

# Trial Design and International Standards

Robert Temple, MD

Deputy Center Director for Clinical Science  
FDA/Center of Drug Evaluation and Research

Presidential Bioethics Commission

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# Major Concerns

## I. The people in the trial

- Use of placebos
- “Best local” vs “best global”

## II. The community where the trial is done and whose interests the trial is serving

# Use of Placebos

In symptomatic conditions, with few exceptions, only a trial showing a difference between treatments, usually a placebo-controlled trial, is informative, a credible basis for showing effectiveness or, with care, lack of effectiveness.

When the WMA in 2000 virtually banned placebos when there was a known effective therapy, it would, had people followed the advice, have prevented development of new symptomatic treatments (unless they were superior, an unusual occurrence).

Let me review the Declaration's placebo reference from 1975, to 2000, to 2008, and also show you ICH E-10's wording on the same subject.

# Declaration of Helsinki, 1975

The 1975 version said:

In any medical study, every patient - including those of a control, if any - should be assured of the best proven diagnostic and therapeutic method

What did the 1975 Declaration mean?

# Ethical Issue

Some (e.g., Rothman, NEJM, 1995) contended that the 1975 Declaration had to be read literally, i.e., that there could never be an acceptable placebo-controlled trial when there was existing effective therapy, and that the condition being treated is irrelevant. Thus:

- No placebo-controlled trials in baldness (Rogaine)
- No placebo-controlled trials in seasonal allergic rhinitis
- No placebo-controlled trials in headache
- No placebo-controlled trials of any duration in insomnia, anxiety, outpatient depression, OCD

Read literally, however, Declaration bars any trial (even active comparison) if there is existing therapy (people receiving the test drug don't receive "best proven" treatment), so its meaning is ambiguous on its face. Perhaps because of this, and despite Rothman and Michels, placebo-controls were performed, and published, by the thousands. Then the Declaration was changed.

# Declaration of Helsinki, 2000

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 exist.

Clearly, the 2000 version was intended to bar placebos whenever there was known effective treatment. And people noticed.

# WMA October 8, 2001

After a lot of criticism (FDA, HHS) WMA “clarified” its guidance in a press release on the use of placebo-controlled trials

The WMA agreed there were circumstances where a [placebo-controlled] trial might be ethically acceptable even if proven therapy was available. The WMA confirmed these circumstances in a formal note of clarification (2002).

These were

- where for compelling and scientifically sound methodological reasons its use was necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- where a prophylactic, diagnostic or therapeutic method was being investigated for a minor condition and the patients who received placebo would not be subject to any additional risk of serious or irreversible harm

Obviously the “or” made this position unethical.

# Finally

In 2008, the Declaration was modified again, still with a needless bias against placebos and failure to appreciate the difficulties of active control non-inferiority studies. It now reads.

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 patients 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.

This is not so different anymore from ICH E-10, although the last gratuitous line is regrettable

# ICH E-10 Guidance (2000)

The principal issue [in use of placebos] is the ethical one. There is no issue when no effective therapy exists. The question is when is it acceptable not to give existing therapy and randomize to drug or placebo.

“In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control.” (Generally, because if treatment is so toxic that people refuse it, a placebo may still be possible.)

# ICH E-10 Guidance (cont)

“In other situations, where there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is non-coercive and patients are fully informed about available therapies and the consequences of delaying treatment... Whether a particular placebo-controlled trial of a new agent will be acceptable to subjects and investigators when there is known effective therapy is a matter of investigator, patient, and IRB judgment, and acceptability may differ among ICH regions. Acceptability could depend on the specific trial design and population chosen.”

As noted, this is now essentially what the Declaration says.

# Best Local vs Best Global

## I. Symptomatic

ICH E-10 refers to “available” therapy but does not specify whether that refers to treatment available where the study is being done, or available anywhere, specifically, in richer countries.

This omission was not accidental.

Note, though, that under ICH E-10 this issue is of interest only if there is a treatment that prevents serious harm (because those are the treatments that must be given). There would never be an impediment to using a placebo instead of an effective symptomatic treatment, whether it was available (e.g., in US) or not available (a developing country), so long as the situation was not coercive and there was valid informed consent.

# Best Local vs Best Global

## II. Important Treatment

Suppose a clinically important treatment is not available in a developing country (this occasionally arises where a developed country chooses not to use a treatment).

And let's suppose a comparison study (non-inferiority study) will not be informative,

Can you study a new drug with the same therapeutic goal as existing therapy in a developing country where the SOC is not available

Very controversial; two treatment cases:

1. The trial serves the interests of the (e.g., it is a therapy they can utilize or afford) developing country
2. The trial has a commercial intent (i.e. there is an intent to market it only in other places.

# Best Local vs Best Global

## II. Important Treatment (cont)

This was an important subject at recent WMA meeting in Buenos Aires. Based on discussion (no written conclusion yet). I'd say there was fair consensus that if the study served the country's interest, e.g.,

- HIV transmission prevention by a short-course AZT regimen (the full 026 regimen could not have been achieved)
- Use of rectal artesunate where full anti-malarial therapy was inevitably delayed
- More generally, any trial needed by the country

a placebo-controlled trial was ethical, if such a trial was scientifically necessary. In the above cases, e.g., the tested treatment was inferior to the best therapy and would fail in an NI study.

# Best Local vs Best Global

## II. Important Treatment (cont)

Far less clear is conduct of a study “making use” of the fact that treatment was not available to do a placebo-controlled drug-development study that could not be conducted in a developed country.

Classic case: Surfactant placebo-controlled study proposed in several Latin American countries

- Surfactant is life saving
- Equivalence (NI) trial won't do (wouldn't be done in Latin America if it had been acceptable)
- Equipment probably makes ALL better than outside the study (but not as good as surfactant)
- No plan, so far as I know, to market in Latin America. Purpose of trial was to gain US approval

# Best Local vs Best Global

## II. Important Treatment (cont)

Public awareness (FDA meeting reported in *Washington Post*) and study abandoned [eventually superior in US study to marketed synthetic (not as good as bovine), but that was not anticipated at the time.]

Everyone was apparently pleased that the people in developing countries were not “used.”

I note, though, that for the people who would have been in the trials, more neonates are now dead.

Arguably, some tension between interests of the patients and a broader view of social justice.

# Who Is Being Served?

There is concern, apart from the others of the trial itself, as to whose interests are being served. Are trials done in poor environments (even if important treatment is not denied):

- Wasting resources that could be better used
- Taking advantage of the poor health care environment (coercive)

Good questions, but it should be noted that such trials, by the thousands, are taking place in Latin America, E. Europe and increasingly, in Asia

- They build infrastructure, a CIOMS goal
- They probably do provide important access for the patients in the trials
- Countries could seek some provision for post-study care
- It seems condescending to think these countries and people can't independently decide whether they want to participate
- The same trials are also done in developed countries