Ethics in Clinical trials

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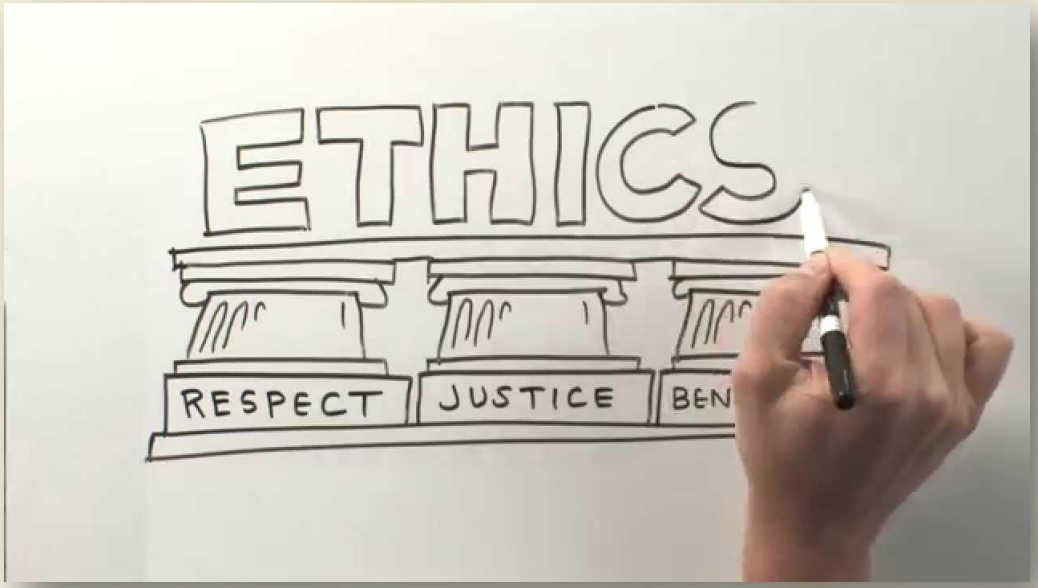
Overview

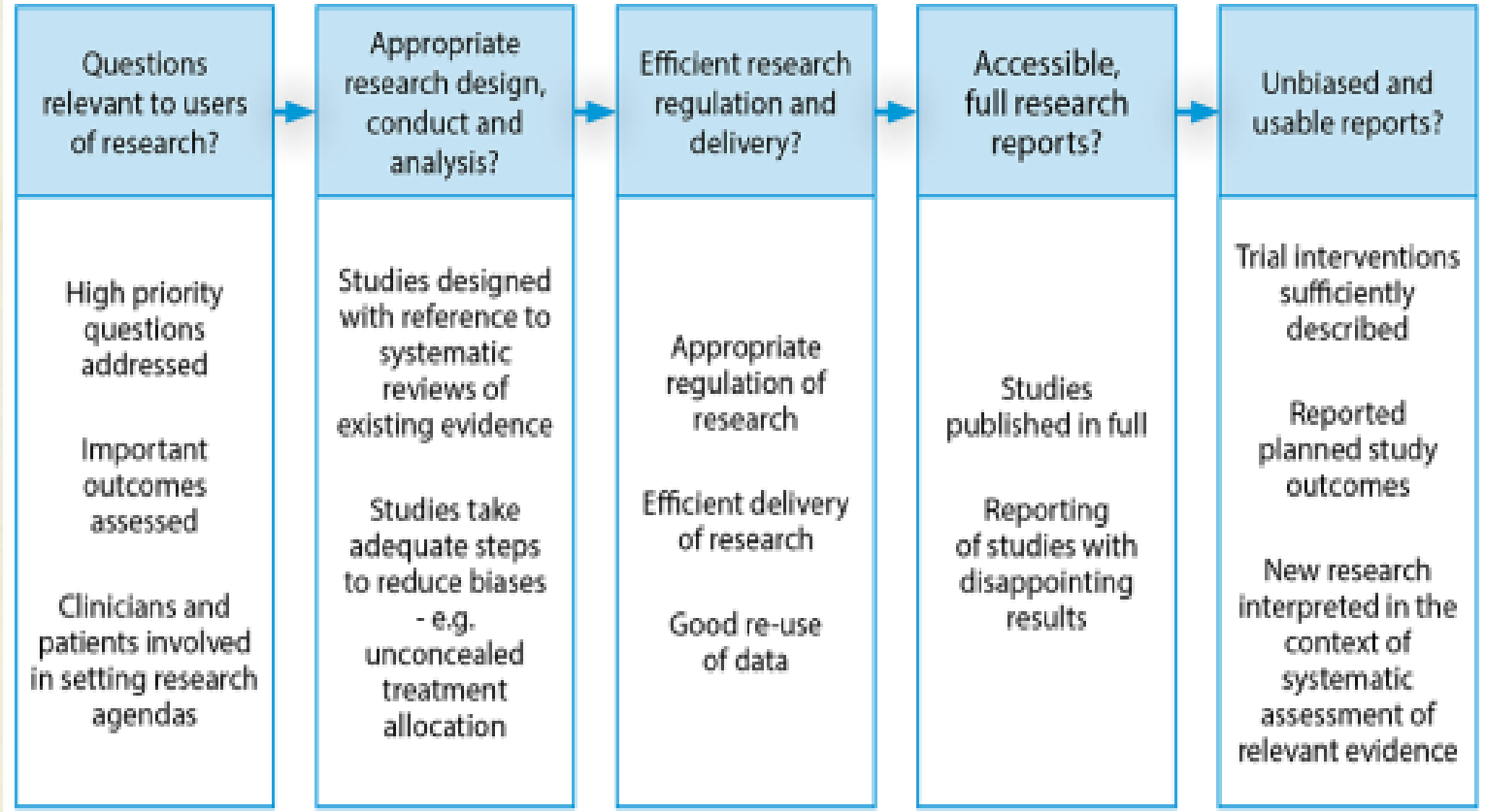
- Definitions.
- Ethical issues of waste in research
- Ethics in clinical trials



Waste in research

- Why does research waste matter?
- When / how does waste occur?
- What harm does research waste do?
- How can we reduce waste in research?

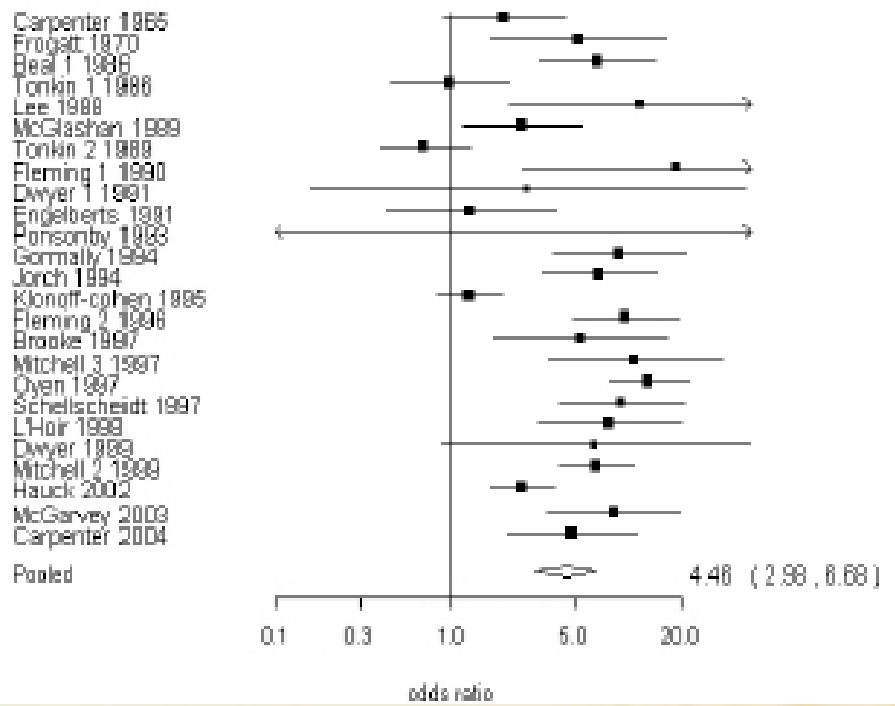
Waste occurs in all stages of research



Ethical impacts

- 1.Asking the wrong questions
- 2.Weak study designs
- 3.Not publishing all research
- 4.Poor reporting quality

Sleeping position and sudden infant death



Individual studies (by year)

1965-2004

increased risk of sudden infant death

- Gilbert et al *Int J Epidemiol 2005;**34:874***

Underpowered studies

- Big problem in preclinical (animal) research
- Risk of not detecting true effect and reporting ‘false positive’ effect
- Systematic reviews found: 3% animal studies in stroke 0% in Alzheimer's / Parkinson's disease reported sample size calculation

Boy, I don't know what they've injected me with, but I feel great!

50% of clinical trials unpublished

- Of EU-funded health research 1998-2006

50% unpublished

- 570 million Euros of research had “no detectable academic output”
- Situation may be improving but evidence-base for most prescribed medicines is badly affected by non-publication

Much published research is unusable

- Of 102 journal articles reporting clinical trials, 62% had a change to the primary outcome stated in the protocol
- Of 88 studies using novel questionnaires only 8% of questionnaire could be accessed
- Of 141 studies of test accuracy, 40% did not report participants' age and sex
- Of 49 AIDS trials, only 33% reported all adverse events

All refs in Glasziou et al *Lancet, 2014*

First question for small group discussion

- How can we reduce waste in research?

- Demand justification of study question
- Support research synthesis so it's clear what is already known
- Enforce trial / study registration
- Use strong designs that maximize the effect-to-bias ratio
- Reward reproducible research
- Reward full and effective dissemination of findings (and re-use of datasets)
- Support use of reporting guidelines

The Belmont Report

- **The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research** - April 18, 1979

- **The Belmont Report** (1979) is the major ethical statement guiding human research in the United States.

The Belmont Report

2. Basic Ethical Principles

- **Respect for Persons**
  - Individual autonomy Protection of individuals with reduced autonomy
- **Beneficence**
  - Maximize benefits and minimize harms
- **Justice**
  - Equitable distribution of research risks and benefits

Respect for Persons

- Treat individuals as autonomous agents
- Do not use people as a means to an end
- Allow people to make choices for themselves
- Provide extra protection to those with limited autonomy
  - *Voluntary Participation*
  - *Informed Consent*
  - *Protection of Privacy & Confidentiality*
  - *Right to Withdraw without Penalty*

Beneficence

- Acts of kindness or charity that go beyond duty
- Obligations derived from beneficence
  - Do no harm
  - Prevent harm
  - Prevent evil
  - Promote good
    - *Risks are justified by the benefits*
    - *Risks are minimized*
    - *Conflicts of interest are managed to avoid bias*

Justice

- Treat people fairly
- Fair sharing of burdens and benefits of research
- Distinguish procedural justice from distributive justice
  - *Vulnerable subjects are not targeted for convenience*
  - *People are not selected as subjects because of their ease of availability or compromised position*
  - *People who are likely to benefit are not excluded*

RANDOMIZED TRIALS

TYPES OF EXPERIMENTAL STUDIES

1. TRUE EXPERIMENTS

-RANDOMIZED TRIALS

2. QUASI-EXPERIMENTS

QUASI-EXPERIMENTS

a. Cross-sectional comparison:
e.g. to comparable communities or groups

b. Temporal comparison:
e.g. before and after the intervention

c. Combinations of the above:
e.g. time-series analysis in community trial.

WHAT MAKES RANDOMIZED TRIALS SO SPECIAL?

5 YEAR MORTALITY IN THE CORONARY DRUG PROJECT

- CLOFIBRATE (N = 1,103 MEN)

  20.0% DIED
- PLACEBO (N = 2,789 MEN)

  20.9% DIED

5 YEAR MORTALITY IN THE CORONARY DRUG PROJECT

- TOOK 80% OR MORE OF CLOFIBRATE PILLS – 15.0% DIED
- TOOK LESS THAN 80% OF CLOFIBRATE PILLS – 24.6% DIED
- TOOK 80% OR MORE OF PLACEBO PILLS – 16.4% DIED
- TOOK LESS THAN 80% OF PLACEBO PILLS – 25.8% DIED

METHODOLOGICAL ISSUES IN RANDOMIZED TRIALS

A. TERMINOLOGY

B. THE RANDOMIZATION PROCESS

C. STRATIFICATION

D. BLINDING

E. CROSS-OVER

F. "PRAGMATIC" TRIALS

G. PURPOSES OF RCT'S

TERMINOLOGY

study population

- **intervention (treatment) arm**
- **control (placebo) arm**

reference population

assignment

intention-to-treat

THE RANDOMIZATION PROCESS

1. **Equal distribution of measured characteristics in trial arms is *optimized* but never absolutely assured.**
2. **Randomization increases the likelihood that *unmeasured* variables are equally distributed between the two arms.**

3. Randomization in assigning the intervention *promotes* avoidance of bias

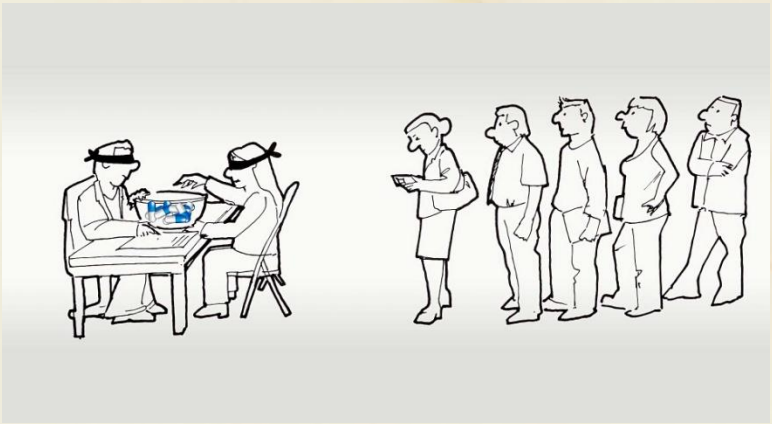
4. Ideally, the randomization scheme, assignment is unknowable in advance. (Systematic sampling is knowable in advance, which is a limitation of this sampling system).

- **5- Randomization applies to *the individuals randomized, not the groups actually receiving treatment or placebo.* Therefore, analysis is *always* by intention to treat; no exclusions after randomization are allowed.**

STRATIFICATION

Can stratify or not. The smaller the sample size, the more advisable is stratification. Common stratification characteristics - age, gender, race, hospital/clinic.

BLINDING



Blinding is not inherent to randomized trials, but should be used whenever possible as placebo effects are powerful. Blinding requires placebo or use of alternate treatment that cannot be distinguished from treatment.

- **Single blinded: patient doesn't know which arm any patient is in.**
- **Double blinded: patient and person administering the intervention don't know.**
- **Triple blinded: patient, interventionist and data analyst don't know.**

CROSS-OVER

The problem that the control arm may get the treatment from other sources. Common problem in screening trials.

“PRAGMATIC” TRIALS

The concept that the trial should ideally reflect real-world conditions. Sometimes may be performed after a more “experimental” trial in a select group of patients.

PURPOSES OF RCT'S

A randomized trial can be of a disease treatment (which may make it not really part of epidemiology), or a primary prevention method (e.g. vaccination), or a secondary prevention method (e.g. screening).

Concept of POWER as applied to RCTs

- **Type 1 error: Falsely *believing* the null hypothesis, or concluding that a difference exists when it does not. P values are designed to protect against this error.**

- **Type II error: Falsely failing to reject the null hypothesis, or concluding there is *no significant difference*, when in fact there is a difference, but it is too small to detect in a trial of this size.**

POWER IS DEFINED AS THE ABILITY OF A STUDY TO AVOID MAKING A TYPE II ERROR

The major problem in RCTs is small studies making type II errors (i.e. studies that have low power). This has happened repeatedly in medicine.

Example: anticoagulants in myocardial infarction.

ETHICAL ISSUES IN RANDOMIZED TRIALS

1. Concept of ***equipoise*** - the point at which you are not sure whether the placebo is better or the treatment is better. This is the point at which a trial is best started.

2. The more information accumulates on a new treatment, the harder it is to do a trial (Randomize the first patient).

3. It can be unethical to deny a new treatment to the placebo group, but the history of trials suggests that it is often better to be in the placebo arm.

Example:

In neonates - sulfa for infections, oxygen for lung disease, steroids for eye disease were all damaging, and this was discovered only via randomized trials

4. It can be unethical *not to perform* a trial, because it prevents new knowledge from being obtained and used.

Example:
Folate for neural tube defects

5. Public health is always best served by proper evaluation, and the best evaluation is by randomized trial.

EFFECT SIZE ESTIMATION *IN RCT'S*

A. If the outcome is dichotomous, there are two common ways to estimate effect size:

1. ***percent reduction* in the *absolute risk* of the outcome.**
2. ***percent reduction* in the *relative risk* of the outcome (less often used).**

percent reduction in the *absolute risk* of the outcome

If mortality is 8% in the placebo arm, and 6% in the intervention arm, then the percent reduction in mortality is:

$$\frac{8\% - 6\%}{8\%} = 25\% \text{ reduction}$$

percent reduction in the *relative risk* of the outcome

If in the placebo arm an exposure carries a relative risk of disease of 3.0, and in the intervention arm 2.0, we calculate the percent reduction in the relative risk

$$\frac{3.0 - 2.0}{3.0} = 33\% \text{ reduction}$$

B. If the outcome is continuous, we usually speak of changes in ***standard deviation units.***

For example, if a special program raises *children's IQ from* 100 to 105, and we know that the standard deviation of IQ in this population is 15 points, then

$$\frac{105 - 100}{15} = 1/3 \text{ of an SD improvement}$$

This is more useful than saying a 5 point improvement, as it tells you how large that 5 point change is relative to the variation of IQ in the population.

NUMBER NEEDED TO TREAT

This is a very useful measure to understand the total value of an intervention

A trial reduces an outcome from 10% to 5%. What is the N needed to treat?

NUMBER NEEDED TO TREAT

- 90% were unaffected because they *didn't* get the outcome in either group
- 5% were unaffected because they did get the outcome in both groups
- 5% had a different outcome, or 1 in 20.
- You needed to treat 20 people to get one outcome you would not have had in the control arm

META-ANALYSIS

A quantitative approach to the summary of research studies, in some views, restricted to randomized trials.

1. Must have strict criteria if pooling of studies is undertaken.
   a. quality of studies
   b. comparability of studies

2. In epidemiology, it is common practice to summarize odds ratios (or relative risks) and confidence intervals in a figure. Diamond used to indicate the pooled odds ratio.
3. Strong trend towards increased use of meta-analysis. Cochrane collaboration is an international network of researchers committed to "meta-analyzing" specific fields of medicine. Most developed field so far is perinatal and neonatal medicine, which has 6-monthly updates of all known RCTs in progress as well as published.

PROSPECTIVE META-ANALYSIS

- A relatively new idea. This is the concept that several groups planning trials around the world get together and, while not doing one trial together, agree to make things similar enough so that pooling will be easy to do across trials at the end. (sometimes trials cannot be done as one because of different funders, different start dates, etc.)

COMMUNITY TRIALS

1. Can and should be randomized, though randomization somewhat less urgent than in individual-level trials. Time-series design, a quasi-experiment, is often used.
2. The only possible trial if the intervention is ecological.

e.g. mass-media, water supply, etc.

3. No selection of individual subjects for study. Savings in cost of individual screening and enrollment.

4. Baseline and follow-up community surveys essential.

5. Ideal to use surveillance systems already in place.

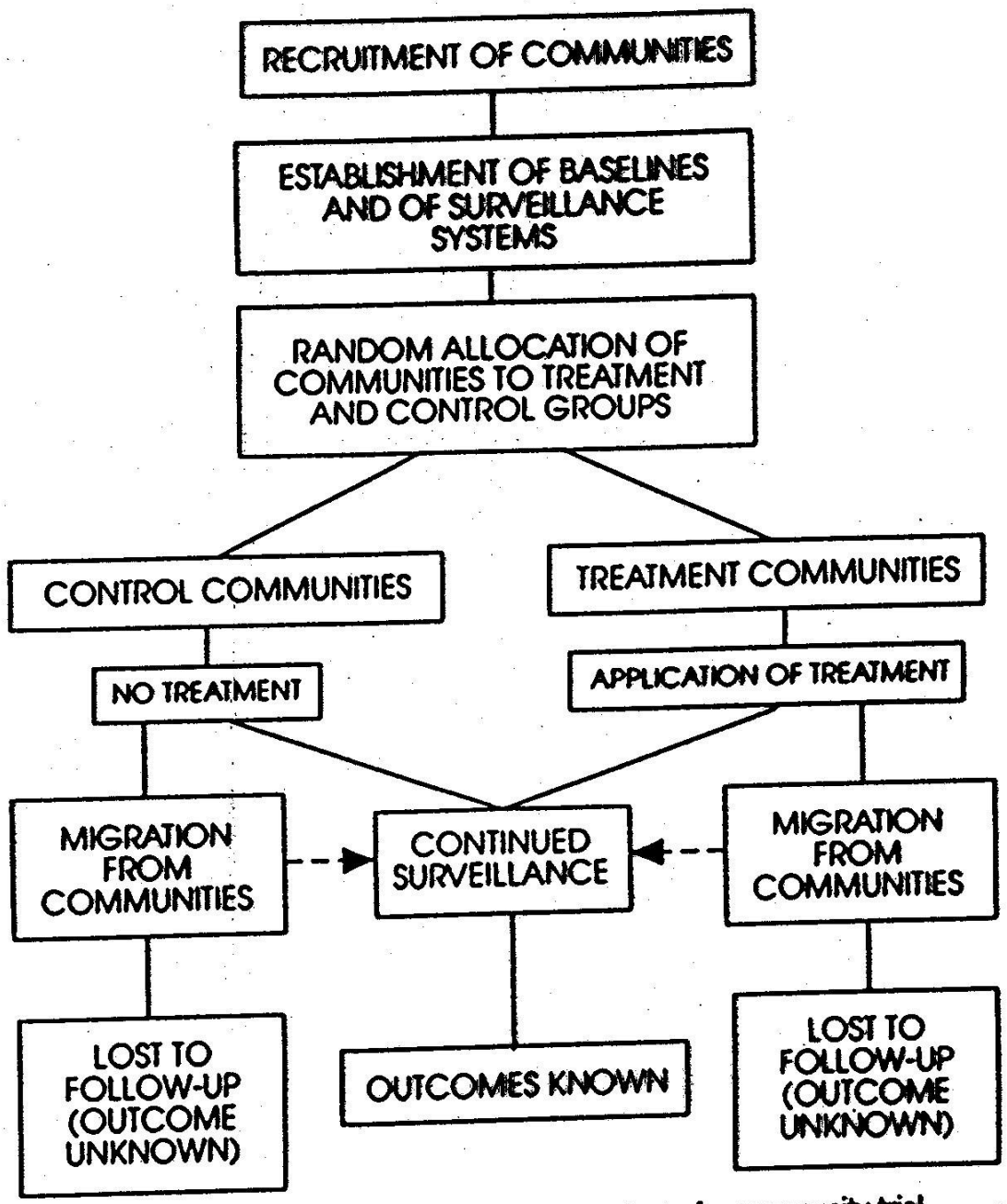


Figure 9–1. Generic diagram of the conduct of a community trial.

Thank You!