The history of human experimentation: the good, the bad and the ugly

Neil W. Schluger, M.D.
Professor of Medicine, Epidemiology and Environmental Health Sciences
Chair, Columbia University IRB 3
STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gauldham, Dr. F. H. G. Heal, Professor A. Bradford Hill, Dr. L. E. Houghton, Mr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tyler, Professor G. S. Wilson, and Dr. P. D'Anci Hart (secretary). The centres at which the trial was carried out and the specialists in charge of patients and pathological work were as follows:

- Brompton Hospital, London—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchell.
- Colindale Hospital (L.C.C.), London—Clinicians: Dr. J. W. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Soothill; Pathologist: Dr. G. H. Evans.
- Harefield Hospital (M.C.C.), Harefield, Middlesex—Clinicians: Dr. R. H. Brunt, Dr. L. E. Houghton; Pathologist: Dr. E. Nasser.
- St. Bage Hospital, Bage, West Leicestershire—Clinician: Dr. J. Blackwell; Pathologist: Dr. Paul Purdie.
- Killingbeck Hospital and Sanatorium, Leeds—Clinicians: Dr. W. S. Gilmour, Dr. A. M. Rees; Pathologist: Professor J. W. McLeod.
- Northern Hospital (L.C.C.), Wickersham Hill, London—Clinicians: Dr. F. A. Nish, Dr. R. Shoullock; Pathologists: Dr. J. M. Allison, Dr. A. Mohun.
- Selly Hospital, Selly, Glenn—Clinicians: Dr. D. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tyler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniel, of the Council's scientific staff, was responsible for the clinical coordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchell on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Illingworth, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944) in the intervening period its power of inhibiting tubercle bacilli in vitro, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapy agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfeiffer, 1946; Keever et al., 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapy agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1946). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberg, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the USA. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled
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The Control Scheme

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre.
STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
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Unethical experimentation on humans: a brief and selective history

- Nazi experiments on concentration camp inmates
- Unit 731 of the Imperial Japanese Army
Evolution of standards for protection of human subject: Nuremberg Code (1)

Principles adopted at the Nuremberg Trials at the end of the Second World War (1947)

• Voluntary consent of the human subject is absolutely essential
• The experiment should be such as to yield fruitful results for the good of society.
• The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease.
• The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury
• No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur.
Evolution of standards for protection of human subject: Nuremberg Code (2)

- The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
- Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
- The experiment should be conducted only by scientifically qualified persons.
- During the course of the experiment the human subject should be at liberty to bring the experiment to an end.
- During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable 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.
Unethical experimentation on humans: a brief and selective history

• Tuskegee experiments
  – Natural history study of syphilis conducted by the USPHS from 1932-1972
  – 600 men (black sharecroppers from Tennessee) were given free medical care, meals, and burial insurance
  – Subjects were not provided treatment even after penicillin was well-established as curative

• Guatemala syphilis study
  – 1946-1948
  – U.S. researchers deliberately infected people with syphilis to study effects of antibiotic therapy
Unethical experimentation on humans: a brief and selective history

- **Chester Southam’s (Sloan-Kettering Institute) cancer studies:**
  - 1952: injected live cancer cells into inmates at Ohio State Prison
  - 1962: injected live cancer cells into elderly patients of the Jewish Chronic Disease Hospital in Brooklyn

- **From the 1950s through 1972, Saul Krugman (NYU) infected mentally impaired children at Willowbrook State Hospital in New York with hepatitis B virus as part of a series of studies leading to the development of a vaccine**

- **Alfred Kligman (University of Pennsylvania) infected hundreds of prisoners at Holmesburg State Prison in Pennsylvania with a variety of pathogens in order to test new therapies in the period from 1951-1974**
The Declaration of Helsinki

- Adopted initially in 1964 by the World Medical Association
- Most recent revision 2008
- Fundamental principles
  - Respect for the individual
  - Right to self-determination
  - Right to make informed decisions regarding participation in research
Foundational principles of bioethics

- Beneficence
- Non-maleficence
- Justice
- Autonomy
Beneficence

• A positive obligation to do good
  — Physicians have a duty to take positive steps to promote the well-being of patients

• A core component of medical ethics

• The only component of medical ethics?
Non-maleficence

• Primum, non nocere: First, do no harm
• A positive obligation to avoid harming patients
  – All medical therapies carry risk, which must carefully be weighed against their potential benefit
• Failure to adhere to the principle of non-maleficence is considered negligence
Justice

• Many philosophical approaches to justice
  – Means based theories
    • Kant
    • Rawls
    • Libertarianism
  – Ends based theories
    • Bentham/Mill
    • Sandel
• At it is generally used in medical ethics, the concept of justice refers to treating every person the same way
Autonomy/respect for persons

- The right of persons to make decisions about their own health and life in the context of medical treatment (and participation in research)
- In medicine, the principle of autonomy is often held in a contrast to paternalism
- Although some persons lack the capacity for rational decision making (infants, persons with diminished mental capacity), they are still deserving of respect and can be assumed to desire relief from harm and suffering, i.e. the lack of agency does not mean a person is not deserving of respect
- The principle of autonomy does not however require physicians to deliver treatments or experimental therapy that they believe is useless or harmful
Prevention of mother-to-child transmission of HIV infection: ACTG 076

• Double-blind, placebo-controlled trial of HIV-infected women enrolled between 14-34 weeks of pregnancy
  – Oral therapy during pregnancy
  – Intravenous therapy during delivery
• Study conducted between 1991-1994 in U.S. and France
• Sponsored by NIH
• Experimental group received zidovudine; control group received placebo
• Infants followed for 18 months after birth

ACTG 076: results

MATERNAL VIRAL LOAD, ZIDOVUDINE TREATMENT, AND THE RISK OF TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 FROM MOTHER TO INFANT

Rhoda S. Sperling, M.D., David E. Shapiro, Ph.D., Robert W. Coombs, M.D., Ph.D., John A. Todd, Ph.D., Steven A. Herman, Ph.D., George D. McSherry, M.D., Mary Jo O’Sullivan, M.D., Russell B. Van Dyke, M.D., Eleanor Jimenez, M.D., Christine Rouzioux, Ph.D., Patricia M. Flynn, M.D., and John L. Sullivan, M.D., for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*

Conclusions  A high maternal plasma concentration of virus is a risk factor for the transmission of HIV-1 from an untreated mother to her infant. The reduction in such transmission after zidovudine treatment is only partly explained by the reduction in plasma levels of viral RNA. To prevent HIV-1 transmission, initiating maternal treatment with zidovudine is recommended regardless of the plasma level of HIV-1 RNA or the CD4+ count. (N Engl J Med 1996;335:1621-9.)
Subsequent trials of prevention of maternal to child HIV infection

<table>
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<th>Study</th>
<th>Year published</th>
<th>Design</th>
<th>Regimen</th>
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<td>DITRAME</td>
<td>1999</td>
<td>Randomized, placebo controlled</td>
<td>Zidovudine vs. placebo</td>
<td>Cote d’Ivoire, Burkina Faso</td>
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<tr>
<td>Wiktor (partial CDC funding)</td>
<td>1999</td>
<td>Randomized, placebo controlled</td>
<td>Zidovudine vs. placebo</td>
<td>Cote d’Ivoire</td>
</tr>
<tr>
<td>PETRA</td>
<td>2002</td>
<td>Randomized, placebo-controlled</td>
<td>Zidovudine + lamivudine at 3 time points vs. placebo</td>
<td>South Africa, Tanzania, Uganda</td>
</tr>
</tbody>
</table>
Were further placebo-controlled trials of maternal to child HIV transmission ethical?

- Studies would not have been allowed in the U.S. or any other resource-rich country
  - Research tourism
    - Not ethical to use a population to get an answer that will be of no benefit to that population
- Informed consent:
  - Largely illiterate subjects
  - Element of coercion: perhaps only way to get care at all was to be in the study
Were further placebo-controlled trials of maternal to child HIV transmission ethical?

• Possible justifications
  – Most women in developing countries breastfeed almost exclusively. Breastfeeding increases risk of HIV transmission, so benefit of prenatal zidovudine unclear in that setting
  – Logistic difficulties of providing zidovudine during pregnancy, since routine prenatal care not available in many developing country settings
  – Intravenous infusions of zidovudine not practical in many developing country settings
  – Cost of zidovudine prohibitive in developing country settings
A TRIAL OF THREE REGIMENS TO PREVENT TUBERCULOSIS IN UGANDAN ADULTS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

Christopher C. Whalen, M.D., John L. Johnson, M.D., Alphonse Okwera, M.B., Ch.B., David L. Hom, M.S., Robin Huebner, Ph.D., M.P.H., Peter Mugyenyi, M.B., Ch.B., Roy D. Mugerwa, M.B., Ch.B., and Jerrold J. Ellner, M.D., for the Uganda–Case Western Reserve University Research Collaboration
METHODS

Study Design

The objective of this randomized, placebo-controlled clinical trial was to determine the efficacy of three daily, self-administered regimens of preventive therapy for tuberculosis in HIV-infected adults. The trial was designed to obtain at least three years of follow-up data on all enrolled subjects, with annual interim analyses to ensure timely detection of risks and benefits to the participants. All subjects gave oral informed consent before screening and enrollment in the study. The study protocol was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee.
A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus

• Study subjects
  – 2736 HIV-infected Ugandan adults
  – Most subjects had positive tuberculin skin tests

• Experimental arms
  – Placebo
  – Isoniazid daily for 6 months
  – Isoniazid and rifampin daily for 3 months
  – Isoniazid, rifampin and pyrazinamide daily for 3 months
A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus

Whalen et al. NEJM 1997; 337: 801-808
Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection

Jean W Pape, Simone S Jean, John L Ho, Alice Hafner, Warren D Johnson Jr

Figure 1: Effect of isoniazid on development of tuberculosis

Pape J, Lancet 1993: 342: 268-272
Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection

Jean W Pape, Simone S Jean, John L Ho, Alice Hafner, Warren D Johnson Jr

Figure 2: Effect of isoniazid on HIV infection in PPD-positive and PPD-negative subjects.

Pape J, Lancet 1993: 342: 268-272
Comments of the NEJM Editor-in-Chief regarding the Uganda TB prevention study

- Whether the study by Whalen et al. was ethical depends, in my view, entirely on the strength of the preexisting evidence. Only if there was genuine doubt about the benefits of prophylaxis would a placebo group be ethically justified.
- It should not be argued that it was ethical because no prophylaxis is the “local standard of care” in sub-Saharan Africa...The fact that Whalen et al. offered isoniazid to the placebo group when it was found superior to placebo indicates that they were aware of their responsibility to all the subjects in the trial.
- The Journal has taken the position that it will not publish reports of unethical research, regardless of their scientific merit. After deliberating at length about the study by Whalen et al., the editors concluded that publication was ethically justified, although there remain differences among us.
- The fact that the subjects gave informed consent and the study was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee certainly supported our decision but did not allay all our misgivings. It is still important to determine whether clinical studies are consistent with preexisting, widely accepted ethical guidelines, such as the Declaration of Helsinki, and with federal regulations, since they cannot be influenced by pressures specific to a particular study.

Angell M. N Engl J Med 1997; 337: 847-849
Investigators’ justification for the Uganda TB prevention trial

- At the time the study began, in March 1993, the protective efficacy of preventive therapy for tuberculosis in patients with HIV infection had not been established. The study in Uganda was designed and begun before the results of the Haiti study had been published.
- The Haiti study was inconclusive because the estimate of a protective effect against tuberculosis was confined to the PPD-positive subjects in the study and was based on only eight cases. Misclassification of only one case in either study group would render the result statistically insignificant.
- After reviewing these results, we concluded that the Haiti study was inconclusive and decided that the placebo group was justified. This decision was supported by the World Health Organization's Therapy of Mycobacterial Disease Steering Committee in April 1994.

The Jesse Gelsinger case

• Jesse Gelsinger was an 18-year old male with ornithine transcarbamylase deficiency, an metabolic defect which leads to an inability to metabolize ammonia
  – Usually X-linked and fatal at birth, but in his case it arose through spontaneous mutation after conception and his clinical syndrome was mild
  – He was enrolled into a gene therapy trial at the University of Pennsylvania
  – On September 13, 1999 he received an injection of an adenoviral vector containing a normal copy of the human gene
  – On September 17, 1999 he died of multiple organ failure as a result of a massive immune response to the viral vector
The Jesse Gelsinger case

- FDA investigation concluded that
  - The University had failed to disclose serious side effects in two prior patients in the trial
  - The University failed to disclose in the consent document, the deaths of monkeys treated with the same adenoviral vector in the pre-clinical phase of testing
  - James Wilson, the principal investigator in the trial, had a commercial interest in the company manufacturing the gene therapy treatment
  - Gelsinger was included only because another volunteer had dropped out
Phase I trial of TGN1412

- TGN1412: monoclonal antibody which binds to CD28 and has agonist functions
- Hypothesis: TGN1412 would lead to an increase in regulatory T cells (Tregs) and therefore lead to an overall down-regulation of T-cell activity. Drug could be useful in a variety of autoimmune and inflammatory disorders, and B-cell lymphoma
Phase I trial of TGN1412

• First-in-human trial in 2006 in England
• Trial conducted by Parexel (CRO) on behalf of TeGenero Immune Therapeutics. Drug was manufactured by Boehringer Ingelheim
• Dose used was $\frac{1}{500}$th of the safe dose in animals (cynomolgus monkeys)
• Study subjects were young (18-34) men, completely healthy
• Subjects were paid £2000 to participate
• Study approved by an independent IRB
Overall, the results of non-clinical studies in rodents and non-human primates have not revealed any potentially serious toxicities that would preclude the use of TGN1412 in healthy subjects. Based on a NOAEL of 50 mg/kg body weight, the clinical starting dose of 0.1 mg/kg body weight represents a safety margin of 500-fold, which is considered to be sufficient to ensure patient safety. The maximum dose in this clinical trial is 5.0 mg/kg body weight, still being 10-fold lower than the observed NOAEL in pre-clinical toxicology studies.
From the TGN 1412 consent document:

There is no definitive information on the side effects of this drug in man. As this is only the first time this drug will be given to man, this study may involve risks that are currently unforeseen. No significant side effects have been seen in the animal studies, and although these are not a precise indicator of what will happen in humans, they give some indications of the possible side effects.

Expert advice from immunologists has been sought in designing the protocol to minimise your risks, including a robust screening process that takes into account your immune status, and repeated thorough assessments of immune function.

It is possible that you will not experience any side effects at all, as the doses used in early human studies are always very small, and increased only gradually, but the following unintended effects may theoretically be encountered during any trial with a monoclonal antibody drug, though they did not occur even at the highest tested doses in animals: immunosuppression (increasing susceptibility to infection, very unlikely after a single-dose), autoimmunity (antibodies being made by your own body against the drug), cytokine release (causing a hives-like allergic reaction), or even anaphylaxis (a generalised allergic reaction that can be life-threatening). Drugs of this type can also cause swelling of the lymph glands, so you will be regularly checked for this. Less specific symptoms such as headache, dizziness and nausea are more common in all drug trials.
<table>
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<tr>
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<th>1</th>
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<td>34</td>
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<td>7.2</td>
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<td>16.0</td>
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<td>11</td>
<td>18</td>
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<td>18</td>
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<td>Bilateral pulmonary infiltrates‡</td>
<td>+</td>
<td>++</td>
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<td>Duration of abnormalities on chest radiography (days)</td>
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<td>6</td>
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<td>&gt;5</td>
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<td>Hemodynamics on transfer</td>
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<td>Blood pressure (mm Hg)</td>
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<td>107/42</td>
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<td>Heart rate (beats/min)</td>
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<td>LVEF on echocardiogram (%)</td>
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<td>(\text{PaO}_2:\text{FiO}_2)</td>
<td>395.5</td>
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<td>329.5</td>
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<td>Muscle weakness‡</td>
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<td>Late myalgia</td>
<td>Calf</td>
<td>Calf and hip adductors</td>
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<td>—</td>
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<td>Neurologic findings</td>
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<td>Headaches and hyperalgesia</td>
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<td>Hyperalgesia and numbness</td>
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Questions raised by the TGN 1412 trial

• Were the preclinical studies adequate to assess safety in humans?
• Did the independent IRB possess the proper expertise to review the protocol?
• Did the informed consent document adequately discuss the risks of the trial?
• Was the provision of a financial incentive coercive?
• Once the trial began, was it conducted ethically?
• Are phase 1 (first-in-human) trials ever ethical, either in healthy or sick volunteers?
Is a research trial ethical?

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Ethical value</th>
<th>Expertise for evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social or scientific value</td>
<td>Scarce resources, nonexploitation (justice, respect for persons, beneficence)</td>
<td>Scientific knowledge; citizen’s understanding of social priorities</td>
</tr>
<tr>
<td>Scientific validity</td>
<td>Scarce resources/nonexploitation</td>
<td>Scientific knowledge</td>
</tr>
<tr>
<td>Fair subject selection</td>
<td>Justice</td>
<td>Scientific, ethical and legal knowledge</td>
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<tr>
<td>Good risk:benefit ratio</td>
<td>Non-maleficence, beneficence</td>
<td>Scientific knowledge</td>
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<tr>
<td>Independent review</td>
<td>Respect for persons</td>
<td>Independent reviewers</td>
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<tr>
<td>Informed consent</td>
<td>Autonomy/respect</td>
<td>Scientific, ethical and legal knowledge</td>
</tr>
<tr>
<td>Respect for subjects</td>
<td>Respect for persons</td>
<td>Knowledge of population</td>
</tr>
</tbody>
</table>

After Emanuel E. JAMA 2000; 283: 2701-2711
How can subjects be harmed in research?

- Their autonomy can be violated through lack of provision of informed consent
- They can suffer physical harm
- They can suffer emotional harm
- They can suffer economic or professional harm
What makes a research study ethical?

• The scientific question being addressed
• The conduct of the trial
• The participant’s willing and informed participation
What makes a research study ethical?

• The scientific question being addressed
  – The study must address a significant scientific question, i.e. a question that has meaning and importance to the general society
  – The study design must be adequate to ensure that if the experiment is completed, meaningful results will be obtained
What makes a research study ethical?

• The conduct of the trial
  – Risks inherent in the research study must be minimized to the extent possible
  – Risks of the research study must be proportionate to any expected benefits from the study
    • Are phase 1 studies ever ethical?
  – Data must be obtained honestly and without fraud
  – There must be equity in the way subjects are recruited and enrolled into the trial
  – The researcher should not have a conflict of interest that could bias the integrity of the study
What makes a research study ethical?

• The participant’s willing and informed participation
  – The purpose of the study must be clear to the subject
  – The procedures in the study must be clear to the subjects
  – Potential risks must be clear to the subject
  – The subject must freely give consent, which can be withdrawn at any time during the study