

CLINICAL TRIALS OF ANTIMICROBIAL AGENTS

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Why do Clinical Trials?

- Only in clinical trials can hypotheses of clinical efficacy and safety, based on in vitro and in vivo preclinical findings, be tested

Problems in Clinical Trials

- Low prestige value
- Patients included are often not representative - results have low external validity
- The investigators; poorly educated, not devoted, biased
- Lack of non-commercial funding - MRC and similar give very little or nothing

Low Prestige

- The academic value of clinical trials often downgraded
- What is more important than proving that a hypothesis based on preclinical findings can be translated into a safe and effective drug?

External Validity

- Patients included in a clinical trial represent a **sample** which ideally should be fully representative for a large **population** from which it was drawn. For example, in a trial of treatment of uncomplicated cystitis, results generated should be valid for all women with cystitis in the world - **THAT IS NEVER THE CASE**

Examples of validity problems:

- In trials of nosocomial pneumonia in ICU patients, mortality is often $<5\%$ - in real life it is $>25\%$
- In trials evaluating ceftriaxone for treatment of *H. influenzae* meningitis 3/400 patients died (2 on CTX and 1 on control regimen) - normal mortality is $\geq 5\%$

The Investigator

- Investigators are often happy amateurs; being a good basic scientist is not enough to make you a good investigator.
- Minimum requirements should include (i) thorough knowledge of the type of disease studied, (ii) familiarity with clinical trials biostatistics, (iii) detailed knowledge of GCP and (iv) willingness to put in time

Acceptance of Bias

- The investigator is always biased
- Reasons for an investigator to engage him/herself in a clinical trials are to prove that A is better than B or vice versa, i.e. we have a preformed opinion of the outcome.
- Bias should be accepted and eliminated through randomisation, controls and, whenever possible, blinding

Consequences of Bias

- In a randomised, open trial comparing 2 injectable cephalosporins, C1 and C2, in the treatment of nosocomial pneumonia, C1 was found to be related to significantly higher mortality than C2 ($\chi^2 = 11, p < 0.01$) using an analysis per protocol, i.e. each patient was analysed as treated.

- It was noted that many patients were had received wrong treatment, i.e. they were randomised to C1 but received C2 or vice versa. An intention-to-treat analysis in which all patients were analysed as randomised showed a χ^2 of 1.5 and a P-value >0.5 .

Lack of Funding

- Clinical trials are expensive
- No reason for industry to support trials of drugs which cannot lead to a patented claim
- NIH and MRC UK support large clinical trials but most similar organisations do not
- Lack of non-commercial support is a major problem

The Ideal Trial

Points to Consider

1. Background knowledge

- Must be documented in the trial protocol
- In 1970 there was published documentation proving reduced morbidity by antibiotic prophylaxis in colorectal surgery, in 1975 reduced mortality was proven. 1975-1979 at least 15 placebo or no treatment controlled trials were published,

- The trial protocol should include an introductory section describing the disease and the drugs studied; adequate references should be added.

2. Rationale and Trial Hypothesis

- The reasons for doing the trials, i.e. the expected benefits, should be described.
- A null hypothesis should be formulated, e.g. “Drug A (test) is not more than 10%-units more effective than Drug B (control) which is expected to be 80% effective with a type I error of 0.05 (2-sided) and a type II error of 0.20 (80% power)”

Type I (alpha) Error

- Risk of falsely rejecting the null-hypothesis; despite a finding of a significant difference, there is no difference in the population.
- Serious error since, if the endpoint is survival or the disease studied is serious, it is ethically difficult to repeat the trial.
- The type I error is normally (and arbitrarily) set at 0.05

Type II (beta) Error)

- The risk of falsely accepting the null-hypothesis, i.e. a difference exists in the population but was not detected in the sample.
- Very common error; too small samples
- Not a serious error - the study can be repeated
- Normally set at 0.1-0.2

3. Trial Design

- All trials should be prospective, controlled, randomised and, preferably, blinded

3.1 Controls

- All studies must be controlled unless standard treatment is known to give 100% result (e.g. gonorrhoea)
- The best control is placebo, which however cannot be used in most infections; when placebo is used the numbers of patients entered can normally be kept low

- Other controls are active drug or dose titrations
- Historical controls should be avoided; medicine changes with time.

3.2 Randomisation

- Allocation of patients to treatment by chance. Normally using computer generated chance sequences. Note that birth date, hospital admission number, every other patient, etc. are not randomisation.
- In open trials, use central randomisation (not envelopes)

3.3 Blinding

- Double-blind always best. Single-blind difficult. The more subjective the endpoint used, the more important to blind the trial. Open trials often necessary when injectable drugs are tested outside the U.S. (no hospital pharmacists)

4. Patient sample

- The sample size depends on the null-hypothesis (appr. 175 patients/group in the example)
- Don't forget exclusions before (not eligible, administrative reasons) or after (protocol requirements not fulfilled) randomisation

- The method by which patients are to be recruited should be described (from patients normally seeking attendance, by referral, by advertisements, etc.)
- The population from which the sample is drawn should be described in detail, e.g. epidemiology of infection studied socio-economic status, race, age, gender, etc.

4.1. Exclusion criteria

- Reasons for exclusion from entry
- Should be as few as possible - the more exclusion criteria, the lower the external validity
- Investigators and sponsors often disagree on exclusion criteria

4.2. Inclusion criteria

- Should be as wide as possible
- Often important to decide if community acquired or nosocomial infections are to be included

5. Trial Procedures

- The more deviations from normal clinical routines, the larger the risk of mistakes
- In trials involving several centres, methods used should be defined and standardised between centres
- Learn and follow GCP rules

5.1 Good Clinical Practice (GCP)

- Set of rules for execution of clinical trials
- Several versions (FDA, EU, etc) - all very similar
- Must be known in detail by all investigators

- Important details: (i) the investigator, not the sponsor has the main responsibility, (ii) all physicians involved in recruitment to a trial are investigators, (iii) CV must be supplied for all investigators, (iv) all data must be registered not only in a case report form (CRF) but also in patient records, (v) all data in CRFs must be verifiable, (vi) all data must be stored for at least 15 years

- All trials can (should) be monitored by the sponsor and/or external agencies
- A well educated research nurse is invaluable in the execution of a trial

5.2 Safety Registration

- Always register adverse events (AEs), i.e. everything which is negative during or after (normally up to 30 days) the trial
- Normal placebo AE frequencies are 25-40%
- Regulators and sponsors require classifications of related and unrelated events - subjective and not meaningful

- For laboratory data decide before the trial (i) normal limits, (ii) which events that are related to the disease treated (e.g. leukocytosis and CRP increase) and (iii) which values that constitute a serious event

6. Endpoints

- Only one can be the main endpoint since it is used for calculation of sample size
- Seek endpoints which are continuous (reduce sample size), e.g. time to death and no.of stools and, above all, objective and verifiable; avoid endpoints such as "cured"

7. Analyses

- In all phase III-V trials an intention-to-treat (ITT) analysis should be included but a per protocol (PP) analysis may very well be the main analysis
- All analyses must be decided upon and described before the randomisation code is broken - all other analyses are principally hypothesis generating

- All patients must be analysed - loss of <5% of patients due to "no data" disqualifies the trial.

7.1 Interim Analyses

- Should be avoided
- Should, when used, be described in detail in the protocol
- Should be performed by an external group
- Should, if possible, be blinded
- Should never be published - no salami!

7.1 ITT

- All patients randomised are analysed in the group to which they were randomised irrespective of treatment given (even if none).
- Results in ITT-analyses should show the same trends as PP-analyses

7.2 PP

- The more restrictive the evaluability criteria, the lower the external validity of the results; sponsors tend to strive for "clean" materials.
- Stepwise analyses - ITT, modified ITT, PP may be of value.

8. Ethics

- All trials must be approved by a research ethics committee; studies which are not prospectively approved should not be published
- All patients must give written informed consent prior to inclusion into the trial

9. Publication

- The protocol should give clear rules for publication of data - (i) who are responsible for manuscript, (ii) who should be authors and (iii) the influence of the sponsor

Conclusions

- Efficacy trials are important scientific projects
- Investigators must be adequately trained and must allocate the time needed
- Accept that you are biased
- Increase the active role of the investigators in design and analyses