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Case Studies And Ethical Issues in Clinical Trial

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Ethics Case Study 1

Cambodian HIV trial halted because of patient rights issues

A major study to determine whether Gilead Sciences' antiretroviral, tenofovir disoproxil fumarate (Viread), would be an effective preventative against HIV infection has been halted because Cambodian sex workers have protested about the terms of the trial. The trial was due to enrol 960 patients in the autumn.

The trial, which is being funded mainly by the US National Institute of Allergy and Infectious Diseases, would have enrolled uninfected female sex workers in Phnom Penh to receive either 300mg of Viread or placebo daily for 12 months.

However, women who became infected during the trial would not be offered treatment, but would be referred to local healthcare services. This was unacceptable to the Cambodian Women's Network for Unity and to the HIV activist group, ACT-UP Paris, which has demanded that "Gilead cease taking sex workers from developing countries as cheap guinea pigs."

The NGO also requests that "persons already included and tested HIV-positive, or who have become HIV-positive in the course of the trial, be entirely taken in charge by Gilead, including medical care, treatment for opportunistic infections and antiretrovirals if necessary". It feels agencies should refuse to organise trials that lack the required financial means if it leads to unacceptable concessions on ethics.



Questions

1. Would you allow such a trial in your country?
2. If no, why not? If yes, how is it ethically justifiable?



Ethics Case Study 2

Chris was recruited to participate in a clinical trial by his oncologist, Dr. Blair. Chris has cancer, and the traditional treatments have been only intermittently successful.

The clinical trial is a randomized, single-blinded, placebo-controlled study of a drug that may be beneficial to patients with the kind of cancer that Chris has. The trial is set to last one year, after which time enough data will have been accumulated to determine the efficacy of the new treatment.

After six months in the study, Chris is not experiencing any signs of improvement, and he may in fact be getting worse. Dr. Blair continues to receive reports about the progress of the research subjects enrolled in both the treatment arm and in the placebo arm, and preliminary data seem to suggest that the drug is beneficial.

During an examination Chris asks Dr. Blair if he is in the treatment arm or the placebo arm. Chris requests that if he is in the placebo arm Dr. Blair switch him to the treatment arm, so that he can receive the possible benefits of the new treatment. Dr. Blair knows that Chris is in the placebo arm.



Questions:

1. Should Dr. Blair respond to Chris's query and inform Chris that he is in the placebo arm?
2. Should Dr. Blair also inform Chris that preliminary data seem to suggest that the new treatment is beneficial?
3. Should Dr Blair switch Chris over to the treatment arm?
4. When is it appropriate for an investigator to remove a subject from a study?
5. What are the dual responsibilities that Dr. Blair has?
6. Which should take precedence in this case, and why?



Ethical problems with Randomized Controlled Trial

Clinical Trial in the form of Randomized Controlled Trial (RCT) is the gold standard method for demonstrating safety and efficacy of treatment.

- Features of RCT design that makes it a gold standard method: controlled, randomized, blinding.
- Yet, the design of RCT presents a spectrum of unique ethical problems.

Levine R. Ethics and Regulation of clinical research.

“In considering the RCT, the average IRB member must be baffled by its complexity and by the manifold problems it represents”



Some problematic ethical issues in Clinical Trial

1. Equipoise: ethical justification of RCT
2. Inherent conflict when Physician is also clinical investigator
3. Ethics of Randomization and Blinding
4. Dealing with preliminary data and emerging trends
5. Ethical use of Placebo
6. Trial in developing countries: Use of “Best current” control treatment and Obligation to continue treatment after trial end.



Ethical justification of controlled trial

In an RCT, a group of subjects receives new Rx under investigation and others receive another therapy or no therapy, the “control” Rx.

Control is required for study validity, to avoid the fallacy of *post hoc ergo propter hoc* reasoning.



Galen AD 130-200

“ **All who drink of this treatment recover in a short time; Except those whom it does not help, who all die. It is obvious, therefore, that it fails only in incurable cases.**”



Ethical problem with Rx comparison

1. What if the new Rx is promising. Then aren't we depriving subjects in the control arm of potential benefit?
2. What if control therapy is known to be efficacious, are we depriving subjects on the Rx arm of potential benefit?



Equipoise

Ethical justification of RCT: “An honest or bona fide null hypothesis”, also referred to as equipoise.

Clinical Equipoise exists if:

In comparing treatment A and B

1. The clinical community agrees there is no **convincing evidence** that A is better or less toxic than B
2. There is no superior therapy C, unless good reason exists to reject C

Hence, doubt about which Rx is superior justifies giving subjects an equal chance to get either one; no one is being assigned to an inferior treatment.



But...

1. **What is convincing evidence”?**

- Statistical significance vs clinical importance
- Often, substantial body of preliminary evidence is available from uncontrolled studies, historical data, pilot trial etc.
- Most investigators and even IRB would demand some preliminary evidence that a new therapy have a potential beneficial effect before agreeing to the trial (ie demonstration of potential, the trial to confirm efficacy)
- Selection of outcome measures or endpoints: different conclusion may be reached depending on which outcome measures



More questions

2. Clinical equipoise and Individual treatment decision

- Not knowing which treatment is better for a group of patients does not preclude judgment about what is best for an individual patient at a particular time.
- It may be possible to make recommendation for an individual in favor of one of 2 unproven treatments based on individual's unique symptoms, side effects, preferences etc.
- Create tension for clinician who is also investigator

And yet more questions...

3. Even if new therapy is superior, what if there **isn't enough** go around?
 - Eg. MRC Streptomycin trial for PTB
 - Randomization is fairest mean to distribute scarce resource
4. Requirement for **independent confirmation** of research
 - Eg. FDA requires 2 pivotal phase 3 trials

Physician as Investigator

	Research	Practice
Goals	Systematic investigation of involving human beings to develop generalizable knowledge	Diagnosis and treatment for an illness in individual or group to meet the health needs
Activities	Test hypotheses, permit conclusion to be drawn	Designed to enhance the well being of a patient and that is likely to succeed.
Sub-jects	Subject may/may not benefit, as the goal of clinical research is to serve a common good by generating knowledge	The individual patient receiving care can expect direct benefit

Ethical problems with dual role

1. The need to make best possible clinical judgment for patient (physician), and need for clinical equipoise in RCT (see above on Equipoise)
2. Dependency relationship invalidate informed consent?
3. Physician sole obligation should be the well being of the patient, yet in the context of trial conduct, the physician has competing obligation to generate high quality data. Trial distracts from "good personal care".

What the guideline says...

Declaration of Helsinki 2000 Paragraph 28

"The physician *may combine medical research with medical care*, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, *additional standards apply* to protect the patients who are research subjects"

What the guideline says...

Declaration of Helsinki 2000 Paragraph 32

"In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, *the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope* of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed"

What should we do and How?

- Be aware of the tension inherent in dual role
- Inform subject accordingly
- Rely on other members of team
- Separating roles of clinician and investigator
- Refer to other investigator for inclusion in trial



Ethics of Randomization and Blinding

RCT has 2 characteristics:

1. Random assignment to 2 or more treatments. That is, selecting treatment by computer rather than based on individual patient's needs and characteristics.
2. Blinding. Neither subjects (single blind) nor investigators (double blind) know which treatment the subject has been assigned to

These are to maximize study validity but has ethical implications?



Ethical problems with Randomization & Blinding

1. Preferences for treatments and information about which treatment a subject is receiving are relevant to autonomous decisions
2. Information about which treatment the subject is receiving may be important in managing an adverse event or a medical emergency, consistent with a concern about safety and welfare of subjects



What should we do and How?

- Informed consent all important: randomization and suspension of knowledge about treatment
- Have procedure to allow breaking of blind
- Have procedure to handle emergency



Preliminary data and emerging trends

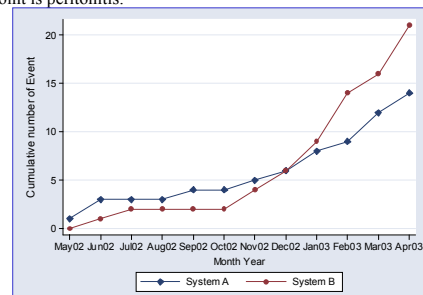
In the course of most RCTs, preliminary data are being accumulated and if subjected to monitoring or even analysis, may indicate

1. One of the therapies seem to be more effective
2. One of the therapy seem to be more safe, or serious AE seem to be associated with one of the therapy, whether causally related or not
3. No emerging trend, and demonstration of treatment effect seems unlikely.



Example: CAPD-2 Trial

270 subjects with ESRF randomized to 2 CAPD systems, A and B. Primary endpoint is peritonitis.



Example: ISIS-2 Trial

17,187 subjects with AMI randomized to streptokinase or placebo. Primary endpoint was mortality at 5 weeks.

Results:

Streptokinase 9.2% vs Placebo 12%. P value <0.0000001

Ethical implication:

Clearly streptokinase would have been shown to be superior long before the trial was concluded.

Sponsor's justification:

“Our ethical responsibility was to report the results when they would be likely to change medical practice in the future.”
Meaning sacrificing current trial participants (those in placebo arm) is therefore acceptable ?



Ethical problems with emerging trends

- Under what circumstances must a RCT be terminated because continuation would be unethical?
- Must subjects be informed of emerging trends indicating superiority of one of the therapies although such superiority is not yet established statistically?
- Must subjects be informed of the possibility of SAE when it has been established that the therapy causes the SAE?



What the guideline says...

Nuremberg Code 1949 2000 Article 10

“During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject “



What the guideline says...

Declaration of Helsinki 2000 Paragraph 17

“Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. *Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results “*



What should we do and How?

Options:

- Full disclosure
- Non-disclosure
- Consent to incomplete disclosure



Full disclosure

- This would jeopardize the integrity of the trial, spell the end of trial.
- Results would be inconclusive, which defeats the purpose of doing the trial in the first place
- Hence Not a serious option



Non-disclosure

Is non-disclosure ethically acceptable?

Probably NOT

- Many would argue that preliminary information is material to the subject's decision to participate in trial (whether as new subject or continuing)
- Society no doubt would benefit from more conclusive results, but
- ICG GCP 2.3 "The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society."



Consent to incomplete disclosure

DHSS rules allow this and consistent with FDA

2 criteria must be satisfied:

1. The protocol submitted for IRB must state explicitly that interim results are to be held confidential
2. Subjects must be informed that interim results are not to be revealed to them or to anybody else until the RCT had reached a conclusion as specified in the original protocol.

But this is just procedural.



Consent to incomplete disclosure

Is this ethically acceptable?

- Is preliminary information that is inconclusive material to the subject's decision?
- But what is conclusive? Current standard of proof relies on statistics ($p < 0.05$). This may be arbitrary but represents current consensus in the scientific community.
- Thus, when subject gives consent to non-disclosure, he or she is called upon to accept or reject the values of the scientific community



Monitoring of accumulative data by IDMC

ICH GCP 1996. 1.25

- Independent Data-Monitoring Committee (IDMC)

(Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

"An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial."



What the guideline says...

ICH GCP 1996. Article 5.5.2

"The sponsor may consider establishing an **independent data-monitoring committee (IDMC)** to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings."



Placebo or "Best current" control treatment

Placebo is a treatment that is identical in all respects to the active treatment under investigation except the active ingredient is absent.

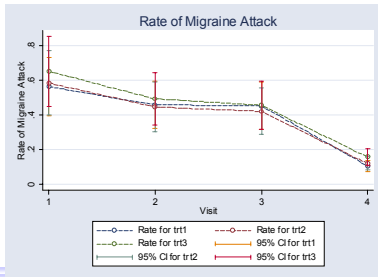
Uses of placebo in RCT:

1. Make blinding possible. This is uncontroversial
2. Allow for placebo effect.
3. Measure of absolute efficacy, whereas cf active control measure relative efficacy only



The Power of Placebo

A 12-week Prospective, Double-Blinded, Placebo controlled, Randomized, Multicenter Study of Low dose AND Medium dose Botulinum Toxin Type A (Dysport®) Injection for Migraine Prophylaxis. Sponsor: Ipsen-Beaufour



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Ethical problem with Placebo

- If effective treatment exists, use of placebo deprive individual of treatment that they may need
- On the other hand, experimental treatment without proof of superiority may cause harm or at best useless.

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What the guideline says...

Paragraph 29 Declaration of Helsinki 2000 Edinburgh

“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.**”

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What should we do and How?

1. Uncontroversial use of placebo:

- No standard treatment
- New evidence has raised doubt standard treatment
- Subjects are people who are refractory to or reject standard treatments

2. Uncontroversial non-use of placebo:

- Definitely NO if outcome for patient receiving no or placebo treatment is death, disability, or serious morbidity.

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Controversial use of placebo?

Can placebo be used even when effective exists?

- Expected consequences to subjects of randomization to one arm or another. Risk may be minimal for placebo, eg symptomatic Rx, short term treatment in chronic disease
- Quality of evidence regarding effect of existing treatment
- Expected variability of spontaneous changes in measured outcomes
- Extent to which treatment effect may be placebo effect

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Para 29 Declaration of Helsinki revisited

Subsequent note of clarification on Paragraph 29 Washington 2002

Placebo may be ethically acceptable even if proven therapy is available under the following circumstances:

1. Where for compelling and scientifically sound **methodological reasons** its use is necessary to determine efficacy or safety of a treatment
2. Where a treatment is being investigated for **minor condition** and patients who receive placebo will not be subject to additional risk of serious or irreversible harm.

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“Best current” treatment in developing countries

- In developing countries, “best current” treatment is NOT freely available
- “Best current” therapy may be difficult to define. Guidelines do differ.
- Too restrictive. Will preclude the testing of low cost treatments, which might yield substantial benefits in developing countries even if they are inferior to best current therapy in developed country.
- Rather than best, better to use “highest attainable” standard of care in the country.



Continuation of treatment after trial ends

- Should subject be allowed access to an intervention that proves beneficial to him or her after completion of the trial?
- Should one assure subject of this, for eg put it in the PIS?
- What about subjects randomized to the inferior treatment (when that is known after the trial)? Should they be switched to the superior treatment?



What the guideline says...

Declaration of Helsinki 2000 Paragraph 30

“At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.”



What should we do and How?

Questions?

- Whose obligation? Investigator or Sponsor
- Treatment eg drug may not be registered yet.
- When is a treatment proven effective? Eg One trial does not establish efficacy, FDA requires 2 pivotal trials
- Does the obligation vary with chronicity of the condition (and hence long term treatment requires)?
- Does the obligation vary with the availability of health care in general? For eg is the obligation the same in developed and developing country?



Thank You

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