

Case Studies And Some ethical problems in Clinical research

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Ethics Case Study 1

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.**

Ethics Case Study 2

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.

Ethics Case Study 3

This is an RCT comparing hypericum (St. John's Wort, a herbal therapy), Sertraline (Zoloft, a SSRI inhibitors with proven efficacy for depression) and placebo (*Hypericum Depression Trial. JAMA 2002;287:1807*).

340 subjects from 12 participating centres were randomized to the three arms of the trial for an 8-week treatment duration. All subjects provide usual informed consent, and were monitored closely and all standard precautions required for placebo controlled trial were taken.

The trial was funded by the NIH (a government research body, NOT pharma company), and all IRBs approved the trial.

What do you think of the ethics of this trial?

Ethics Case Study 4

A rhesus rotavirus tetravalent (RRV-TV) vaccine was licensed in the US after RCT in developed countries showed 60% efficacy in preventing diarrhea. However shortly after FDA approval, the vaccine was withdrawn from US market because of a cluster of cases of intussusception (risk~1 in 10,000).

A similar RCT was being planned in developing countries at the time. Should the trial be allowed to proceed?

(Note: About 600,000 kids died of rotavirus diarrhea in developing countries in spite of ORS)

Ethical Problems in Clinical research

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”

1. The dual hat problem: Physician as investigator
2. Ethics of Randomization & Blinding
3. Ethical issues with preliminary data
4. Ethical use of placebo?

The Dual Hat problem

- Physician primary obligation should be the well being of the patient, but as an investigator in a trial, the physician:
 - Has competing obligation to other ends such as recruiting & retaining patients; generate high quality data; etc that distracts from good personal care
 - Perform non-therapeutic procedures, randomize & blind subjects, administer placebo, adhere to strict protocol, etc that do not serve patients (& might even put them at risk)

So, how is it possible for physicians to fulfill their therapeutic obligation to provide optimal medical & yet conduct trial?

There is a rampant tendency to confuse research with care, the so called therapeutic misconception; a *failure to distinguish between the ethics of clinical research and ethics of medical practice.*

The Dual Hat problem

Thomas Chalmers 1981, described the relationship between the clinical trial & medical care as follows:

“The practice of medicine is in effect the conduct of clinical research . . . Every practicing physician conducts clinical trials daily as he is seeing patients. The research discipline known as the ‘clinical trial’ is the formalization of this daily process.”

Helsinki Declaration, Brazil 2013

Para 4:

It is the duty of the physician **to promote and safeguard the health of patients**, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty

Para 3

“The health of my patient will be my first consideration”... “A physician shall act in the patient's best interest when providing medical care.”

Helsinki Declaration, Brazil 2013

Para 14

The physician **may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value** and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects

Distinction Between Clinical Trials and Medical Care

Clinical trial differs from medical care

1. Purpose
2. Characteristic methods
3. Justification of risks
4. Relationship between investigators and research subjects

Source: Henry Silverman, Therapeutic Orientation to Clinical Trials. University of Maryland School of Medicine Health Research Ethics Training Initiative In Egypt (HRETIE)

Purpose of clinical trial

- To produce generalizable knowledge about treatment efficacy by controlled experimentation in *groups* of patients with the aim of promoting improved medical care.
- Contrasts fundamentally with goal of medical therapy to provide personal care for *particular* patients.

Characteristic Methods

- Clinical trial includes randomization, blinding, placebo controls, protocols restricting treatment flexibility, and research procedures to measure study outcomes.
- All of these methods employed to answer scientific questions are foreign to standard medical care.

Justification of Risks

- Clinical trial includes procedures for scientific purposes that carry risks of discomfort or harm to subjects without a prospect of benefit to them. These are justified by anticipated value of knowledge.
- In medical care, the risks of diagnostic procedures and treatments are justified by potential medical benefits to patients.

Relationship

- In medical care, the physician has a fiduciary relationship creating the obligation to do what is best medically for the patient.
- The investigator cannot have a fiduciary relationship, since the primary focus of the activity is research, and procedures are involved that are not aimed at the best medical interests of patient-subjects.

Distinction Between Research and Medical Care

Therapeutic Orientation to Clinical Trials

| | Medical Care | Research |
|-------------------------------|----------------------|---|
| Purpose | Individualized care | Advance medical knowledge for society |
| Methods | Routine care | Randomization, blinding, restrictive doses, tests to measure study outcomes |
| Justification of Risks | Benefits to patients | Anticipated by the knowledge to be gained |

Source: Henry Silverman, Therapeutic Orientation to Clinical Trials. University of Maryland School of Medicine Health Research Ethics Training Initiative In Egypt (HRETIE)

Ethical Problems

Confusion between Research & Practice

- Interferes with realizing **valid informed consent**
- **Diverts attention from the moral conflict** inherent in clinical research (where patients' and physician's interest are divergent) leading potentially to exploitation (patients induced to enroll under pretext of medical care) or overprotection (unreasonable objections to use of health volunteers, placebo, etc)
- Obstructs development of a conception of **professional integrity proper to clinical research**

What should physician do?

- **Understand** that clinical research, while socially valuable, is ethically challenging. It calls for balancing the pursuit of science and the protection of subjects, and its conduct research requires clarity about how clinical trials differ from medical care.
- **Be aware** of the moral tension inherent in dual role

What should physician do?

- **Inform subject** accordingly
- **Separate roles** of clinician and investigator where possible, : *Separate clinic, rely on other members of team; refer to other investigator for trial*

Ethics of Randomization and Blinding

Randomized Controlled Trial (RCT) has 2 features:

1. Random assignment to 2 or more treatments. That is, treatment assignment 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

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

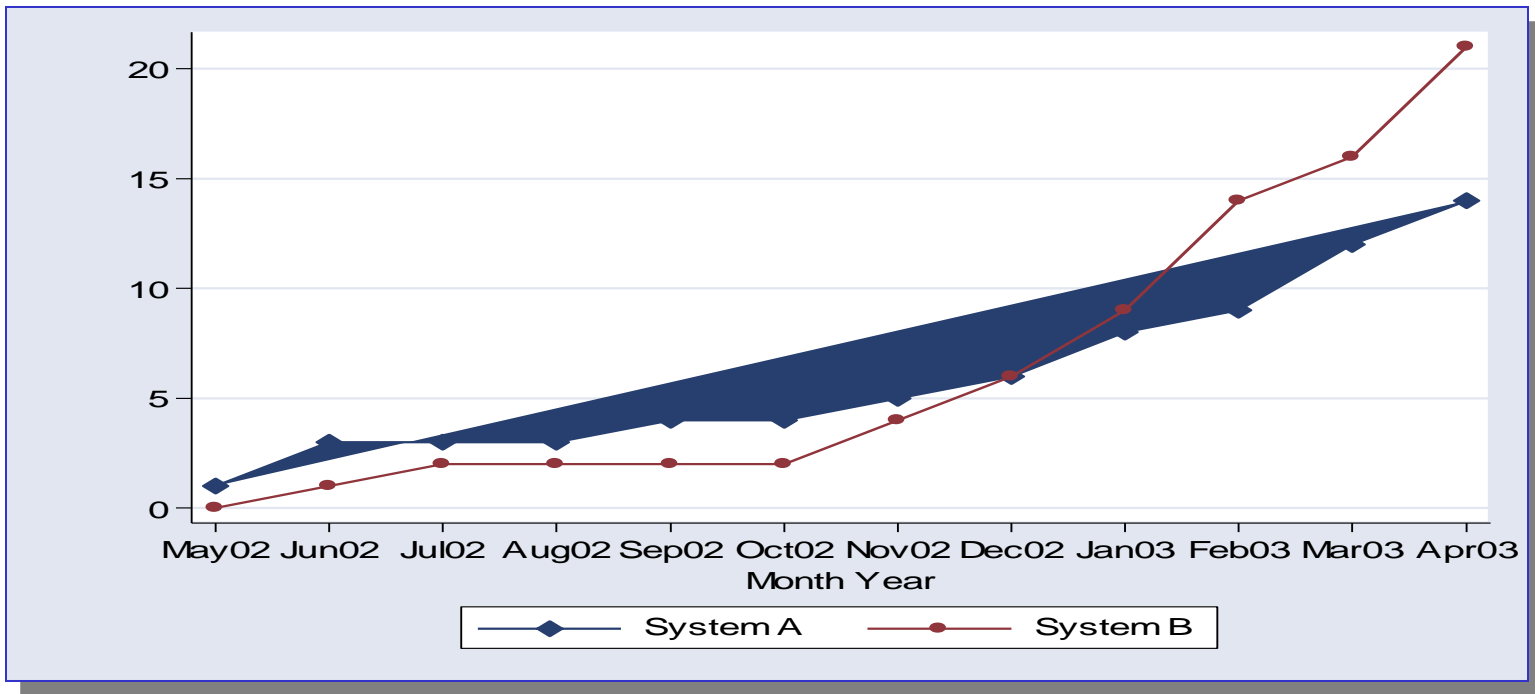
Ethical issues with preliminary data & stopping trial early

In the course of most RCTs, preliminary data are being accumulated and if subjected to monitoring or interim 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: CAPD2 Trial

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



Wong HS et al. A randomised, multi-centre, open label trial to determine peritonitis rate, product defect and technique survival between ANDY-Disc and Ultrabag in patients on CAPD. Am J Kidney Dis 2006; 48(3): 464-472

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 < **0.00000001**

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 2013 Paragraph 18

“Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

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
- **MGCP 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 call upon to accept or reject the values of the scientific community

Monitoring of Accumulative Data by IDMC

MGCP 1.31

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...

MGCP 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.”

Ethical use of Placebo?

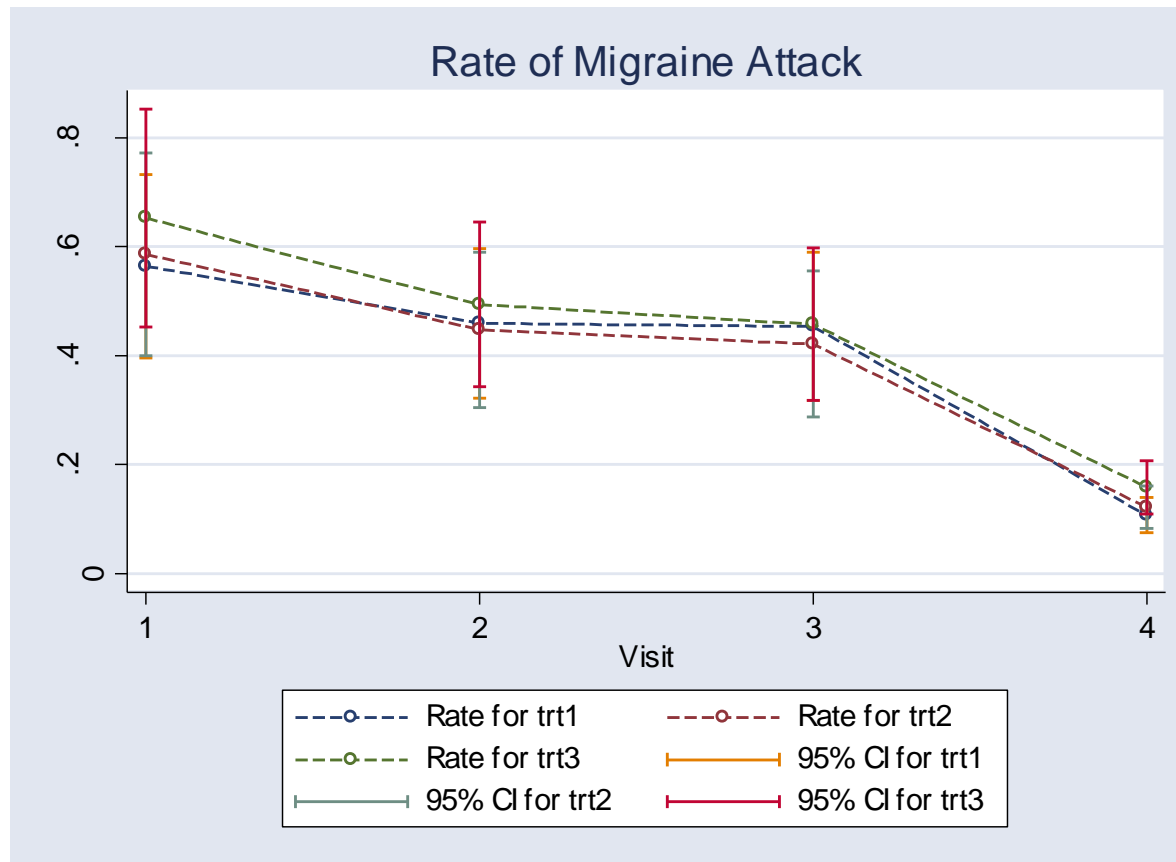
Placebo is a treatment that is identical in all respects to the active treatment under investigation except the active ingredient is absent.

Uses of placebo in clinical trial:

1. Make blinding possible. This is uncontroversial
2. Allow for placebo effect.
3. Measure of absolute efficacy, whereas use of 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*



Which one is the Placebo group?

Ethical Problems 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.

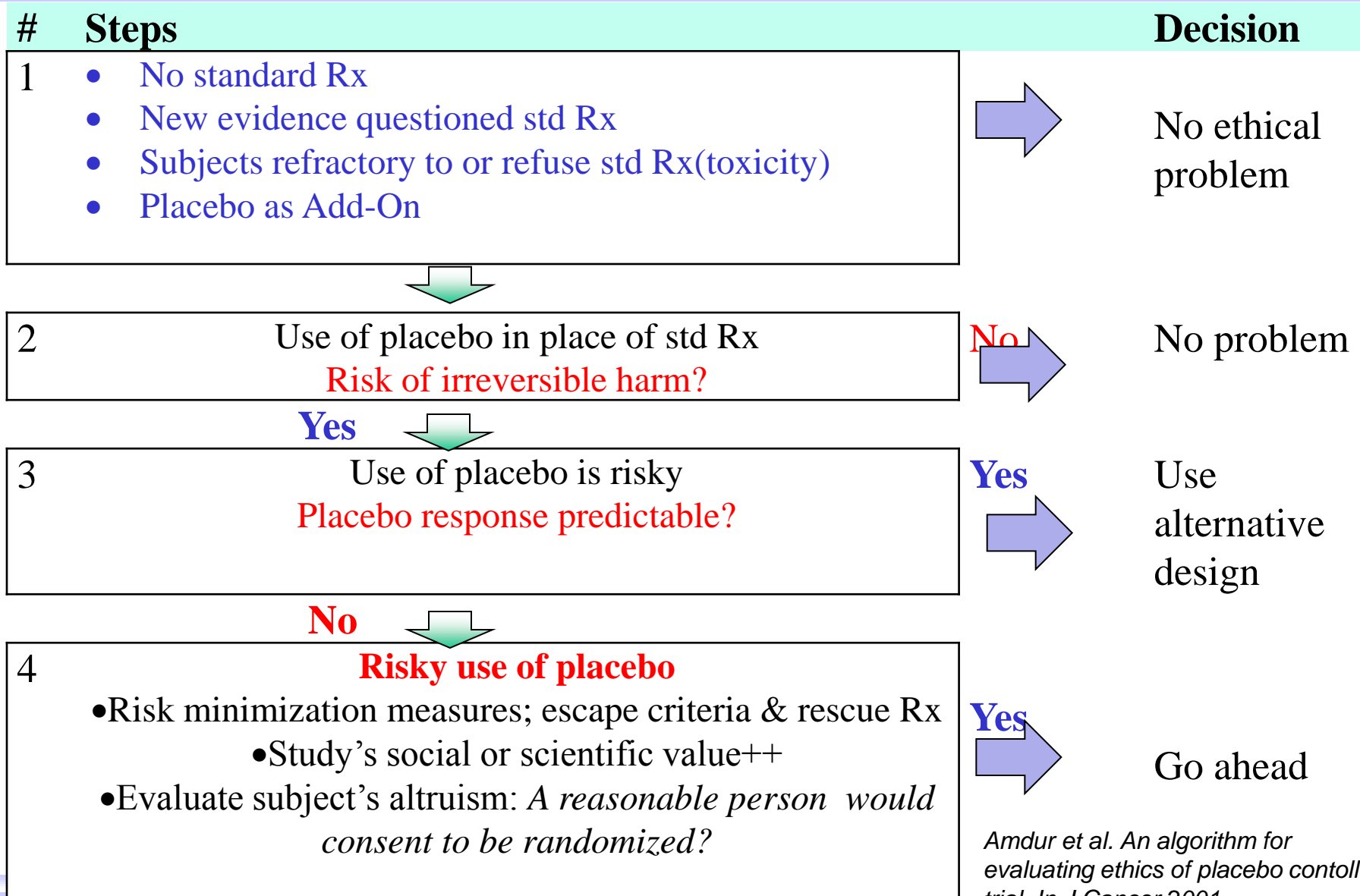
What the guideline says...

Declaration of Helsinki 2013 Para 33

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.**

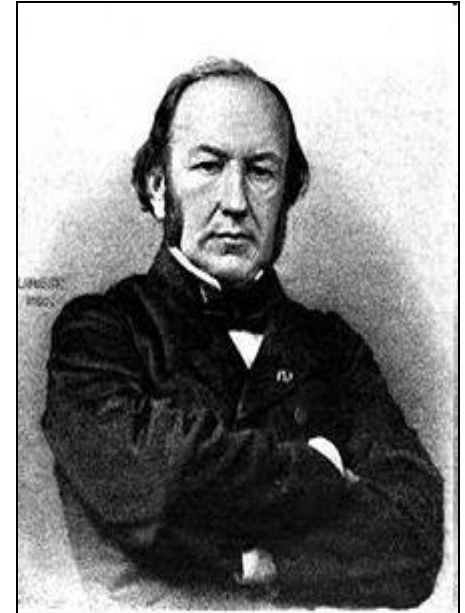
What should we do and How?



Amdur et al. An algorithm for evaluating ethics of placebo controlled trial. In J Cancer 2001

Philosophical vs Procedural

- GCP tends to enforce procedural and documentary, and sometimes neglects philosophical
- *Claude Bernard* (12 July 1813 – 10 February 1878) a French physiologist said, “It is immoral then, to make an experiment on man when it is dangerous to him, even though the results may be useful to others”.
- Was first to suggest the use of *blind experiments* to ensure the objectivity of scientific observations



An Introduction to the Study of Experimental Medicine (1865)

- *Authority vs. Observation.* It is through the experimental method that science is carried forward not through uncritically accepting the authority of academic or scholastic sources. In the experimental method, observable reality is our only authority
- "When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted"

An Introduction to the Study of Experimental Medicine (1865) - 2

- “Theories are only hypotheses, verified by more or less numerous facts. Those verified by the most facts are the best, but even then they are never final, never to be absolutely believed.”
- “proof that a given condition always precedes or accompanies a phenomenon does not warrant concluding with certainty that a given condition is the immediate cause of that phenomenon. It must still be established that when this condition is removed, the phenomenon will no longer appear”

4 Milestone Development

- Industrial Drug Development
 - FDA established **1906**
- Nazi Atrocities
 - Nuremberg Code **1947**
- Declaration of Helsinki **1964**
- Belmont Report **1979**
- Human experiment is no longer just permissible, but ***mandatory*** (can't market it unless safety & efficacy demonstrated)

Conclusions

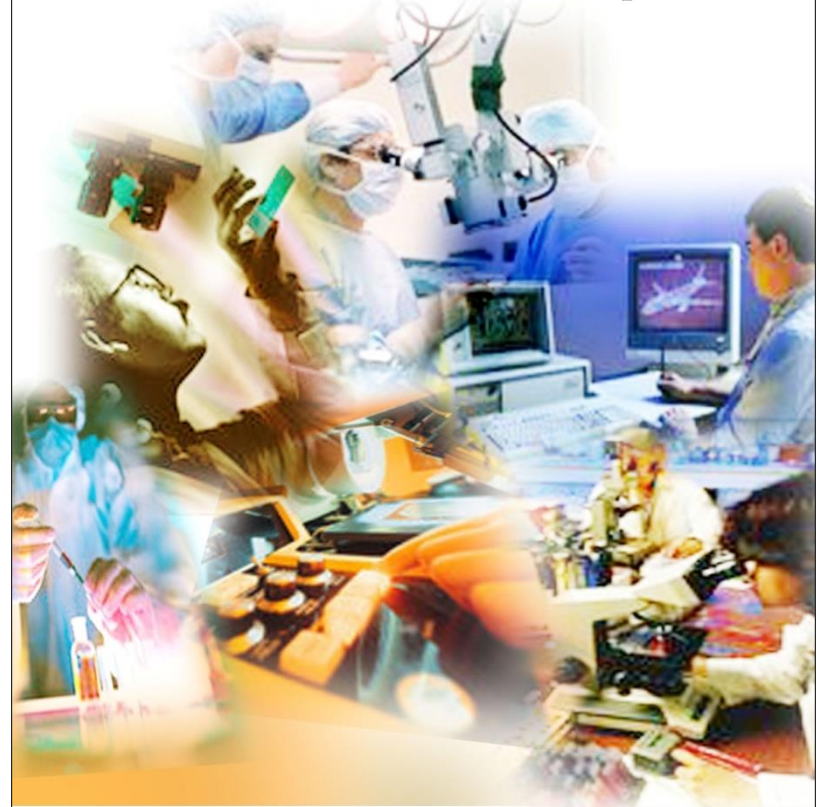
- Ethical boundaries will continue to be challenged
- Investigators tend to become advocates of clinical research, hence, Ethic committees should be more of advocates of research subjects
- Need to be ethically aware and vigilant

Thank You

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The Collaborative Research Experience



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Research that matters to patients

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Research that matters to patients

Quiz 1

A rheumatologist developed a monoclonal Ab that he believe is likely to be effective in RA treatment, and it has successfully moved through Phase 1 & 2 tests. In designing a Phase 3 RCT, comparing to placebo as an add-on therapy for patients already on standard therapy, the ethics of CR require that he...

- A. Can't be involved in the design of this trial, since it would involve an unethical conflict of interest
- B. Can be involved in research design, but can't be involved in enrolling subjects, given his conflict of interest
- C. Can enrol subjects, but only if he can honestly say that he is personally undecided whether or not the new drug is better than placebo
- D. Can enrol subjects into the trial, as long as he can honestly say that the community of rheumatologists is undecided about whether the new drug is effective.

Quiz

When explaining the probability of assignment to trial arms in consent forms, which is true?

- A. FDA requires the probability to be expressed as a percentage chance.
- B. The use of a placebo arm does have to be specifically stated, but not the chance of assignment.
- C. ICH notes that it should be included, but does not specify how the information should be presented.
- D. The probability of assignment should always be stated as being “like the flip of a coin” because subjects can understand that example.

Quiz

The major purposes of random assignment in a clinical trial are:

- I. Ensure that study subjects are representative of the general population.
- II. Create treatment groups that are similar with respect to both measured and unmeasured covariates.
- III. Facilitate double blinding.
- IV. Guard against investigator bias in the allocation of study participants to treatment groups.
- V. Facilitate the measurement of outcome variables.

A. I and II

B. II and IV

C. III and IV

D. I, III and V