1.

Clinical Trial Design and Drug Literature Evaluation

General Principles

Classification of Clinical Studies According to Objective

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 efficacy and safety [selected patients with target disease]	▸ Short-term efficacy / proof-of-concept studies ▸ Dose-response studies ▸ Definition of endpoints for longer-term studies
	IIb	Randomised, controlled trials to evaluate efficacy/safety [usually small-scale studies in patients with target disease]	▸ Comparative efficacy/safety studies (*vs* placebo or other/standard drugs) ▸ Identification of disease subtypes for which drug is particularly effective ▸ Definition of goals for longer-term studies
Therapeutic confirmatory	IIIa	Randomised, controlled trials in relatively large numbers of patients, *or* smaller trials in special groups of patients	▸ Comparative efficacy/safety studies (*vs* other/standard drugs) ▸ Studies of mortality/morbidity outcomes ▸ Evaluations in special populations (e.g. elderly)
	IIIb	Clinical trials that supplement earlier trials and establish risk-benefit profile	▸ Further evaluations of efficacy/safety profile (including comparisons *vs* other drugs) ▸ Quality-of-life studies ▸ Initial pharmaceconomic studies (cost-effectiveness /cost-benefit analyses)
Therapeutic use	IV	Studies to provide additional efficacy/safety data (e.g. risk-benefit profile in special groups), refine dosing recommendations, or identify less common adverse events	▸ Further studies to confirm efficacy/safety in everyday clinical practice (e.g. 'real world' studies) ▸ Postmarketing surveillance studies ▸ Further comparisons *vs* other drugs ▸ Studies of additional endpoints/new indications ▸ Studies of drug utilisation patterns

FTIH = First time in humans

Factors Affecting the Response to Drugs in Individual Patients

- **The natural progression of the disease (deterioration or improvement)**

- **Drug factors:**
  - **pharmacodynamic variability (e.g. differences in receptor sensitivity, altered homeostatic mechanisms)**
  - **pharmacokinetic variability (e.g. differences in absorption, distribution, metabolism, excretory capacity, etc.)**
  - **interactions with other drugs/environmental factors**

- **Non-drug factors:**
  - **personality, beliefs and attitudes of the patient**
  - **the patient's prior experience of doctors and drugs, and his/her expectations of the treatment prescribed**
  - **personality, beliefs and attitudes of the clinician**
  - **the clinician's explanation of the treatment to the patient**

Types of Clinical Trial Designs

1. Single patient group designs

- All patients are treated with the same drug
- Generally open-label/non-randomised
- Not appropriate to demonstrate efficacy *versus* no treatment or placebo, or *versus* other treatment options
- Historical controls can be considered for comparative purposes but are less satisfactory than prospective controls (as many confounding factors and biases may enter the trial and cannot be allowed for)
- Appropriate to study dose-response or concentration-effect relationships, and for long-term toxicity studies (where patients are compared with their own baseline data)

2. Two (or more) patient group designs

a) Parallel-group studies:

- Patients are randomised to one of two (or more) treatment groups, and generally receive the assigned treatment throughout the trial
- Applicable to most clinical situations – most commonly used design for establishing efficacy and/or safety
- Assess between-patient differences
- 'Robust' enough to cope with the many types of problems that occur in clinical trials (e.g. dropouts, missing data, etc.)

b) Crossover studies:

- Patients receive each treatment (randomised to one or the other first, and then crossed over after a 'washout' period between study periods)
- Assess within-patient differences – drug effect is expressed as the differences between responses to the two treatments
- Variability of data obtained is less than with parallel group design, and fewer patients are required to detect differences between treatments
- However, not as 'robust' as parallel group studies (as adversely affected by patient dropouts and missing data, etc.)
- Analysis also requires consideration of a possible 'carryover' effect from one treatment to the next, and a possible 'treatment order' effect

Types of Clinical Trial Designs *(Contd.)*

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

c) Sequential analysis:

- Generally involves the allocation of participants in pairs to two treatments
- Allows a trial to be continually monitored and stopped when a clinical result is achieved
- Numbers of patients needed can be kept to a minimum, and a significant result obtained more rapidly
- However, the design assumes that there is a real difference to be detected
- Not commonly used nowadays (except perhaps for trials in acute diseases)

Clinical Trial Evaluation:
Important Principles

- **Well-controlled clinical trials in diseased patients are mandatory to reliably establish the effectiveness and safety of drugs in clinical practice**

- **Since both clinicians and patients are capable of bias due to previously held beliefs, the *double-blind* technique is an important control measure to prevent bias from influencing the results**

- **However, in assessing such trials, a fundamental problem is the varying "acceptability" of published reports – which makes interpretation and use of the data difficult**

- **The fact that a trial is "double-blind" does not guarantee that its findings will necessarily be beyond reproach**

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

Basic Principles of Clinical Trial Evaluation

- **Any individual trial provides limited information**
- **One study cannot provide all the evidence**
- **Statements made must be critically evaluated**

Important General Requirements of Clinical Trials

- **Appropriate controls to reduce variation and bias**
- **Appropriate and adequate methods of assessing therapeutic effects**
- **Adequate number of patients**
- **Homogeneous population**
- **Appropriate duration of treatment**
- **Appropriate dosage**
- **Appropriate methods of assessing/measuring adverse events**
- **Appropriate statistical validation**

Principles of Assessing Reports of Therapeutic Trials

1. Basic Principles

a) ***Any individual trial provides limited information:***
What happens in a selected group of patients under defined and often very rigid conditions

b) ***One study cannot provide all the evidence:***
The answers to the many questions that may need to be considered in evaluating a drug cannot be provided by any one study

c) ***Statements made must be critically evaluated:***
All statements made and conclusions drawn by the authors cannot necessarily be accepted as read – critical faculties must be maintained at all times

2. Important General Requirements

a) ***Appropriate controls:***
Were the controls adequate or were they not necessary to avoid bias or reduce variation?

b) ***Appropriate and adequate methods of assessing the therapeutic effects:***
Were the methods fully defined, relevant to the aims, and reproducible?

c) ***Adequate number of patients:***
The smaller the difference between two drugs, the greater the number of patients required. Failure to find a difference between two drugs does not necessarily mean that they are equal, but rather that any difference which might exist could not be detected with the methods and number of patients used

d) ***Homogeneous population:***
If two or more drugs are compared, were the treatment groups sufficiently well matched – allocation of patients at random to treatment does nor guarantee like groups

e) ***Appropriate duration of treatment:***
Was therapy sufficiently long for full drug effects (adverse or favourable) and for the nature of the disease?

f) ***Appropriate dosage:***
Were the dosages chosen adequate (if a dose-effect study) or comparable (if two or more drugs being compared)?

g) ***Measurement of adverse events:***
Were the methods of assessment adequate and with a defined protocol – the incidence of adverse events depends on the thoroughness with which they are sought, and by whom and how

h) ***Appropriate statistical validation:***
NB. Elaborate statistics cannot validate a poorly designed or executed trial, make unlike treatment groups equal, or be used to extend the results obtained in a selected group of patients under defined conditions to individualised use of a drug in actual clinical practice

3. Interpretation of the Results and Conclusions

a) ***Are the results clinically significant or acceptable?***
Would the patient derive benefit? Does the result satisfy current desirable criteria?

b) ***Are comparisons with other drug trials (e.g. in the discussion) valid?***
Was a comparison made with the currently accepted treatment of choice? If so, was the comparison valid. If not, was such a comparison unnecessary or was a comparison made against a superseded treatment. Is the discussion a fair review of reliable results?

c) ***Are the authors' conclusions justified?***
Conclusions must be made on the basis of what has been established in the trial and not extended beyond these findings

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**
		If so, are they described? ……...	**Y**	**N**	**D**
3.	**Pharmacological factors: is the following information provided?**				
	3.1	Daily dose? ……..	**Y**	**N**	**D**

(continued over)

3. Pharmacological factors (continued):

3.2	Frequency of administration? ……..	**Y**	**N**	**D**
3.3	Time of day when doses given and results recorded? …….	**Y**	**N**	**D**
3.4	Route of administration? …….	**Y**	**N**	**D**
3.5	Source of drug (i.e. name of manufacturer)? ……..	**Y**	**N**	**D**
3.6	Dosage form (i.e. tablet, syrup, injection, etc.)? …….	**Y**	**N**	**D**
3.7	Timing of drug administration in relation to factors affecting absorption (e.g. meals)? ……..	**Y**	**N**	**D**
3.8	Checks that drug was taken? ……...	**Y**	**N**	**D**
3.9	Were other therapeutic measures employed (either drug or non-drug)? ……...	**Y**	**N**	**D**
	If yes, are they adequately described? ……...	**Y**	**N**	**D**
3.10	Total duration of treatment? ……	**Y**	**N**	**D**
3.11	Dates when trial was begun and completed (especially relevant in seasonal disorders or when 'standards' of therapy have altered)? ……..	**Y**	**N**	**D**
3.12	Drug serum concentrations measured (where appropriate)? ...	**Y**	**N**	**D**

4. Non-pharmacological factors: is the following information provided?

4.1	Person(s) who made the observations? ……...	**Y**	**N**	**D**
4.2	Inpatients or outpatients? ……	**Y**	**N**	**D**
4.3	Setting (e.g. one or several hospitals, clinics, wards, etc.)? …	**Y**	**N**	**D**

5. Methods and additional design factors:

5.1	Are the methods of assessing the therapeutic effects clearly described and are they accepted standard methods? ……...	**Y**	**N**	**D**
5.2	Were control measures used to *reduce variation* that might influence the results? ……...	**Y**	**N**	**D**

If yes, *specify* (more than one descriptor of the method used is possible):

- a) Patient his/her own control . …… ☐
- b) Run-in period to establish baseline …… ☐
- c) Stratification or matched subgroups ..…….. ☐
- d) Concurrent controls ..…… ☐
- e) Historical controls …… ☐
- f) Other …… ☐

5.3	Were controls used to *reduce bias*? …….	**Y**	**N**	**D**

If yes, specify (more than one descriptor is likely):

- a) 'Blind' observers …….. ☐
- b) 'Blind' patients ……. ☐
- c) Random allocation …….. ☐
- d) Matching placebo …… ☐
- e) 'Double-dummy' technique ……. ☐

(continued over)

Part II. Evaluation of the Quality of the Trial Design

6. Assessment of the trial:

6.1	Were the patients suitably selected in relation to the aims (see sections 1 and 2 above)? ……..	**Y**	**N**	**D**
6.2	Were enough subjects used? ……...	**Y**	**N**	**D**
6.3	Was the dosage appropriate? ……..	**Y**	**N**	**D**
6.4	Was the duration of treatment adequate? ……	**Y**	**N**	**D**
6.5	Were the methods of assessment valid in relation to the aim?	**Y**	**N**	**D**
6.6	Were they the accepted standardised methods? ……..	**Y**	**N**	**D**
6.7	Were they sufficiently sensitive in relation to the aim of the trial? …….	**Y**	**N**	**D**
6.8	Were 'carry-over' effects avoided or allowed for where these may have occurred? …….	**Y**	**N**	**D**
6.9	If controls were used, were they adequate? …….	**Y**	**N**	**D**
	Or, if no controls were used, were they unnecessary? ……	**Y**	**N**	**D**
6.10	Was comparability of the treatment groups established? ……	**Y**	**N**	**D**
6.11	Was the overall design appropriate? ……...	**Y**	**N**	**D**
6.12	Are the data presented adequate for assessment? ……	**Y**	**N**	**D**
6.13	If statistical tests were not done, were they unnecessary? …..	**Y**	**N**	**D**
	Or, if statistical tests are reported:			
	a) Is it clear how they were done? ……	**Y**	**N**	**D**
	b) Were they appropriately used? …….	**Y**	**N**	**D**
6.14	If a comparative study, was the comparison made with the currently accepted treatment of choice? ……..	**Y**	**N**	**D**
6.15	Are the authors' conclusions appropriate? ……...	**Y**	**N**	**D**
	a) Is the result as stated by the author(s) clinically significant? ……...	**Y**	**N**	**D**
	b) Are the comparisons with other drug trials made by the author(s) [e.g. in the Discussion] valid or fair? ……	**Y**	**N**	**D**
	c) On the basis of what has been established in the trial, are the authors' conclusions or claims justified? …….....	**Y**	**N**	**D**

Part III. Identifying Areas of Special Importance

Are there any particular areas which are especially important considering the nature of the drug and/or the disease under study?

1. 4.
2. 5.
3. 6.

Have these crucial areas been adequately dealt with?

1. **Y N D** 4. **Y N D**
2. **Y N D** 5. **Y N D**
3. **Y N D** 6. **Y N D**

Part IV. Conclusions as to the Quality of the Information Provided by the Report

On the basis of the above analysis, do you consider that the evidence provided by the report is acceptable?

Definitely yes ☐ Probably ☐ yes No ☐

Controls

- **Whichever control methods are used in a clinical study, they must be both valid and suitable to the aim of the trial**

- **Concurrent controls are preferable to historical controls**

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

- **Random allocation does not guarantee like treatment groups in parallel group studies, and it is ESSENTIAL to show that the treatment groups are comparable (*NB*. not essential in crossover studies but is advisable)**

- **However, the larger the number of patients enrolled in a parallel group study, the greater the likelihood that they will be reasonably well matched**

Interpretation of Clinical Trial Data
Major Perspectives

- **Statistical significance**
  a) On its own, does not provide information on importance for patients (which must be assessed separately)
  b) Often, however, there is a relationship between statistical significance and clinical significance

- **Clinical significance**
  a) Is the response of sufficient magnitude to justify use of the study drug in clinical practice?
  b) Does the drug have a greater benefit: risk ratio than other treatments used for the same indication (i.e. causes a greater change in a critical efficacy parameter or fewer adverse events)?

- **Relevance for medical practice**
  a) How important or relevant are the results for other clinical situations?
  b) Do they have implications for treating other patients (i.e. other than those included in the clinical trial)?

Assessment of Study Bias
(Cochrane Collaboration Criteria)

Six domains of a clinical trial to consider in assessing the risk of bias

Assess each domain as:

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

Type of bias	Potential source of bias	Criteria to assess	Key questions to consider
1. Selection bias	Random sequence generation (for the randomisation procedure)	The 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 used to achieve blinding of the patients and the investigators	? Was knowledge of the interventions adequately prevented*
3. Detection bias	Blinding of outcome assessment	Methods used to achieve blinding of the outcome assessors	? Was knowledge of the interventions adequately prevented*
4. Attrition bias	Reporting of the 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 the pre-specified objectives (as in the trial database listing†)	? Complete or selective reporting of results. If incomplete, are the reasons adequately addressed?
6. Other bias	Any other trial aspect that may lead to bias	Criteria not covered in other domains	? Other problems that may affect interpretation of the results‡

* *Note:* obvious differences in treatment effects or adverse events between interventions can readily unblind a trial.

† For example, in the "ClinicalTrials.gov" database.

‡ For example, the specific study design used; the presence of major baseline imbalance; or early cessation of the trial.

Interpreting the risk of bias for each domain within a trial and across trials

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 creates 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

Common Deficiencies in Clinical Trial Reports

1. Introduction:

- Inadequate description of the aims and objectives
- Excessive background information

2. Methodology:

- Inadequate description of key information on how data were derived
- Omission of some important information (e.g. on trial management)

3. Results:

- Presentation of derived data without adequate information on actual numbers or raw data
- Presentation of data in an ambiguous manner
- Insufficient effectiveness data to permit proper interpretation
- Insufficient adverse effect data to address basic questions

4. Discussion:

- Lack of conciseness and organisation
- Results are only compared with other studies that support the authors' interpretation
- Inadequate consideration of factors that might be expected to influence the results
- Unwarranted extrapolation to other patient populations
- Discussion of too many peripheral/tangential issues

Key Design Issues to Consider in the Overall Analysis of a Clinical Trial (*Summary*)

1. **Patient eligibility**
   - How were patients selected?
   - Was there any potential for 'lead-time' or 'stage migration' bias?
   - Were the patients a narrow/divergent subgroup or a broad population with the disease?
   - If a narrow subgroup, have the results been generalised to all patients with the disease?

2. **Randomisation**
   - Was it adequate to ensure both known and unknown confounders are equally distributed in the treatment groups?
   - Was a valid method used to generate the random allocation sequence?
   - If so, how was it concealed?
   - Has the randomisation procedure ensured homogeneous treatment groups?

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

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

5. **Participant flow**
   - Are all randomised patients accounted for in the presentation of the results?
   - Are the reasons for withdrawals adequately explained?

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

7. **Appropriate endpoints**
   - Were the endpoints appropriate to demonstrate efficacy of the treatment?
   - Was a surrogate endpoint chosen; if so, why?
   - If a surrogate endpoint was chosen, is it sufficiently correlated with the clinical outcome?

8. **Trial duration**
   - Was it adequate to permit a meaningful clinical outcome and detect specific adverse events?

9. **Interpretation of the results**
   - Was the trial designed to demonstrate superiority or non-inferiority of the treatment?
   - Have the results been interpreted correctly and compared with other trials?

Clinical Trial Evaluation: Major Criteria

Trial ……..

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 (efficacy 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?**	

(continued over)

Clinical Trial Evaluation: Major Criteria *(continued)*

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. Efficacy 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)	
	=	**%**

Guide to Scoring of Clinical Trials

Notes:

1. By focusing on individual components of the trial, this scoring system is designed to provide only a *general impression* of the quality of the trial, as it is reported. In the final analysis, the credibility of the evidence may well depend on a specific crucial aspect being satisfied in relation to the aim or particular effect sought, even though this aspect may have scored highly on the scoring system. Such aspects must always be considered when using this scoring system.
2. 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.

Criteria	2 Points		1 Point		0 Points
1. Purpose of the study	Clearly defined	1½	Incompletely defined	½	Not defined
2. Patient selection	Clearly defined	1½	Inadequately or poorly defined	½	Not defined
3. Number of patients	Sufficiently large considering the response obtained with each treatment	1½	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	1½	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	1½	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'	1½	Not long enough for either (a) optimum drug effects or (b) to cover a period of 'risk', *or* only long enough to fulfil *part* of the trial's aim	½	Not long enough
7. Concurrent therapy (drug or non-drug)	None; or, if given, fully described and possible influence on results adequately discussed	1½	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	1½	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	1½	Controls necessary but were inadequate (or of doubtful validity)	½	Controls necessary but not stated or absent

(continued over)

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	1½	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. Efficacy assessment	Fully defined, relevant and reproducible methods adequate to assess efficacy, and full reporting of results	1½	Methods of assessing efficacy 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	1½	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	1½	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	1½	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)	1½	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	1½	Doubtful clinical relevance *or* not all the design criteria met	½	Not clinically relevant or acceptable

Application of Checklist and Scoring System

- **Identifying 'best' results (e.g. in evidence-based medicine assessments)**
- **Identifying reasons for differing results**
- ***Aide-memoire* when evaluating or writing a clinical trial**
- **Identifying missing or deficient areas when refereeing or editing a trial report**
- **Evaluating references provided to support formulary addition requests or promotional claims**

2.

Scientific Report Writing

Making a Good Impression

Planning the Paper:

Initial Considerations

- **What do I have to say?**
- **What is the best format for the message?**
- **What type of publication will it appear in?**
- **Who is the intended audience for the message?**
- **What prose style should I use?**
- **What level of detail should I go to?**

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

***NB*. An <u>outline</u> listing the key points is always advantageous**

Structure of Research Papers

Sequence of the research	Section of report	Elements of 'critical argument'
The question to be answered	• **Introduction**	**The problem (question)**
How the answer was sought	• **Materials and methods**	**Credibility of the evidence**
Findings	• **Results**	**Evidence (the data): initial answer**
Findings considered in the light of findings of other investigators: the answer	• **Discussion and conclusion**	**Supporting evidence (other papers)** **Contradictory evidence (other papers)** **Assessment of conflicting evidence** **Answer**

Some Do's and Don'ts of Prose Style

1. 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

2. Avoid:

- **Professional pomposity** – keep it simple (e.g. “diaphoretic, vasoconstricted and tachycardic with decreased mentation” = sweaty, pale with a fast pulse and confused)
- **Barbarisms** (use of non-existent words or expressions) [e.g. 'anticoagulated']
- **Solecisms** (ungrammatical use of English) [NB. 'data' is always plural]
- **Errors in syntax** (e.g. an ECG is referred to as 'this patient')
- **Use of incorrect or dehumanising words** (e.g. regime/regimen; affect/effect; case/patient)
- **Use of 'empty' phrases or words** (e.g. 'in order to'; 'accounted for by the fact that')
- **Sexism –** it is easiest to refer to patients in a plural sense rather than use 'him/her'
- **Excessive use of abbreviations –** if unavoidable, include a 'glossary of terms'
- **Plagiarism –** avoid at all costs; if quoting another paper, always attempt to do so in your own words

Confused and Misused Word Pairs

Some pairs of words with closely related, but not identical, meanings are frequently misused in the medical/scientific literature. The words defined below are some of the most frequently misused pairs [from *Huth EJ*. How to write and publish papers in the medical sciences. Philadelphia: ISI Press, 1982]:

Accuracy:	the degree to which a measurement or statement is correct
Precision:	the degree of refinement to which something is measured or to which a measurement is reported; *precision* applied to statements implies qualities of definitiveness, terseness, and specificity
Case:	an episode or example of illness, injury, or asymptomatic disease; not a patient (use of *case* in this sense is an example of a 'dehumanising' word)
Patient:	the person cared for by a physician, nurse, or other professional
Dosage:	the amount of medicine to be taken or given over a period of time, or the total amount; not the amount taken at one time
Dose:	the amount of medicine taken or given at one time; the sum of doses may be the *dosage* or *total dose*
Effect:	*as a noun*: the result of an action; *as a verb*: to bring about or cause to come into being
Affect:	*as a noun in psychiatry*: the sum of feelings accompanying a mental state, or the appearance of emotion or mood; *as a verb*: to modify or to elicit an effect
Aetiology:	the study or description of the causes of a disease
Cause:	the agent, single or multifactorial, bringing about an effect, such as inducing a disease
Incidence:	the number of cases developing in a specified unit of population per specified period
Prevalence:	the number of cases existing in a specified unit of population at a specified time
Infer:	to conclude or deduce from an observation or premise
Imply:	to suggest a conclusion to be drawn from an allusion or reference
Pathology:	the study or description of disease; do not use for *disease, lesion, abnormality*
Disease:	lesion, abnormality; not synonymous with *pathology*
Theory:	working hypothesis suggested by experimental observations; do not use loosely for *idea, concept, hypothesis*
Hypothesis:	a proposition for experimental or logical testing
Varying:	*as an adjective*: changing; *as a verb*: causing a change
Various:	having dissimilar characteristics; synonymous with *differing*
Which:	relative pronoun used to introduce a nonrestrictive (nonessential) clause [e.g. ('these diseases, *which* cause most of the deaths each year in the US, are the main subject of this textbook']
That:	relative pronoun used to introduce a restrictive (essential) clause [e.g. 'this is the one lesion *that* is usually fatal']

Empty Phrases and Words

Empty phrase:	Consider shorter equivalent:
a majority of	most
a number of	many
accounted for by the fact that	because
along the lines of	like
an innumerable number of	innumerable
are of the same opinion	agree
as a consequence of	because
at the present time	now
at this point in time	now
by means of	by, with
completely filled	filled
definitely proved	proved
despite the fact that	although
due to the fact that	because
during the course of	during, while
fewer in number	fewer
for the purpose of	for
for the reason that	because, since
from the standpoint of	according to
give rise to	cause
has the capability of	can
having regard to	about
if conditions are such that	if
in all cases	always, invariably
in a position to	can, may
in a satisfactory manner	satisfactorily
in an adequate manner	adequately
in case	if
in close proximity to	near
in connection with	about, concerning
in our opinion, it is not an unjustifiable assumption that	we think
in order to	to
in the event that	if
it is clear that	clearly
it is often the case that	often
it is possible that the cause is	the cause may be
it is worth pointing out that	note that
it may, however, be noted that	but
it would appear that	apparently
lacked the ability to	could not
large in size	large
large numbers of	many
on account of	because
on the basis of	because, by, from
referred to as	called
subsequent to	after
take into consideration	consider
the question as to whether	whether
was of the opinion that	believed
with a view to	to
with regard to	about
with the result that	so that

Terminology/Spelling Differences Between UK and US Journals

There are numerous differences between the UK and US

UK spelling	US spelling
Adrenaline	Epinephrine
Aetiology	Etiology
Analyse	Analyze
Amenorrhoea	Amenorrhea
Anaemia	Anemia
Diarrhoea	Diarrhea
Fetus [*Note:* **not** foetus (Greek)]	Fetus
Fortnightly	2-Weekly ('fortnight' is not used in USA)
Frusemide	Furosemide
Hyperlipidaemia	Hyperlipidemia
Lignocaine	Lidocaine
Noradrenaline	Norepinephrine
Oedema	Edema
Oesophagus	Esophagus
Oestrogen	Estrogen
Paracetamol	Acetaminophen
Pethidine	Meperidine
Phenobarbitone	Phenobarbital
Progestagens	Progestins
Programme	Program
Randomise	Randomize
Rifampicin	Rifampin
Sulphur	Sulfur
Suxamethonium	Succinylcholine
Thiopentone	Thiopental
Tumour	Tumor

Tables and Figures:
Important Considerations

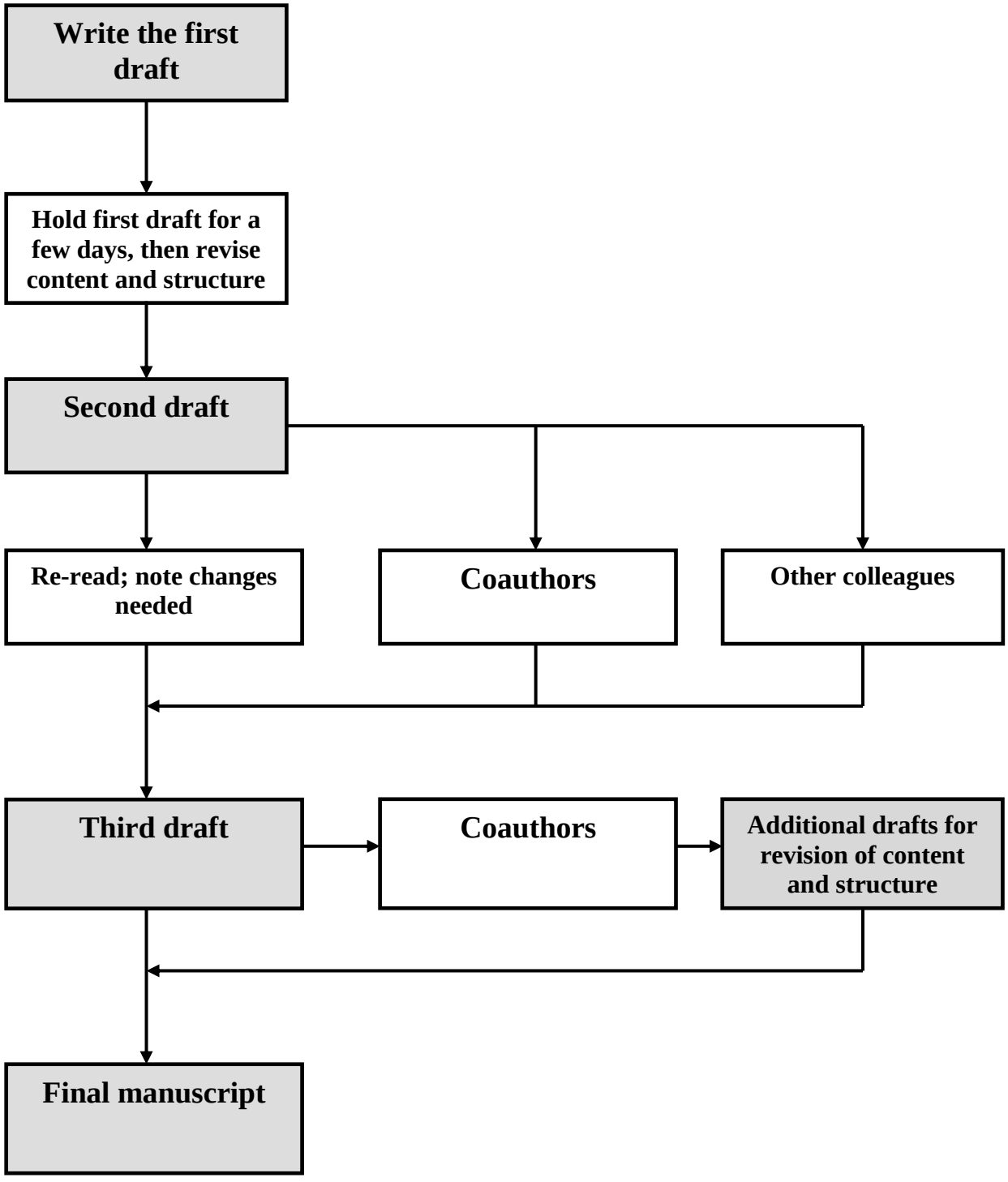
- **If the point a table or figure makes can be made in the text in a few sentences, the table/figure could be omitted**

- **In some instances, however, descriptive information can be more efficiently presented in this form than in the text**

- **The structure of tables and figures should be carefully thought out for logical presentation, and they should relate to each other in a logical sequence**

- **Great care should be taken with proper use of units and clear presentation of the data being summarised**

Revising Manuscripts for Content and Structure



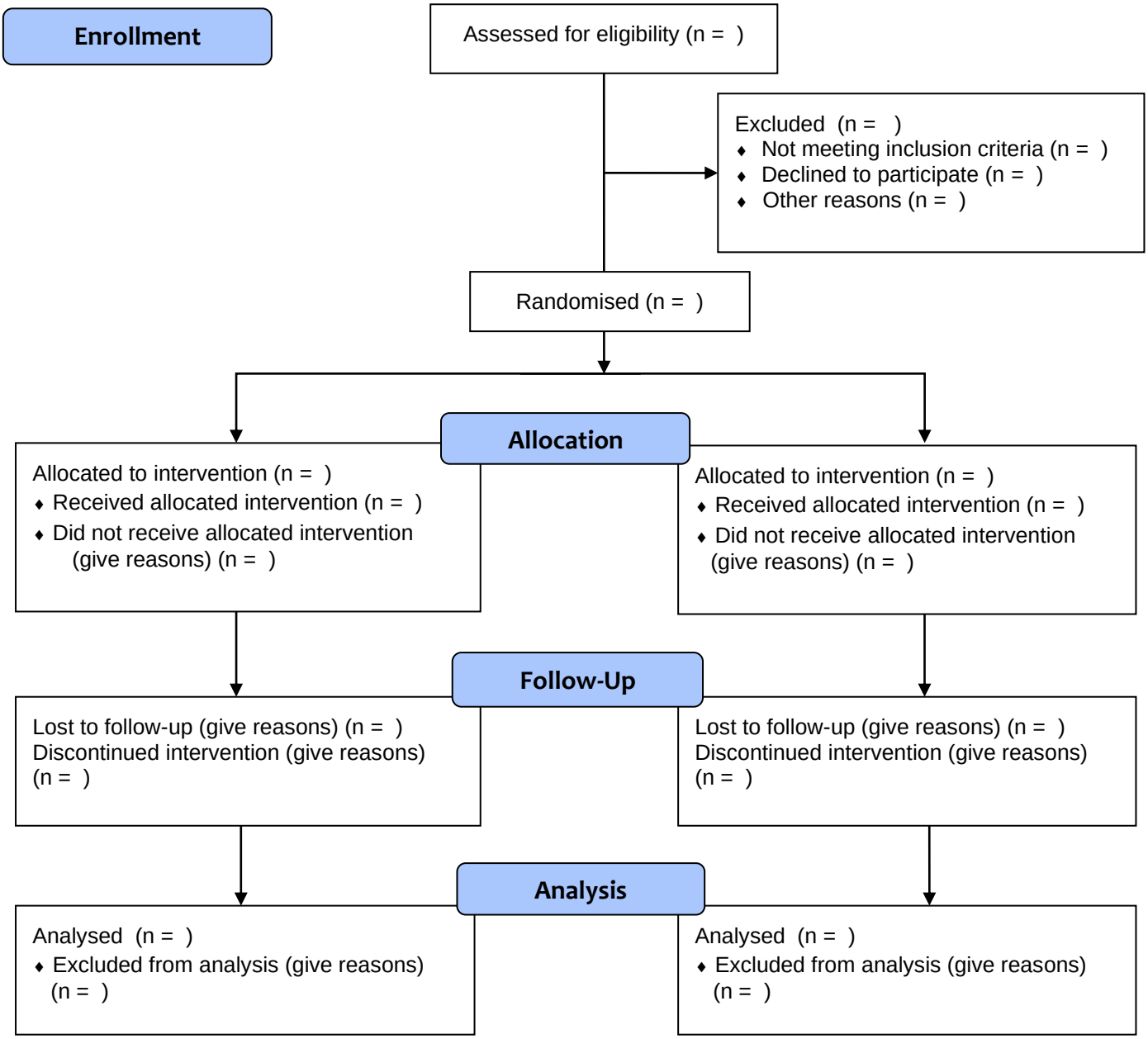
CONSORT (Consolidated Standards of Reporting Trials)
Checklist of Items to Include When Reporting a Randomised Trial

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

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

The CONSORT Patient Flowchart

Flow diagram of the progress through the phases of a parallel, randomised trial of two groups (that is, enrollment, intervention allocation, follow-up, and data analysis)



PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses): Checklist of Items to Include

Section/topic	Item No.	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis

Section/topic	Item No.	Checklist item
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see Item 16])
DISCUSSION		
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users, and policy makers)
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

PICOS = participants, interventions, comparisons, outcomes, and study design.

Writing a Clinical Trial Report

A Checklist for Data that Should be Considered for Inclusion

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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

(continued over)

Materials and methods (contd.)

b) ***Drugs:***

- Description of all drugs and chemicals used (including source or supplier)
- Dosages and duration of therapy
- Dispensing techniques
- Methods used to adjust dosages (increments or decrements), and frequency of adjustments
- Time(s) of drug administration
- Other therapy allowed and not allowed (including appropriate 'washout' periods)

c) ***Study methods:***

- Trial dates (initiation and completion) and location, and individuals responsible for the conduct of the trial
- Basic design (e.g. parallel groups, crossover) and length of each study period
- 'Blinding' procedure (if used) and how maintained – including physical characteristics of drugs and placebo preparations
- Type(s) of control groups used
- Nature and frequency of clinical variable measurements (i.e. the objective and subjective methods of efficacy assessment), and their reproducibility
- Procedure for monitoring safety/adverse events
- Nature and frequency of laboratory measurements (e.g. haematology/ clinical biochemistry parameters), and their reproducibility
- Procedure for monitoring/ensuring patient compliance
- Equipment/analytical reagents used
- Assays used to measure drug concentrations (if included in protocol) and methods used to collect/store samples
- Patient 'drop-outs' and how these are to be handled (e.g. how they are to be replaced and how accounted for in the 'Results')

d) ***Data analysis:***

- Methods used for processing and analysing data
- Criteria for defining patient improvement and/or drug efficacy
- Statistical tests used and power of trial

(continued over)

5. Results:

- Patient accountability data (numbers who entered and completed study, and numbers who dropped out or were withdrawn – with reasons stated)
- Modifications and violations of the original protocol
- Efficacy data (for all patients who completed trial) – show changes in clinical and laboratory assessments for all patient groups
- Pharmacokinetic data (if relevant)
- Safety data (number and severity of adverse events encountered; physical, laboratory, ECG, and x-ray changes, etc.; likely relationship to drug therapy)
- Statistical data (pretreatment comparability of groups, treatment group comparisons, improvement within each treatment group)
- Missing data and problems encountered in the trial

6. Discussion:

- Discussion of results (focusing on those aspects that are of statistical and/or clinical significance, and the advantages and disadvantages of the therapy under investigation)
- Discussion of adverse events – minor, unusual or serious
- Comparison of results with those reported by others (both supporting and conflicting data – with comment on possible reasons for differences)
- Comment on the trial methodology and statistical analyses used (self-critical, if necessary)
- Discuss limitations of the trial and aspects that are unclear or questionable
- Draw conclusions and interpretations/extrapolations from the data presented
- Define questions that the trial does and does not answer
- Discuss how the results might influence future clinical trials or the future practice of medicine
- Propose new questions, hypotheses or models to be studied in future

7. Conclusions:

- Discuss how the results answer the question proposed in the introduction
- Discuss the therapeutic implications of the findings (pros and cons presented as fairly as possible)
- Brief synopsis to conclude report

(continued over)

8. Acknowledgements

9. References:

- Present references in the style of the journal to which the study is to be submitted
- Include references for non-routine methods
- Provide references to review articles (where available) in preference to a series of papers

10. Tables and figure legends:

- Present in the style of the journal to which the study is to be submitted