

Expert Consultation
on the
Use of Placebos in Vaccine Trials



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Abbreviations

CIOMS	Council for International Organizations of Medical Sciences
HIC	high-income country
HIV/AIDS	human immunodeficiency virus / acquired immunodeficiency syndrome
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LMIC	low- and middle-income countries
REC	research ethics committee
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
WMA	World Medical Association

Background

New and improved vaccines to prevent illness and death from infectious diseases are urgently needed, especially in low- or middle-income countries (LMICs). Before they are introduced into widespread use, the safety and efficacy of vaccines are generally assessed in individually randomized controlled trials¹, which are considered the gold standard for such evaluations. Trials of vaccines against diseases for which there are no existing vaccines raise few special ethical issues in relation to the use of placebos. However, it remains unclear under which circumstances, if any, a placebo-controlled clinical trial design is ethically justifiable when an efficacious or partially efficacious vaccine already exists.

A common model for the evaluation and deployment of a new vaccine, against a disease for which there is no existing vaccine, is that it is first tested in a placebo-controlled trial. Then, if the vaccine proves efficacious, it is introduced in the population of the country of development of the vaccine, usually a high-income country (HIC), and later introduced in LMICs. However, there are several examples demonstrating that a vaccine that is effective in one population is not always equally effective in others. The vaccine may have been developed for strains of viruses/bacteria different from those that exist in the target population in the LMIC (e.g. conjugate pneumococcal vaccines). There may also be genetic, epidemiological, demographic or environmental differences affecting the target population that modify the efficacy of the vaccine (e.g. rotavirus vaccines). Additionally, if there are no background epidemiological data on the burden of disease in question for the target population, the extent to which a population will benefit from the introduction of a vaccine that has been found to be effective in another population may be unclear (e.g. uncertainty about the burden of disease due to *Haemophilus influenzae* type b has inhibited some countries from introducing vaccines against this condition).

In such situations, investigators and sponsors have often argued that a further placebo-controlled trial is the best option to determine the effectiveness of the test vaccine in the target population in the LMIC. Another situation in which placebo-controlled trials have been used in LMICs is when an existing (efficacious) vaccine is not available in a country because it is not affordable for the public health system – thus a new locally produced vaccine is tested against a placebo. For example, following the recent trial of ROTAVAC in India, the vaccine will reportedly cost US\$ 1.00 per dose, making it a more affordable alternative to existing rotavirus vaccines.

The prospect of placebo-controlled trials in these situations often raises controversy among members of research ethics committees (RECs), drug regulators, and policy-makers, because current ethics guidelines generally recommend that placebos should not be used as a comparator when an effective intervention already exists. However, the panel of experts noted that some of the guidelines do not take sufficient account of the specific nuances of vaccine research and vaccine trials. The inconsistencies of current ethics guidelines also serve as a source of confusion for researchers – some guidelines state that scientific necessity, to establish

¹ Clinical trials of vaccines are generally conducted in four sequential phases. Phase I trials follow preclinical studies and involve the first use of the product in humans. Their prime purpose is to assess the safety of the vaccine. The vaccine is tested, sometimes at varying dosage levels, in a small number of volunteers (usually under 100). Vaccines that appear to be safe progress to Phase II trials, which test for immunogenicity, and sometimes efficacy, as well as safety in larger numbers of subjects. In Phase III trials, the results of which are required for regulatory approval of a vaccine, and which can involve from several hundred to tens of thousands of participants, researchers assess the safety and efficacy of the vaccine in the target population, that is the population for which the vaccine would be used in a public health programme. Phase IV trials, conducted after regulatory approval and before, in parallel with, or after introduction of the vaccine into public health use, assess safety in larger numbers of individuals and the long-term safety, immunogenicity, and effectiveness of the vaccine.

public health benefit, might justify particular research designs (including placebo-controlled trials) while some national guidelines strictly rule out the use of placebos in all cases where an established effective intervention exists.¹

In 2002, the World Health Organization (WHO) convened a meeting in Accra, Ghana to analyse ethical issues in vaccine trials that include children as study participants. The resulting report, *Ethical Considerations Arising from Vaccine Trials Conducted in Paediatric Populations with High Disease Burden in Developing Countries*,² provided guidance on some key ethical issues related to vaccine research in children. Nevertheless, specific questions regarding the use of placebos in vaccine trials remain unanswered. On the one hand, researchers may avoid conducting placebo-controlled trials if an efficacious vaccine exists – even when such a design is necessary to answer the study question – resulting in the unwanted effect of inhibiting the conduct of potentially justifiable and valuable studies. On the other hand, lack of clear guidance may result in approval and/or conduct of placebo-controlled trials that are ultimately unethical. Additional guidance is therefore needed in this area.

On 17–18 January 2013, WHO convened an expert panel (see Annex 1 for list of participants) to provide recommendations on the ethical issues associated with the development, review and conduct of vaccine trials assessing vaccine efficacy and/or effectiveness, where a placebo is being considered in the study design despite the existence of an efficacious vaccine. The panel was requested to examine these complex issues within the context of existing ethical guidelines, and tasked with developing specific, practical recommendations targeted at a broad audience including researchers, RECs, sponsors, as well as other stakeholders involved in clinical research such as policy-makers, civil society, communities and advocacy groups.³

Day 1 was open to sponsors of vaccine trials in developing countries (or their representatives), and was focused on formal presentations as well as the presentation of case studies along with an ethical analysis of those studies. On Day 2, the experts met in a closed session to develop recommendations for the development, review and conduct of placebo-controlled vaccine trials. Private partners from industry (or their representatives) had no access to the Consultation on Day 2. The WHO Ethics and Health team (now called the Global Health Ethics Unit) served as the Secretariat, which supported the experts in preparing this report.

¹ Use of placebos: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists (Brazil, Conselho Nacional de Saúde, RESOLUÇÃO CNS Nº 404, 2008).

² http://whqlibdoc.who.int/hq/2004/WHO_V%26B_04.04.pdf.

³ Stakeholders are people or organizations affected by the outcome of a trial, negatively or positively, or those who can affect the outcome of proposed research. This includes the population that will be approached to participate in the trial, as well as communities and individuals who are not physically located where the research takes place, including advocates, activists, groups representing specific constituencies such as sex workers, drug users, treatment activists and others. In addition, key stakeholders can potentially include educators, medical professionals, media professionals and, in the immediate community, family members, and people whose age and/or gender make them ineligible for study participation. Policy-makers and leaders of countries where research is taking place are critically important to the research process. All of these groups can provide important input on how to build support for, and conduct an ethical, scientifically sound, and successful trial (Good participatory practice: Guidelines for biomedical HIV prevention trials. Geneva, Joint United Nations Programme on HIV/AIDS, 2007 (UNAIDS/07.30E/JC1364E)).

Introduction

In view of the global burden of infectious diseases that are potentially preventable through vaccines, the experts agreed that there is an ethical imperative to encourage the development and clinical testing of new vaccines that are of high quality for use in LMICs. Recommendations made by this expert consultation should facilitate the conduct of research on vaccines that is ethical, scientifically valid, and addresses important public health needs.

To define the ethical issues relevant to the use of placebos during the conduct of vaccine trials when an efficacious vaccine against the condition under study already exists, the experts examined the issues under three main categories:

- (i) overarching ethics principles that are relevant for all research studies, irrespective of the study design and study population,
- (ii) ethical issues relevant to placebo-controlled trials in general, and
- (iii) ethical issues relevant to placebo-controlled vaccine trials, when an efficacious vaccine against the condition under study already exists.

Case studies were used to illustrate the issues and to develop guidance.

Overarching Research Ethics Principles

The panel emphasized that many of the issues under consideration are relevant to the ethics of research involving human subjects in general, and are not unique to placebo-controlled vaccine trials. For example:

- Research participants must always be respected. In particular, informed consent is necessary, except in highly exceptional circumstances. Participants should also be free to withdraw from the research at any time, for any reason, without penalty.
- The study must be based on a sound scientific rationale, and must be socially valuable and use scientifically valid methods.

Box 1: HIV Vaccine Trials in Thailand

Meeting experts discussed two placebo-controlled trials conducted in Thailand to test the efficacy of a vaccine against human immunodeficiency virus (HIV). In both of these trials, the use of a placebo was clearly ethical because there was no existing effective vaccine. However, to meet the ethical obligation to minimize the risk of developing HIV infection, behavioural interventions that are known to be effective at reducing this risk were provided. The first trial enrolled injecting drug users recruited at 17 drug treatment clinics. Study participants were given counselling on how to reduce HIV risk through the use of condoms, and the use of bleach to clean their syringes between uses (Thai narcotic law prevented the provision of sterile injection equipment). The second trial studied the efficacy of a vaccine in men and women with primarily heterosexual risk of HIV infection. Risk-reduction counselling and condoms were provided to all study participants. HIV acquisition was monitored, and no increase was found.

Other ethical concerns discussed at the meeting included the possibility that the trials might generate social harm – participation might lead to increased risk of HIV infection because participants thought themselves protected by vaccination. Investigators in both trials sought to guard against the possibility that participants might engage in higher-risk behaviour because they believed they were receiving a preventive intervention.

- The research must have a risk–benefit profile judged to be favourable, based on sufficient evidence from previous clinical and non-clinical studies (i.e. the expected benefits of conducting the research must outweigh any associated potential risks). There is an ethical obligation to introduce measures to reduce the risks to all trial participants (see Box 1).
- The benefits and burdens of the research must be justly distributed. For instance, research must not be carried out on vulnerable populations for the benefit of more advantaged populations. Particularly in LMICs, the research must be responsive to local needs.
- Should an intervention be proven efficacious in a trial, research sponsors and other collaborators (such as national or local governments) have a duty to make provisions to ensure reasonable access to the intervention by the population from which the research participants were drawn. All relevant knowledge gained in the trial should also be shared with the host country.

It was, however, recognized that certain research ethics principles are unique to the use of placebos in clinical trials.

Ethical Considerations relevant to the General Use of Placebos

Numerous governmental, intergovernmental and nongovernmental bodies have issued guidelines on the general use of placebos in clinical research, including the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Nuffield Council on Bioethics, the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO, and the World Medical Association (WMA) (see Annex 2). Of these, CIOMS provides the most exhaustive commentary on the use of placebos in clinical trials (Box 2).

- Although there are points of divergence among the documents, there is uniformity on the use of placebos, i.e. that if a proven effective intervention exists, the

Box 2: CIOMS (2002) International Ethical Guidelines for Biomedical Research*

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or “no treatment”.

A placebo may be used:

- when there is no established effective intervention;
- when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects. (There follows a long commentary on ethical controversies related to the last bullet point with respect to interventions against conditions that may result in irreversible harm to the subjects.)

* Guideline 11 (Choice of control in clinical trials): International Ethical Guidelines for Biomedical Research, p54.

trial intervention should generally be tested against it. Failure to do so deprives participants in the “control” arm of an intervention that is likely to benefit them. There are, however, some justifiable exceptions to this practice. For example, if a proven effective treatment exists, use of placebos may be acceptable if foregoing or delaying effective treatment poses only negligible or no serious risks to study participants.

- Guidelines from CIOMS, UNAIDS and WMA stipulate that there must be compelling methodological reasons for the use of placebos, e.g. if using the effective treatment as a comparator would not yield scientifically valid results.
- CIOMS, ICH and UNAIDS guidelines also stipulate that researchers must take steps to minimize any risks associated with the use of placebos.
- The Nuffield Council on Bioethics guidelines state that the use of placebos may be acceptable in LMICs if participants are not deprived of a treatment they would have otherwise received but are provided at minimum with the standard of care that is the best available in the country’s public health system.

Few guidelines specifically address issues related to the use of placebos in vaccine trials, the UNAIDS guidelines being one notable exception. The implications of such use need to be explored.

Ethical Considerations for the Use of Placebos in Vaccine Research

After reviewing existing ethical guidance, several relevant contextual factors were identified that informed the evaluation of ethical issues related to the use of placebos in vaccine research:

- The field of vaccine research is advancing rapidly. New technologies for developing vaccines may be foreign even to the general medical community. It is necessary to explain how and why a new vaccine is likely to protect against disease in ways easily understood by all stakeholders to allow better understanding of the issues associated with proposed trials.

Box 3: Control Vaccines

In place of a placebo, a vaccine against a disease that is not the focus of the trial is given to participants who do not receive the trial vaccine. Typically the control vaccine is a licensed vaccine for which efficacy has been demonstrated and the safety profile is well characterized. The motivation for using active rather than inert “placebos” is to fulfil the ethical duty of beneficence and, sometimes, to avoid giving an injection with an inert substance. A methodological disadvantage, however, is that trials using these types of placebos provide a less perfect control. It may be difficult or impossible to assess fully the safety and reactogenicity of the trial vaccine, although its efficacy can usually be assessed satisfactorily. Such trials may also be less acceptable to regulators. Some regulators and/or public health authorities may prefer data from a placebo-controlled trial on which to make decisions whether or not to approve or adopt a vaccine.

“Add-on vaccine”

In this design, the trial vaccine or placebo product is mixed with an existing vaccine not studied in the trial, and subjects are given either (a) the trial vaccine mixed with the existing unrelated vaccine or (b) the combination of a placebo and the existing unrelated vaccine. The use of an “add-on” vaccine is used to avoid giving an “empty” injection.

- Consideration about the types of potential placebos should be included in the broader discussion on trial design. A true placebo is an inert substance, but in the context of vaccine research, the term placebo is also applied to other types of comparators that are not inert, but are not expected to protect against the disease of interest in a vaccine trial (Box 3).
- Vaccine trials in LMICs may be conducted in the following contexts:
 - a. A vaccine of proven efficacy in HICs is trialled in an LMIC (where it has not already been tested). Examples of these situations include the trials for vaccines against pneumococcal disease, rotavirus and human papillomavirus.
 - b. A new vaccine is trialled in an LMIC for use against diseases that are largely confined to LMICs. Examples of these are trials for vaccines against conditions such as leishmaniasis, dengue fever and malaria.
- When the efficacy of a vaccine is established in HICs, its efficacy in LMICs may remain uncertain and further placebo-controlled trials in LMICs may be necessary.
- There are examples of a public health system not introducing a vaccine found to be beneficial to a specific population after a trial in that country. This has sometimes been due to the failure of the clinical trial sponsors to have prior discussions with policy-makers and health authorities to clarify conditions necessary for the uptake of a new vaccine into the health system.

Acceptability of Use of Placebos

Experts at the meeting identified the circumstances in which the use of placebos is clearly acceptable or unacceptable.

Use of placebos is clearly *acceptable* when:

- no effective vaccine exists *and*
- the vaccine under consideration is intended to benefit the population in which the vaccine is to be tested.

Use of placebos is clearly *unacceptable* when:

- an effective (or partially effective) and safe vaccine exists and is currently accessible in the public health system of the country in which the trial is planned; *and*
- the risk to participants of not receiving the current vaccine cannot be mitigated adequately.

Between these two poles, several examples of ethical ambiguity were identified. It was concluded that the use of placebos may sometimes be justified even if a vaccine of proven efficacy exists and the risks of using the placebo and withholding or delaying administration of the existing vaccine are greater than minimal.

Five Situations where Placebos may be Acceptable

The panel identified the following five situations where the conduct of a placebo-controlled trial may be justified in comparison to alternative study designs, even when an efficacious vaccine exists, provided that (a) the risks of using placebos are mitigated and justified by the scientific and social value of the research, (b) the research is responsive to local health needs, and (c) the general research ethics principles are respected (see page 9, Overarching Ethical Principles).

Resource Constraints (Situation 1)

- A new (low-cost) vaccine is being tested against a placebo, because while the existing vaccine is known (or likely) to be effective in the trial country, it is inaccessible to most of the population and is likely to remain so in the future. Acces-

Box 4: Pneumococcal Vaccine Trial in Bangladesh

Pneumococcal disease causes the deaths of more than one million children annually, with young children in developing countries at greatest risk. Three conjugate vaccines that protect against 7-13 strains of the agents that cause pneumococcal disease have been licensed and have been, or are, widely used in HICs. Although these vaccines are recommended for use worldwide, vaccine programmes against pneumococcal disease have not been implemented in many countries because of financial and logistical constraints. New vaccines based on protein antigens that would protect against many more pneumococcal strains are in development. Experts at the meeting considered options for a potential efficacy trial in Bangladesh of a new protein-based vaccine. Bangladesh has not implemented vaccination programmes against pneumococcal disease, primarily because of the cost of existing vaccines. Options for trial designs analysed were:

- *Placebo-controlled trial (testing the new protein-based vaccine against a true placebo or a control vaccine indicated for prevention of an unrelated disease)*

This option would be ruled out under some existing ethical guidelines because it would deprive participants of an effective alternative (one of the existing conjugate vaccines). It would subject participants who received the placebo/control vaccine to greater than minimal risk that would be difficult

sibility may be hindered by limitations in a health system's ability to provide adequate support in areas such as administration, financing, production, distribution and infrastructure. Testing the new vaccine against the existing vaccine might not provide the desired information, i.e. how effective is the new vaccine compared to no vaccine (if having no vaccine is likely to continue as the local standard of care)? When an existing vaccine is not in use in the trial country because of presumed barriers to access, researchers and sponsors proposing a placebo-controlled design should be prepared to provide evidence to local RECs and other stakeholders that these barriers are unlikely to be overcome in the foreseeable future. Although availability can change quickly when a new product reaches the market, researchers and sponsors should provide evidence that the new trial vaccine will not present the same barriers that have prevented the use of the existing vaccine (see Box 4).

Scientific Constraints (Situations 2–5)

- An existing vaccine is being tested against a placebo to confirm its efficacy in the trial country prior to uptake and introduction into the health system. As there is sometimes insufficient information and lack of consensus about the safety and efficacy of existing vaccines in different settings, the status of the existing vaccine as an “established effective treatment” in the local context may need to be determined.
- A new vaccine is being tested against a placebo because scientific experts and health officials in the host country have determined that the existing vaccine(s) cannot be considered as an “established effective treatment” due to local epidemiological/demographic/environmental conditions, rendering it scientifically inappropriate as a comparator in a trial for the new vaccine (see Box 5). If reliable data on the safety and efficacy of the existing vaccine(s) in the local population are unavailable or unclear, using it as a comparator against a new vaccine in a trial would not provide sufficient information on the new vaccine's efficacy or effectiveness. In such situations, however, sponsors should first consult relevant experts regarding the legitimate reasons to doubt the efficacy or effectiveness of an existing vaccine in

to reduce. However, a counter argument was that a placebo-controlled trial would be acceptable if the existing vaccines were unlikely to be implemented in Bangladesh because of their cost and the new protein-based vaccine would be substantially cheaper and thus implementable in a public health programme in Bangladesh if efficacious.

- *Add-on trial (all trial participants given an existing conjugate vaccine, and participants in the active arm additionally given the trial vaccine)*

Because the provision of the existing vaccine significantly reduces risks for trial participants, this design appeared to be ethically acceptable, but there were significant scientific questions as to whether there would be sufficient disease events to allow evaluation of the new vaccine, and it would not be known if the new vaccine protected against the disease serotypes prevented by the existing vaccine.

- *Head-to-head trial (the new protein-based vaccine tested against an existing conjugate vaccine)*

In this design, the control group is at less risk than in the placebo design. Researchers proposing this design bear the burden of demonstrating that its scientific or social value is superior to the add-on design or a placebo-controlled trial.

the trial population. Once it is established that there are good reasons to doubt the safety and/or efficacy of the existing vaccine in the trial population, the new vaccine may then be tested ethically against a placebo, provided the other conditions described above (see Overarching Ethical Principles, page 9) are met. When there is no reason to doubt the safety or effectiveness of an existing vaccine, testing the new vaccine against both a placebo and the existing vaccine would also provide evidence on the safety and effectiveness of the existing vaccine, while adequately answering the study question.

- The existing licensed vaccine or a new developmental vaccine is being tested against a placebo because the public health significance of the vaccine's introduction (i.e. its effect on the burden of morbidity and mortality due to the target disease) in the trial country is unknown or uncertain. Comparison with a placebo will yield clearer information on whether the introduction of the vaccine would have a public health impact.
- A new vaccine is being tested against a placebo because the existing vaccine is unacceptable to the potential study participants in the trial country (for example, some populations object to vaccines containing porcine gelatine, others reject vaccination administered by injection but will accept nasal sprays).

The five situations noted above present researchers and other stakeholders with ethical ambiguity. The use of placebos in these situations may arguably violate fundamental ethical principles because randomization to a placebo arm deprives research participants of an effective vaccine that investigators could have offered as part of the trial, and placebo use may appear to take unfair advantage of the poverty and vulnerability of participants in LMICs. However, using an active comparator in these situations does not always provide the scientific information (e.g. about the impact, locally, of a new vaccine) that is required by regulators and others responsible for licensure, approval or adoption of a new vaccine.

Trials using an existing vaccine as an active comparator need to be larger and more resource intensive than trials using placebos. Experts agreed that the expense and time entailed by active comparator trials may discourage sponsors and researchers from undertaking them, and result in the delay of availability of new safe and effective vaccines in the very populations that need them most urgently. Efforts to protect research participants (through avoiding placebo-controlled trials as a matter of principle) may thus have the unwanted effect of inhibiting potentially valuable studies, and the "protected" populations may continue to suffer disproportionate disease burdens.

Ethical recommendations must therefore strike a balance between protecting individual research participants from unjustifiable risks of vaccine trials and the ongoing risk that potential trial participants in LMICs already face: the risk of lives lost on a daily basis because of the absence of accessible and effective vaccines. There is an urgent need to conduct timely and beneficial vaccine research for the greater public good, recognizing the tension between the two types of risks mentioned above.

Box 5: Rotavirus Vaccine Trials in India

Rotavirus causes severe diarrhoea and is responsible for approximately 450 000 deaths annually in children worldwide. More than half of these deaths occur in five countries, one of which is India. Two rotavirus vaccines are available and in use in more than one hundred countries. These vaccines demonstrated approximately 85–90% efficacy in clinical trials in the United States of America, Europe, Australia and Latin America, but have shown lower efficacy in Asia and Africa. No trials of these vaccines have been conducted in India and their efficacy in India is uncertain. Although both vaccines have been licensed for use in India, neither is included in the government immunization programme but both are available on the private market at relatively high cost. There is ongoing debate as to whether or not India should implement a national, routine rotavirus vaccine programme using one of the existing products.

Three new vaccines against rotavirus have entered clinical trials in India. Several possibilities existed for the design of efficacy trials of these vaccines in the country, including a placebo-controlled trial of one or more vaccines, a placebo-controlled trial of one (or both) of the licensed vaccines, a trial comparing (a) new vaccine(s) against (an) existing vaccine(s), or placebo-controlled trials including both new and existing vaccines.

In 2011, after extensive consultations, a double-blind, placebo-controlled Phase III trial of one of the new vaccines began, and a similar Phase III trial of another new vaccine began in mid-2013. The ethical justifications for the use of placebos in these trials are that the two existing vaccines are of unknown efficacy in India and are relatively expensive. In addition, trials using an active comparator would be expensive (the trial in India enrolled 6800 participants; a trial using a non-placebo design would require a substantially larger number of participants). A key ethical aspect considered when adopting the placebo-controlled design was that the risks of withholding rotavirus vaccine could be (and were) mitigated by rehydration counselling and regular check-ups. Several ethical and empirical issues related to these trial designs were discussed at the meeting, including whether there is good reason to doubt the efficacy of existing rotavirus vaccines in India; what types of data would be sufficient to answer this question; and whether foregoing an opportunity to obtain efficacy data about the existing vaccines should argue against use of a placebo-controlled design that does not include an active comparator as well as a new vaccine.

Recommendations

Based on these discussions, the experts set forth several recommendations, both procedural and substantive, for assessing the potential use of placebos in the five situations described above. These recommendations concern sponsors and researchers who are considering placebo designs, RECs charged with reviewing the trials, and the local public health authorities, drug/vaccine regulators, and policy-makers in the country where trials are proposed to be conducted. In situations where an efficacious vaccine already exists, researchers and RECs must consider all possible alternative study designs prior to designing or accepting a placebo-controlled trial. Decisions on the design of a trial will largely depend upon the specifics of the vaccine and the particular circumstances of the country where the trial would be conducted.

Procedural Recommendations

For Researchers and Sponsors

- Early and ongoing consultation and collaboration between sponsors and host country stakeholders in government and civil society are essential. Before planning a trial, sponsors should consult with relevant stakeholders in the jurisdiction of the proposed trial about the barriers to use of any existing vaccine as well as the necessary and sufficient conditions for uptake of a new vaccine. This may include formative research (e.g. surveys or interviews to assess the social, political and economic aspects of the health system into which the vaccine may be introduced).
- During the planning and review of a Phase III vaccine trial, sponsors and researchers should be accessible to stakeholders in the trial country to discuss the often complicated scientific and epidemiological questions that are relevant to ethical decision-making, especially about risks and benefits. While there is no single model for how such ethical consultations between sponsors, researchers and trial-country stakeholders should take place, consultation can be ad hoc and trial-specific. Inadequate existing structures for ethical discussions do not justify failure to carry out consultation.
- The task of identifying and assessing risks to research participants typically falls to researchers and sponsors. The rationale for using a placebo-controlled design, along with a description of the possible risks and benefits of such a design, should be clearly outlined in the research protocol. Where possible, sponsors and researchers should consider alternative trials designs (see Annex 3).
- Sponsors and researchers have the responsibility to communicate information about risk in relevant formats to all stakeholders. The risk assessment should be based on available evidence and local context, and should also include the risks of delaying, or not conducting, the trial.

For Health Authorities/Policy-makers

- Health authorities should facilitate ethical discussions among all parties involved in the study prior to approving vaccine trials under their jurisdiction, and should make the outcome of these discussions available to all interested parties.

For Research Ethics Committees

- The task of evaluating risks to research participants, both at individual and population levels, typically falls to RECs. Accurately assessing risks and benefits requires high statistical literacy and a good understanding of the health issues and vaccine research involved. Where necessary, sponsors of proposed studies should be ready to expand the capacities of RECs to make complex assessments. For instance, content experts may present available data to RECs to guide them in their decision-making process when determining the sufficiency of local evidence. It is important to point out that these content experts can be available for advice and discussion without taking part in the REC's actual decision-making process.

Substantive Recommendations

For Researchers and Sponsors

- Researchers should consider whether the risks associated with use of the placebo – that is the risks of the placebo intervention itself and those of withholding or delaying a vaccine with demonstrated efficacy and effectiveness – are minimal, preventable or reversible. Risks greater than this may constrain the use of placebos.
- Researchers proposing to use a placebo in a vaccine clinical trial when a vaccine already exists should explain clearly in the research protocol both the scientific rationale and the social value of using a placebo design. This justification should include articulation of the importance of the research question and details of the trial design, such as the level of effect desired and the merits of alternative trial designs. In particular, justification for the decision not to use an existing vaccine as a comparator should include discussion on the financial barriers, acceptability (e.g. by the local communities), availability and accessibility of the existing vaccine.
- In situations where a vaccine is known to be effective, but the burden of disease in a trial country is uncertain, researchers should first consider study designs other than a placebo-controlled trial that will allow them to demonstrate the burden of disease as well (see Annex 3), keeping in mind that these designs often have methodological or logistical disadvantages compared with individually randomized placebo-controlled trials. In the event that investigators consider that a placebo-controlled trial is required, they should justify why alternative study designs are either scientifically inappropriate or impossible to carry out in the desired setting.
- Sponsors and researchers have a duty to mitigate risks, to ensure adequate treatment for the condition under study and provide information about possible means of prevention. Sponsors and researchers should, as with any other research study, consult with local stakeholders to determine appropriate infrastructure or individual-level measures that can be undertaken to mitigate disease risk. These may include improving sanitation to lower the risk of water-borne illnesses or providing counselling and education on

behavioural prevention strategies. Mitigation of risk may make it more difficult to assess vaccine efficacy as it can reduce disease incidence. However, such measures can assure that the trial has adequately addressed risk minimization and thus attenuated ethical problems related to the use of placebos (see HIV case study in Box 1).

- When the effectiveness of an existing vaccine in the trial population is unknown or uncertain, sponsors and researchers should consult with relevant experts for evidence of legitimate reasons to doubt its effectiveness. Placebos may be ethically acceptable if the existing vaccine's lack of effectiveness in the local population is established and other conditions mentioned in Overarching Ethical Principles (page 9) are fulfilled.
- When a placebo-controlled trial to test a new vaccine is planned in a country where an existing vaccine is not in use due to financial barriers, researchers should be prepared to provide evidence to local RECs and other stakeholders that these barriers are unlikely to be overcome in the foreseeable future. They should also provide evidence that the same financial and/or logistical barriers to accessibility will not be faced by the new vaccine.
- The likelihood that the trial vaccine, should it prove efficacious, will be available in the country where the trial was conducted is a critical consideration. Before submission of a research proposal to an ethics committee, researchers should consult with relevant stakeholders in the jurisdiction of the proposed trial about the barriers to use of an existing vaccine and the necessary and sufficient conditions for uptake of a new vaccine. Sponsors should work with policy-makers to develop a plan for the sustained post-trial availability of the vaccine in the trial country, if it is shown to be efficacious, that addresses these barriers and conditions.

For Research Ethics Committees

- RECs should require a research protocol that provides the scientific rationale and explains why alternative study designs cannot answer the research question. They should have members who are knowledgeable on issues related to sample size and other design-related issues, or be open to obtaining opinion from independent experts when making their assessments.
- They should also review the evidence related to the safety and effectiveness of existing vaccines in the populations under study, and the formative studies conducted in the communities to justify the trial of the vaccine, including its acceptability by the community if found to be effective.
- They must ask for evidence of discussions with policy-makers, regulators, and community members to assure themselves that the existing vaccine is unlikely to be available to the population, and that the trial vaccine, if found to be efficacious, will be acceptable to the community and be made available to the population in which the trial was conducted.
- They must ensure that appropriate steps have been taken to mitigate the risks from the use of placebos, and from the disease itself.
- An REC must record its justification for approving a placebo-controlled trial when an efficacious vaccine exists and must do so in a transparent manner. This will help to ensure trust and confidence in the research ethics system.

Conclusion

The use of placebos in a vaccine clinical trial when there is already an effective or partially effective vaccine raises challenging ethical questions. National and international documents on research involving human subjects have set forth valuable guidelines on the circumstances in which use of placebos is ethically acceptable in a randomized controlled trial. However, none of these documents specifically addresses the use of placebos in vaccine trials. The purpose of the expert consultation described in this report was to address the ethical ambiguity in this area and formulate concrete and practical guidance for action. The critical need to develop new and improved vaccines, especially for use in LMICs that bear the heaviest disease burden, provided the impetus for this consultation and the resulting recommendations.

This report presents a typology of cases in which the use of placebos in vaccine clinical trials may be justified, and offers procedural and substantive recommendations to help trial sponsors and researchers, policy-makers, RECs, and other stakeholders evaluate proposed trial designs. The report specifies five situations in which placebos may be ethically acceptable even in the presence of an efficacious vaccine. In these situations, it is recommended that there be ongoing consultation between trial sponsors and host country actors, thorough assessment of and communication about risks, and consideration of alternative trial designs. Researchers should consider whether risks associated with the use of placebos can be adequately mitigated, and research protocols should explain the scientific necessity and social and public health value of a placebo design. Researchers should also undertake activities to mitigate risks related to the use of placebos. Additionally, the post-trial availability of the vaccine in the trial country should be carefully examined.

This document is not intended to suggest a definitive course of action for all vaccine trials when an effective or partially effective vaccine already exists. Rather, the recommendations set forth here are designed to provide an analytic framework to aid decision-making. Participants at the expert consultation agreed that the ultimate judgement about the use of placebos in these cases will depend on the specifics of the trial vaccine and the circumstances of the country in which the trial will be conducted. A careful weighing of numerous considerations by stakeholders will therefore be required. The overarching goal of these recommendations is two-fold: to assure that participants in vaccine clinical trials are protected from unjustifiable risks, and to facilitate the conduct of beneficial and urgently needed vaccine research. WHO encourages ongoing discussion of these issues and welcomes feedback on the guidance provided here.

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Annex 2: Selected Guidance and Regulations on the Use of Placebos in Clinical Research

International Guidelines

Council for International Organizations of Medical Sciences (CIOMS) (2002).

International Ethical Guidelines for Biomedical Research Involving Human Subjects

http://www.cioms.ch/publications/layout_guide2002.pdf

Council of Europe (2005).

Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research

<http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>

European Commission (2005).

Commission Directive 2005/28/EC of 8 April 2005 Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products for Human Use, as well as the Requirements for Authorisation of the Manufacturing or Importation of Such Products

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>

European Commission (2008).

Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population

http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf

European Group on Ethics in Science and New Technologies (EGE) (2003).

Ethical Aspects of Clinical Research in Developing Countries

http://ec.europa.eu/bepa/european-group-ethics/docs/avis17_en.pdf

European Medicines Agency (EMA) (2001).

Note for Guidance on Choice of Control Group in Clinical Trials

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf

European Medicines Agency (EMA) (2001).

EMA/CPMP Position Statement on the Use of Placebo in Clinical Trials with Regard to the Revised Declaration of Helsinki

http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/12/WC500017646.pdf

European Medicines Agency (EMA) (2004).

EU Standard of Medicinal Product Registration: Clinical Evaluation of Risk/ Benefit – The Role of Comparator Studies

http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/12/WC500017660.pdf

European Medicines Agency (EMA) (2010).

Reflection Paper on the Need for Active Control in Therapeutic Areas Where Use of Placebo is Deemed Ethical and One or More Established Medicines are Available (Draft)

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/01/WC500100710.pdf

European Medicines Agency (EMA) (2012).

Reflection Paper on Ethical and GCP Aspects of Clinical Trials of Medicinal Products for Human Use Conducted Outside of the EU/EEA and Submitted in Marketing Authorisation Applications to the EU Regulatory Authorities

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125437.pdf

European Parliament and the Council of Europe (2001).

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use

http://eudravigilance.emea.europa.eu/human/docs/directives/Dir2001-20_en.pdf

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (2000).

Choice of Control Group and Related Issues in Clinical Trials E10

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf

Joint United Nations Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) (2007).

Guidance Document: Ethical Considerations in Biomedical HIV Prevention Trials

http://data.unaids.org/pub/manual/2007/jc1349_ethics_2_11_07_en.pdf

World Medical Association (WMA) (2008).

Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

<http://www.wma.net/en/30publications/10policies/b3/>

National Guidelines**Conselho Nacional de Saúde, Brazil (2008).**

RESOLUÇÃO CNS Nº 404

http://conselho.saude.gov.br/web_comissoes/conep/aquivos/resolucoes/resolucoes.htm

Indian Council of Medical Research (ICMR), India (2006).

Ethical Guidelines for Biomedical Research on Human Participants

http://icmr.nic.in/ethical_guidelines.pdf

The National Health Research Ethics Council (NHREC), South Africa (2004).

Ethics in Health Research: Principles, Structures and Processes

<http://www.nhrec.org.za/wp-content/uploads/2008/09/ethics.pdf>

The National Health Research Ethics Council, South Africa (2006).

Guidelines for Good Clinical Practice in the Conduct of Clinical Trials with Human Participants in South Africa

<http://www.kznhealth.gov.za/research/guideline2.pdf>

Uganda National Council for Science and Technology (UNCST), Uganda (2007).

National Guidelines for Research Involving Humans as Research Participants

<http://www.uncst.go.ug/dmdocuments/Guideline,%20Human%20Subjects%20Guidelines%20Marc.pdf>

Medical Research Council (MRC), United Kingdom (2004).

MRC Ethics Guide: Research Involving Human Participants in Developing Societies

<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461>

Nuffield Council on Bioethics, United Kingdom (2002).

The Ethics of Research Related to Healthcare in Developing Countries

<http://www.nuffieldbioethics.org/sites/default/files/Ethics%20of%20research%20related%20to%20health-care%20in%20developing%20countries%20I.pdf>

U.S. Department of Health & Human Services, United States of America (1979).

The Belmont Report

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

U.S. Department of Health & Human Services, United States of America (2009).

Code of Federal Regulations Title 45, Part 46 (Protection of Human Subjects)

<http://www.hhs.gov/ohrp/policy/ohrpreulations.pdf>

Food and Drug Administration (FDA), United States of America (2001).

Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf>

The National Bioethics Advisory Commission (NBAC), United States of America (2001).

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries

<http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf>

The National Bioethics Advisory Commission (NBAC), United States (2001).

Ethical and Policy Issues in Research Involving Human Participants

<http://bioethics.georgetown.edu/nbac/human/overvol1.pdf>

Annex 3: Alternative Trial Designs in lieu of Individually Randomized Controlled Trials (including Placebo - Controlled Trials)

Before and after (historical control)

In this design, rates of disease are compared before and after introduction of a trial vaccine. This design does not involve the use of placebos. An example of a trial using this design was the Pneumococcal Conjugate Vaccine Impact Study (PCVIS), which tested the effectiveness of the 10-valent pneumococcal conjugate vaccine (PCV10) in Kenya. This design requires the existence of good surveillance systems and a clear definition of the denominator populations. The main drawback of this design is the fluctuation of disease rates over time, potentially invalidating any conclusions.

Stepped-wedge design

In this design, a trial vaccine is introduced into clusters of participants over a number of successive time periods. An example of a trial using this design was the Gambia Hepatitis Study, which tested the effectiveness of hepatitis B vaccination at preventing liver cancer and chronic liver disease. However, meeting participants recognized that this design does not avoid the ethical concerns resulting from inequitable distribution of risk during the period that a vaccine is introduced.

Cluster randomized trial

In this design, participants are randomized in groups (such as members of a village) rather than individually. An example of a trial using this design was a study in Lombok, Indonesia, that estimated the incidence of Haemophilus influenzae type b (Hib) pneumonia and meningitis, in which children were immunized with the diphtheria-tetanus-pertussis (DTP) vaccine alone or a DTP-Hib combination. Cluster randomized trials can be well-powered and relatively free of bias. As in the stepped-wedge design, participants recognized that this design does not avoid the ethical concerns resulting from inequitable distribution of risk between those in vaccinated and unvaccinated clusters during the trial.

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