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Partnering with Patients in Clinical Trials on Pain Treatments: A Narrative Review

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Introduction

- Patient involvement as partners in various stages of clinical research have been studied in different therapeutic areas

- There is no guidance on best approaches for partnering with patients in planning and conducting clinical trials on pain treatment.

- No consensus on optimal approaches for:
  - Identification
  - Selection
  - Engagement

- Not clear how to optimally engage patients in various stages of trial design and conduct, data analysis, interpretation of results, and research dissemination.

Goals

- ❑ To provide a narrative review of the current literature on engaging patients as partners in clinical studies in general, and in pain-related studies more specifically.

-While recognizing that multiple stakeholders have roles as partners in clinical research, the review primarily focused on <u>patients as research partners</u>.

The evolution of clinical trials – historical perspective

1747: Scurvy trial (James Lind)

1799: Placebo-controlled device study (John Haygarth)

1863: Placebo-controlled pharmacological trial (Austin Flint)

1946: Double-blind controlled curative trial; Streptomycin for Tb (UK Medical Research Council)

1947: Nuremberg Code

1964: Declaration of Helsinki [*current principles of human subject research*]

Methods

- A medical librarian (Lauren Yaeger) created and executed a Scopus search from inception to March 2021 to find relevant citations.

- Search terms for concepts of

  -Patients as partners
  -Stakeholder involvement
  -Clinical trials
  -Pain

- The search was conducted on March 16th, 2021, and was limited to English.

- Katie Holzer and Simon Haroutounian screened all abstracts, and focused primarily on studies from 2011 to March 2021.

- Free search: FDA, EMA, PCORI, NIH, VA, NIHR websites

- Information from the selected sources summarized in a narrative form

Outline

- The Evolution of Patient Engagement in Clinical Trials: National and International Perspectives

- Review of patient engagement practices
    - *Recruitment of Patient Partners*
    - *Perceived benefits of meaningful patient engagement*
    - *Facilitators and Barriers to patient engagement as partners*

- Examples/Landscape of patient engagement in non-pain related therapeutic areas

- Partnering with patients in clinical trials of pain treatments
    - *Examples of patient partnerships*
    - *Evidence of gaps*

- Summary

The Evolution of Patient Engagement in Clinical Trials: National and International Perspectives

United States (some examples)

- ❑ IOM (NAM) 2009 report: *Initial National Priorities for Comparative Effectiveness Research*

- ❑ PCORI

- ❑ VA Health Services Research and Development (HSR&D), 2015
  - *Strengthening Excellence in Research through Veteran Engagement (SERVE) project*

- ❑ FDA
  - 1988: *Office to work with patient advocates*
  - 2012: *FDA Patient Network, patient-focused drug development (PFDD) program*
  - *Office of Health and Constituent Affairs (OHCA)*
  - *The Voice of the Patient reports*
  - *Patient Science and Engagement Program, Patient Engagement Collaborative*
- ❑ NIH:
  - *NCI: National Clinical Trials Network (NCTN)*
  - *Helping to End Addiction Long-term (HEAL) Initiative: Patient Engagement Working Group launched in 2021*

The Evolution of Patient Engagement in Clinical Trials: National and International Perspectives

International (some examples)

- ❑ United Kingdom
  - *-INVOLVE, NIHRs Patient and Public Involvement (PPI).*
  - *-UK Standards for Public Involvement in Research (England, Scotland, Northern Ireland, Wales)*
  - *-NIHR Public Engagement in Clinical Development Service connects science industries with patients*

- ❑ EMA (formed in 1995)
  - *-Getting Involved with the EMA*
  - *-Patient and Consumers' Working Party*
  - *-EUPATI (European Patients' Academy on Therapeutic Innovation): multi-stakeholder partnership with the pharmaceutical industry and the EMA*

- ❑ Canada
  - *-Strategy for Patient-Oriented Research (SPOR) in 2011*

Recommendations for successful patient engagement

Author	Focus	Recommendations
Crowe (UK standards)	Core areas in which specific standards are to be developed	1) Inclusive opportunities; 2) Working together; 3) Support and Learning; 4) Communications; 5) Impact, and 6) Governance
Duffet	Key ingredients to achieve successful patient engagement	1) Thoughtful selection of patients; 2) Clearly defined patient engagement plan, 3) Training and ongoing support for researchers and patient partners, 4) Mutual respect and valuing patients' experiential based knowledge, 5) Starting early and continuing throughout each stage; 6) Including a plan for evaluation of the research program
Kirwan	Guidelines to build capacity for patient-oriented research	1) Establish supportive organizational policies; 2) Cultivate supportive attitudes of researchers and patient partners; 3) Adhere to principles of respect, trust, reciprocity, and co-learning; 4) Address training needs of team members for better communication; 5) Identify tools and resources for successful patient engagement; 6) Recognize value of patient partnerships across all stages of the research cycle.
Supple	Recommendations for effective engagement of patients in research	1) Involve early; 2) Involve deeply; 3) Have patient feedback on project progress; 4) Include patients in the dissemination of results; and 5) Empower patients to convey their own story.
Geissler	EUPATI roadmap: opportunities for meaningful patient engagement across drug R&D	1) Setting research priorities; 2) Designing and planning of research; 3) Conduct of clinical research; and 4) Dissemination and communication, including post-approval activities.
Day	Considerations for partner involvement	1) Methods of engagement most conducive to involving partners throughout the research process; 2) Detailed engagement plans for each stage; 3) Regularly evaluate engagement processes and make appropriate modifications; 4) Academic journals should consider implementing policies about reporting stakeholder engagement; 5) Use consistent terminology to describe patient engagement both among researchers of a specific condition and in clinical trials research in general.

Recruitment of Patient Partners

Three primary models of recruitment infrastructures:

The traditional model

Recruitment occurs on a case-by-case basis, typically driven by the research topic (e.g., pain, HIV).

The third party model

Access to existing patient directories provided by an outside source that allows researchers to search for and match with patients based on their needs.

The directory model

Creation of a local or regional directory of patients who are interested in engaging in research as partners

Strategies in each of these:

- ☐ Social marketing (social media, radio, television)
  - *finding larger groups – e.g., retirees, females*
- ☐ Community outreach
  - *to specific communities, e.g., minorities or cultural groups*
- ☐ Health system recruitment
  - *patients with a particular condition, e.g., recruitment through a specific clinic or center*
- ☐ Partnering recruitment
  - *reaching advocacy groups or charitable organizations*

Vat et al., Research involvement and engagement, 2017

Recruitment of Patient Partners

Additional strategies:

- ❑ Consumer representation in program governance
- ❑ Focus groups and forums that are well-publicized and held at convenient times and locations
- ❑ Educational programs for consumer participants

Perceived benefits of meaningful patient engagement

Perceived Benefits

- Improve relevance of research to patient priorities
- Significant contributions to trial design
- Improved patient information material and/or informed consent documents
- Improved clinical trial enrollment
- Decreased attrition
- Improve dissemination
- Improved implementation of research findings
- Increased public trust in research process and outcomes

Perceived Challenges

- Increased time
- Increased cost
- Fear of symbolism
- Changes to research scope that were not feasible
- Uncertainty on how to resolve conflicts
- Lack of time by both patients and researchers
- Lack of resources and training; minimal preparation

Barriers and facilitating factors to patient engagement as partners

Barriers

- The use of jargon
- Power imbalances between the researcher and patient partners
- Impact of time pressures
- Inability to meet patient needs (e.g., disability accommodations)
- Retention of patient partners when they experience a change in life circumstances or recurrence of disease
- Partners experiencing difficulty identifying their own contributions and understanding how the final research outcomes reflect their input
- Emotional burden
- Shortage of financial resources
- Feared tokenism
- Invisibility (or lack of formal acknowledgement) of experiential knowledge
- Group conflict
- Lack of relationship with the PI
- Lack of procedures for working with PI
- Lack of research skills/training for patient engagement

Facilitators

- Valuing the patient partner role
- Clear role descriptions and responsibilities for patient partners
- Clear expectations of how patient input is acknowledged and considered
- Explicit policies and guiding documentation
- Meeting personal needs of patient partners (e.g., disability accommodations, scheduling adjustments, refreshments, transportation)
- Compensation for time and work
- Atmosphere of camaraderie between researchers and patient partners
- Purposeful recruitment of patient partners through existing organizations
- Sufficient time and space for partnerships
- Flexibility and responsivity, including personal contact and preparedness, of the research team
- Established relationship with research team
- Procedures to support participation in research team
- Training to support collaboration as member of team

Examples/Landscape of patient engagement in non-pain related therapeutic areas

Our literature search: practices in research related to oncology, neurology, infectious disease/HIV, rheumatology, surgery/anesthesiology, and endocrinology

Infectious diseases:
A 2018 systematic review: >100 studies describing stakeholder engagement to inform HIV clinical trials.
-Stakeholder engagement occurred more frequently in the early stages of HIV clinical trials and rarely informed post-trial processes related to trial results and dissemination.

Neurology:
Conference/workshop organization by the Neurological Emergencies Treatment Trials (NETT) Network:
LISTEN (Learning about Investigator-Stakeholder Team Engagement in Neurological) Clinical Trials - a conference about patient engagement in clinical trial design for neurological disorders.

Such workshops or conferences can be an initial step to learn about patient perspectives on their participation in the different stages of research and to develop a plan to actively foster this engagement

Day et al, 2018

Examples/Landscape of patient engagement in non-pain related therapeutic areas

Rheumatology

- ❑ OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) was established in 1992, and have included patient partners in their conferences since 2002.

- ❑ Evaluation of the OMERACT conferences (2013) suggests that their engagement with patients has significantly influenced outcomes research in rheumatology.
  The primary contributions: identification of new scientific domains that patients consider important, the development of patient-informed core outcome measurement sets, and patient-reported outcome measures

- ❑ The European League Against Rheumatism (EULAR) published recommendations in 2011 for inclusion of patient partners in scientific projects, noting the many benefits : improved representation of patients' needs, increased opportunities for funding, empowering patients, incorporating patient priorities to avoid a mismatch between these and the scientific focus, and advantages for dissemination and implementation.

- ❑ Wang et al analyzed articles reporting clinical trials in rheumatology journals (2016 to 2020), but found that reports of patient partner involvement in rheumatology clinical trials is still rare (1.8% of 622 clinical trials).

Examples/Landscape of patient engagement in non-pain related therapeutic areas

Anesthesiology:

Patient engagement in clinical research critically lacking.

☐ Models for future efforts to meaningfully engage patients in anesthesiology research:

-The PCORI-funded multicenter Regional Versus General Anesthesia for Promoting Independence After Hip Fracture (**REGAIN**)- *Neuman et al, NEJM Oct 2021*

-Trajectories of Recovery after Intravenous Propofol vs inhaled VolatilE anesthesia (**THRIVE**)

Partnering with patients in clinical trials of pain treatments: evidence of gaps

- Patient engagement in research as partners in pain studies is not common

- Patient motivations and barriers to participate in trials of rheumatic diseases and chronic musculoskeletal pain (Vogt et al).
    - *-Patients have generally little knowledge about how clinical trials work*
    - *-Patient not aware what trials are available to patients with conditions like theirs*
    - *-Major barriers to participation: concern with adverse effects, being used as "guinea pigs"*

- Patient perspectives and treatment acceptability of telephone-based cognitive behavioral therapy for the prevention of widespread pain (Fraser et al 2019)

  Even among consented participants, many did not understand the objective of the study i.e., prevention of further chronic pain rather than treatments of their current ongoing pain.

Partnering with patients in clinical trials of pain treatments: evidence of gaps

- ❑ Patient partners represent the interests of a study's target treatment population, including individuals from underrepresented groups.
- ❑ Representing groups more vulnerable for developing chronic pain: Women, people of color, and members of the LGBTQ communities have variable representation within chronic pain populations; yet, they may have specific preferences, needs, and concerns.
- ❑ Multicenter clinical trials tend to be conducted in large academic centers, and are likely to misrepresent the interests of people living in rural or otherwise under-resourced communities

Partnering with patients in clinical trials of pain treatments: examples of patient partnerships

- ☐ Help of a patient group to assess the effect of self-care acupressure for women with menstrual pain (Blodt et al, 2013)
  - *Focus group discussion*
  - *Cross-sectional survey among females suffering from self-reported menstrual pain*
  - *A Stakeholder Advisory Group to design the study*
  - *A written Delphi consensus method to define the intervention.*

The feedback helped the researchers realize that preventative acupressure for menstrual cramp prophylaxis would not be feasible, and that the efforts should be focused on treatment only.

- ☐ Engaging patients in the development of a protocol for cannabinoid-based treatment for acute postoperative nausea, vomiting, and pain (Erridge et al 2020).

The partnership helped to refine perceived benefits and harms, consider routes of administration (e.g., smoking will delegitimize the therapeutic value of the intervention) for clinical trial design, and select meaningful outcomes measures.

Partnering with patients in clinical trials of pain treatments: examples of patient partnerships

- ☐ The **Pain Management Collaboratory** (PMC) is a unique example of a broad and transdisciplinary approach, is the collaborative between the NIH, Department of Defense (DOD), and the Department of Veterans Affairs (VA).

- ☐ Intergovernmental agency partnership that supports development, implementation, and testing of 11 large-scale, pragmatic clinical trials evaluating non-pharmacological approaches to management of pain and common co-occurring conditions in military and veteran health systems.

- ☐ Stakeholder Engagement Work Group of PMC: to develop partnerships that will maximize the ability to generate trustworthy, internally valid findings directly relevant to people with pain, front-line primary care clinicians and health care teams, and health system leaders.

Summary

Perceived Benefits and Disadvantages

- Improved trial design and protocol adherence
- Enhanced recruitment and retention
- Relevance of research questions and outcome measures to patients as the end-users
- Improves relevance to public and helps the dissemination of results
- Provides patient-focused value messages and increased opportunities for funding

- Increased time commitment and cost
- Lack of training and methodology in meaningful engagement of patient partners
- Proposed changes to research scope that may not be feasible

Summary

Key Principles of meaningful engagement

- ❑ Goals of clinical trials should align with the priorities of patients
- ❑ The selected patient partners should represent the population of study interest
- ❑ Engagement should be active, purposeful and authentic rather than passive or symbolic
- ❑ Encourage reflection
- ❑ Implement diverse forms of engagement within individual projects
- ❑ Provide ongoing training and support for researchers and patient partners
- ❑ Foster mutual respect and value between patients and researchers
- ❑ Draft detailed engagement plans and regularly evaluate the research program

Summary

Barriers and Facilitating factors

- Time for relationship building
- Financial resources
- Lack of public awareness about the need for and impact of patient engagement
- Lack of consistent terminology to describe patient engagement in research

- Clear role descriptions, responsibilities, and expectations
- Adequate compensation
- Camaraderie between researchers and patient partners
- Sufficient time
- Training for patients and researchers

Summary

- Data from trials testing pain treatments are relatively scarce, but substantial evidence that can be extrapolated from other therapeutic areas to optimize patient engagement in clinical trials of pain treatments

- Early and meaningful involvement of patient partners in clinical research can result in important improvements in clinical trial design, conduct, interpretation, dissemination, and implementation.

- Allowing patient partners to articulate their experience, expectations and needs at the formative stage can ensure the patient-centered focus of the study

- Research output that is transparent and is perceived trustworthy by patients is more likely to be accepted in clinical practice.

- Although formal guidance on patients’ engagement in clinical pain trials is not yet available, offering guidance on the implementation of core principles to optimally fit individual pain studies can elevate the field of pain research toward more meaningful and impactful clinical trials.

Discussion