Focus Article

NIH’s Helping to End Addiction Long-termSM Initiative (NIH HEAL Initiative) Clinical Pain Management Common Data Element Program

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Abstract: The Helping to End Addiction Long-term Initiative (NIH HEAL Initiative) is an aggressive trans-NIH effort to speed solutions to stem the national opioid public health crisis, including through improved pain management. Toward this end, the NIH HEAL Initiative launched a common data element (CDE) program to ensure that NIH-funded clinical pain research studies would collect data in a standardized way. NIH HEAL Initiative staff launched a process to determine which pain-related core domains should be assessed by every clinical pain study and what questionnaires are required to ensure that the data is collected uniformly. The process involved multiple literature reviews, and consultation with experts inside and outside of NIH and the investigators conducting studies funded by the initiative. Ultimately, 9 core pain domains, and questionnaires to measure them, were chosen for studies examining acute pain and chronic pain in adults and pediatric populations. These were augmented with dozens of study-specific supplemental questionnaires to enable uniform data collection methods of outcomes outside of the core domains. The selection of core domains will ensure that valuable clinical pain data generated by the initiative is standardized, useable for secondary data analysis, and useful for guiding future research, clinical practice decisions, and policymaking.

Perspective: The NIH HEAL Initiative launched a common data element program to ensure that NIH-funded clinical pain research studies would collect data in a standardized way. Nine core pain domains and questionnaires to measure them were chosen for studies examining acute pain and chronic pain in adults and pediatric populations.

Key Words: HEAL, Pain, Data, Harmonization, Patient Reported Outcomes.

The opioid and pain crises are embedded in the United States, with 1.6 million Americans living with opioid use disorder and over 81,000 drug overdose deaths occurring in the United States in the 12 months ending in May 2020. Over 50 million Americans experience chronic pain, and half of those suffer from chronic pain daily, with the prevalence of chronic pain among adults increasing from 11.2% in 2012 to 20.4% in 2019. Opioids are widely used to treat acute and chronic pain, but overprescribing and a lack of more effective strategies contribute to misuse. Congress added $500 million to the NIH’s annual base appropriation,
beginning in 2018, to generate scientific solutions to the opioid and pain public health crises.51 The result was the Helping to End Addiction Long-term Initiative, or NIH HEAL Initiative, which has funded over 500 research projects nationwide.

NIH took steps to maximize the value of data collected through NIH HEAL initiative studies, including by mandating rapid public access to findings through a unified public access and data sharing policy.55 Given the urgency of the crises, rapid dissemination of publications and the availability of the primary data promotes knowledge, facilitates reproducibility, and enables researchers to build upon the research to make new discoveries.55 The NIH HEAL Initiative also required that data be findable, accessible, interoperable, and reusable (FAIR) for future novel research, and to this end, NIH supports investigators in the coordination and management of data.55

All applicants for NIH HEAL Initiative funding must submit a Public Access and Data Sharing Plan that details how data will be made publicly available. The initiative is developing a cloud-based-platform that will connect to HEAL-generated data stored in various secured repositories and provide a web interface for searching and analyzing NIH HEAL Initiative results and data.56 To facilitate cross-study comparisons and improve the interpretability of findings, clinical pain grantees collaborate and agree to use common data elements for patient-reported outcomes (PROs). The HEAL common data element (CDE) program is 1 way that NIH is working to achieve the NIH Data Sharing Policy. Pain management experts who have conducted clinical trials and have experience with large datasets advised NIH that it would be easier to ensure HEAL clinical pain data is entered correctly, compatible datasets advised NIH that it would be easier to ensure knowledge, facilitates reproducibility, and enables researchers to build upon the research to make new discoveries.55

The CDE team consisted of NIH program staff from the National Institute of Neurological Disorders and Stroke, Office of Pain Policy and Planning; National Center for Advancing Translational Science, and other institutes that make up the NIH Pain Consortium. The Data Coordinating Center (DCC) at University of Utah assisted with developing the standardized case report forms and CDE detail forms. Throughout the process, HEAL investigators and other clinical pain research experts were asked to provide feedback on the pain domains and questionnaires under consideration.

Materials and Methods

Strategy

The following subsections describe the key steps used to generate core CDEs for PROs to be used by HEAL clinical pain researchers. The general strategy entailed identifying pain domains of interest that were accepted, relevant and feasible to be used in all NIH HEAL initiative clinical pain trials. Consulting the scientific literature, as well as expert groups and stakeholders, a set of PRO measures that would assess the domains were selected. Once finalized, standardized case report forms and CDE detail forms were generated to ensure trial data would be collected uniformly.

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Identifying Pain Domains

A literature review was conducted by NIH staff to identify pain domains that should be assessed within a clinical pain trial. Literature searches were conducted to find articles that discuss pain domains assessed in clinical trials (eg, PubMed, APA PsychInfo, Google Scholar) and to find the most commonly used questionnaires in clinical pain trials to determine which domains have been assessed in previous studies.2, 10, 15-18, 21, 37, 46, 60, 68, 70-72 Some of the most relevant journal articles were written by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a group whose mission is “to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain.”47 NIH staff also reviewed books (eg, Handbook of Pain Assessment73) and standardized U.S. government treatment manuals13, 39, 47 to find frequently used questionnaires and domains. Based on the first review of the literature, 35 pain domains were selected for an initial list.

After these pain domains were selected, NIH program staff began a process to reduce the total number to generate a final list of domains that would be feasible for evaluation in all NIH HEAL Initiative clinical studies. Staff again read the journal articles, IMMPACT articles, books, and government documents that discussed pain domains in clinical pain trials and identified the domains from the initial list that were most frequently cited. As a result of the second review, domains were rank-ordered based on that frequency and the most cited domains were prioritized.
NIH program staff considered the spectrum of HEAL clinical pain research grants and discussed which domains could feasibly be assessed in all HEAL studies. For example, an adverse events domain was considered, but given that the definition of adverse events could vary so greatly across studies, developing consistent questions to help shape a CDE would be difficult. A domain to capture socioeconomic factors was also considered unfeasible due to time and resource burdens that may have imposed on studies and their participants.

Based on these considerations, pain domains that were not widely cited, or could not be realistically assessed in all HEAL clinical pain studies were removed from consideration. NIH program staff merged 2 domains (physical functioning and quality of life) to assess a broader pain domain concept. After considering those criteria, the number of pain domains was reduced to 9.

In addition to the core pain domains, the CDE team selected core demographic domains and variables for each HEAL clinical pain management study to collect. The demographics selected were based on guidance from NIH,5, 6 the Office of Personnel Management,74 and the Clinical Data Interchange Standards Consortium (CDISC),5, 6 a non-profit organization whose standards are required by regulators including the U.S. Food and Drug Administration (FDA).

The core demographic data that must be collected are: date of birth; age; sex at birth; gender identity; ethnicity; race; the highest level of education; employment status; relationship status; annual household income; whether the participant has applied for disability insurance; and pain duration.

NIH HEAL Initiative clinical pain studies also must monitor opioid use (including dosage) by appropriate PROs, electronic health records, or other measures that can capture opioid use at multiple time points.

After the initial selection process, the HEAL CDE team solicited feedback from members of IMMPACT. The group agreed with the list of pain domains the NIH program staff selected and did not recommend adding or removing any domains from the list.

### Identifying PROs

To identify pain questionnaires that would be appropriate for the identified pain domains, a similar process, as discussed in the Identifying Pain Domains section, was undertaken.

NIH staff conducted a literature review to identify the PRO measures that would satisfy the identified pain domains. This review began after the number of pain domains had been reduced to 9. This initial search identified 94 potential questionnaires, of which 23 were excluded because they did not assess 1 of the 9 chosen domains.

NIH program staff familiar with the questionnaires identified in the literature search provided input regarding how the proposed questionnaires have been used and/or validated, and whether the questionnaires have been validated within pain patient populations.

NIH staff prioritized questionnaires that were most frequently used in pain clinical trials and were validated, questionnaires that had been validated within pain patient populations and across pain conditions, and questionnaires that were most frequently used within the field of clinical pain management (eg, the most common sleep, depression, anxiety measures). This included prioritizing questionnaires and/or versions of questionnaires that had fewer questions to minimize the burden on investigators and study participants. To this end, questionnaires that could satisfy multiple pain domains were also prioritized. As a result of this process, the HEAL CDE program identified 9 questionnaires to be included as core CDE measures.

The questionnaires were provided to IMMPACT for review. IMMPACT generally agreed with the questionnaires that were selected but recommended that 2 questionnaires—the 8-item Patient Health Questionnaire (PHQ-8) depression scale and the 7-item General Anxiety Disorder (GAD-7) questionnaire—be replaced with less time-consuming questionnaires that each have 2 items, the PHQ-2 and GAD-2. IMMPACT also advised selecting questionnaires that can assess the effectiveness of pain interventions by demonstrating treatment differences over time in individuals as opposed to differences between treatment groups; therefore, priority was assigned to questionnaires that can detect changes longitudinally. NIH program staff reviewed IMMPACT’s feedback, accepted most of its questionnaire recommendations, and then finalized the core questionnaire battery.

### Reanalysis and Finalization of Pain Domains and PROs

NIH program staff presented the core CDEs at the initial meetings for each of the HEAL and HEAL-related clinical pain programs: the Effectiveness Research Network (ERN), Pragmatic Studies for Pain Management Without Opioids (PRISM), the Back Pain Consortium (BACPAC), Hemodialysis Opioid Prescription Effort consortium (HOPE), Early Phase Pain Investigation Clinical Network (EPPIC-Net), the NIH Common Fund Acute to Chronic Pain Signatures (A2CPS) program, and the biomarker research program. In the future, any new clinical pain management programs that are developed will also be required to use the core and supplemental CDEs and measures. After each of the initial HEAL meetings, principal investigators from the studies in these networks met with the HEAL CDE team to discuss the selected questionnaires and requested that some changes be made to the core CDEs. Several of those recommended changes were considered and approved by the HEAL CDE team.

The HEAL CDE team worked with HEAL clinical pain investigators to integrate their recommendations into the list of core questionnaires, accounting for the input from all investigators, and the criteria described above (Section: Identifying PROs). In general, HEAL investigators agreed with the selected pain domains and did not
recommend any modifications to the pain domains themselves. However, they recommended that CDEs for chronic pain and acute pain, respectively, be organized as separate cores, and that a separate set of core CDEs be created for pediatric studies. The HEAL investigators provided literature to justify these changes, which the HEAL CDE program implemented, when possible.1, 3, 4, 22, 23, 25, 26, 28, 30-32, 34, 36, 41, 43, 61, 64-66, 69, 75, 76, 79

The core adult chronic and acute pain CDEs mostly rely on the same questionnaires, but HEAL investigators recommended using a different questionnaire in chronic pain studies than in acute pain studies for assessing pain intensity and pain interference. The investigators noted that the Pain, Enjoyment of Life and General Activity (PEG) scale, which assesses adult pain intensity and pain interference, is a brief and validated questionnaire but has only been validated in chronic pain studies. Therefore, for the acute pain core CDEs, the Brief Pain Inventory questionnaires for pain severity and pain interference are used for the pain intensity and pain interference domains, respectively. Similarly, investigators also recommended briefer versions of some questionnaires and provided literature to justify changes. Both of those requests were reviewed and approved by NIH program staff.

Some HEAL investigators suggested alternate questionnaires to measure the 9 pain domains and provided literature to support that request. The CDE team again reviewed the literature and contacted experts in the field to consider switching from a validated PRO measure to the Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire. Ultimately, 2 PROMIS questionnaires were added to the core CDEs with the addition of a question from a validated sleep questionnaire, the Pittsburgh Sleep Quality Index (PSQI). Where possible, questionnaires were selected that could be used across a patient’s life span.

Investigators working with pediatric populations agreed with the pain domains that were selected but noted that some of the adult questionnaires have not been validated in children. The HEAL CDE team met with HEAL’s pediatric investigators to confirm that domains were appropriate and to identify evidence-based questionnaires that have been validated in both pediatric and adult populations. The HEAL CDE team and the pediatric investigators conducted a literature review to identify appropriate pediatric questionnaires.8, 9, 11, 14, 20, 24, 33, 35, 38, 42, 44, 45, 49, 77

The HEAL CDE team and HEAL’s pediatric pain researchers prioritized ensuring that questionnaires for parents and children had been validated, rather than the overall number of questions within the core CDEs. Thus, thanks to the input of the pediatric investigators, a separate set of questionnaires was identified for pediatric populations.

Core CDEs were finalized by the HEAL CDE team after reviewing all of the information gathered from several rounds of review from the investigators and other experts in the field (Table 1).

### Creation of Standardized Case Report Forms and Common Data Element Details

Standardized case report forms, or CRFs, and CDE details for the chosen core and supplemental questionnaires were created. The goal was to make the original CRF of the PRO publicly available. Because in some instances investigators were using CRFs for the same questionnaires that had slight variations in wording

| Table 1. Final selection of pain domains and patient-reported outcome (PRO) questionnaires for acute and chronic pain for adults and pediatric patients. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **PAIN DOMAIN**                | **PRO QUESTIONNAIRE**           | **ADULT ACUTE PAIN**            | **ADULT CHRONIC PAIN**          | **PEDIATRIC ACUTE AND CHRONIC PAIN** |
| Pain Intensity                 | BPI Pain Severity                | PEG                             | BPI Pain Severity               |
| Pain Interference              | BPI Pain Interference            | PEG                             | BPI Pain Interference           |
| Physical Functioning/QOL      | PROMIS Physical Functioning      | PROMIS Physical Functioning     | PedsQL Inventory                |
|                               | Short Form 6b                   | Short Form 6b                   |                                 |
| Sleep                         | PROMIS Sleep Disturbance         | PROMIS Sleep Disturbance        | AWS + Sleep Duration Items      |
|                               | 6a + Sleep Duration Question     | 6a + Sleep Duration Question     |                                 |
| Pain Catastrophizing           | Pain Catastrophizing Scale - Short Form 6 | Pain Catastrophizing Scale - Short Form 6 | Pain Catastrophizing Scale for Children |
| Depression                    | PHQ-2                           | PHQ-2                           | For parent: Pain Catastrophizing Scale PHQ-2 (child and parent) |
| Anxiety                       | GAD-2                           | GAD-2                           | GAD-2 (child and parent)        |
| Global Satisfaction with Treatment | PGIC                           | PGIC                           | PGIC                            |
| Substance Use Screener        | TAPS 1                          | TAPS 1                          | NIDA Modified Assist Tool - 2   |

*Pediatric studies will require the child, and in some cases the parent, to complete questionnaires.
from the original questionnaires, it was important that the HEAL CDE team, with support from the Utah DCC, generate standardized CRFs to ensure that domains would be assessed and results recorded uniformly across studies. Each CRF explains how to score responses or calculate a summary score for multiple questions. Each CRF was also formatted to meet accessibility standards under Section 508 of the Rehabilitation Act of 1973 (29 U.S.C § 794 (d)), which “require[s] Federal agencies to make their electronic and information technology (EIT) accessible to people with disabilities.” NIH HEAL Initiative investigators will have access to non-copyrighted supplemental questionnaires before finalizing their measures. For questionnaires that are copyrighted, the initiative will provide instructions for obtaining access.

For each CRF, a CDE detail form was also created. CDE details allow defined variables, standardized variable names and coding, and, when appropriate, links to standards developed by CDISC. Providing CDE details, which will be used to code datasets for HEAL studies, at the beginning of the NIH HEAL Initiative enables harmonization of all HEAL clinical pain research data. The CRF and CDE details associated with the core questionnaires and core demographic questionnaires were the first to be created. As investigators submitted supplemental questionnaires, associated materials (ie, 508 compliant CRFs and CDE detail documents) were created. Demographic CDE details were made CDISC compliant to the extent possible. The CDE team consulted with multiple DCCs to create the demographic CDE details. It was decided that the core and supplemental questionnaires other than the demographics would not be made CDISC compliant. If an investigator needs the variables to be CDISC compliant, they and/or the program DCCs supporting different HEAL studies are responsible for making them so. For each questionnaire, the HEAL CDE team determined licensing information for a questionnaire. HEAL Investigators may request access to NIH's secure cloud storage where non-copyrighted CRFs and CDE details are posted. If a questionnaire is copyrighted and requires a license to be purchased for use, investigators are provided with instructions for how to access the questionnaires within the same website. Spanish-language versions of core CRFs and selected supplemental CRFs are also available.

Discussion

As part of the years-long, government-wide effort to address the national opioid epidemic and address the needs of millions of people with chronic and disabling pain, Congress tasked the NIH, in the words of NIH Director Dr. Francis Collins upon the launch of the NIH HEAL Initiative, with “bringing the full power of the biomedical research enterprise to bear” on these crises.

To do so, lawmakers nearly doubled the funding for research on opioid use disorder and pain, providing $1.1 billion in fiscal year 2018, when the initiative was launched. Given that unprecedented investment and the trust placed in NIH to find solutions for patients and their families, it is essential that the data generated by NIH HEAL Initiative studies be used for the maximum benefit.

The HEAL CDE program is meant to ensure that this happens for the initiative's clinical pain research studies. In close collaboration with researchers and experts inside and outside of NIH, we identified crucial pain domains and selected appropriate questionnaires to assess these pain domains. Stakeholders in the pain research community, particularly the investigators conducting research funded by HEAL, were consulted frequently before the core pain domains and questionnaires were finalized. We set up the necessary infrastructure to harmonize the data collected in these domains to maximize usability beyond the initial HEAL studies.

HEAL clinical pain research investigators are required to use the core CDEs as they conduct their studies and create their datasets. This is the first time the pain research community is being asked to assess 9 core pain domains using the same questionnaires. Since pain is a biological, psychological and social experience, the selected pain domains and questionnaires capture data that are biopsychosocial in nature, to better understand the pain experience of the patients participating in HEAL studies. It is also the first time NIH has standardized the coding of variables for these domains. A core set of domains and questionnaires, with standardized supplemental questionnaires for individual studies, will make it easier to consistently code and harmonize data across studies in a way that is cost-effective and efficient, and provides rapid access to data.

In addition to the core CDEs, HEAL has identified hundreds of potential supplemental questionnaires that may be used depending on a study's subject matter. Investigators also will be asked to submit supplemental questionnaires that they plan to use and that are not already available within the HEAL CDE initiative, to ensure there can be uniform collection of data that ensures compatibility across studies as the field considers unique or innovative research questions. These steps will guarantee that data are preserved in a way that will allow future investigators to access and use them for secondary data analysis.

Increasingly, NIH has recognized the value of providing high-quality scientific data for use beyond their initial purpose. According to the Final NIH Policy for Data Management and Sharing that will go into effect in January 2023, sharing scientific data can accelerate research “in part, by enabling validation of research results, providing accessibility to high value datasets, and promoting data reuse for future research studies”.

Further, NIH believes that sharing data "encourages diversity of analysis and opinion, promotes new research," makes it possible to test new methods of analysis, and can help educate new researchers. The NIH encourages the use of CDEs in part to create "opportunities for comparison or combination of data from multiple studies". Secondary data analysis is used to compare interventions across studies or lend statistical power to subgroup analysis to help find solutions for
minority populations, rare disease patients, or others who are typically underrepresented in research. For example, secondary data analyses have been used to compare outcomes by sex and/or gender to inform more precise treatment guidelines, such as guidelines for blood pressure control.29

To maximize utility and return on investment, NIH is committed to making data generated from HEAL findable, accessible, interoperable, and reusable, or FAIR. In this article we described the process whereby NIH HEAL Initiative staff curated standardized CRFs and CDEs to facilitate the generation of FAIR data by HEAL investigators. The FAIR principles were designed to guide stakeholders on the data-management practices necessary to maximize the utility of scientific data.78

The NIH HEAL Initiative will provide web-based access to clinical pain CRFs and CDE details that can be utilized to conduct secondary analyses. The data will also be linked to the National Library of Medicine’s CDE repository. As the HEAL core pain domains were selected to address biological, psychological, and social factors, the diversity of clinical pain data being collected by HEAL investigators will enable future investigators to conduct secondary data analyses that are biopsychosocial in nature. As a result, this would be the first time secondary data analyses could be conducted to compare biopsychosocial outcomes across a variety of pain management treatment (eg, behavioral interventional strategies, therapeutic devices, medications, and injections).

The CDE program will ultimately have implications for preclinical and translational research, clinical practice, and public policy. It also may encourage clinical pain studies outside of HEAL to adopt the core CDEs. Clinical studies generally build on preclinical observations, however, translation of preclinical findings to novel analgesics or pain treatment strategies is a challenge.40 As other researchers have argued,63 1 potential reason for the lack of translational success in the field of pain is the reliance on lab animals for preclinical data that informs whether an experimental therapy moves into clinical trials. The existence of a large, open-source dataset thanks to the harmonized data from across HEAL-funded pain studies and beyond should make it easier to source this kind of preclinical information from existing human data.

Additionally, the subjective nature of pain poses another barrier to translation, given that single questionnaires, such as a pain threshold test, may not adequately assess the true scope of a patient’s pain. Requiring the full core of pain domains will lead to a more nuanced understanding of how pain affects different patients and how different therapies affect the whole spectrum of pain-related effects.

The standardization of HEAL CDE program clinical pain data and the added statistical power that would come as a result could be used to validate preclinical concepts more easily with clinical data or provide pilot clinical data to justify grant or trial proposals. Among the core questionnaires, all except 3 are in the public domain, which will help increase the utility of collected data when findings are applied to a clinical setting. Uniform data collection, in conjunction with public access to the data generated by NIH HEAL Initiative, will also be useful in the clinical setting, as practitioners might have a better evidence base to help make treatment decisions for patients in minority groups or with underlying health conditions who may not be well represented in individual studies. Similarly, larger, standardized evidence-bases collected with uniform clinical pain measures could help inform coverage decisions by health insurers, and decisions made by federal, state, and local lawmakers, and government officials who are trying to address opioid misuse and pain. The HEAL clinical pain data could also help guide future research in unforeseen ways, as they will be available for hypothesis generation and pilot testing to a community of clinical pain investigators with diverse experience and perspectives.

In summary, the efforts of the HEAL CDE program will lead to a significant influx of high-quality clinical data that will be rapidly infused into the pain research community. The standardized nature of the HEAL CDE program and the generation of FAIR data will facilitate access of this data to all pain researchers, allowing for a wide range of highly powered, secondary analyses to examine a wide range of hypotheses.

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