### 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>
<tbody>
<tr>
<td>Clinical pharmacology</td>
<td>I</td>
<td>Initial (FTIH) safety studies and pharmacokinetic (PK) / pharmacodynamic (PD) characterisations (usually in healthy volunteers)</td>
<td>Single ascending dose (SAD) and multiple ascending dose (MAD) safety studies to determine the maximum tolerated dose (MTD)</td>
</tr>
<tr>
<td>Therapeutic exploratory</td>
<td>Ia</td>
<td>Pilot clinical trials to evaluate efficacy and safety (selected patients with target disease)</td>
<td>Single and multiple dose PK/PD studies to define PK/PD relationship</td>
</tr>
<tr>
<td></td>
<td>Ib</td>
<td>Randomised, controlled trials to evaluate efficacy/safety broadly, and their relationship in patients with target disease</td>
<td>Drug interaction studies</td>
</tr>
<tr>
<td>Therapeutic confirmatory</td>
<td>Ila</td>
<td>Randomised, controlled trials in relatively large numbers of patients with target disease, special groups of patients</td>
<td>Comparative efficacy/safety studies (vs placebo or other standard drugs)</td>
</tr>
<tr>
<td></td>
<td>Iib</td>
<td>Clinical trials that supplement earlier trials and establish risk-benefit profile</td>
<td>Identification of disease subtypes for which drug is particularly effective</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>IV</td>
<td>Studies to provide additional efficacy/safety data (including comparisons vs other drugs)</td>
<td>Comparative efficacy/safety studies (vs other drugs)</td>
</tr>
</tbody>
</table>

### 3. Variability in drug responsiveness may be influenced by numerous factors

**Why well-designed, controlled clinical trials are mandatory to establish efficacy / safety**

Variability in responsiveness may be caused by:

- **The natural progression of the disease** (e.g. relapsing-remitting)
- **Drug factors:**
  - Pharmacodynamic variability (e.g. receptor sensitivity differences)
  - Pharmacokinetic variability (differences in absorption or elimination)
  - Interactions with environmental factors or other drugs
  - Genetic polymorphisms leading to differing drug-gene interactions
- **Non-drug factors:**
  - The personality, beliefs, and attitudes of the patient
  - The patient’s prior experience of doctors and drugs, and his/her expectations of the treatment prescribed
  - The personality, beliefs, and attitudes of the clinician.
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.:
  - The natural progression of the 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

5. Key control measures:

1. Randomisation

- Key design feature to minimise the influence of patient variability
- Randomised allocation of patients to the different study groups helps to ensure that the test treatment and control groups are similar at baseline
- Randomisation minimises the influence of any systematic differences between the study groups that could affect the outcome of the study
- It also eliminates bias in treatment assignment.

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
- Patients: In the absence of blinding, knowledge of the treatment assignment could result in:
  - Patients reporting more/less favourable treatment outcomes
  - Patients being more/less likely to continue their participation in the study
- Investigators: 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
  - The inclusion or non-inclusion of certain results in the analysis.
7. Evidence-based medicine: Levels of evidence in establishing the efficacy/safety of drugs

Levels of evidence

- Ia (meta-analyses of RCTs)
- Ib (individual RCTs)
- IIa
- IIb
- IIIa
- IIIb
- IV
- V

Levels of evidence:

- Evidence-based medicine: Levels of evidence in establishing the efficacy/safety of drugs
- Ia (meta-analyses of RCTs)
- Ib (individual RCTs)
- IIa
- IIb
- IIIa
- IIIb
- IV
- V

8. 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
   - Appropriate to study pharmacokinetics in human subjects, dose-response or concentration-effect relationships, and for long-term toxicity studies – where patients are compared with their own baseline data.

9. Types of clinical trial designs (continued)

2. Two (or more) patient group designs (comparative trials vs placebo or another active drug)
   
   A. Parallel-group studies:
   - Patients are randomised to one of two or more treatment groups, and usually receive the assigned treatment throughout the trial
   - Applicable to most clinical situations – most commonly used trial 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. (an important advantage of this design)
10. Types of clinical trial designs (continued)
2. Two (or more) patient group designs (contd)

B. Crossover studies:
- Patients receive each treatment – randomised to one or other treatment first and then crossed over after an adequate ‘washout’ period (>7 half-lives of the test drug) in between
- Assess within-patient differences – drug effect is expressed as difference between the responses to each treatment
- Variability of data less than with parallel-group studies, and fewer patients are required to detect statistically significant differences between treatments
- BUT, not as ‘robust’ as parallel-group studies as adversely affected by dropouts, missing data, etc.
- Also, statistical analysis requires consideration of possible ‘treatment order’ and ‘carryover’ effects.

11. Parallel-group and crossover trial designs

- Controlled trials comparing 2 drugs/treatments

Parallel-group design
- Drug A
- Randomisation
- Run-in
- Drug B
- Final Assessment
- Assessment 1

Crossover design
- Drug A
- Randomisation
- Run-in
- Drug B
- Washout
- Drug A
- Assessment 2
- Assessment 1

12. Crossover studies – when is this design useful?

Key requirement: Patients must be able to return to the identical pre-treatment 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 appropriate for:
- Studies of long-term effects of drug therapy
- Studies of possible disease cure or prevention of death.
13. **Crossover studies – contd.**

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

1. Analgesics for postoperative pain
2. Analgesics for osteoarthritic knee pain
3. Topical antibiotics for a bacterial skin infection (e.g. impetigo)

14. **Types of clinical trial designs**

(continued)

2. Two (or more) patient group designs (contd.)

C. Sequential analyses:

- Generally involves allocation of study participants progressively to the test treatments (sample size of these trials 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 a difference between the treatments
- Not commonly used nowadays – except perhaps in medical emergency conditions (e.g. head injury) or less common/rare conditions.

15. **Factorial Randomised Controlled Trials**

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

Example: the ISIS-2 Study in Acute Myocardial Infarction (a 2 x 2 factorial study)

17,147 patients with acute MI

Randomisation 1

 ISIS = International Study of Infarct Survival
16. Evaluation of clinical trials:  
**Important considerations**

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

2. Controlled trials vary considerably in their “acceptability”

3. This varying acceptability can make interpretation of their findings difficult

17. Evaluation of clinical trials: **Important considerations (continued)**

4. 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

5. Many factors other than the basic design of a trial influence the adequacy of the results and how they should be interpreted.

18. General principles of clinical trial evaluation

- Any individual trial provides only limited information
- One study cannot provide all the evidence needed to conclude that a drug is effective or safe
- Statements made by authors must always be critically evaluated.
19. Key questions to ask yourself when evaluating a clinical trial

- 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 (if any) reasonable?
- Are the results likely to affect clinical practice or other research activities?
- Overall, how much emphasis should you place on the findings?

20. Overall trial 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 comparative clinical trials

- Appropriate controls (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 (for the disease being studied and type of drug)
- Appropriate dosages of the drugs being compared
- Appropriate methods of assessing/measuring adverse events
- Appropriate statistical validation.
22. Aims and objectives of trials

- The aims may vary from trial to trial, but they should always be very carefully stated at the beginning of the study usually given in the introduction after the rationale for the trial.
- The aim should be to answer ONE precisely framed question or test ONE precisely stated hypothesis.
- 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 various questions posed.

23. 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 the event occurred)
- Require hospitalisation or prolongation of existing hospitalisation
- Result in persistent or significant disability/incapacity
- Qualify as a congenital abnormality or birth defect
- Are considered important or significant (medical judgment) and/or require specific interventions to prevent serious outcomes
25. Adverse events (AEs): relationship to the study drug (treatment-related AEs vs ‘all-cause’ AEs)

- Treatment-emergent AEs (TEAEs) = AEs that are reported during a clinical trial (also known as ‘all-cause’ AEs)
- Treatment-related AEs = categories 1, 2 & 3

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

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

3. Possibly related to drug:
   - Evidence of exposure to drug
   - Temporal relationship reasonable
   - Another cause is 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
   - (If feasible) Rechallenge is negative/unclear

5. Definitely not related to drug:
   - Drug not received or the temporal relationship is not reasonable

26. 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 instances, not appropriate because with the passage of time, many variables may have changed 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 because of the possibility of a ‘treatment order’ effect.)

27. Assessing the adequacy of control measures

- Adequacy of the randomisation procedure:
  - Method used to allocate treatment – computerised random number generation, random number table, an interactive web-based response system or interactive voice response system (IVRS)?
  - Were the patients stratified; if so, how; and was the stratification method valid?
  - How was the randomisation concealed from the investigators – e.g. by 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 completely excluded

- Adequacy of the ‘blinding’ technique:
  - Type of blinding used – e.g. single-blind, double-blind, observer-blind
  - If some key study personnel cannot be blinded, were there independent outcome assessors for the trial, and were they appropriately blinded?
  - How was the blinding of orally active drugs with different administration schedules achieved – e.g. matching drugs or by a ‘double-dummy’ technique?
28. Blinding techniques

Comparison of 2 drugs, X and Y, with different dose frequencies (tid vs bid):

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning: X active + Y placebo</td>
<td>X placebo + Y active</td>
</tr>
<tr>
<td>Midday: X active</td>
<td>Y placebo</td>
</tr>
<tr>
<td>Evening: X active + Y placebo</td>
<td>X placebo + Y active</td>
</tr>
</tbody>
</table>

Matching drugs (X and Y reformulated to look the same, e.g. in opaque capsules)

Double-dummy technique (original forms of X and Y; plus identical X and Y placebos)

5 tablets per day (2 medicine containers/patient)

29. Assessing the 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) population or the "per-protocol" (PP) population, or both?

30. Intention-to-treat (ITT) versus per-protocol (PP) analysis

**ITT analysis**:
- Unbiased method of assessment (analyzes all patients according to the group to which they were originally randomized)
- Assesses the overall consequences of each treatment regimen (takes account of all post-randomisation events, including non-compliance)
- Corresponds to pragmatic management trials (reflects 'real-world' clinical practice)
- "Intention to treat" patients; those who did not receive at least one dose of the study medication, and those with incomplete post-randomisation data
- In such cases, the analysis group may be termed the 'full analysis set' (FAS) or the modified ITT (mITT) population

**Per-protocol "as-treated" 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
- Maximizes opportunity to show efficacy - gives an indication of the 'true effect' of the test drug (since it will have been taken/administered exactly as intended)
- BUT may be biased if non-adherence to the protocol is related to lack of efficacy or the occurrence of adverse events
31. Handling of missing data:
Last observation carried forward (LOCF) analysis

- Data analysis method for patients who discontinue from the trial or for whom 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 discontinue the trial for lack of efficacy.

32. ITT versus per-protocol analysis of the treatment response:
Key points

**ITT analysis** (most commonly applied analytical method in clinical trials):
- Includes results for all patients who are randomised to the treatments
- Takes into account data up to the time of withdrawal for dropouts (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 the “true” drug effect, BUT if more closely reflects everyday, ‘real-world’ clinical practice

**Per-protocol (PP) analysis** (may be fully appropriate in some situations, e.g. trials in hospitalised patients where compliance is supervised):
- 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 (Note: 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 or defaulting by patients)
- Useful as a sensitivity or supportive check of the ITT analysis to evaluate the influence of protocol violations on the results.

33. Assessment of methodological bias in clinical trials
(Cochrane Collaboration Criteria)

Six domains of a clinical trial to consider in assessing 7 potential sources of bias:
1. Adequate: all criteria adequately met = low risk of bias
2. Unclear: 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>Present</th>
<th>Possible Sources of Bias</th>
<th>Key Questions to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias</td>
<td>Random sequence generation (allocation concealment)</td>
<td>Random sequence generation, the allocation sequence method used to generate the sequence</td>
<td>Adequate to produce comparable treatment groups?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allocation concealment method</td>
</tr>
<tr>
<td>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>Detection bias</td>
<td>Blinding of outcome assessment</td>
<td>Methods to achieve blinding of investigators/outcome assessors</td>
<td>Was knowledge of the interventions prevented?</td>
</tr>
<tr>
<td>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>Reporting bias</td>
<td>Selective reporting of results</td>
<td>Results in relation to prespecified hypotheses and the trial database (lack of selective reporting of results)</td>
<td>Complete or selective reporting of results?</td>
</tr>
<tr>
<td>Other bias</td>
<td>Any other trial aspect that may lead to bias</td>
<td>Other biases that may affect the interpretation of results</td>
<td>Other biases that may affect the interpretation of results?</td>
</tr>
</tbody>
</table>
### 34. Assessment of bias

(an example of an assessment of the 7 potential sources of bias for 20 individual studies)

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

### 35. 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>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>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 could create some doubt about the results</td>
</tr>
<tr>
<td>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>

### 36. Major perspectives in interpreting clinical trial data

- Statistical significance of the results:
  - Does not always imply clinical significance for patients
  - Often, however, there is a relationship between statistical significance and clinical benefit.
- Clinical relevance 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?
  - Have the authors used manipulative language (‘spin’) in discussing the relevance of their results (e.g. by focusing on the secondary outcomes of the study rather than the primary outcome, or on subgroup analyses) [i.e. obvious reporting bias?]

37. Summary of 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 statements in the conclusions.

38. Importance of an adequate number of patients in comparative trials

<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>MIAMI (1985)</td>
<td>5778</td>
<td>4.3% (123/2877)</td>
<td>4.9% (142/2901)</td>
</tr>
<tr>
<td>ISIS-1 (1986)</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.

MIAMI = Metoprolol in Acute Myocardial Infarction; ISIS = International Study of Infarct Survival.

39. Absolute benefit of a trial expressed as the number needed to treat (NNT)

1. Trials of mortality reduction:
   \[
   \text{NNT} = \frac{1}{\text{mortality rate with placebo} - \text{mortality rate with active drug} \%}
   \]

2. Trials of therapeutic benefit:
   \[
   \text{NNT} = \frac{1}{\text{response rate with active drug} - \text{response rate with placebo} \%}
   \]
Nine 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 orlength bias? Were the patients a narrow/thin/thin subgroup of a broader population with the disease?
2. **Randomisation**: was a randomisation scheme used to ensure both known and unknown confounders are equally distributed between treatment groups? Did it ensure adequate treatment groups? Was a valid method used to generate random allocation sequences? If so, how was it concealed?
3. **Baseline comparability**: was a randomisation scheme used to ensure both known and unknown confounders are equally distributed between treatment groups? If double blinding was not possible, was there a blinded outcome assessment by independent observers?
4. **Interpretation of the results**: Was the trial's objective taken into account when the investigational treatments to be used in clinical practice - e.g., added therapy compared with placebo? If so, how was it ensured that the investigational treatment compared with the known standard treatment?
5. **Conclusions**: were the endpoints appropriately demonstrated to be equivalent or noninferior? Are the reasons for study withdrawals adequately explained?
6. **Clinical relevance**: Was the analysis performed to demonstrate efficacy of the treatment? Was a surrogate endpoint chosen? Is the study only - if a surrogate endpoint was used, is it sufficiently correlated with the clinical outcome?
7. **Clinical trial evaluation**: was it adequate to permit meaningful clinical outcome and detect specific adverse events?

Clinical Trial Evaluation: Major Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Evaluation points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Purpose of the study</td>
<td>Clearly defined?</td>
<td></td>
</tr>
<tr>
<td>2. Material selection</td>
<td>Clearly defined and appropriate choice?</td>
<td></td>
</tr>
<tr>
<td>3. Number of patients</td>
<td>Adequate to eliminate any differences between substrata? (0 – 2)</td>
<td></td>
</tr>
<tr>
<td>4. Randomisation</td>
<td>Randomised?</td>
<td></td>
</tr>
<tr>
<td>5. Drug therapy</td>
<td>Baseline comparable?</td>
<td></td>
</tr>
<tr>
<td>6. Statistical analysis</td>
<td>Appropriate?</td>
<td></td>
</tr>
<tr>
<td>7. Clinical trial design</td>
<td>Adequate?</td>
<td></td>
</tr>
<tr>
<td>8. Controls adequate?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total = %
### 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>Incompletely defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>2. Methods of assessing</td>
<td>Randomised, double-blind</td>
<td>Single-blind</td>
<td>Open</td>
</tr>
<tr>
<td>3. Number of patients</td>
<td>Suitable, determined with end-points established</td>
<td>Too few patients to allow or given</td>
<td>Too few patients to allow or given</td>
</tr>
<tr>
<td>4. Comparison between groups (method)</td>
<td>Adequately defined and thoroughly described</td>
<td>Inadequately defined or poorly explained</td>
<td>Inadequately or poorly explained</td>
</tr>
<tr>
<td>5. Randomisation</td>
<td>Adequate (e.g. in evidence-based medicine assessments for a specific disease)</td>
<td>Inadequate (e.g. in evidence-based medicine assessments for a specific disease)</td>
<td>Inadequate (e.g. in evidence-based medicine assessments for a specific disease)</td>
</tr>
<tr>
<td>6. Concurrent therapy</td>
<td>Justified and valid</td>
<td>Not justified or not valid</td>
<td>Not justified or not valid</td>
</tr>
<tr>
<td>7. Duration of therapy</td>
<td>Long enough to show statistically significant effect</td>
<td>Not long enough</td>
<td>Not long enough</td>
</tr>
<tr>
<td>8. Drug dosage (including randomisation)</td>
<td>Given a single dosage with titration to an optimum</td>
<td>Too large or too small, not titrated</td>
<td>Too large or too small, not titrated</td>
</tr>
<tr>
<td>9. Other controls</td>
<td>Adequate and fair statistical analysis of all results (with an indication of therapeutic effect (not just a statistically significant effect), and bias)</td>
<td>Incomplete statistical analysis of results</td>
<td>Incomplete statistical analysis of results</td>
</tr>
<tr>
<td>10. Compliance</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>11. Efficacy</td>
<td>Fully defined, relevant results not completely demonstrated</td>
<td>Inadequate or doubtful effects well described</td>
<td>Inadequate or doubtful effects well described</td>
</tr>
<tr>
<td>12. Assessment of adverse events</td>
<td>Clear and detailed</td>
<td>Incompletely defined or incompletely given</td>
<td>Incompletely defined or incompletely given</td>
</tr>
<tr>
<td>13. Authors' conclusions</td>
<td>Justified and valid</td>
<td>Unfair or invalid</td>
<td>Unfair or invalid</td>
</tr>
<tr>
<td>14. Author's conclusions</td>
<td>Doubtful</td>
<td>Doubtful procedure to be followed</td>
<td>Doubtful procedure to be followed</td>
</tr>
<tr>
<td>15. Author's conclusions</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>16. Application of the checklist and scoring system</td>
<td>Identifying “best” results – e.g. in evidence-based medicine assessments for a specific disease</td>
<td>Identifying reasons for differing results between trials</td>
<td>Identifying missing or deficient areas when refereeing or editing a trial report</td>
</tr>
<tr>
<td>17. Protocol and results (e.g. in trials)</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>18. Methods of assessing</td>
<td>Fully defined, relevant methods used, details given</td>
<td>Incompletely defined, or details not given</td>
<td>Incompletely defined, or details not given</td>
</tr>
<tr>
<td>19. Number of patients</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>20. Duration of therapy</td>
<td>Long enough to show statistically significant effect</td>
<td>Not long enough</td>
<td>Not long enough</td>
</tr>
<tr>
<td>21. Drug dosage (including randomisation)</td>
<td>Given a single dosage with titration to an optimum</td>
<td>Too large or too small, not titrated</td>
<td>Too large or too small, not titrated</td>
</tr>
<tr>
<td>22. Other controls</td>
<td>Adequate and fair statistical analysis of all results (with an indication of therapeutic effect (not just a statistically significant effect), and bias)</td>
<td>Incomplete statistical analysis of results</td>
<td>Incomplete statistical analysis of results</td>
</tr>
<tr>
<td>23. Compliance</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>24. Efficacy</td>
<td>Fully defined, relevant results not completely demonstrated</td>
<td>Inadequate or doubtful effects well described</td>
<td>Inadequate or doubtful effects well described</td>
</tr>
<tr>
<td>25. Assessment of adverse events</td>
<td>Clear and detailed</td>
<td>Incompletely defined or incompletely given</td>
<td>Incompletely defined or incompletely given</td>
</tr>
<tr>
<td>26. Authors' conclusions</td>
<td>Justified and valid</td>
<td>Unfair or invalid</td>
<td>Unfair or invalid</td>
</tr>
<tr>
<td>27. Author's conclusions</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>28. Protocol and results (e.g. in trials)</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>29. Methods of assessing</td>
<td>Fully defined, relevant methods used, details given</td>
<td>Incompletely defined, or details not given</td>
<td>Incompletely defined, or details not given</td>
</tr>
<tr>
<td>30. Number of patients</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>31. Duration of therapy</td>
<td>Long enough to show statistically significant effect</td>
<td>Not long enough</td>
<td>Not long enough</td>
</tr>
<tr>
<td>32. Drug dosage (including randomisation)</td>
<td>Given a single dosage with titration to an optimum</td>
<td>Too large or too small, not titrated</td>
<td>Too large or too small, not titrated</td>
</tr>
<tr>
<td>33. Other controls</td>
<td>Adequate and fair statistical analysis of all results (with an indication of therapeutic effect (not just a statistically significant effect), and bias)</td>
<td>Incomplete statistical analysis of results</td>
<td>Incomplete statistical analysis of results</td>
</tr>
<tr>
<td>34. Compliance</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>35. Efficacy</td>
<td>Fully defined, relevant results not completely demonstrated</td>
<td>Inadequate or doubtful effects well described</td>
<td>Inadequate or doubtful effects well described</td>
</tr>
<tr>
<td>36. Assessment of adverse events</td>
<td>Clear and detailed</td>
<td>Incompletely defined or incompletely given</td>
<td>Incompletely defined or incompletely given</td>
</tr>
<tr>
<td>37. Authors' conclusions</td>
<td>Justified and valid</td>
<td>Unfair or invalid</td>
<td>Unfair or invalid</td>
</tr>
<tr>
<td>38. Author's conclusions</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>39. Protocol and results (e.g. in trials)</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>40. Methods of assessing</td>
<td>Fully defined, relevant methods used, details given</td>
<td>Incompletely defined, or details not given</td>
<td>Incompletely defined, or details not given</td>
</tr>
<tr>
<td>41. Number of patients</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>42. Duration of therapy</td>
<td>Long enough to show statistically significant effect</td>
<td>Not long enough</td>
<td>Not long enough</td>
</tr>
<tr>
<td>43. Drug dosage (including randomisation)</td>
<td>Given a single dosage with titration to an optimum</td>
<td>Too large or too small, not titrated</td>
<td>Too large or too small, not titrated</td>
</tr>
<tr>
<td>44. Other controls</td>
<td>Adequate and fair statistical analysis of all results (with an indication of therapeutic effect (not just a statistically significant effect), and bias)</td>
<td>Incomplete statistical analysis of results</td>
<td>Incomplete statistical analysis of results</td>
</tr>
<tr>
<td>45. Compliance</td>
<td>Sufficiently large</td>
<td>Too few or very few patients per group comparability</td>
<td>Too few or very few patients per group comparability</td>
</tr>
<tr>
<td>46. Efficacy</td>
<td>Fully defined, relevant results not completely demonstrated</td>
<td>Inadequate or doubtful effects well described</td>
<td>Inadequate or doubtful effects well described</td>
</tr>
<tr>
<td>47. Assessment of adverse events</td>
<td>Clear and detailed</td>
<td>Incompletely defined or incompletely given</td>
<td>Incompletely defined or incompletely given</td>
</tr>
<tr>
<td>48. Authors' conclusions</td>
<td>Justified and valid</td>
<td>Unfair or invalid</td>
<td>Unfair or invalid</td>
</tr>
<tr>
<td>49. Author's conclusions</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
<td>Doubtful if large enough, stated but not considered or, if not long enough for adequate review of the results and design of management of possible influence on results</td>
</tr>
<tr>
<td>50. Protocol and results (e.g. in trials)</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
<td>Adequate and based on investigators' own results, but no or insufficient discussion of the results and design of management of possible influence on results</td>
</tr>
</tbody>
</table>

The maximum attainable score is 32. A score less than 27 is regarded as unacceptable or the results require confirmation by a further independent trial. A score of 27 to 32 is regarded as satisfactory; and a score of greater than 32 is regarded as excellent.
2. Scientific Writing

Writing Effectively to Make a Good Impression

Important Principles

47. 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 (for presentation at a scientific meeting)
- Research grant application
- Clinical study report (CSR) or other scientific reports for regulatory submission (e.g. to FDA, TGA, or Medsafe)
- Medical news / symposium report

48. Planning the paper: Initial considerations

- What do I have to say?
- What is the best format/structure for the message?
- What type of publication/vehicle 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?
49. 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.

50. 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 specific problem; or
  - To be educated and informed about the topic.

- Consequently, you 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.

51. Structure of scientific papers

<table>
<thead>
<tr>
<th>Sequence of the research</th>
<th>Section of the paper</th>
<th>Elements of critical argument</th>
</tr>
</thead>
<tbody>
<tr>
<td>The question to be answered</td>
<td>Introduction</td>
<td>Question (the problem that the paper will address)</td>
</tr>
<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/results): 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 reasons for contradictory evidence Answer</td>
</tr>
</tbody>
</table>
52. Structure of short commentaries / editorials / opinion articles

- These types of articles have little room in which to deliver their message
- The structure must therefore be well worked out within the word length limitations with the right sequence of 'critical argument' elements:
  - Introductory paragraphs: statement of the problem and a tentative answer
  - Middle paragraphs: evidence in support and counter evidence
  - Closing paragraphs: overall assessment of the evidence and the final answer statement / conclusion

53. 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 (use of non-existent words)
- Solecisms (ungrammatical use of English)
- Errors in syntax (incorrect grammatical arrangement of words)
- Use of incorrect or dehumanising words (e.g. ‘regime’ for regimen; ‘case’ for patient)
- Use of ‘empty’ phrases or words (e.g. ‘in other words’)
- Sexism
- Excessive use of abbreviations
- Plagiarism

54. Avoid Professional Pomposity

“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.”
### Slide 55. 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.

### Slide 56. Abbreviations: don’t assume all readers will know what they mean

**Extreme example:**

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 are often not acceptable in written English.

### Slide 57. 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.
58. Abbeviations may differ in US and UK English

**Transoesophageal echocardiography:**
- UK: TOE
- US: TEE

**Gastro-oesophageal reflux disease:**
- UK: GORD
- US: GERD

59. Abbeviations 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...

60. Tables and figures:

**Important considerations**

- In many instances, descriptive information can be more efficiently presented as a table or figure than in the text.
- However, if the point a table or figure makes can be made in the text in just a few words, the table/figure could be omitted.
- Great care should be taken with proper use of units in tables, and the data summarised should be clearly presented.
- Each table/figure should be understandable on its own. Therefore, always ensure a clear legend is provided to explain what the table/figure shows.
61. Revising the Manuscript for Content and Structure

- **Write the first draft**
- **Second draft**
  - Additional data for the primary analysis and subgroups
- **Third draft**
  - Colleagues
  - Coauthors
  - Hold for a few days, then revise content and structure
- **Final manuscript**

62. Final Manuscript Review (before its submission to a medical/scientific journal)

- Review the manuscript requirements of the journal; ensure it is the right journal (check its aims/scope and the types of articles it publishes)
- Following the **CONSORT checklist** (for clinical trials) or the **PRISMA checklist** (for systematic reviews/meta-analyses) may be compulsory for submission to the target journal (see Notes for these checklists); 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 exactly 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 and its importance
- 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
- Declare that all authors shown on the title page were involved in preparing or reviewing the paper, and that all have approved the final version submitted.

63. CONSORT (Consolidated Standards of Reporting Trials)

<table>
<thead>
<tr>
<th>Section</th>
<th>Topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
<td>1</td>
<td><strong>Introduction</strong> as a successful introduction to the trial: structured summary of trial design, methods, results, and conclusions</td>
</tr>
<tr>
<td>2</td>
<td><strong>Background</strong> and explanation of rationale for the trial and why it was undertaken</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><strong>Methods</strong> of the trial design (such as parallel, factorial, including details of randomization and blinding after trial commencement with competent and unblinding, if any)</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>4</td>
<td><strong>Sample size</strong> calculation where data were collected</td>
</tr>
<tr>
<td>5</td>
<td><strong>Interventions</strong> for each participant, whether random or not, with details of the intervention and its frequency and duration</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>6</td>
<td><strong>Results</strong> (e.g., treatment group and control group)</td>
</tr>
<tr>
<td>7</td>
<td><strong>Analysis</strong> techniques used in the analysis of data and any changes to the analysis after the trial commenced, if any</td>
<td></td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>8</td>
<td><strong>Sample size</strong> calculation using software</td>
</tr>
<tr>
<td><strong>Statistical analysis</strong></td>
<td>9</td>
<td><strong>Statistical analysis</strong> and interpretation of data, including any reasons for protocol deviation and statistical analysis after the trial commenced, if any</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>10</td>
<td><strong>Results</strong> of the statistical analysis, whether random or not, with details of the intervention and its frequency and duration</td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td>11</td>
<td><strong>Discussion</strong> of the results, including how they relate to other relevant studies and what the implications are for future research</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>12</td>
<td><strong>Conclusion</strong> of the results, including how they relate to other relevant studies and what the implications are for future research</td>
</tr>
</tbody>
</table>

**Note:** CONSORT is a checklist of items to include when reporting a randomized trial.
64. CONSORT flow diagram (CONSORT* Group):
Accounting for Patients Enrolled in Clinical Trials
Consolidated Standards of Reporting Trials [http://www.consort-statement.org/]

65. Journal instructions to authors for submission of manuscripts — pay close attention to:
- Page sizes (A4 or US Letter), margins, fonts, line spacing (usually double-spaced)
- Spelling and terminology — US or UK spelling (e.g., edema/oedema, diarrhea/diarrhoea, analyze/analyse, center/centre, etc.)
- Title page instructions, e.g., the length of the title and short running title, the 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 the 'Methods' section
- Limitations, appendixes, and tables/figures
- Acknowledgments, e.g., of the involvement of other people in the study and/or review of the manuscript
- Presentations of the tables and figures (in the required digital format for the figures) and the limitations on the number allowed
67. Reference style

1. Text citations: author name/year OR numbered citations?
   (consider using reference management software such as EndNote)

2. Bibliography: Vancouver or other style, e.g. Harvard, MLA styles?

   **Vancouver style**

   Text citation: [1] or [2]

   **Harvard style**

   Text citation: (Mire et al. 2005)

68. Writing a Clinical Trial Report

A Checklist for Items That Should be Considered for Inclusion

1. Title:
   - Include key words and the drug(s) under investigation
   - Keep concise and clearly reveal, naming key (subject) words are included

2. Summary/Euphoria:
   - Make key findings study in first sentence
   - Provide important details about the conduct of the study (including methodological and statistical information), but keep concise
   - Brief summary of major results and important conclusions/implications

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

4. Materials and methods:
   - Patients:
     - Inclusion/exclusion criteria
   - Setting(s) and number of patients (total and per treatment group)
   - Number of randomization, patients enrolled
   - Methods of randomization
   - Comparability of treatment groups (please patient demographic data in tables)
   - Number of visits per patient
   - Information on ethics committees approval, and procedures for obtaining patient consent

69. Overcoming “writer’s block”

- **Factors that give rise to “writer’s block”**:
  - Anxiety and boredom
  - Defiant attitudes / task inflation
  - A perfectionist attitude and/or 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.