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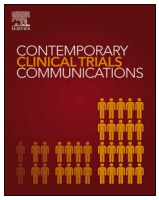

Wearable activity tracker study exploring rheumatoid arthritis patients' disease activity using patient-reported outcome measures, clinical measures, and biometric sensor data (the wear study)

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ABSTRACT

Background: Digital health studies using electronic patient reported outcomes (ePROs), wearables, and clinical data to provide a more comprehensive picture of patient health.
Methods: Newly initiated patients on upadacitinib or adalimumab for RA will be recruited from community settings in the Excellence NEtwork in RheumatoloGY (ENRGY) practice-based research network. Over the period of three to six months, three streams of data will be collected (1) linkable physician-derived data; (2) self-reported daily and weekly ePROs through the ArthritisPower registry app; and (3) biometric sensor data passively collected via wearable. These data will be analyzed to evaluate correlations among the three types of data and patient improvement on the newly initiated medication.
Conclusions: Results from this study will provide valuable information regarding the relationships between physician data, wearable data, and ePROs in patients newly initiating an RA treatment, and demonstrate the feasibility of digital data capture for Remote Patient Monitoring of patients with rheumatic disease.

Trial Registration: ClinicalTrials.gov NCT05603806.

1. Introduction

Digital health technology continues to be widely available, giving patients and their providers greater insight into trends in symptoms and disease activity. Wearable devices have been used to evaluate numerous diseases including atrial fibrillation, asthma, COVID-19 and gout [1].

Rheumatoid arthritis (RA) is a chronic disease characterized by inflammatory activity and joint damage that without adequate treatment over time may lead to disability, pain, limitations in physical function and other impairments important to patients. Patients are typically seen at three-six-month intervals at which point they are often assessed using tender and swollen joint counts as part of the Clinical Disease Activity Index (CDAI), in addition to labs. Although such clinical measures are useful, they may fail to capture the true frequency and severity of pain and flares experienced by patients in between visits. To more comprehensively understand RA disease activity and its manifestations from a patient's perspective, including measure important attributes related to pain and stiffness, it is essential to collect patient reported outcomes (PROs) in addition to physician-derived measures. The addition of remote variables not routinely collected in clinical care allows physicians to better understand what the patient is experiencing including suboptimal treatment response in patients initiating a new medication that may not be feasible with such frequency using current healthcare staff[2,3–5].Recent studies have evaluated the ability of patient-reported outcome measures (PROs) to predict flare in RA patients [6], measure physical activity as a proxy for disease activity [6], and study associations between electronic patient-reported outcomes (ePROs) and passive (wearable/actigraphy) data [7]. These studies also evaluated the ability of RA populations to regularly complete their ePROs and wear their actigraphy devices. There is a lack of

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understanding about how long participants are willing to actively engage in providing data and what forms of encouragement are necessary to ensure high quality participation. Furthermore, there is a lack of consensus on what is considered good adherence to the study protocols for data completeness [8–10].

Using only PROs, wearable data, or clinical measures by themselves to capture RA disease activity is incomplete. Given the lack of research in this area, we aimed to study a large RA population, incorporating physician-derived data (clinical disease activity measures from rheumatologist visits and labs) with PROs and wearable data in patients newly initiating medication.

The primary objective of this study is to evaluate longitudinal associations among biometric sensor data (activity and sleep measures), physician-derived data, and electronically-captured PROs. The hypothesis is that the data sources will show the same information, that patients are improving on new medications. Via increased activity and sleep, improved ePRO scores, and clinician recorded measures.The secondary objectives of this study are to: (1) Explore the reliability and predictive validity of biometric sensor data to classify changes in RA disease activity and associated symptoms, including PROs; (2) To assess adherence and predictors of adherence to study protocol with use of biometric sensor; and (3) Evaluate changes in patients initiating upadacitinib and adalimumab using combined physician, PRO and biosensor data. In this design manuscript, our purpose is to report novel features of the study design, including those related to patient engagement, technology onboarding, and the integration of multiple traditional and non-traditional data sources to achieve these objectives, to serve as a model for future clinical studies where actigraphy devices, out of office PRO, in office PROs, EHR data, and electronic data capture (EDC) system information is integrated together.

2. Methods

2.1. Subject recruitment

Patients are recruited from multiple community practice settings that are part of a newly instantiated practice-based research network (PBRN), the Excellence NEtwork in RheumatoloGY (ENRGY) created in 2022 by Illumination Health (Health). In brief, the ENRGY network consists of approximately 100 private practice rheumatology sites and more than 300 clinicians that are capable of conducting clinical research with well described capacities and a number of shared capacities that promote research efficiency. The features of this PBRN include a) a single electronic health record (EHR), with full access to structured and unstructured data; b) routine use of an in-office tablet app to capture PROs; c) integration with an out-of-office smartphone app (ArthritisPower) [7,11] and the associated wearable data streams used for this study; d) standing linkages to multiple external data sources, including lab data for routine labs, or to a bespoke biorepository (as required); e) external linkage to health plan claims data (if needed); f) an EDC system to capture information from clinicians and study coordinators that would not otherwise be found within the EHR; g) an integrated data warehouse that normalizes all data to a common data model; and f) data visualization and other informatics tools to facilitate periodic or real-time data monitoring. While the overall intention of this study is to evaluate the more newly available upadacitinib we are also recruiting participants using adalimumab to assist with recruitment times and subject availability.

2.2. Inclusion criteria

The following are the inclusion criteria for this study.

- Age ≥19 years
- Diagnosis of RA by a rheumatology provider
- Initiating (with no prior use ever) or planned initiation (i.e. in the next 30 days) of upadacitinib or adalimumab for RA
- Ability to walk without the use of assistive devices
- Owns a smartphone (iPhone or Android)
  - iPhone 4S and later or
  - Android 4.3 and later
- Willing to join the ArthritisPower patient registry and participate in this ancillary study
- CDAI >10

2.3. Variables and measures

Three sources of data are collected for each patient in this study: (1) physician-derived data and lab information, captured by the EDC system; (2) one-time demographic data (at enrollment), plus self-reported daily and weekly PROs through the ArthritisPower app (patient provided) – ArthritisPower data can be provided through a web-based portal and/or a smartphone app (both iPhone, Android); and (3) biometric sensor data passively collected via participant's wearable (transferred via a Fitbit account linked to Fitabase). (Table 1).

Physicians and site coordinators enter the physician-derived clinical data and lab data into the EDC system on the enrollment visit day (or within 24 h of the visit) as well as patient contact information and programmatic tracking measures. Additional clinical data is collected at a follow up appointment 2–6 months after enrollment with further clinical information pulled from the EHR as needed. For patients that see their clinician before the two month follow up visit only a visit that occurs withing the 2–6 month window will be used for clinical data collection.

This study is being conducted as an ancillary study to the ArthritisPower registry infrastructure. ArthritisPower was jointly developed by the nonprofit Global Healthy Living Foundation (GHLF), its associated CreakyJoints arthritis patient community, and rheumatology researchers at the University of Alabama at Birmingham (UAB), and funded through a Patient-Centered Outcomes Research Institute Award (Contract Number PPRN-1306-04811) [7,11]. ArthritisPower currently has over 40,000 consenting participants, about half of whom report a physician diagnosis of RA. As part of their membership in the ArthritisPower registry and participation in the WEAR study, patients download the ArthritisPower app to use for demographic data capture and electronic patient-reported outcome (ePRO) measures collection. ArthritisPower routinely collects ePRO from members in the registry [12]. They separately consent to participate in this ancillary study. The study was conducted in accordance with ethical standards and was approved by Advarra IRB (Pro00047954).

Validated PRO measures from physical, mental, and social health domains are presented to participants at regular intervals (daily, weekly, etc.). Computerized adaptive testing (CAT) versions of the disease-agnostic instruments developed by the National Institutes of Health (NIH) for the Patient-Reported Outcomes Measurement Information System (PROMIS), including measures of pain, fatigue, physical function, anxiety, sleep and social participation, will be used (NIH). Notably, PROMIS Physical Function is now one of the American College of Rheumatology (ACR) recommended measures for functional status for RA [13]. The duration of morning joint stiffness is also collected [14,15–17]. Rheumatoid Arthritis Disease Activity Index (RADAI5) is included as an RA-specific disease activity measure familiar to most physicians (Leeb, Brezinschek et al., 2016).

Biosensor data is collected using a commercial grade Fitbit® device (Versa 3). Participants are provided with preconfigured Fitbit accounts, which they are encouraged to routinely sync, linked by GHLF to the Fitabase platform. Fitabase is a comprehensive data management platform that supports research projects using wearable and internet-connected devices. The Fitabase platform streams participants' activity metrics directly from the Fitbit cloud. This allows the research team at GHLF/UAB to monitor participant synchronizations and send

Table 1
Variables and Measures The following table outlines the specific data elements collected from each source.

SOURCE OF DATA	VARIABLE	FREQUENCY OF COLLECTION	DEFINITION
Clinical Characteristics and EDC Collected Data	•Medical record number	Collected at study baseline and a subset at follow-up 2–6 months from baseline	Medical record number of patient from IEHR
	•Medication initiating upadacitinib or adalimumab)		Medication initiating upadacitinib or adalimumab
	•Providing samples?		Whether the patient is receiving samples
	•If samples, Fitbit ID		The date the coordinator anticipates the participant will start the new medication
	•Anticipated medication start date		Participant's cell phone number (provided by the participant to the coordinator)
	•Cell phone number		Participant's email address (provided by the participant to the coordinator)
	•Email address		BMI as recorded in the EHR
	•BMI		Smoking status as recorded In the EHR
	•Smoking status		Comorbidities as recorded in the EHR
	•Comorbidities – Anxiety, Depression, Fibromyalgia, Diabetes, COPD, Heart Failure, Sleep Apnea/Sleep Disorders		Non autoimmune medication use as recorded in the EHR
	•Non autoimmune medication use		CDAI is a clinical composite score derived from the sum of the swollen joints, tender joints, patient global disease activity measure and the physician global disease activity measure.
	•Clinical Disease Activity Index (CDAI)		Remission $\leq$2.8
	•Physician global assessment		Low Disease Activity >2.8 and $\leq$ 10
	•Patient global assessment		Moderate Disease Activity >10 and $\leq$ 22
	•Swollen/Tender Joint Count		High Disease Activity >22
	•RA Clinical Labs (Rheumatoid Factor and CCP lab results)		Physician Global Assessment is the physician's assessment of overall RA disease activity on a scale of 1–10 where 10 is maximal activity.
	•Past and current prescription medications for RA		Swollen Joint Count is the number of swollen joints, identified by the physician, out of the 28 joints assessed including the shoulders, elbows, wrists, MCPs, PIPs including thumb IP, and knees.
	•Year of first RA diagnosis by rheumatologist		Tender Joint Count is the number of tender joints, identified by the physician, out of the 28 joints assessed including the shoulders, elbows, wrists, MCPs, PIPs including thumb IP, and knee
			Rheumatoid Factor Lab Result shows the amount of rheumatoid factor antibody present in a patient's blood. Positive RF results are values $\geq$ 14 IU/ml, however values 3x greater than 14 (42) are most meaningful.
			Current and past prescription medications for RA will be those identified at enrolment visit.
			The date of the patient's first RA diagnosis code by a rheumatologist.
ArthritisPower Registration	**PARTICIPANT DEMOGRAPHICS**	Once at registry baseline (i.e., variables routinely collected at initial ArthritisPower registration)	Age: Date of Birth
	•Age		Gender: Male/Female
	•Gender		Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple Race, refuse to answer
	•Race		Hispanic Ethnicity: No, Unknown, Yes
	•Hispanic Ethnicity		Zip code: 5-digit U.S. postal code*
	•Zip code		Condition(s): Rheumatoid arthritis
	•Condition(s)		
	BASELINE CLINICAL CHARACTERISTICS & NON-STANDARD ARTHRITISPOWER PARTICIPANT DEMOGRAPHICS	WEAR Study landing page, once at start of *study* registration (i.e., variables NOT routinely collected at initial ArthritisPower registration that will be collected at start of study)	Years since RA diagnosis: Time from the patient's first RA diagnosis code by a rheumatologist.
	•Years since RA diagnosis		Rheumatologist name: NPI lookup by city, state
	•Rheumatologist name (NPI lookup by city, state)		Current rheumatologist: Yes/No
	•Height		Height: feet, inches
	•Weight		Weight: lbs
	•Telephone number (cellular)		Telephone number (cellular): Phone number
	•Shipping address		Shipping address: Address 1, Address 2, City, State, Zip Code
ArthritisPower Study Specific ePROs	•Pain (NRS)	Daily	0-10 at 0.5 intervals
	•Fatigue (NRS)		
	•Duration of Morning Joint Stiffness	Daily	0-24 (hours) at 0.5 intervals
	•Rheumatoid Arthritis Disease Activity Index (RADAI5)	Weekly	0-10 at intervals of 1
	•Patient Global Assessment (PtGA)	Weekly	0-10 at 0.5 intervals
	•PROMIS Pain Interference (CAT)	Weekly	0-100 t-score (Note: most scores are within the 20–80 range)
	•PROMIS Physical Function (CAT)		PROMIS tools anchor on a mean score of 50 (general US population average) and standard deviation (SD) of 10.
	•PROMIS Fatigue (CAT)		
	•PROMIS Sleep Disturbance (CAT)		

(*continued on next page*)

Table 1 (*continued*)

SOURCE OF DATA	VARIABLE	FREQUENCY OF COLLECTION	DEFINITION
	•PROMIS Satisfaction with Participation in Discretionary Social Activities (CAT) •PROMIS Anxiety (CAT)	Monthly	
	•Medication Adherence – ask whether patient has taken medication	Weekly	How many doses have you taken in the last week?: 0, 1, 2, 3, 4, 5, 6, 7, I've stopped taking it.
Passively Collected Participant Biometric Data	**Activity** •Steps •Distance* •Energy expenditure •Metabolic Equivalents** **Activity-derived variables** •Time walking per day •Time in activity intensity categories per day •Active time •Aerobic time	Fitbit continuous, synced to app and Fitabase every <5 days	Steps: Total number of steps taken Distance: Total kilometers tracked Energy expenditure: Total number of estimated calories burned Metabolic Equivalents: Total energy expenditure from basal metabolic rate Time walking per day: Date and time value in mm/dd/yyyy hh:mm:ss format Time in activity intensity categories per day: Value calculated by adding all the minute-level intensity values that occurred within the hour (0 = sedentary, 1 = light, 2 = moderate, 3 = very active) Active time: Minutes spent in Out of range heart rate zone, Fat Burn heart rate zone, Cardio heart rate zone, Peak heart rate zone Minute, hour, day *day – units = miles **METs, minute
	Heart Rate •Beats per minute **Heart rate-derived variables** •Time in heart rate zone of interest based on exercise charts		Mean heart rate value per minute. Date and time value in mm/dd/yyyy hh:mm:ss format.
	Sleep •Time sleeping in last 24 h **Sleep-derived variables** •SleepValue: Time in awake, restless, asleep		Day = Date on which the sleep event started. (in mm/dd/yyyy hh:mm:ss format) Minute = Total number of minutes classified as being "asleep". Value: Value indicating the sleep state, 1 = asleep, 2 = restless, 3 = awake

Data collection schedule and content

participation reminders. Use of wearable activity trackers in studies measuring physical activity in individuals with musculoskeletal diseases such as osteoarthritis, RA, and spondyloarthritis has grown in recent years [8,18], and Fitbit devices have been used in many clinical trials (2022, [19]) and evaluated in a number of validity studies [20,21]. A full list of data elements and their sources are provided in Table 1.

2.4. Data workflow

After physicians determine participant eligibility, the participant is presented with a custom QR code for that site. Scanning the QR code from their smartphone brings them to the registration landing page for the study. Participants are then presented with the necessary information about the study and are able to consent to participation. Once participants have consented clinical site coordinators are able to enter the clinical data into the EDC system. Coordinators are able to enter lab data at a later date if it is unavailable at enrolment.

After participants are enrolled at clinic sites, they return home for a 7-day run-in period. During this time, they will complete daily ePROs (Table 1). Completion of all ePROs for a minimum of 5 out of 7 days in a single attempt are required to successfully advance to the main study. To minimize the missingness of weekly ePRO data and avoid repetition of the same ePROs, the ePRO assessment schedule rotates the weekly and monthly measures that patients see each day while always presenting them with the daily ePROs.

If a participant receives sample medication to initiate at the clinic, they receive their wearable in clinic; otherwise, they will receive their wearable device, along with materials to help with syncing the device, upon successful completion of the run-in period. Patients are expected to wear the device while going about their normal daily routine for up to 24 weeks. Participants agree to wear the device at all times, even when sleeping, and complete daily (approximately 2 min) ePROs via the ArthritisPower app on their smart device or computer.

For participants that are sampled medication the medication start date is imputed as the day of enrollment. For participants that are not sampled medication, they have 30 days to initiate new treatment and are sent daily text messages asking if they have begun their medication. By responding Y to the daily text message medication start date is recorded.

Day 1 of the study is synonymous with the main study start date (i.e. the date that the participant successfully completes the run-in period and has initiated upadacitinib or adalimumab). For the first 12 weeks of the main study period, participants receive automatic and/or manual communications via email, text, lock-screen notifications and/or telephone calls from study personnel. The study team will use a participant communication plan that describes the frequency, type and hierarchy for the types of communication that participants will receive based on the participants' adherence to protocol as described in Communication Plan below (Table 2). For weeks 13–24, also known as the run-out period, participants will not continue to receive automatic or manual communications (Fig. 1).

The ArthritisPower app will collect ePROs from participants via a customized, study-specific user flow within the app. Participants complete ePRO measures every day, the single-item Pain, Fatigue and Morning Joint Stiffness numeric rating scales (NRS), and a once-weekly 'core' set of ePRO measures as well as monthly ePROs that rotate throughout the workflow. Measures of activity, sleep and heart rate are collected passively using the wearable (Table 3). To create day level Fitbit data for participants the following steps will be used: 1. For variables available in 30 s, minutes, and 15 min level, the hourly value will be calculated summing up values to the hourly level (60 min). 2. Hourly values will then be converted to person days by summing the hourly values between 20:00–20:00.

Following the main study period is the three-month run-out period during which no manual or automatic communications to sync the

Table 2
Triggers for contacting participants wPRO = weekly PRO; dPRO = daily PRO.

	Type of Data	Missing Data Trigger	Study Coordinator Action
1	ePRO	ePROs past due 3 days	Text message
2	SLEEP	Wearable wear time <1200 min + No sleep min for 3 days	Text message
3	SLEEP	No sleep minutes for 3 days	Text message
4	WEAR	Wearable wear time for 1–800 min for 3 days	Text message
5	WEAR	Wearable wear time for 0 min for 3 days	Text message
6	SYNC	No Sync 3 days	Auto email/LSN
7	ePRO	ePROs past due 4 days	Text message
8	SLEEP	Wearable wear time <1200 min + No sleep min for 4 days	Text message
9	SLEEP	No sleep minutes for 4 days	Text message
10	WEAR	Wearable wear time for 1–800 min for 4 days	Text message
11	WEAR	Wearable wear time for 0 min for 4 days	Text message
12	SYNC	No Sync 4 days	Text message
13	ePRO	ePROs past due 5 days	Text message
14	SYNC	No Sync 5 days	Text message
15	SLEEP	Wearable wear time <1200 min + No sleep min for 5 days	Phone call
16	SLEEP	No sleep minutes for 5 days	Phone call
17	WEAR	Wearable wear time for 1–800 min for 5 days	Phone call
18	WEAR	Wearable wear time for 0 min for 5 days	Phone call
19	ePRO	ePROs past due ≥6 days	Phone call
20	SLEEP	Wearable wear time <1200 min + No sleep min ≥6 days	Phone call
21	SLEEP	No sleep minutes ≥6 days	Phone call
22	WEAR	Wearable wear time for 1–800 min ≥ 6 days	Phone call
23	WEAR	Wearable wear time for 0 min ≥ 6 days	Phone call
24	SYNC	No Sync ≥6 days	Phone call

Please note that participants are only to be contacted once a day and not sent multiple reminders despite possibly missing multiple data points.

wearable will be sent and no ePRO collection will be prompted. The purpose of the run-out period is to assess the need of reminders/notifications over long periods of time, observe the attrition in wearable use, and assess any changes in wearable measures when not actively solicited.

Participants are compensated for their participation at 4 weeks ($50), 12 weeks ($85), and for attending their follow up visit ($110) to encourage participation and show appreciation for their involvement.

2.5. Data monitoring and Participant communication plan

As part of the procedures that patients consent to, centralized study coordinators (not site study coordinators) contact participants via phone, text or email at any time during the duration of this study to assist them with any challenges or to gather more information about any participation-related or device-related problems that may be encountered while individuals participating in the study. In addition, the study coordinator will be able to contact participants who enroll for the study but do not initiate participation or who may fail to continue providing ePRO or actigraphy data during any of the phases of the study. This will be done to help participants address any difficulties, technical challenges or concerns they may have while enrolled in the study. Such monitoring is done on a continuous basis using a customized electronic query system built by the research team that was designed to facilitate such real-time data monitoring. Triggers include not successfully syncing the wearable device, not continually wearing the wearable device, and not answering PROs. See Table 2 for full list of triggers (i.e. missing data from individual participants) that cause centralized study coordinators to take action, communicating directly with participants.

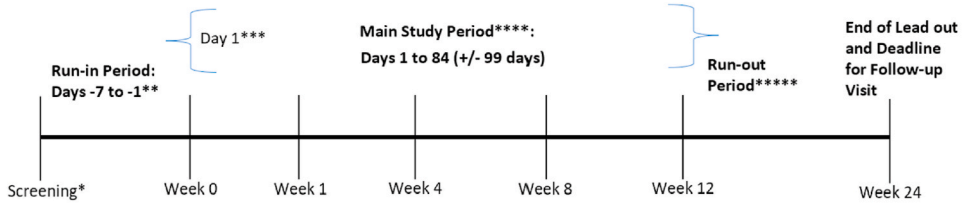
2.6. Analysis

2.6.1. Primary objective

The primary analysis will be a descriptive summary of the correlation between each of the data types: actigraphy data from the wearable, ePRO data obtained via the ArthritisPower app, and clinical data reported at the time of in-office physician visits.

To evaluate the longitudinal associations between the different data sources, summaries to be explored include the average of each measure over the time period, trend, most recent, minimum, maximum, variation, and transformations. Correlations between the PRO, passive measures, and physician-derived data will be quantified using both a simple correlation matrix for each week, as well as repeated measures models over the entire main study period.

Repeated measures models will be implemented using each PRO as the outcome measure, with time (e.g. week as a class factor), baseline measures, and the various passive measures and physician-derived data as potential factors in the model. Normality of the data will be checked and, if necessary, a transformation will be applied (e.g. log or Box Cox). If normality is satisfied, or if sample size allows, the starting model will be a simple main effects model. Penalized logistic regression using LASSO (Least Absolute Shrinkage and Selection Operator) penalty will be used to identify factors associated with high protocol adherence. The reported odds ratios will be based on the unpenalized logistic region including only factors selected by LASSO. For digital measures obtained daily, a repeated measures model will assess the association between the ePROs (outcome), actigraphy measures, and physician-derived data (as appropriate) over time (with day as the time period of assessment rather than week). Daily ePRO data may be lagged by a day if it is observed that most participants are responding in the morning. Due to the large number of days in the study, in this model time will be considered a numeric variable. Simple correlation matrices may also be produced at various time points as for the weekly measures. Also due to the large number of data points statistical significance is not the determining



* Assess eligibility for study participation, enroll participant in Arthritis Power, and provide wearable device to participant if starting samples
** During Run-in period, participants will complete ePROs and perform wearable device set up and sync; an additional 30-day window is to allow time for medication access for non sampled patients
*** To enter Main Study, participant must: (a) initiate medication within 30 days and (b) successfully complete Lead-in (minimum 5 of 7 days of ePROs)
****Participants to wear Fitbit device at all times, even when sleeping, Participants will receive automatic reminders via email, lock-screen notification and/or text
*****Without prompting, participants may continue to complete ePROs using the ArthritisPower app each day as they did during main study period for Day 85-168; Participants may continue wearing Fitbit device at all times; Participants will no longer receive reminders via email, lock-screen notification and/or text

Fig. 1. Overall study design.

Table 3
Data collection schedule.

	Lead-in	Main Study												Lead-out											
	W1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W1	W11	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23	W24
Routine Clinical Encounter													Routine Clinical Encounter												
AP Registration & eConsent	x																								
Non-Standard ArthritisPower Participant Demographics	x																								
Clinical Characteristics													x												
RA Clinical Labs													x												
CDAI													x												
Daily Fatigue		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Morning Joint Stiffness		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Daily Pain		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication Adherence		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient Global Assessment (PtGA)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PROMIS Sleep Disturbance		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PROMIS Fatigue		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PROMIS Pain Interference		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PROMIS Physical Function		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RADAI		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PROMIS Satisfaction with Participation in Discretionary Social Activities		x	x			x				x			x	x				x				x			x
PROMIS Anxiety		x	x			x				x			x	x				x				x			x
Patient Payment					x								x				x								

factor of a trend, instead patterns of association will be reviewed.

2.6.2. Secondary objectives

Reliability and Validity of Passive Measures- The focus of these analyses is not to establish the full validity of the digital measures, as the design of the study does not include the collection of physician-confirmed measures to serve as a standard. However, these analyses will summarize the trends, between-participants and within-participants variability over time and quantify convergent validity and test-retest reliability for select measures. *Assessment of adherence and predictors of adherence with use of technology, and providing ePRO and wearable data*- Descriptive statistics will quantify the adherence/compliance rates for the various measures and technology as well as any differences in the enrolled populations and those compliant with the protocol. Penalized Regression and/or tree-based methods (CART, Random Forests) incorporating cross validation will be utilized to determine the factors most strongly associated with adherence for each type of technology.

Track improvements in upadacitinib and adalimumab patients- The focus of these analyses will be to evaluate mean changes in PROs, physician-derived data and passive data over time (at baseline and at ~3 month follow-up) in upadacitinib and adalimumab patients. Repeated measures models will be implemented using each ePRO and physician-derived data point as the outcome measure, with time (e.g. Week) as a class factor, demographic and baseline clinical characteristics, and each passive measure as potential factors in the model. Machine learning methods (such as decision tree, random forest, XGBoost, support vector machine and elastic-net regression) will be used to build model to classify low-remission vs. medium-high in term of CDAI or regression on CDAI as a continuous variables, potential features will include baseline CDAI, Fitbit data and daily PRO. These analyses will maximize the accuracy of baseline data and longitudinal PROs to correctly classify patients in low disease activity or remission approximately 2–6 months after starting upadacitinib or adalimumab. This will allow for assessment of changes in correlations over time adjusted for participant level, and other, covariates.

2.6.3. Accounting for confounding and bias

The primary analyses in this study are descriptive and thus no adjustment for potential confounding is considered. Participant demographics and baseline characteristics will be summarized to better understand the generalizability of any analyses. Baseline characteristics will be compared between those that qualify for the main study and those that failed the run-in to better understand what can impact digital literacy and being able to participate in a study with remote data collection.

2.6.4. Missingness

As described above, automatic reminders and study coordinators will prompt patients to complete ePROs and sync wearable data during the course of the main study. This is a descriptive analysis and no imputation of outcome data will be performed. *Sample Size*.

The primary objective of this study is to quantify the agreement between passively collected digital measures (e.g. activity), physician-derived data and ePRO data (e.g. pain). To align with the proposed analytic approach in the following section, agreement is quantified by correlations in this sample size determination. Assuming at least 75% of the participants complete the majority of the digital measures, a sample size of 150 was selected to provide at least 80% power to detect correlations between passively collected data via the wearable and the actively collected data from ePRO instruments of at least 0.2 and over 90% power to detect correlations of at least 0.3 at any given time point.

Correlations of 0.3 are generally considered to be moderate correlations [22]. Correlations of up to 0.2 were observed in a prior pilot study of passive measures. From this prior smartphone study in RA patients, complete adherence with ePROs prior to discontinuation was 68%. It is reasonable to anticipate that 75% of the subjects would

complete the daily ePROs [10]. This is not a comparative effectiveness study and it is not planned to compare the participants in each medication subgroup.

2.6.5. Subject withdrawal

Participants may withdraw from the study at any time or may be withdrawn by the study team (categorized as terminated – self terminated, or study team terminated). There are no anticipated withdrawals for safety reasons or non-adherence to protocol requirements.

2.6.6. Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and in compliance with it.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. If this occurs, further surveys will not be collected from the participant.

3. Discussion

Incorporating physician-derived data with passively collected wearable data in conjunction with PROs in a large RA population newly initiating medication expands on efforts of previous studies to help with more informed decision making for both physicians and patients. The ability to register patients for ArthritisPower during a clinical visit while also allowing patients to track their own symptoms cooperatively with their physicians in addition to helping to better understand the relationships between data types makes this a novel study design.

3.1. Strengths

The strengths of this study include the novelty of the design and data being collected, and the efforts made to reduce clinical site burden. Each of these strengths is anticipated to be accompanied by challenges that will lead to learnings for future study development.

The novel study design includes enrolment at site in conjunction with the patient providing data remotely. This will leverage existing physician-patient relationships while nearly all additional data is provided remotely by the patient without needing supplemental clinical visits. The ability to collect data in a mobile fashion will allow for an almost completely virtual/remote study. To ensure participant compliance a combination of automated and direct-customized contact with participants by study coordinators will encourage engagement. This could lead to some confusion by participants about whether they are to contact their physician's office or the study coordinator for any problems that they experience during the study.

While all data in this study has been collected in some form before it is novel in collecting wearable data by participants newly initiating a medication and by combining three different types of data. Additionally, two of the data sources are patient-generated allowing for more frequent data collection points. The use of physician-derived data, in addition to PRO data captured by ArthritisPower, will give a 360-degree view of the participants health status at baseline. While frequent data collection is useful it can also lead to data collection overload resulting in participant fatigue and analytical burden.

This study was developed to reduce clinical site burden. The clinical data being collected is part of routine care and does not require any additional data gathering by the site. All the clinical site coordinator must do is to enter the information into the EDC system. The follow up window is also large to allow for regular scheduling of follow up appointments. Future studies can find ways to pull this information directly from the EHR in order to further reduce burden on clinical site staff. These forms of Remote Therapeutic Monitoring (RTM) are growing since being reimbursed by Medicare and show great potential for future patient provider engagement [23].

3.2. Limitations

This study has a few limitations that should be noted. By not randomizing the use of reminders in the lead-out period we are unable to have a clear coparator group afet the main study period to comparative effectiveness of reminders. Additionally, there may be a selection bias in that only patients that are reasonably comfortable with a smartphone and a consumer-grade wearable device will participate in the study. Although participants will be enrolled and receive assistance with downloading ArthritisPower during the in-person enrollment, participants will continue to use the technology without in-person assistance. However, after enrollment, participants will be able to receive help via phone or email to assist with any technical limitations that they may encounter. While the patient tracking their own symptoms does reduce the burden on physicians it can add to the participants burden of caring for their disease, this is mitigated by hopefully empowering them to better understand their illness. Furthermore, there will be missing data whenever participants fail to complete the workflow on certain days. We have attempted to mitigate this by providing weekly PROs more than once a week to ensure that the information is collected on a regular basis.

Despite these limitations, the findings from this study will help inform similar future efforts in both rheumatology research and clinical care. Patients have long demanded more flexible health care options and the SARS-COV-2 pandemic expanded the opportunity for telemedicine in rheumatology. This includes remote therapeutic monitoring (RTM), where patient-generated data can be tracked in real time for clinical care, such as initiation of new treatment. Indeed, as of 2022, physicians can be reimbursed for remote monitoring. Data from wearables, PROs, and patient measures of disease activity are essential for such clinical tracking of patients' conditions. This additional data has the potential for benefits throughout the health care system: including the potential for better patient outcomes, cost savings for health care systems and patients, and better patient doctor relationships. Studies such as this may promote the continued availability and expansion of remote data collection to serve the needs of clinical researchers, providers, and patients alike.

4. Conclusion

Results from this study will provide valuable information regarding the relationships between physician data, wearable data, and PROs in patients newly initiating an RA treatment.

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CRediT authorship contribution statement

Laura Stradford: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jeffrey R. Curtis:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Patrick Zueger:** Writing – review & editing, Resources, Project administration, Methodology, Investigation. **Fenglong Xie:** Writing – review & editing, Methodology, Formal analysis, Data curation. **David Curtis:** Writing – review & editing, Software, Resources, Methodology, Data curation, Conceptualization. **Kelly Gavigan:** Writing – review & editing, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cassie Clinton:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation,

Conceptualization. **Shilpa Venkatachalam:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Esteban Rivera:** Writing – review & editing, Formal analysis, Data curation. **W. Benjamin Nowell:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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