Slide 1

Drug Literature Evaluation

General Principles

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Type of study	Phase of drug development	Activities undertaken (study objectives)	Study examples
Clinical pharmacology	I	Initial (FTIH) safety studies and pharmacokinetic (PK) / pharmacodynamic (PD) characterisations [usually in healthy volunteers]	▸ Single-ascending dose (SAD) and multiple-ascending dose (MAD) safety studies to determine the maximum tolerated dose (MTD) ▸ Single- and multiple-dose PK/PD studies ▸ Studies of PK-PD relationships ▸ Drug interaction studies
Therapeutic exploratory	IIa	Pilot clinical trials to evaluate effectiveness & safety [selected patients with target disease]	▸ Short-term effectiveness / proof-of-concept studies ▸ Dose-response studies ▸ Definition of endpoints for longer-term studies
	IIb	Randomised, controlled trials to evaluate effectiveness & tolerability [usually small-scale studies in patients with target disease]	▸ Comparative effectiveness/tolerability 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 effectiveness/tolerability 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 effectiveness/tolerability profile (including comparisons vs other drugs) ▸ Quality-of-life studies ▸ Initial pharmaceconomic studies (cost-effectiveness/ cost-benefit analyses)
Therapeutic use	IV	Studies to provide additional effectiveness/safety data (e.g. risk-benefit profile in special groups), refine dosing recommendations, or identify less common adverse events	▸ Further studies to effectiveness/tolerability in everyday clinical practice (e.g. 'real world' studies) ▸ Postmarketing surveillance studies ▸ Further comparisons vs other drugs ▸ Studies of additional endpoints/new indications ▸ Studies of drug utilisation patterns

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Variability in drug responsiveness may be influenced by numerous factors

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

Variability in responsiveness may be caused by:

- The natural progression of the disease (? 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.

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

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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.

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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.

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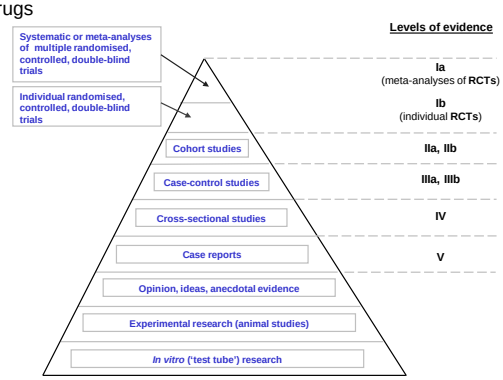
Evidence based medicine

- Levels of evidence in establishing the effectiveness/safety of drugs



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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 effectiveness or safety *versus* no treatment or *versus* other treatment options
- Appropriate to study pharmacokinetics in human subjects, dose-responsiveness or concentration-effect relationships, and for long-term toxicity studies – where patients are compared with their own baseline data.

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Clinical trial designs

2. Two (or more) patient group designs [comparative trials vs placebo or another active drug]

A. <u>Parallel-group studies:</u>

- 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 effectiveness 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).

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Clinical trial designs

2. Two (or more) patient group designs *(cont.)*

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.

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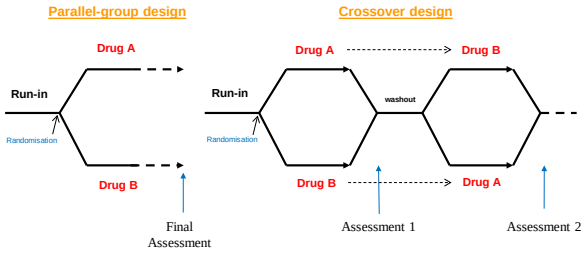
Parallel-group and crossover trial designs

- Controlled trials comparing 2 drugs/treatments



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When are crossover studies 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 appropriate for:
- Studies of long-term effects of drug therapy
- Studies of possible disease cure or prevention of death.

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Crossover studies

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

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

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Clinical trial designs

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

C. Sequential analyses:

- Usually 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 injuries**)** or less common/rare conditions.

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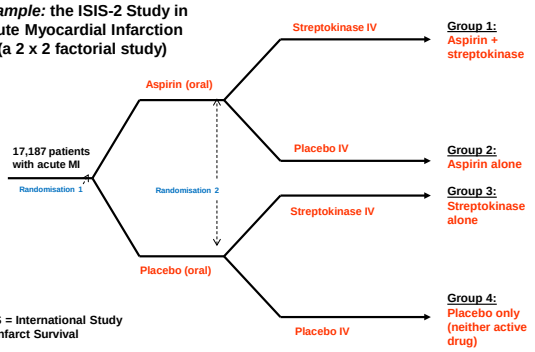
Factorial randomised controlled trials

- 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)**



ISIS = International Study of Infarct Survival

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Evaluation of clinical trials

1. Controlled clinical trials in diseased patients are mandatory to reliably establish the effectiveness and safety of drugs in clinical practice
2. Controlled trials vary considerably in their “acceptability”
3. This varying acceptability can make interpretation of their findings difficult
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.

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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.

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Critical evaluation of 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?

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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

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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 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

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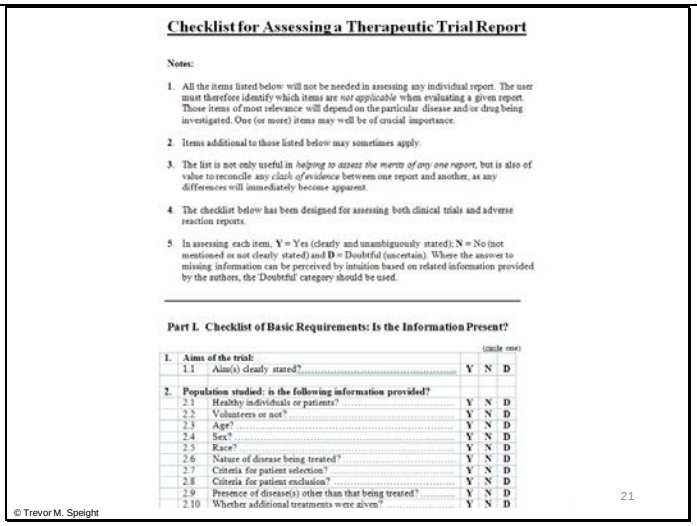

Checklist for Assessing a Therapeutic Trial Report

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?

		(circle one)		
1.	**Aims of the trial:**			
1.1	Aim(s) clearly stated?	**Y**	**N**	**D**
2.	**Population studied: is the following information provided?**			
2.1	Healthy individuals or patients?	**Y**	**N**	**D**
2.2	Volunteers or not?	**Y**	**N**	**D**
2.3	Age?	**Y**	**N**	**D**
2.4	Sex?	**Y**	**N**	**D**
2.5	Race?	**Y**	**N**	**D**
2.6	Nature of disease being treated?	**Y**	**N**	**D**
2.7	Criteria for patient selection?	**Y**	**N**	**D**
2.8	Criteria for patient exclusion?	**Y**	**N**	**D**
2.9	Presence of disease(s) other than that being treated?	**Y**	**N**	**D**
2.10	Whether additional treatments were given?	**Y**	**N**	**D**

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Aims and objectives of clinical 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
- *Generally*, 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.

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Adverse events (AE)

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)

- 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 judgement) and/or require specific intervention(s) to prevent serious outcomes

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AEs: relationship to the study drug (treatment-related AEs *vs* 'all-cause' AEs)

Treatment-emergent AEs (TEAEs) = all 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
   - 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 is equally likely
   - Dechallenge is positive
4. *Probably not* related to drug:
   - Evidence of exposure to drug, BUT
   - Another cause is more likely
   - Dechallenge is negative/unclear
   - Rechallenge is negative/unclear
5. *Definitely not* related to drug:
   - Drug not received or the temporal relationship is not reasonable

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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)

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Adequacy of controls

- Adequacy of the randomisation procedure:
  - What method was used to allocate treatment – computerised random number generation, random number tables, an interactive web-based response system or interactive voice response system (IWRS/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:
  - 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 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?

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Blinding techniques

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

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

	Group A		Group B	
	1. *tid*	2. *bid*	1. *tid*	2. *bid*
Morning:	**X**-active + **Y**-placebo		**X**-placebo + **Y**-active	
Midday:	**X**-active		**X**-placebo	
Evening:	**X**-active + **Y**-placebo		**X**-placebo + **Y**-active	

5 tablets per day
2 medicine containers/patient)

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

	Group A	Group B
Morning:	**X**	**Y**
Midday:	**X**	**Y** (placebo)
Evening:	**X**	**Y**

3 capsules per day
[1 container (e.g. a blister pack) per patient]

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Adequacy of controls

- 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 effectiveness
    - 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 effectiveness and safety?
  - Which patient population has been analysed – the "intention-to-treat" (ITT) population or the "per-protocol" (PP) population, or both ?

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Intention-to-treat vs per-protocol analysis

ITT analysis:

- Unbiased method of assessment **(**analyses all patients according to the group to which they were originally randomised)
- Assesses the overall consequences of each treatment regimen **(**takes account of all post-randomisation events, including non-compliance**)**
- Correspond to pragmatic management trials **(**reflect 'real-world' clinical practice**)**
- *Justifiable exclusions:* those who did not receive at least one dose of the study medication, and those with no 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
- Maximises opportunity to show effectiveness – 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 effectiveness or the occurrence of adverse events

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Missing data: last observation carried forward

- 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 effectiveness.

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Analysis of treatment response

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 (*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 the 'true' drug effect, BUT it 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.

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Cochrane collaboration criteria

- Assessment of methodological bias in clinical trials

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* or criteria only partially met = unclear risk of bias
3. *Inadequate* : criteria not adequately met = high risk of bias

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Cochrane collaboration criteria

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

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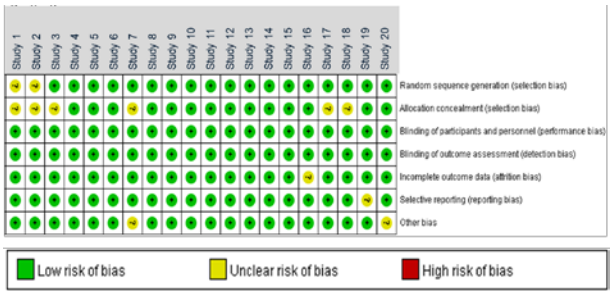
Assessment of bias

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



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Interpreting risk

Risk of bias	Within a trial	Across trials	Interpretation
1. Low risk of bias	Low risk of bias for all key domains	All or most information is from trials at low risk of bias	Bias, if present, is unlikely to have seriously affected the results
2. Unclear risk of bias	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias	There is a risk of bias that could create some doubt about the results
3. High risk of bias	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results	Bias may have seriously affected the results of these trials

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Interpreting clinical 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 (e.g., the change in a disease rating scale) 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., is there obvious reporting bias]?

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Common faults in 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.

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Importance of clinical trial size

- Two Randomised Trials of IV β-Blockers During Evolution of Acute MI

Trial [drug]	No. of patients	Mortality rates:		Mortality reduction & significance
		Active drug	Placebo	
MIAMI (1985)* [metoprolol]	5778	4.3% (123/2877)	4.9% (142/2901)	13% [NS] (p = 0.29)
ISIS-1 (1986)** [atenolol]	16,027	3.9% (313/8037)	4.6% (365/7990)	15% [Sig.] (2p < 0.04)

* 15-day treatment period.
** 7-day treatment period.

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

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Benefit of clinical trials expressed as number needed to treat (NNT)

1. Trials of mortality reduction:

$$NNT = \frac{1}{mortality\ rate\ with\ placebo - mortality\ rate\ with\ active\ drug\ (\%)}$$

2. Trials of therapeutic benefit:

$$NNT = \frac{1}{response\ rate\ with\ active\ drug - response\ rate\ with\ placebo\ \%)}$$

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Design issues in clinical trial analysis

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
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-drug comparative trial, was the investigational treatment compared with the best available alternative treatment ?)

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Design issues in clinical trial analysis

5. Participant flow (are all randomised patients accounted for in the presentation of the results?; are the reasons for study 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 effectiveness 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 ?).

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41. **Clinical Trial Evaluation: Major Criteria**

Criteria	Evaluation points	Score (0 – 2)
1. Purpose of the study	□ Clearly defined?	
2. Patient selection	□ Clearly defined and appropriate criteria? □ Diagnosis confirmed? □ Homogeneous patient group? □ Exclusions defined and appropriate? □ Prior therapy defined?	
3. Number of patients	□ Adequate to detect any differences between treatments?	
4. Randomisation	□ Yes/no? □ Appropriate methodology? □ Group comparability established? □ Influence of any differences discussed?	
5. Drug dosage(s)	□ Defined and appropriate? □ Comparable relative effects?	
6. Duration of therapy	□ Long enough to show maximum effect of drug (effectiveness and/or tolerability)?	
7. Concurrent therapy (drug or non-drug)	□ Full details reported? □ Possible influence discussed?	
8. Controls to reduce variation (e.g. run-ins, placebo, standard comparator, crossover design, washouts)	□ Yes/no? □ Baseline established? □ Controls adequate?	

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Criteria	Evaluation points	Score (0 – 2)
9. Controls to reduce bias (blinding)	□ Yes/no? □ Method of maintaining blindness stated?	
10. Compliance	□ Compliance checks performed? □ Methods stated and adequate? □ Influence, if any, on results discussed?	
11. Effectiveness assessment	□ Parameters fully defined? □ Parameters relevant and reproducible? □ Results fully reported? □ Adequate follow-up? □ Stratification performed, when appropriate?	
12. Assessment of adverse events	□ Protocol clearly defined? □ Number and type fully reported? □ Severity stated? □ Likely relationship to therapy discussed?	
13. Statistical evaluation	□ Yes/no? □ Methods stated and valid?	
14. Author's discussion	□ Full discussion or all results? □ Fair review of others' work? □ Self-critical, if necessary?	
15. Author's conclusions	□ Conclusions clearly stated? □ Conclusions valid/justified?	
16. Clinical relevance of results	□ Trial design and conduct acceptable? □ Any fatal flaws? □ Any major inadequacies?	
	Total (out of 32) =	 %

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Guide to Scoring of Clinical Trials

Criteria	2 Points		1 Point		0 Points
1. Purpose of the study	Clearly defined	1 ½	Incompletely defined	½	Not defined
2. Patient selection	Clearly defined	1 ½	Inadequately or poorly defined	½	Not defined
3. Number of patients	Sufficiently large considering the response obtained with each treatment	1 ½	Doubtful if large enough, or infrequent occurrence of disease limits number of available patients	½	Too few patients to show statistically significant differences, if any, between treatments
4. Randomisation of patients to treatment (and group compara-bility)	Adequate method used, and group comparability detailed and fully established	1 ½	Doubtful randomisation method, or groups stated to be comparable but no or insufficient details given	½	No randomisation procedure, or group comparability not established
5. Drug dosage(s)	Comparable dosages (established by earlier studies) or dosages titrated for each patient	1 ½	Doubtful if dosages comparable (or no titration of dosages to ensure comparability)	½	Inadequate or noncomparable dosages
6. Duration of therapy	Long enough to show optimum drug effects and assess tolerability, or to cover a period of 'risk'	1 ½	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	½	Not long enough
7. Concurrent therapy (drug or non-drug)	None; or, if given, fully described and possible influence on results adequately discussed	1 ½	Allowed or given, but with inadequate details and no discussion of possible influence	½	Information missing or unclear
8. Controls to reduce bias (blinding)	Double-blind protocol; procedure used detailed and appropriate	1 ½	Doubtful procedure to ensure double-blind, or single-blind protocol	½	Open-label (no blinding procedure)
9. Other controls to reduce variation	Controls adequate or were not necessary	1 ½	Controls necessary but were inadequate (or of doubtful validity)	½	Controls necessary but not stated or absent

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Criteria	2 Points		1 Point		0 Points
10. Compliance	Definite: checks made (by an appropriate method), or serum levels measured, or parenteral route of administration, or inpatients	1 ½	Probable: stated but details not given or methods used not adequate to ensure compliance	½	Not considered or, if outpatients, no checks made (or stated)
11. Effectiveness assessment	Fully defined, relevant and reproducible methods adequate to assess effectiveness, and full reporting of results	1 ½	Methods of assessing effectiveness inadequately or incompletely defined, or results not completely reported	½	Inadequately defined or irrelevant or non-reproducible methods, or inadequate reporting of results
12. Assessment of adverse events	Clearly defined protocol, effects well described (with an indication of severity), and relationship to therapy discussed	1 ½	Protocol and results given, but neither fully detailed	½	Neither protocol nor results given (or poorly detailed)
13. Statistical evaluation	Full details of methods provided, and adequate statistical analysis of all results	1 ½	Incomplete details of methods used, and/or incomplete statistical analysis of results	½	No statistical analysis of results
14. Author's discussion	Adequate and fair discussion of the study's results, plus adequate review of the results of other investigators	1 ½	Reasonable discussion of own results, but no or poor review of the results of other investigators	½	Unfair or invalid discussion of own or others' work, or no discussion at all
15. Author's conclusions	Adequate and based on the results and design of the study (i.e. fully justified and valid)	1 ½	Inadequate or doubtful conclusions, or none made	½	Not based on the results demonstrated, too far-fetched, or irrelevant
16. Clinical relevance of results	Clinically relevant therapeutic effect (not just a statistically significant effect), and all design criteria met	1 ½	Doubtful clinical relevance or not all the design criteria met	½	Not clinically relevant or acceptable

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.

Slide 46	## Application of the checklist and scoring system • Identifying “best” results – e.g. in evidence-based medicine assessments for a specific disease • Identifying reasons for differing results between trials • *Aide-memoire* when evaluating or writing a clinical trial • Identifying missing or deficient areas when refereeing or editing a trial report • Evaluating the references that are provided to support promotional claims (e.g. in advertisements). 46 	
Slide 47	# Scientific writing James Morse Department Pharmacology and Clinical Pharmacology 	
Slide 48	## Types of scientific papers • Clinical trial or other original research paper • Review article – e.g. literature review, systematic analysis, meta-analysis, 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 	

Slide 49	**Planning a paper** • 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 © Trevor M. Speight	
Slide 50	**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 © Trevor M. Speight	

Slide 51	**Scientific paper structure**
	• 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.
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	© Trevor M. Speight	

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Scientific paper structure

Sequence of the research	Section of the paper	Elements of 'critical argument'
The question to be answered	• Introduction	Question (the problem that the paper will address)
How the answer was sought	• Materials and Methods	Credibility of the evidence
Findings	• Results	Evidence (the study data/ results): initial answer
Findings considered in the light of other investigators' findings: the answer	• Discussion and Conclusions	Supporting evidence Contradictory evidence Assessment of reasons for contradictory evidence Answer

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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:

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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 (see notes for examples)
- Sexism
- Excessive use of abbreviations
- Plagiarism.

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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".

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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.

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Do not assume readers will understand abbreviations

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 / 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.

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Slide 58	**Abbreviations can have multiple meanings** 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 © Trevor M. Speight	
Slide 59	**Abbreviations may differ between US and UK English** Transoesophageal echocardiography: • UK: TOE • US: TEE Gastro-oesophageal reflux disease: • UK: GORD • US: GERD 59 © Trevor M. Speight	
Slide 60	**Tables and figures** • 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. 60 © Trevor M. Speight	

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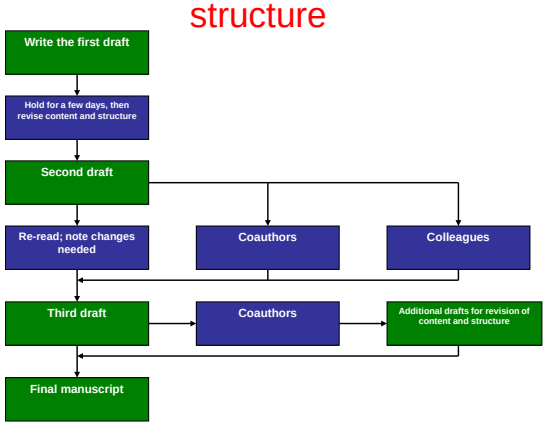
Revising a manuscript for content and structure



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Final manuscript review

- Review the manuscript requirements of the journal, and 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 <u>all</u> authors shown on the title page were involved in preparing or reviewing the paper, and that all have approved the final version submitted.

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63.

CONSORT (Consolidated Standards of Reporting Trials)
Checklist of Items to Include When Reporting a Randomised Trial

Section / topic	Item No.	Description
Title and Abstract	1	• Identification as a randomised trial in the title • Structured summary of trial design, methods, results, and conclusions
Introduction: Background and objectives	2	• Scientific background and explanation of rationale • Specific objectives or hypotheses
Methods: Trial design	3	• Description of trial design (such as parallel, factorial), including allocation ratio • Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4	• Eligibility criteria for participants • Settings and locations where the data were collected
Interventions	5	• The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6	• Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed • Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7	• How sample size was determined • When applicable, explanation of any interim analyses and stopping guidelines
Randomisation – Sequence generation	8	• Method used to generate the random allocation sequence • Type of randomisation; details of any restriction (such as blocking and block size)
Randomisation – Allocation concealment mechanism	9	• 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
Randomisation – Implementation	10	• Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11	• If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how • If relevant, description of the similarity of interventions
Statistical methods	12	• Statistical methods used to compare groups for primary and secondary outcomes • Methods for additional analyses, such as subgroup analyses and adjusted analyses

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Section / topic	Item No.	Description
Results:		
Participant flow (Note: a diagram is recommended)	13	• For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome • For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14	• Dates defining the periods of recruitment and follow-up • Why the trial ended or was stopped
Baseline data	15	• A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	• For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17	• For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) • For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory
Harms	19	• All important harms or unintended effects in each group
Discussion:		
Limitations	20	• Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	• Generalisability (external validity, applicability) of the trial findings
Interpretation	22	• Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information:		
Registration	23	• Registration number and name of trial registry
Protocol	24	• Where the full trial protocol can be accessed, if available
Funding	25	• Sources of funding and other support (such as supply of drugs), role of funders

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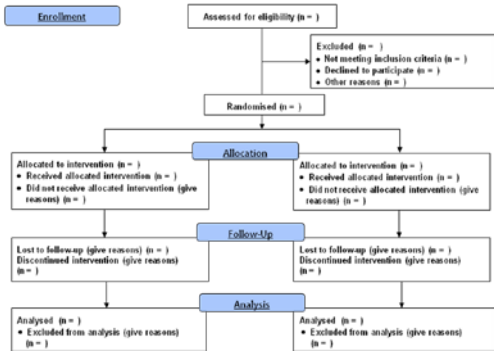
'CONSORT' flow diagram

- Accounting for patients enrolled in clinical trials



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Instructions to authors

- 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.) [other examples: see *Notes*]
- 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 for the work, etc.
- Declarations that all authors were involved in preparing the paper
- *Not e* : All authors should have participated in: (1) the planning and/or execution of the study; (2) the collection and analysis of the study data; (3) writing of the manuscript *OR* critical review of the manuscript; and (4) reading and approving the final version submitted
- 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
- Maximum allowable word length and tables & figures (*Note:* tables and figures may be equated to approx. 250 words by some journals, which will reduce the allowable total word length)
- Acknowledgements, e.g. of the involvement of other people in the study and/or review of the manuscript (including people who provided editorial assistance)
- Presentation of the tables and figures (in the required digital format for the figures), and the limitations on the number allowed

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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, AMA styles?

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

1. Mire DE, Silfani TN, Pugsley MK. A review of the structural and functional features of olmesartan medoxomil, an angiotensin receptor blocker. J Cardiovasc Pharmacol. 2005;46(5):585-93.

Harvard style **Text citation: (Mire et al. 2005)**

Mire, D.E., Silfani, T.N. & Pugsley, M.K. (2005) A review of the structural and functional features of olmesartan medoxomil, an angiotensin receptor blocker. *J. Cardiovasc. Pharmacol.*, 46(5), 585-593.

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68.

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' (indexible) 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.

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Overcoming "writer's block"

- Factors that give rise to "writer's block":
  - Anxiety and boredom
  - Defeatist 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.

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Overcoming “writer's block”

- 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.