1. Drug Literature Evaluation

General Principles
## 2. Classification of Clinical Studies According to Objective

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Phase of drug development</th>
<th>Activities undertaken (study objectives)</th>
<th>Study examples</th>
</tr>
</thead>
</table>
| Clinical pharmacology | I | Initial safety studies and pharmacokinetic (PK) / pharmacodynamic (PD) characterisation [usually in healthy volunteers] | ➤ Dose-tolerance studies  
➤ Single- and multiple-dose PK/PD studies  
➤ Studies of PK-PD relationships  
➤ Drug interaction studies |
| Therapeutic exploratory | IIa | Pilot clinical trials to evaluate efficacy and safety [selected patients with target disease] | ➤ Short-term efficacy / proof-of-concept studies  
➤ Dose-response studies  
➤ Definition of endpoints for longer-term studies |
| | IIb | Randomised, controlled trials to evaluate efficacy/safety [usually small-scale studies in patients with target disease] | ➤ Comparative efficacy/safety studies (vs placebo or other/standard drugs)  
➤ Identification of disease subtypes for which drug is particularly effective  
➤ Definition of goals for longer-term studies |
| Therapeutic confirmatory | IIIa | Randomised, controlled trials in relatively large numbers of patients, or smaller trials in special groups of patients | ➤ Comparative efficacy/safety studies (vs other/standard drugs)  
➤ Studies of mortality/morbidity outcomes  
➤ Evaluations in special populations (e.g. elderly) |
| | IIIb | Clinical trials that supplement earlier trials and establish risk-benefit profile | ➤ Further evaluations of efficacy/safety profile (including comparisons vs other drugs)  
➤ Quality-of-life studies  
➤ Initial pharmaceconomic studies (cost-effectiveness/cost-benefit) |
| Therapeutic use | IV | Studies to provide additional efficacy/safety data (e.g. risk-benefit profile in special groups), refine dosing recommendations, or identify less common adverse events | ➤ Further studies to confirm efficacy/safety in everyday clinical practice  
➤ Further comparisons vs other drugs  
➤ Studies of additional endpoints/new indications  
➤ Postmarketing surveillance studies  
➤ Studies of drug utilisation patterns |
3. Why Well-designed Controlled Clinical Trials Are Mandatory:

Responses to Drugs in Individual Patients May be Affected by Numerous Factors

- The natural progression of the disease (relapsing-remitting)
- Drug factors:
  - pharmacodynamic variability – e.g. differences in receptor sensitivity, altered homeostatic mechanisms
  - pharmacokinetic variability – inter-individual differences in absorption, distribution, metabolism, excretion (ADME)
  - interactions with environmental factors or other drugs
  - differing drug-gene interactions
- Non-drug factors:
  - personality, beliefs and attitudes of the patient
  - patient’s prior experience of doctors and drugs, and his/her expectations of the treatment prescribed
  - personality, beliefs and attitudes of the clinician
  - the clinician’s explanation of the treatment to the patient.
4. Purpose of Controls in Clinical Trials

- Controls allow patient outcomes due to the test treatment to be differentiated from outcomes due to other factors, e.g.:
  - natural progression of disease
  - patient or clinician expectations
  - other treatments

- Control group experience tells us what would have happened to patients had they not received the test treatment

- In this regard, a concurrent control group – one chosen from the same population as the test group – is preferable to an historical control group in most situations (as circumstances, e.g. natural history of the disease and treatments may have changed over time).
5. Key Control Measures:

(1) Randomisation

- Key design feature to minimise the influence of patient variability
- Random allocation of patients to the different study groups helps to ensure that the test treatment and control groups are similar at the start of the study (baseline)
- Randomisation minimises the influence of any systematic differences between the study groups that could affect the outcome of the study (including either known or unknown baseline variables)
- Randomisation also eliminates bias in treatment assignment and helps ensure like treatment groups
6. **Key Control Measures:**

(2) **Blinding (masking) of treatments**

- Blinding minimises the possibility of biases, either on the part of the patient or the investigator, affecting the outcome of the study.
- In the absence of blinding, knowledge of the treatment assignment could result in patients:
  - reporting more/less favourable treatment outcomes
  - being more/less likely to continue their participation in the study
- Knowledge of the treatment assignment could influence investigator decisions regarding:
  - assessment of the therapeutic response
  - assessment of adverse events
  - the need for ancillary treatments during the study
  - the thoroughness of patient follow-up
  - inclusion or non-inclusion of certain results in the analysis.
7. Types of Clinical Trial Designs

1. Single patient group (single-arm) designs – sometimes referred to as ‘observational cohort studies’:
   - All patients are treated with the same drug (open-label design – no randomisation or blinding)
   - Not appropriate to establish efficacy or safety versus no treatment or versus other treatment options
   - For comparative purposes, historical controls can be considered but are less satisfactory than concurrent controls – as confounding factors and biases may enter the trial and cannot be allowed for
   - Appropriate to study dose-responsiveness or concentration-effect relationships, and for long-term toxicity studies – where patients are compared with their own baseline data.
8. Types of Clinical Trial Designs (continued)

2. Two (or more) patient group designs

A. Parallel-group (parallel-arm) studies:

- Patients are randomised to one of two (or more) treatment groups, and usually receive the assigned treatment throughout the trial (though not always; sometimes there may be a crossover of treatments, e.g. placebo to active drug, in one treatment group).

- Applicable to most clinical situations – most commonly used design for establishing efficacy and/or safety.

- Assess between-patient differences.

- ‘Robust’ enough to cope with the many problems that occur in clinical trials – e.g. dropouts, missing data, etc.
2. Two (or more) patient group designs (contd.)

B. Crossover studies:

- Patients receive each treatment – randomised to one or other first, and then crossed over after an adequate ‘washout’ period in between.
- Assess within-patient differences – drug effect is expressed as difference between responses to the two treatments.
- Variability of data less than with parallel-group studies, and fewer patients are required to detect statistically significant differences between treatments.
- However, not as ‘robust’ as parallel-group studies as adversely affected by dropouts, missing data, etc.
- Also, statistical analysis requires consideration of possible ‘carryover’ and ‘treatment order’ effects.
10. **Parallel-group and Crossover Trial Designs**

Controlled trials comparing 2 drugs/treatments

**Parallel-group design**

- Run-in
- Randomisation
- Drug A
- Drug B
- Final Assessment

**Crossover design**

- Run-in
- Randomisation
- Drug A
- Drug B
- Washout
- Drug B
- Drug A
- Final Assessment 1
- Final Assessment 2
11. **Crossover studies – when is this design useful?**

*Key requirement:* Patients must be able to return to the identical pretreatment state for the second phase (or as close to it as possible)

**Useful in:**
- Chronic stable conditions, e.g. asthma, epilepsy, migraine
- Studies of short-term effects of therapy
- Bioequivalence investigations

**Not useful in:**
- Studies of long-term effects of drug therapy
- Studies of possible disease cure or prevention of death.

For which of the following could a crossover design be considered for studying drug efficacy?

1. Analgesics for postoperative pain
2. Analgesics for menstrual pain
3. Topical antibiotics for a bacterial skin infection (e.g. impetigo)
2. Two (or more) patient group designs (contd.)

C. Sequential analysis:

- Generally involves allocation of study participants progressively to the test treatments (sample size may not be fixed in advance)
- This design allows a trial to be continually monitored and stopped, in accordance with pre-defined stopping rules, when a clinically significant result is achieved or when significant harm is detected
- Numbers of patients needed can be kept to a minimum, and a significant result can often be obtained more rapidly
- However, the design assumes that there is a significant difference to be detected. There may not be
- Not commonly used nowadays – except perhaps in medical emergencies (e.g. head injury) or less common/rare conditions.
14. Factorial Study Design

Allows the evaluation of more than one intervention in a single study

ISIS-2 Study in Acute Myocardial Infarction (2 x 2 Factorial Study)

Patients with acute MI

Randomisation 1

Group 1:
Aspirin + streptokinase

Aspirin (oral) → Randomisation 2

Group 2:
Aspirin alone

Placebo inj.

Group 3:
Streptokinase alone

Streptokinase inj.

Group 4:
Placebo only (neither)

Placebo inj.

Placebo inj.
15. Evaluation of Clinical Trials: Important Principles

- Controlled clinical trials in diseased patients are mandatory to reliably establish the efficacy and safety of drugs in clinical practice.

BUT . . . .

- Controlled trials vary considerably in their "acceptability".

- This varying acceptability can make interpretation of their findings difficult.
16. Evaluation of Clinical Trials: Important Principles (continued)

- The fact that a trial is stated (in the title) to be a “randomised” and/or “double-blind” study does not guarantee that the results will automatically be beyond reproach.

- Many factors other than the basic design of a trial influence the adequacy of the results and how they should be interpreted.
17. General Principles of Clinical Trial Evaluation

- Any individual trial provides only limited information
- One study cannot provide all the evidence
- Statements made by authors must always be critically evaluated.
## Improvement Rates Reported in 239 Clinical Trials of Antidepressant Drugs:
### An Example of a Misleading Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of trials</th>
<th>Percentage of patients improved (via rating scale assessment)</th>
<th>Median %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10-19</td>
<td>20-29</td>
</tr>
<tr>
<td>Imipramine</td>
<td>92</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>31</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Desipramine</td>
<td>28</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>13</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>30</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>22</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
19. Key Questions in Evaluating Clinical Trials

- What is the value of the trial in terms of new knowledge?
- What is the overall quality of the data?
- Does it adequately address the aims and objectives and support the conclusions reached?
- Were the endpoints appropriately chosen, and were the data analyses reliably performed?
- Are the interpretations and conclusions justified?
- Are the extrapolations reasonable?
- Are the results likely to affect clinical practice or other research activities?
- Overall, how much emphasis should be placed on the findings?
20. Overall Assessment

- Well-conducted study providing acceptable and clinically relevant results
  *Major emphasis*

- Adequate study but some aspects missing or unclear – some doubts about acceptability or clinical relevance of the results
  *Medium emphasis*

- Poorly conducted study and/or results not clinically relevant or acceptable
  *Low emphasis*
21. Important General Requirements of Clinical Trials

- Appropriate controls (e.g. to minimise interindividual variability and potential biases)
- Appropriate methods of assessing therapeutic effects (i.e. clinically relevant outcome measures were used)
- Sufficient number of subjects (to give it adequate statistical power)
- Homogeneous population
- Appropriate duration of treatment
- Appropriate dosages
- Appropriate methods of assessing/measuring adverse events
- Appropriate statistical validation.
Checklist for Assessing a Therapeutic Trial Report

Notes:

1. All the items listed below will not be needed in assessing any individual report. The user must therefore identify which items are not applicable when evaluating a given report. Those items of most relevance will depend on the particular disease and/or drug being investigated. One (or more) items may well be of crucial importance.

2. Items additional to those listed below may sometimes apply.

3. The list is not only useful in helping to assess the merits of any one report, but is also of value to reconcile any clash of evidence between one report and another, as any differences will immediately become apparent.

4. The checklist below has been designed for assessing both clinical trials and adverse reaction reports.

5. In assessing each item, Y = Yes (clearly and unambiguously stated); N = No (not mentioned or not clearly stated) and D = Doubtful (uncertain). Where the answer to missing information can be perceived by intuition based on related information provided by the authors, the 'Doubtful' category should be used.

Part I. Checklist of Basic Requirements: Is the Information Present?

<table>
<thead>
<tr>
<th>Aims of the trial:</th>
<th>Y</th>
<th>N</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Aim(s) clearly stated?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population studied: is the following information provided?</th>
<th>Y</th>
<th>N</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Healthy individuals or patients?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.2 Volunteers or not?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 Age?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 Sex?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 Race?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6 Nature of disease being treated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.7 Criteria for patient selection?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8 Criteria for patient exclusion?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9 Presence of disease(s) other than that being treated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.10 Whether additional treatments were given?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

etc.
23. Aims and Objectives of Trials

- The aims may vary from trial to trial but must always be very carefully formulated before the start of the study.
- The aims should be to answer ONE precisely framed question or test ONE precisely stated hypothesis – with perhaps one or two subsidiary questions/hypotheses.
- *As a generalisation*, the more questions that are posed initially, the more complicated the trial becomes and the more likely it is to break down in practice and not answer the questions posed.
### Frequency of Adverse Events by Method of Questioning

<table>
<thead>
<tr>
<th>Method of eliciting adverse events</th>
<th>Reported to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physician</td>
</tr>
<tr>
<td>Patients asked how they felt and if any physical complaints experienced</td>
<td>72</td>
</tr>
<tr>
<td>Patients asked about any specific organ effects (e.g. anything in chest, etc.)</td>
<td>34</td>
</tr>
<tr>
<td>Observer reads off a checklist and asks whether patients had experienced these events</td>
<td>353</td>
</tr>
</tbody>
</table>
25. Adverse Events (AEs): Severity versus Seriousness

Severity of AEs:
- Mild – the AE is easily tolerated and does not interfere with usual activity
- Moderate – the AE interferes with daily activity but the patient is still able to function
- Severe – the AE is incapacitating and/or the patient is unable to work or complete usual activities

Serious AEs (SAEs) – untoward occurrences that:
- Result in death
- Are life-threatening (patient is at risk of death at time event occurred)
- Require hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/ incapacity
- Qualify as a congenital abnormality or birth defect
- Are considered important or significant (medical judgement) and/or require specific intervention(s) to prevent other serious outcomes
26. Adverse Events (AEs): Relationship to Study Drug (all-cause vs drug-related AEs)

- Treatment-emergent AEs = all categories
- Treatment-related AEs = 1, 2 or 3

1. **Definitely related to drug:**
   - Evidence of exposure to drug
   - Temporal relationship reasonable
   - Most likely explanation for event
   - Dechallenge is positive
   - Rechallenge (if feasible) is positive

2. **Probably related to drug:**
   - Evidence of exposure to drug
   - Temporal relationship reasonable
   - Event more likely due to drug than to other causes
   - Dechallenge is positive

3. **Possibly related to drug:**
   - Evidence of exposure to drug
   - Temporal relationship reasonable
   - Another cause equally likely
   - Dechallenge is positive

4. **Probably not related to drug:**
   - Evidence of exposure to drug
   - Another cause is more likely
   - Dechallenge is negative/unclear
   - Rechallenge is negative/unclear

5. **Definitely not related to drug:**
   - Drug not received or temporal relationship not reasonable
27. Controls

- Whichever control methods are used in a trial, they must be both valid and suitable to its aim(s).

- Patients: concurrent controls are preferable to historical controls.

- Historical controls are, in most cases, not appropriate since with the passage of time, many variables may have changed during the course of the disease or influenced the outcome of treatment.

- Randomisation: random allocation does not necessarily guarantee like groups of patients in parallel-group studies, and it is ESSENTIAL to show that the treatment groups were comparable before the trial began.

[Note: Not essential for crossover studies, but it is advisable to show that the groups receiving the different treatments first are comparable].
28. Adequacy of Control Measures

- **Adequacy of randomisation procedure:**
  - What method was used to allocate treatment – computerised random number generation, random number tables, interactive web-based or voice response system (IWRS/IVRS)? Were the patients stratified?
  - How was the randomisation concealed from the investigators – e.g. non-specific medication labels; sequentially numbered containers?
  - This information should be provided (albeit briefly) in the study report – if not, “selection bias” can’t be totally excluded

- **Adequacy of “blinding” technique:**
  - Is the type of blinding stated – e.g. single-blind, double-blind, observer blind. If some key study personnel cannot be blinded, were there independent outcome assessors and were they appropriately blinded?
  - How was blinding achieved – e.g. matching drugs or a double-dummy technique?
29. **Blinding Techniques**

Comparison of 2 drugs, X and Y, with different dose frequencies:

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>‘Double-dummy’ Technique</strong></td>
<td>1. <strong>tid</strong> 2. <strong>bid</strong> X-active + Y-placebo</td>
<td>1. <strong>tid</strong> 2. <strong>bid</strong> X-placebo + Y-active</td>
</tr>
<tr>
<td><strong>Morning:</strong></td>
<td>X-active + Y-placebo</td>
<td>X-placebo + Y-active</td>
</tr>
<tr>
<td><strong>Midday:</strong></td>
<td>X-active</td>
<td>X-placebo</td>
</tr>
<tr>
<td><strong>Evening:</strong></td>
<td>X-active + Y-placebo</td>
<td>X-placebo + Y-active</td>
</tr>
</tbody>
</table>

5 tablets per day
[2 containers per patient]

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>‘Matching Drugs’</strong> (X and Y reformulated to look the same, e.g. in opaque capsules)</td>
<td>1. <strong>tid</strong> 2. <strong>bid</strong> X-active + Y-placebo</td>
<td>1. <strong>tid</strong> 2. <strong>bid</strong> X-placebo + Y-active</td>
</tr>
<tr>
<td><strong>Morning:</strong></td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Midday:</strong></td>
<td>X</td>
<td>Y (placebo)</td>
</tr>
<tr>
<td><strong>Evening:</strong></td>
<td>X</td>
<td>Y</td>
</tr>
</tbody>
</table>

3 capsules per day
[1 container (e.g. a blister pack) per patient]
30. Adequacy of Control Measures (continued)

- Patient exclusions after randomisation:
  - were any patients excluded during the trial?
  - if so, are the reasons stated – e.g.:
    - protocol deviations, dropouts, losses to follow-up, etc.
    - withdrawals due to adverse events
    - withdrawals due to lack of efficacy
    - poor compliance (compliance within the range 80% to 120% is generally considered ‘acceptable’ in clinical trials)
  - have patient exclusions been taken into account in analysing the results, both for efficacy and safety?
  - which patient population has been analysed – the “intention-to-treat” (ITT) or the “per-protocol” (PP) population, or both?
31. **Intention-to-treat (ITT) versus Per-protocol (PP) Analysis**

**ITT analysis:**
- Unbiased method of assessment (analyses all patients according to the group to which they were randomised)
- Assesses the overall consequences of each treatment regimen (takes account of all post-randomisation events, including non-compliance)
- Corresponds to pragmatic management trials (reflects everyday clinical practice)
- *Justifiable exclusions:* those who did not receive at least one dose of study medication, and those with no post-randomisation data. If so, the analysis group may be termed the ‘full analysis set’ (FAS) or the ‘modified ITT’ (mITT) population

**Per-protocol analysis:**
- Includes only those patients who complied with the protocol and provided primary clinical endpoint data, without major violations
- Patients who deviate from the protocol and may therefore influence estimation of the true drug effect are excluded
- Maximises opportunity to show efficacy – gives an indication of the true effect of the test drug since it will have been taken as intended
- May be biased if non-adherence to the protocol is related to lack of efficacy or the occurrence of adverse events
32. Handling of Missing Data: Last Observation Carried Forward (LOCF) Analysis

- Data analysis method for patients who discontinue from the trial or where data are missing
- Uses the last recorded parameter – or a mean of the last parameters – as the value applicable at the time of discontinuation
- Attempts to provide the best estimate of the patient’s condition at the time of discontinuation
- Important for those patients who discontinued for lack of efficacy.
33. **ITT versus Per-protocol Treatment Response Analysis: Key Points**

**ITT analysis** (most commonly applied method in clinical trials):
- Includes results for all patients who are randomised to treatment
- Takes into account data up to the time of withdrawal for dropouts *(NB. if LOCF technique applied, the last recorded values are used)*
- Tends to underestimate actual treatment effect in practice *(renders a more conservative result than PP analysis, and doesn’t quantify true drug effect, but may more closely reflect everyday clinical practice)*

**Per-protocol (PP) analysis** (may be fully appropriate in some situations):
- Includes results only for patients who completed the study and for whom full follow-up data are available
- Missing values for major protocol violators/non-compliers are disregarded *(NB. these patients must be differentiated from treatment failures and withdrawals due to adverse events)*
- Tends to overestimate the actual treatment effect in practice *(doesn’t take into account possible non-compliance/defaulting by patients)*
- Useful as a sensitivity or supportive check of the ITT analysis to evaluate the influence of protocol violations on the results.
34. Assessment of Study Bias: (Cochrane Collaboration Criteria)

Six domains of a clinical trial to consider in assessing the risk of bias. Assess each as:

1. Adequate: all criteria adequately met = **low risk** of bias
2. Unclear or criteria only partially met = **unclear risk** of bias
3. Inadequate: criteria not adequately met = **high risk** of bias

<table>
<thead>
<tr>
<th>Type of bias</th>
<th>Potential source of bias</th>
<th>Criteria to assess</th>
<th>Key questions to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Selection bias</td>
<td>Random sequence generation (randomisation procedure)</td>
<td>Method used to generate the allocation sequence</td>
<td>? Appropriate to produce comparable treatment groups</td>
</tr>
<tr>
<td></td>
<td>Allocation concealment method</td>
<td>Method used to conceal the allocation sequence</td>
<td>? Were treatment assignments adequately concealed</td>
</tr>
<tr>
<td>2. Performance bias</td>
<td>Blinding of patients and study personnel</td>
<td>Methods to achieve blinding of patients and investigators</td>
<td>? Was knowledge of the interventions prevented</td>
</tr>
<tr>
<td>3. Detection bias</td>
<td>Blinding of outcome assessment</td>
<td>Methods to achieve blinding of outcome assessors</td>
<td>? Was knowledge of the interventions prevented</td>
</tr>
<tr>
<td>4. Attrition bias</td>
<td>Reporting of outcome data</td>
<td>Completeness of the results for each main outcome</td>
<td>? Were reasons for attrition or exclusions of patients stated</td>
</tr>
<tr>
<td>5. Reporting bias</td>
<td>Selective reporting of results</td>
<td>Results in relation to prespecified objectives (? trial database listing)</td>
<td>? Complete or selective reporting of results</td>
</tr>
<tr>
<td>6. Other bias</td>
<td>Any other trial aspect that may lead to bias</td>
<td>Criteria not covered in other domains</td>
<td>? Other problems that may affect interpretation of results</td>
</tr>
</tbody>
</table>
35. **Assessment of Bias Example**
(for 20 individual studies)

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
<th>Study 6</th>
<th>Study 7</th>
<th>Study 8</th>
<th>Study 9</th>
<th>Study 10</th>
<th>Study 11</th>
<th>Study 12</th>
<th>Study 13</th>
<th>Study 14</th>
<th>Study 15</th>
<th>Study 16</th>
<th>Study 17</th>
<th>Study 18</th>
<th>Study 19</th>
<th>Study 20</th>
</tr>
</thead>
</table>

**Notes:**
- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

**Legend:**
- ![Low risk of bias]
- ![Unclear risk of bias]
- ![High risk of bias]
36. Risk of Bias Summary

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

[Diagram showing risk levels: Low risk of bias (green), Unclear risk of bias (yellow), High risk of bias (red)]
37. Interpreting the risk of bias for each domain within a trial and across trials

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Within a trial</th>
<th>Across trials</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low risk of bias</td>
<td>Low risk of bias for all key domains</td>
<td>All or most information is from trials at low risk of bias</td>
<td>Bias, if present, is unlikely to have seriously affected the results</td>
</tr>
<tr>
<td>2. Unclear risk of bias</td>
<td>Low or unclear risk of bias for all key domains</td>
<td>Most information is from trials at low or unclear risk of bias</td>
<td>There is a risk of bias that creates some doubt about the results</td>
</tr>
<tr>
<td>3. High risk of bias</td>
<td>High risk of bias for one or more key domains</td>
<td>The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results</td>
<td>Bias may have seriously affected the results</td>
</tr>
</tbody>
</table>
### Randomised Trials of IV β-Blockers During Evolution of an Acute MI

<table>
<thead>
<tr>
<th>Trial [drug]</th>
<th>No. of patients</th>
<th>Mortality rates:</th>
<th>Mortality reduction &amp; significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Active drug</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>MIAMI</strong> (1985)* [metoprolol]</td>
<td>5778</td>
<td>4.3% (123/2877)</td>
<td>4.9% (142/2901)</td>
</tr>
<tr>
<td><strong>ISIS-1</strong> (1986)** [atenolol]</td>
<td>16,027</td>
<td>3.9% (313/8037)</td>
<td>4.6% (365/7990)</td>
</tr>
</tbody>
</table>

* 15-day treatment period.
** 7-day treatment period.
39. Major Perspectives in Interpreting Clinical Trial Data

- **Statistical significance of the results:**
  - does not always imply clinical significance for patients (are statistics being used as a drunken man might use a lamp-post for support rather than illumination)?
  - often, however, there is a relationship between statistical significance and clinical benefit

- **Clinical importance of the results**
  - is the response of sufficient magnitude to justify use of the drug in clinical practice?
  - does the drug have a greater benefit: risk ratio than other treatments used for the same indication?

- **Relevance for medical practice**
  - how important are the results for other clinical situations?
  - are there implications for treating other patients?
40. Major Faults of Clinical Trials

- Inadequate controls (e.g. in eliminating bias)
- Non-like treatment groups (in parallel-group studies)
- Dosages of trial drugs not equivalent
- Inadequate number of subjects*
- Erroneous or extravagant conclusions.
41. 9 Key Design Issues to Consider in the Overall Analysis of a Clinical Trial (Summary)

1. **Patient eligibility** (how were patients selected?; was there any potential for ‘lead-time’ or ‘stage migration’ bias? Were the patients a narrow/divergent subgroup or a broad population with the disease?; if a narrow subgroup, have the results been generalised to all patients with the disease?)

2. **Randomisation** (was it adequate to ensure both known and unknown confounders are equally distributed in the treatment groups?; has it ensured homogeneous treatment groups?; was a valid method used to generate the random allocation sequence?; if so, how was it concealed?)

3. **Degree of blinding/masking** (was it adequate to eliminate performance bias?; if double-blinding was not possible, was there a blinded outcome assessment by independent observers?)

4. **Selection of control group** (was the control group appropriate for the trial’s objective, taking into account how the investigational treatment is to be used in clinical practice – e.g. added to or in place of existing treatment?; if an active-controlled trial, was the investigational treatment compared with the best available alternative treatment?)

5. **Participant flow** (are all randomised patients accounted for in the presentation of the results?; are the reasons for withdrawals adequately explained?)

6. **Analytical method** (was intention-to-treat analysis used?; if not, why not?; does the study have adequate statistical power?; was the statistical analysis of the data appropriate?)

7. **Appropriate endpoints** (were the endpoints appropriate to demonstrate efficacy of the treatment?; was a surrogate endpoint chosen?; if so, why?; if a surrogate endpoint was used, is it sufficiently correlated with the clinical outcome?)

8. **Trial duration** (was it adequate to permit a meaningful clinical outcome and detect specific adverse events?)

9. **Interpretation of the results** (was the trial designed to demonstrate superiority or non-inferiority of the treatment?; have the results been interpreted correctly and compared with other trials?)
## Clinical Trial Evaluation: Major Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Evaluation points</th>
<th>Score (0 – 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Purpose of the study</td>
<td>□ Clearly defined?</td>
<td></td>
</tr>
<tr>
<td>2. Patient selection</td>
<td>□ Clearly defined and appropriate criteria?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Diagnosis confirmed?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Homogeneous patient group?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Exclusions defined and appropriate?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Prior therapy defined?</td>
<td></td>
</tr>
<tr>
<td>3. Number of patients</td>
<td>□ Adequate to detect any differences between treatments?</td>
<td></td>
</tr>
<tr>
<td>4. Randomisation</td>
<td>□ Yes/no?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Appropriate methodology?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Group comparability established?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Influence of any differences discussed?</td>
<td></td>
</tr>
<tr>
<td>5. Drug dosage(s)</td>
<td>□ Defined and appropriate?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Comparable relative effects?</td>
<td></td>
</tr>
<tr>
<td>6. Duration of therapy</td>
<td>□ Long enough to show maximum effect of drug (efficacy and/or tolerability)?</td>
<td></td>
</tr>
<tr>
<td>7. Concurrent therapy (drug or non-drug)</td>
<td>□ Full details reported?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Possible influence discussed?</td>
<td></td>
</tr>
<tr>
<td>8. Controls to reduce variation (e.g. run-</td>
<td>□ Yes/no?</td>
<td></td>
</tr>
<tr>
<td>ins, placebo, standard comparator,</td>
<td>□ Baseline established?</td>
<td></td>
</tr>
<tr>
<td>crossover design, washouts)</td>
<td>□ Controls adequate?</td>
<td></td>
</tr>
<tr>
<td>Criteria</td>
<td>Evaluation points</td>
<td>Score (0 – 2)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>9. Controls to reduce bias (blinding)</td>
<td>□ Yes/no?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Method of maintaining blindness stated?</td>
<td></td>
</tr>
<tr>
<td>10. Compliance</td>
<td>□ Compliance checks performed?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Methods stated and adequate?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Influence, if any, on results discussed?</td>
<td></td>
</tr>
<tr>
<td>11. Efficacy assessment</td>
<td>□ Parameters fully defined?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Parameters relevant and reproducible?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Results fully reported?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Adequate follow-up?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Stratification performed, when appropriate?</td>
<td></td>
</tr>
<tr>
<td>12. Assessment of adverse events</td>
<td>□ Protocol clearly defined?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Number and type fully reported?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Severity stated?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Likely relationship to therapy discussed?</td>
<td></td>
</tr>
<tr>
<td>13. Statistical evaluation</td>
<td>□ Yes/no?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Methods stated and valid?</td>
<td></td>
</tr>
<tr>
<td>14. Author’s discussion</td>
<td>□ Full discussion or all results?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Fair review of others’ work?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Self-critical, if necessary?</td>
<td></td>
</tr>
<tr>
<td>15. Author’s conclusions</td>
<td>□ Conclusions clearly stated?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Conclusions valid/justified?</td>
<td></td>
</tr>
<tr>
<td>16. Clinical relevance of results</td>
<td>□ Trial design and conduct acceptable?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Any fatal flaws?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Any major inadequacies?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(out of 32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>=</td>
<td>%</td>
</tr>
</tbody>
</table>
### Guide to Scoring of Clinical Trials

<table>
<thead>
<tr>
<th>Criteria</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Purpose of the study</td>
<td>Clearly defined</td>
<td>1½ Incompletely defined</td>
<td>½ Not defined</td>
</tr>
<tr>
<td>2. Patient selection</td>
<td>Clearly defined</td>
<td>1½ Inadequately or poorly defined</td>
<td>½ Not defined</td>
</tr>
<tr>
<td>3. Number of patients</td>
<td>Sufficiently large considering the response obtained with each treatment</td>
<td>1½ Doubtful if large enough, or infrequent occurrence of disease limits number of available patients</td>
<td>½ Too few patients to show statistically significant differences, if any, between treatments</td>
</tr>
<tr>
<td>4. Randomisation of patients to treatment (and group comparability)</td>
<td>Adequate method used, and group comparability detailed and fully established</td>
<td>1½ Doubtful randomisation method, or groups stated to be comparable but no or insufficient details given</td>
<td>½ No randomisation procedure, or group comparability not established</td>
</tr>
<tr>
<td>5. Drug dosage(s)</td>
<td>Comparable dosages (established by earlier studies) or dosages titrated for each patient</td>
<td>1½ Doubtful if dosages comparable (or no titration of dosages to ensure comparability)</td>
<td>½ Inadequate or noncomparable dosages</td>
</tr>
<tr>
<td>6. Duration of therapy</td>
<td>Long enough to show optimum drug effects and assess tolerability, or to cover a period of 'risk'</td>
<td>1½ Not long enough for either (a) optimum drug effects or (b) to cover a period of 'risk', or only long enough to fulfil part of the trial's aim</td>
<td>½ Not long enough</td>
</tr>
<tr>
<td>7. Concurrent therapy (drug or non-drug)</td>
<td>None; or, if given, fully described and possible influence on results adequately discussed</td>
<td>1½ Allowed or given, but with inadequate details and no discussion of possible influence</td>
<td>½ Information missing or unclear</td>
</tr>
<tr>
<td>8. Controls to reduce bias (blinding)</td>
<td>Double-blind protocol; procedure used detailed and appropriate</td>
<td>1½ Doubtful procedure to ensure double-blind, or single-blind protocol</td>
<td>½ Open-label (no blinding procedure)</td>
</tr>
<tr>
<td>9. Other controls to reduce variation</td>
<td>Controls adequate or were not necessary</td>
<td>1½ Controls necessary but were inadequate (or of doubtful validity)</td>
<td>½ Controls necessary but not stated or absent</td>
</tr>
<tr>
<td>Criteria</td>
<td>2 Points</td>
<td>1 Point</td>
<td>0 Points</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10. Compliance</td>
<td>Definite: checks made (by an appropriate method), or serum levels measured, or parenteral route of administration, or inpatients</td>
<td>Probable: stated but details not given or methods used not adequate to ensure compliance</td>
<td>Not considered or, if outpatients, no checks made (or stated)</td>
</tr>
<tr>
<td>11. Efficacy assessment</td>
<td>Fully defined, relevant and reproducible methods adequate to assess efficacy, and full reporting of results</td>
<td>Methods of assessing efficacy inadequately or incompletely defined, or results not completely reported</td>
<td>Inadequately defined or irrelevant or non-reproducible methods, or inadequate reporting of results</td>
</tr>
<tr>
<td>12. Assessment of adverse events</td>
<td>Clearly defined protocol, effects well described (with an indication of severity), and relationship to therapy discussed</td>
<td>Protocol and results given, but neither fully detailed</td>
<td>Neither protocol nor results given (or poorly detailed)</td>
</tr>
<tr>
<td>13. Statistical evaluation</td>
<td>Full details of methods provided, and adequate statistical analysis of all results</td>
<td>Incomplete details of methods used, and/or incomplete statistical analysis of results</td>
<td>No statistical analysis of results</td>
</tr>
<tr>
<td>14. Author’s discussion</td>
<td>Adequate and fair discussion of the study’s results, plus adequate review of the results of other investigators</td>
<td>Reasonable discussion of own results, but no or poor review of the results of other investigators</td>
<td>Unfair or invalid discussion of own or others’ work, or no discussion at all</td>
</tr>
<tr>
<td>15. Author’s conclusions</td>
<td>Adequate and based on the results and design of the study (i.e. fully justified and valid)</td>
<td>Inadequate or doubtful conclusions, or none made</td>
<td>Not based on the results demonstrated, too far-fetched, or irrelevant</td>
</tr>
<tr>
<td>16. Clinical relevance of results</td>
<td>Clinically relevant therapeutic effect (not just a statistically significant effect), and all design criteria met</td>
<td>Doubtful clinical relevance or not all the design criteria met</td>
<td>Not clinically relevant or acceptable</td>
</tr>
</tbody>
</table>

The maximum attainable score is 32. A score less than 16 (<50%) denotes a trial that is not acceptable or the results require confirmation by a better designed study. A score of ≥16 to 22.5 (≥50% to 70%) denotes a fair trial where some important features are considered to be inadequate; a score of >22.5 to 27 (>70% to 85%) denotes a good to very good trial where the important elements are considered to be satisfactory; and a score of >27 to 32 (>85% to 100%) denotes an excellent or highly acceptable trial.
46. Other Scoring Systems: Modified Jadad* Criteria for Randomised, Controlled Trials

[Max. score = 5; <3 denotes low methodological quality]


<table>
<thead>
<tr>
<th>Criteria</th>
<th>Source of bias</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation</td>
<td>Selection bias / confounding (i.e. differences in comparison groups)</td>
<td>Adequate = 1; Inadequate/nil = 0</td>
</tr>
<tr>
<td>Concealed allocation</td>
<td>Selection bias / confounding</td>
<td>Adequate = 1; Unclear/not described = 0; Inadequate/nil = 0</td>
</tr>
<tr>
<td>Blinding of receipt (recipients)</td>
<td>Performance bias (i.e. differences in other treatments provided)</td>
<td>Adequate, described = 0.5; Unclear/not described = 0.25; Inadequate/nil = 0</td>
</tr>
<tr>
<td>Blinding of provision (providers)</td>
<td>Performance bias</td>
<td>Adequate, described = 0.5; Unclear/not described = 0.25; Inadequate/nil = 0</td>
</tr>
<tr>
<td>Follow-up of participants</td>
<td>Attrition bias (i.e. differences in withdrawals from trial)</td>
<td>Adequately accounted for = 1; Unclear/not described = 0; Inadequate/nil = 0</td>
</tr>
<tr>
<td>Blinding of assessment</td>
<td>Detection bias (i.e. differences in outcome assessment)</td>
<td>Adequate = 1; Unclear/not described = 0; Inadequate/nil = 0</td>
</tr>
</tbody>
</table>
47. Application of the Checklist and Scoring System

- Identifying “best” results – e.g. in evidence-based medicine assessments
- Identifying reasons for differing results
- *Aide-memoire* when evaluating or writing a clinical trial
- Identifying missing or deficient areas when refereeing or editing a trial report
- Evaluating references provided to support formulary addition requests or promotional claims.
48. Criticism of Clinical Trials: A Note of Caution

- It is easy to criticise the conduct or design of a trial for the sake of criticism.
- It is much more difficult to distinguish situations where criticism is warranted from those where the perceived short-comings are not likely to have affected the outcome.
- In the overall assessment, determine which criteria are of particular importance and which are of lesser or no importance. Shift the emphasis accordingly.
2. Scientific Writing

Writing Effectively to Make a Good Impression

Important Principles
50. **Types of Scientific Papers**

- Clinical trial or other original research paper
- Review article – e.g. literature review, state-of-the-art disease management review, drug monograph, etc.
- A commentary, editorial or leading article
- Abstract / summary of original research paper
- Poster
- Research grant application
- Clinical study report (CSR) or other scientific report for regulatory submission
- Medical news / symposium report.
Planning the Paper: Initial Considerations

- What do I have to say?
- What is the best format/structure for the message?
- What type of publication will it appear in?
- Who is the intended audience for the message?
- What prose style should I use?
- What level of detail should I go to?
52. The Value of an Outline

- You should be able to clearly define the point(s) you wish to make before starting.

- An outline listing the key points is particularly advantageous – even though this may change as you proceed and new points emerge.
53. Basic Structure of Scientific Papers

When considering structure, remember that the reader of a scientific paper will be looking for:

- the answer to a question or solution to a problem; or
- to be educated and informed about the topic

Consequently, the author must convince the reader, through critically sifted evidence arranged in a logical sequence, that the conclusions drawn are correct.

This content of the paper is known as its 'critical argument'.

‘Critical argument’ is built around the sequence of: question, evidence and answer.
## Sequence of the research

<table>
<thead>
<tr>
<th>The question to be answered</th>
<th>Introduction</th>
<th>Question (the problem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How the answer was sought</td>
<td>Materials and Methods</td>
<td>Credibility of the evidence</td>
</tr>
<tr>
<td>Findings</td>
<td>Results</td>
<td>Evidence (the study data): initial answer</td>
</tr>
<tr>
<td>Findings considered in the light of other investigators’ findings: the answer</td>
<td>Discussion and Conclusions</td>
<td>Supporting evidence Contradictory evidence Assessment of contradictory evidence Answer</td>
</tr>
</tbody>
</table>
These types of articles have little room in which to deliver their message.

The structure must therefore be well worked out with the right sequence of the elements of ‘critical argument’.

Otherwise, the brevity of the article may expose all too clearly any flaws in the argument.
## Basic Structure of Commentaries and Leading Articles/Editorials

<table>
<thead>
<tr>
<th>Paragraphs</th>
<th>Elements of ‘critical argument’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introductory paragraphs</td>
<td>Statement of the problem: tentative answer</td>
</tr>
<tr>
<td>Middle paragraphs</td>
<td>Evidence in support and counter evidence</td>
</tr>
<tr>
<td>Closing paragraphs</td>
<td>Assessment of all evidence: final answer</td>
</tr>
</tbody>
</table>
Some Do’s and Don’ts of Prose Style

*Do’s – essential requirements of good prose:*
- **Accuracy** – use the right words to convey your meaning
- **Clarity** – don’t obscure what you have to say by how you say it
- **Brevity** – keep it concise; avoid repetition

*Don’ts – avoid:*
- Professional pomposity
- Barbarisms
- Solecisms
- Errors in syntax
- Use of incorrect or dehumanising words
- Use of ‘empty’ phrases or words
- Sexism
- Excessive use of abbreviations
- Plagiarism.
“The utilisation of inordinately inflated prose in the attempt to convey technically-oriented concepts among professionals in the various scientific/technical fields is, in the opinion of the present author, a major obstacle to the successful completion of the communication process”

- Don’t obscure what you have to say by how you say it
- Remember the KISS principle – “keep it simple, stupid”.
Avoid Excessive Use of Abbreviations

- Abbreviations reduce verbosity and can improve text flow, but don’t assume all readers will necessarily know what an abbreviation means.
- Abbreviations can mean different things to different people.
- Always spell out abbreviations at first mention in the text.
- If there are a large number of abbreviations and their frequent use is unavoidable, consider a ‘glossary of terms’ somewhere in the article.
The patient with ASHD and PHMI, SPCABG had an episode of BRBPR PTA for ERCP

- **Translation:**
  The patient with /atherosclerotic heart disease/ and /a past history of myocardial infarction, status post-coronary artery bypass graft/ had an episode of /bright red blood per rectum/ prior to admission for /endoscopic retrograde cholangiopancreatography/

- Abbreviations might be acceptable in spoken English, but they may not be in written English.
Abbreviations Can Mean Different Things to Different People

Possible meanings of “PAS”:

- Para-aminosalicylic acid
- Periodic acid-Schiff
- Pulmonary artery stenosis
- Pregnancy advisory service
- Patient attitude scale
- Professional activities study
- Pulmonary adaptation syndrome.
Abbeviations May Differ in US and UK English

Transoesophageal echocardiography:
- UK: TOE
- US: TEE

Gastro-oesophageal reflux disease:
- UK: GORD
- US: GERD.
63. Abbreviations Are Not Words in Their Own Right

NPWT – negative-pressure wound therapy:
- **Wrong**: Patients who received NPWT therapy had . . .
- **Right**: Patients who received NPWT had . . .

NSAID – nonsteroidal anti-inflammatory drug:
- **Wrong**: An NSAID drug is the first-line of treatment in . . .
- **Right**: A NSAID is the first-line of treatment in . . .
  
or  NSAIDs are the first-line of treatment in . . .
64. **Tables and Figures: Important Considerations**

- If the point a table or figure makes can be made in the text in a few sentences, the table/figure could be omitted.
- In many instances, however, descriptive information can be more efficiently presented in this form than in the text.
- If tables/figures are included, their structures should be carefully thought out for logical presentation, and they should relate to each other in a logical sequence.
- Great care should be taken with proper use of units and clear presentation of the data being summarised.
- Each table/figure should be understandable on its own. Ensure a clear legend is provided to explain what the table/figure shows.
65. Revising the Manuscript for Content and Structure

- Write the first draft
- Hold for a few days, then revise content and structure
- Second draft
  - Re-read; note changes needed
  - Coauthors
  - Colleagues
- Third draft
  - Coauthors
- Final manuscript
  - Additional drafts for revision of content and structure
66. **Final Manuscript Review**

*(Before submission to a medical/scientific journal)*

- Review the manuscript requirements of the journal. *Note:* following the **CONSORT** checklist (for clinical trials) or the **PRISMA** checklist (for systematic reviews/meta-analyses) may be mandated by the journal.
- Review the final version of the paper to ensure that it contains all the needed elements, and that these are in accord with the journal’s requirements.
- Ensure the manuscript is written and presented in accord with the journal’s requirements.
- Prepare a submission letter that will give the editor the information he/she will require about the author(s) and what the paper contains.
- Enclose any items that have to be sent with the manuscript – e.g. figure artwork, ‘permission’ letters, etc.
- Declare any sources of funding and/or potential conflicts of interest.
<table>
<thead>
<tr>
<th>Section / topic</th>
<th>Item No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and Abstract</td>
<td>1</td>
<td>• Identification as a randomised trial in the title&lt;br&gt;• Structured summary of trial design, methods, results, and conclusions</td>
</tr>
<tr>
<td>Introduction: Background and objectives</td>
<td>2</td>
<td>• Scientific background and explanation of rationale&lt;br&gt;• Specific objectives or hypotheses</td>
</tr>
<tr>
<td>Methods: Trial design</td>
<td>3</td>
<td>• Description of trial design (such as parallel, factorial), including allocation ratio&lt;br&gt;• Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
</tr>
<tr>
<td>Participants</td>
<td>4</td>
<td>• Eligibility criteria for participants&lt;br&gt;• Settings and locations where the data were collected</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>• The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6</td>
<td>• Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed&lt;br&gt;• Any changes to trial outcomes after the trial commenced, with reasons</td>
</tr>
<tr>
<td>Sample size</td>
<td>7</td>
<td>• How sample size was determined&lt;br&gt;• When applicable, explanation of any interim analyses and stopping guidelines</td>
</tr>
<tr>
<td>Randomisation – Sequence generation</td>
<td>8</td>
<td>• Method used to generate the random allocation sequence&lt;br&gt;• Type of randomisation; details of any restriction (such as blocking and block size)</td>
</tr>
<tr>
<td>Randomisation – Allocation concealment mechanism</td>
<td>9</td>
<td>• Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
</tr>
<tr>
<td>Randomisation – Implementation</td>
<td>10</td>
<td>• Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
</tr>
<tr>
<td>Blinding</td>
<td>11</td>
<td>• If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how&lt;br&gt;• If relevant, description of the similarity of interventions</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>• Statistical methods used to compare groups for primary and secondary outcomes&lt;br&gt;• Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
</tr>
<tr>
<td>Section / topic</td>
<td>Item No.</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant flow</td>
<td>13</td>
<td>• For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
</tr>
<tr>
<td>(Note: a diagram is recommended)</td>
<td></td>
<td>• For each group, losses and exclusions after randomisation, together with reasons</td>
</tr>
<tr>
<td>Recruitment</td>
<td>14</td>
<td>• Dates defining the periods of recruitment and follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Why the trial ended or was stopped</td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>• A table showing baseline demographic and clinical characteristics for each group</td>
</tr>
<tr>
<td>Numbers analysed</td>
<td>16</td>
<td>• For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17</td>
<td>• For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory</td>
</tr>
<tr>
<td>Harms</td>
<td>19</td>
<td>• All important harms or unintended effects in each group</td>
</tr>
<tr>
<td><strong>Discussion:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitations</td>
<td>20</td>
<td>• Trial limitations; addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
</tr>
<tr>
<td>Generalisability</td>
<td>21</td>
<td>• Generalisability (external validity, applicability) of the trial findings</td>
</tr>
<tr>
<td>Interpretation</td>
<td>22</td>
<td>• Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
</tr>
<tr>
<td><strong>Other information:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>23</td>
<td>• Registration number and name of trial registry</td>
</tr>
<tr>
<td>Protocol</td>
<td>24</td>
<td>• Where the full trial protocol can be accessed, if available</td>
</tr>
<tr>
<td>Funding</td>
<td>25</td>
<td>• Sources of funding and other support (such as supply of drugs), role of funders</td>
</tr>
</tbody>
</table>
69. ‘CONSORT’ Flow Diagram (CONSORT* Group):
Accounting for Patients Enrolled in Clinical Trials
* Consolidated Standards of Reporting Trials [ http://www.consort-statement.org/ ]
70. **Instruction to Authors:**

Pay attention to:

- Page margins, font, line spacing
- Spelling and terminology – US or UK spelling
- Title page instructions, e.g. length of title, short running title, address for correspondence, etc.
- Declarations of conflicts of interest, sources of funding, etc.
- Abstract structure and word length (commonly 250 words maximum)
- Key words (for indexing)
- Presentation of the text and what to include in each section, e.g. statements on Ethics Committee approval for the research in ‘Methods’
- Total text word length *(Note: Tables and figures may be equated to approx. 250 words, which will reduce the allowable length)*
- Acknowledgements, e.g. statements that all authors were involved in writing or reviewing the text and are in full agreement with it
- Presentation of tables and figures / limitations on numbers allowed
- References style, and limitations on maximum number.
71. Reference Style

1. Author name/year or number citations in text? 
   [If numbers, considering using reference management software such as EndNote]

2. ‘Vancouver’ or other style, e.g. Harvard, AMA?

**Vancouver style**  
Text citation: [1]

**Harvard style**  
Text citation: (Mire et al. 2005) 
Writing a Clinical Trial Report
A Checklist for Data that Should be Considered for Inclusion

1. Title:
   - Include type/design of study and the drug(s) under investigation
   - Keep concise and easily readable, ensuring 'key' (indexable) words are included

2. Summary/synopsis:
   - State key facts about study in first sentence
   - Provide important details about the conduct of the study (including essential background information), but keep concise
   - Brief summary of major results and important conclusions/implications

3. Introduction:
   - Review historical background and relevant literature (including previous experience with the drug under investigation)
   - Statement of the problem and the primary (and secondary) objectives of the trial
   - Rationale for approach taken
   - Define clearly the question being asked or hypothesis to be tested

4. Materials and methods:

   a) Patients:
      - Inclusion/exclusion criteria
      - Source(s) and numbers of patients (total and per treatment group)
      - Number of trial sites where patients enrolled
      - Methods of randomisation
      - Comparability of treatment groups (show patient demographic data in 'Results' section)
      - Number of clinic visits per patient
      - Information on ethics committee approval, and procedure for obtaining patient consent

   etc.
Factors that give rise to “writer’s block”:
- anxiety and boredom
- defeatist attitudes / task inflation
- perfectionism and unrealistic expectations – *NB.* first draft won’t be perfect

Eliminate all sources of distraction:
- create right environment for concentrating on task
- keep a regular schedule – preferably begin when mind not cluttered and energy levels are highest
- set daily time limits or goals for writing.
Overcoming “Writer’s Block” (continued)

- **Outlining ideas / brainstorming:**
  - helps to decide where you are going and what to say
  - gives a sense of the length, difficulty, time required
  - try “free-writing” initially – jotting down ideas

- **Draft quickly, revise slowly:**
  - avoid temptation to edit draft as you write
  - consider writing and editing as entirely separate tasks

- **Start writing at whatever point you like:**
  - begin with sections you know best – e.g. in middle
  - leave introduction and discussion sections until later
  - write conclusions and summary last.
Levels of evidence

Ia
(meta-analyses)

Ib
(individual RCTs)

IIa, IIb

IIla, IIlb

IV

V

Randomised, controlled double-blind trials

Cohort studies

Case-control studies

Cross-sectional studies

Case reports

Opinion, ideas, editorials

Experimental research (animal studies)

In vitro (‘test tube’) research