Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Mini lecture:

Conducting and managing randomized controlled trials (RCTs)

Tracy Glass

Conflicts of Interest

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I have received funding for membership on Data Safety and Monitoring Boards and for the preparation of educational materials from:

Gilead Sciences

Novartis

Janssen-Cilag

Introduction – study design

We often wish to investigate the efficacy of new treatments and interventions on patient outcomes

In this session, we shall consider a study design commonly used to answer such questions – Randomized Controlled Trials

The following session will consider when it is appropriate to use other types of studies (observational studies)

Outline

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- The basic idea
- Important features of well performed RCTs
- The CONSORT statement

Randomized Controlled Trials

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Experimental, longitudinal, prospective

Randomized – ensures that treatment groups are similar (in both measured and unmeasured factors) at start of trial; any differences are due only to chance

Controlled – control group allows us to conclude that any improvement in outcome is due to the experimental treatment rather than some other factor

Experimental and Control group

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Experimental arm: can be

- a new drug/regimen
- an intervention (counseling, delivery method)
- combination of things

Control arm: can be

- Placebo (if ethical)
- Standard of care

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Trial Populations

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Explicit and objective inclusion and exclusion criteria are required for any RCT

Narrow and restrictive inclusion criteria can allow us to focus on people most likely to benefit from treatment, and reduce variability in the outcome

However, we want the included participants to be representative as far as possible of those who may receive treatment in the future

Discuss trial and assess eligibility

Example – Trial populations

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Does immediate ART result in a reduction in new AIDS events, non-AIDS events and death compared to deferred ART?

Inclusion criteria:

- age ≥18 years
- Karnofsky performance score ≥ 80
- no previous AIDS
- no previous serious non-AIDS
- not currently pregnant or breast feeding

Generalizable to all HIV-positive individuals?

INSIGHT START Study Group; N Eng J Med 2015

Informed consent

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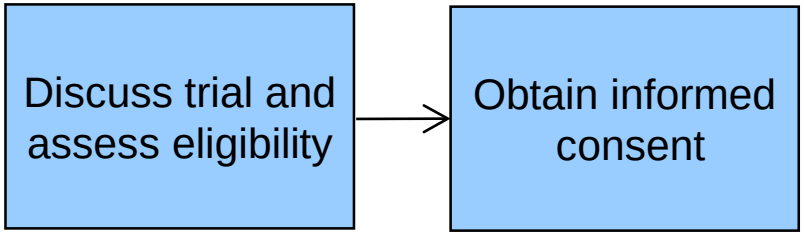
Medically, a patient should be aware of the potential immediate, early and late health outcomes after an operation, and the risks involved. (brief!)

Legally, consent is required to enable fair consideration of liability should complications arise or patient expectations not be met. (encyclopaedic!)

Balance has to be struck between the ethical aims of the informed consenting process and the potential negative consequences of overloading patients with information.



Randomization

What does it mean to randomize patients?

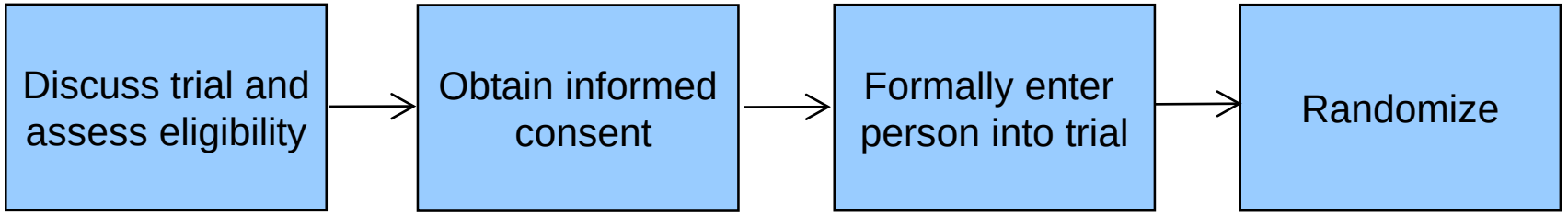
- roll a die?
- flip a coin?
- alternate day of the week?

Other considerations:

- blocks (ensures size of both arms is the same)
- stratification (ensures balance in an important prognostic factor)

Key points:

1) It should not be possible to guess the arm for which the next person will be assigned
2) You need sufficient numbers for the randomization to work



Treatment allocation

A person's treatment allocation should not be known before they are entered into a trial

If there is no concealment of treatment allocation, this may influence the decision to recruit, leading to imbalances

ex., list with assignment is available to recruiting person in advance of randomization

"Successful randomisation in practice depends on two interrelated aspects—adequate generation of an unpredictable allocation sequence and concealment of that sequence until assignment occurs."

CONSORT Explanation and Elaboration, *BMJ* 2010;340:c869

Example - Baseline characteristics

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Immediate-Initiation Group (N=2326)	Deferred-Initiation Group (N=2359)	All Patients (N=4685)
Median age (IQR) — yr	36 (29–44)	36 (29–44)	36 (29–44)
Female sex — no. (%)	624 (26.8)	633 (26.8)	1,257 (26.8)
Race or ethnic group — no. (%)†			
Asian	198 (8.5)	190 (8.1)	388 (8.3)
Black	702 (30.2)	708 (30.0)	1,410 (30.1)
Latino or Hispanic	320 (13.8)	318 (13.5)	638 (13.6)
White	1,015 (43.6)	1,071 (45.4)	2,086 (44.5)
Other	91 (3.9)	72 (3.1)	163 (3.5)
Geographical region — no. (%)			
Africa	499 (21.5)	501 (21.2)	1,000 (21.3)
Asia	179 (7.7)	177 (7.5)	356 (7.6)

INSIGHT START Study Group; N Eng J Med 2015

Blinding

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Once randomized, bias can occur if a patient, treatment team, assessor are aware of treatment allocation

1. Patient: psychological effect, adherence to treatment
2. Clinical team: treatment modifications, additional treatments, intensity of examination
3. Assessor: recording of responses to treatment and adverse events

The extent of the bias may depend on the intervention and the nature of the outcome measure

Blinding

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Blinding is not always possible, but in most trials some element can be introduced

Double-blind: neither patient nor clinical team know which treatment patient is receiving

Single-blind: only patient does not know which treatment s/he is receiving

Blinding is particularly important for subjective endpoints; Increasing use of independent review committees to adjudicate endpoints

Study endpoints

All clinical trial protocols should state one (sometimes two) pre-defined primary endpoint(s)

Main conclusions should be based on the results from the primary endpoint(s)

Pre-defined secondary endpoints can also provide supportive data

Exploratory endpoints can provide ideas for future research

Example – START Trial

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Primary Endpoint (Composite outcome):

1. Serious AIDS-related event* or death from AIDS
2. Serious non–AIDS-related event~ or any death not attributable to AIDS

Secondary Endpoints:

1. Major components of primary endpoint

   Serious AIDS-related events; Serious non–AIDS-related events, death, TB, Kaposi's sarcoma, lymphoma, cancer, CV disease

2. Grade 4 events
3. Unscheduled hospitalizations for reasons other than AIDS

*1993 CDC definition excluding non-fatal HSV and oesophageal candidiasis and including Hodgkin's lymphoma); ~ CVD (MI, stroke or coronary revascularisation), ESRD (starting dialysis or transplantation, decompensated liver disease, NADC (excluding basal-cell or squamous-cell skin cancer)

INSIGHT START Study Group; N Eng J Med 2015

Loss to follow-up

The validity of trial results are dependent on complete follow-up of randomized patients

All patients who were randomized should be accounted for when the results are reported

Ideally, all patients who were assessed for eligibility should be accounted for, as this may impact on the generalizability of the trial

Analyzing data

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Intent-to-treat analysis (ITT): gold standard

All individuals are included in analysis and according to which arm they were assigned

On treatment analysis (OT): only individuals who complete the study and adhere to the protocol are included

- Also known as per-protocol analysis

What could be the difference between these approaches?

How do we account for missing data?

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Missing = Failure analysis (M=F):

- Those lost to follow-up are considered as virological failures from that time point onwards
- Those with missing study visits are considered as virological failures at that time point

Missing = Excluded analysis (M=E):

- Those lost to follow-up are excluded from analyses from that time point onwards
- Those with missing study visits are excluded from analyses at that time point

How do we account for treatment changes?

Switch=Failure (S=F):

- individuals who make drug changes are considered as virological failures

Switch=Ignored (S=I):

- drug changes are ignored; patients are categorised according to virological response

Ethical considerations

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Trials must be reviewed and approved by ethics committee(s) – even trials conducted in other countries have to be reviewed by local authorities where principal investigator is located

They are looking for whether a trial is ethical:

- Good reason/motivation
- Feasible
- Patient informed
- Patient data protected

Must have a state of equipoise (uncertainty about which intervention condition will work best) which is the ethical justification for conducting a trial.

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Where to go for guidance

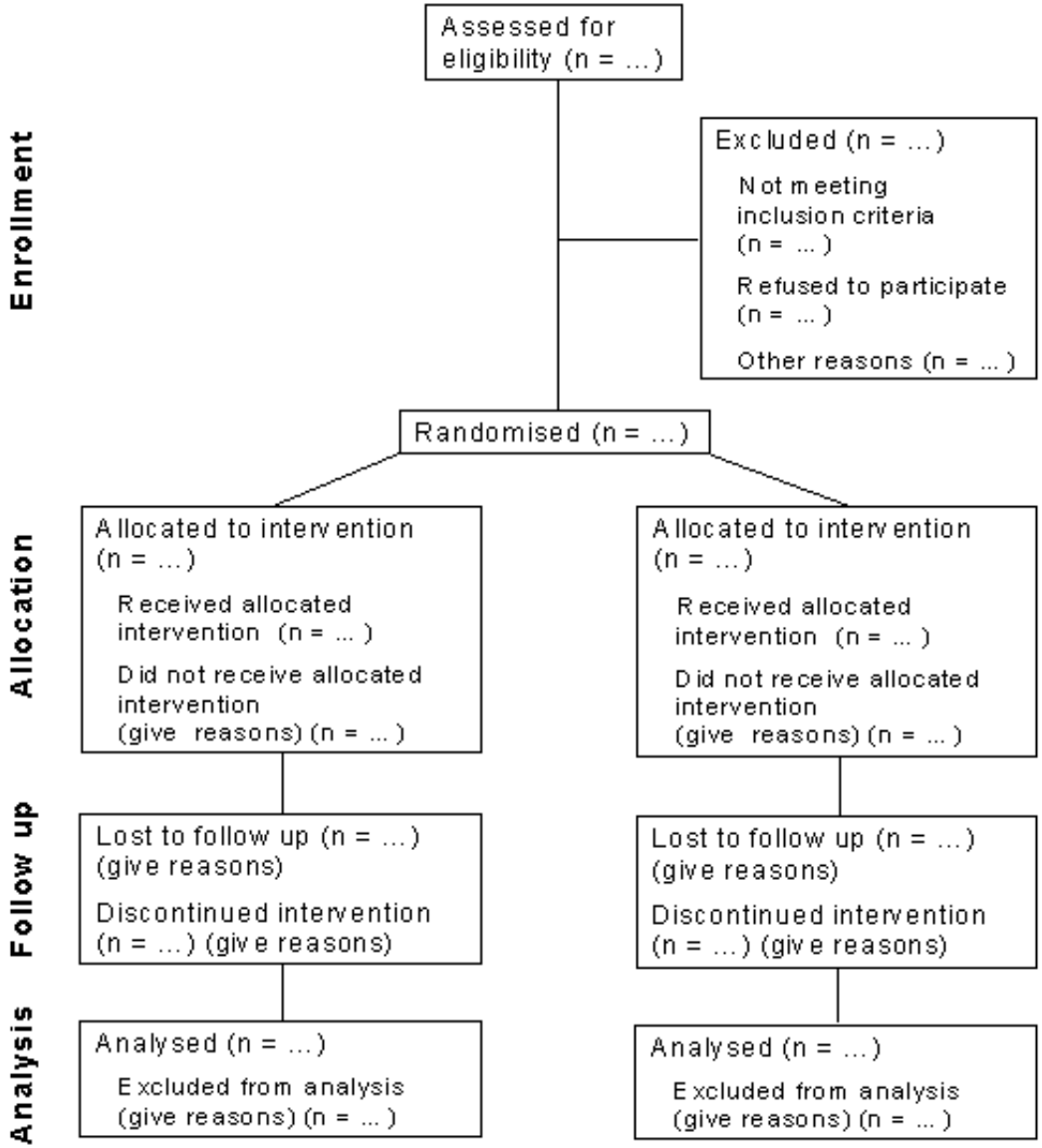
The Consolidated Standards of Reporting Trials (CONSORT) Group was set up to ensure transparency in the reporting of RCTs

Their main output is the CONSORT Statement which is an 'evidence based, minimum set of recommendations for reporting RCTs'

It includes a checklist and flow diagram, which can be very helpful both for conducting and appraising RCTs

www.consort-statement.org

CONSORT flow diagram



CONSORT

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The CONSORT checklist for reporting and appraising RCTs

Table. **CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial***

Section/Topic	Item Number	Checklist Item	Reported on Page Number
Title and abstract	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [21, 31])	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	