First in human trials: Are there any benefits of including placebo treatments?

Sir,

The first administration of drugs to human subjects serves as a bridge between animal testing and efficacy study in the target patient population. Hence, it is the stage where the postulated safety in animal testing is proved in man on a small sample size before progression unto larger sample size in future phases. During this phase, safety is assessed in investigating the pharmacokinetic and pharmacologic activity of the drug in healthy volunteers or patient subjects where appropriate.[1] The trial design employed at this stage usually employ within-subject control (crossover design) or between subject controls (parallel group design). There are different available control groups namely; placebo, no treatment, dose-response, active, external, and multiple controls. However, these control groups are appropriate for a particular trial objective. For first in human (FIH) trials placebo and sometimes no treatment control groups are used. Nonetheless, placebo is preferred to no treatment control due to associated high dropout rate of the latter.[2] The purpose of placebo is to control for the placebo effect which is described as an improvement achieved as a result of the idea of taking a medicine and not the pharmacological effect of the medicine.[1] Considering the primary focus of FIH trials; safety, the inclusion of a placebo is intended to control for the influence of the idea in a trial on the safety tolerability and pharmacokinetics parameters other than improvement of disease state which is the case of efficacy study.

However, the use of placebo has raised ethical concerns under conditions where patient subjects are employed, and there are available standard treatments. Furthermore, because the placebo is not an active intervention, it limits the new intervention to noninferiority study. Despite the limitations, placebo-controlled trials are beneficial in FIH trials and the preceding paragraphs seek to discuss some of these benefits.

First and foremost, it is highly relevant for noninferiority trials of FIH trials to determine the safety profile of the new medicine. Placebos are considered inert in that they lack the inclusion of the pharmacologically active substance and consequently expected to be free from the adverse effects associated with the new medicine.[1] Since, the focus of Phase 1 trials is the evaluation of safety in man, the objective of this noninferiority trial is to show that the new medicine is as safe as the placebo. One such trial conducted on amoxicillin by Le Saux *et al.* in children with otitis media was able to conclude that the adverse effects associated with amoxicillin was not significant compared with the placebo which, in other words, means the safety is comparable to the placebo.[3]

Furthermore, a placebo-controlled trial contributes to the efficiency of FIH trials. The sample size of FIH trials are usually small requiring about 20–80 subjects in order to limit the exposure to any potential toxicity.[1] This implies that the choice of a control group should be able to detect treatment effects within smaller sample size. Placebo-controlled trials are known to be efficient in detecting treatment effects with smaller sample size due to internal assay sensitivity which does not require external inferences and thus appropriate control for FIH trials. Other concurrent controls such as active controls require larger sample size to detect effect differences and consequently less efficient in FIH trials.[2] An example of Phase 1 placebo-controlled trial to evaluate the safety of 3% SPL7013 Gel (VivaGel®) enrolled 54 volunteers across USA and Kenya.[4] On the other hand, a larger sample size; 254 volunteers were enrolled in an active-controlled trial comparing the safety of vernakalant to amiodarone.[5]

A review conducted by Rosenzweig *et al.,* on 109 studies involving 1228 healthy volunteers showed that 19% of the volunteers on placebo experienced adverse effects.[6] Hence, in addition to its efficiency, placebo controls helps to ascertain absolute adverse effects associated with the new intervention.[2] As part of the informed consent, trial subjects are usually brief of possible adverse effects prior to the trial. This, therefore, results in "subject expectancy effect" whereby subjects will encounter adverse effects because they have been made aware of other than the intervention itself causing it.[1] Furthermore, there may be other adverse effects associated with the formulation excipients other than the pharmacologically active ingredient. In such cases, placebo is useful in controlling these expected effects so that the absolute effect of the intervention can be obtained. For patient subjects, adverse effects may also be interfered by the underlining course of the disease which requires a control group on placebo to account for this influence.[2]

Usually, biases in FIH trials are controlled by blinding and randomization.[2] However, these measures cannot be achieved in a single arm cohort where all subjects are assigned to the same intervention. This is also difficult

to attain when a no-treatment control group is employed, which leads to an open-label trial where both investigators and subjects are aware of their intervention assignments resulting in biased outcomes. Since, comparative efficacy study is not the main focus of FIH studies and thus active control is rarely used, the placebo control serves to introduce an intervention arm between which randomization and blinding can be introduced instead of the no-treatment control group. Eliminating bias from both investigators and trial participants will in effect increase the sensitivity of the trail to detect effects caused exclusively by the intervention.

Moreover, the inclusion of placebo is useful in controlling uncontrollable effects posed by the experimental setting. Such effects include sleep latency, psychometrics, hemodynamic parameters, and change in metabolism. For instance, a review Rosenzweig *et al.*, on the sleep latency of nine hospitalized healthy volunteers in a placebo-controlled trial showed that on the average, a sleep latency of < 20 min was recorded on the 1st day.[6] As the trial progressed, the sleep latency increased to more than 40 min on day 16. However, upon discharge and continuation of the placebo on day 17, the sleep latency returned to the baseline value. These changes are likely to alter some pharmacokinetic parameters. In their study, Rumble *et al.* found out that, sleep or posture change altered the mean residence time of paracetamol and its metabolites.[7] In addition Rosenzweig *et al.*, observed the influence of hospitalization and inactivity on the increase in C-peptide levels on trial day 16 compared with day 1 in one of their review studies. Including a placebo will, therefore, control for these inherent effects induced by the experimental setting which blinding and randomization are less likely to eliminate.[6]

Finally, the nature of FIH trials is such that comparator medicines are often not employed. Hence, the limited options that present the investigator are either a placebo or a no treatment group. Bearing in mind that a smaller sample is used, the choice of control should be one that will encourage participation and retention of participants throughout the trial period. Subjects recruited onto no treatment arm tend to drop out quickly from the trial because they tend to lack commitment as a result of not being on an intervention.[2] On the other hand, since participants are randomly assigned to in placebo-controlled trial, retention rate tend to increase because they are unaware which treatment arm of assignment with the hope of being assigned to the new intervention arm.

To conclude, it can be seen from the above discussion that there are more reasons to employ a placebo control than not to employ in FIH trials, however, the appropriate decision lies in the context ethical approval and the ultimate assuring safety of participants.

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Conflicts of interest
There are no conflicts of interest.

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References

1. Chin R, Lee BY. Principles and Practice of Clinical Trial Medicine. Burlington: Elsevier Inc.; 2008.
2. European Medicines Agency (EMA). ICH Topic E 10: Choice of Control Group in Clinical Trials; 2001. Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf. [Last accessed on 2013 Apr 13].
3. Le Saux N, Gaboury I, Baird M, Klassen TP, MacCormick J, Blanchard C, *et al.* A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. CMAJ 2005;172:335-41.
4. Cohen CR, Brown J, Moscicki AB, Bukusi EA, Paull JR, Price CF, *et al.* A phase I randomized placebo controlled trial of the safety of 3% SPL7013 Gel (VivaGel®) in healthy young women administered twice daily for 14 days. PLoS One 2011;6:e16258.
5. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, *et al.* A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. J Am Coll Cardiol 2011;57:313-21.
6. Rosenzweig P, Brohier S, Zipfel A. The placebo effect in healthy volunteers: Influence of experimental conditions on physiological parameters during phase I studies. Br J Clin Pharmacol 1995;39:657-64.
7. Rumble RH, Roberts MS, Denton MJ. Effects of posture and sleep on the pharmacokinetics of paracetamol (acetaminophen) and its metabolites. Clin Pharmacokinet 1991;20:167-73.

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