessment of chronic conditions may represent one aspect of how healthcare services can modify patient interaction and enable appropriate management of people with multi-morbidity.

7.5 Future research implications

The findings of my thesis also have a number of implications for how future research (not just mHealth research) could be carried out. In particular, the impact of high volumes of longitudinal data on study power, developed code for accelerometer data processing, the ability to identify "digital biomarkers" related to flare occurrence, and potential role in the context of the COVID-19 pandemic are noteworthy.

The demonstration of high engagement and collection of high volumes of useful data from a small cohort may incentivise the wider uptake of remote monitoring methods in other areas of research, both within and outside the IIMs. Recruitment to IIM observational and interventional studies have, to date, been limited by the rarity of the disease, thus impacting overall study power. Increased international collaboration and data sharing has been posited as a potential solution[261], however incipient political barriers may limit the ability of UK researchers to benefit from such collaboration[262]. Frequent remote data collection could perhaps improve the accuracy of parameter measurement in inevitably small study populations, thus enhancing overall study power without increasing cohort size.

The field of processing and analysing high frequency accelerometer data is rapidly expanding. The provision of reproducible code for accelerometer data analysis may encourage wider participation of researchers outside this area. In turn, this may open the opportunities of remote monitoring to other disease areas, thus widening the patient benefit. Further, publication of code can enhance transparency of methods and boost confidence of researchers and other stakeholders in reported results and future opportunities[216–218]. This can encourage and enable other researchers to complete subsequent steps necessary in the implementation of continuous remote gait pattern measurement, without having to commit time and resources to the development of their own code.

Chapter 5 demonstrated the utility of daily PROM/symptom data collection in characterising IIM flares in a detailed manner. This approach could potentially be applied in other disease areas, such as systemic lupus erythematosus (SLE). Much more is known about SLE flares than IIM flares, however a number of unmet needs remain. For example, no validated biomarkers for SLE flare or increased disease activity exist[263]. The availability of a biomarker that could accurately predict or confirm an SLE flare could considerably enhance and focus SLE management. Previous studies have aimed to identify biological biomarkers, such as type-1 interferon induced chemokines, where the association with flares and disease activity is not consistent between study populations

[264–269]. A "digital biomarker" based on daily symptom/PROM data could perhaps provide a more accurate and user-friendly method of SLE flare prediction, possibly in combination with biological biomarkers. Daily PROM/symptom data collected in a prospective SLE cohort along with gold-standard disease activity (i.e. Systemic Lupus Erythematosus Disease Activity Index[270,271]) and treatment data could provide preliminary insights into candidate digital biomarkers for SLE flares. Of course, this approach of digital biomarker identification could be applied and tailored to a multitude of chronic diseases where flare research is warranted or digital biomarkers may enhance clinical care or research.

Finally, almost every aspect of society has been impacted by the COVID-19 pandemic. Clinical research has been particularly affected, thus stymying advances in healthcare[272]. Infection control measures have prevented potential study participants from being able to attend clinical research facilities, thus halting a wide number study types, such as clinical trials and observational studies. Remote monitoring could perhaps provide a novel method of data collection without the associated risk of COVID-19 transmission. Indeed, smartphone-based app data collection has allowed COVID-19-specific research to take place, for example with the COVID Symptom Study App[108], as described in the introduction. As described earlier, a number of steps are necessary before widespread remote symptom/gait parameter monitoring in IIM and other participants is possible, however the urgent need for innovative approaches may expedite efforts and funding in this frontier. It is perhaps possible that the COVID-19 pandemic may act as a catalyst, progressing the implementation of innovations related to the digital healthcare revolution into clinical and research settings[273].

7.6 Final remarks

My thesis has addressed a number of preliminary steps necessary in the eventual implementation of frequent remote symptom/gait pattern monitoring in the IIMs. I have delineated the unmet need, demonstrated feasibility, and provided preliminary insights into the clinical/research utility. Additionally, I have envisaged the potential future benefits that this approach could confer and outlined a research agenda.

We can never know what Sherlock Holmes may have made of the opportunities posed by the digital healthcare revolution, however we can perhaps assume that he would have looked fondly upon the ability granted to clinicians and researchers to be able to view diseases and their consequences in a more objective manner.

“All things should be seen exactly as they are.”

Sherlock Holmes

The Adventure of the Greek Interpreter[274]

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9 Appendices

9.1 Appendix to Chapter 1 - IMACS Core Set Measures

IMACS FORM 02: PHYSICIAN GLOBAL ACTIVITY ASSESSMENT

Subject's IMACS number _____

Assessor _____

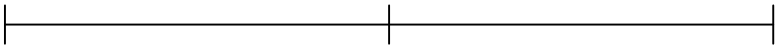
Date of assessment (mm/dd/yy) _____

Assessment number _____

Physician Global Activity Assessment

Disease Activity is defined as potentially reversible pathology or physiology resulting from the myositis. Clinical findings known or suspected to be due to another disease process should not be considered in this evaluation. The global assessment of disease activity is to be judged from all the information available to you today including the subject's appearance, history, physical examination, diagnostic laboratory testing and your resultant medical therapy.

Please rate your global (overall) disease activity assessment by drawing a vertical mark on the 10-cm. line below according to the following scale: left end of line = no evidence of disease activity, midpoint of line = moderate disease activity, and right end of line = extremely active or severe disease activity.



No evidence of disease activity

Extremely active or severe disease activity

Also rate global disease activity on a 5-point Likert scale:

___0 = none
___1 = mild activity
___2 = moderate activity
___3 = severe activity
___4 = extremely severe activity

IMACS FORM 03: PATIENT/PARENT GLOBAL ACTIVITY ASSESSMENT

Subject's IMACS number _____

Assessor _____ _____

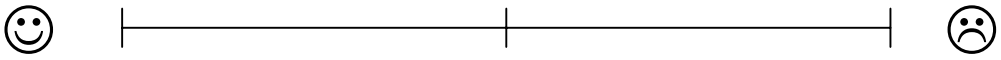
Assessor's relationship to subject: Patient; Mother; Father; Other (specify):_____

Date of assessment (mm/dd/yy) _____

Assessment number _____

Your myositis is the result of the combined effects of many disease processes. One of these is disease activity, which is active inflammation in your/your child's muscles, skin, joints, intestines, heart, lungs or other parts of your body, which can improve when treated with medicines.

1. Considering all the ways that myositis affects you/your child, please rate the overall activity of your/your child's disease today by placing a mark on the line below.



No evidence of disease activity

Extremely active or severe disease activity

IMACS FORM 04: Manual Muscle Testing Scoring Sheet

Subject's IMACS number _____

Assessor _____

Date of assessment (mm/dd/yy) _____

Assessment number _____

Muscle Groups	**Right (0 – 10)**	**Left (0 – 10)**	**Axial (0 – 10)**
Axial Muscles (0 – 20)			
Neck Flexors**	-	-	
Neck Extensors	-	-	
Proximal Muscles (0 – 160)			
Trapezius			-
Deltoid middle**			-
Biceps brachii**			-
Gluteus maximus**			-
Gluteus medius**			-
Iliopsoas			-
Hamstrings			-
Quadriceps**			-
Distal Muscles (0 – 80)			-
Wrist Extensors**			-
Wrist Flexors			-
Ankle dorsiflexors**			-
Ankle plantar flexors			-
MMT8 score (0 – 80)**			
Total MMT26 score (0 – 260)			

****MMT8** is a set of 8 designated muscles tested unilaterally (potential score 0 – 80), generally on right side (unless cannot be tested on right, then use left side)
Axial score: 0 – 20 potential range: sum of neck flexors and extensors
Proximal score: 0 - 160 potential range; 8 muscle groups tested bilaterally
Distal score: 0 - 80 potential range; 4 muscle groups tested bilaterally
Total score (MMT26): 0 - 260 potential range; sum of axial, proximal and distal scores

IMACS FORM 05a: HEALTH ASSESSMENT QUESTIONNAIRE

Subject's IMACS number_____
Person Completing: ___Patient ___Other: Relationship_____
Date of assessment (mm/dd/yy)_____ Assessment number_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
DRESSING & GROOMING				
Are you able to:				
-Dress yourself, including tying shoelaces, and doing buttons?	☐	☐	☐	☐
-Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
-Stand up from a straight chair?	☐	☐	☐	☐
-Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
-Cut your meat?	☐	☐	☐	☐
-Lift a full cup or glass to your mouth?	☐	☐	☐	☐
-Open a milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
-Walk outdoors on flat ground?	☐	☐	☐	☐
-Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any if these activities:

- ☐ Cane
- ☐ Walker
- ☐ Crutches
- ☐ Wheelchair
- ☐ Devices used for dressing (button hook, zipper pull, shoe horn, etc.)
- ☐ Special or built up utensils
- ☐ Special or built up chair
- ☐ Other (specify:_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Dressing and Grooming
- ☐ Arising
- ☐ Eating
- ☐ Walking

Subject's IMACS number_____Person Completing: ___Patient ___Other
Date of assessment (mm/dd/yy)_____Assessment number_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty[0]	With SOME difficulty[1]	With MUCH difficulty[2]	UNABLE to do[3]
HYGENE				
Are you able to:				
-Wash and dry your body?	☐	☐	☐	☐
-Take a tub bath	☐	☐	☐	☐
-Get on and off the toilet	☐	☐	☐	☐
REACH				
Are you able to:				
-Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
-Bend down to pick up clothing from floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
-Open car doors?	☐	☐	☐	☐
-Open jars which have been previously opened?	☐	☐	☐	☐
-Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
-Run errands and shop?	☐	☐	☐	☐
-Get in and out of a car?	☐	☐	☐	☐
-Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

Please check any AIDS or DEVICES that you usually use for any activities:

- ☐ Raised toilet seat
- ☐ Bathtub bar
- ☐ Bathtub seat
- ☐ Long-handled appliances for reach
- ☐ Jar opener (for jars previously opened)
- ☐ Long-handled appliances in bathroom
- ☐ Other (specify_____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Hygiene
- ☐ Gripping and opening things
- ☐ Reach
- ☐ Errands and chores

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A <u>VERTICAL</u> (|) MARK ON THE LINE TO INDICATE THE SEVERITY OF PAIN

NO PAIN	**SEVERE PAIN**
0	**100**

IMACS FORM 06: SERUM LEVELS OF MUSCLE ENZYMES

Subject's IMACS number _____
Date of assessment (mm/dd/yy) _____
Assessment number _____

Blood laboratories:	Result	Normal Range
Creatine kinase (IU/L)	_____	_____
Aldolase (IU/L)	_____	_____
SGOT (IU/L)	_____	_____
SGPT (IU/L)	_____	_____
LDH (IU/L)	_____	_____
Creatinine (mg/dl)	_____	_____

IMACS FORM 07A: MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL (MDAAT) – 2005, VERSION 2

General Guidelines for Completion:

This is a combined tool that captures the physician's assessment of disease **activity** of various organ systems using (1) the 0-4 scale described below and (2) a visual analog scale (VAS). Please assess the clinical features (items 1-26) of each organ system based upon:

a) The presence of clinical features or symptoms **within the previous 4 weeks that are due to active disease** (i.e. use your clinical judgment to determine how active the myositis-associated clinical feature has been **within the previous 4 weeks**)

b) The judgment that the feature is due to the myositis disease process (i.e. clinical findings known or suspected to be due to another disease process or due to therapy should **NOT** be considered in this evaluation)

c) The concept that disease activity is defined as a potentially reversible finding

d) A clinical, functional, and laboratory assessment for each organ system:

NA = Cannot be assessed
0 = Not present in the last 4 weeks
1 = Improving - clinically significant improvement in the last 4 weeks compared to the previous 4 weeks
2 = The same - manifestations that have been present for the last 4 weeks without significant improvement or deterioration compared to the previous 4 weeks
3 = Worse - clinically significant deterioration over the last 4 weeks compared to the previous 4 weeks
4 = New - in the last 4 weeks (compared to the previous 4 weeks)

Also, rate your overall (global) assessment of the ongoing disease activity over the past 4 weeks for each organ system on the 0-10cm VAS scale (which precedes the listed clinical features) by drawing a **vertical** mark on the 10cm line according to the following guidelines:

- left end of line = no evidence of disease activity
- midpoint of line = moderate disease activity
- right end of line = extreme or maximum disease activity

Please review the glossary as you score each listed clinical feature. The VAS score for each organ system integrates the severity of activity based upon all of the clinical features listed for that particular organ system.

NOTE: The "Extramuscular Global Assessment" is very important as this is a Core Set Measure encompassing an overall evaluation for the disease activity in all the extramuscular organ systems and excludes muscle disease activity.

Guidelines for scoring mild, moderate, severe:

First, identify the category of mild-severe **using the glossary as a guide**. Then score what has happened in the last 4 weeks compared to the previous 4 weeks. Note that with worsening (3) or new (4) activity in the designated category, the same degree of activity should be ascribed in the items that are "less severe." For example:

- In a patient developing new moderate muscle inflammation (see glossary for definition) in the last 4 weeks, "moderate muscle inflammation" (25b) would score a 4 as would "mild muscle inflammation" (25c)
- If "severe muscle inflammation" worsened in the last 4 weeks, then the severe (25a), moderate (25b) and mild (25c) muscle inflammation categories would all score a 3

If a patient had severe muscle inflammation at last visit one month ago and improves to a moderate category over the past 4 weeks (based on the glossary definition), then score the severe category (25a) as a 1 (improving) and score moderate (25b) and mild (25c) as either a 1 or 2 (this would depend on just how much improvement has occurred over the last month so the glossary should be reviewed for this). If one month later the symptoms have further improved, then score the severe category (25a) as a 0 and the moderate (25b) and mild (25c) categories as a 1.

IMACS FORM 07a: MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL – 2005, Version 2

Subject's IMACS number:_____ ASSESSOR:_____ Date Assessed:_____Assessment number:_____

Constitutional Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Severe fatigue or malaise resulting in being bed bound and an inability to perform self care

1.	Pyrexia – documented fever > 38◦ Celsius	0	1	2	3	4	NA
2.	Weight loss – unintentional > 5%	0	1	2	3	4	NA
3.	Fatigue/malaise/lethargy	0	1	2	3	4	NA

Cutaneous Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** - Ulceration to muscle, tendon or bone; - Extensive erythroderma

4.	Cutaneous ulceration	0	1	2	3	4	NA
5.	Erythroderma	0	1	2	3	4	NA
6.	Panniculitis	0	1	2	3	4	NA
7.	Erythematous rashes:						
	a. **with** secondary changes (e.g. accompanied by erosions, vesiculobullous change or necrosis)	0	1	2	3	4	NA
	b. **without** secondary changes	0	1	2	3	4	NA
8.	Heliotrope rash	0	1	2	3	4	NA
9.	Gottron's papules/sign	0	1	2	3	4	NA
10.	Periungual capillary changes	0	1	2	3	4	NA
11.	Alopecia:						
	a. Diffuse hair loss	0	1	2	3	4	NA
	b. Focal, patchy with erythema	0	1	2	3	4	NA
12.	Mechanics hands	0	1	2	3	4	NA

Skeletal Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Severe arthritis with extreme loss of function (bedridden, inability for self care)

13. Arthritis:							
a. Severe active polyarthritis	0	1	2	3	4	NA
b. Moderately active arthritis	0	1	2	3	4	NA
c. Mild arthritis	0	1	2	3	4	NA
14. Arthralgia	0	1	2	3	4	NA

Gastrointestinal Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Major abdominal crisis requiring surgery or intensive care

15. Dysphagia:						
a. Moderate/severe dysphagia	0	1	2	3	4	NA
b. Mild dysphagia	0	1	2	3	4	NA
16. Abdominal pain related to the myositis disease process:						
a. Severe	0	1	2	3	4	NA
b. Moderate	0	1	2	3	4	NA
c. Mild	0	1	2	3	4	NA

Pulmonary Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Active interstitial lung disease or respiratory muscle weakness requiring ventilatory support

17. Respiratory muscle weakness **without** interstitial lung disease (ILD):						
a. Dyspnea at rest	0	1	2	3	4	NA
b. Dyspnea on exertion	0	1	2	3	4	NA
18. **Active reversible ILD** (i.e. not just ventilatory abnormalities due to pulmonary fibrosis): *Read glossary for scoring pulmonary function tests and score each item below (a,b and c).*						
a. Dyspnea or cough due to ILD	0	1	2	3	4	NA
b. Parenchymal abnormalities on chest x-ray or high resolution CT scan (HRCT) and/or ground glass shadowing on HRCT	0	1	2	3	4	NA
c. Pulmonary Function Tests: ≥ 10% change in FVC OR ≥ 15% change in DLCO	0	1	2	3	4	NA
19. Dysphonia:						
a. Moderate to severe	0	1	2	3	4	NA
b. Mild	0	1	2	3	4	NA

Cardiovascular Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Myocarditis, pericarditis or severe arrhythmia requiring intensive care unit

20. Pericarditis	0	1	2	3	4	NA
21. Myocarditis	0	1	2	3	4	NA
22. Arrhythmia:						
a. Severe arrhythmia	0	1	2	3	4	NA
b. Other arrhythmia, except sinus tachycardia	0	1	2	3	4	NA
23. Sinus tachycardia	0	1	2	3	4	NA

Other Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Extreme disease activity with major impact on function

24. Specify:_____	0	1	2	3	4	NA

Extramuscular Global Assessment	**(Absent)** ——— **(Maximum)** __ __ . __ cm	Overall evaluation for disease activity in all extramuscular systems **(EXCLUDING MUSCLE DISEASE ACTIVITY)**

Muscle Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	**Examples of maximal score** Severe muscle weakness resulting in being bed bound and an inability to perform self care

25. Myositis:						
a. Severe muscle inflammation	0	1	2	3	4	NA
b. Moderate muscle inflammation	0	1	2	3	4	NA
c. Mild muscle inflammation	0	1	2	3	4	NA
26. Myalgia	0	1	2	3	4	NA

Global Disease Activity	**(Absent)** ——— **(Maximum)** __ __ . __ cm	Overall evaluation for the totality of disease activity in ALL systems, (**INCLUDING MUSCLE DISEASE ACTIVITY)**

9.2 Appendix to Chapter 3 - Baseline interview topic guide

Interview topic guide: patient participant baseline interview

Study Title: The Myositis Physical Activity Device (MyoPAD) Study

Views and opinions on relationship between IIM (referred to as "myositis" throughout) disease activity and physical activity:

- Do you think your myositis and physical activity capability are linked?
- What particular physical activities do you think myositis affects?
- Do you think your walking pattern is affected by myositis?
- Do you think your walking speed is affected by myositis?
- Does reduction in physical activity from your myositis affect your day-to-day activities?
- Has this affected your social life, relationships with family, friends or work colleagues?
- Do you think myositis affects your mood?
- Do you think your physical activity capability is related to treatment for your myositis?
- Do you think you can tell when your myositis is getting better or getting worse?

Views and opinions on using a smartphone app to collect data and the potential value:

- What are your views about storing and sharing health data collected by monitoring symptoms etc by smartphone apps?
- Do you have any concerns about this method?
- What do you think are the benefits of this type of monitoring?
- Do you think the MyoPAD app will affect how you manage your condition/health?
- Do you think the MyoPAD app will affect how clinicians manage your condition/health?

Previous experience of monitoring symptoms and activity, and use of health apps:

- Have you done any previous monitoring of symptoms and physical activity? If so, can you give examples?
- Have you any experience of using other health related apps? If so, can you give examples and describe how you found using them?

The interviewer will give a University of Manchester smartphone to the interviewee. The smartphone will have a prototype version of the MyoPAD app installed.

The interviewer will also give a SENS Motion Plus accelerometer patch to the interviewee.

First impressions and expectations of using the MyoPAD app and SENS Motion Plus accelerometer patch:

- How do you think you will find using the MyoPAD app?
- Do you think you will be happy to wear the patch?
- Do you anticipate any problems using the MyoPAD app and patch?

Views about symptom monitoring using the MyoPAD app:

- What are your first impressions of the app?
- Do you think you will you be happy to complete the app's questions every day?
- Do you think you will be happy to complete the app's questions every day for a 90 day period?
- Are there any other questions that you would like to see in the app?

Changes to app:

- Are there any other aspects of myositis that you would like to be assessed by the MyoPAD app?
- Are there any alterations to the app's interface that you could suggest?

Any other issues you would like to raise?

9.3 Appendix to Chapter 4 - Follow up interview topic guide

Topic guide: patient participant follow up interview

Study Title: The Myositis Physical Activity Device (MyoPAD) Study

Experience of using the self-completed components of the MyoPAD app:

- How have you got on overall using the app? Was it easier or more difficult than you expected?
- Which aspects of the app did you find most useful and why?
- Which aspects were not useful or did not work well?
- Was the frequency of questions appropriate? If not, how often would be appropriate and why?

Content and scoring:

- Were any of the questions difficult to answer?
- Was there anything you would change about the questions?

Experience of passive monitoring:

- How did you feel about the accelerometer patch being able to track your movements? Was this any different to what you expected at the beginning?
- Do you think the accelerometer patch captured a true reflection of your movements? Has it had any impact on how you move around?
- How did you find wearing an accelerometer patch? Did you wear it all the time, whether at home or outside? If not, why not?

Impact of MyoPAD app and accelerometer patch for medical management:

- Has taking part in the pilot study made you think about your myositis symptoms more often than usually? How has this made you feel?
- Have you been more aware of your physical activity since wearing the accelerometer patch?
- Do you think this data is potentially useful for health professionals, and for discussions between you and your health professionals?

Additional technical/ usability issues:

- Did the daily prompt act as a useful reminder to complete your questions?
- How did you find the battery life on your smartphone? How often did you find yourself having to charge your smartphone? How did you feel about this?
- How easy or difficult did you find changing the accelerometer's adhesive patch?

Support:

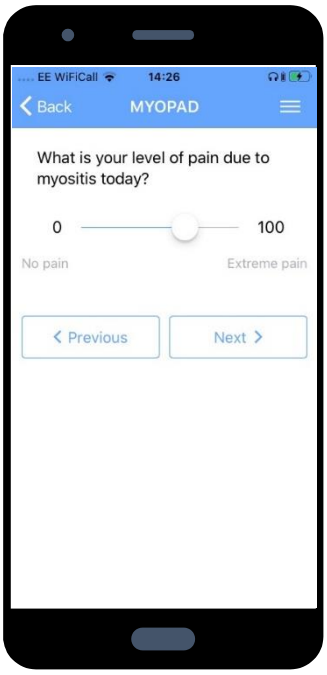
- Do you think you received sufficient support for using the app and accelerometer device?

Sustaining prolonged use:

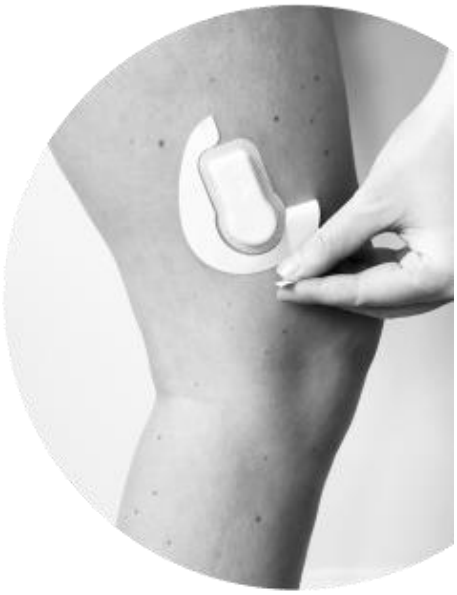
- Could you envisage using the app and accelerometer patch over a longer period of time (one year possibly). Why/why not?
- Do you think there are any reasons why some people may not want to use the app and accelerometer patch over a long period of time?
- What do you think could act as an incentive for people to take part in a larger trial over a longer period of time?

9.4 Appendix to Chapter 4 - Smartphone-based app screenshots, images of accelerometer sensor and participant instructions

A - Screenshot from smartphone-based MyoPAD app - daily overall pain question



B - Images of accelerometer sensor being applied to leg



C - MyoPAD study participant instructions for app and sensor use

The Myositis Physical Activity Device (MyoPAD) study:

Smartphone app and accelerometer sensor user guide

Many thanks for agreeing to take part in the "Myositis Physical Activity Device (MyoPAD) Study". The MyoPAD Study aims to develop and test a new method that can measure how active a person's myositis is in a continuous and remote manner.

The developed method will involve a combination of:

1. A specially designed smartphone app, through which myositis-specific questions can be answered
2. A wearable adhesive sensor that can continuously monitor walking pattern

This document will describe how to use both the smartphone-based app and the accelerometer sensor.

Please take time to read the following information carefully. Email the study team (alexander.oldroyd@manchester.ac.uk) if there is anything that is not clear.
Thank you for taking the time to read this.

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Smartphone-based app

The smartphone-based app is designed to allow you to answer a small number of questions that relate to how "active" your myositis is that day. You will be asked to complete these questions once a day, over a 90 day period.
The app is available on iPhones and Androids and is called "MyoPAD".
This guide will explain how to use the app to answer the daily questions. It will also explain what to do if you have any questions or difficulties.

Step 1 - Opening the app
Open the main screen on your smartphone and press the MyoPAD app symbol.

Step 2 –
Login using your username and password.

Step 3 –
Up to three questionnaire sets will be available – daily, weekly and monthly sets.

Step 4 –
Select "Start Task" on any available questionnaire.

Step 5 - Enter responses
Please complete each question by selecting the most appropriate response or sliding the marker along the line.

Step 4 - Completion
Your will see the "Thank you!" screen once you have completed all questions. All of your answers have been saved automatically.
You can now close the app.

Alerts
You will receive a single alert at the same time each day reminding you to complete that day's questions.

Accelerometer sensor

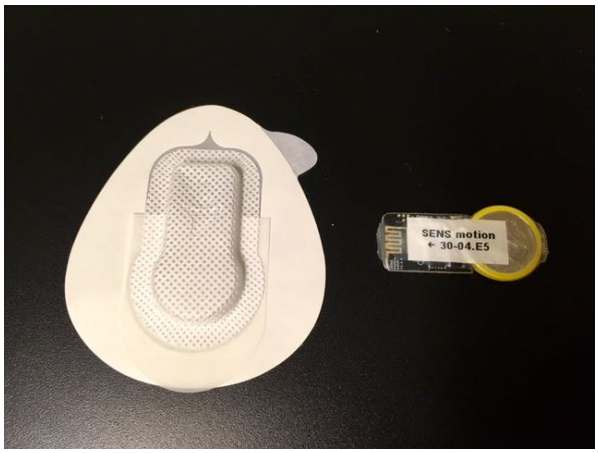
The accelerometer sensor is designed to continuously measure your walking pattern. The sensor can be inserted into an adhesive “patch” and attached to the side of your leg.

Please note that the adhesive patch typically lasts for over 14 days (2 weeks). After 14 days of wearing, the patch can be removed from your leg, the sensor removed and inserted into a new patch.

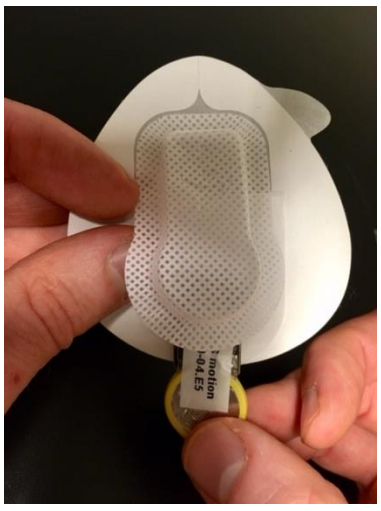
This guide will explain how to insert the sensor into the patch and attach it to the side of your leg. It will also explain how to remove a patch, extract the sensor and insert it into a new patch.

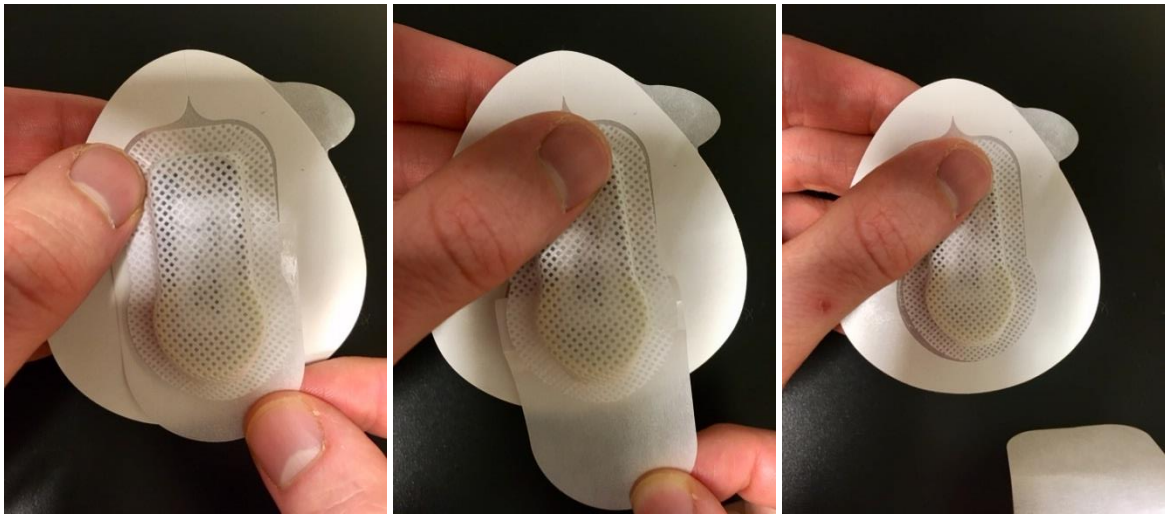
The sensor’s smartphone-based app can be installed onto your smartphone – it is called “SENS motion”. As described later, the app will automatically transmit data from the sensor to the University of Manchester.

Step 1 -
Remove the sensor and patch from the box



Step 2 - Inserting the sensor into the patch
The patch has three different coverings that can removed. Insert the sensor into the patch. Then remove the inner adhesive covering. Then close the patch so that the sensor is contained within the patch.





Step 3 - Attaching the patch to your leg

The patch should be attached to the side of your right leg, about 10cm (4 inches) above your knee. Please ensure that the skin is clean and does not have a rash or any form of cut or wound to it. Remove the adhesive covering on the back of the patch. Then gently but firmly press the patch onto the skin. Please ensure that the patch is attached with the narrow part pointing upwards towards your torso and the broad part pointing towards your knee.
Finally, the white outer covering can be removed.

Attachment is now complete. The sensor will automatically collect information about your walking pattern and transmit data to the university through your smartphone-based app. You should not need to interact with the sensor or the app until patch replacement is required.
Please note that the patch **and** sensor are both waterproof, therefore showing, bathing and swimming can be continued as normal.

Patch replacement -
The patch only needs to be replaced if the adhesive has worn off, the patch has become soiled or if you desire for it to be removed.

Step 1 - Removing the patch
Carefully remove the adhesive patch from your skin. A small amount of moisturiser can aid in removing a patch that has adhered strongly.

Step 2 - Removing the sensor from the patch
You will be required to remove the sensor from the old patch. You can either:

- Carefully open the old patch
- "Push" the sensor out of the old patch
  Or
- Carefully cut open the old patch using a pair of scissors

The sensor is then ready to be inserted into a new adhesive patch. Please follow Steps 2 to 3 above to do this.

Data transmission
Data collected by the sensor will be automatically sent to the University of Manchester via the smartphone-based app. This will happen automatically and you should not need to interact with the app. You may, however, periodically be asked to open the SENS motion app to check that data transmission occurs.

FAQs

"Are the sensor and patch waterproof?"
Yes.

"Will the sensor interfere with airport security scanners?"
No.

"Can I have a break from wearing the sensor and patch when I remove it?"
Yes, you can have a break from wearing the patch, though please ensure that the break lasts a maximum of 1 day.

"Will the sensor be able to identify exactly what activities I will be doing?"
No. The sensor can't identify specific activities. However, we are interested in analysing walking pattern and will therefore identify walking data for further analysis.

"Can I swap which leg I place the patch and sensor onto?"
Yes, though please inform the study team that you have done this so we can adjust our data interpretation.

"How long is the battery life of the sensor?"
The battery lasts for at least 4 months, which is longer than the study period. We can remotely monitor if a sensor's battery is running out and will supply a new sensor in this circumstance.

Contact details for help or assistance

In case of need for help or assistance, please contact the MyoPAD Study team on alexander.oldroyd@manchester.ac.uk or call 0161 275 1614.

Instructions for the end of the study

You will be invited to attend Salford Royal Hospital sometime after the 90 day study period has been completed. The smartphone-based apps will be uninstalled from your smartphone and the sensor will be collected from you.

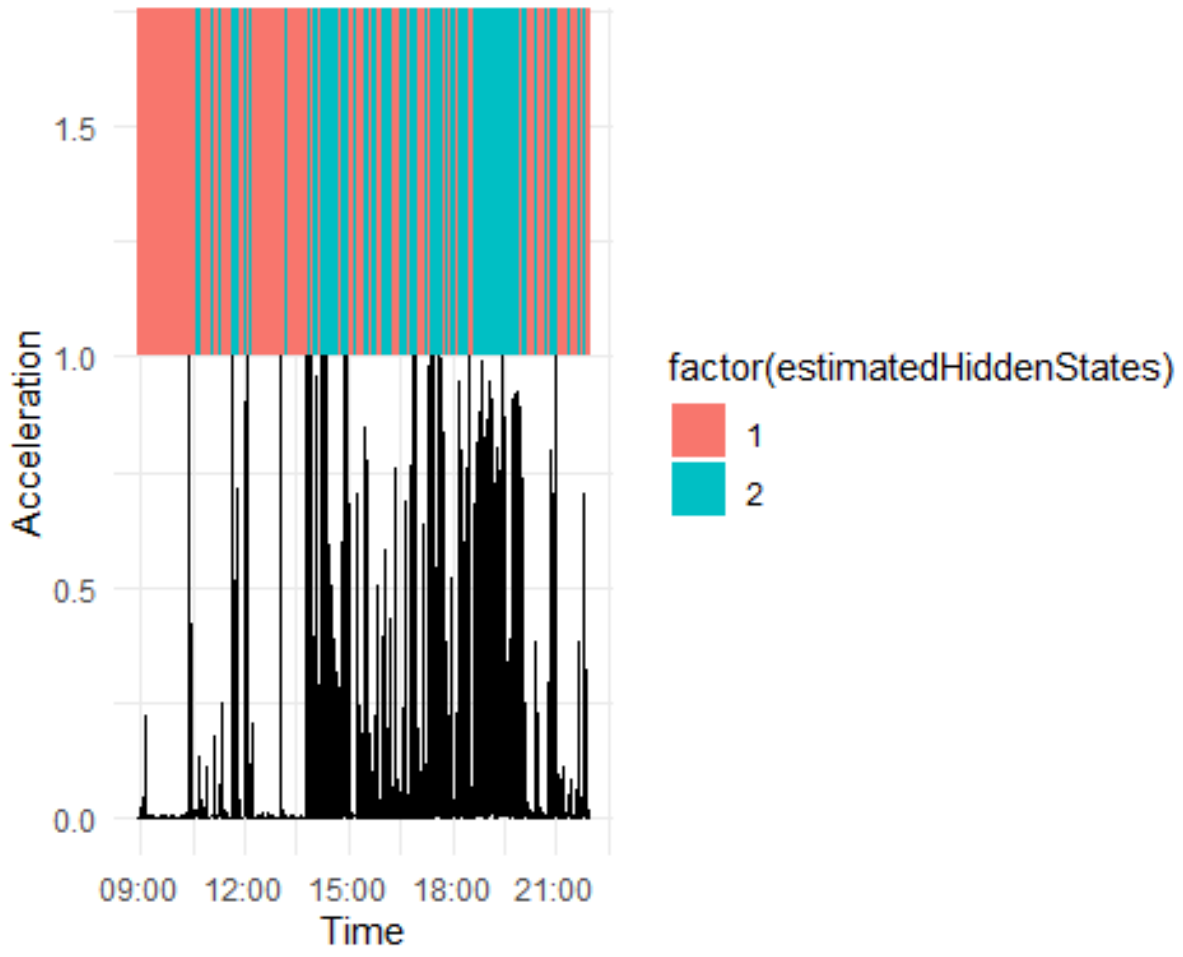
9.5 Appendix to Chapter 6 - R code for processing accelerometer data

R script for processing accelerometer data

```
# Set working directory
setwd("D:/Acc data/22")

library(usethis)
library(processx)
library(devtools)
library(l1tf)
library(cluster)
library(factoextra)
library(anytime)
library(Rcpp)
library(ggplot2)
library(lubridate)
library(reshape2)
library(ggplot2)
library(plotly)
library(ggthemes)
library(zoo)
library(depmixS4)
library(scales)
library(dplyr)
library(magrittr)
library(tibble)
library(tidyr)
library(readr)
library(pracma)
library(tidyverse)
library(glue)
library(tidyselect)
library(data.table)
library(hexView)

#######
# Import data
# Data should be downloaded as “hexadecimal” data
#######

fileBlock <- readRaw("22_1.HEX", width=24, signed=TRUE)
data<-blockValue(fileBlock)
data2<-as.data.frame(data)
df2 <- as.data.frame(matrix(data2[,1], byrow=TRUE, ncol = 25))
df2$zero<-"0x"

# Organise time variable

df2$time <- paste(df2$zero,df2$V1,df2$V2,df2$V3,df2$V4,df2$V5,df2$V6,df2$V7,df2$V8,df2$V9,d
f2$V10,df2$V11,df2$V12, sep="")
df2$time<-as.numeric(df2$time)
options(digits.secs=6)
df2$time2<-as.POSIXct(df2$time/1000, origin="1970-01-01", tz="GMT")

# Organise X axis data
df2$x<-paste(df2$V13,df2$V14,df2$V15,df2$V16, sep="")
```

```
df2$x2 <- strtoi(df2$x, base=16)
df2$x3 <- ifelse(bitwAnd(df2$x2, 0x8000) > 0, -0xFFFF-1, 0) + df2$x2
df2$x3<-df2$x3*0.008
# Organise Y axis data
df2$y<-paste(df2$V17,df2$V18,df2$V19,df2$V20, sep="")
df2$y2 <- strtoi(df2$y, base=16)
df2$y3 <- ifelse(bitwAnd(df2$y2, 0x8000) > 0, -0xFFFF-1, 0) + df2$y2
df2$y3<-df2$y3*0.008

# Organise Z axis data
df2$z<-paste(df2$V21,df2$V22,df2$V23,df2$V24, sep="")
df2$z2 <- strtoi(df2$z, base=16)
df2$z3 <- ifelse(bitwAnd(df2$z2, 0x8000) > 0, -0xFFFF-1, 0) + df2$z2
df2$z3<-df2$z3*0.008
###
finaldata<-data.frame(time=df2$time2, x=df2$x3, y=df2$y3, z=df2$z3)
data<-finaldata

#######
#Set time origin
#######

options(digits.secs=7)
data$time<-as.POSIXct(data$time, origin="1970-01-01", tz="GMT")
df<-data

#######
#Calculate and plot Euclidean norm
#######

df$euclideannormminus1<-sqrt(df$x^2+df$y^2+df$z^2)-1

#######
#Remove gravitational component via L1-trend filtering
#######

df$l1tfx<-l1tf(df$x, lambda = 50)
df$filteredx<-df$x-df$l1tfx
df$l1tfy<-l1tf(df$y, lambda = 50)
df$filteredy<-df$y-df$l1tfy
df$l1tfz<-l1tf(df$z, lambda = 50)
df$filteredz<-df$z-df$l1tfz

#######
#Calculate and plot the vector magnitude
#######

df$euclideannorm<-sqrt(df$filteredx^2+df$filteredy^2+df$filteredz^2)
options(digits = 15)
df$time2<-as.numeric(df$time)
newdata <- subset(df, select=c(euclideannorm, filteredy, filteredx, filteredz, time, time2)
)

#####
# Hidden Markov Model
#####
expectedNumberOfStates <- 2
set.seed(6)

# Create model
```

```
myModel <- depmix(list(euclideannorm~1), data=newdata,
                  nstates=expectedNumberOfStates,
                  instart = c(1,0),
                  trstart = runif(expectedNumberOfStates^2),
                  family = rep(list(gaussian()),1))

# Fit the model

fittedMyModel <- fit(myModel, verbose = FALSE)
## converged at iteration 34 with logLik: 2067667.45993604

newdata$estimatedHiddenStates <- as.character(posterior(fittedMyModel)$state)
newdata$estimatedHiddenStates <- factor(newdata$estimatedHiddenStates, c("1", "2"))

# Make plot of states

ggplot(newdata) +
  geom_line(aes(time, euclideannorm)) +
  geom_rect(aes(xmin = time, xmax = dplyr::lead(time), ymin = 1, ymax = Inf, fill = factor(
estimatedHiddenStates)), alpha = 1) +
  theme_minimal()+
  scale_x_datetime() + xlab("Time") + ylab("Acceleration")

## Warning: Removed 1 rows containing missing values (geom_rect).
```



```
#####
#####

## Remove non-walking part of time series
newdata$estimatedHiddenStates<-as.numeric(newdata$estimatedHiddenStates)
walkingdata<-newdata[newdata$estimatedHiddenStates==2,]
walkingdata$estimatedHiddenStates<-as.factor(walkingdata$estimatedHiddenStates)

######
# Calculate number of days between each row
######

B <- newdata %>%
  mutate(timediff = time - time[1])
B$timediff<-as.numeric(B$timediff, units="days")
#####
newdata2 <- data.table(B)
##
walkingdata<-newdata2
totalwalkingdata<-walkingdata
totalwalkingdata$day<- trunc(walkingdata$timediff)
#####

######
# Identify toe-off and heel-strike events
######

walkingdata<-totalwalkingdata
x <- data.frame(findpeaks(walkingdata$euclideannorm,minpeakdistance=10, nups=1, ndowns=1, n
peaks=Inf, minpeakheight=0.5, sortstr=FALSE))
x<-data.frame(euclideannorm=x$X1, peak=1)
endata0<-c(walkingdata$euclideannorm[walkingdata$day==0])
y <- data.frame(findpeaks(-endata0,minpeakdistance=10, nups=1, ndowns=1, npeaks=Inf, minpea
kheight = -0.5, sortstr=FALSE))
###
y$X1<-abs(y$X1)
y<-data.frame(euclideannorm=y$X1, trough=1)
walkingdata<-merge(walkingdata, x, by="euclideannorm", all.x=TRUE)
walkingdata<-merge(walkingdata, y, by="euclideannorm", all.x=TRUE)
#####
walkingdata1<-walkingdata[!is.na(walkingdata$peak),]
walkingdata2<-walkingdata[!is.na(walkingdata$trough),]
walkingdata3<-rbind(walkingdata1, walkingdata2)
walkingdata3$trough[walkingdata3$peak==1]<-2
walkingdata3 <- walkingdata3[order(walkingdata3$time),]
walkingdata3$trough2 <- c( "NA", walkingdata3$trough[ - length(walkingdata3$trough) ] )
troughdata<-walkingdata3[walkingdata3$trough2==2 & walkingdata3$trough==1,]
troughdata <- subset(troughdata, select = -trough2)
troughdata$peakint<-NA
troughdata$countedpeak<-NA
##
peakdata<-walkingdata1
peakdata <- peakdata[order(peakdata$time),]
peakdata$peakint <- c(NA, diff(peakdata$time))
peakdata$countedpeak[peakdata$peakint<2]<-1
##
peaktroughdata<-rbind(peakdata, troughdata)
peaktroughdata<-data.frame(time=peaktroughdata$time, truepeak=peaktroughdata$peak, truetrou
gh=peaktroughdata$trough, peakint=peaktroughdata$peakint, countedpeak=peaktroughdata$counte
dpeak)
##
```

```r
peaktroughdata <- peaktroughdata[order(peaktroughdata$time),]
peaktroughdata$countedtrough[lag(peaktroughdata$countedpeak)==1 & peaktroughdata$truetrough
==1] <-1
##
walkingdata<-merge(walkingdata, peaktroughdata, by="time", all.x=TRUE)
#####
######







######
### Calculate gait parameters
######

# Calculate step time - difference (in seconds) between peaks
meansteptime1<-mean(walkingdata$peakint[walkingdata$countedpeak==1], na.rm=TRUE)
sdsteptime1<-sd(walkingdata$peakint[walkingdata$countedpeak==1], na.rm=TRUE)

# Calculate swing time - difference between peak and trough
walkingdata1<-walkingdata[!is.na(walkingdata$countedpeak),]
walkingdata2<-walkingdata[!is.na(walkingdata$countedtrough),]
walkingdata3<-rbind(walkingdata1, walkingdata2)
walkingdata3 <- walkingdata3[order(walkingdata3$time),]
walkingdata3$peaktroughint <- c(NA, diff(walkingdata3$time))
walkingdata3$peaktroughint[is.na(walkingdata3$countedtrough)] <-"NA"
walkingdata3$peaktroughint<-as.numeric(walkingdata3$peaktroughint)

## Warning: NAs introduced by coercion

meanswingtime1<-mean(walkingdata3$peaktroughint, na.rm=TRUE)
sdswingtime1<-sd(walkingdata3$peaktroughint, na.rm=TRUE)

# Stance time - time between trough and peak
walkingdata1<-walkingdata[!is.na(walkingdata$countedpeak),]
walkingdata2<-walkingdata[!is.na(walkingdata$countedtrough),]
walkingdata4<-rbind(walkingdata1, walkingdata2)
walkingdata4 <- walkingdata4[order(walkingdata4$time),]
walkingdata4$troughpeakint <- c(NA, diff(walkingdata4$time))
walkingdata4$troughpeakint[is.na(walkingdata4$countedpeak)] <-"NA"
walkingdata4$troughpeakint<-as.numeric(walkingdata4$troughpeakint)

## Warning: NAs introduced by coercion

meanstancetime1<-mean(walkingdata4$troughpeakint[walkingdata4$troughpeakint<2], na.rm=TRUE)
sdstancetime1<-sd(walkingdata4$troughpeakint[walkingdata4$troughpeakint<2], na.rm=TRUE)
###
steptime<- walkingdata %>%
  group_by(day) %>%
  summarise(meansteptime = mean(peakint[countedpeak==1], na.rm=TRUE),
            sdsteptime = sd(peakint[countedpeak==1], na.rm=TRUE))

## `summarise()` ungrouping output (override with `.groups` argument)

swingtime<- walkingdata3 %>%
  group_by(day) %>%
  summarise(meanswingtime = mean(peaktroughint, na.rm=TRUE),
            sdswingtime = sd(peaktroughint, na.rm=TRUE))

## `summarise()` ungrouping output (override with `.groups` argument)
```

```r
stancetime<- walkingdata4 %>%
  group_by(day) %>%
  summarise(meanstancetime = mean(troughpeakint[troughpeakint<2], na.rm=TRUE),
            sdstancetime = sd(troughpeakint[troughpeakint<2], na.rm=TRUE))

## `summarise()` ungrouping output (override with `.groups` argument)

steptime

## # A tibble: 1 x 3
##     day meansteptime sdsteptime
##   <dbl>        <dbl>      <dbl>
## 1     0         1.20      0.207

swingtime

## # A tibble: 1 x 3
##     day meanswingtime sdswingtime
##   <dbl>         <dbl>       <dbl>
## 1     0         0.576       0.524

stancetime

## # A tibble: 1 x 3
##     day meanstancetime sdstancetime
##   <dbl>          <dbl>        <dbl>
## 1     0          0.672        0.212

gaitsummary <- left_join(steptime, swingtime, by = "day")
gaitsummary1 <- left_join(gaitsummary, stancetime, by = "day")

gaitsummary1$day2<-1

# Display calculated gait parameters
gaitsummary1

## # A tibble: 1 x 8
##     day meansteptime sdsteptime meanswingtime sdswingtime meanstancetime
##   <dbl>        <dbl>      <dbl>         <dbl>       <dbl>          <dbl>
## 1     0         1.20      0.207         0.576       0.524          0.672
## # ... with 2 more variables: sdstancetime <dbl>, day2 <dbl>

#######
##
#######
```