Clinical Trials from Concept to Management

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Overview of lecture

- Introduction
- Why and when to do trials
- Randomised Control Trials
  - Controls
  - Blinding
  - Size
- Small trials and systematic reviews
- Life history of a trial
- Selected issues of trials in 21st Century
  - Surrogate endpoints
  - Consent

The Controlled Clinical Trial

"The aim of the controlled trial is very simple: it is to ensure that the comparisons we make are as precise, as informative and as convincing as possible."

A. Bradford Hill

1st Modern-day Clinical Trial
Acute progressive pulmonary tuberculosis

- MRC (1948)

Patients:	aged 15-30 satisfying the criteria defined
Treatments: (by random allocation)	S = streptomycin 2g i.m. per day plus bed rest C= bed rest alone 109 patients from 7 hospitals, 2 exclusions
Radiographic evaluation:	blind, without knowledge of allocated treatment, by 2 radiologists and 1 clinician

1st Modern-day Clinical Trial
Acute progressive pulmonary tuberculosis

Outcome: after 6 months of treatment

	S	C
Total patients	55	52
Considerable radiographic Improvement	28 (51%)	4 (8%) (P < 0.001)
Deaths	4 (7%)	14 (27%) (P < 0.01)

Conclusion: Strong evidence that streptomycin is an effective therapy in acute progressive disease

Why do we do trials?

- to evaluate the risks and benefits of new interventions, often drugs or vaccines
- to compare the new treatment with the current “best” treatment, if there is one
- to evaluate the impact on patient assessed outcomes such as quality of life
- to assess the cost-effectiveness of the new treatment

When to do trials?

- enough data to indicate new treatment might work and be tolerable , but
- still enough uncertainty about its benefits
- "window of opportunity" before clinical practice changes - sometimes without good evidence

Types of Trials

- Phase I: pharmacology & drug safety
  in healthy human volunteers

- Phase II: in people with the disease
  first investigations of activity and safety

- Phase III: risks and benefits
  comparison of new treatment with current standard in a large number of people

- Phase IV: post-marketing surveillance
  after approval, additional large scale trials for adverse event monitoring

Trial Designs

Four main types of trial design:

- Parallel arm
  - 'standard' A vs B trial
- Cluster randomised
  - Randomise by unit (GP surgery, family, community)
- Cross-over
  - Every patient has both treatments (i.e A then B or B then A).
- Factorial
  - Tests all combinations of two or more treatment regimens

	A	Placebo A
B	A + B	B + pA
Placebo B	A + pB	pA + pB

Treatment Comparison

If you are comparing two different treatments, what do you want to know?

- Superiority
  - used to demonstrate that one treatment is better than another
- Equivalence
  - used to demonstrate that a treatment is no better or worse than an existing treatment
- Non-inferiority
  - used to demonstrate that effect is not worse by more than a pre-specified amount

What design and comparison would you use to answer the following research questions?

- Can ART be safely given to symptomatic HIV infected adults in Africa with clinical monitoring alone, in the absence of regular viral load and CD4 measurements and laboratory monitoring for toxicity?

- Parallel arm, equivalence trial (DART)

- Does isoniazid prophylaxis therapy given to gold-miners in South Africa on a community-wide basis reduce the incidence of TB.

- Cluster randomised, superiority trial (Thibela TB)

- To compare different combinations of ART drugs to see which is the best to start with in children AND to decide what to do if the viral load rises again in the blood (change immediately or wait until virus levels are higher).

- Factorial, superiority (PENPACT1)

- To establish whether rapid and early intravascular volume expansion with saline results in a lower mortality than standard slow replacement in critically ill children AND to establish whether rapid and early intravascular volume expansion with albumin is better than saline in reducing mortality.

- Parallel – three arms, superiority (FEAST)

Design issues (1)

- randomise: to remove selection bias
- blinding: to remove bias in assessment or management (usually by use of placebo but may not be feasible)

Aims

- any differences in outcome between groups receiving X and not receiving X is due to the intervention X itself
- randomisation ensures groups similar at the start of the trial (baseline)
- what about differences during follow-up?
  - **is management the same?**
  - **is outcome assessed the same?**

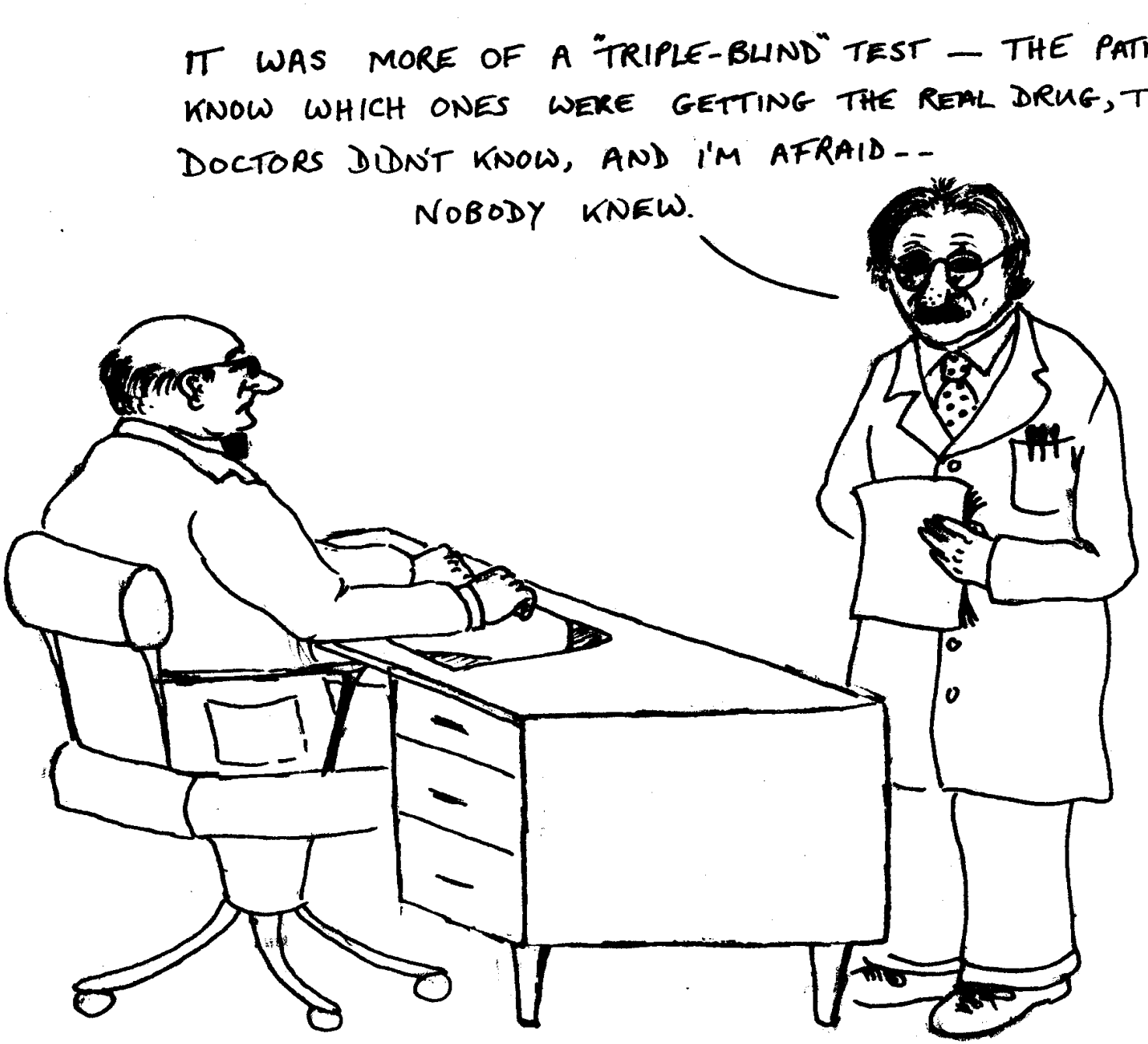
- Using a blinded control group enables groups to be treated similarly throughout the trial.
  - **Objective measures**
  - **'blinded' assessors**
  - **Double blinding**

Blinding

- Double blind
  - Neither doctor nor patients knows who has what
- Single blind
  - Doctor knows but patient doesn’t
- Prevents outcome being influenced by
  - Placebo effect
  - Doctor treating patients differently
  - Differential assessment of study endpoints
- Not always possible
  - surgery vs no surgery
  - complex chemotherapy trials
  - radiotherapy

The Double Blind Trial: How blind should it be?

- Medicament
- Allocation
- Patient
- Physician
- Clerk
- Laboratory
- Statistician


IT WAS MORE OF A "TRIPLE-BLIND" TEST — THE PATIENTS DIDN'T KNOW WHICH ONES WERE GETTING THE REAL DRUG, THE DOCTORS DIDN'T KNOW, AND I'M AFRAID--
NOBODY KNEW.

Design Issues (2)

- outcome measures: objective and well defined
- size: big enough to reliably detect a moderate but clinically important effect

Trial Size

- How many patients are required for each treatment group?
  - estimation process - drives trial design, cost and duration.
  - too few - miss treatment effect. Too many - waste
  - needs to have scientific reasoning and be justified in terms of practicality and expense.
  - the power calculation is the usual method of determining trial size, based on information gleaned from literature/clinical experience and also based on expected levels of adherence.

Calculation Requirements

- What is the primary outcome? This can be:
  - continuous e.g change in mean calcium levels.
  - binary e.g favourable response: yes or no
  - survival time to a certain event e.g death
- The primary outcome chosen depends on clinician's opinion as to what outcome is the most important.
- Sometimes >1 primary outcome typically:
  - Efficacy
  - Adverse effects
  - Costs

Requirements (cont'd)

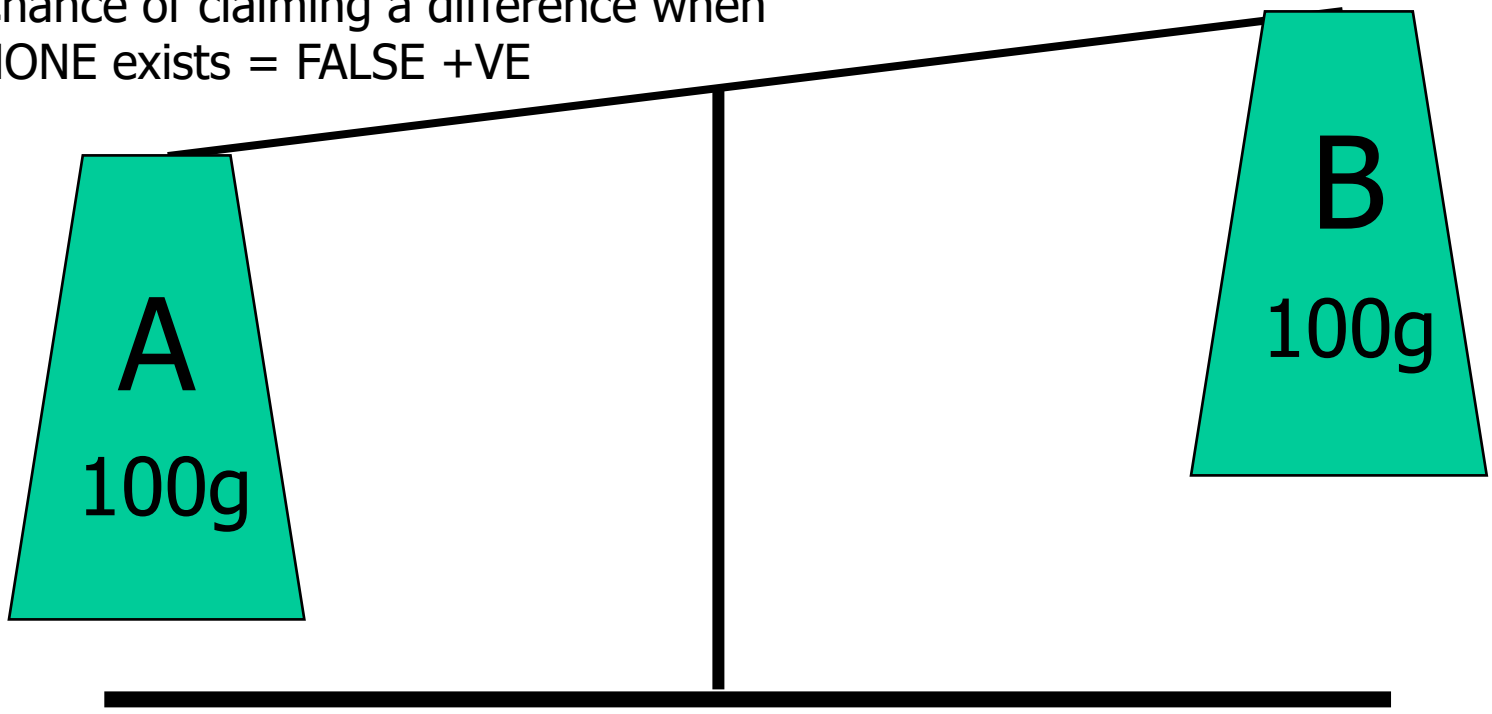
- How small a treatment difference do you want to detect? This should be large enough to be clinically important.
- What is current level of the outcome on standard treatment?
- What level of errors will you choose?
  - These are aspects of design that set the degree of certainty of the observed treatment effect.

Type I error -

α

Conclusion: A is heavier than B

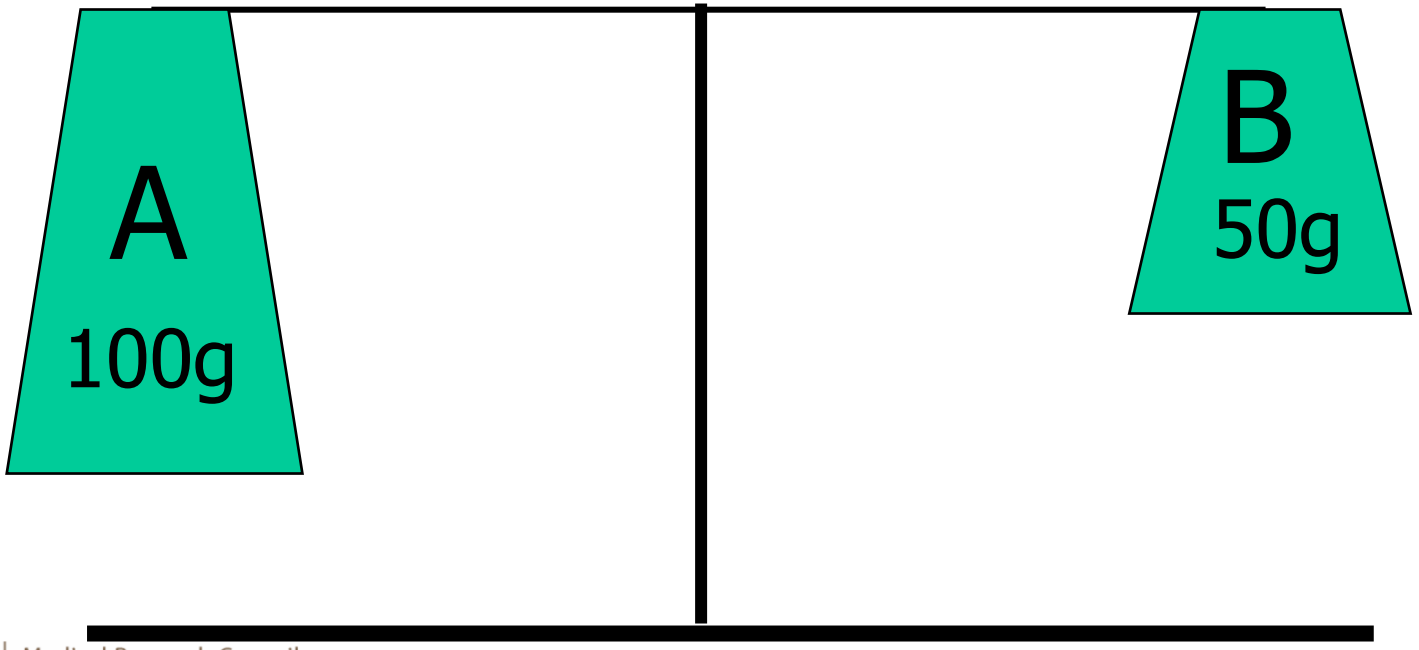
Chance of claiming a difference when NONE exists = FALSE +VE



Type II error - β

Conclusion: A and B weigh the same

Chance of claiming NO difference when a difference DOES exist = FALSE -VE

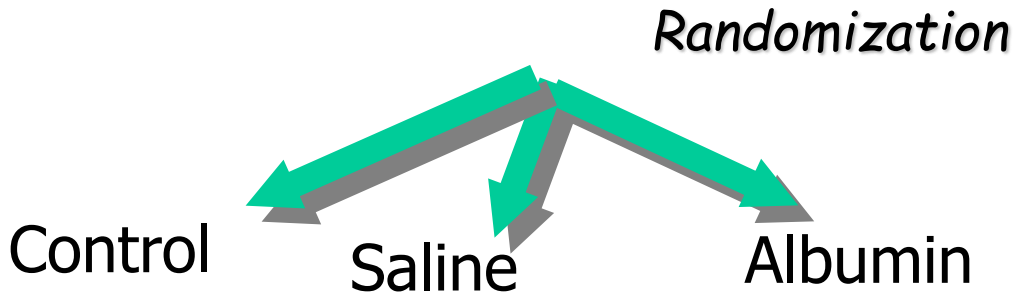


α, β and power

- The value of α chosen is arbitrary, usually set to 0.05 (1 in 20).
- Determines the acceptable chance of wrongly declaring a difference when none exists.
- The power of a trial measures how likely the trial is to detect a significant difference given a true difference exists. This is normally set to at least 80% and is equal to 100-β.

The power calculation

Example of a three arm randomised trial, comparing 3 proportions. FEAST – Fluid Expansion As Supportive Therapy for critically ill African children.



Outcomes: Success = Alive at 48 hours.

Power calculation (cont'd)

Calculation based on:

- Preliminary findings and assumptions
  - **Baseline mortality at 48 hours of eligible children is 15%**
  - **67% of those with inclusion criteria will have *P.falciparum* parasitaemia**
  - **Bolus 0.9% saline reduces mortality by 30% compared to maintenance fluids**
  - **Bolus HAS reduces mortality by 40% compared to 0.9% saline**
  - **Power 80% and α = 0.05, adjusted for two primary comparisons (saline versus maintenance fluids and HAS versus saline).**

Importance of adherence and loss to follow up

- if participants do not take the trial treatment:

  the true effect may be underestimated and the result of the trial inconclusive

- if patients are lost from follow up:

  the results will be less reliable and may be biased if there is a difference in the rate of loss between the treatment groups

Challenges: Small Trials

- selection of new drugs or combinations to take into large trials
  - using surrogate or intermediate endpoints

- large trial impossible
  - rare disease
  - subgroup of common disease
  - complex or expensive therapy

Behind every large trial there is at least one small trial!

Why we need systematic reviews

Totality of evidence

- Evaluations should be based on results of all trials
- Results of any one trial should be interpreted in context of all relevant evidence
  - *consistency / inconsistency*
  - *applicability / generalisability*

Synthesis

- Need systematic reviews to reliably summarise existing information

Power and Precision

- Often benefits of new treatment are moderate
- Usually RCTs recruit too few patients to detect such differences with reliability

Systematic Reviews

- **Systematic Review**
  - means of reviewing clearly formulated questions, using explicit methodology, to minimise bias in the location, selection, critical evaluation and synthesis of research evidence

    (may or may not involve quantitative synthesis)

- **Meta-analysis**
  - means of quantitatively combining the results of research studies to provide overall summary statistics

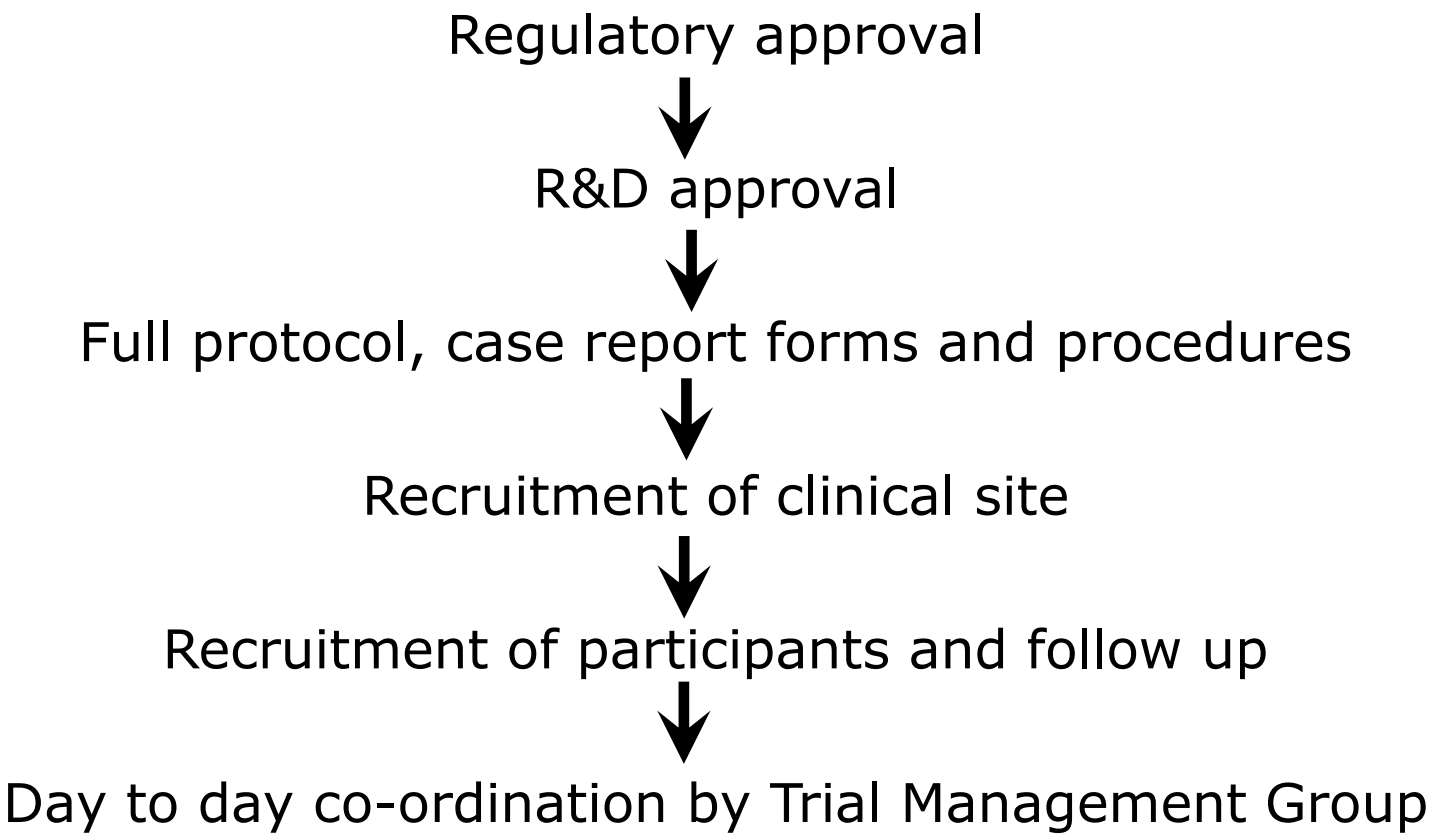
    (good quality MA will also be a SR)

Systematic Reviews

Are only as good as the trials
on which they are based

Life history of a trial

Life history of a trial (cont'd)



Life history of a trial (cont'd)

Independent supervision by Trial Steering Committee

↓

Review by Data & Safety Monitoring Committee

↓

Analysis of data and reporting of results

↓

Dissemination of results

Selected issues in trials in the 21st century

- Surrogate endpoints
- Consent
- Ethical issues in resource poor countries
- Consumer involvement

Surrogate endpoints

- What ultimately matters to patients is the duration and quality of life
- However often difficult to do trials with clinically important endpoints and surrogate endpoints enable studies to have smaller sample sizes and shorter follow-up.
  - e.g. recent HIV drugs licensed on basis of virological effect over 48 weeks
- But need to be very careful in choosing appropriate surrogate endpoints/markers.

Current ethical issues

- **consent:**
  - children and incapacitated adults
  - Difficult in trials in emergency situations

- **resource poor countries:**
  - definition of standard care
  - provision of treatment at the end of the trial

Ethical issues:
Memories of the first randomised trial

- "Of course, there were no ethical problems in those days: we did not ask the patient's permission or anybody's permission. We did not tell them they were in a trial - we just did it"

- " I think it is wrong to shift the entire consent-giving responsibility on to the shoulders of patients who cannot really be informed or know what weight relatively to put upon the technical information provided concerning risks and benefits"

– Sir Austin Bradford Hill
Controlled Clinical Trials
1990;11:77-79

- Trials are governed with principles and guidance set out from:
  - **Declaration of Helsinki**
    - International recommendation on the conduct of medical research on human subjects. Drawn up in 1964 but has been revised 5 times. All clinical trials should comply with these recommendations
  - **International Conference on Harmonisation Good Clinical Practice**
    - ICH - GCP is a set of rules designed to protect research subjects and validate data across the world
    - Publishes very detailed guidance on conduct, monitoring, auditing, recording, analyses and reporting of clinical trials

Involvement of consumers and the public

- key role of consumers at all stages of the trial process from design through recruitment to dissemination of results

- importance of increasing public understanding of trials - from schools to patients

Randomised controlled trials today

- Foundation of evidence-based medicine
- Increasing options in many diseases
  but, as cure is rare - need better treatments
- Most benefits only modest - need large trials to detect them reliably
- Need to decide which interventions to take into large trials

What are the main challenges?

- appropriate design to produce an unbiased reliable result
- enthusiasm from the clinical teams
- enough participants willing to join
- maintain adherence to trial treatment
- minimise loss from follow up
- sufficient funding!

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Any
Questions?