Abstract

There is longstanding debate on the use of placebo control in clinical trials. Critics of placebo-controlled trials argue that using placebo sacrifices the welfare of patients and is unethical if a proven therapy exists. Proponents argue that placebo control is crucial for proving the safety and efficacy of new treatments because it is more scientifically rigorous.

The heterogeneous physiology of pain adds an additional layer of complexity to the debate because the measurement of pain is inherently subjective. Analgesia studies are further complicated by the potential effects of a robust placebo response, not only because of the subjectivity of pain measurement, but also due to the variability in patient responses to both analgesics and placebo. This white paper reviews the regulatory, ethical, cultural, and even financial considerations surrounding the issue of placebo control in analgesia clinical trials.
Introduction

Pain is a significant health problem that impacts quality of life and imparts high costs to society. Despite intense research effort and progress in our understanding of the mechanistic and molecular basis of pain, there has been a lack of real breakthroughs in novel analgesic drug development over the past fifty years. One major obstacle to the development of novel pain medicines is the difficulty of planning and executing analgesia clinical trials which meet the expectations of regulatory authorities, ethics committees, and other key stakeholders.

In the United States, the Food and Drug Administration (FDA) typically expects sponsors to conduct two separate placebo-controlled trials in order to be eligible for marketing authorization. However, in the EU, the European Medicines Agency (EMA) will not accept two-arm, placebo-controlled trials if a proven intervention is available. In addition, authorities in the EU are increasingly requiring sponsors to demonstrate that new drugs are not only effective, but also offer improvement over the existing standard of care. This white paper provides an overview of the use of placebo control in pain studies in the EU, as well as strategies for developing rigorous placebo-controlled analgesia clinical trials.

Rationale for Placebo Control

Choosing a control group is a critical decision in designing any clinical trial. The choice of control group affects nearly every aspect of the trial, from its ethical acceptability and endpoints to the credibility of results and eventual marketing authorization. Factors to consider when selecting a control group include availability of standard therapies, ability to justify the study design, and ethical considerations. The main purpose of control groups is to allow discrimination of patient outcomes caused by the study drug from outcomes caused by other factors, such as disease progression, observer or patient expectations, or other treatment.

Critics of placebo-controlled trials argue that placebo control potentially violates clinical equipoise when a proven effective therapy is available. Clinical equipoise refers to situations where clinicians are not sure whether a new treatment is as good as standard of care. In these cases, it could be argued that placebo use compromises the patient’s right to receive the best care possible. However, proponents of placebo-controlled trials counter this argument by pointing out that placebo-controlled trials are scientifically and ethically justified when they are supported by sound methodological considerations and do not expose patients to excessive risk.

Modifications to Placebo Control

Using placebo control does not necessarily mean leaving patients untreated. Modifications of study design and combinations with rescue medication or other controls may resolve ethical or practical issues. Studies that include three arms – study drug, active control, and placebo – are common. Other modifications include:

- ‘Add-on’ designs in which all patients are given a standard therapy in addition to either study drug or placebo
- ‘Early escape’ designs in which a study plans for rescue treatment in patients whose clinical status worsens or fails to improve
- ‘Limited-placebo’ designs in which a placebo group is used for a short period at the beginning of an active control to establish assay sensitivity and then discontinued
- ‘Randomized withdrawal’ designs in which all patients receive the study drug for a specified time before being randomized to continued treatment with the study drug or with placebo

The ICH E10 Guideline describes the general principles involved in modifying placebo control, but does not address the regulatory requirements in any region.
EMA Guidance on the Use of Placebo Control in Analgesia Studies

It is the official position of the Committee for Proprietary Medicinal Products (CPMP) and the EMA that continued availability of placebo-controlled trials is necessary to satisfy public health needs, as long as ethical use is clearly understood and implemented.\(^5\)

Guidance on choosing control groups is provided by the ICH E10 guideline, as well as the various guidelines developed for specific therapeutic areas.\(^3\) The Committee for Medicinal Products for Human Use (CHMP) of the EMA has issued separate guidelines on the clinical development of new drugs for nociceptive and neuropathic pain. These guidelines are currently being merged, and the new guidance is expected later in 2012.

Guidelines for Nociceptive Pain

In general, the CHMP guidance on nociceptive pain acknowledges the value of placebo control in analgesia trials, but emphasizes that ethical and cultural considerations may limit placebo use. The guidance recommends the use of placebo control with appropriate use of rescue medication for trials that are not intended to show superior efficacy to an active comparator. The guidance recognizes that three-armed trials, where the study drug is evaluated against both placebo and an active comparator, are usually the most informative.\(^6\)

Guidelines for Neuropathic Pain

The guidance on neuropathic pain requires randomized, placebo-controlled trials in the chronic pain setting. It also states that, in cases where there is an established treatment, a third arm with the active comparator is required.\(^7\)

Placebo Control in Practice

In the EU, the decision to require placebo and/or active control studies for analgesia has been, and will continue to be, taken on a case-by-case basis, although some fundamental principles apply. In practice, the EMA prefers for sponsors to demonstrate that new treatments are superior to existing therapy in order to win marketing approval. The use of an active or best-available-therapy control group in addition to placebo control has become the standard for pain indications where a proven therapy already exists.

However, there may be methodological limitations in using an active comparator. For example, in a non-inferiority trial, it may be difficult to demonstrate similarity to an existing therapy, especially in pain studies where the study drug’s mechanism of action, analgesic effect, and likely responders had not yet been defined. The need for sponsors to provide additional supporting information often results in added arms to secure regulatory approval. While adding arms to a placebo-controlled study is costly, it is likely more cost-effective and persuasive than conducting a separate trial due to the risk of study-to-study variability.

General Considerations

Availability of Standard Therapy

When no proven effective therapy exists, the use of placebo control is routinely accepted. Placebo-controlled trials become controversial when patients randomly assigned to receive placebo forego or delay treatments that are known to be effective.\(^8\)

Pain Intensity

Pain intensity should be considered when determining whether or not placebo control is appropriate. Placebo control is not appropriate in a post-surgical moderate to severe acute pain setting. However, in a chronic pain setting, it is appropriate to evaluate placebo versus a study drug as an adjunct to standard therapy.
Placebo Effect

Placebo effects are genuine psychobiological events that can be attributed to multiple factors, including the patients’ expectations of relief. The placebo effect is particularly problematic in pain studies with a symptom-based approach, where placebo-related analgesic responses may occur in up to 60% of study participants and may have a long duration.\(^\text{10}\)

Figure. Considerations for use of placebo controls.\(^\text{11}\)

<table>
<thead>
<tr>
<th>Question</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Is there effective treatment?</td>
<td>Placebo control acceptable</td>
</tr>
<tr>
<td>Is active control equivalence study informative?</td>
<td>Active control acceptable</td>
</tr>
<tr>
<td>Does treatment affect survival or irreversible morbidity in population to be studied?</td>
<td>Placebo control acceptable</td>
</tr>
<tr>
<td>Can add-on study provide information?</td>
<td>Add-on study</td>
</tr>
<tr>
<td>Can short-term study that is ethically acceptable provide needed evidence?</td>
<td>Short-term placebo-controlled study</td>
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<td>Is “effective” treatment accepted uniformly as standard treatment?</td>
<td>Placebo-controlled trial where doubts exist</td>
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<tr>
<td>Might new treatment prove superior to active control?</td>
<td>Active control (superiority) study</td>
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Three-arm studies are recognized to give the fullest assessment of efficacy and safety, for a number of reasons:\(^\text{8}\)

1. Comparison of active control versus placebo provides an internal standard for assay sensitivity
2. Situations where active control is no better than placebo may indicate flaws in study design, such as the choice of pain model, rather than lack of analgesic efficacy
3. Comparison of study drug versus placebo can be used to measure the effect of the study drug
4. Comparison of active control versus study drug relative to placebo can be used to demonstrate superiority or non-inferiority

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Ethical Considerations

According to the biomedical research guidelines published by the Council for International Organizations of Medical Sciences, a clinical trial cannot be justified from an ethical standpoint unless it is capable of producing scientifically reliable results.\textsuperscript{12} Scientifically invalid research is inherently unethical because it exposes patients to risk without any benefit. European Union Council Directive 75/318/EEC also specifies that “all clinical trials should be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki.”\textsuperscript{4}

While the Declaration of Helsinki emphasizes that extreme care must be taken not to abuse the use of placebo control, it also leaves the concept of ‘proven intervention’ open to interpretation. There may also be room to challenge established therapies if the supporting data for those therapies were not very strong.\textsuperscript{11}

In addition to the Declaration of Helsinki, the ICH E6 Guideline and Directive 2001/20/EC on Good Clinical Practice also provide information on the ethical use of placebo control.\textsuperscript{14, 15} Special ethical considerations that are pertinent to the pediatric population can be found in ICH Topic E11 Clinical Investigation of Medicinal Products in the Paediatric Population.\textsuperscript{16} Finally, when designing protocols, it is important for sponsors to recognize that ethical positions on the use of placebo control in analgesia are influenced by cultural norms and may vary from country to country within the EU.

Cultural Considerations

Pain is a culturally-defined physiological and psychological experience. Sociocultural factors can influence pain perception, tolerance, and coping style. Cross-cultural studies have shown significant differences in the meaning of pain in different countries. Studies have shown that people who find meaning in their pain show less suffering than those who find pain to be meaningless. While some cultures are characterized by stoicism, others view pain as an inevitable part of life or as an important component of healing. Comparative studies of pain response in different ethnic and cultural groups have revealed significant differences in pain tolerance and coping strategies. Some cultures utilize religious faith as a powerful coping strategy and pharmacological interventions to reduce pain may be inappropriate.\textsuperscript{17}

Sponsors must account for, and be sensitive to, potential sociocultural influences when designing clinical trials. Due to cultural variability in the experience of pain, pain scales that measure pain intensity may be less important than scales that measure a patient’s degree of satisfaction about how pain is being managed.
Endpoint or Outcome Considerations

Analgesia clinical study development requires a well-defined, scientifically-acceptable definition of effective analgesia. Variability in outcome measures across analgesia clinical trials can hinder evaluations of the efficacy of treatment. In an effort to develop a standard set of outcome measures, the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommended six core domains that should be considered when designing chronic pain clinical trials. These core domains were:

- Pain
- Physical Functioning
- Emotional Functioning
- Patient-Reported Ratings of Improvement & Satisfaction with Treatment
- Symptoms and Adverse Events
- Disposition: Adherence to Treatment or Reasons for Early Study Withdrawal

These suggested core domains address the issue of patient-related benefit and may be particularly useful in demonstrating therapeutic advantage in terms of safety, tolerability, or compliance.

Financial Considerations

The requirement for an active comparator could potentially impact analgesic development and, eventually, marketing. Sponsors of novel analgesics that demonstrate non-inferiority/equivalence when compared to best available therapy may choose to invest in other compounds, rather than continue to develop a ‘me too’ drug that fails to win marketing approval or favorable pricing.

The Issue of Reimbursement

Changes to the drug reimbursement structure in the EU may impact clinical trial design, even if a study has already received approval by regulatory authorities and independent ethics committees. Healthcare decision-makers and payers increasingly require sponsors to demonstrate that new drugs are not only effective, but also improve on standard of care, in order to secure higher reimbursement. In Germany, the largest EU market, a law was passed in January 2011 requiring sponsors of new drugs to submit a cost-benefit dossier to the Federal Joint Committee (G-BA), the highest healthcare decision-making body in Germany. G-BA may consult with the Institute for Quality and Efficacy in Health Care (IQWiG) to assess patient-related benefit as part of the drug pricing process. IQWiG’s decisions reflect a strong skepticism of surrogate markers and a preference for active comparators and patient-relevant outcomes in different clinical trial populations. In order to secure a favorable price point, sponsors should consider adding patient outcome measures as trial endpoints, particularly because the price set in Germany is referenced by other countries in price negotiations.
Strategies for Conducting Successful Placebo-Controlled Analgesia Trials

Regulatory and ethical issues regarding the appropriate use of placebo should be addressed early on in the analgesic development program, with appropriate scientific advice and protocol review by competent authorities in the EU. Sponsors have access to multiple sources of information on protocol design, including EMA guidance and best practice guidelines published by physician groups. The CHMP has made scientific advice available to industry to aid in generating scientifically robust and reliable data for the assessment of comparative efficacy for individual products under development. Sponsors may also benefit from partnering with a research organization with analgesia experience, or reviewing the development programs and protocols of recently-approved drugs in a similar therapeutic area to gain insight into successful study designs.

Addressing Ethical Concerns

The overarching ethical concern in using placebo control in analgesia studies is the risk of exposing patients to unacceptable levels of pain or allowing the patients’ pain experiences to break through the provided treatment regimen. It is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort, provided that there is no coercion and patients are informed about available therapies and the potential consequences of delaying treatment. However, some clinicians or patients may not be comfortable deferring the treatment of pain. The use of appropriate rescue medication helps to mitigate ethical concerns, as well as clinician and patient concerns, about placebo use.

Selecting Clinical Sites

Identification and selection of clinical sites with proven track records in enrollment and quality, as well as experience with analgesia trials, is a critical factor for success.

Accessing Local Knowledge

As ethical positions and perceptions of pain are influenced by cultural norms, discussions with independent ethics committees and other competent authorities are a critical step in analgesic clinical trial design. Sponsors should consider having their protocol reviewed by local key opinion leaders for acceptability and feasibility. Sponsors should also be aware that cultural influences are not limited to the general public. There are also distinct medical cultures that influence the perception and treatment of pain, and these biases in clinical practice vary from country to country. The variability in ethical and cultural positions within the EU makes it valuable for sponsors to have access to local expertise on the ground.

Conclusion

Pain is the most common symptom for which patients seek medical attention, and there is an unmet need for new analgesic drugs. In recent years, pain studies have favored the development of products whose pharmacokinetic, safety, and efficacy profiles are already well-established. In the EU, the increasing emphasis on comparison to existing therapies and evidence of patient-related benefit has significant implications on clinical trial design, marketing, and reimbursement. In order to conduct rigorous trials of novel analgesic drugs, sponsors need to understand the current regulatory and ethical environment, as well as the cultural and financial factors, that influence the use of placebo control.
DEVELOPING ANALGESIA STUDIES: Use of Placebo Control in the EU

References

About Premier Research

Premier Research is a leading global contract research organization (CRO) serving biotech, pharmaceutical, and medical device corporations. Its services include clinical research and regulatory outsourcing in the areas of analgesia; neurology; infectious, cardiovascular, and respiratory disease; dermatology; and oncology. The company also has a wealth of experience in medical device and pediatric research.

Premier Research has 21 offices (seven in North America, 14 in Europe) and operates in 23 countries. It employs 1,000 clinical professionals dedicated first and foremost to fulfilling each client's requirements in a timely, accurate, and cost-effective manner. This includes a strong international network of monitors and project management professionals combined with regulatory, data management, statistical, scientific, and medical experts, and staff at its well-established network of dedicated clinical sites.

Michael Kuss, BS
Vice President, Analgesia

Mr. Michael Kuss is the therapeutic leader in analgesia and rheumatology and focuses on building and reinforcing our depth in analgesia. Mr. Kuss has been with the company since 2001 and has worked as an Executive Director, Clinical Trial Management and Senior Director, Analgesia and Rheumatology. He is responsible for working with clients to help develop clinical development plans, provide therapeutic expertise to internal and external clients', write protocols, manage study teams to conduct clinical trials, and participate in the preparation of clinical study reports.

Prior to joining Premier Research, Mr. Kuss worked for Pharmacia (formerly G.D. Searle) in various positions with the last being Director of Research and Development. Mr. Kuss was responsible for clinical development of several COX-2 inhibitors (celecoxib, valdecoxib and parecoxib) and NSAIDs (oxaprozin, oxaprozin potassium, diclofenac/misoprostol) as part of the Arthritis and Inflammation team. Prior to G.D. Searle, Mr. Kuss worked as a Clinical Research Associate at Abbott Laboratories and as an Infectious Diseases Research Technologist.

Mr. Kuss graduated from Wright State University in Dayton, Ohio with a BS in Medical Technology. He received a certification in Medical Technology from the American Society of Clinical Pathology. He is a member of the American Pain Society and Drug Information Association. He is a frequent presenter at annual meetings of the American Pain Society and American College of Rheumatology annual meetings. He has presented at the DIA annual meeting and at several DIA sponsored symposia. He is an author on many publications and posters in the areas of analgesia, rheumatology and infectious disease.

Jim Lees
Senior Director, Analgesia, Europe

Mr. Jim Lees is currently the Senior Director, Analgesia, at Premier Research. In this role, Mr. Lees works with our global team of directors who add value throughout the project life-cycle. This responsibility extends from sales lead generation, through proposal development, bid defense meeting, project execution to final deliverables and acquisition of repeat business.

Prior to joining Premier Research, Mr. Lees served as Clinical Development Manager with PAION UK, Ltd; a company specializing in the development of innovative drugs for hospital-based treatment in indications for which there is a substantial unmet medical need. In this role, he was responsible for the design and implementation of clinical development plans for PAION’s lead developmental compounds in the fields of analgesia and anesthesia. Prior to his eight years with PAION, Mr. Lees was based in Japan as Global Co-ordination Associate with Chugai, responsible for harmonization of global clinical operations across the United States, Europe and Japan. He has also held the positions LCRA at Chiltern and Clinical Data Manager with Monsanto and Quintiles.

Mr. Lees earned his Bachelor’s degree of Medical Science from the University of St. Andrews.
Susan Bhatti, PhD  
Executive Director, Regulatory Affairs, Study Start-Up and Medical Writing  

Dr. Susan Bhatti joined Premier Research Germany as Director Regulatory Affairs in 2007 and she is now Executive Director European Regulatory Affairs, Study Start-Up and Medical Writing. She is responsible for managing all European regulatory, start-up and medical writing activities and supervising the staff in these departments. Prior to this she spent eight years working as a regulatory manager in the pharmaceutical industry, where she gained experience in both national and European submission procedures. Dr. Bhatti has more than 15 years of experience working in the pharmaceutical and CRO industries.

Dr. Bhatti has performed regulatory submissions for many products covering a wide range of therapeutic areas and dosage forms, such as: antibiotics, biosimilars, cardiovascular medicines, dermatological products, products to treat central nervous system disorders, products in the area of oncology, products to treat metabolic diseases, respiratory disease products, and products for the treatment of osteoporosis. She has also written and/or reviewed many submission documents such as clinical and non-clinical overviews, protocols, study reports, and investigator brochures; and has also advised several companies on their Pediatric Investigation Plans, given in-house and external training and prepared and submitted PIPs to the PDCO. Her experience in pharmacovigilance covers both clinical trial reporting requirements as well as post-marketing requirements, e.g. pharmacovigilance systems and periodic safety update reports.

Dr. Bhatti obtained her PhD in Cell Biology at the J. W. Goethe University in Frankfurt in 1991. Prior to this she had completed a degree course in Biology at the J. W. Goethe University in Frankfurt and obtained a 1st class honors degree in 1984. She was educated in England and is bilingual in German and English.