Placebo and drug kits in clinical trial design

New and improved medicinal products are continuously needed throughout the world to prevent and treat diseases. Good quality clinical trials are key in bringing new safe and effective medicines to patients. Some information is outlined below on specific aspects of conducting clinical studies, namely the use of placebo as a control intervention and the use of drug kits for effective blinding of trials.

Introduction
Before novel medicinal products are introduced into widespread use, they must be assessed in clinical trials. Randomized controlled trials (RCTs) are often considered the gold standard in this regard, although other study designs can also yield valid research results. Clinical trials should be designed in such a way that the effects of the experimental intervention are compared with those of a control intervention. In a controlled trial, the subjects in the study and control group should be drawn from the same population, and should preferably be assigned to the groups by randomization to remove bias in the allocation of participants. Where feasible, clinical trials should be blinded, so that the subjects – and in double-blinded studies also the researchers – are unaware of who is receiving which intervention. This helps to avoid behaviour changes that may influence the study outcomes.\(^1\)

Two questions are discussed below that commonly arise in developing and evaluating clinical trial designs, namely in what situations it is acceptable to use placebo in the control arm, and how to achieve effective blinding.

The use of placebo
A placebo has been defined as “an inert substance or sham procedure that is provided to research participants with the aim of making it impossible for them, and usually the researchers themselves, to know who is receiving an active or inactive intervention.”\(^1\)

Placebos typically consist of the ingredients employed in the medicinal product under study minus the active ingredient, making them inert. The inactive ingredients (excipients) employed in a pharmaceutical product must be “generally recognized as safe”\(^1\) for use in humans, otherwise a medicinal product would not be authorized for use.

In vaccine research, the term “placebo” is also applied to non-inert substances. In this context, an existing vaccine not studied in the trial is added to both the investigational and the control product in order to avoid giving an “empty” injection to the subjects in the control group. A disadvantage of this approach is that it complicates the

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\(^1\) The U.S. Food, Drug, and Cosmetic Act makes provision for food additives to be shown to be “Generally Recognized As Safe” (GRAS) through scientific procedures. Similar approaches are used in other jurisdictions.

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evaluation of the safety and reactogenicity of the vaccine under study.\(^{(2)}\)

As the risks associated with the placebo product are typically very low or non-existent, the use of placebos is generally uncontroversial where there is no established effective intervention for the issue being researched. Where an established effective intervention exists, on the other hand, the use of placebo often raises controversy among members of research ethics committees (RECs), regulators, and policy-makers. The CIOMS Guideline 5, Choice of control in clinical trials, advises as follows:

“As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention. Placebo may be used as a comparator without providing the established effective intervention to participants only if:

- there are compelling scientific reasons for using placebo; and
- delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.”

Risks and benefits of other study interventions and procedures should be evaluated according to the criteria set out in Guideline 4 – Potential individual benefits and risks of research.\(^{(1)}\)

A WHO expert group has identified five situations when placebos may be acceptable in the context of vaccine trials despite the existence of an effective intervention, namely when the existing vaccine: (1) is not affordable or not accessible to the target population, (2) has not been proven effective in the target population, (3) has been proven ineffective in the target population, (4) has an unknown or uncertain public health impact in the target population which is to be evaluated against a placebo; or (5) is not acceptable to target population (e.g. a vaccine containing porcine gelatine in populations that have religious restrictions on the consumption of pork). However, the risks and benefits of conducting a placebo-controlled design should always be weighed against those of alternative trial designs such as response-adaptive designs, observational studies, or historical comparisons.\(^{(1,2)}\)

The use of placebo may require risk mitigation even if no established effective intervention exists. For example, in the Ebola vaccine trial conducted in Guinea the use of a placebo or an unrelated vaccine in the control group was deemed ethically unacceptable as it would leave vulnerable individuals unprotected against Ebola virus disease when a potentially effective investigational vaccine was available. Instead, vaccination of control subjects was delayed by 21 days, the minimal delay that would enable researchers to determine vaccine efficiency.\(^{(3)}\)

The use of drug kits

Specifically for researching new pharmaceuticals, clinical trials should preferably have a randomized double-blind design. Blinding can take place at several levels: it may apply to the researchers who assign subjects to groups, the subjects themselves, the health care workers who take care of patients in a study, and the researchers who record and assess the outcomes.\(^{(4)}\)

A method of blinding clinical trials is the use of drug kits, in which the investigational or control product is packaged for distribution to investigational
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sites. Each kit is labelled with a neutral ID, without indication of its content, enabling investigators to administer study or control drug to subjects in a blinded manner without the assistance of an unblinded pharmacist. (5) Each kit contains sufficient product for a extended period, typically two or three weeks, (6) although the quantity will vary depending on the study design.

The key component to the successful use of drug kits is the creation of a kit list, where kit IDs are randomly assigned to kit types (investigational or control). This kit list is used at the time of manufacture to label the kits, during shipping to track the kits, and during the study to assign kits to patients. (6)

Many trials involve multiple clinical sites. To avoid the need for an unblinded pharmacist at each site, use is often made of a randomization centre to randomize study subjects and manage the supply of drug kits *i.e.*, track drug kit inventory at each site, ship kits to sites, and assign kits to patients. In this way, information on whether a kit contains test or control product does not accompany the kit but is available from the randomization centre. (6)

The coding used in creating the kit list and the distribution patterns and resupply methods employed are key factors in blinding a clinical trial. A good design should achieve a balance between kit efficiency and successful blinding. This can be illustrated by two simple scenarios. In a trial where each kit handed out to a subject triggers a replacement by a single kit of the same type, no kits are wasted but the researcher can deduce that the patients dosed with these two kits belong to the same study arm. In the opposite scenario the randomization centre would send two replacement kits (one active and one control) for each kit handed out to a patient, and would inactivate one of the two when a kit is assigned to the next patient. This is successful blinding at the expense of wasting one kit per subject. (5)

An analogous approach to the “waste-one-kit” method could be used to blind a trial where the control subjects receive a delayed intervention, by scheduling additional visits in both groups. In the Ebola vaccine trial conducted in Guinea this was not possible due to operational challenges; instead, to reduce the risk of bias arising from behaviour changes that might follow vaccination, participants were informed that it is not known if the vaccine works, and that they must still take steps to avoid infection. (3)

In practice, the design of algorithms for coding and supplying blinded drug kits will take into account a range of factors specific to each study, such as any additional trial arms, kit inventory size, enrolment rate at the sites, and times between subject enrolments in relation to shipment time for replacement kits. Operational characteristics of different types of kit lists (6) and supply methods (5) have been discussed in published literature. A criterion has also been proposed for evaluating the strength of blinding in a clinical trial, even if the researcher has been unblinded to the contents of one or more kits. This is of interest because it is not uncommon for an investigator to be unblinded to a subject’s treatment assignment for safety reasons or from the subject’s adverse event or efficacy profile. (5)

Conclusions

With today’s swift pace of product development in a globalized market, designing, assessing, and authorizing clinical trials can be challenging. Cooperation among regulators, ethics committees, and sponsors to reach consensus on key ethical
and regulatory questions is essential, and has proved particularly valuable in situations of urgency and in low-resourced environments.\(7\)

Efficient conduct of the trials without unnecessary regulatory barriers is equally important. Excessively cumbersome regulations, for example on importation and dispensing of placebos for clinical trials, could delay access to effective and sometimes lifesaving medicines. WHO stands ready to assist countries in identifying well-balanced approaches for clinical trials, including those requiring the use of placebos.

Lastly, well-designed clinical trials must be complemented by reliable post-approval safety assessment mechanisms. Many new medicinal products are introduced early and/or exclusively into countries with limited pharmacovigilance capacities. New guidance has become available on safety surveillance of vaccines, proposing a structured process for evaluating whether significant knowledge gaps exist, whether passive safety surveillance is adequate, and if not, how active vaccine safety surveillance studies can be designed and implemented.\(8\)

References