Study protocol and statistical analysis plan

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Background

Self-management is a key component of successful chronic disease management [1]. Broadly, it is a process where patients are actively participating in a variety of activities that contribute to lessening of the physical and emotional impact of their illness. Such activities include adhering to their treatment plan, being physically active, and seeking medical help when the treatment target is not met. It is important to make self-management a priority as patients can benefit from learning about how their daily activities and treatments correlate with their symptoms and health status on an ongoing basis. This contextualized health data provides a baseline for patients to determine if their symptoms warrant seeking medical attention and could inform their decisions about daily activities. For example, a patient who is aware of how much pain and fatigue they experience following a day of housework will know to pace their activities the next day.

Chronic disease self-management is hard work; it can be difficult to follow treatment regimes in the context of busy lives and fluctuating symptoms. There is a need to develop a multifaceted approach that can promote self-management and adherence to recommended treatments. As an example, for people with RA, there is ample evidence to support early and persistent use of disease-modifying anti-rheumatic drugs (DMARDs) [2]. However, for people who started RA medications, the adherence rates are as low as 30% [3]. Furthermore, despite the compelling evidence supporting a physically active lifestyle in reducing symptoms [4-7], the majority of patients do not meet the minimum recommended level of moderate-to-vigorous physical activity (MVPA) [8].

In general, patients feel a moral obligation to "manage well" [9]. However, some become disengaged from self-management activities [10] because of a frustration from managing their

health on a trial-and-error basis [11]. The current practice relies on patients applying their self-management knowledge and skills in daily life with little feedback on their performance or how their actions affect their health. In light of these findings, we believe that there is a need for a multifaceted approach that provides support in terms of knowledge, skill development and timely advice from health professionals, as well as motivational support for patients to be engaged in their care and to stay physically active.

OPERAS web application

The OPERAS web app was designed to engage patients in monitoring and managing their health. Building from two existing software programs, the Arthritis Health Journal (AHJ) [12] and FitViz [13], OPERAS allows users to track symptoms, self-management goals, medication use, and physical activity. The latter is automatically measured by Fitbit. Using OPERAS, a physiotherapist (PT) will provide remote counselling to guide the user in setting realistic physical activity goals. Based on the users' goals, the PT can adjust parameters of physical activity intensity and duration to provide automated personalized feedback on their goal attainment.

The objectives of this study are to: 1) assess the efficacy of OPERAS at improving self-management ability of people with RA in a 6-month randomized controlled trial (RCT); 2) explore the effect of OPERAS on disease status, pain, fatigue, depressive symptoms, and characteristics of habitual behavior; and 3) assess barriers to implementation and sustainability of OPERAS from the perspectives of participants involved in the study.

Methods/design

Study Design

The *Empowering active self-management of arthritis: Raising the bar with OPERAS (an On-demand Program to EmpoweR Active Self-management)* project will use a mix of quantitative and qualitative research methods. The RCT will employ a delayed control design, whereby participants will be randomly assigned to start the 6-month intervention immediately (Immediate Intervention [II] group) or 6 months later (Delayed Intervention [DI] group) using a 1:1 allocation ratio. Participants will be assessed 3 times throughout the study (Fig. 1.). At the end of the intervention, we will invite a sample of participants to be interviewed regarding their experiences.

Participants

Individuals are eligible for the study if they have: 1) a rheumatologist confirmed diagnosis of RA; 2) no joint surgery in the past 6 months; 3) no history of acute injury to any joints in the past 6 months; 4) an email address and daily access to a computer or mobile device; 5) the ability to speak and understand English; and 6) not previously participated in studies involving the AHJ or physical activity counselling. We will exclude people who should not be physically active without medical supervision, as identified by the Physical Activity Readiness Questionnaire (PAR-Q) [14]. If participants fail the PAR-Q, a physician's note will be required to determine if they are eligible.

Participants will be recruited from rheumatology clinics in Metro Vancouver, and through the network of patient groups including Arthritis Consumer Experts, and Arthritis

Research Canada's Arthritis Patient Advisory Board. We will also post study information in social media (Facebook, Twitter, Kajiji, Craigslist) and Arthritis Research Canada's website.

Once participants complete the screening process and are deemed fully eligible for the study, the study coordinator will provide detailed information on the study, and a consent form will be emailed to the participant. When a signed consent form is obtained (e-signature or scanned copy), the participant will be enrolled. All potential and consented participants will be assigned a study ID which links to their personal and contact information. This information will be stored in a password-protected file on a secure database only accessible to the research team.

	STUDY PERIOD				
	Enrolment	Baseline	Post-allocation		
Weeks	-1 to 0	0 (T0)	1	27 (T1)	53 (T2)
ENROLMENT:					
Eligibility	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Immediate Group (N= 67)			♦—	—♦	
Education Session			X		
Access to OPERAS web-app and Fitbit (Weeks 1-53)			♦—	—	—♦
PT Phone Calls (Weeks 2- 26)			♦—	—♦	
Delayed Group (N=67)				♦—	—♦
Education Session				X	
Access to OPERAS web app and Fitbit (Weeks 27-53)				♦—	—♦
PT Phone Calls (Weeks 29-52)				♦—	—♦
ASSESSMENTS:					
Patient Activation Measure (PAM)		X		X	X
Rheumatoid Arthritis Diseases Activity Index (RADAI)		X		X	X
Fatigue Severity Scale (FSS)		X		X	X
McGill Pain Questionnaire (MPQ-SF)		X		X	X
Patient Health Questoinnaire-9 (PHQ-9)		X		X	X
Self-Reported Habit Index (SRHI)		X		X	X
SenseWear Mini		X		X	X

Fig 1 Standard protocol items: recommendation for interventional trials (SPIRIT) figure

The Intervention

Participants randomized into the II group will receive the 6 month intervention immediately. They will attend a 2-hour in-person session where they will: 1) participate in a group education session from a study PT about self-management and physical activity for people with RA, 2) receive a Fitbit Flex 2 and an orientation to the OPERAS web app, and 3) receive

individual counselling from a PT trained in motivational interviewing [15]. All study PTs will follow the Brief Action Planning approach [16], whereby participants will be guided to set their own physical activity goals, develop an action plan, and identify barriers and solutions.

We will ask participants to wear the Fitbit throughout the intervention period, and use the OPERAS app to record their RA disease activity, symptoms, treatment use, and self-management action plans. If participants experience any discomfort wearing the Fitbit, we will advise them to stop wearing it but continue using the OPERAS web app. Disease activity will be tabulated from participants' self-reported measures, including the Rheumatoid Arthritis Disease Activity Index [RADAI], Visual Analogue Scale [VAS], and the Health Assessment Questionnaire [HAQ]. Participants will record their symptoms twice a week during periods of more active disease (i.e., a disease activity score above 4), and once every 2 weeks during periods of stable disease (i.e. no sudden increases in disease activity score). They will also be asked to log on and review their physical activity goal achievements at least once a week. Participants who have not recorded their disease activity for more than 2 weeks will receive an email reminder from the research team.

II participants will receive a phone call from their PTs at weeks 2, 4, 6, 8, 13 and 26 to review their physical activity goals and accomplishments. PTs will coach participants to modify their goals if they are ready.

The DI group will receive the same intervention in week 27. Participants will receive a monthly newsletter of arthritis news, which are unrelated to disease management prior to the intervention period.

After the six-month intervention period, both II and DI participants can keep the Fitbit and their OPERAS app account, but will not have access to a PT. There is no requirement for

participants to stop their medical treatments and non-pharmacological care during their participation in the study.

Measurements

All participants will be assessed 3 times throughout the study: at baseline (T0), week 27 (T1), and week 53 (T2). Baseline measurements will be completed before randomization. Research personnel performing data analysis will be blinded to the group assignment. We will not be blinding the group assignment to the study coordinator, who will be facilitating delivery of the intervention, nor the participants who will be receiving it.

Outcomes

Primary Outcome

Self-management ability will be assessed through the Patient Activation Measure (PAM), a 13-item self-reported measure of individual's confidence in managing chronic diseases [17,18]. Each item has a 4-point response, with 1 being strongly disagree and 4 being strongly agree, and the aggregate raw score is converted to 0-100 [15]. Hibbard et al [17] described a 4-stage activation model based on the standardized scores of PAM: 1) believing an active role is important (PAM score <47); 2) having confidence and knowledge to take action (47.1 - 55.1); 3) taking action (55.2 - 67); and 4) maintaining healthy behaviors despite setbacks (> 67.1). PAM has demonstrated internal consistency (Chronbach's $\alpha > 0.85$) [17], and construct validity with health status measures (e.g., SF-36 [24]) and healthy behaviours such as exercise, healthy eating and medication adherence [19].

Secondary Outcomes

We will assess disease status through the RADAI which categorizes disease activity into remission, low, moderate, and high states [20]. RADAI has 5 components, including 1) global disease activity; 2) joint tenderness/swelling; 3) pain; 4) morning stiffness; and 5) number/severity of painful joints. Its validity was supported by moderate correlations with physicians' assessment of disease activity (r = 0.54), swollen joint count (r = 0.54), and C-reactive protein value (r = 0.43) [18].

Pain will be measured with the McGill Pain Questionnaire (MPQ-SF), which consists of 15-pain related words that can be rated from 0 to 3, with the higher number being more severe [21]. We will measure fatigue using the Fatigue Severity Scale (FSS), a 9-item questionnaire that has demonstrated internal consistency (Cronbach's α=0.89) [22]. The FSS is also moderately correlated with pain (r=0.68) and depression (r=0.46) [23]. We will also assess participants' mood using the Patient Health Questionnaire-9 (PHQ-9) [24] which consists of 9 questions that correspond to the diagnostic criteria for major depressive disorder. A total score of greater than 11 indicates the presence of major depressive disorder [25].

The Self-Reported Habit Index (SRHI) will be used to measure characteristics of habitual behavior. It is a 12-item scale, rated on a 7-point Likert scale, with higher scores indicating a stronger habit or behavior that is done frequently, automatically, and done without thinking about it [26, 27]. Participants will rate their strength of habit for 3 specific behaviors, including sitting during leisure time at home, sitting during usual occupational activities, and walking outside for 10 minutes or more.

We will measure participants' time spent in physical activity and sedentary activity with SenseWear Mini. It integrates tri-axial accelerometer data, physiological sensor data and

personal demographic information to estimate steps, energy expenditure and Metabolic Equivalent of Tasks (METs). Tierney et al. [28] has showed that the SenseWear is an appropriate tool in estimating energy expenditure during activities of daily living in people with arthritis (intraclass correlation coefficient (ICC) = 0.72). Participants will wear the SenseWear monitor over their triceps on the non-dominant arm for 7 days. Almeida et al [29] recommended that a minimum of 4 days is required to reliably assess energy expenditure from different levels of physical activity in people with RA (ICC > 0.80).

We will calculate: 1) the mean time spent in bouted MVPA per day. A bout is defined as $\geq$ 10 consecutive minutes at the level of $\geq$ 3 METs (i.e., the lower bound of MVPA), with allowance for interruption of up to one minute below the threshold [30]. 2) Mean daily time spent in sedentary behaviours, with an energy expenditure of $\leq$ 1.5 METs, occurring in bouts of > 20 minutes during waking hours [31, 32].

Implementation Assessment

At the end of the 6 month intervention, we will conduct one-hour interviews with a purposive sample of participants to include both men and women and have different duration of experience in using health-related apps (Novice: <2 years; Avid $\geq$ 2 years). The interview guide will explore three topics: 1) the participants' experiences with the intervention, probing to understand their views of each aspect of the program; 2) barriers and facilitators to using OPERAS; and 3) the nature of activities they engaged in with the program.

The OPERAS app will collect program usage data of all participants and these data will be securely stored on the Arthritis Research Canada server. Information collected include: 1) participants' frequency of using OPERAS app; 2) duration of each use; 3) adherence to using the

Fitbit; and 4) adherence to the PT counselling session. The app is designed to allow researchers to obtain usage data without access to the personal health information, protecting particpants' health information privacy.

Adverse Events and Data Monitoring

In the follow-up questionnaires at Month 6 and Month 9, participants will be asked to note any serious adverse events, including falls and cardiovascular/ musculoskeletal events [33]. Adverse events will be reviewed by the Data and Safety Monitoring Committee, which will recommend terminating the study, if warranted. Additionally, at any time during the study period, participants will report any serious adverse events directly to the study coordinator. In the event of a severe adverse event due to participation in the study, participants will be recommended to follow-up with their family doctor as well as have the option to meet with a rheumatologist (DL), or a physiotherapist (LCL).

The Data and Safety Monitoring Committee will also be in charge of auditing trial conduct, reviewing trial processes and documents to ensure that research activities comply with the requirements of the protocol. It will review screening and consent documentation to ensure ethical trial conduct. Committee members will meet, in person or via teleconference, quarterly or when 25%, 50% and 75% of the participants are enrolled, whichever is sooner.

Sample Size Calculation

Our primary outcome measure is self-management ability as measured by the (PAM) [17,18]. In a study by Turner et al., it was reported that patients with chronic diseases who completed a 7-week self-management program would have their mean PAM score improve from

52.2 to 60.2 at 6 months (standardized effect size = 0.65) [34]. Based on a difference of 8 points, an estimated SD of 12.4, and a 2-tailed analysis of covariance (ANOVA), a total of 102 participants (51 per group) would be needed (90% power; α-level 0.05). We plan to recruit a total sample size of 134, with 67 participants in each group, to allow for a ~24% attrition rate.

For the implementation assessment, we will conduct qualitative interviews with 7-10 participants in each of the 4 purposive sampling strata, including gender (2) and experience in using health-related apps (2). Hence, 28 – 40 people will be interviewed.

Data Analysis

The data collected will be de-identified and password protected. All research personnel involved with data analysis will have access to the data files. The study coordinator will oversee the data sharing process.

Efficacy Analyses

The intervention efficacy will follow an intention-to-treat approach. We will analyze the outcomes measured at weeks 26 and 52 in the II and DI groups. We will employ Generalized Linear Mixed-effect Models (GLMM), adjusting for baseline value on the outcome variable and sex as covariates. These models are the most efficient and recommended statistical methods for analyzing longitudinal clinical trial data with missing data [35, 36] and can account for data missing at random without the need to perform explicit imputations of the missing values [37]. Binary indicators of group and months since baseline, will allow us to test their interaction ($p <$ 0.05 for 2-tailed Wald test), which addresses if the outcome post-intervention is significantly better in the II than DI group. Data transformation, if needed, will be applied to continuous

outcomes to satisfy the assumption of normality. The sandwich estimators for GLMMs [38] will be used to compute empirical standard errors that are robust to model specifications and distributional assumptions. An unstructured variance–covariance matrix will be used to model the within-subject error variance-covariance for continuous outcomes. The quality of statistical inferences will be substantiated through rigorous model checking and validation techniques.

Implementation Analysis

For the qualitative interviews, we will conduct an iterative content analysis, whereby codes will be identified and revised as interviews are analyzed. Initial open coding will be followed by clustering the labels into thematic categories [39]. Quotes representative of the thematic categories will be identified to illustrate experiences of participants with the intervention, as well as barriers and facilitators in meeting their physical activity goals. If distinct themes based on gender or age are apparent, data will be reanalyzed within subgroups. Descriptive analysis will be conducted for all participants' usage data from the OPERAS app.

An iterative content analysis will be used to identify and revise codes in the qualitative interviews. We will start with an initial open coding and then cluster the labels into thematic categories [40]. Quotes representative of the thematic categories will be identified to illustrate experiences of participants in using OPERAS, as well as barriers and facilitators in using the program. We will reanalyze the data within subgroups if there are distinct themes based on gender or age. We will also conduct a descriptive analysis for all participants' usage data.

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