Ethical issues in international collaborative research: the standard of care debate

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Issues in international research

• Issues of different ethical standards and regulatory requirements

• What types of trials can one do in resource poor settings?
  – Post trial access to intervention studies

• Are researchers obligated to provide additional care to trial subjects?
  – Ancillary care

• What is the appropriate standard of care for the control group in a clinical trial?
Helsinki, 2013, article 33

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

• Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

• Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.
Scientific necessity criterion

• Cases where we do not know what the “no treatment effect is” and it varies among populations
  – If we compare
    • Established intervention against new intervention with the following results:
      – Established intervention has 30% survival
      – New intervention similarly has 30% survival
      – No treatment previously results in 20% survival
    – We cannot conclude that new intervention is effective without a placebo group
## Equivalence trials

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<th>Established, effective intervention</th>
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With placebo arm

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Scientific necessity criterion

- Cases where we do not know what the “no treatment effect is” and it varies among populations
  - If we compare
    - Established intervention against new intervention with the following results
      - Established intervention has 20% survival
      - New intervention has 30% survival
      - No treatment in this population has 30% survival
    - We cannot conclude that new intervention is effective without a placebo group
No serious harm criterion

- Clinical trial of an anti-histamine against runny nose
- Minor elevations of blood pressure
- Depression – Perhaps controversial
- Psychosis - Controversial
- Death – Definitely prohibited
The perinatal HIV transmission studies

• It had been shown that a long course of AZT treatment reduced transmission from around 30% to less than 10%
• This intervention was expensive and logistically difficult in resource poor settings
• Urgent need to develop a more suitable intervention
• A number of short course trials initiated. All but one tested against placebo
• It was argued that the design was scientifically necessary
Helsinki criteria satisfied?

• Was a placebo controlled trial scientifically necessary?
  – There was variability in the no intervention transmission rate

• There was a “best proven intervention” demonstrating reduction in HIV-infection from 30% to below 10%
  – HIV infection is serious harm
Helsinki criteria satisfied?

• Was a placebo controlled trial scientifically necessary?
  – There was variability in the no intervention transmission rate

• There was a “best proven intervention” demonstrating reduction in HIV-infection from 30% to below 10%
  – HIV infection is serious harm

• BUT this intervention is not implementable in resource poor settings
Dilemma

• There is a known effective intervention against a major health problem in a resource poor setting
• This intervention cannot be made available in the foreseeable future
• It is desirable/necessary to introduce cheaper alternatives
• But testing these involves violating international research ethics regulations
  – Or the ethical principle “do no harm”

This principle of comparing a new intervention with the best current proven intervention seems reasonable at first sight, but it has given rise to much controversy. The controversy has centred on global ‘best’ interventions that are neither currently available nor likely to become available to the population in which the trial is being conducted, either because of their cost or because of the feasibility of implementing the intervention (for example, radiotherapy for conditions in countries in which there is little or no provision for such treatment). The ‘purists’ hold that, if the global ‘best’ intervention is not included as the control arm, then the trial is unethical and should not be conducted. The pragmatists, who often have experience of conducting trials in LMICs, hold that this position is itself ‘unethical’, as it prevents research investigations that may lead to important public health benefits in deprived populations.
Example: prevent HIV infection after delivery

- Interventions such as nevirapine dramatically reduced transmission during pregnancy and delivery
- But transmission still can occur after delivery if mother breastfeeds baby
- In rich countries: HIV positive mothers should not breastfeed babies, but use bottle feeding. This eliminates transmission after birth
- In resource poor settings: recommendation is still that HIV mothers breastfeed
  - Overall this is best for the children
    - Lack of clean water
How to prevent infection in Low income countries?

- Best proven intervention is bottle feeding
- According to the Declaration of Helsinki this intervention should be provided in the control group
- Let us say we have a drug that might prevent infection. We should then have the following design
  - The intervention group is a breastfeeding group with the drug
  - The control group is bottle fed
Problems

• Will this design provide results that are useful for Low income countries?
  – We want to know whether drug treatment is better than breast feeding, not how much worse drug treatment is compared with bottle feeding

• The intervention group also receives sub-optimal care: breast feeding with a drug intervention. There is no reason to believe that this overall is as good as bottle-feeding (even within the context of the clinical trial).
Challenge

• According to the Declaration of Helsinki, we are not allowed to do this research, even if it could lead to dramatic health improvements in low income countries.
  – Nevirapine trial in fact did do so
Placebos permitted

If scientifically necessary for trivial conditions
- Hair loss
- Nasal congestion

If scientifically necessary and if causing temporary harm or non serious harm
- Migraine headaches
- Minor elevations of blood pressure
An exception to the general rule is applicable in some studies designed to develop a therapeutic, preventive or diagnostic intervention for use in a country or community in which an established effective intervention is not available and unlikely in the foreseeable future to become available, usually for economic or logistic reasons. The purpose of such a study is to make available to the population of the country or community an effective alternative to an established effective intervention that is locally unavailable.
Also, the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population. In these circumstances an ethical review committee can approve a clinical trial in which the comparator is other than an established effective intervention, such as placebo or no treatment or a local remedy.
3 conditions for exception

1. The results of the trial will be relevant to the study population/country in which the study is carried out or there is a reasonable likelihood that the new intervention will be implemented
   – AND
2. No alternative designs are possible AND
3. Participants are not denied treatment they would ordinarily receive
• The view of the pragmatists, including ourselves, is that, if an effective intervention is known, but its cost is beyond that which would make it feasible to introduce it into the local health care system (and there is little prospect that the cost can be reduced by means such as shifting production of pharmaceuticals to generic manufacturers), then it may well be acceptable to exclude it from consideration as a possible comparison intervention in a trial. In some circumstances, it may be acceptable to try to test a new intervention that might be, at best, equivalent to an existing intervention or may even be inferior to it if, for example, it is cheaper or simpler to apply, or more stable, or associated with fewer adverse reactions, or is more acceptable to the community than the existing intervention. In such circumstances, the purpose of the trial might be to show that the efficacy of the intervention was ‘equally good or not much worse than’ the existing intervention.

  – Field trials of health interventions. A toolbox
Case: Pertussis vaccine trials in Sweden/Italy

- Previously vaccine used based on whole killed bacterium
- Various side effects, relatively low protective effect
- Acellular vaccine developed in the early 1990s.
  - Test design: placebo controlled trial
  - Deemed unethical in the US
- NIH funded placebo controlled trial carried out in Italy and Sweden (four armed trial, with 10% of children in the placebo group).
  - Sponsor argued placebo group is necessary
  - Sweden and Italy had discontinued their whole cell vaccination program. 10% of infants vaccinated in Sweden, 40% in Italy
Two unresolved issues

• Sweden had used a locally produced whole cell vaccine previously that was known to be inferior to the one used in the US

• Many pediatricians in Sweden disagreed with the official government position of no whole cell pertussis vaccine
  – Lots of pertussis cases in Sweden after discontinuation of vaccination
  – Experts advising government likely be the same who had an interest in participating in the US sponsored clinical trial
• The low level of vaccination in the two countries is an important factor in designing an ethically acceptable trial, said Dr. Mark Siegler, director of the Center for Clinical Medical Ethics at the University of Chicago. "Since only 4 in 10 Italian children are immunized, it seems that any trial that assured 9 out of 10 participants were likely to receive a safe and effective pertussis immunization is an ethically appropriate trial," he said.

• But Dr. Siegler said to avoid all criticism, the best approach would be to offer all parents interviewed for the study a chance to get the recommended vaccinations first, and then try to enroll those who declined.
Lessons from the Pertussis case

• The question of whether to do a trial with a lesser standard of care in a country may delay introduction of a recognized standard of care in that country
  – It was generally recognized that the lack of a pertussis vaccination program in Sweden was not justified

• How much information about the «controversy» should be provided to potential participants in the trial
  – In particular that the recognized standard of care was readily available to anyone who wanted it
Case: oral rehydration

- In the late 1960s standard intervention for cholera in adults and diarrhea in children was intravenous liquid
  - Perception was that oral rehydration was useless, even dangerous, because liquids could not be absorbed from the gut
- Intravenous administration difficult in resource poor settings, war situations, and epidemics
- A number of researchers in Bangladesh and India started research that led to the current standard, oral rehydration, which has saved millions of lives
- Control group?
- Is any study acceptable?
Key trials

• Beginning of 1960s: 30-40% mortality of mortality in villages. Hospital intravenous fluids, around 1%
• Basic studies of roles of Sodium and sugar in transport of fluids from intestines in cholera patients
• 1967 Richard Cash and David Nalin, two US physicians arrive in Dacca. Both are interns/residents, 26 year old. September 1967 cholera epidemic. Failed oral rehydration trial in field conditions. No deaths, but not adequate rehydration.
• Second protocol carried out in hospital in Dacca
Adults

Sickest patients selected

First stabilized intravenously

Then maintained on oral fluids
  - Some wanted to continue iv fluids

Safeguards of hospital setting
Field trial in rural East Pakistan

- Treatment center
- Stabilized on IV
- Then maintained on oral fluids
- Next trial (from Calcutta group) using ORT in refugee camp during war.
Use of an Oral Glucose-Electrolyte Solution in the Treatment of Paediatric Cholera—
A controlled study
by D. MAHALANBIS, M.D.;; R. B. SACK, M.D., M.C.;; B. JACOBS, M.D., A. MONDAL, M.B., CH.B.,
and J. THOMAS, M.A.

From the Johns Hopkins International Centre for Medical Research and Training, and the Infectious Disease Hospital, Calcutta, India

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Abstract
A controlled trial of oral glucose-electrolyte therapy in children with cholera was performed in Calcutta, India. Fifteen children were treated by standard intravenous methods and 17 by a combination of intravenous and oral glucose-electrolyte fluids. Oral fluid replacement was found to be effective maintenance therapy in spite of large stool losses (up to 9.5 lit. per kg.day). Persistent vomiting was the main problem encountered during oral therapy, but this occurred almost exclusively in children with the more severe diarrhoea whose initial deficits were only partially corrected intravenously. Oral fluid replacement was shown to be a useful additional form of therapy in paediatric cholera, although it was uniformly successful only when initial deficits had been completely corrected intravenously. Oral glucose-electrolyte solutions have been used successfully to treat cholera in adults, both in hospital and in field conditions. The main advantages of oral therapy are a marked reduction in the need for intravenous fluids, as the extent of 80 per cent in severe cases, and thereby a reduced need for trained personnel to administer therapy under difficult field conditions.

Lack of intravenous fluid and lack of trained personnel are major handicaps to successful cholera therapy in many parts of the world. The use of oral hydration in children would be an important addition to the treatment of paediatric cholera under such circumstances. Studies on the efficacy of oral replacement in paediatric cholera, however, are few[11] and as yet no controlled study in children has been reported. Intravenous fluids have been shown by us in previous studies[11] to be satisfactory therapy for most pediatric patients. Oral therapy, however, would further obviate the need for needle punctures and restraints, and sterile pyrogen-free fluids.

This study was undertaken (1) to evaluate the use of an oral glucose-electrolyte solution in replacing part of the initial fluid deficit and virtually all of the subsequent stool losses, and (2) to define the practical problems involved in carrying out such treatment in infants and children with cholera.

Materials and Methods

Patients
The study was conducted in Calcutta during the "cholera season", April through July, 1970. Male children age six years and under, with a history of watery diarrhoea of less than 24 hours duration, with no history of antibiotic medication, and presenting with dehydration estimated by clinical assessment to be approximately 10 per cent of body weight were admitted to the study. Each child was then randomly assigned to either a control or oral therapy group. All studies were performed on metabolic beds for accurate stool and urine collections.

The control group was initially hydrated intravenously (IV) with a hypotonic electrolyte solution in 5 percent dextrose (Na+ 106; Cl− 74; and HCO− 32 mEq/litre)10. 100 ml/kg body weight given over the first 8 hours. The same solution was used to replace, on a volume-for-volume basis, all stool losses occurring after admission. To meet the obligatory water needs, 5 per cent glucose water was given ad libitum by mouth.

Children in the oral therapy group were initially partially rehydrated with 1/2 Ringer's lactate solution, 50 ml/kg body weight, over a 3-hour period, at which time the IV was discontinued and oral glucose-electrolyte (GE) solution started (Glucosal A) to replace the initial fluid deficit

- Trial in children in 1970 in Calcutta
- IV group as control
- Intervention group initially rehydrated with iv solution, then maintained on oral rehydration
- If oral rehydration failed, iv rehydration resumed
Lessons from the oral rehydration trials

• Even if the vast majority of people in Bangladesh did not have access to state of the art IV replacement fluids, it was felt to be unjustified not to provide it to clinical trial participants

• «Hybrid designs» were used so that people were stabilized using state of the art treatment, and only then was oral rehydration started in some patients

• Nevertheless, everyone who received oral rehydration therapy received a «lesser standard of care», but the trial was justified that this intervention was more feasible in resource poor settings