Clinical Trials

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Learning objectives

-How to approach designing a clinical trial

-How to identify a good idea for a clinical trial

-How to add research values to a clinical trial through sub-studies

Definition of clinical trial

‘A research activity involving the administration of a test regimen to humans to evaluate its efficacy and safety’.

The term is subject to a wide variation in usage, from the first use in humans without any controlled treatment to rigorously designed and executed experiment involving test and controlled treatment and randomisation

Types of treatment that can be tested in clinical trials

- Drugs
- Devices
- Surgery, Radiotherapy, physiotherapy etc
- Management strategies e.g. home vs hospital
- Alternative medicine e.g. homeopathy, acupuncture
- Disease prevention measures: drugs, vaccines, life-style interventions, education

Designing a trial

A clinical trial is (most) like…..

Similarities…… (positive)

- A (well-done) trial can have a transformational effect on scientific knowledge / (clinical practice)

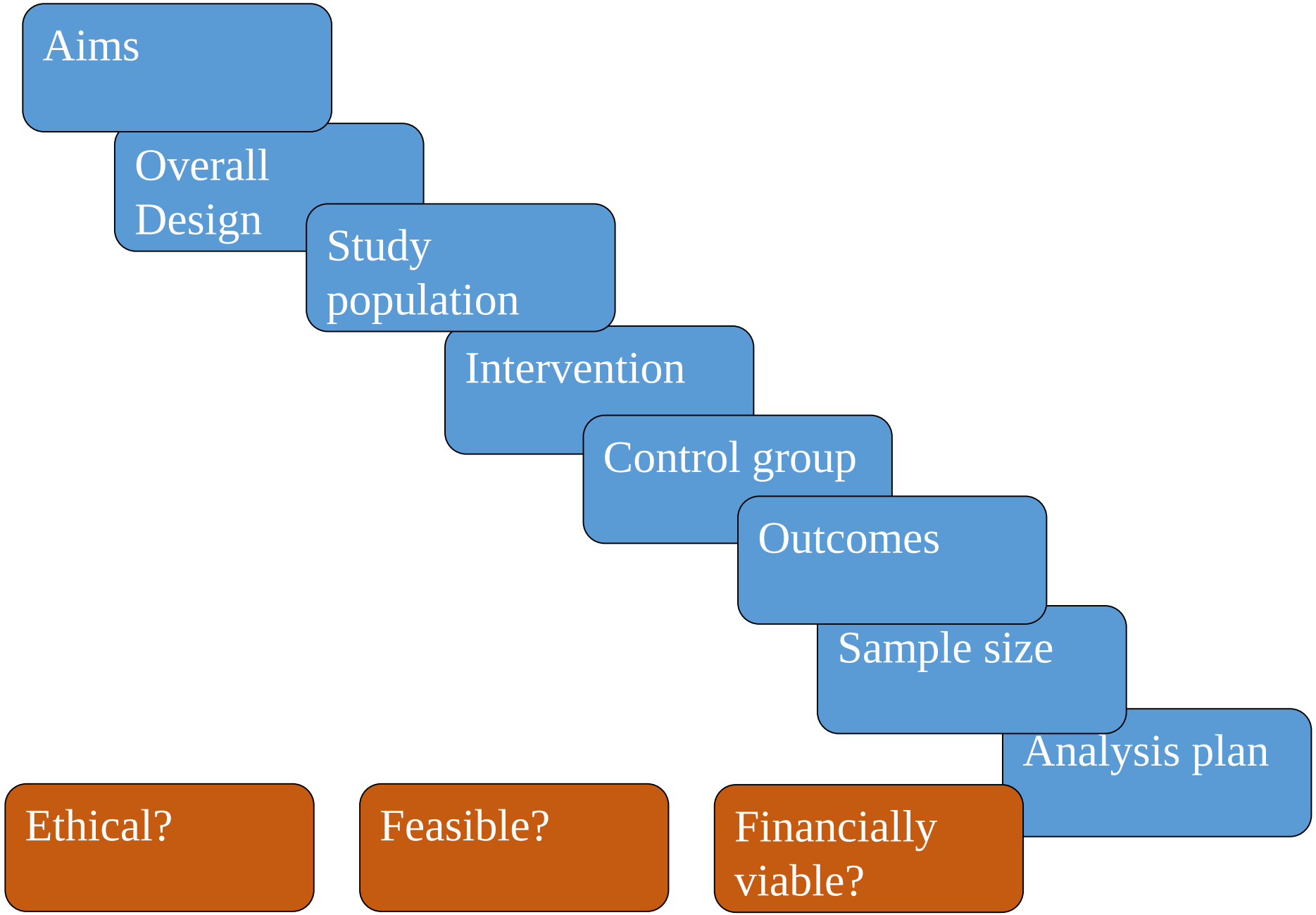
Similarities……(negative)

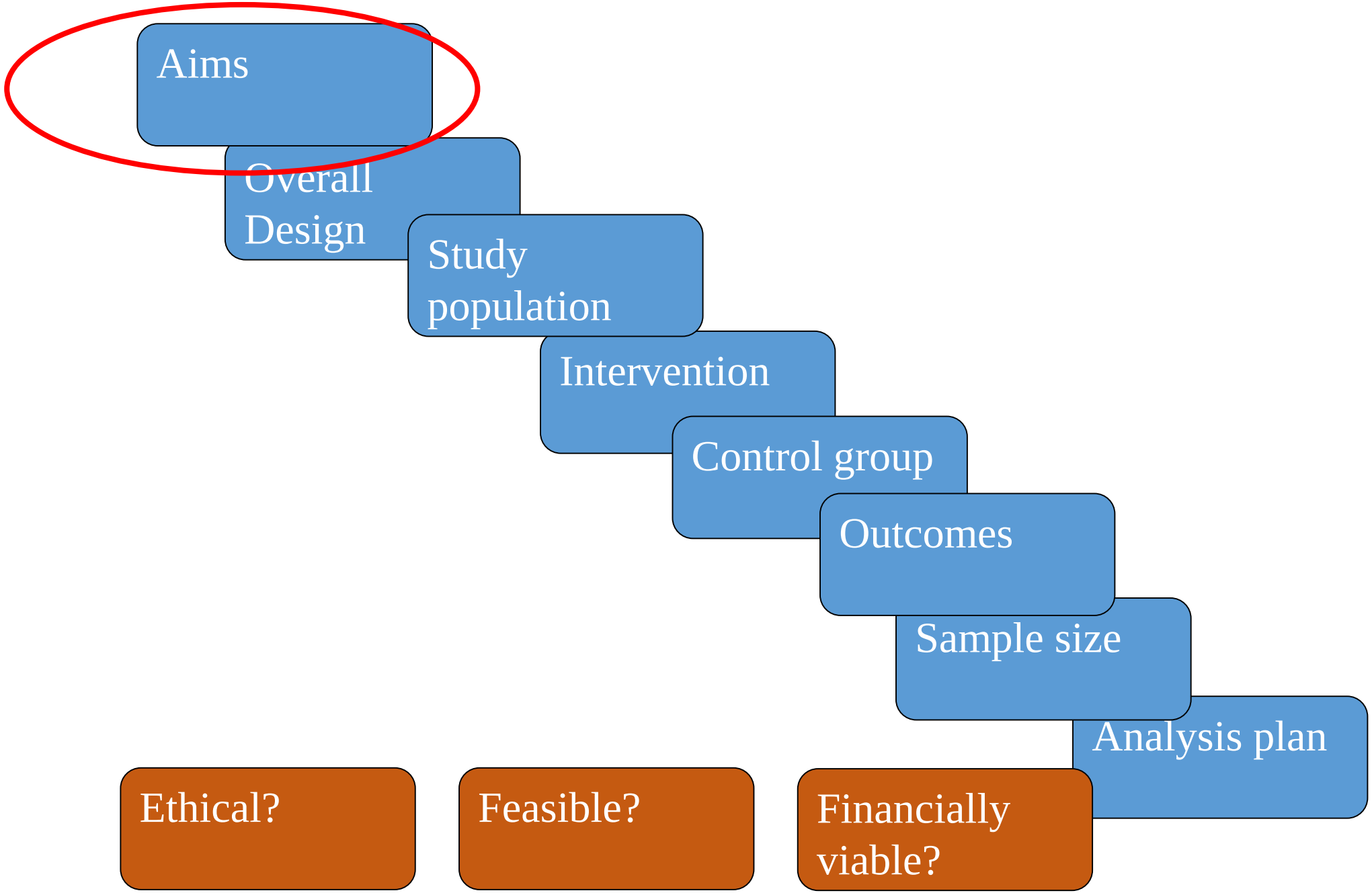
- Very expensive to do
- Very hard to get off the ground
- Very easy to go wrong when it gets off the ground
- Very hard to fix once its off the ground
- If it goes wrong can cause serious harm including…..

Colossal waste of money

Can give you a bad reputation!

- **Which of the following is <u>always</u> important in designing a clinical trial?**
- Defining exact characteristics of the trial participants
- Deciding on only one outcome to measure
- Including either an active or placebo control group
- Using an online sample size calculator to estimate sample size precisely
- Taking time to consider thoroughly all alternative design parameters


Aims
Overall Design
Study population
Intervention
Control group
Outcomes
Sample size
Analysis plan
Ethical?
Feasible?
Financially viable?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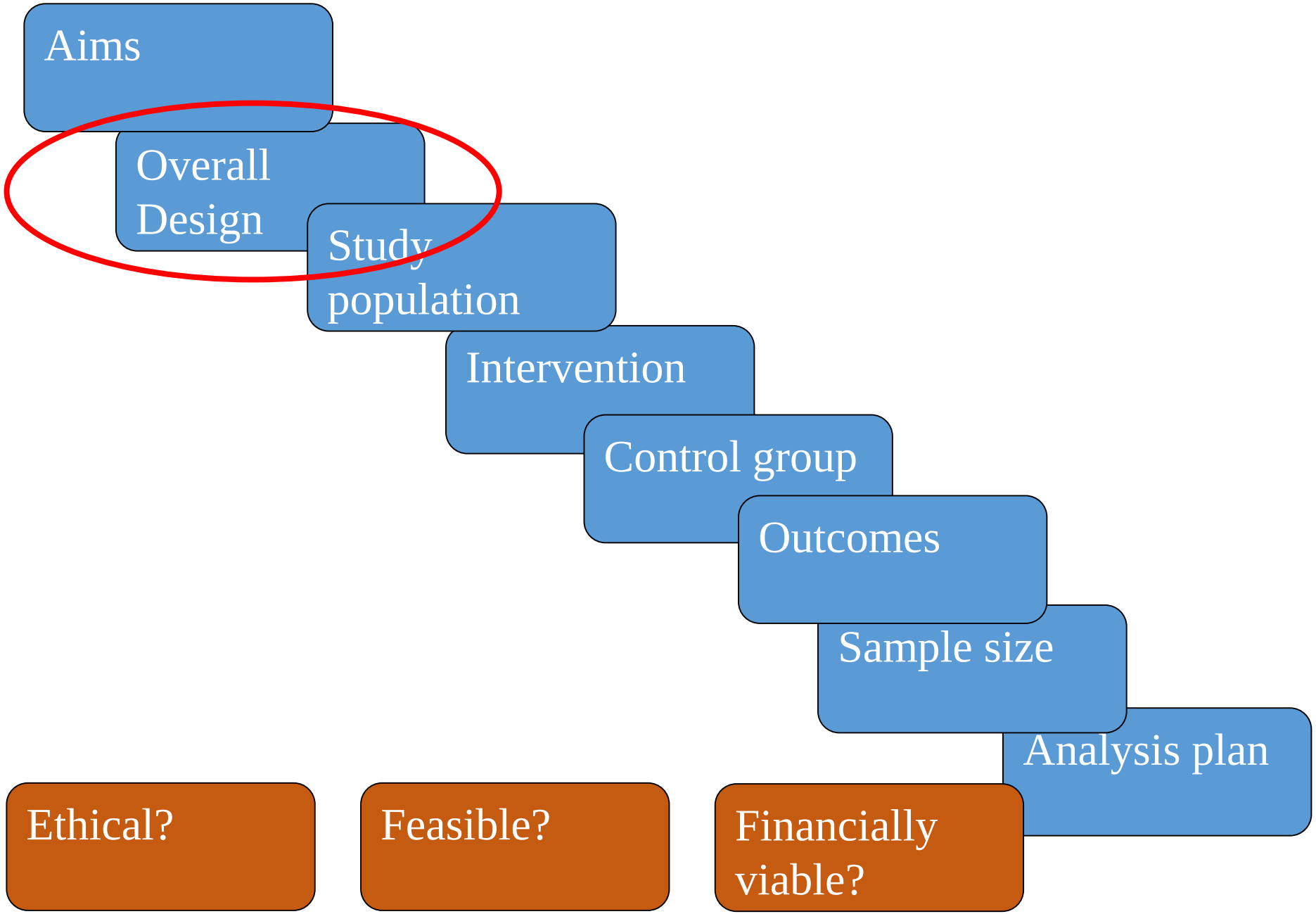
Defining aims

- What’s the question?
- Try to be as precise as possible – write it down.
- Keep referring to it when the debating aspects of the design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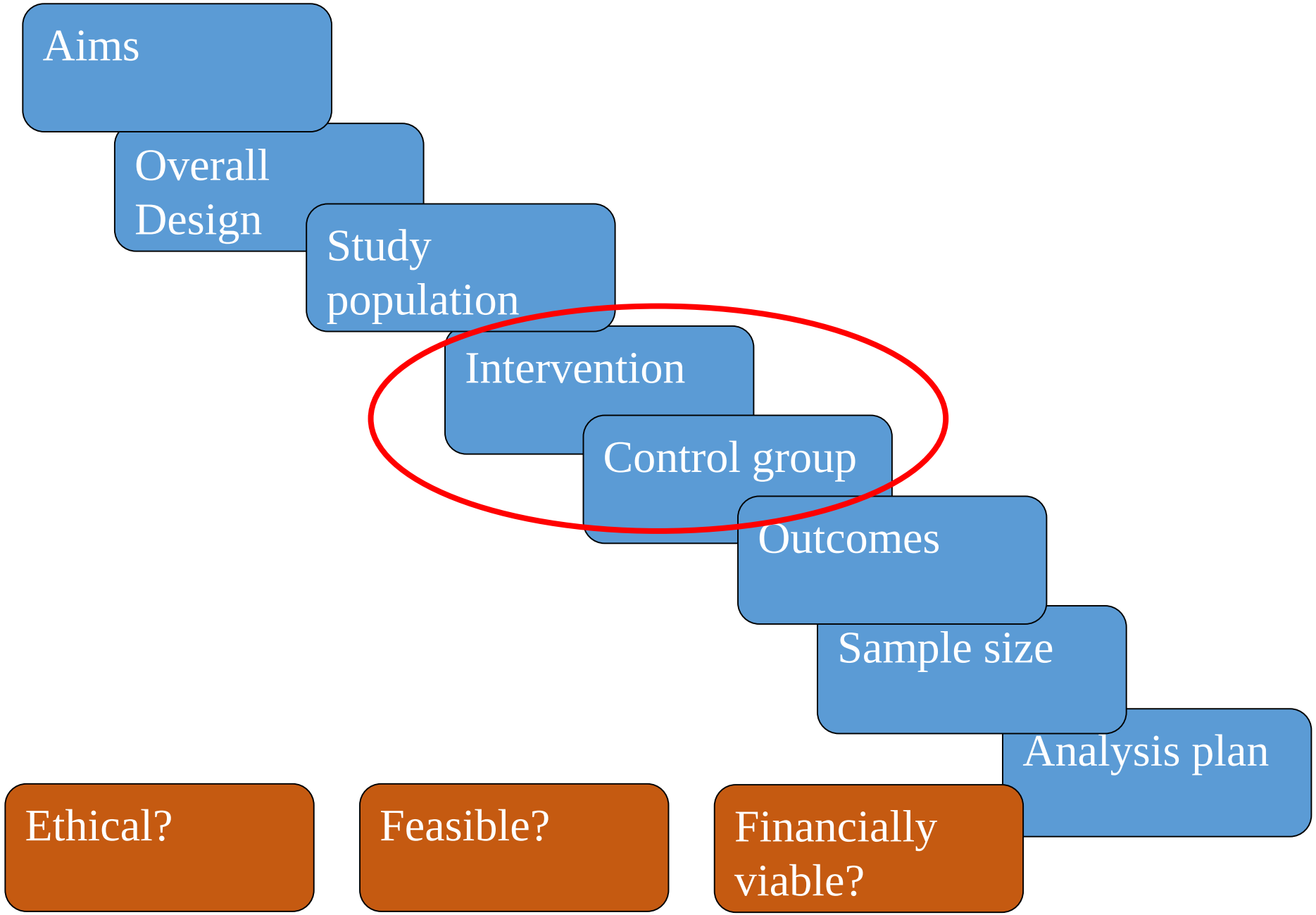
Overall design

- Single arm or control arm
- Parallel or crossover
- Superiority, non-inferiority, (equivalence)
- Phase
- Randomised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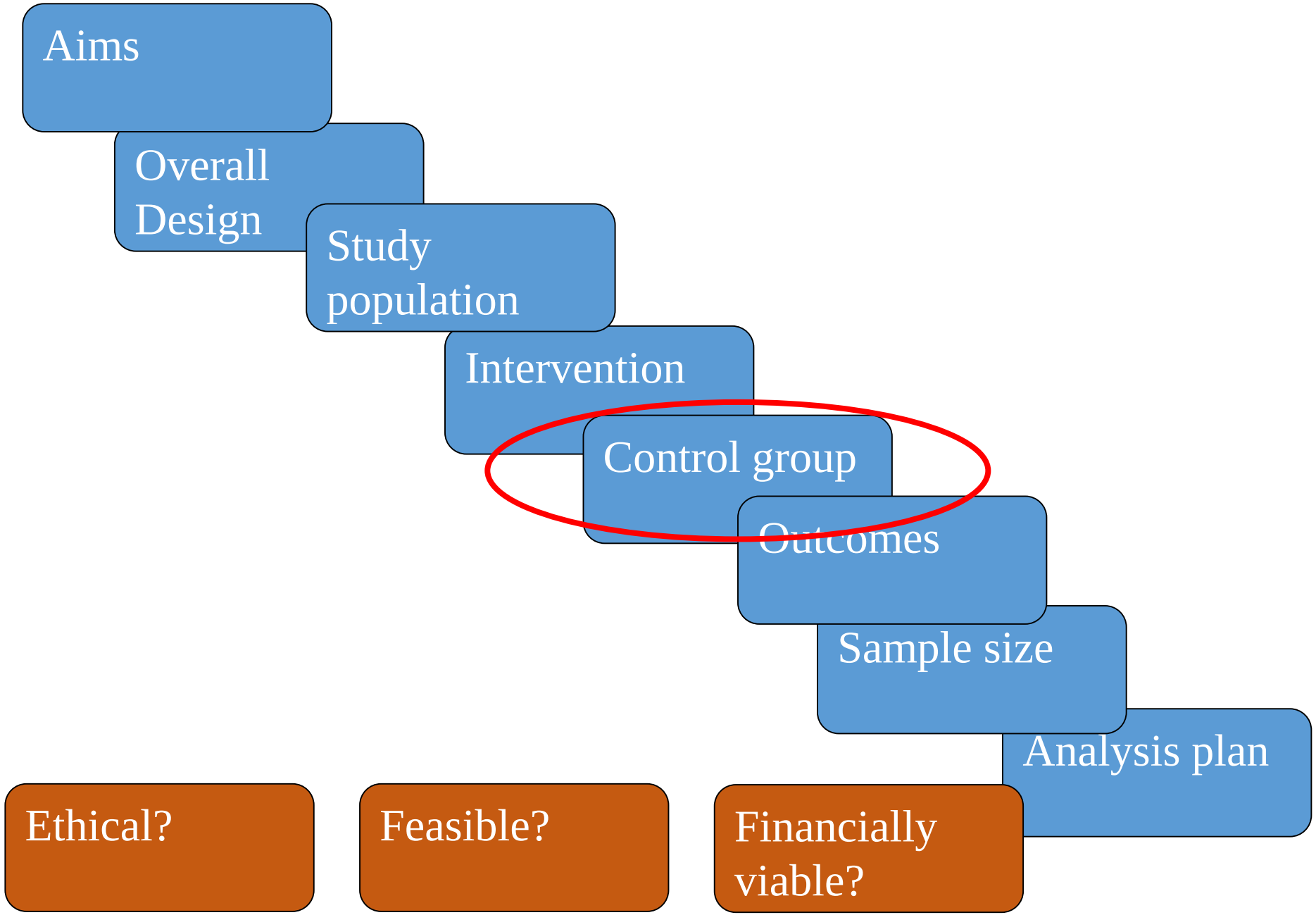
Intervention

- Defining the intervention
- Needs to be sufficiently precise to be replicable
- What's included in the "package"
  - Even with a drug trial may need to define other aspects of the intervention e.g. adherence, resistance testing selection of drugs
- Can be a complex intervention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Why need a control group?

- Without a control group cannot distinguish the effect of new treatment from:
  - spontaneous improvement over time
  - regression to the mean
  - placebo effect (increased care and attention)

Control group: historical

- Start using intervention X and compare outcomes with intervention Y that was in use before
- Multiple confounding factors:
  - Changes in practice over time
  - Changes in disease over time
  - Selection bias of patients given treatment : highly motivated, healthy lifestyle etc ….
  - Historical controls may not have same quality of follow up

Randomised Controls

Advantages of **randomisation**:

- Exclude selection bias

- Ensures no systematic differences between the treatment and control groups in known and unknown variables influencing the prognosis (confounding)

- Ensures that any difference in outcome between the different groups is due to differences in treatment

- And…..

Randomised controlled trial…

… sounds really great!

What is Randomisation?

- Allocation of patients to intervention and control (or 2 different interventions) by a purely chance process
- Not haphazard allocation
- Clinician should not be able to predict the allocation of the next participant

Randomisation practicalities

- Draw up randomisation list
- Then:
  - Codes in sealed opaque envelopes to be opened at site
  - (Consecutive drug allocation in pharmacies)
  - Administered by coordinating trial unit /pharma …sites fax or phone patient details to central office to get patient allocation

Randomisation difficulties

- Drug A vs Drug B…usually easy
- Drug vs placebo ….less easy
- Surgery vs no surgery

- Patient consent….want ”best treatment”
- Investigators’ prior beliefs: may refuse to randomise some / all patients
- Observational “evidence”, positive pilot study, animal studies ……

  do not give definitive answers, but may affect belief and make definitive trials hard to do
- Conflict between science (need to find out what’s best for future patients) and medical ethics (what’s best for the care of this next patient)

Blinding

‘Blinding aims to reduce the possibility of bias in the interpretation of symptoms and signs and in the management of the patients resulting from the knowledge of the therapy which the patient is receiving’

Blinding

- Open (label)
- Single blind
- “Double” blind: patient + treatment provider +
  - Those evaluating response
  - Data management team
  - Drug company / sponsor
  - Statistician?
  - Trial report writer?

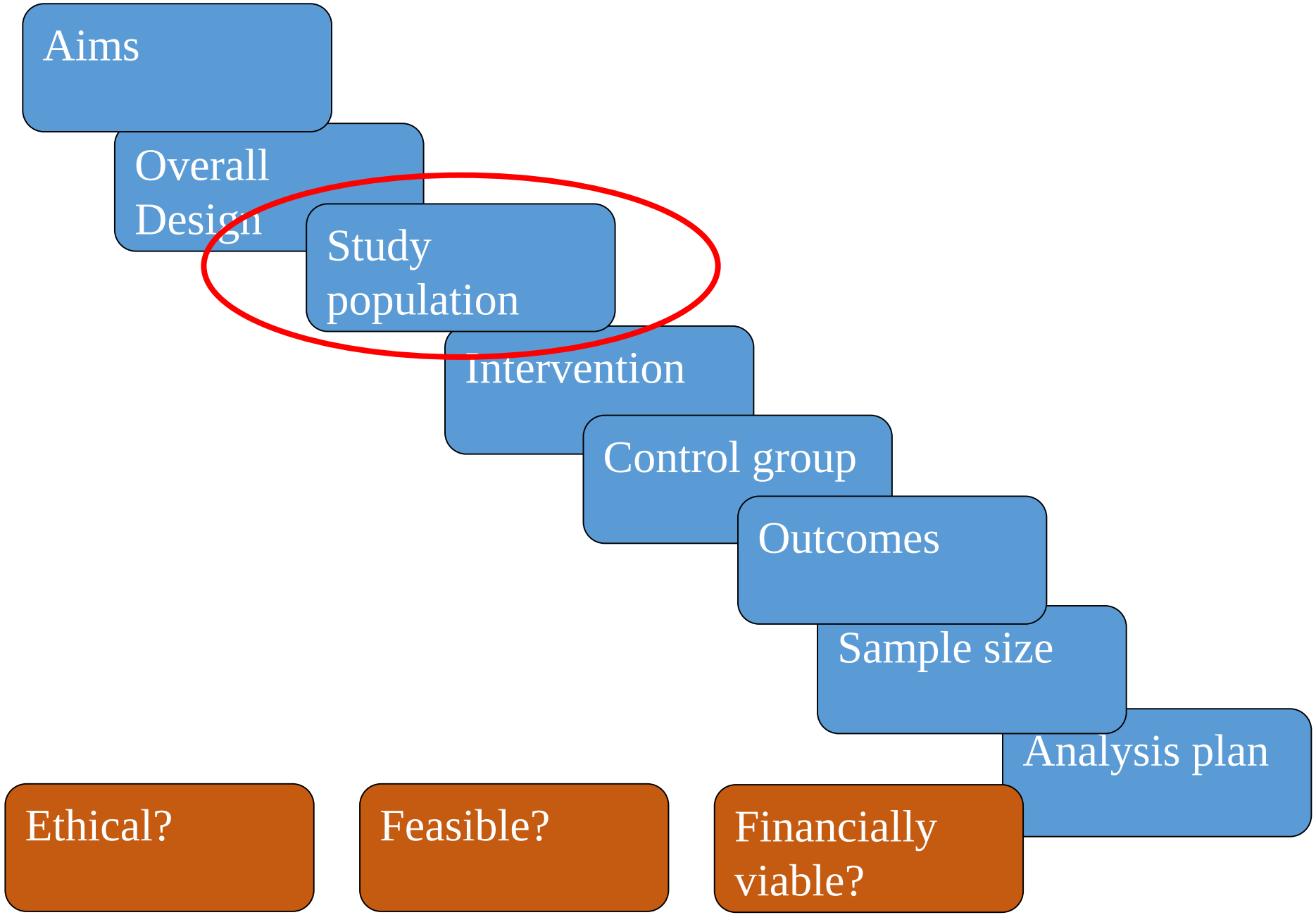
Blinded treatment packages prepared by central pharmacy

Code kept secret until end of trial

Can break code for individual patient safety

Blinding in drug trials

- Drug trials often double blind using placebo (identical in appearance to drug, but inactive)
- Problems with placebo:
  - unmasking of treatment e.g.. Taste, side effects
  - pooling of trial medication… may affect efficacy of treatment
  - Cost
  - May get complicated e.g. double dummy if comparing two treatments with different schedules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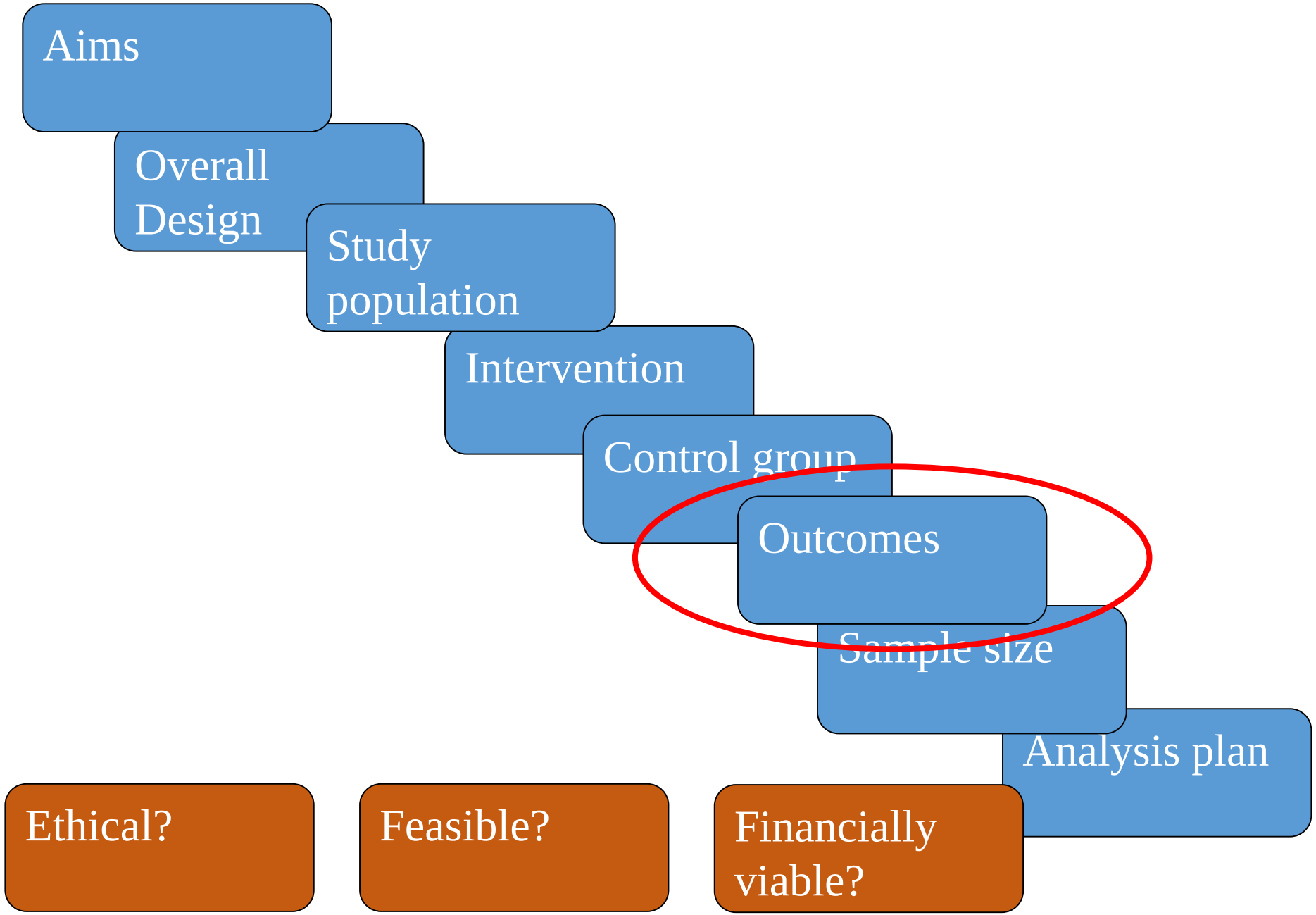
Defining the patient population

- Efficacy vs effectiveness trial
- Very tight criteria = may reduce variability so best chance of getting a clear answer (good for efficacy trial), but will reduce generalisability of trial results and make the trial recruitment harder
- Define population by inclusion and exclusion criteria (characteristic should appear in one list only)
- Should not be discriminatory (ethical issues)
- Should avoid vulnerable populations (unless clearly justified)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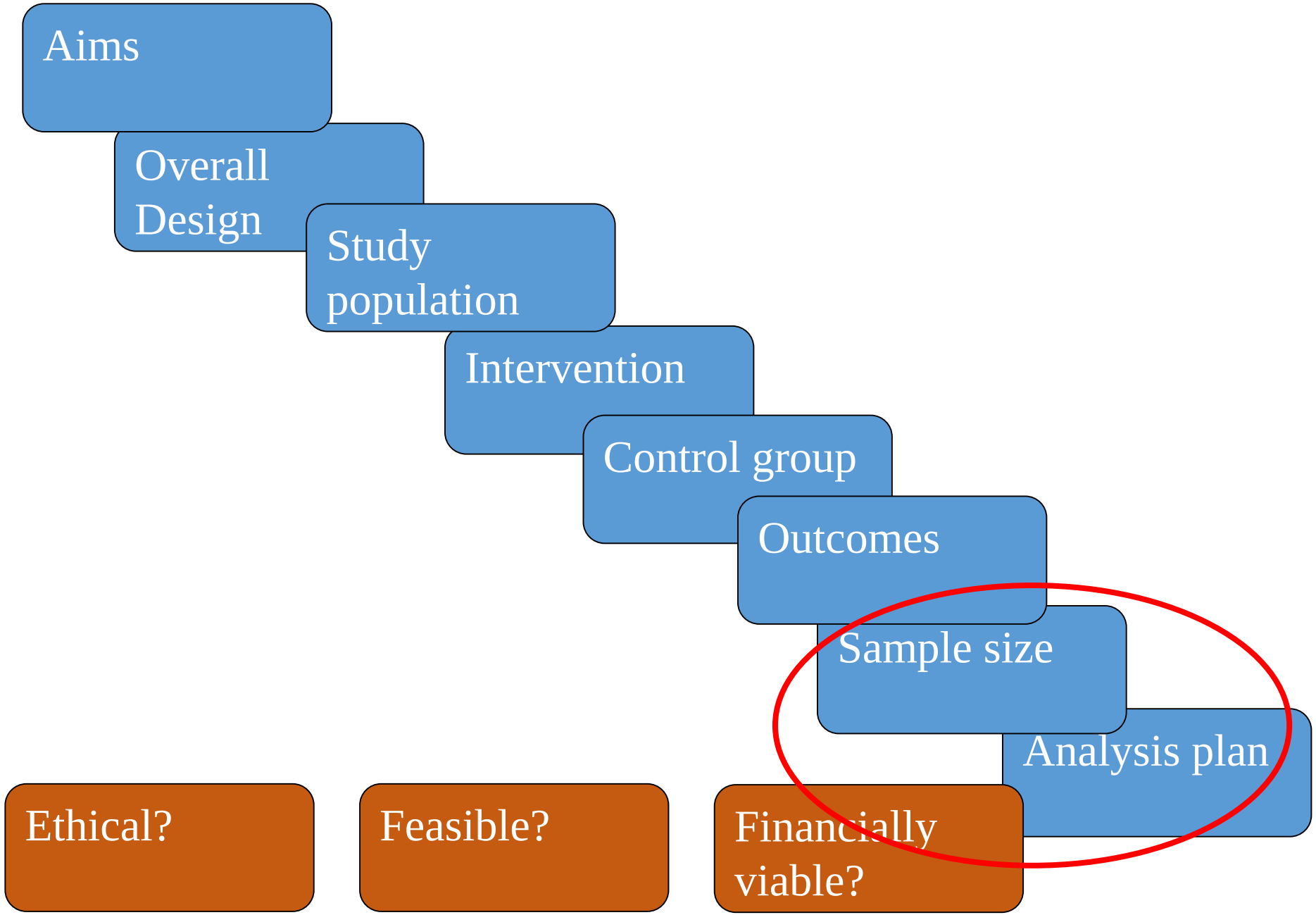
Define outcome parameters

- Clinical – which one?
  - Death
  - AIDS
  - Drug-related serious events?
  - Other serious clinical events
- Surrogate markers
  - CD4
  - VL
  - Other lab parameters

  - May have 20-30 endpoints
  - Need to define a single primary endpoint (can be a well-defined composite endpoint)
  - Other endpoints classified as secondary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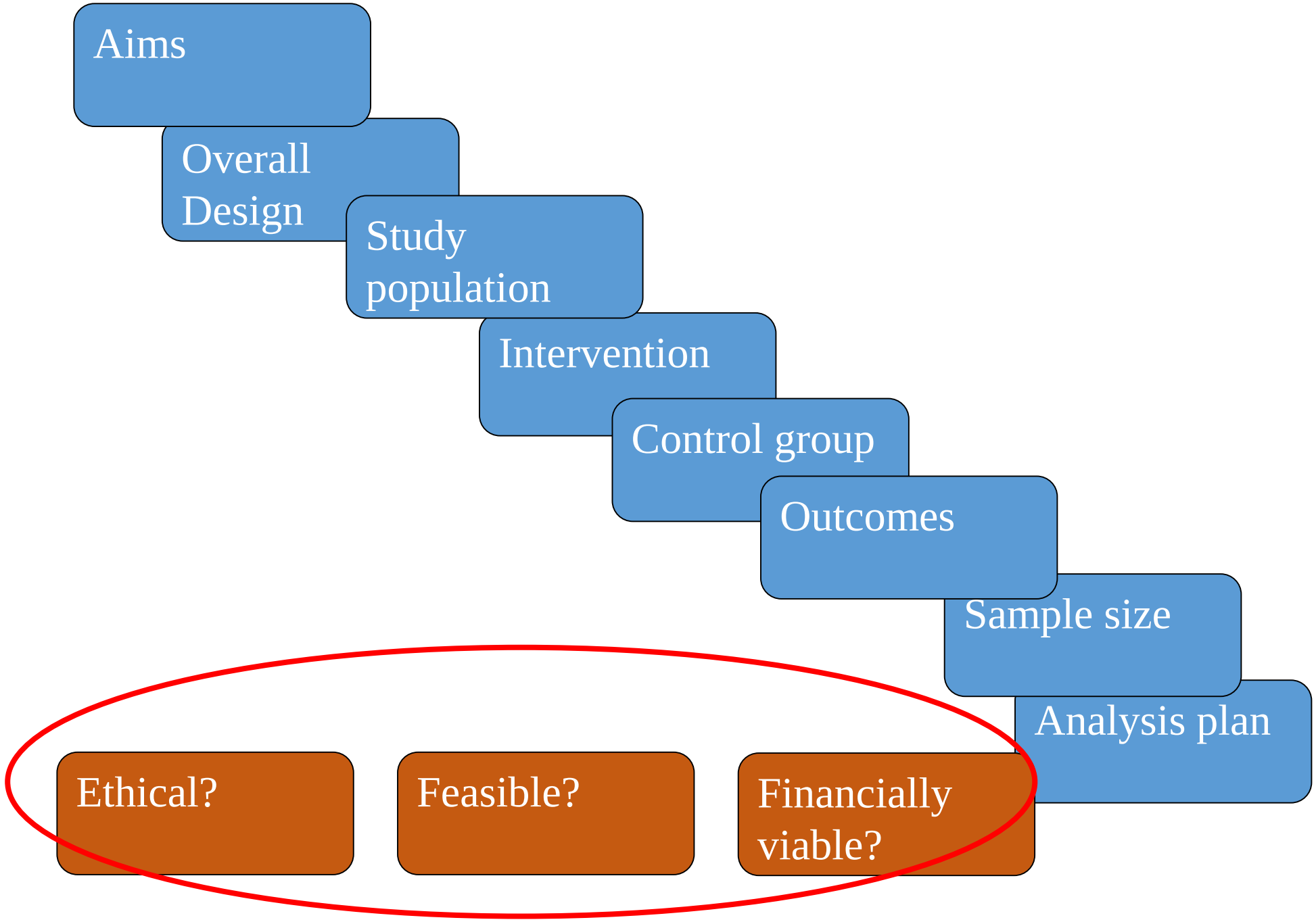
Sample size and analysis plan

Can do sample size yourself (online calculators) …but always check it with a statistician.

Have a statistician involved from the study design stage (especially if you're writing a grant!)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- Need to consider ethics,, feasibility and financial viability in parallel with designing the trial to end up with a viable trial

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Ultimately the key to success in a randomised controlled trial is ……

- Having a good idea
- Having lots of money
- Being able to survive on 6 hours sleep per day
- Something else?……

Ultimately the key to success in a randomised controlled trial is ……

Collaboration!

Why bother with all this?

- Well-designed and well-conducted RCTs
  - Are a huge amount of work
  - Are enormously costly
  - Are run to a scientific standard that is unparalleled in most other biomedical research
  - BUT
  - Provide the most rigorous clinical evidence
  - Change clinical practice
  - In the long run, are highly cost-effective