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The Suitability of End Point Designs for Health Technology Assessment in Chronic Pain Studies

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ABSTRACT

Objectives: To identify the pain instruments and study end points most commonly used in clinical trial settings and to provide insight into the extent to which outcome measures in clinical studies are meeting payer needs. **Methods:** A literature review was conducted to identify published clinical studies and ongoing/recently completed registered trials in chronic pain. Inclusion criteria were interventional study, chronic pain in adults, and pain measured within the primary end point. **Results:** Of 1256 PubMed citations and 3006 clinical trial registry entries, 356 reported large clinical studies in pain populations (e.g., malignant, neuropathic, functional, and musculoskeletal). Studies were designed for superiority in 28% of PubMed citations and 8% of registry entries. The primary end points of most studies were single-dimension pain instruments, such as the numerical rating scale (n = 131) and the visual analogue scale (n = 69). In cases in which multidimensional pain end points were used, this was most commonly the Brief Pain Inventory (n = 37). Payer-relevant end points were typically limited to secondary end points, and were limited and/or reported inconsistently in published studies and ongoing/recently completed studies: preference-weighted quality of life (36% and 42%), resource use (2% and 8%), physical function (28% and 39%), and psychological function (25% and 24%). **Conclusions:** Most pain trials were not designed to show superiority to an active comparator, and they used single-dimension pain scales as their primary end point in combination with a broader selection of secondary end points. The inclusion of payer-relevant end points among clinical trials was inconsistent.

Keywords: chronic pain, end points, health technology assessment, literature review.

Introduction

The burden of chronic pain includes a quality-of-life impact for individual patients and an economic impact on society. For patients, chronic pain interferes with sleep, employment, and everyday activities and is frequently associated with depression [1]. For society, chronic pain has a direct impact on health care resource use and an indirect economic burden through missed workdays and reduced productivity in the workplace. In European countries, pain is estimated to cost economies between 1% and 10% of gross domestic product (GDP) [1]. The GDP of the European Union (EU) was estimated to be worth €14 trillion (US $18.5 trillion) in 2014 [2]; as such, a conservative estimate of the burden of pain in the EU is at least €140 billion (US $185 billion). US estimates are also high; according to the Institute of Medicine, in 2010, costs associated with pain were US $560 million to US $630 billion [3]. In spite of this substantial burden and a large recent investment in therapy development, there has been little progress in developing new, efficacious, and safe analgesics [4].

This limited development of new chronic pain therapies is a multifaceted issue. Although partly due to the complexity of pain pathways and the subjective nature of pain, research in this area is also hindered by a lack of efficacy, a potentially substantial placebo effect, end points that are not sufficiently sensitive, and the selection of end points that are not considered relevant to payers. *'Payers'* are broadly defined here as those responsible for financing or reimbursing health care services and health technology assessment bodies. This situation is reflected in a recent

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review on pain relief in America by the Institute of Medicine, in which it calls for new diagnostic measures and improved clinical research methods to determine the efficacy of pain treatments [3].

To justify any increased expenditure over existing standards of care, in pain, as in any therapeutic area, a payer-relevant patient benefit must be demonstrated to result from the use of the new treatment. Often, this requires the demonstration of superiority on primary and secondary end points in relevant trials. In some circumstances, however, payers may accept demonstration of other benefits in terms of improvements in specific, but often subjective, patient-related end points within the context of a noninferiority study. Which payer-relevant end points are accepted may differ by jurisdiction but frequently include efficacy (e.g., reduction in pain), preference-weighted quality of life (e.g., EuroQol five-dimensional (EQ-5D) questionnaire, short-form 36 health survey, or a measure that can be mapped to the EQ-5D questionnaire, especially in markets requiring cost-utility analyses), patient function (e.g., physical function, psychological function, and, in some markets, work impairment), and/or resource use (e.g., hospitalization and physician visits) [5–11].

To consider the need, design, and application of *de novo* outcome measures, or to create suitable combinations of existing outcome measures for the assessment of pain, it is essential to first identify the types and frequency of the measures currently used in trials of pain therapies. The present study identified these measures by means of a structured and comprehensive literature review of published and ongoing/recently completed clinical trials in chronic pain and reported the type of end points included within each study design. By grouping the end points into broad domains that may be of interest to payers, we attempted to understand the extent to which the use of end points in clinical studies may be meeting the needs of payers. In documenting how clinical studies are currently designed, how researchers are attempting to demonstrate the value of their products, and how payer-relevant end points are used, this research aimed to inform efforts to improve value demonstration in pain trials and thus to help improve patient access to novel pain treatments.

Methods

A structured, comprehensive literature review of published clinical studies in PubMed and of ongoing/recently completed registered trials in clinical trial registries was conducted to identify clinical studies in areas of chronic pain, which could be malignant, neuropathic, functional, or musculoskeletal in origin.

PubMed Searches for Published Clinical Studies

For searching PubMed, terms were selected using Medical Subject Headings (MeSH) in the first instance. MeSH terms were identified for the general areas of chronic pain (e.g., malignant, neuropathic, functional, and musculoskeletal), instruments to assess pain, quality of life, and clinical studies (randomized controlled trials [RCTs] and non-RCT studies). Once suitable MeSH terms were identified for these areas, each MeSH term was investigated to identify the entry terms that were associated with each. As such, a combination of MeSH terms and text words was used to identify relevant articles.

The searches were limited to human studies. Comments, letters, news articles, editorials, case reports, preclinical studies, *in vitro* studies, review articles, and studies in children were excluded.

The searches were limited to English-language articles only. To restrict the literature review to the most recent studies in pain, and to keep the search results manageable, the search for RCTs was limited to articles published from 2009 onward (i.e., approximately 5 years). Because the search for non-RCTs was considered supplementary to the RCT search, the search was limited to articles published from 2012 onward (i.e., approximately 2 years). The full search strategy used to search PubMed is presented in Appendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.07.001. The search in PubMed was conducted on April 24, 2014.

Trial Registry Searches for Ongoing/Recently Completed Clinical Trials

Three clinical trial registries were searched:

- ClinicalTrials.gov: http://clinicaltrials.gov
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP): http://apps.who.int/trialsearch/
- EU Clinical Trials Register: https://www.clinicaltrialsregister.eu

Using the terms identified for the PubMed searches already described, a search strategy was devised for the clinical trial registries using a combination of terms for chronic pain, for instruments, and for quality of life. MeSH terms are not available for the trial registries; therefore, only a combination of text words and filters was applied. In addition, the search facilities in the registries are not as sophisticated or do not allow the same search string length as in PubMed; thus, it was not possible to use all the same search terms. As such, the primary search terms were used as a basis to create search strategies for the registries.

The search strategy required slight modifications for each registry to allow for the differences in search capabilities between the registries. These search strategies are presented in Appendix A in Supplemental Materials (see Appendix Table 2 for ClinicalTrials.gov, Appendix Table 3 for WHO ICTRP, and Appendix Table 4 for the EU Clinical Trials Register). The searches were conducted on March 17, 2014 (ClinicalTrials.gov), March 31, 2014 (WHO ICTRP), and April 3, 2014 (EU Clinical Trials Register).

Screening of Articles and Trial Entries

Titles and abstracts of identified citations from PubMed and the list of relevant clinical trials from registers were screened for relevance by one researcher against prespecified inclusion/exclusion criteria (Table 1). In particular, strict screening criteria were used in relation to the population to manage the volume of literature in this widely researched therapy area. Specifically, studies in children were excluded because the focus of this review was pain in adults; studies in acute pain were excluded because this review is focused on long-term chronic pain conditions; studies in healthy volunteers were excluded because this review is focused on the treatment of pain in patients with the condition; and studies conducted in fewer than 100 patients were excluded to focus on the larger, more robust studies.

For the articles from PubMed, in cases in which a decision could not be reached on the basis of the abstract, the full-text article was retrieved and reviewed by one researcher against the same inclusion/exclusion criteria. If a decision could still not be reached, a second researcher reviewed the full-text article, and the reviewers discussed their observations to reach a consensus. The inclusion and exclusion processes were recorded, including the completion of a Preferred Reporting Items for Systematic