Human Subjects Protocol

VA Puget Sound IRB

Effects of Physical Activities on Pain and Functional Recovery in Low Back Pain

Funding Agency: VA RR&D

Principal Investigator: Pradeep Suri MD MS

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Abstract

Objective:
Low back pain (LBP) is second only to hearing problems as a reason for Veteran disability, and it is the most common cause of disability globally. Although general activity is encouraged in the treatment of LBP, there is no empirical information available on the ***specific*** types of activities that are beneficial or harmful for patients seen in primary care for LBP. This study will identify those physical activities with short-term (transient) effects on LBP exacerbations (or "flares" of LBP), as well as identifying the long-term (cumulative) effects of such activities on functional recovery.

Research Design and Methodology:
The proposed research will use a novel approach to distinguish the short-term effects on LBP of physical activities from the long-term effects of such activities, by conducting a longitudinal case-crossover study nested within a cohort study. This design accounts for measured and unmeasured confounds by using each case as his/her own control- an entirely observational study that is analogous to a crossover experiment- capitalizing on modern mobile health and actigraphy technology. The primary exposures of interest are 10 self-reported physical activities commonly performed during work and activities of daily living, and actigraphy-assessed physical activity. The primary outcomes are participant-reported "flares" of low back pain (Aim 1) and participant-reported back-related functional limitations (mobility and activities of daily living [ADLs]) at 1-year follow-up, as measured by the Roland-Morris Disability Questionnaire. This observational study will include up to 730 Veterans with LBP aged 18 and older recruited from the VA Puget Sound Health Care System (VAPSHCS). The study will not affect Veterans' medical care in any way. After verbal informed consent, recruitment, and baseline data collection, study participants will complete frequent, serial electronic "e-Questionnaires" using their own personal electronic devices (personal computer [PC], tablet, or smartphone) over the 1-year period of follow-up. Participants may also wear ActiGraph units for the 1st 4 weeks of follow-up. Long-term outcomes will be assessed by extended e-Questionnaires completed at 1-year follow-up. Aim 1 analyses will examine the short-term effects of 10 specific activity categories on participant-reported flares across all study assessments over 1-year follow-up. Aim 2 analyses will examine associations between the frequency of exposure to 10 specific activity categories over weeks 1-4 of follow-up, and long-term functional recovery at 12 months as defined by the RMDQ. All analyses will use a biopsychosocial framework accounting for potential confounders (sociodemographics, psychological factors, etc.) and effect modifiers, and will include sensitivity analyses to examine the robustness of findings and important study assumptions.

Relevance to VA Mission:
This work will provide completely new, foundational information that will support Veterans with LBP in navigating the complex process of recovery. It will also help VA clinicians to make recommendations regarding return to work and activities for those with LBP. These findings will also inform the development of future activity-based educational treatments for optimizing functional recovery for Veterans with LBP.

List of Abbreviations

AE	Adverse Event
CDW	Corporate Data Warehouse
CPRS	Computerized Patient Record System
CSQ	Coping Strategies Questionnaire
DMAP	Data Management and Access Plan
EHR	Electronic Health Record
EMR	Electronic Medical Record
ERIC	Epidemiologic Research and Information Center
FLAReS	Flares of Low Back Pain with Activity Research Study
HIPAA	Health Insurance Portability and Accountability Act
HR	Human Resources
HSR&D	Health Services Research & Development
ICD	International Classification of Diseases
IRB	Institutional Review Board
IRQ	Initial Review
JIT	Questionnaire Just-In-Time
LBP	Low Back Pain
LSRS	Lumbosacral Radicular Syndrome
NIH	National Institutes of Health
NRS	Numerical Rating Scale
OASC	Organizational Assessment Sub-Committee
OR	Odds Ratio
PACT	Patient-Aligned Care Team
PC	Personal Computer
PCL-C	Post-traumatic Stress disorder Checklist
PCP	Primary Care Provider
PHI	Protected Health Information
PHQ-8	8-Item Patient Health Questionnaire
PI	Principal Investigator
PRAF	Project Revision/Amendment Form
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Post-Traumatic Stress Disorder
RMDQ	Roland-Morris Disability Questionnaire
RR&D	Rehabilitation Research & Development
RTW	Return to Work
SAE	Serious Adverse Event
SISQ	Single Item Stress Questionnaire
SLSS	Symptomatic Lumbar Spinal Stenosis
TSK	Tampa Scale of Kinesiophobia
UAP	Unanticipated Problem
UW	University of Washington
VA	Veterans Affairs
VAPS	VA Puget Sound
VAPSHCS	VA Puget Sound Health Care System
VISTA	Veterans Information Systems and Technology Architecture

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Effects of Physical Activities on Pain and Functional Recovery in Low Back Pain

Lay Title: Flares of **L**ow Back Pain with **A**ctivities **Re**search **S**tudy ('FLAReS')

1.0 Study Personnel

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Professor, Department of Rehabilitation Medicine, University of Washington

Collaborators:

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Associate Professor, Department of Rehabilitation Medicine, University of Washington

Mark Jensen, PhD (at UW, no affiliation with VA Puget Sound Health Care System, no contact with participants or study data other than in aggregate form such as published in medical journals, not covered under the VA IRB approval. Due to this lack of engagement from a VA human subjects perspective, Dr. Jensen is not listed on IRB or R&D documents other than the protocol).

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Patrick Heagerty, PhD (at UW, no affiliation with VA Puget Sound Health Care System, no contact with participants or study data other than in aggregate form such as published in medical journals, not covered under the VA IRB approval. Due to this lack of engagement from a VA human subjects perspective, Dr. Heagerty is not listed on IRB or R&D documents other than the protocol).

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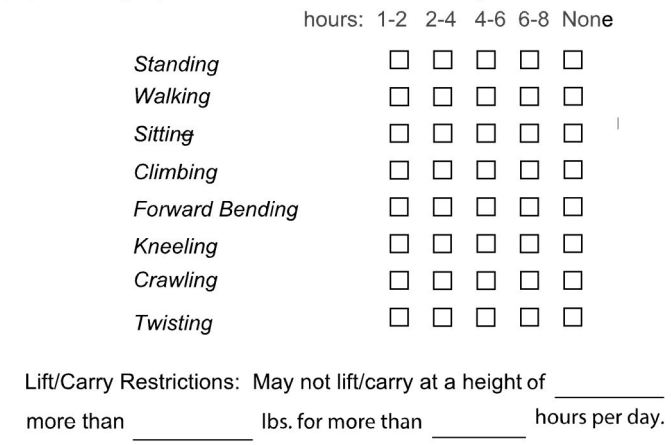
2.0 Introduction

Low back pain (LBP) is the #1 cause of disability worldwide and a leading cause among Veterans. The general advice to remain active when experiencing acute or chronic LBP is a key part of clinical practice guidelines. However, existing guidelines provide no specific recommendations about the types of activity (e.g., lifting, bending, etc.) that should be engaged in or avoided ("Which?") or the duration/intensity of such activities should they be performed ("How?"). The guidelines therefore do not address a major concern of patients with LBP, which is that certain activities may have short-term effects on pain exacerbations or "flares", or cause sustained detrimental effects on pain or function. The distinctions between healthy, benign, and detrimental activities are also important to clinicians, who are often called upon to complete "work restriction forms" as part of the process of making return-to-work (RTW) decisions. An ideal set of work restrictions for persons with LBP would limit only those activities that are likely to cause flares of pain (***transient*** effects) or poor overall functional recovery in the longer term (***cumulative*** effects). However, there exist no empirically derived data concerning the transient vs. cumulative effects of specific activities during LBP, with which to guide work restrictions.

A typical "work restriction form" excerpt from California state is shown in **Figure 1**, listing 10 categories of activities relevant to LBP. These activities can occur commonly in the workplace, or in other aspects of everyday life. In the absence of empirical data, primary care providers' work restrictions mirror their general practice style[1,2] or personal beliefs[1], which may conflict with evidence-based care,[3] and may limit functional recovery if overly restrictive. Primary care providers (PCPs) may feel compelled to choose restrictions that avoid conflict with patients.[2,4,5] These factors combine to create a situation where most PCPs feel ill-prepared or conflicted when making work restrictions.[6] **Our proposed work will yield objective data regarding the risks associated with specific types of activities during LBP, meeting an important need of both Veteran patients and PCPs.**

Figure 1. CA State work restriction form



The expected age range of study participants is 18 years of age and older. We expect the general health status of the subject population to be about average for Veterans' ages. We will not include patients from special classes of subjects or vulnerable populations such as pregnant women, children, cognitively impaired persons, or prisoners due to possible coercion. We will not otherwise make any exclusions based on gender, sex, race, ethnicity, or any minority group designation. VA employees may be enrolled in the study; however, if enrolled, they cannot complete assessments on their VA paid time. "Questionnaires" or "e-Questionnaires" as

referred to in this Protocol do not fall under the definition of “surveys” as used in the VA Survey Guidance document. As such, OASC and local VAPS HR will not be notified if a VA employee enrolls in this study. The term “e-Questionnaires” is used in materials related to human subjects approvals, but the term “e-Surveys” is used in participant-facing materials, due to the simplicity and brevity of the term “e-Survey”.

3.0 Objectives

Aim 1: Estimate the *short-term* effects (□24 hours) of specific physical activities on pain flares in Veterans with LBP.

Research question #1: What are the short-term (transient) effects (<24 hours) of specific types of physical activities on pain flares in Veterans with LBP?

We will conduct a longitudinal case-crossover study with 1-year follow-up to identify activities that trigger flares among up to 730 Veterans of working age (18-65 yrs) seen in VA primary care for LBP. The predictors of interest are 10 activity categories relevant to LBP that are commonly included in work restriction forms used for RTW determinations. The primary outcome is a validated flare definition characterized by pain and functional impact. Analyses will use a biopsychosocial framework accounting for key potential confounders and moderators, such as pain characteristics, work-related factors, catastrophizing, fear of movement, depression, stress, post-traumatic stress, and analgesic use.

Aim 2: Estimate the *long-term* effects of specific physical activities among Veterans with LBP.

Research question # 2: What are the long-term (cumulative) effects of specific types of physical activities on functional recovery at 1-year follow-up?

In analyses of the longitudinal cohort within which the Aim 1 case-crossover study is nested, we will examine associations between the frequency of activities for 10 specific activity categories over the first 4 weeks of follow-up, and long-term LBP-related functional recovery as defined by the Roland-Morris Disability Questionnaire (RMDQ) at 1-year follow-up (primary outcome). Analyses will account for a range of important potential confounders and moderators, using a biopsychosocial framework, as in Aim 1. Secondary outcomes will include average pain intensity, lost work productivity, and quality of life, and analgesic use at 12 months.

These study aims will produce tables of evidence-based estimates contrasting the short-term risks of specific physical activities on LBP flares with the long-term effects on functional recovery. These data will then be used to design educational interventions to optimize physical activity, considering both the short- and long-term effects of physical activities.

Recruitment in additional populations (project modification, January 2023)

In December 2022, we obtained sponsor approval from ORD RR&D to expand the target population of recruitment (beyond Veterans who have recently been seen in for back pain in VAPSHCS primary care, the "*original target population*"), in order to achieve the original recruitment goal of 440 Veterans who complete 1-year follow-up. In the current project modification, we expand recruitment to other Veterans with low back pain who have been seen in VAPSHCS (the "*expanded target population*"), but may not have had recent visits for back pain in VAPSHCS primary care. We will not contact individuals who have already been contacted once as part of recruitment efforts using the Information Statement (targeted to the original target population). The approach and analyses for the main study aims as stated above will not change; these main study aims will involve only the study sample recruited from the *original target population* (Veterans seen for low back pain in primary care). However, we will also conduct separate, analogous analyses, among Veterans recruited from the *expanded target population*. For certain analyses where exposure-outcome relationships do not differ between samples recruited from the original target population vs. the expanded target population, we will conduct secondary analyses pooling the two samples.

Overview of the Overall Study Approach

The content of subsequent sections warrants an introduction to the overall approach to the research involved. The research as a whole involves two separate but related components: (1) **a VA component** involving all VA recruitment, VA data collection, and all processes involving VA data (addressed by the current VA IRB application and referred to as the "VA component"), and (2) **a non-VA component** involving non-VA data collection that occurs entirely outside the VA and does not involve any VA data. This means that the current human subjects application and the VA informed consent processes described in this application pertain only to the VA component of the research (the VA research processes). Separate from the VA component of the research is the non-VA component, which will be carried out by researchers at the University of Washington (UW). Participants in the VA component of this research will be provided information that they can use to initiate contact, screening, and possible enrolment in the non-VA component conducted by UW researchers. The non-VA component of the research will run in parallel with the VA research processes, yet involves non-VA data collection only. The UW research processes will undergo a separate process of IRB approval at UW, including a separate process of informed consent. This non-VA data collection will include all e-Questionnaires described above, administered by a private (non-VA) data collection company specializing in secure HIPAA-compliant and 21 CFR 11-compliant electronic questionnaire administration (DatStat). DatStat has a successful track record for conducting secure electronic questionnaire administration for another current UW research study. Acquisition of e-Questionnaire data in this proposed manner- in partnership with UW researchers- permits the ability to conduct frequent serial assessments with quasi-randomized timings via e-Questionnaires, since at the current time there exist no feasible processes to collect such data as VA data using VA devices. At interim time points during the VA component of this study, e-Questionnaire data being collected by UW researchers as part of the non-VA component of this study will be downloaded by VA research study staff involved with this VA research study, at which time such data will become VA data and will not subsequently be shared outside the VA during the study. **In summary, no VA data produced as part of this VA research study will be shared outside of the VA at any point during the conduct of this VA research. However, non-VA data collected by researchers at the UW will be shared with this VA research team.** Thus, the flow of research data in this VA research study is only into the VA, and never out of the VA.

Most aspects of the proposed research as described in this human subjects research application pertain to the "VA component" of the study (VA data collection and VA research processes). However, in order to provide a complete picture of what the study entails for reviewers of this

protocol/application, the protocol also provides information about aspects of data collection occurring as part of the non-VA (UW) component of the study. From this point on in the protocol, data collection or study processes relevant only to the non-VA (UW) component of the study are provided in blue font such as this, to emphasize aspects that are not covered by the VA human subjects review processes (i.e. by the VAPSHCS IRB), but will be covered by the UW human subjects review processes (i.e. by the UW IRB). In addition, communications with the IRB Director, Information Systems Security Officer, and Privacy Officer resulted in the recommendation during the initial IRB approval process that we provide to potential VA participants a "Summary of UW Research" processes (Attachment S) to ensure that participants are fully aware from the outset about all aspects of being a study participant, including both VA and non-VA components of the research. Attachment S was previously approved with the original IRB submission, and a revised version is submitted with PRAF 1. As appropriate in the future, we will submit to the VAPSHCS IRB any documentation pertinent to study processes at UW and relevant documentation from the UW IRB**.**

4.0 Resources and Personnel

- This research will be led by Dr. Pradeep Suri at VA Puget Sound Health Care System (VAPSHCS). Dr. Suri is the PI and will be responsible for study planning and broad oversight; supervising study procedures; integrity of data collection; interpretation of findings; and all subsequent steps including manuscript preparation and submission. He will have access to protected health information (PHI).
- Ms. Tanus is the research coordinator. She will supervise research assistants and other study staff. She will be involved in recruiting subjects; obtaining informed consent; mailings to participants and from participants; coordinating provision of or receiving the ActiGraph units; tracking participants; and all other study procedures involving recruitment, data collection, and data management. She will have access to protected health information.
- Dr. Korpak, Mr. Timmons, Mr. Baraff, and Mr. Forsberg are study biostatisticians. They will be involved in data analysis; and in manuscript preparation and submission. They will not have access to PHI.
- Ms. Fox, Mr. Morelli, Ms. Wicks, Ms. Scott and Mr. Peterson will function as data managers. They will obtain data from the Corporate Data Warehouse and/or assemble that data into a format ready for analyses. They may have access to PHI at one stage in the study, when VA administrative data is obtained from the Corporate Data Warehouse (CDW) or from any future repository that replaces the CDW after the Cerner electronic health record (EHR) transition. Subsequently, any use of data will not involve interaction with PHI.
- Ms. Irimia, Ms. Brubeck, and Ms. Dhillon are research assistants. They will be involved in recruiting subjects; obtaining informed consent; mailings to participants and from participants; coordinating provision of or receiving the ActiGraph units; tracking participants; and all other study procedures involving recruitment, data collection, and data management. They will have access to protected health information.

5.1 Study Design

This will be an ***observational***, longitudinal case-crossover study nested within a cohort study, following up to 730 Veterans seen for LBP in VA primary care prospectively for 12 months. Study procedures will not make changes to nor in any way affect the typical medical care for LBP provided at VAPSHCS. All study assessments following recruitment will be "*e-Questionnaires*" that participants complete using their own personal electronic devices (smartphones, tablets, or PCs, not provided by the study). There are two types of e-Questionnaires that participants will complete: "*scheduled e-Questionnaires*" and "*flare window e-Questionnaires*. Scheduled e-Questionnaires are quasi-random, 'cue-elicited' frequent assessments that will be repeated numerous times throughout the 1-year follow-up period. Cues to complete scheduled e-Questionnaires are automated "e-Alert" notifications sent by text
message and email at the start of each "*scheduled assessment window*", the 3-hour period during which a scheduled e-Questionnaire may be completed. ***Scheduled e-Questionnaires will occur three times each week during weeks 1-4 of follow-up, once a week during weeks 5-8, and twice a month during months 2-12***. Participants will also complete unscheduled "*flare window e-Questionnaires*" on an *ad hoc* basis, if they experience new flares of LBP at any time during the 1-year follow-up period. At study entry, participants will receive training on how to complete flare window e-Questionnaires, if they experience flares of pain, by logging on to a secure Participant Portal (the **F**lares of **L**BP with **A**ctivity **Re**search **S**tudy or "FLAReS" website) within 3 hours after the onset of a new pain flare. In addition, all scheduled e-Questionnaires will remind participants to complete a flare window e-Questionnaire if they have a new pain flare. Scheduled e-Questionnaires and flare window e-Questionnaires generally contain the same question items, however, scheduled e-Questionnaires inquire about activity exposures *preceding the start of the scheduled assessment window* (when e-Alert notifications are sent), and flare window e-Questionnaires inquire about activity exposures *over the time period preceding the flare onset*. Each e-Questionnaire will begin by prompting the participant with the definition of a LBP flare. Participants will then report whether or not they are experiencing a flare, the primary outcome for Aim 1 of this study. E-Questionnaires will also inquire about activity exposures that have occurred over the 24-hour period prior to the assessment window start and - *if* an activity is reported – ask for further clarification of whether the activity was performed in the 2-hour period prior to the assessment window start. Further questions included in every e-Questionnaire are time-varying pain and psychological covariates (pain intensity, depression, catastrophizing, stress, etc.) assessed using brief, validated measures. All e-Questionnaires are inherently time lagged for activity-flare relationships, since they capture *current* flare status at time=*t*, and activities in the 24-hour period *before* the start of the assessment window/flare onset (*t*-1). Participants may also be offered to wear the optional ActiGraph wGT3X-BT unit continuously for weeks 1-4 of the study. Due to the participant burden involved with frequent serial e-Questionnaire assessments, a run-in period during weeks 1 and 2 of follow-up will exclude those individuals unable to maintain compliance with these assessments. Aim 1 analyses will examine the short-term effects of 10 specific activity categories on participant-reported flares across all study assessments over 1-year follow-up. Aim 2 analyses will examine associations between the frequency of exposure to 10 specific activity categories over weeks 1-4 of follow-up, and long-term functional recovery at 12 months as defined by the RMDQ. All analyses will use a biopsychosocial framework accounting for potential confounders (sociodemographics, psychological factors, etc.) and effect modifiers, and will include sensitivity analyses to examine the robustness of findings and important study assumptions.

Please see "Overview of the Overall Study Approach" subsection in 3.0 above. As mentioned, the study as a whole involves two separate components: (1) a VA component involving all VA recruitment, VA data collection, and all processes involving VA data (addressed by the current VA IRB application and referred

to as the "VA component"), and (2) a non-VA component involving non-VA data collection that occurs entirely outside the VA and does not involve any VA data. Non-VA data collection involves e-Questionnaires (referred to as "e-Surveys" in participant-facing materials). e-Questionnaires are to be administered as part of the non-VA (UW) research processes and are therefore provided to the VA IRB for completeness, but not for VA review. E-questionnaires are labelled as Attachments Q1-Q3.

ActiGraph units will not be available for participant use by the time when recruitment could otherwise be started. ActiGraph-related research questions are separate from the primary study aims which rely on participant-reported data, and are therefore non-essential and optional for participant use. Participants may or may not be offered to wear an ActiGraph and use of this device is optional. Due to the expected unavailability of ActiGraph units at the time when recruitment is started, potential participants approached at times when Actigraphs are not available will be offered the opportunity to participate without wearing the ActiGraph. With the current version of the protocol, we provide a revised Information Statement document that describes participation in the study either with or without participation in that component of the study that involves the ActiGraph. In other words, the revised Information Statement is now applicable whether or not the participant wears the ActiGraph as part of their study participation.

Description of Potential Risks and Risk vs. Benefit

Both VA and non-VA components of this study are entirely observational. Risks pertaining to the VA component of this research study involve those related to the obtaining, storage, and analysis of VA research data, and any possible inadvertent disclosures.

Physical risks: Participants who wear ActiGraphs may find it uncomfortable or inconvenient in general to wear the ActiGraph during the day or while sleeping. There is no risk of electrical shock while wearing the activity monitor. The Actigraph will not be able to track where participants are physically located. Participants may experience sweating or skin irritation while wearing the activity monitor if they have sensitive skin. We will provide participants with tips on how to mitigate any discomfort or inconvenience due to the positioning/wear of the unit, such as shifting the unit positioning when feasible.

Psychological risks: Participants may experience fatigue and/or boredom while completing the research assessments. Some participants may also experience mild anxiety, frustration, and/or stress while reporting on their pain and mood during the research assessments.

Social, Legal, Privacy, and Other Risks: There are research risks to participants' privacy associated with inappropriate disclosure of data. Specifically, there is a risk that a participant's identity and participation in the study may be discovered by an outside party. However, we will take steps as described elsewhere in this document to ensure that the likelihood of such risk is negligible.

Risks pertaining to the non-VA component of this research study also involve those related to the obtaining, storage, and analysis of non-VA research data, and any possible inadvertent disclosures. Such risks relevant to the non-VA component of the research are covered in the separate human subjects approvals processes at UW, and also in the "Summary of UW Research" (Attachment S) provided as part of the VA research processes so that VA participants are aware from the start of both VA and non-VA components of the overall research. Following any future substantive modifications to the UW IRB application (for example, study staff modifications at UW would not be considered substantive), we will provide the relevant updated UW IRB documentation (including participant-facing materials) and approvals back to the VAPSHCS IRB.

Description of Study Population/Expected Enrollment/Vulnerable Populations:

We expect to recruit up to 730 Veterans in the proposed study in order to obtain at least 440 Veterans who complete 1-year follow-up. Further details of inclusion/exclusion criteria are provided below in Table 1 (see Section 5.4). All participants recruited will be Veterans. We will recruit Veterans from primary care clinics and other clinic encounters (including telephone visits) occurring at VAPSHCS. The anticipated age range of participants is between 18 years and 65 years of age. In expanded recruitment as part of a project modification (January 2023), recruitment was also expanded to other Veterans with low back pain who have been seen at VAPSHCS or through VA-associated community care, but not necessarily in VAPSHCS primary care specifically. Patients with severe and major active medical and psychiatric comorbidities will be excluded since they will likely be unable to complete the study procedures, particularly the requirements for frequent serial assessments in the first 4 weeks of follow-up. Otherwise, we expect the general health status of the subject population to be about average, for Veterans' ages. We will exclude Veterans from special classes of subjects or vulnerable populations such as pregnant women, children, cognitively impaired persons, or prisoners, to avoid possible coercion of vulnerable populations. We will not otherwise make any exclusions based on gender, sex, race, ethnicity, or any minority group designation. The study inclusion and exclusion criteria are specifically defined to capture the broadly-defined target population of Veterans seen for LBP seen in primary care, who are of working age (18-65 years), irrespective of whether participants are actually currently employed. We will re-contact any participants who were interested in the study and screened, but failed criteria from a prior version of the Screening Checklist, provided that they meet all criteria on the currently approved version of the Checklist.

5.2 Recruitment Methods

We will recruit up to 730 participants from among Veterans seeking care at VAPSHCS. The eligibility and exclusion criteria are defined to capture the medically eligible target population of Veterans seeking care for LBP.

Where not stated or indicated otherwise in blue font (signifying UW [non-VA] research processes), all aspects of the descriptions below pertain to the VA component of the proposed research.

5.2.1 Recruitment and Informed Consent

We will conduct in-person recruitment at the time of primary care clinic visits for LBP (Mode 1), and by identifying potential participants using ICD-10 codes, with subsequent screening and recruitment conducted by telephone (Mode 2); both modes can be combined if some aspects of in-person recruitment (Mode 1) cannot be completed at the time of the visit for LBP. In Mode 1 (in-person recruitment), research staff will only have an initial contact with the patient if the patient is first introduced by non-study personnel (primary care staff), or if the participant approaches research staff on their own initiative. Research staff will not interact with potential participants while they are waiting for an appointment or while they are in an appointment, unless a participant has approached research staff on their own initiative. No designated vulnerable populations are included in this research. In Mode 2 (telephone-based recruitment), participants will receive an information packet by mail, and research staff would only speak with potential participants if the potential participant subsequently initiates a contact with research staff. Recruitment will begin with Mode 2 only. As restrictions due to COVID-19 change, we may shift over time to incorporate Mode 1 recruitment. We will notify

the IRB prior to shifting to Mode 1 recruitment. If any concerns arise due to restrictions related to COVID-19, recruitment may shift back to only Mode 2 recruitment, and we will notify the IRB in this case as well. Up to 100,000 Veterans will be pre-screened using VA administrative data, and those potentially eligible will be contacted via Mode 1 or Mode 2 recruitment. An Information Statement will be used in lieu of a written and signed Informed Consent document. Veterans who were previously sent an invitation letter at a time when our consent processes required written informed consent (i.e., prior to 9/10/2021) may be recontacted with 1 additional mailing packet (Mode 2 Recruitment). Additionally, if a potentially eligible Veteran initiates contact with our staff with the interest of possibly joining the study, we would begin screening and enrollment processes as indicated in this document. We will not recontact anyone who has previously informed us they were not interested in participation, or who was previously enrolled in the study.

The consent process will occur at a time deemed mutually feasible for the Veteran patient and staff member and coordinated on a case-by-case basis. If the consent process is conducted by Mode 1 (in-person) it will take place in a private location at VAPSHCS where possible (e.g., a medical exam room or private conference room). We will work with the primary care clinics, other outpatient clinics, and the Rehabilitation Care Services (RCS) service line to create a list of private spaces within a short distance of the primary care clinics that can be used for this purpose. These locations will vary depending on the half-day of the week and week of the month, and a list of these locations/times will be compiled into a “private space schedule”. Research staff will consult the private space schedule when potential participants are identified by Mode 1 (in-person) recruitment. If no private space is available at a given time when a potential participant is identified by Mode 1, but there is space within the primary care waiting room (at the time of) where no other individuals are seated within a distance where conversations can realistically be overheard, we will offer potential participants the option of talking about the study, and undergoing informed consent (if appropriate), in the primary care waiting room itself. The large size of the primary care waiting room, its typically low occupancy at any given time, and the fact that there is a second area of the primary care waiting room on the western edge of the clinic space that is often entirely unoccupied by patients, makes the option of such staff-patient interactions possible while still permitting private discussions. If the primary care waiting room occupancy at a given time does not permit such staff-patient interactions, or any other barrier to private discussion presents, participants will be provided written materials and can opt to initiate Mode 2 recruitment (telephone-based) should they be interested in participation. If the consent process is conducted by Mode 2 (telephone), the VAPSHCS research staff member will make the telephone call from a VAPSHCS telephone in a private room.

5.2.2. Recruitment Mode 1 (in-person recruitment): Although labeled “Mode 1”, due to COVID-19-related precautions, in-person recruitment will serve as the secondary mode of recruitment, with telephone-based recruitment as the primary recruitment mode. Mode 1 recruitment will involve research staff members situated in the primary care clinics at VAPSHCS Seattle campus where the patient-aligned care teams (PACTs) are collected. Research staff will maintain a physical presence and intermittent contacts with PACT clinicians (physicians, nurse practitioners, physician assistants) as well as support staff. Flyers (Attachment A – Recruitment Flyer) will be posted in clinical areas of outpatient clinics. If a PACT clinician or clinical staff identifies a Veteran with LBP who is a potential candidate for the study, they will inquire with the Veteran regarding whether the Veteran would be interested and willing to discuss the study with a research staff member. If the Veteran expresses interest, clinical staff will then notify a research staff member (“handoff from a clinician”) to approach a Veteran after their clinic appointment is completed. If there is a handoff from a clinician, or if a Veteran initiates contact with a research staff member on their own, research staff will explain the study to the Veteran at the initial patient contact (on the day of the index LBP visit). Research staff will describe the study; its observational nature; the high volume of study assessments; use of electronic questionnaires (e-Questionnaires) via personal computer (PC), tablet, or smartphone; the system of e-Alert notifications or “cues” to complete e-Questionnaires via email and text messages; answer participant questions; confirm eligibility with screening criteria; and involve the study-associated clinician or PI where

eligibility criteria determinations warrant a physician determination or evaluation. Specific instructions will be provided to potential participants about the two separate components involved in the research: (1) the VA component involving data collection within the VA, and that is part of this VA research; and (2) the UW component of electronic data collection (e-Questionnaires) that occurs outside the VA, and would be covered under a separate human subjects approval process for UW. Research staff will explain that participants' VA medical care for LBP will not be affected in any way by participation in this study. Where potential participants wish to do so, informed consent will be offered and completed at the time of the index LBP visit for those study procedures involved in this VA research, using the Information Statement. This informed consent process is described in further detail below in section 5.3. If potential participants wish to have time to consider their involvement in the VA component of this study further before completing informed consent, or if some component of the study screening or education cannot be completed in-person, the remainder of recruitment procedures that are not yet completed can be done using recruitment Mode 2 methods as below. Following informed consent, participants will be provided with other study materials, including the "Key Points" document (Attachment K) which consists of the main points contained in the Information Statement and serves as a quick reference for participants; the instructions for completing e-Questionnaires document (Attachment I); and an activation code that allows access to the Participant Portal.

5.2.3 Recruitment Mode 2 (remote recruitment by telephone): *Although labeled "Mode 2", due to COVID-19-related precautions, remote recruitment will serve as the primary mode of recruitment, with in-person recruitment taking place only if/when determined to be safe and feasible by the study team, consistent with VA and local restrictions in place at that time.* On a recurring basis during the recruitment phase, research study staff will identify potentially eligible patients seen in primary care using ICD-10 codes indicating LBP or related spinal disorders. Data collection is expected to span the start time of the transition of the electronic health record (EHR) from the Computerized Patient Record System (CPRS) to Cerner. Prior to the Cerner transition, we will identify participants with ICD-10 codes indicating LBP by one of several possible mechanisms, such as Veterans Information Systems and Technology Architecture (VISTA) queries, or using Corporate Data Warehouse (CDW) data. After the Cerner transition, we will identify participants with ICD-10 codes indicating LBP using methods that have yet be determined; however, VAPSHCS research staff have been informed in seminars related to the Cerner transition that methods to identify potential research subjects in this way will be available after the Cerner transition. Potentially eligible Veterans with new ICD-10 codes indicating a recent LBP visit will be mailed information packets. Information packets will include a cover letter (Attachment L), the Information Statement document, and the summary of UW research processes (Attachment S). Information packets will describe study eligibility, the study assessments, and what study participation would entail. Packets will prompt interested Veterans to contact research staff by telephone. Once research staff are contacted by telephone, staff will administer the same procedures for providing study information, answering questions, screening, and training as described above for in-person recruitment (Mode 1), but such procedures will instead be completed by telephone. Veterans who complete all screening procedures and meet study criteria will be offered the chance to have any questions about the study answered by study staff. Those interested in participating will be offered informed consent for VA research processes, completed over the telephone, while referring to the Information Statement hardcopy included with the mailed information packet. Participants will be considered enrolled in the VA component of the study once the Information Statement content has been reviewed, questions have been answered, and the Veteran verbally agrees to participate in the study. Following this, participants will be mailed other study materials, including the "Key Points" document (Attachment K) which consists of the main points contained in the Informed Consent and serves as a quick reference for participants; the instructions for completing e-Questionnaires document (Attachment I); and an activation code that allows access to the Participant Portal; participants will also be called by phone to provide the activation code.

5.2.3.1 Email notifications: To supplement mailed recruitment, we will email potential research subjects using Veterans' email addresses (see HIPAA waiver) after the date when physical mailings are sent. The email content (Attachment LE) does not contain any identifying information about individual Veterans other

than the email address; it does not contain any information that could identify Veterans' health conditions, but it does describe what study participation would entail in general terms. Emails of this type will be sent via Microsoft Outlook, using bcc, using an email address that cannot be replied to and is not monitored. Individuals who receive the email are prompted to call the study phone numbers for more information. Prior to this IRB submission, we have had discussions regarding these processes with IRB administrators Gage Doehlert and Amy Marsh (see correspondence).

Because email notifications may result in a greater burden of phone calls received by study staff, if study staff numbers are diminished due to staff attrition or leave, email notifications may need to be stopped for periods of time or permanently.

5.2.3.2 Recruitment from an expanded target population: Through a modification submitted to the VAPS IRB in January 2023, recruitment is to be expanded to other Veterans with a history of back pain-related conditions who have been seen in VAPSHCS (the "expanded target population") but may not have had recent visits for back pain in VAPSHCS primary care specifically. Within the expanded target population of Veterans with back-related conditions are subgroups of individuals with certain "specific" spine conditions, such as (1) "lumbosacral facet-mediated" back pain, (2) "sacroiliac joint-mediated back pain", and (3) spondylolytic spondylolistheses. We will use CDW data (or other approved VA processes involved the electronic health record should these change, such as following the transition to Cerner) to identify Veterans enrolled at VAPSHCS on 10/1/2015 or anytime thereafter who have had ICD-10 or CPT codes indicating back pain-related conditions, to be approached as potential study participants. These individuals in the expanded target population will then be contacted using the same processes as described above in sections 5.2.3 and 5.2.3.1, with the exception that potential participants will not be identified on a recurring basis dependent on recent primary care visits associated with ICD-10 codes indicating LBP or related spinal disorders. Instead, they will be identified based on past diagnostic codes or procedure codes indicating past LBP or spinal disorders since 10/1/2015 and approached in separate batches of mailings and emails. No individuals who have previously been contacted as part of the original target population and been sent a mailing containing the Information Statement will be contacted as part of the expanded target population.

5.2.4 Informed Consent for research processes involving UW

As mentioned above, separate from the processes for VA research described in this application to conduct VA human subjects research, participants will undergo a separate UW informed consent process as part of UW human subjects approval processes. These processes are not part of the current VA human subjects research application. Following any future substantive modifications to the UW IRB application (for example, study staff modifications at UW would not be considered substantive), we will provide the relevant updated UW IRB documentation (including participant-facing materials) and approvals back to the VAPSHCS IRB.

5.2.5 Run-in period

Participants who join the study may subsequently fail requirements of the 2-week run-in period and be withdrawn from the study. A run-in period is needed for a study of this type to ensure that participants are able to complete the frequency of data collection that is necessary for the study to be valid. Criteria for failing the run-in period include (1) not completing the baseline e-Questionnaire, (2) not completing at least 4 of 6 e-Questionnaires in the 2-week run-in period, with an adequate proportion of e-Questionnaire items completed within surveys, as the definition for completion, or (3) not completing the UW informed consent for the (non-VA) UW component of the study; although listed separately to be explicit, completing the UW informed consent (3) is necessary before a participant is able to complete (1) and (2). These criteria could be waived or more time allotted if participants report a major life event (unexpected illness, injury, etc.) preventing a criterion from being met or are otherwise determined to be eligible by research staff on a case-by-case basis.

5.2.6 Materials used to Recruit Subjects

Recruitment materials that we have submitted include the Recruitment Flyer (Attachment A), the introduction (cover) letter document that will be included with the mailing sent to potential participants identified by Mode 2 recruitment (Attachment L), an introduction email letter document that will be sent to potential participants identified by Mode 2 (Attachment LE), a study Key Points document (Attachment K), instructions for completing e-Questionnaires (Attachment I), and the Information Statement. Of note, after IRB review of the PRAF submitted at the same time as this version of the Protocol, we request that the cover letter (Attachment L) and instructions for completing e-Questionnaires (Attachment I) be provided back to the research team in an editable format to permit mail merges. Any content to be included in future recruitment materials to be developed will be modeled after and be consistent with the content of the Information Statement.

5.2.7 Payment to Participants

Participants will be compensated for the time taken to complete the informed consent process, and for completion of each e-Questionnaire. Compensation will be paid by check or by direct deposit (EFT). The amounts of compensation will include the following: $20 for completion of informed consent procedures, $12 for the baseline e-Questionnaire, $7 each for scheduled e-Questionnaires (up to 36 for each participant), $7 for the first 10 flare-period e-Questionnaires, $4 for the 2nd set of 10 flare-period e-Questionnaires completed (that is, #11-20 completed), and $2 for the 3rd set of 10 flare-period e-Questionnaires completed (that is, #21-30 completed). Participants will have the option to complete more than 30 flare-period e-Questionnaires if they wish, but the study will not compensate them for flare-period e-Questionnaires beyond the first 30. The decreasing payment for higher numbers of completed elective flare-period e-Questionnaires was specifically introduced to address a prior scientific reviewer suggestion (in the 1st round of formal peer review by RR&D) that the research processes employed reduce incentives for spurious flare over-reporting. There is also a $15 compensation for the exit e-Questionnaire, and a $30 incentive for return of the ActiGraph unit. A larger ($50) incentive for ActiGraph return may be offered if an ActiGraph unit is not initially returned. This contingency plan for a higher compensation amount if the ActiGraph unit is not initially returned will not be disclosed to participants in the informed consent documents, since it would incentivize participants to delay returning the ActiGraph. This means that the amount listed for total possible compensation in the Information Statement document ($459) is $20 *less* than the amount listed for total possible compensation in the IRQ ($479) and other documents in this human subject application. For participants not wearing ActiGraphs, the total study compensation will be up to $429.

Payments will be bundled together to minimize inconvenience to participants and for reasons of feasibility, into 3 payment periods after the end of month 2, month 7, and months 12 (completion of study). If a participant withdraws from the study at another time that is not close in time to these 3 payment periods, a payment will be initiated at the time of withdrawal. The time points for payments and spacing between payments are motivated by our experience with current and recent VAPSHCS studies, including that it sometimes takes approximately 5 months after a payment is sent before we can confirm with the participant that the payment has been received. Tracking of non-VA (e-Questionnaire) data collection completion by VA staff for the purposes of participant payments is feasible because a researcher-facing portal for participant tracking will be accessible to VA research staff as part of the non-VA study processes. This portal can be accessed when needed to determine the applicable payment amounts at the time of each payment period.

5.2.8 Periodic contacts by phone, when needed Participants may be contacted by study staff via telephone in certain instances where data indicates participant misunderstanding about aspects of data collection or the study in general, or to respond to participant-initiated questions left on the study voicemail. During these conversations, research staff will be guided by the content provided in the Reminder Call Script (Attachment R). Participants may be contacted if they attempt to complete a Flare-window e-Questionnaire while also reporting that they are not having a flare (indicating misunderstanding about the flare definitions being used, or the expectations for reporting); for repeated missed Scheduled e-Questionnaires; for not completing any

flare-window e-Questionnaires; for reporting non-wear of the ActiGraph during 2 or more assessments during the 1st 4 weeks; for problems related to the ActiGraph or returning the ActiGraph, or other questions prompting an a direct telephone contact; or similar occurrences reflecting a misunderstanding of or lack of compliance with study processes. Some telephone contacts with participants are advantageous to allow participant-staff interactions and maintain connectedness with the study, beyond what can be achieved electronically. These contacts thus ensure validity of the study findings.

5.3 Informed Consent Procedures

A Waiver of Informed Consent has been obtained to cover screening/recruitment procedures, that will allow research study staff to approach patients. Informed consent for study participation is as described below. Informed consent will be offered following screening/completion of a Screening Checklist. The Screening Checklist is provided (Attachment AA). The Screening Checklist consists of the Inclusion/Exclusion criteria stated below in Table 1. A Waiver of Documentation of Informed Consent has been approved to use an Information Statement in lieu of requiring a signed consent form.

A. Informed Consent:
In the section below, all uses of the words 'patients' or 'participants' prior to completion of the informed consent process using the Information Statement refers to potential candidates for study participation. Please see the Information Statement document.

Informed consent gives patients the opportunity to choose whether or not they want to participate in a study. Informed consent will be administered by research study staff (research assistants, research coordinator, or research specialist) who are or will be named as part of this study protocol and human subjects documentation. Research staff will have completed the necessary human subjects protections training per VA policy to engage in human subjects research and will remain current with such trainings during the study period. Any new study personnel added to the study in the future will also have been trained on VA consent procedures, and will be trained on informed consent for this study by existing research staff for this study. Adequate informed consent requires the disclosure of relevant information about the research, assurance of patient understanding of the information, and the patient's voluntary agreement to participate. Research staff will explain the study to potential participants and answer questions. If questions cannot be answered by research staff, the PI (Dr. Suri) will be consulted to answer additional questions.

Participants will be informed that their decision whether or not to participate in the study would not affect the medical care they receive at the VA in any way. Participants will be informed that participation will involve completing frequent, serial e-Questionnaires using their own personal electronic devices (PC, tablet, or smartphone) over a 1-year period of follow-up. All data collection after the time of recruitment will involve these electronically administered e-Questionnaires. E-Questionnaires will include questions on sociodemographics, back specific functional status, pain, physical activities, health-related quality of life, mood, stress, and other study measures. Participants will be informed that joining the study is entirely optional.

Potential candidates will also:

i. Receive detailed information concerning the overall study goals from a research staff member. It will be explained that participants' involvement in this observational study will not affect their medical care at the VA in any way.

ii. Receive adequate time to raise questions and voice concerns.

iii. Be questioned to assure that they understand all information provided. Potential participants will be asked to repeat back understanding of this material, as necessary. Individuals will not be permitted to participate if there is any question as to whether a person is able to provide informed consent.
iv. Potential participants will be provided with as much time as needed to review the Information Statement and ask the research staff member questions about the Information Statement, their rights as participants, and participation in the study. Potential participants will be fully informed of all risks and benefits prior to giving their verbal informed consent and prior to enrollment in the study. Participants will be asked if they need some time to consider their involvement before providing consent. If so, a time will be scheduled to continue the discussion at a later date using Recruitment Mode 2 (telephone), or participants will be asked to call research staff using the study telephone number, if they wish to complete informed consent and participate in the study in the future.
iv. Following the above, potential participants will provide verbal consent to participate in the study procedures.
v. If informed consent procedures are being performed remotely by telephone interactions with research study staff (as in Mode 2 described above), the information packet sent to Veterans recruited in this manner will contain 1 copy of the Information Statement. The Information Statement can be retained by the participant for their records.
vi. Be informed about the run-in period requirements (see above in section 5).

During the informed consent process, study staff will explain to potential participants that participation in the VA component of this study will (1) involve data collection within the VA, which will produce VA data that will not subsequently leave the VA; and (2) data collection outside the VA. Data collected outside the VA will later be downloaded to the VA, at which point it becomes VA data and will not subsequently leave the VA during the study. The informed consent process (and the Information Statement submitted with this application) will briefly describe study processes involved with the non-VA component of this study, while clarifying that the VA informed consent process potential participants are completing at the time does not cover or apply to the non- VA component of the study.

During informed consent study staff will clarify the following

(1) Data collection within the VA will include several parts:

a. Information needed for participant screening, including the initial conversation between Veteran and research study staff, and subsequent interactions until and including informed consent.
b. Obtaining participants VA electronic medical record data from existing administrative data sources (e.g. CPRS, Vista, the Corporate Data Warehouse [CDW], Cerner, etc.). This data will be used for analyses at VA, and will not leave the VA.
c. Any data obtained from sources outside the VA (as described immediately below) that enters the VA. Once such data enters the VA, it becomes VA data and subsequently will not leave the VA.

(2) Data collection outside the VA will include the following:

a. Electronic survey data collection conducted by a non-VA private company (DatStat, Inc.) specializing in secure HIPPA-compliant electronic data collection using participants' own personal electronic devices (smartphone, tablet, and/or PC). e-Questionnaires will not include sensitive medical information. e-Questionnaires will involve self-reports of pain, physical limitations, physical activities, mood, and recent treatments for low back pain.
b. This component of electronic data collection will be led by researchers at the University of Washington (UW). The involvement of UW will entail a separate informed consent process for UW.

The consent process for VA research processes will occur at a time deemed mutually feasible for the Veteran patient and staff member and coordinated on a case-by-case basis. If the consent process is conducted by Mode 1 (in-person), we will follow the processes described above in section 5.2.1 to ensure that the staff-patient discussions take place in a private location at VAPSHCS (e.g., a medical

exam room or private conference room) or another location where a private discussion can be ensured. If the consent process is conducted by Mode 2 (telephone), the VAPSHCS research staff member will make the telephone call from a VAPSHCS telephone in a private room to minimize the possibility of coercion or undue influence. Prospective subjects will be informed that all study personnel will have completed the necessary human subjects protections training per VA policy. Informed consent will be conducted in English. Prospective subjects will be asked if they are able to understand English and whether they feel comfortable speaking it.

If during the course of this contact the potential participant has questions that cannot be addressed by research staff, another research staff member, the PI, or another study investigator will follow up with the potential participant to answer the questions. Potential participants may take time to think about participating and render a decision at a future time.

A waiver of HIPAA authorization has been approved for all study procedures, which allows the research team to view and analyze participant administrative data (CPRS, Cerner, or other data sources maintained by the VA) for the purposes of recruitment. In addition, the waiver of HIPAA authorization allows for analyses of VA administrative data for those individuals who do not respond to mailing packets, for the purpose of weighting the study sample of participants back to represent the target population of Veterans who were participants and those who did not respond to the mailing. The waiver of HIPAA authorization does NOT apply to individuals who contact the study to opt out of the study, or to participants who contact the study but decide not to participate in the study.

The same general study-related information content provided by study staff at the screening visit/informed consent will also be made available to participants throughout the study period on the participant-facing website Participant Portal (the 'FLAReS' website, or flares.datstat.com/portal/), which will be run by the non-VA (UW) component of this research study. The FLAReS website was set up by the private (non-VA) data collection company mentioned earlier (DatStat/R1) specializing in secure HIPAA-compliant electronic questionnaire administration, and processes related to the website will be covered through the UW component of the proposed research and the related UW human subjects processes.

5.4 Inclusion/Exclusion Criteria

Low back pain is defined as pain occurring between the lower posterior margin of the rib cage and the horizontal gluteal fold. Low back pain intensity will be measured using the numerical rating scale (NRS) See **Table 1** below for a complete and detailed list of inclusion and exclusion criteria, and justification/rationale for exclusion.

Table 1: Study Inclusion/Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
• Veterans age 18-65 years seen in VA primary care for LBP (the original target population); ***or*** (as part of expanded recruitment): Veterans age 18-65 years who otherwise have had health care for LBP since 10/1/2015, and report current back pain (Justification: adults of working age)	• 'Red flag' spine conditions (spinal cord injury, infection, malignancy, fracture) or spondyloarthropathy (Justification: red flag conditions are a distinct medical condition)* • Pregnancy (Justification: exclusion of potentially

• Must have regular access (every day, during most hours of the day) to a computer, tablet, or smartphone with internet access at home or at work (not via a public resource such as the public library). (Justification: needed for e-Questionnaire component of data collection occurring as part of UW research processes) • Basic computer literacy, including the ability to navigate simple websites (Justification: needed for e-Questionnaire component of data collection occurring as part of UW research processes) • Having a mobile phone capable of receiving alerts using text messages (Justification: needed for e-Questionnaire component of data collection occurring as part of UW research processes) • Must be able to understand and read English, sufficient to provide informed consent and validly complete the study assessments. (Justification: needed for informed consent and validity of study assessments) • Participants must enroll in the parallel study conducted at UW prior to the 2-week run-in period, and complete run-in period requirements for e-Questionnaire completion. Run-in period requirements including (1) completing the baseline e-Questionnaire, (2) completing at least 4 of 6 e-Questionnaires in the 2-week run-in period with an adequate proportion of e-Questionnaire items completed within surveys, and (3) completing the UW informed consent requirements for the (non-VA) UW component of the study. (Justification: run-in period is needed to identify participants capable of completing study procedures, including frequent and repeated data collection)	vulnerable populations) • Prisoners or incarcerated (Justification: exclusion of potentially vulnerable populations) • Severe active medical comorbidities or psychiatric illness likely to be a barrier to study participation including completing frequent, serial assessments (e.g., metastatic cancer). (Justification: exclusion due to likely being unable to complete study procedures)* • Prior diagnoses for psychotic or major thought disorder or unstable or severe psychiatric/behavioral conditions (e.g. delirium, mania, psychosis) as identified in EHR data (CDW, Cerner, etc.)* (Justification: exclusion due to likely being unable to complete study procedures)* • Diagnoses indicating cognitive limitations that might limit study participation (such as dementia)* • Thoracolumbar spine surgery in the past 1 year • Other ***major*** orthopedic surgery potentially impeding normal physical activities in a material way (such as surgeries involving the hip, knee, ankle, shoulder, elbow, wrist joints) within the past 6 months, or major abdominal or chest surgery within the past 6 months.* • Planned major orthopedic, abdominal, or chest surgery in the next 2 months.

*Evaluated partially or primarily by review of EHR data (CDW or other administrative data) to identify potential participants with back pain and without red flags or other exclusions (prior to contacting potential participants)

5.5 Study Evaluations

Screening

At the time of Mode 1 and/or Mode 2 recruitment as described above, research study staff will administer the Screening Checklist (Attachment AA). The Screening Checklist is comprised of the Inclusion/Exclusion criteria stated below in Table 1. The screening checklist will also questions specific to two of the subgroups included in the expanded target population. The Screening Checklist may be completed as a paper version or entered directly into a database. Screening and informed consent will typically be conducted during the same session, for potential participants that meet study criteria and proceed on to informed consent.

EHR data collection

Prior EHR and administrative data for study participants will be obtained from the CDW or other VA data repositories that are established after the VA's transition to the Cerner system. Participants will be informed that in this study, research staff will need to periodically look up participants' information in the electronic health record. This will be so for the duration of this study, a period that may last up to 2 years after a participant begins the study. This includes looking up such information from participants' health records after the 1-year follow-up period. If a participant decides to withdraw from this study, however, and informs the research team not to access his/her health record after that time, we will not access that participant's health record after that time. EHR reviews will be conducted to ascertain participants' status with regards to the subgroups in the expanded target population as described above (facet-mediated pain, SIJ-mediated pain, spondylolysis) and the other subgroups described below in 5.6.2.a (LSRS and LSS).

ActiGraph data collection

Study participants may be provided with an ActiGraph wGT3X-BT unit at or after the time of recruitment, depending on whether an ActiGraph unit is available for use at the time of recruitment. Potential participants who do not want to wear the ActiGraph or express hesitancy about their ability to use the ActiGraph will be offered study participation without the component of wearing the ActiGraph. Thus, this paragraph pertains to those participants who wear the ActiGraph. Participants recruited by Mode 1 (in-person) recruitment will be provided an ActiGraph and a thigh strap at the time of recruitment. Otherwise, ActiGraphs will be mailed to study participants. The ActiGraph wGT3X-BT is a triaxial accelerometer that has been validated as a measure of walking in LBP[7] and for the measurement of other types of activity when worn on the thigh (sitting, standing, lying supine, and running).[8-10] The ActiGraph does **not** display step counts or activity levels, limiting participants' capacity to be influenced by this data. Participants who receive the device will wear the ActiGraph on the thigh all day except when in water. After wearing the ActiGraph for the 1st 4 weeks of follow-up, participants will mail back the unit in a prepaid delivery box that will be sent to participants in advance of the 4-week follow-up time point. Once ActiGraph units are received back, data will be downloaded from the ActiGraph using VA-approved software, and all data erased before subsequent use. According to the plan previously agreed to by the VA ISSO Sharon LePage-Erwin, data is downloaded first to a VA-approved external hard drive, and then transferred to the VA network. We will use existing ActiGraph algorithms for distinguishing types of activities (sitting, standing, lying supine, and running).[10] No wireless or remote data sharing will be enabled on the ActiGraph, so no data can be transmitted in this way, safeguarding data and participants' privacy. ActiGraphs will be periodically tested for proper functioning by being worn by participant staff and the ActiGraph output examined.

All other study evaluations as described immediately below will be conducted as part of the e-Questionnaires that are <u>non-VA</u> data collection. These are presented here for the sake of completeness, although their initial conduct/acquisition are not a part of the VA component of the research. After acquisition as part of the non-VA component of this research, the data will be shared with the VA study team, and henceforth will become VA data. The baseline e-Questionnaire will be administered within 2 days of a participant completing informed consent. Scheduled e-questionnaires will be administered 3 times weekly during weeks 1-4, once a week during weeks 5-8, and twice a month from months 2-12. The exit e-Questionnaire will be administered at 1-year follow-up. Flare window e-Questionnaires are completed on an ad hoc basis during the 1-year follow-up period, and are participant-initiated (not on a set schedule)

Baseline e-Questionnaire

The baseline e-Questionnaire to be administered as part of the UW (non-VA) study is provided

(Attachment Q1). Of note, only the content of the e-Questionnaires can be provided, not the actual e-Questionnaires, since they are administered electronically. Below we list some of the study measures that are included in the baseline e-Questionnaires. Other measures may be added to this list in future PRAFs. The citations provided for these measures provide detailed descriptions of the measures, including validity and reliability.

- *Roland-Morris Disability Questionnaire (RMDQ):* The RMDQ is a back pain specific functional status questionnaire adapted from the Sickness Impact.[11] The RMDQ consists of 24 yes/no items, which represent common dysfunctions in daily activities experienced by participants with low back pain. A single unweighted score is derived by summing the 24 items, with higher scores indicating worse function with 0 (no disability) to 24 (maximum disability). The RMDQ was designed for paper administration, and is also well-suited for electronic device-based administration or telephone use.

- *Pain Numerical Rating Scale (NRS):* We will measure back pain using a 0-10 pain NRS (0=no pain and 10=worst pain imaginable) assessing average pain over the past week and pain "right now". Numerical rating scales of pain intensity are valid, reliable, and sensitive to detecting change in pain intensity after treatment.[12,13] We will also ask participants to make a second report of what they expect their NRS rating for back pain would be if they were not currently or recently taking medications for pain (analgesics).

- *PROMIS Short Form 10:* The NIH Task Force on Research Standards for Chronic Low Back Pain[62] recommended using PROMIS Short Form items to assess the constructs of depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and satisfaction with participation in social roles.

- *Tampa Scale of Kinesiophobia (TSK):* The TSK is a 17-item scale developed to measure the fear of movement related to chronic lower back pain.[14]

- *UW Concerns about Pain Scale 8-item SF* (previously called the UW Pain Appraisal Scale). Ths is a validated 8-item scale, described further at: https://uwcorr.washington.edu/measures/uw-cap/

- *PROMIS depression short-form (PHQ-8):* The *PROMIS depression short-forms have been previously validated*

- *The Single-item Global Measure of Depression* This single-item self-report measure of depression has been validated as compared to the Clinically Useful Depression Outcome scale, which involves 16 items assessing the DSM-IV inclusion criteria for major depressive disorder.[17]

- *Post-traumatic stress disorder (PTSD) Checklist, civilian version (PCL-C):* The PCL is a standardized self-report rating scale for PTSD comprising 17 items that correspond to the key symptoms of PTSD.[18]

- *Single-item stress question (SISQ*) The SISQ has been shown to have content, criterion, and construct validity in comparison to comprehensive measures of stress, well-being, psychological symptoms, and sleep disturbances.[19,20]

- *Chronic Pain Acceptance Questionnaire:* This 20-item scale was designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce unsuccessful attempts to avoid or control pain and thus focus on engaging in valued activities and pursuing meaningful goals.[21]

- *UW Pain Self-efficacy Questionnaire:* This questionnaire was developed to assess the confidence people with ongoing pain have in performing activities while in pain (https://uwcorr.washington.edu/measures/uw-prse/).

- *Medications:* Patients will report medications they have taken for pain in the past 24 hours.

Other variables to be included in the baseline e-Questionnaire include: low back pain history characteristics, work-related factors (receiving disability or compensation, or planned applications, hours/days off work at baseline, job satisfaction ratings, physical demands at work), smoking and vaping history, and questions with regards to current typical number of alcoholic beverages consumed per week and cannabinoid use.

Scheduled e-Questionnaires

We have now provided an updated version of the Scheduled e-Questionnaire content (Attachment Q2-Scheduled e-Questionnaire). As mentioned above, this e-Questionnaire is part of the UW (non-VA) study processes. Only the *content* of the e-Questionnaire can be provided, not the actual e-Questionnaire, since it is an electronic questionnaire. Variables included in both Scheduled and Flare Window e-Questionnaires include several of the measures listed immediately above under "Baseline e-Questionnaire", such as: numerical rating scales of low back pain intensity[23,24], analgesic use[25], the 2-item version of the Coping Strategies Questionnaire[15], the 2-item version of the TSK[26], the 1-item global measure severity of depression[17], the 2-item version of the PCL-C scale[18], the single-item stress question (SISQ)[19,20], hours of lost work[27], other variables related to work quality/quantity,[28] recent cigarette smoking, vaping history, number of alcoholic beverages consumed and cannabinoid use.

Flare Window e-Questionnaires

The flare window e-Questionnaire material **includes the same content as the Scheduled e-Questionnaire content** (Attachment B-Scheduled e-Questionnaire), but the wording of items are slightly different, to indicate the reference time period occurring prior to flare onset (instead of prior to the expected Scheduled e-Questionnaire start time). This e-Questionnaire (to be administered as part of the non-VA study processes) is submitted to the VAPSHCS IRB currently (see Attachment Q3). Only the content of the e-Questionnaire can be provided, not the actual e-Questionnaire, since it is administered electronically.

Exit e-Questionnaire

The exit e-Questionnaire to be administered as part of the non-VA study processes will be provided to the VAPSHCS IRB at a future PRAF. The exit e-Questionnaire materials include many of the same measures as contained in the baseline e-Questionnaire, but omit some measures that need only be assessed at baseline (and not at final follow-up). The exit e-Questionnaire will also include measures of global perceived improvement and satisfaction, which were not included on the baseline e-Questionnaire.

Brief Telephone-based Exit Survey

For participants who have been unable to compete the Exit e-Questionnaire, we will offer a brief telephone-based Exit Survey. The brief telephone-based Exit Survey is limited to 25 questions, 24 of which are yes/no questions, and 1 of which is a 10-point scale. Participants will already be familiar with these items from prior surveys they have completed in the study, and the telephone-based Exit Survey should take between 5-10 minutes to complete. We will make up to 2 phone contacts in which a voicemail can be left, or if a participant declines the brief telephone-based Exit Survey (whichever comes first).We provide the questions for the new telephone-based Exit Survey in Attachment ZZ. Participants completing the brief telephone-based Exit Survey will be compensated the same amount as if they had completed the full electronic Exit e-Questionnaire.

VA data storage.

See Section 7.0 for further information relevant to data storage.

Part of the VA research records will be stored in paper form in a locked file cabinet (in the locked office space of the Seattle ERIC at VA Puget Sound) and part will be stored electronically. The file cabinets and computers will be locked and are housed in rooms that are locked when unoccupied. Other information will be stored electronically. All electronic data will be stored in encrypted, password-protected files on the VA secure research server with access restricted to VA research staff on this study team. Data will not be stored on any laptops or computers outside VA Puget Sound.

5.6 Data Analysis

5.6.1 Sample Size Calculations: Of the recruitment goal of 730 Veterans, we expect that 290 Veterans (40%) will have limited data available (i.e. they will fail the run-in period, be non-compliant with e-Questionnaire data collection, be lost to follow-up, or withdraw). All data analysis will be conducted using VA data (including e-Questionnaire data that has been downloaded to the VA and has become VA data) by the biostatistical team from the Seattle ERIC listed in this human subjects application (Korpak, Timmons, Baraff, Forsberg). Key determinants of statistical power for the Aim 1 case-crossover analysis include the (1) activity exposure effect size, (2) activity frequencies (expected to be 5-

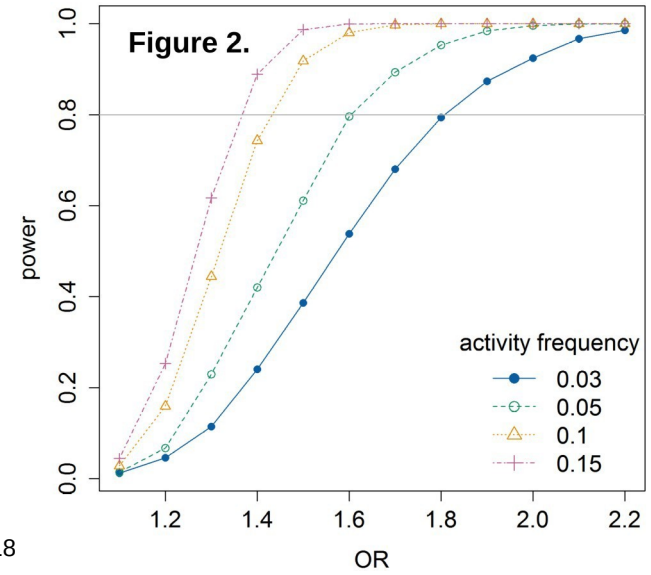


Figure 2.

25% based on a previously conducted pilot study[29]), (3) number of case/control periods, and (4) proportion of participants who are statistically informative (with both case and control periods). Given the transient nature of flares, in our view, only activity exposures with moderate magnitude effects (ORs of 1.5-2.0) will have a meaningful impact on the population level. Informed by the characteristics of activities, flares, and missing data from our pilot[29], we estimated power using simulated data with 1000 replications, assuming □=0.005 (Bonferroni-corrected for 10 activity groups), comparing different assumptions for sample size determinants, including activity frequencies as low as 3%. A sample size of n=440 yielded □90% power to detect ORs of 1.5 for activity frequencies □10%, 80% power to detect OR=1.6 at activity frequency=5%, and 80% power for OR= 1.81 given activity frequencies as low as 3% (**Figure 2.**). Allowing for 40% of participants not being analyzed due to having limited data available (loss to follow-up, fail run-in period, etc.), this yielded ***a planned sample size of n=730 for Aim 1***. These power estimates are highly conservative, since (1) they use data from scheduled e-Questionnaires only and assume no data from *ad hoc* flare-window e-Questionnaires, and (2) they assume no information at all from the n=290 with limited data. Moreover, they are based on binary activity exposures, and analyses using continuous exposures (incorporating duration and frequency) will have greater power. As a point of comparison, the previously conducted pilot study was able to detect ORs ≥2.5 and p-values< 0.001 despite having ~9x *fewer* participants than the currently proposed study.[29] For Aim 2, using the same data simulated for Aim 1, and assuming an expected mean (standard deviation) 1-year RMDQ scores of 8.8 (6.4) from a prior study,[30] Bonferroni-corrected □=0.005, activity frequencies □20%, and n=440 without missing data (from n=730 initially recruited), we estimated power over a range of scenarios where we varied the strength of the association between the *change* in activity frequency over the 1st 4 weeks of follow-up (for each of the 10 activity categories) and a minimum clinically important change in 1-year RMDQ of 2.5 points.[31] We found ≥80% power to detect a 2.5-RMDQ-point difference at 12 months in scenarios where a 65% change in activity frequency over the 1st 4 weeks produced a 2.5-RMDQ-point difference at 12 months, and in all scenarios where the activity frequency-RMDQ relationships was *more* extreme (e.g., if a smaller % change in activity frequency produced a 2.5-RMDQ-point difference at 12 months. This confirms adequate power with ***a planned sample size of n=730 for Aim 2.***

5.6.2. Analytic approach: All analyses will be conducted at VA by members of the Seattle ERIC biostatistical team, by research staff member biostatisticians named on this protocol as above. It is expected that Dr. Anna Korpak and Mr. Andrew Timmons of the Seattle ERIC will conduct all analyses involved. If needed, other members of the Seattle ERIC biostatistical team named above as study personnel may be called upon for analyses, such as Mr. Baraff and Mr. Forsberg. Senior biostatistical oversight will be provided by Dr. Patrick Heagerty at UW; however, Dr. Heagerty will not interact directly with study data and/or PHI, and will only see results in aggregate format such as would be presented for publication to a scientific journal.

We will conduct analyses to identify patterns of missing data that may indicate whether they are ignorable.[10] Approaches to deal with missingness will vary depending on patterns of missingness and may change completely from the initial approach specified here. If >5% of outcome data are missing, the sample will be divided into two groups (missing vs. not missing) and fully observed variables will be examined to determine if they predict missingness on the affected outcome. Depending on this analysis, the missingness may be considered “observed at random” thus meeting some criteria for

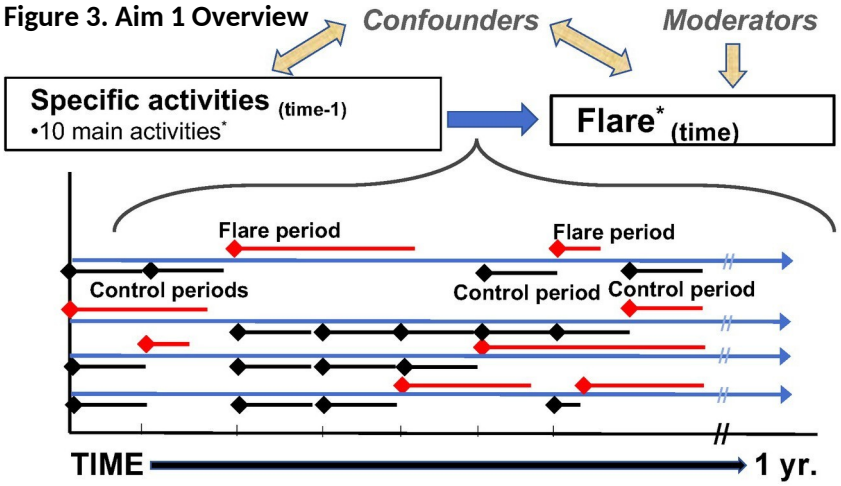
"missing at random" assumptions. Multiple imputation procedures will then be implemented. If data missingness is not ignorable, we will use Heckman's selectivity models or pattern-mixture models with multiple imputation to model the missingness.[10] These methods for dealing with missing data may change based on the actual nature of the data and missingness.

We will characterize the study sample using descriptive statistics and graphical techniques such as frequencies, means, medians, histograms and box plots. Quantitative variables (e.g., ActiGraph data) will be transformed as needed (e.g., log transformations for positively skewed long-tailed distributions, or conversion to categorical variables based on clinical rationale or distribution). All analytic approaches as stated below are preliminary plans, and may change depending on developments in the field, new statistical innovations, and the nature of the data at hand.

$$\log\left[\frac{Pr(Y_{ij}=1)}{1-Pr(Y_{ij}=1)}\right] = \beta_{0i} + \beta_w x_{i(j-1)} + \gamma C_{i(j-1)}, i = 1,2,...,n; j = 1,2,...,n_i \quad (1)$$

5.6.2 a. Aim 1 analyses: We will examine associations between activity group exposures and the participant-reported flares outcome in conditional logistic regression models, using data from all scheduled and flare window e-Questionnaires over 1- year. There will be one model for each of the 10 primary activity categories. Models will include activity categories as time-varying predictors as in **equation 1**, where *Y* is the outcome (flare vs. no flare), *x* is the activity exposure (yes vs. no), and C represents potential time-varying confounders (psychological factors, other activities). The letter *i* indicates the *i*th individual (*i* =1,2,. . . n), *j* indicates the *j*th time of follow-up (*j* =1,2,. . . ,n_i) and $x_{i(j-1)}$ indicates an activity that was performed in the exposure window prior to the *j*th time (either the start of the control window [scheduled e-Questionnaire] or time of flare onset [flare window e-Questionnaire]). As previously noted, the survey methods are such that activity exposure and flare outcome are inherently time-lagged, with exposure preceding outcome. β_w represents the association of activity *x* with flare outcome Y within individuals (the 'within-individual effect'), or the expected odds of a flare with change in the activity exposure for a given individual. These analyses will yield odds ratios (OR) and 95% confidence intervals for within-individual 'effects' of activity triggers on an LBP flare. The initial analytic approach (**Figure 3**) will examine the association between binary activity exposure and binary flare outcome, with explicit adjustment for pain NRS and number of prior flares measured at time=*j*-1, and time-variant confounders selected based on conceptual importance; *by design*, the case-crossover method uses each person as their own control, accounting for known and unknown confounds that are fixed or relatively stable over time (i.e., age, sex, sociodemographics, medical and LBP history, work-related factors, and underlying psychological predispositions). We will use a Bonferroni-corrected threshold of *p*=0.005 for each

Figure 3. Aim 1 Overview



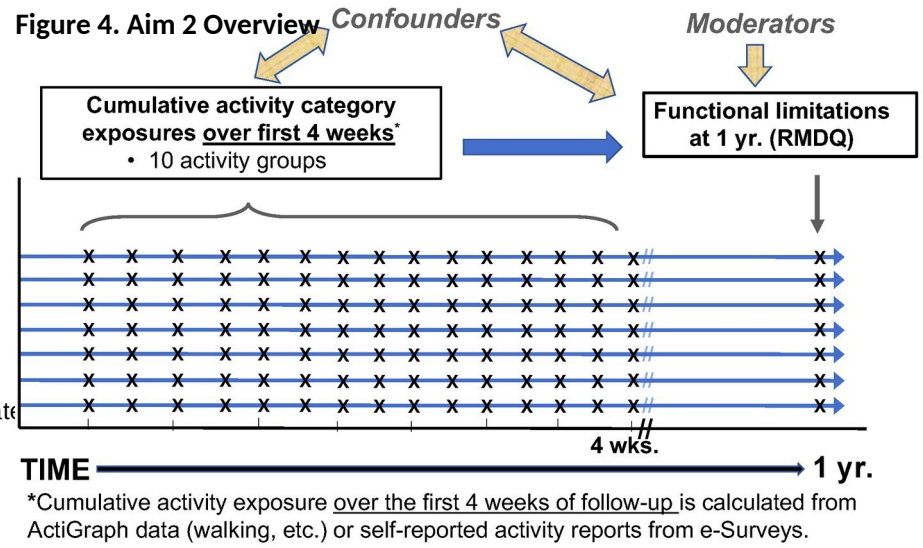
*Analysis includes all scheduled and flare window e-Surveys. Activity exposures over prior 24-hr and 2-hr effect periods, and current flare status, are inherently time-lagged.

primary activity-

flare comparison to account for 10 statistical comparisons (one for each of the 10 activity categories). We will further examine for activity-flare associations after accounting for important relationships based on theory and clinical knowledge, including the following: dose-response relationships; work- specific activity-flare associations; multivariate analyses including other potential confounders (other time-varying activities, depression, PTSD, stress, catastrophizing); potential moderators; different effect-periods of activity exposures (i.e., 24 vs. 2 hours); possible biases (e.g., conscious activity avoidance and carry-over effects); and clinical subgroup analyses (lumbosacral radicular syndrome [LSRS] symptomatic lumbar spinal stenosis [SLSS] diagnosed by a specialist, ascertained by chart review). We will also conduct similar subgroup analyses as secondary analyses, targeting the expanded target population subgroups described above (facet-mediated pain, SIJ-mediated pain, spondylolysis, ascertained by EHR review). We will analyze the reliability and accuracy of these subgroups. Of note, the primary analysis of walking, standing, and sitting will use the ActiGraph data (which are only obtained for the 1st 4 weeks of follow-up); secondary analyses will use the self- reported data for these 3 groups over the entire 1-year follow-up, and will also examine the association between ActiGraph and self-reported data. After these analyses using the binary flare outcome, we will use an analogous approach to examine relationships between activity categories and the secondary (continuous) outcome of NRS LBP intensity, with linear mixed-effects regression. These analyses account for potential biases that might be introduced by participant self-identification of flare status; if no such bias exists, we would expect the direction of effects to be similar to those obtained in the initial analysis of flares.[8,9]

5.6.2b. Aim 2 analyses: We will examine associations between the frequency of activity during scheduled e-Questionnaires (% of periods during which each of the 10 primary activity categories were reported over the 1st 4 weeks of follow-up), and the outcome of long-term LBP-related functional limitations at 12 months as reflected by the RMDQ,[31] using a Bonferroni-corrected threshold of p=0.005 (**Figure 4**). Activity over the 1st 4 weeks is the exposure of interest for the Aim 2 analysis because activity restriction is most expected early in an episode of LBP, and because of our previously-stated reasoning that early changes in activity may be particularly important in determining long-term/overall activity-function relationships. The percentage of periods with each activity category over the 1st 4 weeks will be calculated from self-reported activity information and ActiGraph output. The main multivariate model for each activity category will explicitly adjust for a range of potential confounders based on prior knowledge and conceptual rationale, including baseline RMDQ score, and all psychological predictors and other baseline covariates. We will then conduct secondary analyses analogous to that done for Aim 1 to examine activity-1-year-RMDQ associations after accounting for important relationships based on theory and prior knowledge: potential moderation by baseline employment status, compensation status, or job satisfaction; potential moderation by analgesic use over the first 4 weeks of follow-up; sensitivity analyses contrasting associations with cumulative activity exposure early (weeks 1-2) vs. late (weeks 3-4 or weeks 5-8)

Figure 4. Aim 2 Overview



during follow-up; and clinical subgroup analyses (LSRS and SLSS subgroups). We will use the same approach for the secondary outcomes of LBP intensity, lost work productivity, quality of life, and analgesic use at 1-years.

Analyses for Aims 1 and 2 will use VA administrative data to weight the sample of participants back to represent the target population of Veterans with back pain (including those who did not respond to the study).

5.6.3. Interpretation: Aims 1 and 2 will yield tables of risk estimates for (1) the *short-term effects* of the 10 specific activity categories on flares and (2) the *long-term effects* of such activities on functional recovery as reflected by the 1-year RMDQ score. We expect that different activities will have different patterns of short-term vs. long-term effects. In instances where short-term and long-term effects are in the same direction, potential implications for activity recommendations may be straightforward. For example, if heavy lifting confers both greater short-term risk of pain flares and greater long-term risk of functional limitations at 1-year follow-up, the clinical implication may be that that lifting should be avoided for those with LBP. In some instances where the short-term vs. long-term effects of activities differ, however, implications may depend on personal priorities and preferences. For example, if walking increases the short-term risk of a flare but has no effect on functional recovery at 1 year, the decision of whether or not to walk during a new LBP episode might be guided by a patient's preferences. In other instances where the short-term vs. long-term effects of activities differ in direction, the latter may take priority (i.e., if walking improves functional recovery at 1 year, but causes a small magnitude increase in pain flares, walking should likely be encouraged).

5.7 Withdrawal of Subjects

Participant withdrawals

We will record termination/withdrawal information for participants who decide to leave the study. Participants may leave the study at their own discretion, by contacting the research team and notifying them of the decision to leave the study. Participants may be withdrawn from the study without their consent if they become incarcerated during the study, or if the researchers feel that the study is in some way negatively affecting the participant's health or wellbeing. Participants may be withdrawn from the study without their consent if their responses to surveys are consistent with systematic non-compliance such as consistent non-completion or non-response to surveys not explained by other factors; findings indicating false data such as e-Questionnaire completion times that are too fast to be possible; or inappropriate and repeated completion of *ad hoc* flare window surveys even after explanation/clarification. Participants may also not be offered participation, or be withdrawn from the study, if they demonstrate threatening behaviors or potentially harmful behaviors towards research study staff.

Although not considered 'withdrawal' per se, participants who are consented may be subsequently excluded, if they fail the 2-week run-in period requirements as described above. For the purposes of the Information Statement, to simplify understanding for potential participants, we do not distinguish between withdrawals and these pre-randomization exclusions.

6.0 Reporting

There are no study-related processes in this purely observational study that would be expected to cause serious adverse events. E-Questionnaires inquire about musculoskeletal pain conditions and treatments, other diagnoses, sociodemographic factors, and factors related to healthy living and lifestyle. We do not anticipate these to pose any significant effect on a participant's health or well-being, although it is theoretically possible (although highly improbable) that some questions may cause emotional distress or discomfort due to participants paying more attention to areas where musculoskeletal pain may or may not be present. Any possible discomfort or distress is expected to be negligible, and of note e-Questionnaires do not include question items pertinent to sensitive issues such as suicide risk, stigmatized behaviors, sexual trauma, etc. We will take the steps outlined in the IRQ to mitigate any possible discomfort or distress for participants when answering questions in the e-Questionnaires.

We will collect safety information regarding problems that are reported in an *ad hoc* basis to study staff by participants who complete informed consent for the VA component of this study as described in this human subjects application. Safety information will be collected via any applicable means (verbal and/or written communication) at the time of occurrence, but we will suggest that participants contact research staff by telephone. Safety information, including unexpected serious adverse events or problems, will be reported in accordance with VHA Handbook 1058.01. Collection of safety information will begin at study initiation. Collection of safety information will end at study closeout. Study staff will report safety information to the PI Dr. Pradeep Suri at the time of occurrence. Events will be communicated via any applicable means (verbal and/or written communication). An adverse event or problem will be communicated to the IRB in writing using forms such as the 1) Unanticipated Serious Adverse Event or Problem Report, or 2) Continuing Review Questionnaire or Research Project Termination Report. An adverse event or problem will be communicated to the IRB in writing 1) within 5 business days of becoming aware of any serious unanticipated problem involving risks to subjects or others in VA research, or 2) at the time of study renewal or closure, whichever comes first, if the event is not serious or unexpected. Unauthorized research-related access, use, disclosure, transmission, removal, theft, or loss of VA sensitive information, including but not limited to PHI, individually-identifiable private information, confidential information, and Privacy Act-protected information will be reported within 1 hour of becoming aware of the event. Data for reporting will be compiled at the time of study renewal or closure.

7.0 Privacy and Confidentiality

The study will use participants' Protected Health Information (PHI) for the purposes of participant payment by mailed checks to the participant's current address. Also, PHI will be used to contact participants via telephone (as outlined above). PHI will be contained in the crosswalk file that links participant identifiers with the study-specific StudyID. No PHI will be disclosed at any point in the study.

We will take multiple steps to protect participants' privacy, confidentiality, and inappropriate disclosure of data, under strict VA security guidelines. All study staff will maintain current on required

VA trainings for privacy and confidentiality. Data will be stored in Participant Data Files that will be de-identified, labeled with a code number that is unique to each patient in the study ('study-specific StudyID'). The study-specific StudyID will be a unique numerical code consecutively numbered in order of approach/screening. We will NOT include any protected health information (PHI) in the Participant Data Files. The Participant Data Files will be stored in a secure password-protected electronic location on the VA servers (expected to be the in the J: drive on the Health Services Research & Development (HSR&D) server), accessible only to study staff members and authorized personnel. Staff will maintain a Master List key code that links participants with the study-specific StudyID. This Master List key code will be stored in a secure password-protected electronic location on the VA servers, separately from all other study data. All hard copy files such as signed informed consent forms (from prior to the time when these were replaced by Information Statements) .will be stored in locked filing cabinets in the locked/secured offices of the Seattle ERIC, while all electronic data will be stored in password-protected files in a limited access folder (to research staff) on a secure VA network drive. Only IRB-approved study personnel will have access to Participant Data Files or Informed Consent Forms. We will only analyze data that does NOT contain PHI, and will report participant data in aggregate form only- no PHI will be entered into analyses or reports.

If improper use or disclosure of research data occurs, the ISSO and Privacy Officer will be notified within one hour of the improper use or disclosure, and we will also adhere to any other local policies regarding improper use or disclosure.

Of note, no wireless or remote data sharing will be enabled on the ActiGraph, so no data can be transmitted in this way, safeguarding data and participants' privacy.

8.0 Communication Plan

This study involves VAPSHCS as the coordinating center and UW as a participating site. When the initial application to conduct human subjects research (related to the non-VA component of this study) was submitted to the UW IRB by UW researchers, we provided a letter notifying the UW IRB of the existing VAPSHCS IRB approval and a copy of the VAPSHCS IRB approval letter. For any future modifications to the UW IRB-approved research processes, we will coordinate with UW researchers who will submit documentation to the UW IRB if appropriate; due to the study's minimal risk, the UW IRB has indicated that they only want to receive updated documentation if major, substantiative changes are made to the study processes. If such changes occur, we will provide the appropriate documents to the UW IRB.. If we are told a particular document cannot be shared with the UW IRB and UW researchers, we will share a summary of the document's contents instead.

At the time of any PRAF or modification submitted to the VAPSHCS IRB, we will submit relevant human subjects approvals from UW and documents approved by the UW IRB that have changed since the last PRAF or modification. Conversely, at the time of any modification submitted to the UW IRB, we will share the most recent VAPSHCS IRB approval letter unless previously shared, and either pertinent VAPSHCS IRB-approved documents, or summaries of such documents, according to the guidance provided by the VAPSHCS IRB or IRB administrators. In instances where we are told that VAPSHCS

IRB-approved documents or summaries are not required with UW IRB modifications, we will not submit such documents.

There are no expected AEs or serious AEs involved with this purely observational research. We will work with UW researchers to ensure that UW researchers report SAEs or unanticipated problems (UAPs) to our VAPSHCS research team within 5 days of becoming aware of the SAEs or UAPs. The study design does not permit the sharing of individual-level VA data outside of the VA during the study. Therefore, if SAEs or UAPs are reported to or otherwise learned of by VA research staff, we will advise participants to contact UW research staff and report this information. Where applicable, information on SAEs or UAPs can also be shared with UW researchers in aggregate form.

9.0 Information Security and Data Storage/Movement

Research data pertaining to this application are VA data. These data would only remain within the VA, and would not be moved or shared outside the VA. Non-VA data produced by e-Questionnaires will be shared by UW researchers with VA researchers on the VA study team, at which time this data will become VA data and will not be moved or shared outside the VA.

Hard-copy (print) documents include completed screening checklists and signed informed consent forms. Electronic data include databases of parameters obtained during screening/recruitment, ActiGraph data, and VA administrative data obtained from the CDW or any such proxy that comes into use after the Cerner EHR transition. Additional electronic databases include non-VA data that are shared to the VA research team, at which time that non-VA data will become VA data. These non-VA data will be downloaded by VA researchers. This is one-way sharing, since once this becomes VA data it will not be shared outside VAPSHCS except as mandated by provisions for potential sharing of anonymized datasets once enterprise-level resources for this are available (described below). Of note, data from participants who completed informed consent using an Information Statement (without written *documentation* of informed consent) cannot be shared outside the federal government even after enterprise-level resources are available.

Any hard-copy documents involved will be stored in locked file cabinets in the locked/secured offices of the Seattle ERIC. These will be retained for six years after study closure, until destroyed in accordance with VA procedures, and will not be moved from the ERIC, since there is no need for movement of the documents (unless they need to be locally archived according to local R&D processes).

Similarly, the electronic databases/files described above will be maintained locally in a secure manner until enterprise-level resources become available for long-term storage and access. Once enterprise-level resources become available for long-term secure electronic storage, we will use those resources. Electronic databases will be retained for six years after study closure, at which time they will be destroyed in accordance with VA procedures. We will update the above plan as needed if VA procedures and requirements change in the future. We will ensure that data is destroyed/sanitized in accordance with VA Directive 6500.

Current VA requirements mandate provisions for making the final data sets resulting from VA funded research available outside the VA. As stated in the submitted DMAP document, once enterprise-

level resources become available for electronic access, we will use those resources to make de-identified, anonymized datasets available to approved applicants under a formal written agreement. Only completely deidentified and anonymized versions of datasets would be shared. Sharing will only take place under a written agreement prohibiting the recipient from identifying or re-identifying (or taking steps to identify or re-identify) any individual whose data are included in the dataset. Of note, data from participants who completed informed consent using an Information Statement (without written *documentation* of informed consent) cannot be shared outside the federal government even after enterprise-level resources are available. We will update the above plan as needed if VA procedures and requirements change in the future.

Participants' involvement in the UW (non-VA) research processes will result in deidentified and anonymized UW datasets containing participants' e-Questionnaire responses that UW researchers will retain. Those datasets will not include several components of data that are part of the VA datasets, such as ActiGraph data, EMR data, and data collected during initial screening.

10.0 References

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