



Placebo use in research: What do the guidelines say?

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Trial design

- For research to be ethical, it must have scientific and social value
- Randomized, placebo-controlled trials normally provide the best evidence

The placebo problem

- When a proven treatment exists, using a placebo deprives participants in the control group of treatment known to be beneficial
- The important research question is normally whether a new treatment is better than the existing one

Review of guidelines

- **International guidance** WMA, WHO / UNAIDS, CIOMS, ICH, CoE, EC, EGE, EMA
- **Influential national guidance and regulations** FDA, NBAC, Nuffield Council, UK MRC
- **National guidance from selected emerging and developing countries** India / ICMR, Brazil / BCNS, South Africa / SA DoH, Uganda / UNCST

Limitations

- Existing guidelines reflect the controversy surrounding placebo use in research
 - “The commentary to the Guideline concerned (11) recognizes the unresolved, or unresolvable, conflict” CIOMS
- Some guidelines may be outdated and/or are currently under revision
- Almost no vaccine-specific guidance

Acceptable placebo use

- Scientific and social value
 - Reasonable risk-benefit ratio
 - Informed consent CIOMS, ICH, EMA
 - Respect right to withdraw EMA
 - Post-trial access UNCST
 - Ethical review CIOMS, EGE, EMA, SA DoH
 - Community involvement ICMR
- } All guidelines / regulations

Risk-benefit considerations

- All research
 - Default to test against proven effective treatment
 - Placebo acceptable if
 - No proven effective treatment
 - Delaying or foregoing proven effective treatment poses negligible / no serious / justifiable risks
 - Risks of placebo are minimized
- Research in resource-poor settings

1) Default

- Default to test against proven effective treatment WMA, CIOMS, EGE, EMA, NBAC, SA DoH
 - As a general rule CIOMS
 - Presumption in favor of active controls NBAC
 - Any exception must be justified EGE

2) No proven effective tx

- Placebo acceptable if there is no proven effective intervention for the condition under study WMA, CIOMS, WHO/UNAIDS, ICH, CoE, EMA, EC, NBAC, ICMR, BCNS, SA DoH, UNSCST

3) Negligible risks

- Placebo acceptable if delaying or foregoing treatment poses negligible risks
CIOMS, EC, SA DoH, UNCST
 - At most temporary discomfort or delay in relief of symptoms (e.g. no treatment of relatively trivial conditions) CIOMS
 - No more than minimal adverse effects that are entirely reversible UNCST

4) No serious risks

- Placebo acceptable if delaying or foregoing treatment poses no serious risks
ICH, EMA, NBAC
 - No additional risk of irreversible harm EMA
 - No serious harm NBAC

5) Justifiable risks

- Placebo acceptable if 1) delaying or foregoing treatment poses no serious risks *and* 2) there are compelling methodological reasons for using placebo WMA, CIOMS, UK MRC, UNCST
 - Use of established effective intervention as comparator would not yield scientifically reliable results, placebo does not add any risk of serious or irreversible harm CIOMS

6) Risks minimized

- Placebo acceptable if some or all of the above conditions are satisfied *and* risks are minimized CIOMS, EC, WHO/UNAIDS, ICH,
 - Placebo use should be associated with measures to minimize exposure and avoid irreversible harm EC

Risk-benefit considerations

- All research
- In research in resource-poor settings
 - Placebo acceptable if
 - Participants not deprived of interventions they would otherwise receive
 - Compelling methodological reasons for using placebo *and* responsiveness* to local health needs *and* reasonable risk-benefit ratio

1) No worse off

- Placebo acceptable if participants are not deprived of interventions they would otherwise receive Nuffield
 - Minimum standard of care offered to the control group should be the best intervention available for that disease as part of the national public health system Nuffield

2) Local social value

- Placebo acceptable if 1) there are compelling methodological reasons for using placebo *and* 2) the research is responsive* to local health needs *and* 3) the risk-benefit ratio of the study is reasonable CIOMS, EGE, NBAC, SA DoH

Local social value ctd.

- CIOMS view of responsiveness* to health needs: responsiveness *and* reasonable availability *and* established effective intervention unlikely to become available / implementable / affordable in the foreseeable future (*and* study initiated by local health authorities)

Summary

- Widespread agreement that placebo use is acceptable when there is no proven effective intervention
- Many guidelines accept placebo use when a proven effective intervention exists if delaying / foregoing treatment poses only very limited risks (*inconsistent with clinical norms AND requirements for research*)

Summary ctd.

- Placebo use in studies in resource-poor settings remains controversial and raises difficult questions about research under non-ideal circumstances
 - Standard of care
 - Responsiveness / reasonable availability
 - Research as a remedy for overcoming high drug prices?