Expert Consultation on Ethical Aspects of Placebo Controlled Vaccine Trials

Les Pensières Conference Centre, Annecy, France

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This was an important meeting discussing a controversial issue, the use of placebo as a control arm in clinical studies.

Annette Rid presented a review of what various international and influential guidelines recommend. Brazilian regulation on this subject is radical and forbids without exception placebo on clinical studies when there is a proven and effective treatment for the disease under study, which has been interpreted as any effective intervention, available. This means that trials for second generation products may need to be based on head to head comparisons. For most guidelines on the subject there is some kind of flexibility, but there is plenty of room for interpretations and discussion. The Helsinki declaration establishes that the comparator should be "the best current prophylactic, diagnostic, and therapeutic methods". Still some guidelines say that this should be the "best local available treatment". CIOMS says: "when there is no established effective intervention". Another version is:"a clinical trial is ethically acceptable, if proven treatment exists and the control group receives a placebo and there is only a minimal burden or no risk of serious or irreversible harm to the participants". So, there are many possibilities and guidelines should be more precise.

Kim Mulholland discussed in great detail several study designs and how to address the placebo alternative in each one of them. For example, cluster randomization and stepped wedged trial designs permit to have temporary placebo controls, while they end up with all volunteers receiving the intervention.

Anat Bhan discussed risk and benefit from the point of view of populations, instead of individual risk. This raises important politicy issues. For example: is it valid to develop a vaccine that is not better than the current vaccines? Is cost-benefit a valid consideration? Should population risk-benefit be taken into account and not only individual risk-benefit?

Pieter Neels discussed clinical trials conducted outside the EU, and supported the concept that the ethical considerations should be the same regardless of the country involved. He also stressed that regulators do not consider costs or cost-benefit as part of their evaluations.

Alan Fix, Punee Pitisuttithum, Rosanna Lagos, exemplified ethical issues in several clinical trials, including HPV vaccines.

Many of the ethical discussions interface with policy issues, such as validity of non-inferiority studies and cost-benefit considerations.

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