Placebos are a key component of many clinical trials. However, the ethics behind their use are widely debated. Despite the continuous development of new treatments, availability of efficient and safe methods remains a great unmet need. This term, ‘methods’, refers to the vast range of approaches to chemical and biologic medications, cell-based therapies, medical devices, psychotherapy and so on. Testing new procedures against placebo is thought to provide the most reliable data on the value of a new solution.

However, it is not unusual that this comparison is unfeasible for technical or practical reasons or because it is considered unethical. The latter especially affects the development of treatments for severe diseases or for vulnerable populations, where the use of a placebo instead of an active comparator or standard-of-care may be dangerous for the subject. In some cases, the use of placebos can also be linked with a risk to other people, for example, due to an increased possibility of aggressive or asocial behaviours.

These considerations have fuelled many years of debate over the use of placebos in clinical trials. Regulators, opinion leaders, patient advocates and journalists express their opinions on this matter – noticing a disagreement between the stakeholders is easy.

Conflicting Objectives

While key regulators EMA and FDA endorse placebo-controlled trials remaining compliant with the World Medical Association’s 2013 edition of the Declaration of Helsinki and with a less restrictive ICH E10, opinion leaders and medical societies seem more reluctant. Patients are not happy with the placebo option at all, and journalists publish negative sentiments on their use in severe disease research (1). Additionally, for some indications, a purely placebo-controlled design cannot be considered at all, as in the case of epilepsy.

Furthermore, although a prevailing strategy, the use of this approach is not always adequately justified by companies. In a review of the records of one Finnish hospital published in 2015, Keränen et al found that only one third of the protocols provided justification for the use of placebo, and, in most of those cases, this was due to the scientific rationale or to comply with regulatory guidelines (2).

The use of a placebo in disorders affecting central nervous systems (CNS) is particularly commended for schizophrenia, major depression, dementia and epilepsy. The most important regulations are the Declaration of Helsinki, ICH, FDA and EMA recommendations, which underline that the use of a placebo can be accepted in certain circumstances.

While these represent cautious, yet endorsing, approaches, some authorities reject or limit the possibility to accept a placebo-controlled trial in such indications (3). All parties have valid reasons and, in scientific publications, articles defending the use of placebos can be found alongside medical societies trying to restrict its application in some populations.

Even though opinions are mixed, the likelihood of obtaining trial authorisation in individual countries is unpredictable, as the decision may depend on the actual expert personnel requested by the regulatory authorities to evaluate the application. When planning a clinical study in such a condition with a placebo control, performing a profound country-level feasibility check and discussing the chances of protocol approval by the Ethics Committee and regulatory authorities with selected principal investigators in the candidate locations is important.

Paradoxically, in some cases, performing an efficacy study without a placebo can also be considered unethical, thus risking a lack of valid conclusions.
Interestingly, despite having a clear endorsement for placebo-controlled design, a search in public databases for pure (ie not an add-on) placebo-controlled studies in some indications, such as schizophrenia, reveals quite specific patterns. The US is in a leading position when considering the number of trials run, which is typical for almost every case (4). Surprisingly, well-developed European countries are invisible in these results. Central Europe is showing a slow uptake.

This most probably reflects an increasing number of scientifically active physicians seeking a balance between the conservative avoidance of placebos and the need to continue development of new antipsychotics, for example for patients with predominant negative symptoms. The geography of placebo-controlled trials in psychiatry – specifically in studies of schizophrenia – reveals that most of them have recently been run in Baltic countries, CEE, the Far East and the US, as presented in Figure 1.

**Regional Patterns**

Regulators and opinion leaders suggest some mitigation measures to alleviate the risks associated with placebo use in these patients. Special study designs are proposed, such as:

- Randomised withdrawal
- Use of a well-documented standalone active comparator instead of a placebo
- Running the trial in a hospital or otherwise controlled environment
- Limiting the time on placebo
- Extension of short-term placebo studies
- Three-arm studies using placebo and active comparator (‘gold standard’)
- Permission of co-medications
- Add-on designs

**Figure 1:** Placebo use in clinical trials of schizophrenia: the geographic distribution of completed, Phase 3 clinical trials (N=30) conducted in schizophrenia with conventional placebo arm globally (A) and across countries (B). Out of 175 records identified to include placebo component, only 30 studies had placebo arm not combined with add-on medications. Data retrieved from clinicaltrials.gov on 16 June 2017
The need for adequate assessment and high dropout rates may impact the scientific value of the collected data.

The key drawbacks of using placebos include an increased number of adverse events—these are linked to the discontinuation of so-far treatment, withdrawal and relapse of disease symptoms—which will trigger at least a temporary study stop until Data Safety Monitoring Board or regulatory authorities grant the green light. Such disruptions can cause an obvious impact on trial timelines and, in consequence, upon the marketing of the product. Another potential problem may be the dropout rate caused by placebo use leading to the deterioration of health/onset of symptoms. Furthermore, the lack of certainty regarding treatment received (i.e., active or placebo) may translate into a subjective perception of feeling worse, thus masking the effect of the active investigational medicinal product when taken while the patient thinks he/she is on placebo.

However, another frequently highlighted issue is the potential of the control to ‘generate’ positive effects, concealing the disparity between the studied drug and the lack of treatment. The latter is, in fact, very different to the use of a placebo, which can be strong enough to disable the possibility of demonstrating the superiority of potentially active treatment.

**Final Thoughts**

The challenges related to the presence of placebo in CNS clinical research are significant. As a result, such studies require particularly careful design and cautious biostatistical planning that considers:

- Time-to-event design
- Run-in periods
- Alternative and non-pharmacological treatment allowance

Generally, the careful selection of countries and sites minimises the risk of the study application’s rejection due to ethical considerations, and, although questions from the Ethics Committees and regulatory agencies are likely in placebo-controlled studies, these are largely manageable. Additional rationale and risk mitigation solutions can be implemented and the study can be conducted.

**References**

1. Visit: www.huffingtonpost.ca/marvin-ross/ schizophrenia-placebo-study_b_7839894.html

Other publications used in the process of this article preparation and relevant for this subject:

- Chaturvedi SK, A review of Indian publications on ethical issues regarding capacity, informed consent, and placebo controlled trials, The Internet Journal of Mental Health 5(2): 2007
- Tashiro S et al, Ethical issues of placebo-controlled studies in depression and a randomized withdrawal trial in Japan: Case study in the ethics of mental health research, The Journal of Nervous and Mental Disease 200(3): pp255-9, 2012
- Visit: www.intechopen.com/books/contemporary-issues-in-bioethics/placebo-use-in-depression-research-some-ethical-considerations
- National Collaborating Centre for Mental Health, Schizophrenia: Core interventions in the treatment and management of schizophrenia in primary and secondary care, British Psychological Society: 2009
- Lee BI, Ethical issues of using placebo in antiepileptic drugs trials in Asia, Neurology Asia 15(1): pp29-31, 2010
- Committee for Medicinal Products for Human Use, Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia, European Medicines Agency: 2012

**Dr Piotr Piotrowski** is a Medical Director at KCR and holds a PhD in neurology. He is responsible for cross-therapeutic oversight of new and ongoing company projects from a medical perspective. Piotr’s professional experience includes more than 10 years in medical affairs, preclinical research, clinical development and regulatory affairs in the environment of the world’s top pharma industry and academic entities.

**Dr Magdalena Czarnecka** is a member of the Commercial Project Support Team at KCR, responsible for landscaping and development of clinical documentation. She gathered her professional experience during preclinical research at Georgetown University in Washington DC, US, and her work for a consulting firm focused on medical technology assessment. Magdalena holds a PhD in physiology and biophysics.

**Dr Anna Baran** is a Chief Medical Officer at KCR. She leads the organisation’s early stages of study operations and provides cross-functional support to all service areas, ensuring the smooth integration of medical affairs and regulatory and business development efforts. Throughout her career, Anna has worked closely with recognised authorities across Eastern Europe and has been involved in developing national legislation for clinical trials registration.

Email: info@kccro.com