Understanding flare in axial spondyloarthritis: novel insights from daily self-reported flare experience

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Data availability statement: Due to confidentiality agreements, supporting deidentified participant data can only be made available to bona fide researchers subject to approval and implementation of a data sharing agreement, as determined by the Royal National Hospital for Rheumatic Diseases, Royal United Hospitals, Bath (data custodians). Requests for data would be evaluated on the basis of the research objectives of the intended project and any conflict of interests involved. Enquiries about the Project Nightingale dataset should be directed to Rosemarie Barnett via: rlb60@bath.ac.uk.

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Abstract

Objectives

Our objective was to explore daily self-reported experience of axial spondyloarthritis (axSpA) flare based on data entered into the Project Nightingale smartphone app (www.projectnightingale.org), between 5th April 2018 - 1st April 2020.

Methods

Paired t-tests were conducted for mean_flare_on and mean_flare_off scores for each recorded variable. Mean estimated difference between flare and non-flare values for each variable was calculated with 95% confidence intervals (CI). Mean, standard deviation (SD) and range were reported for flare duration and frequency. Participants with ≥10 days of data entry were included for affinity propagation cluster analysis. Baseline characteristics and mean flare on versus flare off values were reported for each cluster. Welch's t-test was used to assess differences between clusters.

Results

143/189 (75.7%) participants recorded at least 1 flare. Each flare lasted a mean of 4.30 days (SD 6.82 days, range 1–78 days), a mean frequency of once every 35.32 days (SD 65.73, range 1-677 days). Significant relationships were identified between flare status and variable scores. Two clusters of participants were identified with distinct flare profiles. Group 1 experienced less severe worsening of symptoms during flare in comparison to Group 2 ($p<0.01$). However, they experienced significantly longer flare duration (7.2 versus 3.5 days, $p<0.01$); perhaps indicating a prolonged, yet less intense flare experience. Groups were similar in terms of flare frequency and clinical characteristics.

Conclusions

Two clusters of participants were identified with distinct flare experiences, but similar baseline clinical characteristics. Smartphone technologies capture subtle changes in disease experience, not currently considered in clinical practice.

Key words

Axial spondyloarthritis, ankylosing spondylitis, flare, symptoms, remote monitoring, patient-reported outcomes

Key messages

- Daily self-reported smartphone data identified two distinct clusters of people living with axSpA who had different flare experiences.
- Despite differences in flare duration and symptoms, baseline clinical measures were similar between clusters.
- Smartphone technologies capture subtle changes in disease experience not currently considered in clinical practice.

Manuscript

Introduction

Axial spondyloarthritis (axSpA) is a chronic, inflammatory disease characterised by alternating periods of flare and more stable disease activity. Flares are often both unpredictable and debilitating, and a greater understanding of their nature and outcome is therefore important to both those living with axSpA and clinicians (1, 2). Over the last decade, although rapid advances have been made in terms of our understanding of axSpA, the natural history of the disease remains elusive. It has been hypothesised that the presence of early, severe disease flares (often associated with a worsening of symptoms or increased disease activity) may allow for early identification of people living with axSpA who may develop more severe disease (3-6). Indeed, severe flare has been identified as a poor prognostic factor in axSpA, particularly in early disease (4). It has therefore been suggested that early, aggressive treatment of severe flares in axSpA may improve long-term outcomes.

Despite the frequent use of the concept "flare" within rheumatic condition terminology, an accepted, consistent definition of a flare does not yet exist for axSpA. In recent years, there have been attempts to define flare in both axSpA and other chronic rheumatic conditions such as rheumatoid arthritis, based upon validated composite indices, or through qualitative retrospective investigation of flare states (3, 7-9). Indeed, there is a growing interest in the concept of flare, and in characterising the lived experience behind this multidimensional phenomenon (1, 6, 7, 9-17). Such understanding is critical to better characterise the natural history of the condition and in future may facilitate optimisation/ personalisation of available treatments. The problematic nature of defining a flare in axSpA in part lies in the multifaceted, heterogenous nature of the disease. This problem was clearly demonstrated by Gossec and colleagues, whereby, in a preliminary attempt to classify flare, 27 different flare definitions were identified among just 38 publications on axSpA (7).

In prior studies investigating flare experience, those living with axSpA have often been asked to recall history of flare or prior experience of flare (3-6). However, this retrospective characterisation is subject to recall bias and may not provide an accurate picture of the lived day-to-day reality. Recently introduced smartphone technologies for the daily monitoring of disease symptoms and activity provide a unique insight into the daily experiences of individuals with chronic, fluctuating conditions (18-25). Such technologies may allow for a more accurate investigation of flare experience (12, 16, 17).

In the present study, we conducted an exploratory analysis on a dataset of participants entering daily symptoms and behaviour into the Project Nightingale (uMotif) app (www.projectnightingale.org). Our objective was to explore individual's self-reported experience of flare. We hoped to characterise the constituents of flare, the frequency and duration of flare, and whether people living with axSpA could be clustered based on their similar experiences. We then attempted to further characterise these clusters of participants, to provide detailed insights into potential distinct subtypes of flare experience.

Methods

Overview of Project Nightingale

Since April 2018, people living with axSpA under the care of the Royal National Hospital for Rheumatic Diseases (RNHRD), Royal United Hospitals NHS Foundation Trust (RUH), Bath, have been eligible to participate in Project Nightingale. Project Nightingale was created to allow people living

with axSpA to track daily symptoms and behaviour via their smartphone device and gain further insights into the nature of their condition.

All participants are invited to track 10 variables via the uMotif smartphone app, including 8 fixed and 2 optional variables. Fixed variables are tracked by all participants and include pain, mood, fatigue, sleep, stress, flare, recommended exercise, and anti-inflammatory use. While 2 optional variables are chosen by each participant from the following: caffeine intake, hot flushes, adherence to medication, screen time, confidence in self-management, eyesight, hydration, chest pain, flare of psoriasis, impact of menstrual cycle, red painful eyes, smoking habits and blood in stool. The variables and associated scales were designed by the lead consultant for axSpA at the RNHRD to optimise clinical relevance, following years of regular, detailed and empathetic interaction with people living with axSpA.

Participants are asked how they are feeling each day via the app. They rate each variable on a 5-point Likert scale. The interface for recording each outcome is displayed as a flower-like visualisation, whereby each petal represents one of the ten tracking variables (Supplementary Figure 1). Participants are required to drag their finger from the centre of the flower to the outer edge of each petal to record their symptoms. For each variable, a score of 1 equates to the less healthy or desirable outcome, whereas a score of 5 represents the most healthy/positive outcome or behaviour. For example, for pain: 1=debilitating pain; 5=no pain. The flower-motif recording interface acts as a visual metaphor, whereby a full flower represents the most healthy or optimal outcomes. Participants receive daily reminders for data entry as a notification to their smartphone if data has not already been entered. In the uMotif app settings, participants can choose to opt out of reminders or alter their time and frequency.

Data collection

For the present study, we utilised smartphone data collected via the Project Nightingale (uMotif) app between 5th April 2018 and 1st April 2020. South West - Central Bristol UK local research ethics committee for National Health Service research approved the study, and all patients provided written informed consent (The Bath Spondyloarthritis Biobank; REC reference: 13/SW/0096). Clinical data was collected based on routine assessment at the RNHRD. Baseline measures were extracted at visit date closest to Project Nightingale registration – restricted to visit dates within 90 days of Project Nightingale registration. Data from participants' wearable and smart device applications were downloaded regularly and incorporated into the patient record.

Statistical methods

For participants with at least one flare and non-flare set of recorded variables, data was aggregated to one row per participant, containing mean values with and without flare for each petal variable. For example, Participant 1 would have an 'average_pain_flare_on' feature and an 'average_pain_flare_off' feature for each variable. Paired t-tests were conducted for each variable, to investigate which variables correlated with flare status. The difference between the 'flare_on' and 'flare_off' features were taken for each pair to create a set of 'difference' features, to capture the effect of a flare on each petal variable for each participant. The mean estimated difference between flare and non-flare values for each variable was calculated with 95% confidence intervals (CI). The mean, standard deviation (SD) and range were reported for flare duration and flare frequency. For the flare duration calculation, two logged periods of flare occurring within three days were to be considered as one period of flare if missing one day of data between entries.

For the cluster analysis, Project Nightingale participants with <10 days of data entry were excluded. 'Difference' features for each variable for each participant were normalized to between -1 and 1,

and then used for clustering. Affinity propagation was used as the clustering algorithm via the 'apcluster' R package (26). negDistMat(r=2) was used for the similarity matrix, squaring the distance measures between participants to calculate similarities (27). q=0 was used to minimize the number of clusters found. Given the size of the dataset (129 participants), it was decided to lower the number of clusters in order to achieve a meaningful sample size for each cluster (28).

Baseline characteristics and mean flare on versus flare off values were reported for each cluster. Welch's t-test was used to assess differences between clusters.

Patient and public involvement (PPI) statement

Project Nightingale was established through a strong collaboration between the RNHRD (RUH, Bath) and consultant Dr Raj Sengupta, engagement with relevant stakeholders (people living with axSpA/HCPs), the charity White Swan and the Bath Institute for Rheumatic Diseases (BIRD). This has facilitated PPI from project initiation. Petal tracking variables were determined by Dr Raj Sengupta, based on decades of clinical experience and interactions with people living with axSpA. Additional optional variables were also added to the scope, based on patient feedback at Project Nightingale information days. These regular Project Nightingale & axSpA information days organised by BIRD have facilitated patient-HCP-researcher discussion, knowledge exchange, participant feedback and dissemination of results. Such interactions/collaboration have informed advancement of future Project Nightingale research plans and app innovation.

PPI has been maintained during the COVID-19 pandemic via regular Project Nightingale patient-HCP-researcher discussions during the well-established RNHRD axSpA rehabilitation course. A Project Nightingale BIRD podcast episode and Facebook Live event with the National Axial Spondyloarthritis Society have also facilitated PPI. The Project Nightingale blog and twitter has facilitated regular research updates/ dissemination of results to the wider axSpA community. This has allowed for further patient participation and discussion of experiences (29, 30).

Results

Between 5th April 2018 and 1st April 2020, 189 patients consented for research and logged a mean of 156.78 (SD=199.60) days of data (range=1 - 711 days). 143/189 (75.7%) participants recorded at least 1 flare, with 1,349 flares recorded in total. Each flare lasted a mean of 4.30 days (SD 6.82 days, range 1–78 days), with a mean frequency per participant of once every 35.32 days (SD 65.73, range 1-677 days). Significant relationships were identified between flare status and variable scores (Table 1). Small but significant ($p<0.01$) estimated differences were found between flare and non-flare scores for pain, fatigue, sleep quality, exercise, mood, anti-inflammatory use, stress, confidence in self-management and chest pain.

Between 5th April 2018 and 1st April 2020, 129 patients had registered for participation in Project Nightingale and provided 10 or more days of data entry suitable for the cluster analysis. Two clusters of participants were identified based on distinct profiles of uMotif petal symptom scores during flares, using non-flare scores as a baseline comparator (Figure 1, Table 2). Group 1 appeared to experience less severe worsening of pain, fatigue, sleep, mood and stress during flare (versus non-flare) in comparison to Group 2 ($p<0.01$). However, this group also experienced significantly longer flare duration (7.2 versus 3.5 days, $p<0.01$) (Supplementary Table 1); perhaps indicating a more prolonged, yet less intense flare experience. Although not reaching significance due to small sample size, Group 2 also demonstrated a more severe decrease (worsening) in score for chest pain, confidence in self-management, eyesight, flare of psoriasis, impact of menstrual cycle and screen time. Changes in anti-inflammatory use and recommended exercise during flare versus non-flare

appeared similar between the two groups; perhaps suggesting similar behaviours while attempting to resolve flares.

Group 2 reported slightly (petal score difference of <0.5) better sleep quality (p=0.022) and very slightly higher levels of recommended exercise (p=0.026) than Group 1 when not in flare; despite worse scores for pain (p=0.043), fatigue (p=0.001), mood (p=0.031) and stress (p<0.001) during flare (Table 3). No significant differences were found between groups for pain, fatigue, mood, anti-inflammatory use or stress when not in flare.

The baseline (at Project Nightingale registration) characteristics of participants in each cluster group are presented in Table 4. Both groups were similar in terms of gender, HLA-B27 status and other clinical characteristics such as spinal mobility (BASMI). However, Group 1 had a significantly greater proportion of smokers (p<0.001). Group 2 had a significantly greater proportion of people who had never smoked (p<0.05).

Discussion

To our knowledge, this is the first study to investigate, characterise and group daily self-reported flare profiles in people with axSpA, utilising a smartphone application and remote data collection. Two distinct clusters of participants were identified. Whereby, one group reported significantly shorter flare duration (p<0.01), however experienced a significantly greater worsening of pain, fatigue, mood, sleep and stress during flare (p<0.01). Perhaps indicating a shorter, although more intense, flare experience. Number and frequency of flares were similar between clusters. As were baseline clinical measures such as BASMI, BASDAI, BASFI and quality of life (measured through ASQoL). Smartphone technologies therefore have the potential to capture subtle, potentially critical changes in disease activity that are not currently considered in clinical practice. Although the long-term significance of these is yet to be explored, such work is planned in our future research agenda. Furthermore, the study of such daily self-report data may in future allow for prediction of flare based on patterns of symptoms/behaviour or enable a greater understanding of behaviours that lead to earlier resolution of flare. This may facilitate earlier targeting and prevention of flares to reduce flare frequency and duration – to ultimately improve quality of life for patients.

Prior qualitative work by Brophy and Calin in 2002 also identified two types of flare, localised and generalised, based on group discussions with 214 patients, over the period of one year (3). All participants had experienced a localised flare, involving pain and immobility in one area, sometimes accompanied by fatigue and emotional symptoms. In contrast, only 40% (85/214) of participants had experienced generalised flares, involving the whole body. This was described as an infrequent event whereby all symptoms were experienced to the extreme. Individuals reporting generalised flares described the localised flares as not a “true” flare – perceiving localised increases in disease activity as incomparable to the crippling, acute and devastating phenomenon of a whole-body flare. Similar experiences of localised (minor) or generalised (major) flares have been characterised in later studies also – by Stone and colleagues in 2008 (6) and a follow-up study in 2010 (5). In the present study, we were unable to determine the location of flares. However, our results appear broadly consistent in terms of one group of patients experiencing more intense, debilitating flares, with greater changes in symptoms such as pain, fatigue, mood, sleep and stress. In the present study, this group experiencing more severe flares again appeared to involve the minority of participants (26% of participants in the present study, 33/129).

Our average flare duration may appear less than previously reported. In 2002, Brophy and Calin described the majority of flares as short-term (days to weeks) – broadly in agreement with the present study (3). However, in 2010, Cooksey and colleagues reported a mean flare duration of 2.4

weeks (5). In comparison to an average duration of 7.2 and 3.5 days for Group 1 and Group 2 respectively in the present study. This is likely because our flare duration calculation was quite strict, in that a flare required subsequent days of uMotif flare entries to be considered as 'continued'. Just 1 day of missing data was permitted. For example, if a participant recorded a flare on a Monday and Wednesday but with missing data on Tuesday, this would be recorded as a single period of flare. However, if a participant recorded a flare on a Monday and Thursday with 2 missing days of data, this would be considered as two separate periods of flare. This was defined in alignment with a more recent study by Jacquemin and colleagues, whereby the majority of reported flares lasted ≤3 days (14). However, this definition may have considerably underestimated the flare duration in the present study. The past 10-20 years have shown dramatic advances in our understanding of axSpA, including the introduction of the widespread use of biologics, improved treatment strategies and a change in definition of disease (to include non-radiographic axSpA in addition to ankylosing spondylitis). Therefore, this may have contributed to the differences in flare duration seen in the present study and the study by Jacquemin and colleagues (2017). Indeed, both earlier studies (Brophy and Calin, Cooksey and colleagues) included only people with ankylosing spondylitis, not non-radiographic axSpA also, perhaps further contributing to the disparity in flare duration.

It is also important to note that, despite short flare duration in the present study, the mean flare frequency per participant was once every 35.32 days (SD 65.73). This suggests that there is still a need for optimisation/personalisation of treatments in axSpA in order to reduce the frequency of debilitating flare, and potential associated poor clinical outcomes and work impairment (4, 6, 31, 32).

Beyond the importance of flare characterisation in clinical practice, flare also represents an important endpoint to consider in clinical trials. As a potential indicator of disease severity, flare assessment is vital to understanding disease status or treatment efficacy and is of particular importance in tapering or discontinuation trials (33-36). There has recently been an attempt to quantify a single definition of flare based on validated composite indices for the purpose of harmonising trial designs in axSpA (7, 37). However, it is important to distinguish between the necessarily stricter, arbitrarily homogenous definition of flare that is required in clinical trials, versus the highly variable, highly individualised flare experience of those living with axSpA. In clinical practice, in order to move towards optimisation and personalisation of treatments, the latter definition as explored in the present study may arguably be of greater significance. This may be supported by the fact that in the present study, although Group 2 reported significantly worse flare experience via the uMotif app, we found no significant difference in baseline spinal mobility, disease activity or function as measured by validated BASMI, BASDAI and BASFI measures between the two groups. Highlighting the power of smartphone technologies to capture potentially critical fluctuations in disease severity that are too subtle to be observed by traditional, infrequent measurement of existing validated indices. Indeed, future integration of daily self-reported health data into the electronic health record may allow for greater optimisation and personalisation of treatment outcomes, through more accurate reporting of disease experience (38).

A limitation of the present study is with regard to adherence. Upon registration, participants were encouraged to enter data every day. However, they were told that any data entry may be useful, including restarting after inactive periods. Prior qualitative and quantitative evidence suggests that patients with worse disease experience in axSpA may be more likely to adhere to self-tracking behaviour (39). Therefore, our results may be biased towards those with more severe disease. Similar results have been reported in the literature for other inflammatory, rheumatic conditions

such as rheumatoid arthritis; whereby, it has been suggested that patients may primarily use self-tracking apps in the case of impending flares (40).

Another potential source of bias in the present study is that the RNHRD is a tertiary hospital, receiving both local and specialist referrals. Therefore, our cohort may be more severely affected by axSpA or less likely to experience a down-period between flares. However, both our own data and data from prior studies from the RNHRD suggest that our cohort of patients reflect the full spectrum of axSpA disease (6, 41). For example, the population included in the present study showed a range of BASDAI scores from 0-8.6, and BASMI scores ranging from 0-7.8. Disease duration (from age of onset to age at study consent) ranged from 4 years to 68 years. Furthermore, it is now common practice and recommended for General Practitioners to refer all suspected axSpA diagnoses to a specialist centre (42).

Conclusions

The results of the present study yield novel insights into the characterisation of flares in axSpA. Significant relationships were identified between a variety of patient-reported symptoms and flare, including variables that to our knowledge, have not yet been explored in axSpA. Clustering of daily self-reported symptom data has identified two clusters of people with axSpA who have distinct flare profiles. One group appears to experience significantly longer flare duration. However, this group also experiences less dramatic worsening of pain, fatigue, sleep, mood and stress during flare in comparison to non-flare. Although we observed differences between the two groups in terms of flare experience, clinical differences in BASMI, BASDAI and BASFI were not identified. Highlighting the potential of smartphone technologies to capture subtle, potentially critical changes in disease activity that are not currently considered in clinical practice.

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Tables and figures

Table 1. Paired t-tests: flare vs. non-flare scores for each variable

Estimated difference^	p-value	95% CI (lower limit)	95% CI (upper limit)	N	Variable
-0.788*	0.000	-0.898	-0.679	143	Pain
-0.599*	0.000	-0.706	-0.491	143	Fatigue
-0.228*	0.000	-0.303	-0.153	142	Sleep quality
-0.296*	0.000	-0.416	-0.177	143	Recommended exercise
-0.381*	0.000	-0.463	-0.298	143	Mood
0.140*	0.000	0.090	0.191	143	Anti-inflammatory use
-0.343*	0.000	-0.459	-0.228	143	Stress
-0.038	0.348	-0.119	0.043	59	Caffeine intake
-0.404	0.012	-0.709	-0.100	19	Hot flushes
-0.018	0.685	-0.106	0.071	26	Adherence
-0.289	0.092	-0.630	0.053	18	Screen time
-0.500*	0.000	-0.693	-0.307	36	Confidence in self-management
-0.123	0.121	-0.281	0.035	24	Eyesight
-0.136	0.123	-0.311	0.038	51	Hydration
-0.419*	0.006	-0.707	-0.131	28	Chest pain
-0.024	0.681	-0.238	0.191	3	Flare of psoriasis
-0.310	0.175	-0.781	0.161	13	Menstrual cycle
0.101	0.599	-0.345	0.547	7	Red painful eyes
0.132	0.704	-1.163	1.427	3	Smoking today
0.224	0.371	-1.655	2.104	2	Blood in stool

N= number of patients with both a flare and non-flare entry for each variable; CI=confidence interval. Higher variable scores indicate more positive outcomes (e.g. a higher pain score indicates less pain).
**p<0.01.*
^Estimated difference between flare and non-flare entries (e.g. on average, the mean pain score of a flare entry is 0.67 [0.56– 0.78 CI] less than a non-flare entry).

Figure 1. Differences (normalised to [-1,1]) in petal values between two clusters of patients recording self-reported flare in the Project Nightingale (uMotif) app

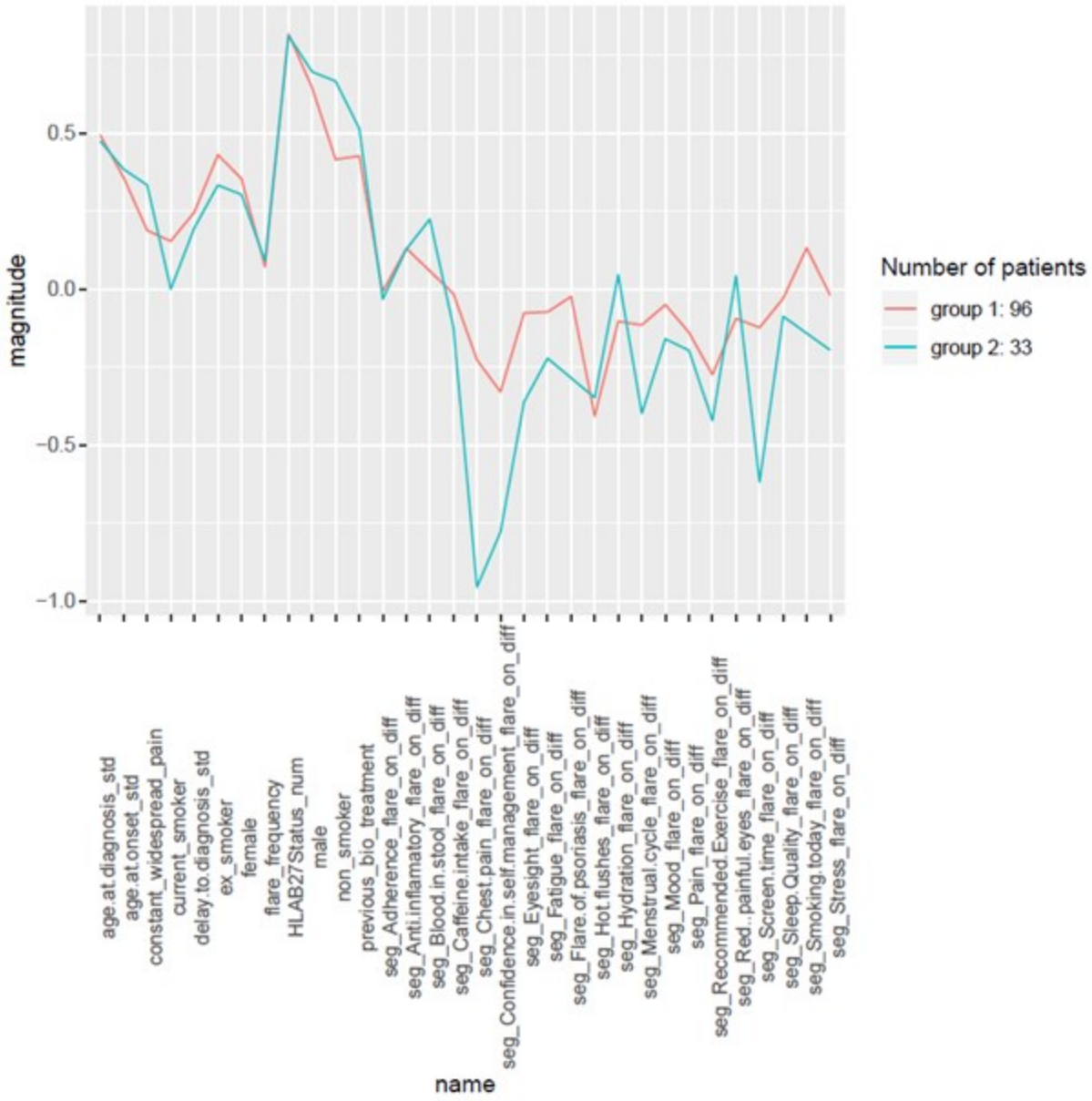


Table 2. Absolute differences in petal values between flare and no flare values for two clusters of patients recording self-reported flare in the Project Nightingale (uMotif) app

Petal Variable	Group 1 (N=96)		Group 2 (N=33)		p-value
	Difference*	N	Difference*	N	
Pain_flare_on_diff	-0.694	96	-0.984	33	0.007
Fatigue_flare_on_diff	-0.368	96	-1.111	33	0.000
Sleep.Quality_flare_on_diff	-0.151	96	-0.438	33	0.000
Recommended.Exercise_flare_on_diff	-0.274	96	-0.422	33	0.300
Mood_flare_on_diff	-0.251	96	-0.800	33	0.000
Anti.inflamatory_flare_on_diff	0.131	96	0.128	33	0.960

Stress_flare_on_diff	-0.101	96	-0.980	33	0.000
Caffeine.intake_flare_on_diff	-0.015	43	-0.122	11	NA
Hot.flushes_flare_on_diff	-0.408	17	-0.348	1	NA
Adherence_flare_on_diff	-0.008	13	-0.032	11	NA
Screen.time_flare_on_diff	-0.124	12	-0.619	6	NA
Confidence.in.self.management_flare_on_diff	-0.330	23	-0.779	9	NA
Eyesight_flare_on_diff	-0.077	18	-0.362	4	NA
Hydration_flare_on_diff	-0.103	32	0.046	14	NA
Chest.pain_flare_on_diff	-0.227	19	-0.956	4	NA
Flare.of.psoriasis_flare_on_diff	-0.024	3	NA	0	NA
Menstrual.cycle_flare_on_diff	-0.115	8	-0.399	2	NA
Red..painful.eyes_flare_on_diff	-0.094	4	0.043	2	NA
Smoking.today_flare_on_diff	0.132	3	NA	0	NA
Blood.in.stool_flare_on_diff	NA	0	0.224	2	NA

**Absolute difference from baseline (non-flare)*
NA=sample size too small to determine statistical significance

Table 3. Mean flare on and flare off values for two clusters of patients recording self-reported flare in the Project Nightingale (uMotif) app

Petal Variable	Group 1 (N=96)		Group 2 (N=33)		p-value
	Mean	SD	Mean	SD	
Flare on					
Pain	3.083	0.638	2.850	0.529	0.043
Fatigue	3.077	0.967	2.555	0.614	0.001
Sleep Quality	3.177	0.594	3.192	0.668	0.910
Recommended Exercise	3.219	1.152	3.513	0.994	0.166
Mood	3.051	0.799	2.693	0.801	0.031
Anti-inflammatory Use	0.552	0.408	0.575	0.373	0.770
Stress	3.875	0.720	3.070	0.902	0.000
Flare off					
Pain	3.777	0.581	3.834	0.590	0.635
Fatigue	3.445	0.805	3.666	0.657	0.122
Sleep Quality	3.328	0.545	3.630	0.657	0.022
Recommended Exercise	3.494	1.019	3.934	0.934	0.026
Mood	3.302	0.740	3.494	0.708	0.191
Anti-inflammatory Use	0.421	0.402	0.447	0.398	0.753
Stress	3.977	0.657	4.049	0.716	0.609

Table 4. Baseline characteristics of two clusters of patients recording self-reported flare in the Project Nightingale (uMotif) app*

	Group 1 (N=96)			Group 2 (N=33)			
Baseline* values	Mean	SD	N	Mean	SD	N	p-value

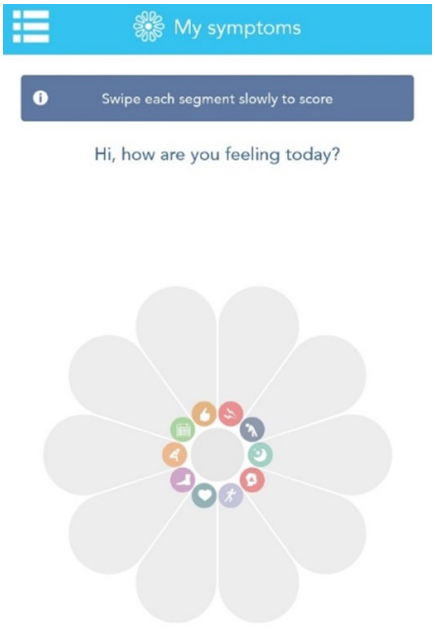
Mean (SD) BASMI score	3.173	2.069	59	3.533	2.082	18	NA
Mean (SD) BASDAI score	3.680	1.733	70	3.852	2.081	21	0.732
Mean (SD) BASFI score	3.627	2.568	66	3.715	2.214	20	0.882
Mean (SD) EQ-5D	0.618	0.191	53	0.659	0.240	20	0.499
Mean (SD) EQ-5D Pain and Discomfort	2.585	0.663	53	2.400	0.940	20	0.427
Mean (SD) EQ-5D Anxiety and Depression	1.906	1.005	53	1.600	0.754	20	0.167
Mean (SD) Patient-global	4.018	2.057	57	3.429	2.420	21	0.329
Mean (SD) ASQoL	8.060	4.716	59	7.935	5.234	21	0.924
Mean (SD) work productivity impairment	3.640	2.691	25	4.000	3.162	13	NA
Mean (SD) activity impairment	4.240	2.722	50	3.950	2.964	20	0.708
Proportion of employed	0.592	0.497	49	0.650	0.489	20	0.658
Proportion of females	0.354	0.481	96	0.303	0.467	33	0.592
Proportion of males	0.646	0.481	96	0.697	0.467	33	0.592
Proportion HLA-B27 +ve	0.818	0.388	88	0.813	0.397	32	0.945
Proportion of current smokers	0.154	0.364	65	0.000	0.000	21	0.001
Proportion of ex-smokers	0.431	0.499	65	0.333	0.483	21	0.431
Proportion of non-smokers (never smoked)	0.415	0.497	65	0.667	0.483	21	0.047
Proportion ever treated with bDMARDs	0.427	0.497	96	0.515	0.508	33	0.391
Proportion with CWP	0.188	0.392	96	0.333	0.479	33	0.121

**at visit date closest to Project Nightingale registration – restricted to visit dates within 90 days of Project Nightingale registration date*
SD=standard deviation; CWP=chronic widespread pain

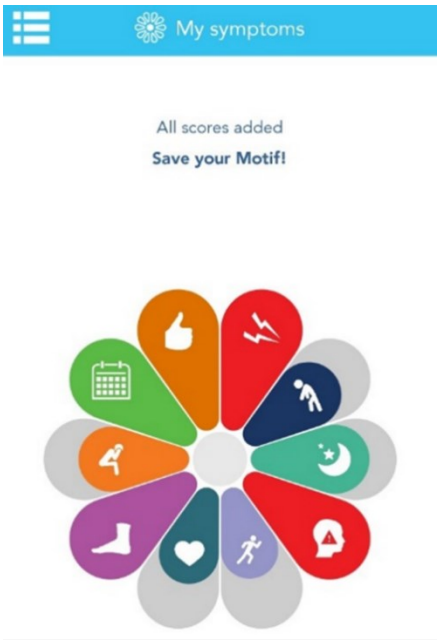
Supplementary material

Supplementary Figure 1A & 1B. Screenshots from the Project Nightingale smartphone app - daily completion of the motif

A)



B)



Supplementary Table 1. Flare characteristics of two clusters of patients recording self-reported flare in the Project Nightingale (uMotif) app

Variable	Group 1 (N=96)			Group 2 (N=33)			p-value
	Mean	SD	N	Mean	SD	N	
Number of flares	10.385	12.267	96	10.091	13.689	33	0.913
Mean number of active days (days reporting symptoms in the app)	223.906	210.692	96	188.818	201.750	33	0.398
*Mean flare frequency^*	0.072	0.069	96	0.091	0.084	33	0.249
Mean flare duration (no. of days)	7.208	10.188	96	3.530	2.756	33	0.002

^ Flare frequency reported as a proportion of each participants' number of active days.