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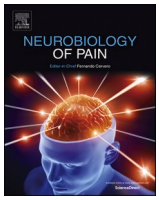

Original Research

Clinical and biobehavioral phenotypic assessments and data harmonization for the RE-JOIN research consortium: Recommendations for common data element selection

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ABSTRACT

Background: The Restoring Joint Health and Function to Reduce Pain (RE-JOIN) Consortium is part of the Helping to End Addiction Long-term® (HEAL) Initiative. HEAL is an ambitious, NIH-wide initiative to speed scientific solutions to stem the national opioid public health crisis. The RE-JOIN consortium's over-arching goal is to define how chronic joint pain-mediating neurons innervate different articular and *peri*-articular tissues, with a focus on the knee and temporomandibular joints (TMJ) across species employing the latest neuroscience approaches. The aim of this manuscript is to elucidate the human data gathered by the RE-JOIN consortium, as well as to expound upon its underlying rationale and the methodologies and protocols for harmonization and standardization that have been instituted by the RE-JOIN Consortium.

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Methods: The consortium-wide human models working subgroup established the RE-JOIN minimal harmonized data elements that will be collected across all human studies and set the stage to develop parallel pre-clinical data collection standards. Data harmonization considerations included requirements from the HEAL program and recommendations from the consortium's researchers and experts on informatics, knowledge management, and data curation.
Results: Multidisciplinary experts – including preclinical and clinical researchers, with both clinician-scientists-developed the RE-JOIN's Minimal Human Data Standard with required domains and outcome measures to be collected across projects and institutions. The RE-JOIN minimal data standard will include HEAL Common Data Elements (CDEs) (e.g., standardized demographics, general pain, psychosocial and functional measures), and RE-JOIN common data elements (R-CDE) (i.e., both general and joint-specific standardized and clinically important self-reported pain and function measures, as well as pressure pain thresholds part of quantitative sensory testing). In addition, discretionary, site-specific measures will be collected by individual institutions (e.g., expanded quantitative sensory testing and gait biomechanical assessments), specific to the knee or TMJ. Research teams will submit datasets of standardized metadata to the RE-JOIN Data Coordinating Center (DCG) via a secure cloud-based central data repository and computing infrastructure for researchers to share and conduct analyses on data collected by or acquired for RE-JOIN. RE-JOIN datasets will have protected health information (PHI) removed and be publicly available on the SPARC portal and accessible through the HEAL Data Ecosystem.
Conclusion: Data Harmonization efforts provide the multidisciplinary consortium with an opportunity to effectively collaborate across decentralized research teams, and data standardization sets the framework for efficient future analyses of RE-JOIN data collected by the consortium. The harmonized phenotypic information obtained will significantly enhance our understanding of the neurobiology of the pain-pathology relationships in humans, providing valuable insights for comparison with pre-clinical models.

Introduction

The Restoring Joint Health and Function to Reduce Pain (RE-JOIN) Consortium is part of the Helping to End Addiction Long-term® (HEAL) Initiative, an ambitious, NIH-wide effort to speed scientific solutions to stem the national opioid public health crisis (Restoring Joint Health and Function to Reduce Pain (RE-JOIN) | NIH HEAL Initiative, 2024). RE-JOIN's overarching goal is to define how various types of neurons innervate articular and *peri*-articular tissues, and how these neurobiological patterns change as a function of pain, biological sex, age, or physical function. RE-JOIN's initial focus is on the knee and temporomandibular joints (TMJ), with longer-term goals of expanding developed workflows and state-of-the-art neuroscience technologies to other joint types to identify both common and joint-specific pain pathways. Clinical pain presentation at the knee joint and TMJ are highly heterogenous and are leading sources of chronic pain in the United States (Cui et al., 2020; Valesan et al., 2021).Both pain presentations contain multifactorial components that can range from acute to chronic and from mild to severe, significantly compromising quality of life and leading to high disability across an individual's lifespan.

To map and characterize how joint disease alters knee and TMJ innervation, RE-JOIN will take a transdisciplinary, neuroscience team science approach, combining preclinical joint disease models with data obtained from human patients. The RE-JOIN consortium consists of five multisite projects, which include preclinical and clinical investigators. While all study sites will perform pre-clinical work, a subset of RE-JOIN sites will also recruit human patients who are undergoing surgical procedures of the knee or TMJ, such as elective total joint replacement of these joints (Fig. 1). Specifically, RE-JOIN teams at the following geographical sites were funded to collect human tissues and data: a) Duke University (North Carolina, TMJ); b) the University of Texas Health Science Center – San Antonio (TMJ), and its partner site at Karolinska Institutet (KI) (TMJ); c) Rush University Medical Center (Knee) partnered with the Hospital for Special Surgery (HSS)(Knee), Scripps Research (Knee), and Rockefeller University Hospital (Knee); and d) the University of Florida (UF) (TMJ and Knee) and partner University of Pittsburgh (TMJ) Table 1.

Prior to surgery, joint pain and function will be evaluated using

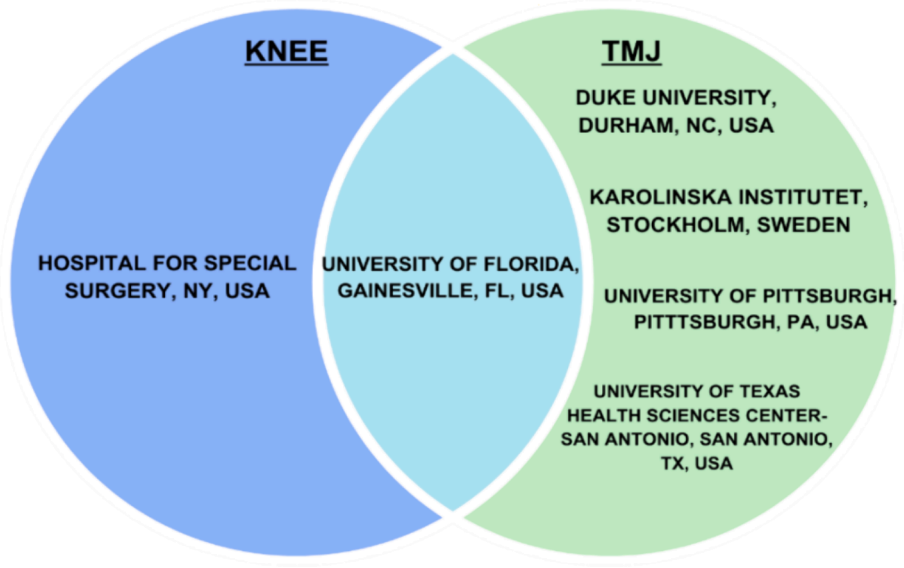

Fig. 1. Sites for human tissue collections in the RE-JOIN consortium by joint type studied.

multi-modal self-reported and performance-based measures, while tissues retrieved at the time of surgery will be evaluated using translational research approaches to identify innervation and molecular pain signatures. The RE-JOIN Consortium created the human models working subgroup to harmonize clinical data collection across RE-JOIN human study sites and establish common measures, clinical paradigms, and data dictionaries. This multidisciplinary team combines researchers and clinicians with expertise in knee osteoarthritis (OA) and TMJ/orofacial pain conditions across the translational continuum. The consortium-wide human models working subgroup established harmonized data elements that will be collected across all human studies and set the stage to develop parallel pre-clinical data collection standards. The details of the pre-clinical data collection are not included here and will be presented elsewhere. Given that clinical and research settings vary across study sites collecting human data, the human models working subgroup collectively agreed on a Human Models RE-JOIN minimal dataset which include both HEAL-required Common Date Elements (CDEs) and a number of RE-JOIN Common Data Elements (R-CDEs). In addition, we determined discretionary, site-specific measures as presented below (Fig. 2).

Methods

Harmonization efforts across RE-JOIN sites were facilitated by multidisciplinary group discussions and literature reviews. The committee included 6 clinical researchers (4 clinician-scientists), 7 pre-clinical researchers (2 clinician-scientists), and 3 data curation and integration experts spanning 9 institutions. Consensus was reached via discussions in biweekly meetings and email communications. NIH HEAL defines common data elements (CDEs) (Common Data Elements (CDEs) Program | NIH HEAL Initiative, 2024) as: a) fields describing the data to be collected (i.e., identifying specific variables), b) instructions on how to gather the data from the participants, and c) how the response should be represented (i.e., allowable responses or variable coding) (Common Data Elements (CDEs) Program | NIH HEAL Initiative, 2024; Wandner et al., 2022). All clinical research studies funded by the NIH HEAL Initiative are required to capture a core group of CDEs related to pain with the aim to harmonize data across all sites and to enable downstream *meta*-analysis at scale (9 domains at the time of our study) (Common Data Elements (CDEs) Program | NIH HEAL Initiative, 2024). The human models working subgroup led the development of the RE-JOIN clinical data standards by expanding the HEAL CDEs to include elements specific to knee OA and TMJ conditions or the RE-JOIN-Common Data Elements (**R-CDEs**). The HEAL-CDE and the R-CDE are minimal clinical datasets collected on every patient enrolled in RE-JOIN across all study sites. The group also identified additional discretionary measures that will be collected at some, but not all clinical RE-JOIN sites. These discretionary domain-specific measures were created with the potential for future collaborative efforts across sites where different teams can gain knowledge and expertise from those already collecting the data.

Depending on data type, harmonization efforts ranged from creating R-CDEs and accompanying data standards to identifying standardized protocols for data collection, file naming, and data submission. Consortium-wide harmonization also included standardized naming of unique subject identifiers, naming and numbering of study visits, and standardization of date variables for optimal data export and sharing. The data informatics and curation experts and the consortium's administrative core (Baylor College of Medicine, TX) worked alongside the human models working subgroup to create a secure central data repository and computing infrastructure for managing data governance and sharing within RE-JOIN to further advance the NIH's mission of facilitating cross-study comparisons and improving the interpretability of findings.

RE-JOIN minimal clinical dataset (HEAL-CDE+R-CDE)

The human models working subgroup was tasked with developing the minimum required elements to faithfully represent clinical datasets in accordance with the findable, accessible, interoperable, and reusable (FAIR) principles of data sharing. These include the HEAL CDEs, R-CDEs and discretionary measures for broad use across the various clinical projects. Consensus around a harmonized set of required and discretionary measures was reached through a combination of literature review followed by internal discussion within the human models working subgroup.

First, the human models working subgroup reviewed the required HEAL-CDEs and agreed upon those most appropriate for the RE-JOIN consortium and its objectives. Next, the human models working subgroup recommended minimum joint-specific medical history and participant-reported descriptive information to be collected, while acknowledging that other research teams would expand upon this minimum dataset in accordance with their own respective study aims, such as for deep phenotyping purposes. The human models working subgroup placed emphasis on minimizing overlap of collected information between the HEAL-CDEs, R-CDEs, and any site-specific discretionary data elements, while also reducing participant burden. Beyond those included in the R-CDE, the human models working subgroup incorporated measures of self-reported and experimental pain, psychosocial and behavioral factors important in chronic pain, as well as knee/TMJ joint pathology with recommendations for specific assessment instruments.

Data curation process

Members of the data coordinating group (DCG) are also part of the Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, which is specifically funded to support various studies part of the NIH HEAL Initiative. DCG members also part of the human models working subgroup helped identify and implement standards, provided guidance on harmonizing data, as well as specifying study, dataset, and variable level metadata for the RE-JOIN Program. The resulting RE-JOIN Data Dictionary governs how data will be collected and harmonized from each domain across the consortium, with

Table 1
RE-JOIN Consortium information.

Joint	Knee	Knee/TMJ	TMJ			
Clinical Site PI	Bella Mehta	Yenisel Cruz-Almeida	Alejandro Almarza	Armen Akopian	Malin Ernberg	Shad B. Smith
Clinical Site	Hospital for Special Surgery, New York, NY	University of Florida, Gainesville, FL	University of Pittsburgh, Pittsburg, PA	University of Texas Health Science, San Antonio TX	Karolinska Institutet, Stockholm	Duke University, Durham, NC
UC2 Contact PI	Anne Marie Malfait	Kyle Allen		Armen Akopian		Christopher Donnelly
UC2 Institution	Rush University Medical Center, Chicago, IL	University of Florida, Gainesville, FL	University of Pittsburgh, Pittsburg, PA	University of Texas Health Science, San Antonio TX	Karolinska Institutet, Stockholm	Duke University, Durham, NC

Fig. 2. The three different human data collection levels across clinical and research settings of the RE-JOIN consortium.

specific focus on structured metadata (e.g., variable format, naming, and coding, and tracking of unique subject identifiers). DCG curators worked with the RE-JOIN researchers to fulfill all SPARC and HEAL standards and to capture experimental information that adds context to the dataset. Data will be uploaded to a secure data sharing platform and will be findable through both the HEAL Platform and the SPARC Portal, where the data will also be accessible. Datasets on SPARC are published in a meaningful way; they are well documented, standardized, semantically annotated, and accompanied by detailed experimental protocols. This puts the dataset in context and encourages reuse, integration, and further collaboration.

Results, considerations, and recommendations for RE-JOIN outcomes

HEAL Common data elements

The RE-JOIN human models working subgroup came to a consensus for collecting the HEAL-CDEs after consideration of patient burden on answering questions when combining the HEAL-CDEs and the R-CDEs, both of which are collected by each clinical research site prior to surgery as the RE-JOIN minimal clinical dataset. Some sites chose to administer longer versions of the HEAL-CDEs as described below. The consensus on the HEAL-CDEs collected by the consortium employing a standardized REDCap are in alignment with the HEAL Core CDEs for Adult Chronic Pain to satisfy the *nine core pain domains*, demographics, and opioid use (Adams et al., 2023; Wandner et al., 2022):

1. Patient **Global Unique IDentifier (GUID)** is unique study subject number used to identify the subject and their corresponding samples within and across study sites.
2. The **Subject Demographics** are a set of demographic questions standardized across all HEAL studies to gain background information on subjects, such as age, sex, gender, race, ethnicity, pain duration, and other socioeconomic factors. For domestic sites, HEAL requires collection of zip code to determine the Rural Urban Commuting Area (RUCA) code. RE-JOIN will utilize a tool created by the HEAL Integrative Management of chronic Pain and Opioid Use Disorder for Whole Recovery (IMPOWR) study to determine the RUCA code (IMPOWR MIRHIQL Data Commons Portal, 2024).
3. The **Pain, Enjoyment, General activity (PEG)** Pain Screening Tool is a brief self-reported questionnaire designed to assess two key domains related to pain: *pain intensity* (P) and *pain interference* with (E) enjoyment of life and (G) general activity. It consists of three items, each scored on a scale from 0 to 10, with higher scores indicating greater severity or interference (Krebs et al., 2009).
4. The **Pain Catastrophizing Scale 6 (PCS-6)** consists of six items that assess the HEAL core domain of *pain catastrophizing* along three dimensions: rumination, magnification, and helplessness. Higher scores reflect higher levels of catastrophic thoughts (Franchignoni et al., 2022; McWilliams et al., 2015).
5. The Patient-Reported Outcomes Measurement Information System **(PROMIS) Physical Function 6b** scale assesses self-reported level of difficulty in carrying out the daily task requiring *physical functioning and its impact on quality of life* through a grading scale of daily living activities. Scores range from 6 to 30 with lower scores indicating more physical impairment (Cella et al., 2010; Reeve et al., 2007).
6. The HEAL core domain of *sleep* is assessed through the **PROMIS Sleep Disturbance 6a** scale. It measures self-reported perceptions of sleep quality, sleep depth, and any difficulties related to sleep in the past 7 days.[11] Scores range from 6 to 30 with higher scores reflecting greater perceived sleep disturbance. HEAL also requires that **Sleep Duration** be collected, which is define as the average amount of sleep the subject received each night, over the last month (Yu et al., 2011).
7. The **Generalized Anxiety Disorder 2 (GAD-2)** is an initial screening tool for the HEAL core domain of *anxiety* and consists of two items that represent core anxiety symptoms. Scores range from 0 to 6, with higher scores indicating greater anxiety symptoms. The GAD-2 has been recommended as a brief screening tool to use in primary care (Delgadillo et al., 2012; Kroenke et al., 2007).
8. The **Patient Health Questionnaire 2 (PHQ-2)** measures the frequency of depressed mood and anhedonia over the past two weeks with scores ranging from 0 to 6. Higher scores indicate greater depressive symptomology to satisfy the HEAL core domain of depression (Kroenke et al., 2003).
9. The **Tobacco, Alcohol, Prescription medications, and other Substance (TAPS)** is used as the HEAL core domain for substance use (SU) screening. This tool consists of four items that asses unhealthy tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year. The tool has been shown to be acceptable to patients and can be self-administered. Cutoff scores for problem use and SU disorder are generated (McNeely et al., 2016).

   Prescription Opioid Use is assessed by employing the HEAL instrument to capture the name, dose, prescription duration, total days exposed and morphine milligram equivalents (MME). MME is expressed in terms of the amount of morphine that would provide equivalent pain relief to a specific dose of another opioid. This standardized measurement is essential for prescribing opioids safely and effectively, as it helps healthcare providers calculate appropriate doses and manage opioid therapy, considering differences in potency and potential side effects among different opioid medications (Common Data Elements (CDEs) Repository | NIH HEAL Initiative, 2024).

RE-JOIN Common data elements (R-CDE)

The human models working subgroup came to consensus on cross-condition measures that should be collected at all sites (Table 2). In addition, all investigators studying knee OA and/or TMJ conditions converged on joint-specific measures that should be collected on all patients within the corresponding conditions (Table 2). Investigators reached consensus on the following measures based on the literature and feasibility of collection at clinical and research sites.

Measures Collected on All Knee and TMJ Subjects:

Table 2

RE-JOIN Domains	RE-JOIN-CDEs
Anthropometric	Height, Weight, Calculated BMI
Pain Severity	Brief Pain Inventory- Pain Severity Subscale
Clinical & Medical History	Charlson Comorbidity Index (CCI)
Pain Location & Descriptors	Joint-specific Homunculus
Quantitative Sensory Testing (QST)	Joint-specific Pressure Pain Thresholds (PPT)

1. The **Brief Pain Inventory (BPI)** short form is a widely used, concise and reliable questionnaire comprised of two subscales designed to assess the interference and severity of pain and its impact on daily functioning (Pain assessment: global use of the Brief Pain Inventory, 2024). This nine-question survey is used by HEAL to assess these two core pain domains for acute pain patients. All RE-JOIN subjects will receive the pain severity subscale of the BPI, while some sites will administer the full BPI short form.
2. **Charleston Comorbidity Index (CCI):** Patient-reported or the electronic medical records will be used to derive the CCI to quantify the burden of comorbid conditions in patients by assigning scores to various medical conditions, providing a comprehensive assessment of overall health status (Charlson et al., 1987). The CCI evaluates the presence of 19 comorbid conditions, each assigned a specific score based on its severity and impact on mortality. Each comorbid condition is assigned a score ranging from 1 to 6, with higher scores indicating greater severity and higher mortality risk. The total CCI score is calculated by summing the individual scores for each comorbidity present in the patient. These conditions include:
   a. Myocardial infarction
   b. Congestive heart failure
   c. Peripheral vascular disease
   d. Cerebrovascular disease
   e. Dementia
   f. Chronic pulmonary disease
   g. Connective tissue disease
   h. Ulcer disease
   i. Mild liver disease
   j. Moderate or severe liver disease
   k. Diabetes mellitus
   l. Hemiplegia or paraplegia
   m. Renal disease
   n. Cancer
   o. Moderate or severe liver disease
   p. Diabetes mellitus
   q. Hemiplegia or paraplegia
   r. Renal disease
   a. Cancer
   b. Metastatic solid tumor
   c. AIDS/HIV
3. RE-JOIN clinical sites will also collect information about pain quality and location using RE-JOIN specific homunculus focused on **anatomical orofacial and lower body sites** (Fig. 3). These areas were chosen based on consensus discussion and the existing literature (Sengupta et al., 2006; Thompson et al., 2009; Wood et al., 2007), as well as to best align the tissue collected during surgery to determine direct pain-pathology relationships. Our working group modified the knee pain homunculus from the NIH-funded Multicenter Osteoarthritis Study (MOST) (Macri et al., 2020). The orofacial pain homunculus was adapted from the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Clinical Protocol and Assessment Instruments (Ohrbach and Durham, 2017). Patients are asked to indicate painful locations on the homunculus and then asked to describe their pain using one or more of the following descriptors: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting, tiring-exhausting, sickening-nauseating, fearful, punishing-cruel (Melzack, 1975).
4. All study sites will administer Quantitative Sensory Testing (QST) evaluated by **pressure pain thresholds** at multiple body sites. For the knee joint, 2 sites on the surgical knee will be evaluated on the medial and lateral knee lines 2 cm from the patella on either side, and center of the patella. For the TMJ, 3 sites on the surgical side of the face will be evaluated (i.e., temporalis, TMJ, masseter). Control sites may be also tested including the ipsilateral tibialis anterior, thenar eminence, and the extensor digitorum (i.e., forearm). If the patient is undergoing bilateral surgery, testing will be conducted on the patient-reported most painful side. Procedures will be demonstrated on a practice test site located between thumb and index finger on the dorsal side of the hand to ensure the participant understands the procedure. For testing on the knee, the participant will be reclined with knees supported by a pillow. A handheld digital pressure algometer (AlgoMed, Medoc, Israel, or Somedic Sales, Sweden) will be applied at a constant rate of 30 kPa/second and the participant will be instructed to press a button when the sensation “first becomes

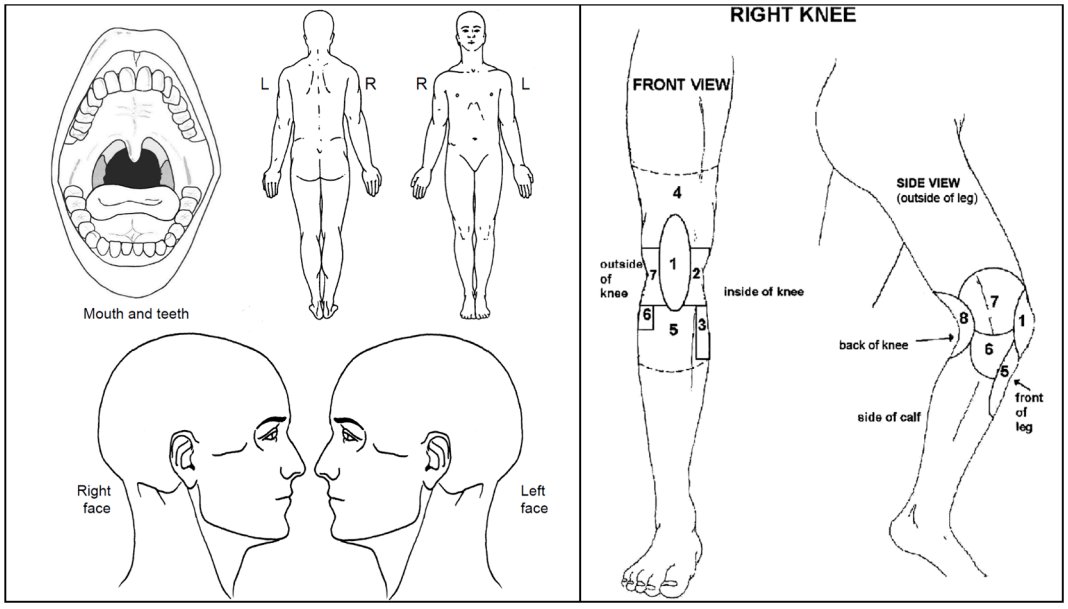

Fig. 3. Homunculus for the RE-JOIN consortium clinical sites.

painful." The amount of pressure (kPa) that first produces a painful sensation will be recorded. The pressure pain threshold procedure will be repeated 3 times for each body site to create an average pressure pain threshold for the site. The maximum pressure for the face is 400 kPa, and 600 kPa for the knee and control sites. If participants do not report pain at the maximum pressure level, the procedure is terminated and a score of 400/600 kPa will be assigned for that trial.

*Knee-Specific Measures (*Table 3*):*

1. **1986 American College of Rheumatology (ACR) Knee Osteoarthritis Classification Criteria:** ACR has established classification criteria for knee OA to aid researchers in assuring consistency and improve communication in reporting knee OA (Altman et al., 1991). All patients with knee OA in the RE-JOIN consortium need to meet at least one of the three ACR criteria for classification of KOA below:
   a. Clinical and Laboratory Criteria
   b. Clinical and Radiographic Criteria
   c. Clinical Criteria
2. The **Knee injury and Osteoarthritis Outcome Score (KOOS)** (Roos and Lohmander, 2003) will be collected across study sites including individuals undergoing knee joint surgery. The KOOS is a widely used self-administered questionnaire specifically designed to assess the outcomes of knee injury and osteoarthritis. It evaluates various dimensions of knee health and function. The KOOS questionnaire covers five main domains related to knee health: Pain, Symptoms, Function in Daily Living (ADL), Function in Sports and Recreation (Sport/Rec), and Knee Related Quality of Life (QOL). Each domain assesses different aspects of knee function and well-being. The KOOS is commonly used in clinical research and practice. Overall, the KOOS provides a comprehensive and patient-centered assessment of knee health and function, allowing healthcare providers to better understand the impact of knee injuries and osteoarthritis on patients' lives and tailor treatment approaches accordingly. The KOOS has been extensively validated and shown to have good reliability, validity, and responsiveness to change over time. It is considered a valuable tool for assessing knee outcomes in both research and clinical settings. Overall, the KOOS provides a comprehensive and patient-centered assessment of knee health and function, allowing healthcare providers to better understand the impact of knee injuries and osteoarthritis on patients' lives and tailor treatment approaches accordingly. The human models working subgroup chose this measure given its relevance to multiple OA models – including younger patients with anterior cruciate ligament injuries and post-traumatic OA, primary OA – as well as to track patients longitudinally in OA or post-arthroplasty. Also, this measure is particularly relevant for RE-JOIN as there is increasing interest to understand early onset of OA and leverage across the study sites employing post-traumatic OA (PTOA) pre-clinical models. While the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is frequently used in studies of knee OA, the KOOS provides data necessary for computing WOMAC pain, stiffness, and function scores, in addition to other relevant subscales (Roos and Toksvig-Larsen, 2003). Accordingly, the implementation of KOOS aligns with the emphasis of the human models working subgroup by reducing patient burden while providing a rich data source (Roos and Lohmander, 2003).
3. Study sites collecting data on individuals undergoing knee surgery will obtain a **Kellgren-Lawrence (KL) score** (Kellgren and Lawrence, 1957), a widely used radiographic disease severity grading system based on the degree of structural damage and joint space narrowing in knee OA through X-ray imaging. The KL score categorizes knee OA into five grades (0 to 4) based on the severity of radiographic changes observed on X-rays. Higher KL grades indicate more severe knee OA, with grade 4 representing the most advanced stage of the disease. The KL score is commonly used in research studies and clinical practice to assess the severity of knee OA, monitor disease progression over time, and guide treatment decisions. While the KL score is valuable for assessing structural changes in knee OA, it may not always correlate well with symptoms or functional limitations experienced by patients. Some individuals may have significant pain and disability despite having a relatively low KL score, while others with higher KL scores may have minimal symptoms.

Table 3

RE-JOIN Domains	Knee-CDEs	TMJ-CDEs
Diagnostic Criteria	1986 American College of Rheumatology (ACR) Knee Osteoarthritis Classification Criteria	Diagnostic Criteria for Temporomandibular Disorder (DC/TMD)
Disease Stage	Kellgren-Lawrence (KL Score)	–
Joint-Specific Pain Limitations	Knee injury and Osteoarthritis Outcome Score (KOOS)	Jaw Functional Limitation Scale (JFLS)

TMJ-Specific Measures:

1. **Diagnostic Criteria for Temporomandibular Disorder (DC/TMD):** The DC/TMD is a diagnostic tool used to assess and diagnose TMDs, (i.e., conditions affecting the TMJ and the muscles of mastication), developed by the International Research DC (RDC)/TMD Consortium Network (Schiffman et al., 2014; Ohrbach and Durham, 2017). It consists of two axes, Axis I used for clinical diagnoses of the most common TMDs and Axis II that assess psychosocial function. Axis I consists of a standardized exam which includes a comprehensive evaluation of various aspects related to TMDs, including confirmation of pain location, evaluation of mandibular range of movements and pain upon movement, TMJ sounds, and pain on palpation of the TMJ and masticatory muscles, and ensures consistency and reliability in diagnosing TMDs using validated criteria. Axis II involves a detailed history of the patient's symptoms, including onset, duration, modification of pain and headache by jaw movements, function or parafunctions, and other instruments that assess pain intensity, pain interference and emotional distress.
2. Given the overlap of the HEAL-CDEs and R-CDEs with most of the Axis II assessments, only the Jaw Functional Limitation Scale will be included across study sites testing individuals undergoing TMJ surgery (Schiffman et al., 2014; Ohrbach and Durham, 2017). The **Jaw Functional Limitation Scale (JFLS)** part of the DC/TMD Axis II is a questionnaire designed to assess the functional limitations experienced by individuals with temporomandibular disorders or other jaw-related conditions by measuring the impact of jaw dysfunction on an individual's ability to perform various activities such as eating, speaking, yawning, opening the mouth wide, and other activities that require jaw movement. The JFLS is commonly used in clinical settings, particularly by oral health professionals and orofacial pain/temporomandibular disorder specialists, to assess the severity of jaw dysfunction and to monitor changes over time. The JFLS is reliable and valid tool for assessing jaw functional limitations (Ohrbach et al., 2008). It is considered a valuable tool for both research and clinical practice by providing a structured approach to assessing the functional impact of jaw disorders on daily activities, helping healthcare providers better understand the patient's experience and tailor appropriate treatment plans.

RE-JOIN discretionary measures (Table 4)

1. The **Patient Global Impression of Change (PGIC)** measures a patient's perceived change of their health condition over a

certain amount of time on a single-item scale ranging from 0 to 7, with higher scores indicating more perceived improvement. Although this is a required HEAL CDE, only clinical study sites following participants longitudinally after surgery will collect this information (Dworkin et al., 2005).

2. **Anatomical pain location, and widespread pain** will be queried by participants marking their painful sites (pain on most days in the past 3 months) on a body manikin divided into 45 sections on the front and on the back (Dragioti et al., 2017; Grimby-Ekman et al., 2015; Margolis et al., 1986). These sections will be calculated and denoted as the number of pain sites (NPS), ranging from 0 to 45. High values indicate higher spreading of pain. Furthermore, anatomical pain sites (APSs) will be defined as pain equally marked on the front and back of the manikin (e.g., knee, shoulder, and arm) or at least on one of them. In addition, our assessment considered, for example, that an upper extremity comprises four anatomical sites according to the distribution of sections on the manikin (i.e., hand, forearm, upper arm, and shoulder). This span of APSs constitutes the most pain possible to experience within an extremity. Hence, we will localize pain to 23 body regions as follows: foot right, foot left, lower leg right, lower leg left, thigh right, thigh left, hand right, hand left, forearm right, forearm left, upper arm right, upper arm left, shoulder right, shoulder left, neck/throat, head right, head left, stomach, chest, gluteal, low back, upper back, and genitals.
3. **Pain History Interview:** In a face-to-face pain history interview, participants will provide details concerning all pain problems that had been present for $>$ 3 months on most days. The interview will be based on previous studies (Cruz-Almeida et al., 2009; Lipat et al., 2023; Valdes-Hernandez et al., 2021). Specific characteristics will be defined for each distinct pain problem regarding pain quality, intensity, temporal characteristics, and previous treatments.
4. **The Chronic Overlapping Pain Conditions Screener (**COPCS): The COPCS is a logic-driven electronic instrument that screens for the 10 COPCS identified by the Institute of Medicine (Relieving Pain in America, 2011). These include fibromyalgia, TMD, chronic low back pain, migraine headache, tension-type headache, myalgic encephalomyelitis/chronic fatigue syndrome, irritable bowel disorder, urologic chronic pelvic pain, vulvodynia, and painful endometriosis. The subject marks all painful areas on body mannequins. Depending on which regions that are marked modules are "triggered" with question for the specific pain conditions (based on published criteria). The COPCS is reported to be valid showing good agreement with diagnostic criteria administered by physician interview (Schrepf et al., 2024).
5. **NIH Low Back Pain Minimal Dataset Questionnaire:** Based on the high prevalence of chronic low back pain around the world, this standardized set of questions developed by the NIH will collect essential information for research and clinical purposes related to low back pain (LBP). The questionnaire aims to gather standardized data on various aspects of low back pain to facilitate research, clinical assessment, and treatment planning. The questionnaire includes questions covering several domains specific to low back pain such as pain intensity (severity and location), pain duration, functional limitations, previous treatments, and impact on quality of life. The NIH Low Back Pain Minimal Dataset Questionnaire is used in both clinical practice and research settings to collect standardized data on LBP (Dutmer et al., 1976). Given the high prevalence of co-occurring LBP in knee OA patients, this data will improve understanding of the impact of LBP on knee pain outcomes and innervation patterns.
6. **Medication Quantification Scale (MQS) Version III:** MQS score will be used to determine classes and doses of medications and is calculated for each medication by taking a consensus-based detriment weight for a given pharmacologic class and multiplying it by a score for dosage (Harden et al., 2005). The calculated values per medication are then summed for a total MQS score. The MQS was developed and validated for clinical and research use and provides a measure of medication usage for any medication regimen.
7. **Utilization of medications and non-pharmacological interventions:** Pain is often self-managed by a variety of interventions with increasing prevalence (Pritchard et al., 2022). Similar to previous work in older individuals (Johnson et al., 2022), we will further assess over the counter medication usage as well as utilization of non-pharmacological interventions.
8. The **Hopkins Verbal Learning Test – Revised (HVLT-R)** is a verbal learning and memory test. The current HVLT-R offers six alternate forms. Each form contains 12 nouns, four words each from one of three semantic categories (e.g., precious gems, articles of clothing, vegetables, etc.), to be learned over the course of three learning trials. Approximately 20–25 min later, a delayed recall trial and a recognition trial are completed. The delayed recall requires free recall of any words remembered. The recognition trial is composed of 24 words, including the 12 target words and 12 false-positives, 6 semantically related, and 6 semantically unrelated (Hopkins Verbal Learning Test–Revised | HVLT-R, 2024). The administration and scoring manual are available through Psychological Assessment Resources (PAR).
9. The **Trail Making Test (TMT)** is a timed, neuropsychological test that involves visual scanning and working memory. The TMT has two parts: the TMT-A (rote memory) and TMT-B (executive functioning). In each test the participant is asked to draw a line between 24 consecutive circles that are randomly arranged on a page. The TMT-A uses all numbers, whereas the TMT-B alternates numbers and letters, requiring the patient to switch between numbers and letters in consecutive order. The TMT is scored by how long it takes to complete the test. The time includes correction of errors prompted by the examiner. If the person cannot complete the test in 5 min, the test is discontinued (Ciolek and Lee, 2019).
10. The **Stroop Color and Word Test** is a neuropsychological test extensively used to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute, well-known as the Stroop Effect. The test booklet and accompanying professional manual acquired from Psychological Assessment Resources (PAR) provides normative information to obtain education-corrected scores (Scarpina and Tagini, 2017).
11. The **F-A-S Test** assesses phonemic verbal fluency by requesting an individual to orally produce words that begin with the letters F, A and S. Individuals are typically given 1 min to name as many words as possible beginning with one of the letters. The procedure is then repeated for the remaining two letters. This is then repeated for categorical fluency requesting the names of as many animals as possible (Patterson, 2011).
12. The **Ruff Figural Fluency Test (RFFT)** will be administered to examine planning strategies, fluid and divergent thinking, and ability to flexibly shift cognitive set in relation to non-verbal fluency. The participants will be asked to draw as many unique designs as possible within 60 s by connecting the dots in different patterns for each of the five parts. The total number of unique designs drawn constitutes the main score (i.e., Total Unique Designs). The Error Ratio score accounts for the number of repetitions of the same pattern drawn by the participants providing a measure of the individual's ability to minimize repetition while maximizing unique productions. The test booklet and accompanying professional manual acquired from Psychological Assessment Resources (PAR) provides normative information to obtain education-corrected values for Total Unique Designs and Error

Ratio scores (Lysne et al., 2019; PAR | RFFT | Ruff Figural Fluency Test, 2024).

13. A measure of **Intermittent and Constant Osteoarthritis (ICOAP)** is an 11-item measure that assesses pain in individuals with hip or knee OA, considering both constant and intermittent pain experiences which differentiates it from the commonly utilized KOOS measure. It was developed as part of a collaboration between the international organizations Osteoarthritis Research Society International (OARSI) and Outcome Measures in Rheumatology (OMERACT), the OARSI-OMERACT collaboration. It captures constant and intermittent pain variability in OA and serve as a tool to track KOA progression and potentially help mitigate the structure symptom discordance in OA (Hawker et al., 2008).
14. **Knee OA Disease Clinical History:** This includes history that would not be captured by the standard patient reported questionnaires described above. These were finalized by consensus and would include questions such as duration of diagnosis, duration of symptoms and duration of pain, OA diagnosis in other joints, history of osteopenia and osteoporosis, injections in the knee which include steroid injections, hyaluronic acid injections or platelet rich plasma injections, history of arthroscopy. Some of the therapies will be available via review of electronic medical records.
15. **Upper Limb Strength:** To determine grip strength, participants are asked to hold a dynamometer (Jamar Plus Hydraulic hand dynamometer; Sammons Preston) in their hand, with the elbow bent at a right angle to the body and the elbow tucked into the side of the body with feet flat on the ground. The handle of the dynamometer will be adjusted to fit hand size with the base resting on the first metacarpal, while the handle rests on the middle of the four fingers. The subject will then squeeze the dynamometer with maximum isometric effort and maintain the contraction for about 5 s before releasing their grip. No other body movement will be allowed. The subject will be strongly encouraged to give a maximum effort. Three trials will be performed on each hand and the average will be recorded as in previous work (Peterson et al., 2023).
16. **Short Physical Performance Battery (SPPB):** The SPPB is a performance-based measure used to assess lower-extremity physical function. Participants will be asked to complete three tasks: (1) a balance task that involves completing a double-footed balance task, a semi-tandem balance task, and a tandem balance task (10 s each); (2) sit to stand task in which the participants have to stand up out of a chair and back to a seated position for five consecutive attempts; and (3) a walking task in which the participants will be timed for a 10-meter walk task at their normal walking speed. These tasks will be scored from 0 to 4, with higher scores representing increasing ability. Scores will be summed for a total performance score ranging from 0 to 12 (Guralnik et al., 1994).
17. **Gait Analysis:** A GAITRite (Cir Systems Inc., Franklin, NJ, USA) will be used to analyze participant spatiotemporal gait performance. Participants will be instructed to complete three trials of walking at their normal pace across the 7-meter-long mat. Walking trials will begin 1.5 m before the start of the mat and end 1.5 m after the mat ends to ensure only steady state walking is analyzed. Spatiotemporal gait performance will be characterized by average gait speed (m/s), stride length (m), step width (cm), swing time (s), double support time (% cycle), and swing time variability (coefficient of variation). Gait parameters will be averaged across legs and trials. Gait speed, stride length, and step width will be normalized for leg length. Coefficient of variation (CV) will be calculated as: 100 x (standard deviation/mean) (Lipat et al., 2022; Lipat et al., 2023; Menz et al., 2004; Ogawa et al., 2020).
18. **painDETECT:** A simple, easy to use screening questionnaire. The questionnaire consists of 9 items and is completed by the patient with no clinical examination is required. There are 7 weighted sensory descriptor items (never to very strongly) and 2 items relating to spatial and temporal pain characteristics. A total score of 19 or more is indicative of more likely neuropathic pain (Freynhagen et al., 2006).
19. **Graded Chronic Pain Scale-Revised (GCPS-R):** GCPS-R identifies persons with chronic pain and grades chronic pain severity (mild, bothersome, high impact chronic pain). Chronic pain has been operationally defined as pain present on at least half the days over 3, 6, or 12 months. High impact chronic pain has been defined by sustained pain-related limitations in work, social and self-care activities. GCPS-R employs 2 simple questions to identify chronic pain and high impact chronic pain (Von Korff et al., 2020).

Quantitative Sensory Testing (QST): An expanded multi-modal standardized QST battery may be administered by some study teams to assess neurophysiological processing of pain. QST can detect alterations in the nervous system processing of sensory information that could be associated with chronic pain and response to treatment (Bordeleau et al., 2024; Cruz-Almeida and Fillingim, 2014). Furthermore, QST is hypothesized to be related to joint innervation. Experts from each of the RE-JOIN sites incorporated tests validated in KOA and TMJ. Efforts were made to balance the feasibility and comprehensiveness of these psychophysical assessments across clinical and research settings. Experimenters will locate body test sites in relation to the appropriate bone landmarks and will mark each body site while avoiding drawing on open wounds or on top of existing scars. As experimenters palpate and draw each body site, participants will be asked to rate their pain at each body site right now on a scale of 0–100 (where 0 is no pain and 100 is the most pain imaginable), and pain ratings will be recorded. All testing will occur on the surgical knee. The thenar eminence located between the thumb and index finger will be used to practice and demonstrate each stimulus to the participant. For the TMD participants testing will be done on the TMJ, the temporalis and masseter muscles of the surgical side, or of the most painful side if surgery is bilateral. Skin temperature will also be recorded at all body sites before performing any procedures. The standardized battery (Table 5) is based on prior work (Cruz-Almeida et al., 2013; Cruz-Almeida et al., 2014; Johnson et al., 2021; Rolke et al., 2006; Wilson et al., 2022) and includes:

- **Dynamic and Static Mechanical Allodynia:** Participants are asked whether they feel numb, tingling, hot & cold pain, tenderness around their knee. If they respond yes, then testing is performed using a calibrated SENSELab Brush-05 and a nylon Semmes–Weinstein monofilament with 100 g of force (Touch TestTM Sensory Evaluator; North Coast Medical, Inc., Morgan Hill, CA), respectively. Dynamic mechanical allodynia will be tested by the experimenter bringing the brush in contact with the skin and a 1-second-long stroke moving the brush 40 mm until the brush filaments slightly bend, after which the brush is lifted. Static mechanical allodynia will be tested by the experimenter holding the handle of the von frey monofilament parallel to the skin and applying the monofilament at a 90-degree angle to skin. The experimenter will press the monofilament slowly down until it bends, and then hold for 1–2 s and remove it the same way it was applied. The experimenter will repeat these procedures enough times to cover the areas reported. Participants will be asked each time how painful it feels on a scale from 0 to 100 where 0 is no pain and 100 is the worst pain imaginable.
- **Vibratory Detection Thresholds (VDTs):** A handheld VSA-3000 circular probe with a 1.22 cm2 circular probe (Medoc Ltd, Ramat Yishai, Israel) will be used to measure VDT for a 100 Hz stimulus frequency at all body sites. Vibratory sensations will begin at 0 μm

Table 4

REJOIN Domains	Measure	Joint	Study Location
Self-reported Improvement with Treatment	Patient Global Impression of Change (PGIC)	All	HSS, KI, UF
Clinical Pain Characteristics	Pain History Interview	All	HSS, Pittsburgh, UF
Clinical Disease History	Knee OA Disease Clinical History	Knee	HSS, UF
Clinical Pain Characteristics	Anatomical pain location, Widespread pain	All	HSS, Pittsburgh, UF
Clinical Pain Characteristics	Intermittent and constant pain score (ICOAP)	Knee	HSS
Overlapping Pain Conditions	Chronic Overlapping Pain Conditions Screener (COPCS)	All	Duke, KI, Pittsburgh, UF
Low Back Bain	NIH Low Back Pain Dataset Questionnaire	All	Pittsburgh, UF
Pain Interference	Brief Pain Inventory- Pain Interference Subscale	All	Pittsburgh, UF
Drug Class Equivalency	Medication Quantification Scale (MQS)	All	HSS, Pittsburgh, UF
Other Treatments	Medications including over the counter medications and non-pharmacological interventions	All	Pittsburgh, UF
Performance-Based Physical Function	Upper Limb Strength Short Physical Performance Battery (SPPB) GAITRite	Knee	UF
Performance-Based Cognitive Function	Hopkins Verbal Learning Test – Revised (HVLT-R) Trail Making Test (TMT) F-A-S Test Stroop Color and Word Test Ruff Figural Fluency Test	All	Pittsburgh, UF
Neuropathic Pain Screening	painDETECT	All	UF
Pain Impact	Graded Chronic Pain Scale-Revised (GCPS-R)	All	Pittsburgh, UF
Experimental Pain	Quantitative Sensory Testing (QST)	All	KI, Pittsburgh, UF

Table 5

RE-JOIN QST Domains	Category	Joint	Study Location
Pressure Pain Thresholds	R-CDE	All	Duke, HSS, KI, Pittsburgh, UF
Dynamic and Static Mechanical Allodynia	Discretionary	All	Pittsburgh, UF
Vibratory Detection Thresholds	Discretionary	All	Pittsburgh, UF
Thermal Detection and Pain Thresholds	Discretionary	All	KI, Pittsburgh, UF
Pinprick Pain Detection	Discretionary	All	KI, Pittsburgh, UF
Mechanical Temporal Summation	Discretionary	All	KI, Pittsburgh, UF
Conditioned Pain Modulation	Discretionary	TMJ	KI, UF

and will be increased at 0.5 μm/second until a maximum of 130 μm is reached. Each participant will indicate when s/he first feels a vibratory sensation, and this value will be recorded. This procedure will be conducted 3 times at each site and averaged.

- **Thermal Detection and Pain Thresholds:** A thermode (0.4 cm^2 stimulation surface at UF, Pitt; 9 cm^2 stimulation surface at KI) will be applied to all body sites (TCS-2, QSTLabs, France, or Medoc Pathway, Israel). The thermode temperature starts at 32 °C and either gradually decreases (i.e., cold detection) or increases (i.e., warmth detection) at a rate of 1 °C/second until the participant states the stimulus is first perceived as cold or warm, respectively. This procedure will be repeated until the participant reports the stimulus as first painful (i.e., cold pain threshold and heat pain threshold) with a cutoff value of 0 °C for cold pain threshold and 50 °C for heat pain threshold. Participants will be asked to rate the pain intensity of each cold and heat pain threshold trial on a 0–100 numerical rating scale (NRS), where 0 represents "no pain" and 100 represents "the worst pain imaginable." The thermal detection and pain procedures will each be repeated 3 times for both cold and warmth at each site and the average will be obtained for each test.
- **Pinprick Pain Detection:** A sterile standardized Neurotip will be applied to body sites and the patient is asked to report whether they feel the sensation, and if so, whether it feels sharp or dull. Pinprick Pain Detection test helps to assess the presence, quality, and localization of pain sensation and can identify abnormalities in peripheral nerve function, such as neuropathy or nerve damage, which may manifest as altered or reduced sensitivity to pinprick stimuli.
- **Mechanical Temporal Summation:** A calibrated nylon Semmes–Weinstein monofilament with 300 g of force (Touch TestTM Sensory Evaluator; North Coast Medical, Inc., Morgan Hill, CA) will be applied to each anatomical site in a randomized order. First, the single stimulus will be delivered, and participants will rate the pain intensity using the 0–100 NRS. Next, a series of 10 punctate stimuli will be administered twice at a rate of one contact per second and participants will verbally rate the highest pain intensity. The single pain intensity ratings will be subtracted from the series of 10 pain rating at each anatomical site to provide a measure of pain facilitation.
- **Conditioned Pain Modulation:** The subject immerses the non-dominant hand in a container with water at 8 °C for 60 s. Thirty seconds after immersing the hand in the water bath and immediately after removal of the hand from it, the subject rates the pain intensity on a 0 "no pain" to 100 "worst pain imaginable" Numerical Rating Scale. The maximum recalled pain intensity during hand immersion is also assessed. The pressure pain threshold (PPT) of the volar side of the forearm (dominant side) is used as test stimulus. The PPT is recorded before and immediately after removal of the hand from the water bath. In each evaluation, PPT is determined as the arithmetic mean of three consecutive measurements. The absolute (kPa/s) and percent (%) differences between PPT values before and after hand immersion are calculated. Negative values indicate an increased PPT or reduced experimental pain sensitivity.

RE-JOIN data organization and harmonization

Each RE-JOIN study site is currently focused on collecting and coding data to be submitted as standardized metadata and study data to the DCG for publication on the SPARC Portal once studies are completed. The DCG will continue to work with the HEAL Initiative Data ecosystem to link study level information across the platforms and is in the process of working with the HEAL Initiative Data ecosystem on linking variable level metadata with an initial focus on the HEAL CDEs (About the HEAL Data Ecosystem | NIH HEAL Initiative, 2024; HEAL Data Stewardship Group | HEAL Data Stewards, 2024). Several of the RE-JOIN research teams met frequently with members of the DCG to develop their electronic databases. Specifically, the RE-JOIN research teams chose to use the Research Electronic Data Capture (REDCap) system to collect clinical data for several key reasons: 1) the REDCap platform can collect variable level metadata in a secure, robust way to maximize data integrity; 2) ubiquity and accessibility of the REDCap platform to researchers optimizes and facilitates harmonizing variable level metadata, by providing out of the box features to re-use the data dictionary across all sites; 3) REDCap is approved for collection and storing protected health information (PHI) by our institutions and approved by our human subjects protections committees (Institutional Review Boards, IRBs) allowing for secure subject data collection and tracking and providing built-in tools to export limited or anonymized data; 4) REDCap is well-suited to distribute surveys to human subjects both in-person electronically via iPads or computers and remotely, which both streamlines and maximizes data collection (About the HEAL Data Ecosystem | NIH HEAL Initiative, 2024; HEAL Data Stewardship Group | HEAL Data Stewards,

2024). Taken together, these integral steps allow for the development and curation of a rich and accessible data set that can be used to inform research and clinical care beyond the initial RE-JOIN consortium.

RE-JOIN data portal

The efforts outlined here between the study DCG and RE-JOIN study teams supports the future integration of clinical and biobehavioral phenotypic data with data acquired from the tissues and structures of the TMJ and knee joints, resulting in a unique data environment. Through this process, data informatics will provide seamless data integration within and across RE-JOIN study sites to achieve the goals of the consortium. While in the early stages of this process, our combined efforts have laid a solid foundation for data integrity and sharing to provide a rich resource to the scientific and clinical community.

RE-JOIN accompanying documentation

HEAL's annotated case report forms, SPARC metadata specification files and sample datasets exemplifying the data standards were made available to all research groups to use and modify to serve the needs of their studies. This resulted in harmonized data collection methods. The DCG also provided guides for data standards and accompanying documentation. NIH HEAL Initiative grant requirements dictate that all studies be FAIR, and this is a priority for the RE-JOIN Consortium with creation of shared code (in SAS and R programs) that are used to clean and check datasets to ensure their quality.

Discussion

The collaborative team efforts within RE-JOIN's human working subgroup members led to the creation of the RE-JOIN-Common Data Elements (R-CDE), the discretionary domain-specific data collection recommendations, standardized operating procedures (SOPs) for data collection and reporting, data standards for aligned data elements, and the RE-JOIN Data Portal for collaborative research endeavors. The successful implementation of these initiatives across national and international research units and clinical environments required substantial input, coordination, collaboration, and cooperation among members of the human working subgroup, RE-JOIN Consortium leaders and administrators, and the NIH. These recommendations complement the CDEs mandated for all NIH HEAL-funded studies and will streamline the integration of demographic and pain-related data from participants across various RE-JOIN clinical study sites. Because we established and implemented RE-JOIN's minimal clinical datasets or the R-CDE at the onset of our studies, prior to clinical and pre-clinical data collection, these datasets will be obtained for all subjects enrolled as part of RE-JOIN clinical studies across sites. By integrating data from harmonized measures, data analyses will become more efficient due to larger sample sizes, while pooling participant data from diverse sites enhances the generalizability of findings. Furthermore, the current work will allow for the development of collaborative research proposals for integrated analyses of RE-JOIN data, leveraging the unique structure of the consortium studies and their datasets to advance precision pain medicine and translational pain science. Together, RE-JOIN's clinical datasets will set the stage for integrated, cross-study analyses that will reveal commonalities and differences in pain presentation profiles of patients with various types of joint disease.

Outcome measure harmonization across various clinical data domains within the RE-JOIN Consortium serves to achieve multiple objectives. By conducting pooled analyses of demographic and descriptive data from the R-CDE, it becomes possible to characterize patient phenotypes and identify subgroups for two distinct and highly heterogeneous pain conditions—namely, TMJ and knee OA. Additionally, utilizing data from discretionary domain-specific recommendations, along with deep phenotyping of a subset of study participants including joint pathophysiology enables the examination and exploration of additional biobehavioral measures that characterize each condition and have the potential to predict future outcomes. The harmonized phenotypic information obtained will significantly enhance our understanding of the neurobiology of the pain-pathology relationships in humans, providing valuable insights for comparison with pre-clinical models. For example, RE-JOIN investigators will use the latest neuroscience methodologies including microscopy, immunohistochemistry, tracing studies, electrophysiology, molecular and genetic techniques, as well as functional and behavioral studies to map the origin and termination, structure and function of nerve fibers innervating the human joint tissues. However, a noteworthy limitation of the RE-JOIN Consortium is that patient representatives were not intentionally included as part of the research teams. The inclusion of patients as research stakeholders is a broadly recognized domain of research since patient impact is the ultimate goal of the research.

Future work for the RE-JOIN Consortium includes publishing more detailed guidelines for the collection and use of clinical data standards, and their integration with large amounts of mechanistic pathophysiological and histological data obtained from the corresponding human tissues. In addition, ongoing harmonization efforts between the human working subgroup and RE-JOIN's preclinical researchers in joint-focused working groups will identify experimental paradigms that translate between human and preclinical studies. Together, these efforts will enable in-depth, cross-species analysis of the molecular and cellular changes that take place in articular and *peri*-articular tissues at various stages of joint disease, and how these changes may impact clinical pain presentation. Ultimately, the concerted and collaborative efforts among national and international preclinical and clinical translational scientists, as well as patients, will significantly advance our understanding of these conditions, while also advancing efforts of truly *trans*-disciplinary translational team science approaches in these complex pain conditions.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RE-JOIN Consortium investigators reports financial support was provided by National Institutes of Health. Yenisel Cruz-Almeida reports a relationship with Journal of Pain that includes: board membership and consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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