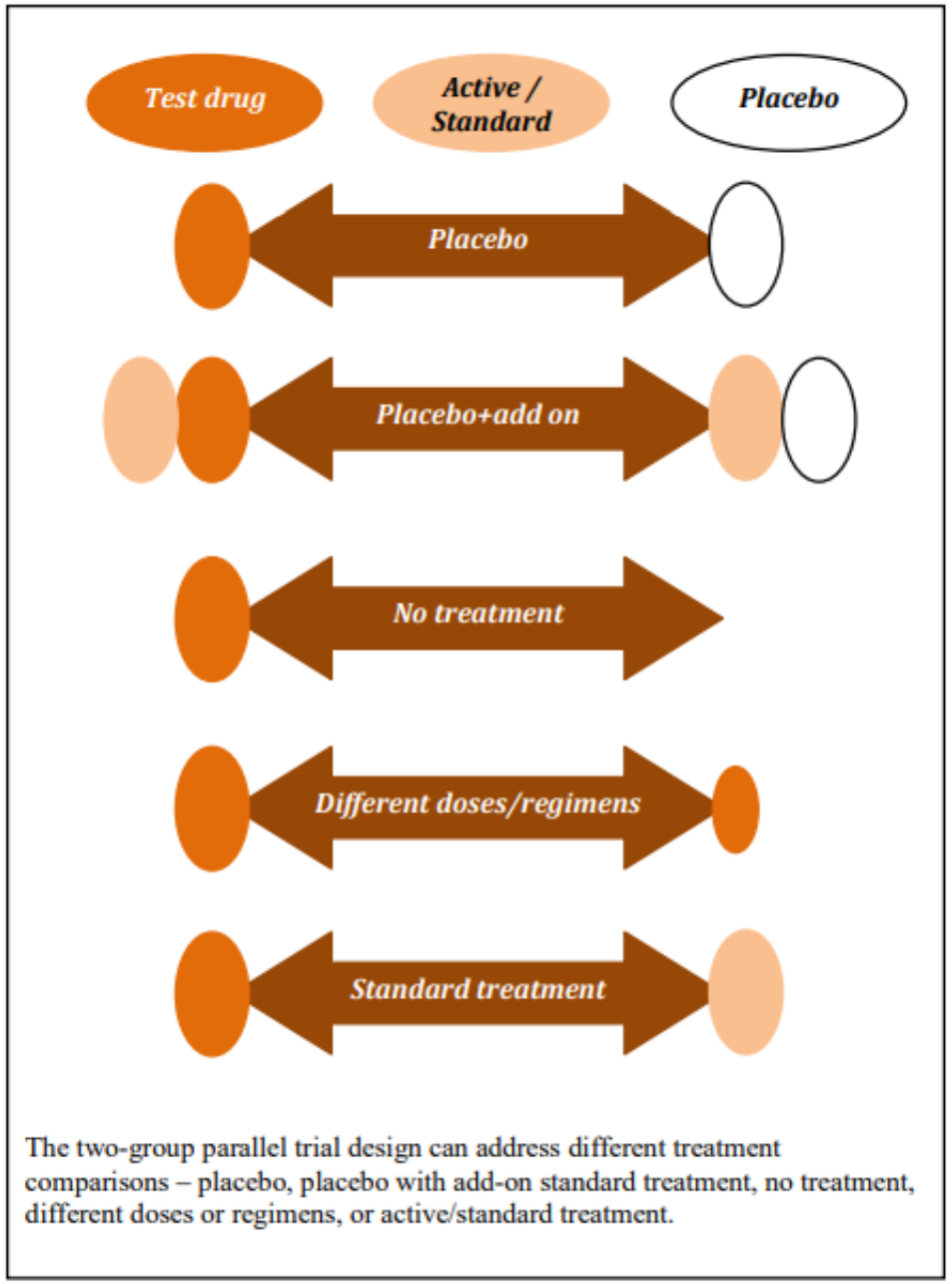
Controls of Clinical Trials

2.3 Controls of Clinical Trials

The control group experience tells us what would have happened to participants if they had not received the test treatment – or if they had received a different treatment known to be effective. A control group is chosen from the same population as the test group and treated in a defined way as part of the same trial studying the test treatment. Test and control groups should be similar at the initiation of the trial on variables that could influence outcome, except for the trial treatment. Otherwise, bias can be introduced into the trial.

The ICH Topic E10 Choice of Control Group in Clinical Trials states: “The choice of control group is always a critical decision in designing a clinical trial. That choice affects the inferences that can be drawn from the trial, the ethical acceptability of the trial, the degree to which bias in conducting and analyzing the trial can be minimized, the types of participants that can be recruited and the pace of recruitment, the kind of endpoints that can be studied, the public and scientific credibility of the results, the acceptability of the results by regulatory authorities, and many other features of the trial, its conduct, and its interpretation.”

The type of control can be (1) placebo, (2) no treatment, (3) different dose or regimen of the trial test treatment, or (4) the standard treatment:



The two-group parallel trial design can address different treatment comparisons – placebo, placebo with add-on standard treatment, no treatment, different doses or regimens, or active/standard treatment.

Controls of Clinical Trials *(2)*

- In a placebo-controlled trial, participants are randomly assigned to a test treatment or to an identical-appearing treatment that does not contain the test drug. Such trials are almost always double blind.
- In a no treatment-controlled trial, participants are randomly assigned to test treatment or to no trial treatment. Here, participants and investigators are not blind to treatment assignment. This design is needed and suitable only when it is difficult or impossible to use blinding.
- In a randomised, fixed-dose, dose-response trial, participants are randomised to one of several fixed-dose groups. Dose-response trials are usually double-blind.
- In an active control trial, participants are randomly assigned to the test treatment or to an active control treatment. Such trials are usually double-blind, but this is not always possible as blinding to the two treatments may be impossible. Active control trials can have two objectives with respect to showing efficacy: to show efficacy of the test treatment by showing it is as good as the standard treatment, or by showing superiority of the test treatment to the known effective treatment.

Controls of Clinical Trials *(3)*

An externally controlled trial compares a group of participants receiving the test treatment with a group of participants external to the trial. The external control can be a group of participants treated at an earlier time (historical control) or a group treated during the same period but in another setting. Such trials are usually considered uncontrolled. It is possible to use more than one kind of control in a single trial. Trials can, for instance, use several doses of a test drug and several doses of an active control, with or without placebo.

Choice of participants – trial sample – should mirror the total participant population for which the drug may eventually be indicated. However, this is not the case for early phase trials, when choice of participants is influenced by research questions such as human pharmacology. However, for confirmatory late phase trials, the participants should closely mirror the target patient population. However, how much the trial participants represent future users may be influenced by the medical practices and level of standard care of a particular investigator, clinic, or geographic region. The influence of such factors should be reduced and discussed during interpretation of the results.

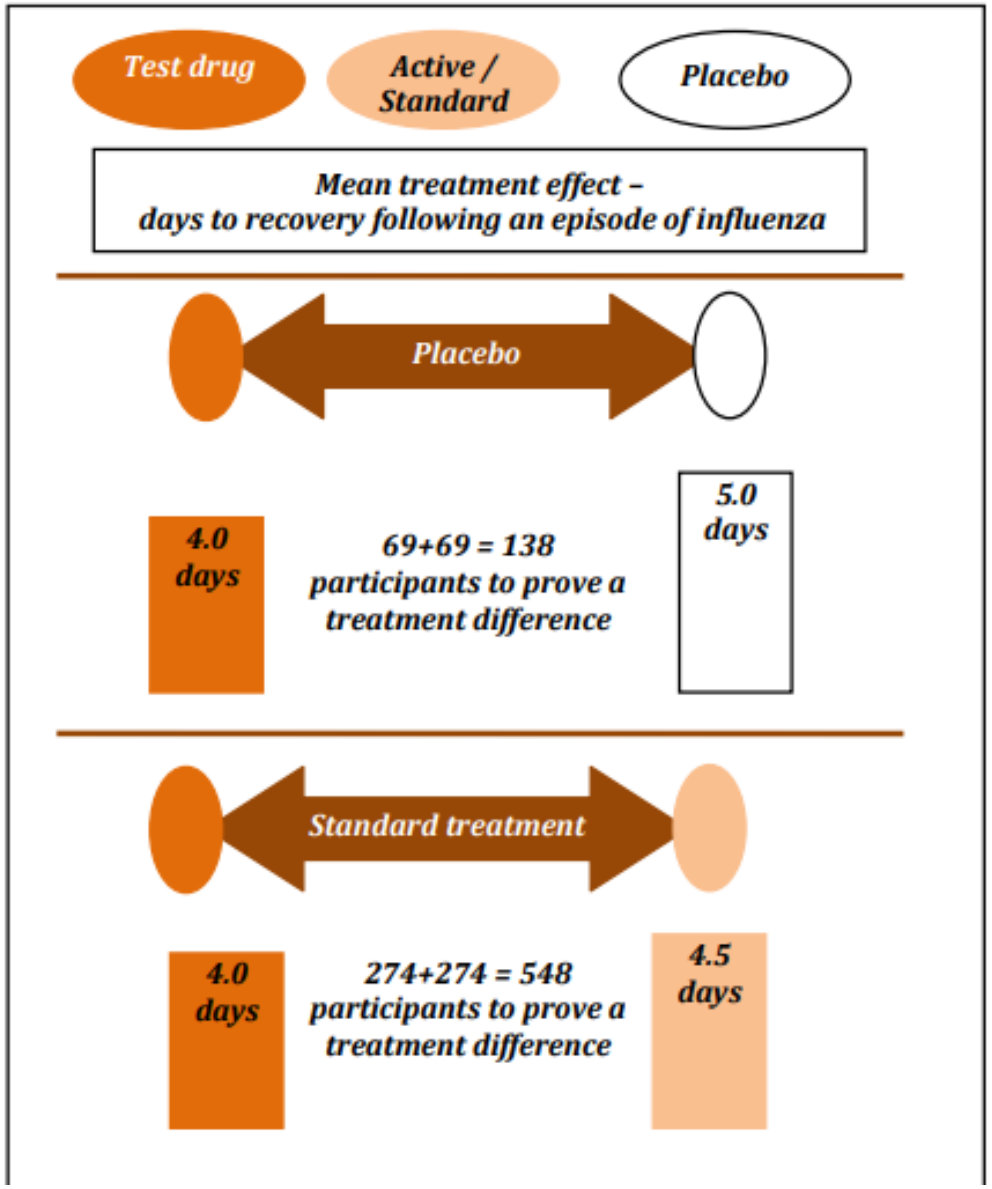
Placebo Treatment

The Declaration of Helsinki states: "The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the participants who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option." There is no ethical problem in using a placebo group if a new treatment is being tested for a disease for which there is no known effective treatment. However, using a placebo control may pose ethical concerns if an effective treatment is available. When the available treatment is known to prevent serious harm, such as death or irreversible morbidity, it is most often inappropriate to use placebo control. An exception is, for instance, when the standard therapy has such severe toxicity that participants will not accept it. When a placebo-controlled trial is not associated with serious harm, it is by and large ethically sound to use a placebo-controlled trial design, even with some discomfort, assuming that the participants are fully informed about available therapies and the consequences of delaying treatment.

Placebo Treatment (2)

Opinions on the acceptability of using placebo controls are in any event controversial. In the end, it is up to investigators, participants, and ECs to decide. Placebo or no-treatment control does not mean a participant does not receive treatment at all. The best supportive available care will normally be provided, plus the same clinical follow-up as the active treatment group. Placebo-controlled trials can also be conducted as add-on trials where all participants receive a standard therapy.

Placebo-controlled trials measure the total mediated effect of treatment while active control trials, or dose-comparison trials, measure the effect relative to another treatment. They also make it possible to distinguish between adverse events caused by both the drug and underlying disease. Placebo-controlled trials can detect treatment effects with a smaller sample size (see example below). However, it is also arguable that they represent an artificial environment, producing results different from real-world effects. It should also be noted that they provide little useful information about the comparative effectiveness of standard treatment.



Placebo and sample size:
The sample size of a trial is influenced by the type of comparison. Here we illustrate that a placebo treatment group design will require 138 study participants in total, compared with 548 when utilising a standard treatment control group.

Placebo Treatment (3)

Placebo and sample size: Assume that “normal” recovery from influenza – without any specific influenza treatment – takes on average 5.0 days. However, when standard treatment is used, the mean duration to symptom recovery is 4.5 days. A drug company has developed a promising new anti-influenza drug and would like to proceed with a first-into-human, exploratory, proof-of-concept phase II trial. Theoretically, the new test article is more effective, being able to reduce the average number of days to recovery to 4.0 days. If the comparison is against standard treatment, to show a statistical difference between the two treatment groups, we need to recruit 274 participants for each (the calculation is based on certain assumptions not described in detail). But only 69 participants are needed per group if no treatment – placebo – is used as a comparison. In this scenario, 410 extra participants are put at risk of harm when standard treatment is used as a comparison. Yet in fact we do not know whether the test article has any effect at all or is safe when given to participants. So, three times more participants are put at risk of harm, and the trial budget may increase by as much as US$4 million.