Standard of Care and Placebo Controlled Trials

The views expressed are my own. They do not represent the position or policy of the NIH or the US government.

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Readings

Wendler D, Emanuel EJ, Lie R. American Journal of Public Health 2004; 94:923–928

Angell M. N Engl J Med 1997;337:847–849

Kitua, et al. J Med Ethics 2010;36:116e120

Observation

- In some cases, patients experience improvements that are not due to specific medical interventions.

- A patient with lower back pain goes to his doctor and feels better, even though the doctor did not give the patient any treatment.

Possible Reasons

- Natural history of some diseases, such as prostate cancer, is variable.
- Some diseases, such as depression and back pain, can go away on their own.
- Patients get better because they expect to get better.
- Getting attention from doctors and nurses can make patients (feel) better.

Implication

- Improvements in patients who receive an experimental intervention may be due to the intervention, or to other factors.

- To assess the efficacy of experimental interventions, it can be important to include a control arm.

Method

- Randomize subjects to the experimental intervention or to a control intervention.
- Compare the results in subjects who receive the experimental intervention to subjects who receive the control intervention.
- In some trials, the control intervention is a placebo (or no treatment).

Concern

- Patients are interested in obtaining access to treatment for their conditions.
- However, placebo controls and no treatment controls deny some (e.g. half) of the patients in the trial a potentially beneficial treatment.

IL-2 and HIV

- Treatment with IL-2 was found to result in increases in CD4 counts for HIV infected patients.
- Treatment with IL-2 is also associated with often significant flu-like symptoms.

ESPRIT Study

- Randomize patients to antiretrovirals with IL-2 or antiretrovirals and no IL-2.
- Critics objected that this trial was unethical because it denied IL-2 to some participants.

Results

- The study found that IL-2 led to “substantial and sustained increase in CD4+ cell count.”
- IL-2 yielded no clinical benefits.
- Side effects, GI disorders and psychiatric concerns were greater in the IL-2 arm.

N Engl J Med 2009; 361:1548-1559

Balanced Worries

- Placebo trials seem acceptable when the chances they deny subjects a beneficial treatment and the chances they give subjects a harmful treatment are about equal.

- In that case, it is unknown whether it is better to receive the experimental treatment or receive a placebo.

Freedman

Clinical equipoise obtains when there exists a "controversy among the community of expert clinicians concerning the relative therapeutic merits of each treatment within the trial—including placebo—if the study includes a placebo control."

Standard View

- Some argue that equipoise is an ethical requirement: Studies are ethical only when there is disagreement in the expert community about what is best for patients.

- There are good reasons to hold this view.

Explanation

- It is vital to ensure research subjects are not exposed to excessive risks.

- Requiring equipoise provides a way to do this: it ensures that subjects will not receive an intervention that is known to be worse than the best standard of care.

Dilemma

- In some cases, an effective treatment exists, but it is not available in the host country.
- Example: Long-course AZT to prevent transmission of HIV from mother to fetus
- What is the appropriate control to use in these cases?

Shapiro and Meslin

"In our view, an experimental intervention should normally be compared with an established, effective treatment…whether or not that treatment is available in the host [developing] country."

Declaration of Helsinki

New interventions must be tested against the best proven interventions, except when: no proven intervention exists or for compelling reasons the use of a less effective intervention is necessary and patients who receive the less effective intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Paragraph 33 (2013)

Non-beneficial Research

- DoH permits subjects to be exposed to some risk of serious or irreversible harm in the context of non-treatment trials.

- For example, it is widely agreed that it can be acceptable to do a study involving a purely research lumbar puncture, even though it poses some risks of serious harm.

Inconsistency

- This suggests an inconsistency: some risk of serious harm is permitted in non-treatment trials, but not in treatment trials.
- This seems odd.
- However, it might be good policy if there is no other way to protect subjects of treatment trials from excessive risks.

Long-course AZT Example

- Country A cannot afford to provide its citizens with long-course AZT, which is the best treatment to block vertical transmission of HIV.
- An investigator develops a possible treatment that is affordable, and may be effective, although not as effective as long-course AZT.

Two Possible Designs

- Comparing the experimental treatment to long-course AZT may show that the experimental treatment is not effective.

- A placebo controlled trial could show that the experimental treatment is effective (even if not as effective as long-course AZT).

Host Country Relevance

- The placebo controlled trial has greater potential to produce results that are relevant for the host country.

- Thus, the placebo controlled trial seems to better satisfy the ethical requirement for host country value.

Potential for Exploitation

- Allowing such trials creates the potential for investigators to conduct placebo controlled trials in developing countries of medications that will be used only in developed countries.

- To address this potential for exploitation, safeguards are need for trials that propose to include less than the best proven treatment.

Framework

- IRBs should assume a default of requiring equipoise with the world wide best methods in their studies.

- However, IRBs should be willing to allow exceptions to this rule that satisfy the following 4 conditions.

Wendler, Emanuel, Lie. AJPH 2004; 94:923-927.

Necessity and Relevance

- **Scientific Necessity**: investigators must use less than the best methods to answer the question posed by the trial.

- **Relevance**: answering the question posed by the trial addresses an important health need of the host community/country.

Fair Benefit and Nonmaleficence

- **Sufficient Host Community Benefit**: the trial will produce a fair level of benefit for the host community/country.

- **Nonmaleficence**: the trial will not make subjects and the community worse off than they would be in the absence of the trial.

Conclusion

When these conditions are satisfied, the trial will address an important health need of the host community, offer the host community a fair level of benefits, and not make the host community or subjects worse off.

Objection #1: Double Standard

- "A double standard permits research designs (in developing countries) that are unacceptable in the sponsoring country."

Lurie, Wolf. NEJM 1997; 337:853-856.

Response: Differences in circumstances across countries imply that different designs may be necessary to ensure an ethical trial (require a signature in some communities but not others; use bovine derived drugs in some communities, but not others).

Consistency

- One needs to look to the overall goals of the study: respect and host country value.
- Use of less than the world wide best methods may be necessary to meet the goal of ensuring that trials are socially valuable and provide sufficient benefit to the host community.

Objection #2: Obligations

Trials using less than the world wide best methods violate clinicians' obligations to provide the best treatments for their patients.

NBAC, Marcia Angell, Peter Lurie

Reality

- Clinicians do not have an obligation to provide the best care when there is a good reason not to do so.

- For example, it is acceptable to provide less than the best methods in order to train new physicians; save money that can be used to help other patients; allow nurses to eat; ensure integrity of clinical trials.

Summary

- This framework allows trials to use less than the best methods only when necessary to address an important health need of the host community.

- Insisting on the best methods would involve the cost of not addressing the health concern in question. When this cost is high, such trials can be ethically acceptable.

CASE

Delays in treating malaria increase mortality.

Treatment, intravenous or deep intramuscular injections of quinine, need to be administered in a hospital.

OBSTACLES

Delay in getting treatment can be due to the distance or to parents deciding not to take the child to the hospital.

Parents may not realize the seriousness of the disease, seek traditional healers, or have experience that drugs are not available.

STUDY

Test a rectal suppository of artesunate in rural areas of Bangladesh, Ghana, and Tanzania.

Can be administered by village practitioners who can easily be trained.

STUDY DESIGN

Placebo controlled trial of rectal artesunate.

When parents present with a sick child, they will be given information about the trial, told they should seek hospital care, but if they decide they do not want to do that, given the option of entering the trial.

Questions

Would you approve the trial with this design?

Why or why not?

If not, are there any changes in the design that you would recommend?