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Session I: Welcome and Overview of the Workshop

This meeting aimed to inform the behavioral and social sciences research community, stakeholders, and NIH Institutes and Centers about cutting-edge ways to measure chronic pain and what research is needed to develop, test, and validate the next generation of pain measures. Objectives included describing major influences on current pain measurement instruments and identifying steps to move toward more accurate and comprehensive measurement of pain experiences.

Session I addressed the main topics and themes of pain measurement and its social, behavioral, and biological factors. Although many innovations have been developed, the zero-to-10 pain scale still is most used, which does not provide precision measurement or account for the subjectivity of the pain experience and the factors that may affect how people self-report their pain. Item response theory tests and environmental momentary assessments (EMAs) both are able to capture more complexity than the standard pain scale, but further innovation is needed. Wearable devices and sensors in mobile phones are beginning to be used for innovative tests and monitoring, and their use is likely to expand. The meeting served as a space to inform researchers in the field about existing technologies and encourage discussion about unmet needs. Participants were encouraged to think multidimensionally and multimodally, given that pain is a complex condition that likely does not match a single mechanism.

A previous workshop, in 2018, discussed how to investigate non-addictive pain therapeutics, as well as identify objective measures and biomarkers for pain. Although pain biomarker research remains in its early stages, comprehensive measurement is needed to address the complex, interconnected experience of chronic pain, which can vary throughout the day or with a person's experiences. Because pain is a subjective and individually variable experience, providers are unable to verify how much pain a person is experiencing. They often also ask questions that people experiencing pain are unable to answer specifically—for example, a person's "average" pain level may vary dramatically throughout the day, between days, or depending on activities. Science does not currently have a good understanding of how interactions between various factors influence a person's pain level. Many people who experience pain say that current pain measurements are somewhat useful but do not capture the full pain experience; a paradigm shift is necessary to transition pain care to match what people actually experience.

Session II: Setting the Stage: Advances and Challenges

Session II presenters emphasized that pain must be considered in a broader context than a number on a scale. Pain is temporally dynamic, and a conceptual, testable framework is needed to measure it accurately. One option to move toward developing such a scale is to identify biopsychosocial and genomic biomarkers, which can help move the field toward individualized pain care. However, barriers to translating what is known about pain into new thought processes that will advance the understanding of pain in a broader context exist. Current models fail to capture the heterogeneity of pain and its temporally dynamic changes, which may be caused by environmental influences on the genetic code that influence the many biochemical pathways that lead to the symptoms that can be assessed in the clinic. Various components of these pathways interact to create non-anatomically-specific overlapping conditions. The biological phenotypes that can be assessed are influenced by intrinsic protein cascades influenced by up- or downregulation of a variety of genes. Many environmental exposures are contributors, and the pain field has very few tools to assess these and a very poor understanding of them. Presenters outlined studies in which reproducible clusters of various pain intensities were defined using biopsychosocial perspectives; categorizing heterogenous patients into more homogeneous clusters in this way could help researchers more succinctly identify biomarkers.

In addition to the clinical issues involved in assessing pain, interactions between the scientific understanding of pain and the legal domain create ethical issues of which researchers should be aware. Pain is the most common reason people resort to legal action, but the legal system has a long-standing tradition of seeking verification and quantification that does not correlate with the heterogeneity of pain. Quantifying pain may undercount important associated issues—such as social distress, sleep dysregulation, cognitive function, and so on—that are not measured on a pain scale, as well as undercounting people whose pain is less quantifiable, and the legal system may overcount people with tissue damage. Because pain frequently is unrelated to tissue damage, the legal system may require evidence that does not currently exist; this is an area in which the identification of many specific biomarkers for pain could be helpful in validating constructs. Although wearable devices have great potential to help collect information about wearers' pain, most are not covered by current medical data privacy laws. A person's data could be used to predict future health status, so frameworks for the ethical use of data must be considered to prevent discrimination in the marketplace. In legal and cultural spheres, terms like "psychological" and "subjective" can be used negatively, when in the clinical field, these terms are used without connotation. Adjudicators are allowed to discount phenomena that are "merely subjective" or "merely psychological." Researchers and clinicians need to be aware that these terms are used and understood differently outside their own field, so they should be urged to contextualize their writings.

Providers also have an ethical imperative to address sociocultural factors that affect a patient's pain. Pain is not a simple input-output function, but rather is the sum of a person's life experiences. Lived experience over time creates physiological changes that then create changes in the presence of a painful stimulus. Despite this understanding, providers cannot alter much of this life experience by the time an individual presents with pain, which makes primary prevention much earlier in life critical. Sociodemographic factors—such as housing, cultural norms, stigma, and politics—all contribute to pain and must be addressed, in addition to clinical factors to meet the ethical imperative for treatment. Pain is not only an individual product but

also is a product of culture, so it could be considered as a tool for social justice before individuals develop their own atomized pain conditions.

The Session II panel discussed the importance of asking the right question to capture the experience and complexity of pain. The pain research field needs to bring together large data sets, but *All of Us*℠ likely is too broad to be useful for this question. Researchers have much information from cohort studies that allows them to make primary assessments in the clinic, but appropriate tools that currently exist have not yet been implemented effectively. An ideal tool would be able to capture the pain experience broadly across symptoms as well as specifically for certain conditions. Current assessments fail to capture the many layers of the pain experience, and researchers are trying to measure something that is not well understood scientifically. Responsivity in a measurement also requires context, such as the difference between physical functioning at rest and during movement and the fundamental variability of pain as a condition.

Session III: Chronic Pain Measurement: Beyond the Visual Analog Scale

Session III included background on the history of pain self-reporting. Pain and tissue injury do not correlate, and the realization that pain is a multidimensional experience led to multidimensional methods. However, self-reporting is not only an assessment method but also a behavior, and as such it is influenced by emotions, thoughts, experiences, and context. People may be asked to remember their pain, but memory is not reliable, and current pain and mood can affect the memory of past pain. Additionally, other factors often associated with pain can be worse than the pain itself, and these are not easy to measure. The most recent advances in pain reporting have standardized stimuli and allow self-reports in natural settings, allowing the development of a moving average and collection of other factors that might affect pain, which helps providers assess variations in a more sophisticated way. Although pain is a dynamic process encompassing more than self-reporting can capture, current self-reporting methods are the best available to learn about an individual's experience of pain.

Pain is always subjective, and because it is—by definition—unpleasant, pain is both a physical and emotional experience. Any sensation an individual experiences as painful counts as pain, regardless of the correlation with tissue damage or nociceptive pathways. Animal studies can be used to measure nociceptive response, but the results cannot be considered as pain because animals cannot report their experiences. Researchers are trying to assess the experience of pain, which also is not the same as the report of pain. How researchers ask questions and the scale they use are critical—functioning can be a useful outcome or goal, and people who experience pain can differentiate between kinds of pain and how the pain affects their life and abilities. Variability often is considered an error in research, but in pain studies, responses might reflect the true variability of the condition and the effectiveness of the treatments. Validated questionnaires can be used to establish an individual's baseline, but tests must be sensitive to individual differences.

The concept that pain is subjective can be used to suggest the pain is not real or valid, both in legal situations and in the general population, and this mindset causes great harm to patients and society by creating the idea that treatment must correct broken parts of a body, despite the long-standing knowledge that this mindset is not accurate or effective in medicine. Attendees discussed how to convey to the public the importance of such cultural transformation. Although

attitudes have changed in some cases, such as the growing acceptance of fibromyalgia, pain conditions are diverse and largely still undersupported. Additionally, although the effect size of psychosocial predictors is relatively small, the effects might be very different for certain subgroups, and little research has been conducted on this topic. Participants emphasized that identifying contributing factors is only part of the solution, given the heterogeneity of pain and the need to study multifactor effects. Current inclusion criteria for clinical trials often allow only a narrow group of participants for each diagnosis, leading to studies that do not capture the breadth of the pain experience.

Session IV: Co-Morbidities on Chronic Pain Measurement and Potential Impact on Outcome Measures

Session IV presenters reiterated that pain is a complex physical and emotional experience with no correlation between physiological markers and pain reporting. Mental health also is a critical factor—people with chronic pain are more likely to develop depression or anxiety, and people with depression or anxiety are more likely to develop chronic pain. Pain catastrophizing is associated with mental processes, such as ruminating on the pain, and the relationship between pain and mental processes often has temporal dimensions, with many people developing pain and depression simultaneously. Early increases in catastrophizing have been shown to influence later increases in pain. Emotional awareness and expression therapy are new strategies that, although not effective at improving pain, have shown slight improvements in depression. Because mood issues and pain experiences are integrated, separating them for treatment may not be effective.

Presenters emphasized that a single solution to all pain problems is unlikely; researchers are much more likely to be able to identify multiple mechanisms and ways to address complications. Current understanding of both pain and its treatments are limited. People with pain often have poor sleep quality, and these symptoms have distinct mechanisms. Questionnaires can identify sleep problems, but they can measure only the consequences of the problems, not the problems themselves. Devices, such as smartwatches, similarly measure proxies for sleep, such as movement during the night. Animal models demonstrate the complicated interactions involved in these cases—sleep fragmentation in otherwise healthy animals leads to mood disorders and impaired recovery. Sleep disturbances can be considered pain outcomes, and the consequences of disturbance can be measured and are less likely to be influenced by environmental factors.

Session IV panelists discussed the variation in sleep disturbance depending on the type of pain and noted that sleep problems likely are much more common than researchers know. Participants discussed how to move the knowledge that social constructs create unique intersectionalities into pain measurement. Although researchers measure variables with the best methods they have, good tools to dissect the interactions of these variables are not available. Participants also emphasized the importance of keeping in mind that people who report more pain likely also experience more pain.

Session V: The Social and Cultural Factors Influencing Chronic Pain and Clinical Performance Measures

Session V presenters emphasized that pain prevention should start early in the lifespan—children experience chronic pain at similar rates to adults. Such pain impacts children's daily lives in

much the same way that it does adults' lives, but at their age, pain can affect school attendance or performance, which affects lifelong achievement and social participation. Although children must be asked directly to assess their own pain—rather than using adults as proxies—children live in the context of their families, and other family members may experience effects—such as depression, anxiety, financial burden, and so on—that become important aspects of treatment. Childhood chronic pain is associated with later opioid misuse, which indicates that the childhood pain experience affects their functioning in adulthood. Social and family vulnerabilities may lead to the continuation of pain from childhood to adulthood. Despite these associations, few data are available that correlate across age groups and can be used to study similarities between adult and childhood pain. Further research is needed on broader family dynamics, and more common ways of discussing and measuring pain across the lifespan must be developed.

Pain catastrophizing involves multiple primary sensory and associative brain networks, which in normal functioning activate and deactivate as distinct assemblies. The default mode network is more active in a resting state, and the salience network regulates executive function. Studies of brain activation during pain show that gradual pain stimulus changes the connectivity of the brain networks. Individuals with greater connectivity between networks are more likely to engage in pain catastrophizing. Catastrophizing may reduce the brain's ability to switch between active networks and blur the networks that are normally distinct.

Panelists discussed the lack of methods for tracking children's pain, particularly when most children and young adults with pain do not visit pain clinics. When people with pain are not effectively tracked, they also often are not prepared for what will happen after they leave the clinic, and they are not followed well after treatment. Pain clinics often do not operate under the same mindset that is used for management of other chronic diseases.

Participants noted that catastrophizing may be an appropriate coping strategy in its initial stages; however, over time, it gathers context that can become detrimental for the person experiencing it or their family members. The day-to-day effects of catastrophizing vary widely between individuals and are highly malleable; teaching individuals how to feel more effective and solve problems may reduce catastrophizing. Although longitudinal studies may provide models to study causality of pain and catastrophizing or allow researchers to assess the change in markers over time and across multiple outcomes, current causal data often are not available for chronic pain. The source of catastrophizing may be external, but once it starts, it will be an internal, interoceptive process. Some behavioral therapies may be able to modulate the process. Attendees pointed out that protective and resiliency factors are understudied in the pain field; researchers should be assessing positive interventions. Attendees discussed whether catastrophizing has any positive effects—for example, if the purpose of catastrophizing is to call for help, researchers should study whether people improve when that call is answered. This may require studies of the social dynamics around catastrophizing.

Participants noted that language used in the pain field, including "catastrophizing," has derogatory connotations and suggested a consensus conference at which those in the pain field could decide on replacements for terms that have become stigmatizing. People in the field also should be encouraged to disengage the activity from the identity of the individual by using person-first language. Investigating the source of the negative stigma around these terms could be helpful.

Session VI: The Use of Technologies to Inform Pain Outcomes

Session VI presenters reviewed the current tools for measuring functional outcomes and how these relate to pain, which often is paired with a functional measure. Although such functional measures in rehabilitation may not be linked to pain directly, they describe how a person with pain is able to move and go about their life. Many current wearable devices allow the measurement of motion; gait can be monitored by providers as a functional activity and predictor of fall risk, but an accelerometer is more accurate at describing fall risk. These devices provide more granular data on functional measures, allowing researchers to identify some impairments that might be missed in visual assessment. They also provide more data on the most basic functional activities, such as walking and standing, that people with pain often change to compensate for their pain. Virtual reality can be used to help track function in people with lower back pain, who often have a warped kinetic awareness, and to improve their motivation and outcomes. Additionally, biofeedback in mobility training can extend the rehabilitation outside the clinic into an individual's daily life. Future developments likely will move the field toward complete wearable monitoring with such technologies as garment-based technology and smart skin sensors.

In addition to physical effects, pain has emotional and other peripheral experience aspects that can modulate the behavior of people who experience it. Pain associated with injury often heals over time, and it may be treatable with cardiovascular exercise. Interventions to treat pain may be able to shift the connectivity in the brain, and brain metrics may help provide valuable outcomes for patients. Measuring the peripheral experience of pain associated with injury adds value, especially when patients often have been disbelieved for a significant amount of time. Data also can be collected outside the clinics by the people experiencing pain; these data can inform treatment between the individual's sporadic touchpoints within the health system. Individuals can use apps to track their wellness and participate in research studies. Step counts can be used to study the evolution of an illness in a population that changes activity levels, and individuals with chronic pain who are engaged with technology can use these apps to provide real-world data not readily available in the clinic. Data from these apps add to the growing body of evidence that African Americans are disproportionately burdened by chronic pain, regardless of their activity levels. These apps also can be used to measure interference, or how much pain affects behavior, and these data negatively correlate with pain self-reports regardless of race—people feeling more pain walk less. Presenters reiterated the need to make recommendations specific to the individual given the highly individualized nature of pain; personal data tracking can help providers understand how each individual is affected by pain differently.

Participants noted that data from tracking apps are better for determining averages over time than for studying specific endpoints; corrections are available for slight areas of missing data over time, and validation tests are available for basic interferences. Wearable devices can gather data for a small number of key variables, but these must be validated clinically with practice guidelines and parameters to correlate with behavior. Participants noted that early monitoring of patterns, such as adjustments in movements to compensate for pain, can lead to the possibility of prevention. However, the degree of heterogeneity involved requires researchers to first determine what patterns exist and which contribute to later problems before they can use these patterns to screen for future outcomes. Some of the standard tests have normative values for certain age groups, but these tests are few and far between. Participants pointed out that the population that

seeks treatment for pain is far smaller than the likely actual population, and wearable devices might help providers find more of this population. Additionally, data from devices would provide the opportunity to compare an individual to their past self, rather than to a normative average. Often, little is known about an individual's baseline before pain; data from wearable devices might help researchers identify trackable triggers for some types of pain. Participants also suggested excluding low-affinity binders when studying microglial interaction in neurodegenerative disease. Positron emission technology scans can provide some signals for pain intensity, but because pain is a personal experience similar to emotions, this experience cannot be inferred from sensors.

Session VII: The Role of Technologies in Clinical Trials and Measurement Development

Session VII presenters described quantitative sensory testing, which attempts to standardize the test without removing the inherent subjectivity of the pain experience. Delivery systems and responses are standardized as much as possible, but the ability to localize responses is limited. These tests operate under the hypothesis that the clinical phenotype of pain reflects the underlying mechanism, although the reality is not that simple. However, an identified mechanism can be matched to a drug mechanism for potential treatment. The mechanism of pain often is as important as the actual condition, if not more. Some trials have shown that some mechanism-based approaches are effective, but this result is not universal across trials. Other potential tests are available that use psychophysical principles and easy-to-access equipment. Results of these studies support the phenotyping of participants in all trials, which would help researchers pool data across studies with multiple mechanisms.

One measurable mechanism for assessing function is the step, which is a summary mechanism of many processes that occur prior to movement and also is easily interpretable and intuitively scalable for people of differing abilities. Mobility is inversely proportional to pain, regardless of whether that pain is musculoskeletal or another form, such as migraines. Tracking step activity shows that habitual activities predominate in the data for most people; these can outline an individual's activity baseline, ideally over 1–2 weeks, that then is changed by interventions. An individual with pain is likely to reduce their activity, but this leads them to report less pain because they have reduced activity to avoid pain—measurement of activity is an indicator not of a person's pain, but of whether they are compensating for it. Depression also can reduce physical activity, which may be a confounder in pain studies but can indicate a need to alter the treatment.

Presenters emphasized that providers must remember that, between symptoms and cure, an individual is experiencing pain and must be treated respectfully. Most current interventions do not cure pain and only sometimes reduce it; additionally, animal models have shown wide variability in how different kinds of pain respond to treatment. Psychological variables, beliefs, social factors, and other biopsychosocial variables affect pain but are difficult to measure. A self-report can indicate what the patient considers important, but may not be fully accurate to the pain experience; similarly, how a patient appears in the clinic might not be representative of their natural state, but their behavior can provide clues. Currently, interreliability of data across multiple studies is lacking, and those in the pain field have not agreed on the necessary components of any assessment, which may not be the same as the components currently collected on clinical records. Presenters encouraged providers to determine the minimum values that should be gathered for all studies to begin to move toward data that can be aggregated.

Constructs and reporting measures also must be standardized, and the NIH can play a role in encouraging researchers to develop consensus on these items.

Participants discussed the lack of knowledge around mechanisms and ways to tailor treatments; patients are not well phenotyped in pain trials, and no standard approach has been sufficiently adopted. Additionally, people with the same phenotype may have different pain signatures, and researchers do not yet have sufficient granularity to elucidate the connection between phenotype and mechanism. Many treatments have been developed based on trials with only a small portion of the pain population, and some clinical trials fail when moving from a more generalized approach to a more complicated understanding of pain. Researchers currently may be too limited in trying to assess the underlying mechanisms of pain, and many psychosocial variables are understudied. One outcome of this workshop could be to encourage those in the pain field to assess the domains in which more precision is needed. Participants commented that many pain researchers are focused on their areas of expertise, but pain is a complicated condition that requires collaboration across disciplines. The context of pain is critical for determining the best measures, and overarching support is needed to move the field toward harmonization.

Session VIII: What Is Efficacy in Pain Clinical Trials?

Session VIII presenters outlined the regulatory perspective, which includes prioritization of patient-focused outcomes in clinical trials. Efficacy assessments are used to demonstrate the clinical benefit using all available tools, and digital health technologies are increasingly used to collect outcomes from patients' daily lives. Regardless of the type of assessment, strong measurement principles are used to consider content validity, construct validity, reliability, and the ability to detect and interpret change. Such assessments have implications for how drugs are developed and can help those in the pain field capture what matters to people with pain in their daily lives, as well as reducing the barrier to clinical trial participation. A patient-focused drug development initiative recognizes the role that patients and caregivers have in affecting the development of drugs—patients can provide advice on what measures are meaningful to them. Patients also have participated in conferences specific to various chronic diseases, providing perspectives that providers and researchers might not previously have recognized. Future directions for the regulatory sphere include continuing to elicit patient input on trials, increasing multistakeholder collaboration to advance the science, and increasing the role of technology.

Although many strong ideas were discussed at this workshop that will affect the way drugs are developed, great ideas often take a long time to become reality. One useful objective in clinical trials that helps in the short term is to improve the tolerability of the trial itself. Without a biomarker for pain, biomarkers for pain response can be used to improve trial design. Pain severity can be defined operationally using intensity and pain distress in daily activities, and these severity measurements will be available as extensions in the International Classification of Diseases 11th Revision. To match the right drug with the right patient, the first stage of a trial could identify responders to the treatment or responders to the placebo and include or exclude them for the second stage. This method allows trials to use the signal-to-placebo rate as a proof of concept in Phase II, although this measure is less useful for Phase III. Quantitative sensory testing also can be used to identify a patient's pain phenotype and screen patients, but this testing likely would be cost-prohibitive for any outcome measures. Biomarkers have been used effectively in certain contexts, but identifying the appropriate question is important to determine

which biomarkers will have construct validity. Presenters expressed optimism that accurate and generalizable biomarkers will improve treatment development.

EMA is another measurement method that can augment other standard measures, which rely on recall. EMAs are collected in a real-world environment and focus on a subject's momentary state. Multiple assessments over time can provide a clearer picture of a person's pain experiences. EMAs allow the characterization of a specific period of time and the assessment of dynamic, temporal associations between variables. Because pain is variable over time and across patients, EMAs can be useful in illustrating individual variability. Patients in real-world settings also are likely to focus on different aspects of pain than clinicians often ask about.

Participants discussed the need for a continuum of common scales used in clinical practice and trials. They emphasized the importance of harmonization to define a common metric by which clinicians can assess patients. Adequate controls are critical for gathering evidence that can be used in the regulatory field.

Session IX: Toward a Complex Composite Measurement for Chronic Pain from Behavioral, Social, and Biological Measurements

Panelists first provided remarks on the overall question of how to define a complex composite measurement. They reiterated that measurement depends on the use of complex questions, but a practical approach must be developed that will provide a realistic opportunity to learn about the prevalence of certain variables in pain. Factors affecting pain depend partially on the nature of the pain condition, but researchers also must think about commonalities across pain conditions and determine whether different biological or sociological factors should be considered. The NIH could provide support to identify the best ways to measure a variety of constructs.

Attendees suggested that clinicians should be encouraged to screen every chronic pain patient for psychosocial distress. Clinicians and researchers also must recognize that people are different and continually educate other providers to look at more individually variable factors, such as personal data sets over time, than any average response. Patients repeatedly stress the importance of certain domains, like the ability to function in daily life and participate in social activities, which providers and researchers should recognize when considering how to study and treat pain. Providers also should discuss the recovery expectation, which is a critical aspect of the pain treatment experience that is not well measured and not frequently addressed in the clinic. Individual patients may have different levels of meaningful change in response to their treatment. Attendees reiterated the need for a data repository specific to pain researchers with standardized data and optimal sharing, suggesting that virtual pain centers could help integrate the community and develop the desired constructs for measurement.

Attendees commented that those in the pain field currently are missing a major opportunity to understand how reports of pain vary as a function of the social context in which the reports are gathered. People suffering from persistent pain are in a wide variety of social situations, and some interactions have a dramatic effect on reducing pain. Providers and researchers have an opportunity to improve their understanding of what people tell them about their pain and develop better interventions. The social context and patient perspective must be integrated more meaningfully with current measures. Regardless of how carefully providers collect data, these

data must be validated against an individual, subjective experience of a complex condition; no simple measurement of these factors exists, and providers often are not trained in interpreting the data that these measures provide. Providers also must resist the tendency toward oversimplification of such a complicated, multivariable condition that remains poorly understood. Attendees reiterated the importance of acknowledging the complex and individual nature of pain as a critical aspect defining the path to better measures and treatment.