ACTTION Special Issue on Clinical Trials of Pain Treatments
Introduction (part 1)

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The ACTTION Guide to Clinical Trials of Pain Treatments: standing on the shoulders of giants

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"If ye speak truth, Oh ye Schools, that ye can cure any kind of Fevers without evacuation, but will not fear of a worse relapse; come down to the contest ye Humorists: Let us take out of the Hospitals, out of the Camps, or from elsewhere, 200, or 500 poor People, that have Fevers, Pleurisies, etc. Let us divide them in Halfes, let us cast lots, that one half of them may fall to my share and the other to yours; I will cure them without bloodletting and sensible evacuation; but do you do as ye know (for neither do I tye you up to the boasting, or of Phlebotomy, or the abstinence from a solutive Medicine) we shall see how many Funerals both of us shall have… Here your business is decided."

–John Baptiste Van Helmont, 1662[4]

The World Health Organization has defined a clinical trial as "any research study that prospectively assigns human participants or groups of humans to 1 or more health-related interventions to evaluate the effects on health outcomes" (https://www.who.int/topics/clinical_trials/en). This definition includes double-blind randomized clinical trials (RCTs), which are considered the highest level of scientific evidence in the evaluation of treatment interventions because they provide assessments of treatment efficacy and safety that are substantially more informative with respect to causal effects on outcome and less prone to bias than those from nonrandomized, uncontrolled, and unblinded studies.[14] Despite the advantages of RCTs, however, it is important to recognize that multiple types of bias involving methods, analyses, and conclusions can be present, and that these must be critically evaluated when designing clinical trials and interpreting their results.

The ACTTION Guide to Clinical Trials of Pain Treatments consists of a series of articles that is intended to serve as a basis for designing, conducting, analyzing, interpreting, and reporting the results of RCTs of treatments for acute and chronic pain. The primary intended audience for these articles is clinician investigators interested in the major issues that should be considered when conducting clinical trials of pain treatments. The ACTTION Guide will also be valuable to early career clinician investigators and trainees interested in pursuing careers involving the conduct of clinical trials. In addition, these articles will be of value to clinicians who would like to improve their ability to understand and interpret the results of published clinical trials.

The articles in this series focus on randomized trials investigating the efficacy and safety of treatments for acute and chronic pain. Relatively limited attention has been devoted to the analysis and interpretation of adverse events and to benefit–risk assessments, both of which often involve complex issues and require close collaboration between biostatisticians and clinician investigators.

Clinical trials involve research on human participants, and all individuals involved in such studies must become familiar with applicable ethical principles and regulatory obligations. These include the responsibilities of investigators and the importance of informed consent, as well as institutional and national regulations for study review and approval. Rowbotham and McDermott[12] begin part I of the ACTTION Guide by discussing several important ethical considerations involving clinical trials of pain treatments. Although these RCTs share numerous ethical considerations with clinical trials in many other medical conditions, there are also unique challenges; for example, rescue pain treatments should be provided for patients with unacceptable levels of pain, but doing so has the potential to reduce the study's ability to show a difference between the active and the placebo or sham intervention.

Campbell et al.[3] discuss the design and execution of proof-of-concept clinical trials. Such early investigations play a crucial role in the development of new treatments, often providing preliminary evidence of the efficacy and safety of different treatment regimens and of the feasibility of various research methods and outcome

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measures. Given the large number of novel treatment targets and interventions, proof-of-concept studies often serve as a basis for "go-no go" decisions involving future investigations and efforts. In such circumstances, the risks of making incorrect decisions must be balanced against what are often limited resources and small sample sizes in this phase of the treatment's development.

The biopsychosocial model of pain has provided a unifying perspective for clinicians and researchers for well over half a century. Although this model has had a broad range of important influences on treatment interventions and research advances, perhaps, its greatest impact has been the foundation it has provided for the development of several major treatment approaches. Edmond et al.[6] discuss the aspects of clinical trial design and execution that trials of behavioral treatments share with other types of RCTs and highlight the unique considerations presented by such trials, including choice of comparison interventions, strategies for patient and provider blinding, and intervention fidelity and therapist adherence to treatment protocols.

It is well known that many patients with chronic pain fail to respond adequately to existing pharmacologic and various nonpharmacologic (eg, behavioral) treatments. For such patients, invasive therapies may provide meaningful pain relief. Cohen et al.[5] discuss the substantial challenges of conducting RCTs of such interventions, not least of which are selection of comparison groups and methods for conducting such trials in a double-blind manner. A recent RCT of a surgical intervention for shoulder pain with sham and no treatment comparison groups illustrates that these challenges can be met when the investigators have the motivation and resources to do so.[2]

These initial articles in the ACTTION Guide focus on clinical trials conducted in adults. There are appreciably fewer RCTs conducted in children and adolescents, which is very unfortunate given that chronic pain can begin in childhood and sometimes persists through adolescence into adulthood. Palermo et al.[11] review the major issues encountered when designing and conducting chronic pain trials in children and adolescents, including the unique ethical concerns and limitations in communication involved in studying pain treatments in minors. As they emphasize, the evidence base for the treatment of pediatric chronic pain is limited, and much greater effort must be devoted to conducting well-designed RCTs and thereby providing a foundation for treatment guidelines.

Most of the articles in the ACTTION Guide emphasize RCTs of chronic pain. Clinical trials of pharmacologic treatments for acute pain have a longer history, beginning in the middle of the 20th century. This history has made possible a level of research design standardization, investigator expertise, and assay sensitivity that has often eluded chronic pain RCTs. Building on this legacy, Gilron et al.[8] discuss prospects for future advances, including improved outcome assessments and greater recognition that there are clinical settings and patient types that are much more complex than those in the dental and bunionectomy RCTs that have played such an important role in analgesic drug development.

One of ACTTION's major objectives is to encourage and support early career investigators and trainees interested in exploring a career that includes conducting basic or clinical research on pain. Adams et al.[1] provide a wide-ranging overview of the opportunities and challenges for junior investigators who are considering becoming involved in clinical trials. As these authors emphasize, conducting such studies in many academic settings can be difficult, given that financial support is often limited and that there are almost always competing clinical and administrative responsibilities. The gratification that can come from working to identify improved treatments, however, can be substantial, and for many junior and senior investigators more than offsets these challenges.

There has been increasing attention to the existence of major deficiencies in the reporting of clinical trials in peer-reviewed publications. Publication of CONSORT checklists and the requirement of many journals that articles must adhere to these guidelines have provided a strong foundation for greater standardization and more complete reporting of RCT methods and results. Gewandter et al.[7] provide a pain-specific supplement to the CONSORT guidelines, emphasizing the aspects of chronic pain RCTs that must be described for readers to be able to adequately evaluate sources of bias and misleading interpretations of results. Transparent reporting of methods and results will contribute to ensuring that clinical trials are as rigorous, reproducible, and informative as possible.

There is 1 aspect of conducting clinical trials that we want to especially emphasize. We believe strongly in the importance of clinical trial registration on authoritative websites such as www.clinicaltrials.gov or www.clinicaltrialsregister.eu. Prospective registration of clinical trials before the beginning of enrollment has multiple benefits, including impeding selective reporting of outcomes and analyses, reducing publication bias resulting from failure to publish trials for which the treatment effects were not statistically significant, and increasing transparency of trial methods and results to investigators, patients, and the general public. Importantly, the information provided during initial registration must be updated when protocols and prespecified analysis plans are revised and when results become available. Unfortunately, there are still journals that either do not require such registration or permit retrospective registration of completed trials, a practice that negates the benefits of prospective registration and that has limited if any value.[13]

We are optimistic that the prospects for major advances in understanding the neurobiologic and psychosocial mechanisms of pain and in developing improved treatments and preventive interventions have never been better. As a consequence of the opioid crisis in the United States, considerable funding for basic and clinical research on pain has become available from the National Institute of Health's Helping to End Addiction Long-term initiative (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative). In addition, the accomplishments of ACTTION (www.acttion.org) and the European Union Innovative Medicines Initiative EuroPain (http://www.imieuropain.org) and PainCare (https://www.imi-paincare.eu) programs have demonstrated that public–private partnerships have great potential to improve knowledge of pain mechanisms and patient responses to pain treatments.

As indicated by our subtitle, we want to acknowledge the landmark contributions of an earlier generation of analgesic clinical trialists. As Lasagna[9] emphasized in a historical overview, the anesthesiologist Henry Beecher and statistician Frederick Mosteller at Harvard University, and physician pharmacologist Raymond Houde, psychologist Stanley Wallenstein, and nurse Ada Rogers at Memorial Sloan-Kettering Cancer Center provided an enduring foundation for studying the efficacy and safety of pain treatments. Major contributions were also made by William Beaver, Stephen Cooper, Howard Fields, William Fordyce, Louis Lasagna, Eugene Laska, Henry McQuay, Andrew Moore, Nancy Olsen, Bernard Schachtel, Soren Sindrup, Abraham Sunshine, Peter Watson, and others too numerous to mention. We dedicate the ACTTION Guide to Clinical Trials of Pain Treatments to Mitchell Max who, when designing and conducting analgesic

clinical trials back in the mid-1980s, addressed critically important methodologic and statistical issues that remain inadequately recognized to this day.[10]

Disclosures

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