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Research Letter

INTEGRATE-Pain: a transatlantic consortium to advance development of effective pain management

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Dear Editor,

Introduction

Pain is among the most frequent reasons for seeking medical care worldwide and across all socioeconomic levels.[1] Although many pain conditions are not immediately life-threatening, pain can significantly impact an individual's daily life and wellbeing long-term.[2–4] Despite significant advances in the understanding of pain mechanisms and ways to improve pain diagnosis, the currently available options for effective pain treatment and management inadequately address the scope of the pain burden.

Methods

The INTEGRATE-Pain Consortium (Innovative Medicine Initiative [IMI] – National Institutes of Health [NIH] Transatlantic Emphasis Group on Research and Translation-to-care Efforts for Pain) was created in 2020 as a US-EU (United States–European Union) consortium to advance the pain field, to enhance development of treatments, and to facilitate transfer of existing and new treatments into clinical practice, ultimately improving the lives of people with lived pain experience in the United States and European Union. The similarities in aims and scopes of the work being conducted by IMI-PainCare and NIH staff inspired the establishment of the INTEGRATE-Pain Consortium. While the consortium does not develop or discuss funding opportunities within pain research, members discuss current projects, potential advancements, and published work.

Figure 1 shows the INTEGRATE-Pain Consortium's composition, with staff at the US NIH and the European IMI-PainCare Consortium. The NIH is the largest public funder of medical research and houses the largest medical research institute in the world. NIH staff involvement in pain research spans preclinical pain research to workforce enhancement and human clinical trials.[5] The IMI-PainCare Consortium, composed of 41 partner organizations,[6] is established within the IMI's framework.[7] IMI is a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). It is engaged in the development of patient-reported outcome measures (PROM), development of functional biomarkers, and on improving the understanding of chronic pelvic pain.

NIH and EU leadership met with the INTEGRATE-Pain Consortium in September 2020 to discuss potential collaborative opportunities to advance the pain field. Based on existing

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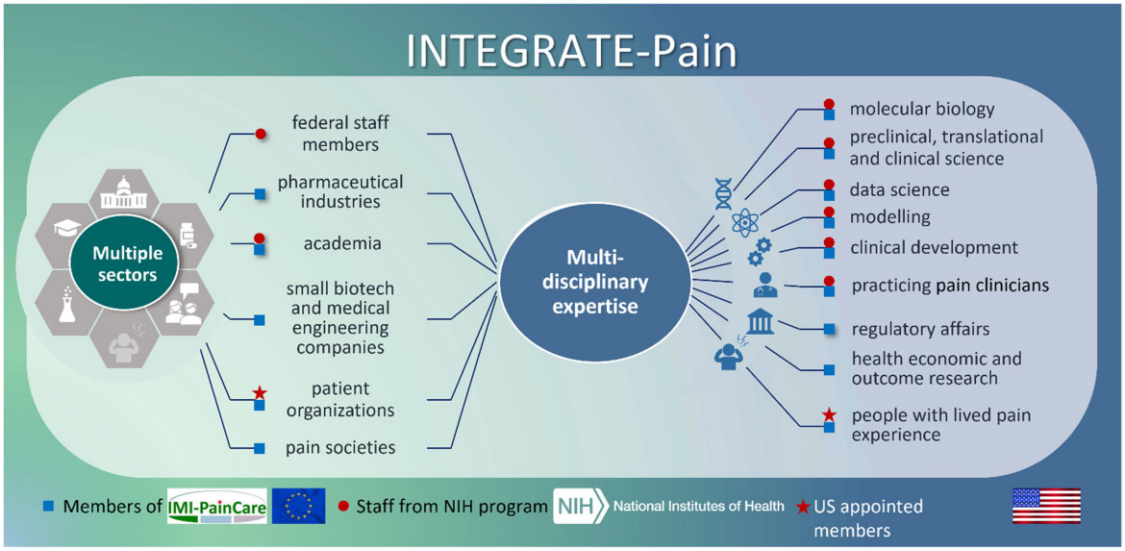

Figure 1. The INTEGRATE-pain consortium.

Formed by IMI-PainCare members and NIH program staff, INTEGRATE-Pain united multiple stakeholders from several sectors (pictured left) and with a broad spectrum of multidiscilinary expertise (pictured right) way to create a transatlantic US-EU ecosystem for advancing pain science and clinical management. IMI-PainCare members (indicated by blue squares) are involved in academia, industry (i.e., pharmaceutical and biotech/engineering), advocacy. IMI-PainCare also has multiple European societies related to pain involved in their initative. NIH staff members (incdicated by red circles) are involved in intramural research, federal policy, federal health science program administration; some staff members also have academic appointmentships, and/or are practicing clinicians. Further, NIH staff have appointed people with lived experience of pain as members of the consortium (indicated by red stars). On an ad-hoc basis, other stakeholders who are not INTEGRATE-Pain members have been or will be invited to participate in events to expand stakeholder representation in intiativites, such as US-based health economics, regulatory affairs, industry represenativites, and practicing clinicians.

core outcome set (COS) projects within the NIH and IMI-PainCare,[8,9] leadership encouraged the consortium to establish overarching pain COS to enhance clinical pain management (ie, patient reported outcomes (PRO) and PROM for use in research and clinical practice) among the United States, European Union, and—eventually—globally. Leadership also expressed support of collaborations in: (1) studies on pain and co-morbidities across populations, (2) preclinical cooperation, back-translation, and multisite evaluation, (3) biomarker identification and validation, and (4) preclinical cooperation and clinical infrastructure for testing new non-addictive pain therapeutics.

Results

Achievements: The establishment of the INTEGRATE-Pain Consortium has led to cross-cultural exchange of information and ideas. Such partnerships are increasingly important, as they can help leverage resources and develop pain treatments with broad global impact. Next, based on the feedback from leadership, the consortium has prioritized establishing four overarching pain COS (acute—eg, post-surgical pain, transition, recurrent/episodic—eg, sickle cell disease, and chronic pain—eg, fibromyalgia) that indicate the minimal set of domains that should be used within clinical research and practice. A systematic literature review (SLR) helped inform a three-round Delphi voting process, which included 616 relevant stakeholders (eg, people with lived experience, researchers, and clinicians) throughout each step (Figure 2A). Most stakeholders were not INTEGRATE-Pain members, and although all continents were represented, most stakeholders resided in North America or Europe at the time of voting. Delphi voting ended in early 2023, and the aims, methods, and results from this process will be reported as a separate article.

Next Steps: Once the four COS have been disseminated to the research community, clinical organizations, and advocacy organizations, the consortium's immediate next step is to determine an appropriate set of PROMs corresponding to each COS. This process will likely include a SLR, assessment of the psychometric properties of existing PROMs, and the conduct of a stakeholder-engaged Delphi process.[10] Discussions among consortium members across the translational research spectrum has also highlighted the importance of back-translating the clinical COS into preclinical approaches for testing pharmacological and non-pharmacological interventions. Endpoints useable for such purposes (eg, facial pain expression or home-cage-analysis in animal models) may be verified in ongoing or future projects. Finally, an anticipated long-term next step for this consortium, as well as the pain community, might include continuing to refine and validate preclinical endpoints and disease models in multiple centers internationally. Refinements to preclinical studies based on back-translation can facilitate forward-translation into revised clinical outcomes. Having clinical and preclinical COS that reciprocally inform each other is a novel approach that bridges existing gaps. Figure 2B–D depicts these next steps and potential long-term impacts.

Discussion

The INTEGRATE-Pain Consortium is a group of scientists spanning the translational pain research spectrum and people with lived experience that aims to improve pain care globally. A unique asset of this group is the diversity of perspectives stemming from members' disparate training backgrounds,

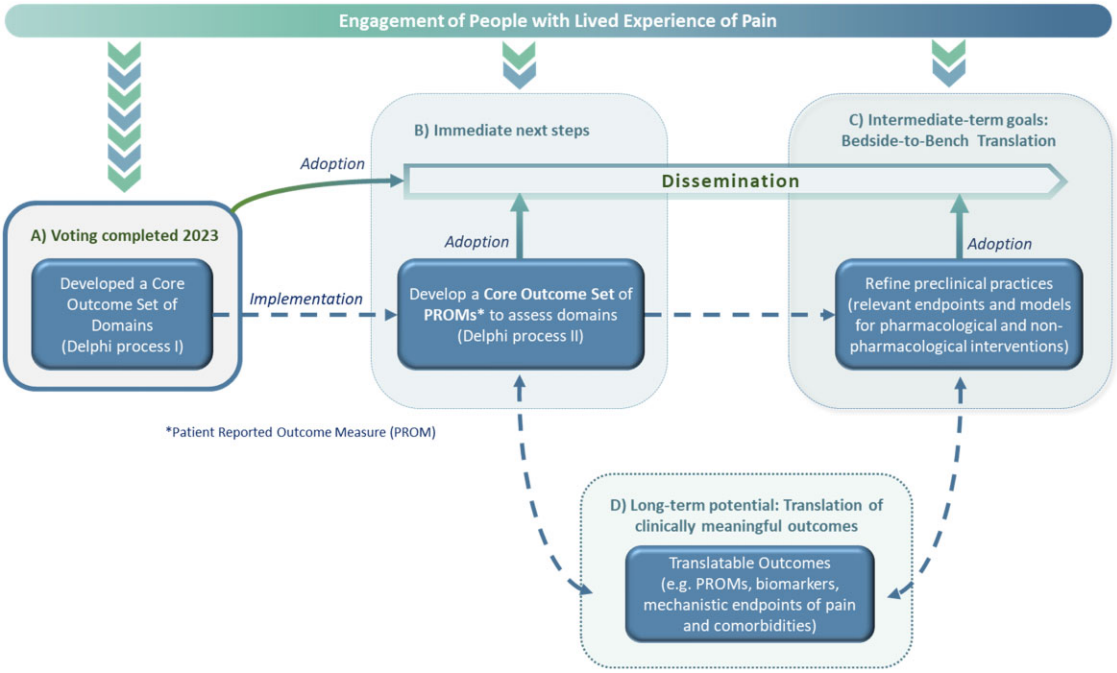

Figure 2. Potential for the field to build off of INTEGRATE-Pain accomplishments.

INTEGRATE-Pain has completed one major effort and has additional short- and long-term goals. Because partnering with people who have lived experience of pain improves the relevance and impact of initiatives related to pain research and care, these stakeholders have been included early on and throughout the entire process of INTEGRATE-Pain s initiatives, deliverables, and events. A: In early 2023, INTEGRATE-Pain completed the final round of a Delphi process to achieve consensus on Core Outcome Sets (COS) of domains for pain research. B: The immediate next steps for consortium members will be to disseminate the results of the Delphi process to interested stakeholders. This includes two journal articles in preparation, presentations at scientific meetings, webinars for research, clinical, and advocacy organizations, and educational materials for people with lived experience of pain that will be co-produced with lived experience expert members of our Advisory Committee. To ultimately implement the COS, consortium members or other stakeholders, will determine an appropriate set of patient-reported outcomes (PROM). C: These COS can inform ongoing efforts for bedside-to-bench back-translation to refine condition-specific preclinical models and validate clinically relevant endpoints to better model the experience of pain in humans. D: To advance the field in the long-term, collaborative pre-clinical and clinical approaches of INTEGRATE-Pain and the international pain community might further improve clinically meaningful outcomes for pain conditions and comorbidities. The model undertaken by the INTEGRATE-Pain Consortium integrates deliverables from all levels of pain research and pain care to ultimately produce and deliver clinically meaningful outcomes for people living with pain.

cultural differences, and roles within pain research and engagement. Although not all sectors are currently represented among INTEGRATE-Pain members across the European Union and United States (eg, health economics, implementation science), future efforts will expand representation as relevant to the initiative. The consortium's diversity has contributed to several strengths and considerations for future consortiums to heed. Strengths include information sharing across countries that has helped align pain research efforts broadly and creativity in generating novel pain research ideas. Pooled COS across countries, for example, can identify treatment targets with the broadest potential impact. Our experience confirms the importance of continuously refining expectations and goals, especially for large consortia. Similarly, identifying potential differences in cross-national regulatory processes early in the consortium facilitates collaborations. Consortia might also consider continuous collaborative approaches to integrate disease-specific preclinical models, clinically relevant models and endpoints, and people with lived pain experience in pain research and care. Finally, this and other consortia should strive to incorporate voices from countries and cultures across all continents to facilitate global equity in pain care. In sum, cross-continent, multiple stakeholder partnerships, such as this consortium, are becoming increasingly feasible and imperative to spark innovative solutions that will address longstanding, global pain care needs.

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