

Ethics of research designs and methods

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Outline

- Why study design is important for ethics and ethical review
- Variety of research designs:
 - Observational studies
 - Interventional studies
 - Ethical issues: some cross-cutting, some specific to particular designs
- Classic study design types: observational designs, RCTs, phase I, II and III, and more
- Complex and innovative designs: cluster randomized trials, adaptive designs, challenge studies, and more
- Conclusion

Why understanding study design is important for ethics and ethical review

- Poorly designed or scientifically inadequate studies are inherently unethical—waste of time and resources, fail to produce reliable results, possibly expose individuals to risks or burdens with no useful outputs
- Even with proper design, each type of study has its own ethical challenges and tensions, risks and burdens
- Ethics committees and other reviewers need to be cognizant of the demands and limitations of study designs
 - Offer appropriate recommendations and critiques
 - Adjudicate ethical tensions and pressure points

Interventional

Observational

This is nowhere near a complete list—just examples!

Large pragmatic trials

Phase IV postmarketing studies

Disease registries

Phase III RCT

Surveillance

Standard of care clinical trials

Quasi-experimental studies

Population level epidemiology

Phase II

Case control studies

Phase I

Lab analyses of specimens

Cohort studies

Pharmokinetic studies

Qualitative studies

Survey research

Observational versus interventional (experimental) studies: ethical issues

Principles common to both

- Requires sound scientific design
- Needs appropriate expertise for the type of study, research question, and population (e.g. pediatricians in study with children)
- Requires protection of confidentiality of individually identifiable data

Different ethical issues—a few examples

Observational studies:

- Researchers may identify needs in study population but difficult or impossible to respond;
- Issues of stigmatized or illegal behavior can raise concerns

Interventional studies:

- Assessing and managing risks of intervention
- Equipoise—we will talk about this
- Determining standard of care and control groups
- Study management, stopping rules, interpretation of efficacy

Biomedical research

note: biomedical studies can be either interventional or observational

Product development pathway (drugs, biologics, vaccines)

- Phase I: pK, safety
- Phase II: expanded safety, some efficacy
- Phase III: efficacy/effectiveness
- Phase IV: post-marketing studies

Basic science/mechanistic studies

Examples:

- lab analysis examining immunologic responses to vaccines;
- study of genetic factors influencing disease pathway

Phase I studies—some ethical challenges

Healthy volunteers

- Concerns about risks to volunteers without benefits (pK or first in human studies)
- Healthy volunteers typically motivated to enroll to receive compensation or study-provided benefits—undue inducement?
- Some volunteers covertly enroll in more than one study simultaneously—unsafe and bad for science

Patients with advanced disease

- Typically in cancer trials and other chronic diseases, early phase trials conducted in patients who are refractory to standard treatment
- Risks of early phase trial may seem worth it because no other options
- Concerns about fragile patients, excessive optimism (~5% of phase I trials go on to show benefit in future trials)

RCTs:

Basic structure and terminology

- **Blinding:** participants are not told which arm of the study they are assigned to, so as to avoid subjective reporting on the part of the participant
- **Double-blind:** both participants and physicians/investigators are unaware of treatment assignment—again to avoid subjectivity
- **Confounding:** variables that are present among the study population and potentially influence the outcome measure
- **Randomization** is used to create groups that are equivalent with regard to known baseline variables and unknown confounders
- **Predetermined statistical tests** are used to assess whether the intervention has had a significant effect
- **Stopping rules:** set of instructions regarding what statistical tests and results would trigger a decision to stop the trial and announce the results

Randomized controlled trials--RCTs

Considered “gold standard” for measuring efficacy in health research

- RCTs given higher status in systematic evidence reviews and in clinical practice guidelines development;
- Essential for regulatory approvals of new products (usually 2 well powered RCTs showing efficacy required by US FDA);

Strengths of RCTs

- Reduce influence of confounding variables through randomization
- With blinding, reduce influence of bias in reporting or assessing outcome measures
- Methodology well known and understood among many key stakeholders: researchers, physicians, regulators, policy-makers, journals, funders;

RCTs: some limitations

- RCTs create artificial environment and use highly selected patient population—**may not be generalizable** or relevant to real world clinical practice conditions
- **RCTs are very expensive** to conduct—large RCTs in the 10s of millions of USD
- **Randomization can be problematic** in some circumstances—e.g. where patient preference is highly relevant; or where there is disagreement about what constitutes adequate standard of care; **disagreements about equipoise**;
- **Selection of control groups** can be controversial
- **Long time frame** to plan and conduct an RCT—handling external evidence and changing evidence base is challenging

Debates about placebo use

- Placebo gold standard
- Makes research results very clear
- Makes research cheaper to conduct
- Yet goes against the “duty to care” and “best known treatment”
- Debates surrounding trials of preventing PMTCT in Africa
- Placebo used because alternative too expensive and yet alternatives were standard of care in US

RCT Use of placebo

- Beneficial when assessing new drug or intervention
- Unethical in most circumstances when standard therapy exists
- If standard therapy unproven, may use placebo and standard therapy
- HIV vaccine and microbicides

POSSIBLE INTERVENTIONS IN CONTROL GROUP

- The best diagnostic, preventive or therapeutic intervention available:
 - Anywhere in the world?
 - Locally?
- Placebo
- Nothing

Best standard of care available

- What is a standard of care?
- Best standard where?
- What if there is no local standard available
- Is no standard a standard?
- Issues about costs of providing the available standard
- Excuse of lack of capacity to administer standard locally.
- Hence studies such as DART (clinical arm vs lab arm)
- Recent structured interruption studies

Use of comparator

- Use a comparator is appropriate compared to placebo.
- Placebo only acceptable where there is no alternative
- At the end if proven useful those on placebo should be given the new product
- In Vaccine and microbicide trials of HIV there is currently no comparator – but a combination prevention package is a requirement including PrEP.

Equipoise

Clinical equipoise occurs if there is genuine uncertainty within the expert medical community about the relative merits of the two or more arms of a trial; and if none of the study arms is known to be inferior to standard clinical care.

(Paraphrasing) Freedman, B. (1987) 'Equipoise and the ethics of clinical research'. *The New England Journal of Medicine*, 317, (3):141–145



Behavioral science

- The full range of methodologies also apply to behavioral science studies: observational, RCT, etc.
- Behavioral science may face challenges with regard to standardization of methods and outcome measures;
- For example: use of methods like cognitive behavioral therapy in controlled trials requires standardization
- Standard assessment tools may need to be translated or adapted to different populations

Adaptive designs

- **Designs in which decisions about changes to trial design are made as data are gathered, in midstream**
- Adaptive trials are designed to be more efficient and more responsive to changing evidence base, but they may be more difficult to interpret and explain
- **Example: outcome-adapted trials** adjust randomization if one arm of a trial performs better than another. Study subjects are randomized in higher proportion to the “better” arm of the study.
- This may raise questions:
 - If later study participants differ from early ones, this could introduce bias;
 - Disclosure about changes in randomization scheme could unblind the study and introduce bias;

Ethical issues : Stepped Wedge designs

- A **stepped-wedge trial** is a form of trial that involves sequential rollout of an intervention over multiple time periods.
- The term "stepped wedge" due to the stepped-wedge shape that is apparent from a schematic illustration of the design.
- The crossover is in one direction, typically from control to intervention, with the intervention not removed once implemented.
- The stepped-wedge design is more commonly used as a cluster randomised trial (CRT).

Stepped wedge trial ethical issues

- Design requires adequate justification
- Delays in implementation of intervention for communities in later groups
- The design is advantageous when simultaneous roll-out is impractical
- Potential for interference in ordering of communities.
- Design also faces ethical questions similar to those faced by CRTs

Cluster randomized trials

- **Randomization is used to assign treatment and control to groups (called clusters) rather than individuals**
- E.g., a cluster could be a town, or a hospital, or another type of group; and each cluster is assigned to treatment or control condition
- Specific statistical methods are needed to account for correlation of individuals within a cluster, in addition to comparison of clusters to each other;
- Ideally the clusters should be matched in terms of baseline characteristics; if the number of clusters is small, this may be difficult or impossible;

Cluster trials

- Entire groups or communities randomised to intervention or non intervention
- Appropriate when intervention is difficult to provide at individual level or group effects may be important
- Examples – counselling study, aerial spraying, water treatment experiments

Ethical issues

Cluster randomised trials pose difficult ethical issues because of features of their design

- 1. CRTs involve groups rather than individuals
- 2. The units of randomisation, experimentation, and observation differ within any given trial
- 3. Clusters may be randomised before cluster members may be approached for informed consent
- 4. Intervention may be directed at the level of the individual or the level of the cluster

Challenges with CRTs

- Researchers currently lack authoritative guidance to aid design and conduct cluster trials according to the highest ethical standards
- Research ethics committees and regulators have no single international standard to guide their review of cluster trials
- Predictably, the lack of authoritative guidance has resulted in uncertainty and markedly different interpretations as to permissible practices in cluster trials.

Ethical analysis

- 1. Who is the human research subject?
- 2. From whom, how, and when must informed consent be obtained?
- 3. Does clinical equipoise apply to CRTs?
- 4. How do we determine if the benefits outweigh the risks of CRTs?
- 5. How ought vulnerable groups be protected in CRTs?
- 6. Who are gatekeepers and what are their responsibilities?

Challenge studies

(controlled human infection models)

- **Studies involve intentional exposure of trial volunteers to an infectious agent**, e.g. malaria, or bacterial or viral pathogen
- Studies use controlled infection to assess vaccine efficacy or effectiveness of new treatment methods
- **Example: RTS/s malaria vaccine**
- Tested in controlled human infection model prior to field trial
- Challenge model allows for extremely efficient assessment of preventive or treatment methods
- E.g. can use 10 -20 participants, 3 month trial, versus 100s of participants, 2-3 year trial.

History of challenge studies in the US

Challenge studies were conducted in the US in the 1940's with prisoners

PROCEDURES USED AT STATEVILLE PENITENTIARY FOR THE TESTING OF POTENTIAL ANTIMALARIAL AGENTS¹

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(Received for publication December 23, 1946)

INTRODUCTION

The need for normal human subjects to use in appraising the activity of antimalarial drugs led, in 1944, to the establishment of a clinical research unit at the Illinois State Penitentiary, Stateville, Illinois. Through an arrangement with the Department of Public Safety,³ one floor of the prison hospital and a portion of a second floor were placed at the disposal of the Malaria Research Project. Approximately 500 inmates volunteered to act as subjects.

The studies were designed primarily to yield in-

formation concerning the effect of potential anti-malarial agents upon the relapse rate of sporozoite-induced *vivax* malaria. The observations also furnished information on the prophylactic and suppressive effects of the drugs tested, as well as data on their toxicology and pharmacology in man. The Chesson strain of malaria was selected for study because its short latent period between attacks (1) made feasible the rapid accumulation of information. An abundance of normal volunteers, in the younger age groups, living under standard conditions of diet and daily routine, made controlled clinical testing of antimalarial drugs possible. The institution being in a non-endemic area, accidental reinoculation was not a problem.

¹This investigation was carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Develop-

In the 1940's,
P. vivax strains were
maintained in
institutionalized
mentally ill patients

Malaria parasite. The Chesson strain of *P. vivax* (2) was isolated from a military patient who presumably had acquired his infection in New Guinea and was under treatment at the Harmon General Hospital, Longview, Texas (3). This strain is characterized by a high relapse rate when treated with noncurative drugs such as quinine and quinacrine, by a short period of latency between successive attacks, and by almost complete absence or delayed primary attacks (1, 4). The strain was maintained in psychotic patients at the Manteno State Hospital, Manteno, Illinois* chiefly by blood inoculations from donors who had manifested high gametocyte densities during trophozoite-induced infections. Not infrequently, however, donors were Stateville volunteers, whose malaria had been sporozoite-induced.

Present day challenge studies

- Studies are currently conducted using controlled human infection models (CHIM) for malaria, bacterial and viral pathogens, for example:
 - *P. falciparum*, *P. vivax*
 - *Salmonella typhi*
 - *Shigella* spp.
 - Cholera
 - RSV
 - BCG
 - Influenza
- Most studies are conducted in high income countries (US, UK) and rarely in low or middle income countries
- Issues of cost, acceptability, and regulatory issues are at play

Ethical challenges of challenge studies

- **Risks: important to assess both short term and long term risks of infection**
 - E.g. recent review of proposal for Zika challenge studies concluded that risks are too high and long term consequences uncertain;
- Even treatable infections may result in complications
- **Inducement: potential volunteers usually motivated by financial compensation**
- **Mechanisms for follow up for safety reasons:** in malaria challenge study, participants need to agree to follow up to ensure treatment has completely eradicated infection
- **Questions about which populations chosen for challenge studies**
 - Some ethics committees will not approve these studies

Malaria challenge study for *Plasmodium vivax* vaccine

- Study subjects infected with *P. vivax* in vaccine study (vaccine group and control group); all subjects treated with primaquine to eliminate infection;
- One subject had recrudescence after primaquine treatment and was retreated several times.
- Further analysis identified CYP2D6 genetic polymorphism which resulted in inadequate drug metabolism, leading to ineffective treatment
- The result was unfortunate for the participant—although he was ultimately successfully treated
- Led to significant development for the field, as the CYP2D6 mutation is present in populations exposed to *P. vivax*; was not known previously that it affect drug effectiveness
- Bennett, Jason W., et al. "Primaquine failure and cytochrome P-450 2D6 in *Plasmodium vivax* malaria." *New England Journal of Medicine* 369.14 (2013): 1381-1382. latively common in populations susceptible to *P. vivax*;

Ethics of CHIMs

- For what diseases are CHIMs justified?
- Need adequate justification for use of CHIMs
- The risks to the participants should be identified and minimised
- Studies require thorough monitoring eg through admission to a hospital ward
- Volunteers need to be adequately informed

Challenge studies

- Challenge studies, like all research, must above all protect subjects' health while advancing scientific inquiry;
- The temptation to use challenge studies due to their greater efficiency and reliability, compared to field studies or other trials.
- Always need to remember that not all risks can be completely accurately predicted;

Summary: Study design and ethics

- Choice of study design and careful planning are the most important parts of any scientific project
- For human subjects research, consideration of human welfare and choice (autonomy) impact the choice of study design and the particular structure of every project;
 - Some scientifically interesting and valuable studies simply cannot be done due to ethical constraints
 - At the same time, limitations on design should be based on well-justified ethical arguments
 - As science advances, new designs may become possible (for example, due to better assays or new ways to handle risks); also, some designs will become obsolete
 - Design of clinical studies will continue to become more sophisticated