

How to write a research protocol

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A research protocol is best viewed as a key to open the gates between the researcher and his/her research objectives. Each gate is defended by a gatekeeper whose role is to protect the resources and principles of a domain: the ethics committee protects participants and the underlying tenets of good practice, the postgraduate office protects institutional academic standards, the health authority protects provincial resources etc. The protocol must explicitly address the issues likely to be raised by these gatekeepers, demonstrating evidence of a clear understanding of the issues involved and that all components of the research plan have been addressed. The purpose of this paper is to add flesh to the skeleton provided in step six ('write the protocol') of the Biccard and Rodseth paper of 2014, orientated towards the first-time researcher working towards the MMed degree. Although occasional reference will be made to qualitative approaches, it is likely that the majority of these studies will be quantitative designs and these form the focus of this paper.

Keywords: MMed, protocol, protocol design, research, research design

Introduction

The introduction of compulsory research for medical specialist registration with the HPCSA has challenged those institutions that historically used the Colleges of Medicine (CMSA) examinations as a route to specialisation. Without the resources of a fully developed MMed programme (a coursework Masters with a practical research component), some departments have battled to accommodate the increased workload, especially with an inadequate number of experienced research supervisors. Students are faced with the tasks of finding a research area of interest, identifying and developing a research topic, formulating a research question into a suitable protocol, conducting the study, analysing the results and writing the paper or dissertation, against the background of the demands of clinical training, service provision, and preparation for the rigorous examinations of the CMSA.

Biccard and Rodseth examined the research process from the point of view of the novice researcher and presented a nine-step process for taking a research idea to the protocol stage,¹ and provided an invaluable guide to our students. One of the stumbling blocks in the process is the writing of a 'winning' protocol that passes through postgraduate and ethical review with minimum delay and successfully garners research funding. A well-written protocol ensures timely approval and smooth running of the research process, facilitates subsequent writing of the research report, and permits completion within the allotted time.

This paper assumes that the student has a clear idea of what interests him/her, where the knowledge gap lies (from literature review) and has framed either a research question or hypothesis, even if not fully developed (steps 1–4, Biccard and Rodseth¹). Although requirements for protocol format vary between academic centres, we have kept largely to the structure recommended by Biccard and Rodseth, with slight modification (Table 1).

Introduction and statement of purpose

The introduction is a very brief summary of the literature review consisting of a short paragraph identifying the clinical problem, outlining the areas of equipoise and previous research approaches to them. For example:

'Pulmonary aspiration of acid gastric contents has been shown to be an important cause of mortality with general anaesthesia for caesarean section. Efforts to decrease the volume and acidity of gastric contents have included reduced oral intake, active pre-operative gastric emptying and the use of neutralising antacids, with varying degrees of success. One possible method of reducing the incidence of acid aspiration might be the preoperative administration of a histamine H₂ receptor antagonist to reduce gastric acid secretion.'

The statement of purpose then outlines exactly *what is to be studied* in the proposed study, *how* it is to be studied, *in whom*, *where* and *when*. Although this normally develops from the subsequent background and literature review, it is a useful initial declarative statement that crystallises the nature of the study in both the reviewer's and student's mind and directs the review to relevant questions that are best addressed by the student beforehand.

For a quantitative study the format (adapted from Cresswell²) would be:

'The purpose of this ... (*observational/descriptive, comparative, correlational, survival, analytical etc.*) study is to ... (*explore, describe, compare etc.*) the ... (*central focus, i.e. what you are actually measuring*) for/of/in ... (*population sampled*) at/in/presenting to ... (*location*) from/ over/ for the period ... (*Dates, time period*)'

Table 1: Recommended protocol structure

Introduction and statement of purpose
Background to the study
<ul style="list-style-type: none"> • Clinical problem • Literature review • Research question
Aims and objectives
Method
<ul style="list-style-type: none"> a. Design b. Setting c. Sampling strategy: Inclusion and exclusion criteria d. Outcome assessment and measurements e. Data collection and statistical analysis. Follow-up. f. Sample size, statistical power and variable selection
Methodological challenges
<ul style="list-style-type: none"> • Selection bias • Loss to follow-up
Feasibility
<ul style="list-style-type: none"> • Recruitment • Study team • Participating centres • Study funding and progress
Study organisation and ensuring data quality
<ul style="list-style-type: none"> • Organisation and management • Investigator responsibilities • Central coordination • Ethical considerations • Ensuring data quality
Ethical considerations
Study significance

Students use this template to create their own purpose statements. For example:

'The purpose of this *double blind randomised controlled* study is **to compare** the *pH and volume of gastric contents in term parturients presenting for Caesarean section receiving preoperative glocatidine compared to saline controls presenting to St Elsewhere's Hospital for the period January to July 2015.*

The importance of this statement is that it creates boundaries in addition to providing direction. Any further statement or section of the protocol must fall within the limits of purpose; the background/literature review must demonstrate the research problem and equipoise to which this purpose is the natural consequence. The direction from the statement naturally leads to specific objectives and thence to requisite items within the research instrument (data sheet). It also directs the investigator (and reviewer) to pertinent statistical and research ethics issues. The combination of *purpose* (represented by aims and objectives) and *direction* constitutes a 'golden thread' that binds the protocol together.

If a summary of the proposed research is requested in an institutional protocol format, grant application form, or ethical review application form, this statement is what is required. Do *not* 'cut and paste' the opening sentences of the background; this is not helpful to the reviewer.

Background and literature review

The function of the background and literature review is to encapsulate the clinical problem in such a way that the research question or hypothesis naturally emerges.

- *Clinical problem.* The background declares and explains the clinical problem and summarises existing epidemiological, socioeconomic and health systems knowledge (etc.) globally (from the world literature), and locally (from our regional literature and local audits). In the above example, the background would include evidence of a problem (for example acid aspiration syndrome) in this specific group of patients that is a known cause of morbidity or mortality globally and its relevance to local circumstances (for example as highlighted by enquiries into maternal deaths).
- *The literature review* (again starting globally and reducing to local experience, i.e. contextualisation) is a critical, objective summary of the known extent of the problem and confirms that the research question is appropriate. Reference should be made to the findings of studies performed internationally and locally to address the problem. Novel methods and those particularly suited to local circumstances should be highlighted. By the end of the review it should be clear that the researcher has a thorough understanding of the problem and why the proposed study design has been chosen, based on gaps in knowledge and conflicting results (*equipoise*).

The protocol literature review should be brief but incisive, and there may be stipulated requirements (e.g. 500 words, and 5 references). However, investigators should develop a more extensive review, kept as a separate document and repeatedly reviewed throughout the study (up to the day of submission of the report, in which a more extensive review is required).

- *The research question (or hypothesis)* should naturally emerge from the background and literature review but must also appear as an explicit statement under a separate sub-heading at the conclusion of this section.

Aims and objectives

Confusion may arise concerning these two terms; semantically they are so close as to be virtually indistinguishable and not all centres will insist on both. However, we value the distinction as it assists in clarifying thought processes within the research design.

Aims are what you hope to achieve in your research project and objectives are the steps you need to take in order to achieve your aims.³ Aims must directly relate to the research question or hypothesis. Objectives must relate to the aims. For example:

Research question: What are the risk factors for TB in children aged 5–7 years in Limpopo Province?

Aim: To investigate risk factors for TB associated with birthweight, socio-demographic factors and pre-school care in Limpopo Province

Objectives: To determine the relationships between:

- (1) birthweight and incidence of TB in 5-year-old to 7-year-old children;
- (2) day-care facility, type of caregiver and TB;
- (3) socio-demographic factors and TB.

Methods

This is the most important section of the protocol. It must convey exactly *what you are going to do, in whom, where, when, and how*. Methods must relate directly to and only to the specific objectives of the study.

In the above example, recording the birthweight of all participants and a history of TB between the ages of 6 and 9 years would address objective 1. Testing for HIV status would not address any of the objectives as stated, so cannot be included in the methodology. Adding this as an 'afterthought', before the study commences, can only happen if the role of HIV status is included in a rewritten background and literature and added as an additional objective in the protocol, which would then have to be resubmitted. Once the study has commenced, any additions or changes cannot be made to the protocol without ethical review.

The methods section is written in the future tense. It should be written so that anybody can use it to reproduce your study exactly (although perhaps with different results). Scrupulous adherence to well-written methods enables complete 'cut and paste' transfer to a report, simply changing future to past tense.

Each of the following must be addressed:

a. Study design. Figure 1 shows a decision tree that can be used to categorise types of study as possible research designs. Note that there are several different types of observational study (case reports, series, prevalence, questionnaires, incidence, audit and reviews) and that some of them include analytical elements.

N.B. This is not intended to be exhaustive and space does not permit detailed descriptions of each design. Readers are encouraged to consult more comprehensive sources, such as the *Lancet* epidemiology series by Grimes and Schulz of 2002 and 2005, the introduction to which⁴ covers most of the content of Figure 1 and provides a brief introduction to the commoner designs. The full series is a useful guide to the various research designs and includes articles on issues common to all. It is available as a *Lancet* publication.⁵ The titles of the articles/chapters have been included as references.⁶⁻²⁰ An additional reference to stepped wedge designs has been included.²¹

b. Setting. This states *where* you will be conducting your study, for example a tertiary care dermatology clinic. Remember that many research settings (and all that are institutional) will require site or gatekeeper permission to conduct your research. Have you obtained such? If not, why not? An acceptable reason might be 'Hospital management has been approached, and they have deferred approval until provisional Human Research Ethics Committee (HREC) approval has been granted' (remember to attach any correspondence as an Appendix 1 to your HREC application).

c. Participant selection and sampling strategy. This describes *whom* you are investigating (the population of interest, e.g. all people with hypertension), the sampling frame used to access the population (e.g. the telephone numbers or postal addresses of all people living within a geographical area, or all the patients

attending a particular clinic) and your sampling strategy (i.e. which of the various probabilistic methods or non-probabilistic methods will be used), with inclusion and exclusion criteria.

The reviewer will be checking that:

i. the methods used will ensure that the sample (and sampling frame) matches the population in which the problem has been identified and the research question asked (*Representativity*). Where uneven distributions of a variable are known within a population (e.g. disease distributions related to age, gender or geographical distribution), a probabilistic (random) sampling process should match these via stratified or cluster sampling. In non-probabilistic sampling, methods should be used to demonstrate avoidance of *sampling error* by ensuring adequate proportional sampling of the known characteristics of the population;

ii. any comparisons of a variable will be made between similarly constructed sample groups (*Comparability*). When random allocation is used, sufficient relevant demographic data must be recorded to enable subsequent comparability testing. With non-probabilistic sampling the protocol must document methods used to prevent selection bias;

iii. all relevant social groups are included (*Social justice*). Unless the research problem has been identified as unique to a specific social group, all social groups should be included in the sampling strategy.

Randomisation and blinding procedures should be included if relevant.

The protocol should include a process of handling missing data, patients lost to follow-up, and protocol violations. The reviewer will be looking for a commitment to an initial intent-to-treat analysis using the full data-set and before group identification in a double-blind study.

d. Outcome assessment and measurements. Here you provide details of *what you are going to measure* (the outcome variables), the methods of measurement to be used and what steps you are going to take to avoid measurement error (random and systematic error). These details determine the *internal validity* of the study. Remember that what you measure *must* relate to the objectives of the study and *may not* relate to an unstated objective. All outcomes/measurements must be clearly defined and the primary outcome identified, which will be used for sample size calculations (in large studies secondary outcomes may also be used).

e. Data collection and statistical analysis. This must be planned in detail. The reviewer will be looking for specific information that must be included (Table 2). All outcome variables should be in a clear logical format on your data-collection tool. Statistical analysis is part of the methodology and as such misuse, abuse, misapplication and inappropriate testing fall within the ethical domain.²² You are likely to require statistical advice, either from a professional statistician or an experienced, knowledgeable member of your department. Do

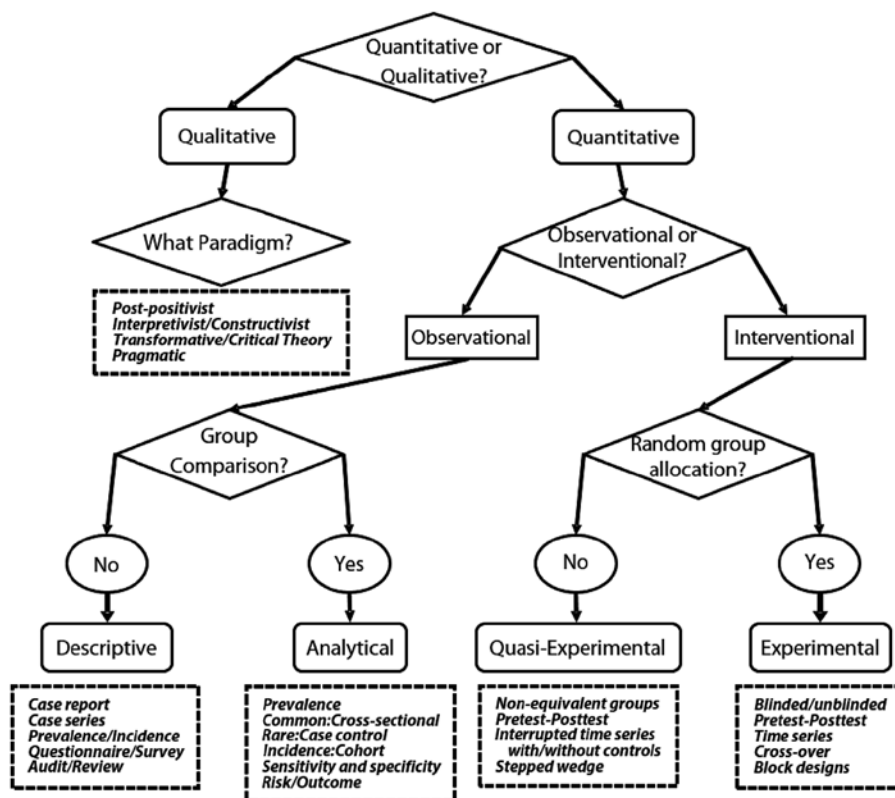


Figure 1: Decision tree defining research designs, with various examples.

not use vague statements such as ‘statistical analysis will be performed’. Be specific, for example:

‘Descriptive statistics (mean and standard deviation or median and interquartile range as appropriate) will be used to describe the sample groups. Continuous variable group means will be compared using unpaired t-tests for normally distributed data, otherwise non-parametric (Mann–Whitney U) methods will be used. A *p*-value of < 0.05 will be regarded as statistically significant.’

If relevant (or indeed possible), any planned participant follow-up should be included at the end of this section and the purpose of the follow-up identified. If supplementary data are to be sought they should be described here and included on the data form to accompany the protocol.

f. *Sample size, statistical power and variable selection.* Statistical advice should be sought. Sample size calculations can depend upon circumstances. For example:

1. Sufficient resources (personnel, time, funding and a high prevalence or incidence) and an estimate of the mean and standard deviation of your outcome variable of main interest may be available. In this case you can calculate the required size of a comparative study to achieve a given statistical level of significance for a predetermined difference of clinical importance between means. You will need to have an estimate of:

- the control mean;
- an important clinical difference (Δ or effect size, ES);

- standard deviation (σ , sd) of your variable;
- your chosen α (probability of accepting a result as a statistically significant difference when in reality there is no difference);
- required statistical power (probability that a study will detect an effect when there is an effect there to be detected).

These are the estimates the statistician will request in order to assist with the calculation.

The control mean may be known (e.g. from previous research, or a physiological value such as a systolic pressure of 120 mm Hg), and similarly the standard deviation. In which case, the ‘standard’ chosen values of α of 0.05 and power of 0.8 might be used (N.B. these ‘standard’ values are by convention, not rule; there are situations, e.g. differences in mortality, where you would want to be more certain and therefore choose a smaller value of α and/or a higher power).

Defining an important clinical difference is more of a challenge, but it represents your only justifiable method of obtaining a study size matched to your resources. Strictly speaking, the important clinical difference *is the smallest difference that would make you change your practice*. The most commonly used calculable estimate is known as the *standardised mean difference (ES)*:

$$ES = \frac{\bar{X}_1 - \bar{X}_2}{SD}$$

The difference from your control mean ($X_1 - X_2$, desired effect size) can be altered until the difference divided by the control standard deviation represents an appropriate value for the primary outcome measure of the study.

Table 2: Statistical treatment: what the reviewer will be looking for (adapted from Bland *et al.*²²)

- (1) The study design and aims must be appropriate to the proposed statistical treatment that will depend upon issues such as randomisation, number of groups, whether repeated measures are to be used, possible confounding or interacting factors etc.
- (2) The types of data (continuous, discrete, nominal etc.) to be collected should be specified, to ensure that the proposed statistical analysis is appropriate, with clear identification of the outcome variable(s) of main interest on which any power analysis is based
- (3) The number of outcome measures that are to be recorded should be stated, to avoid or adjust for issues of multiple testing
- (4) Any power analysis to estimate required sample sizes for the outcome of interest must be based upon the statistical test identified for use in its subsequent evaluation
- (5) The information used in any power analysis (means, proportions, standard deviations, effect size, proposed alpha and power etc.) must be included to permit the reviewer to repeat the calculation
- (6) Confirmation that the investigator has the required knowledge to perform the subsequent analysis, or whether assistance will be provided by a statistician or person with the necessary expertise

A general view of the values of ES might be:

- ≤ 0.2 : a very small effect, of negligible importance;
- 0.5: of moderate importance;
- 0.8: a large difference of considerable importance;
- ≥ 1 : cannot be ignored.

But again, this is context specific. If your primary outcome measure is death, an effect size of 0.2 is important, whereas if the outcome were a readily treatable decrease in systolic blood pressure (say from 120 to 108) then an effect size of 1 might not be considered very important.

2. Alternatively, you may have few resources and not know the size and range of the variable of interest and wish to describe it in a pilot study for future research. You should, however, have some idea of how many potential participants you will be able to see in the time available (e.g. from a clinic's records).

In this case, statistical calculations can *indicate how accurate* your estimates of average and range will be. This is important in a descriptive study, and explains why protocols containing 'this is a descriptive study only and requires no statistical analysis' may be rejected by reviewers. To underscore this point, Figure 2 depicts the upper and lower 95% confidence bounds on a proportion of 0.1. Assuming a true prevalence of 0.1, if samples of 10 were repeatedly taken 95% of these estimates would be found between 0.0025 and 0.445, which represent a large range of possible answers far removed from the real one. This would not represent an adequate sample size for a useful description of an outcome measure, in contrast to repeated samples of 200 (95% confidence limits 0.062–0.15).

Variables selected for documentation and analysis should be kept to the minimum necessary to achieve the aims and objectives of the study and answer the research question. Avoid the temptation to over-test, either by multiple testing of the same variable, or unnecessary testing of additional variables (usually in pursuit of critical *p*-values). Just as buying several lottery tickets increases the probability of winning a prize, so multiple testing increases the probability of finding an erroneous statistically significant difference (type I error). This is a particular problem with predictive observational outcome studies when too many risk factors are added to a multiple logistic regression analysis. If using this type of study design, the reviewer will check the anticipated outcome incidence to ensure an appropriate

number of positive outcomes (about 5–10) for each risk factor added to the regression. An additional problem with this type of study is the confounding effect of two or more related variables (e.g. height, weight and body mass index).

Methodological challenges and study limitations

This should be a concise, realistic view of the challenges to achieving the aims and objectives of the study. It should be long enough and detailed enough to demonstrate to the reviewer that the study team has insight into what it is doing, but not so long and detailed as to suggest that the project has no hope of success. Each challenge presented must be accompanied by a summary of how the protocol meets the challenge. For example:

- How have response rates to questionnaires been improved?
- What efforts have been put in place to select a representative sample?
- Can the results be generalised?

Feasibility

a. *Time lines and project management.* It must be demonstrated that the study can be completed in the time available. All stages of the research must be included and time allocated to literature search, protocol preparation and realistic turnaround time for necessary review following submission, recruitment and data collection, data collation and entry into electronic format, statistical analysis and review, and finally write-up; use of a Gantt chart is recommended. The project manager (usually the principal investigator) is responsible for ensuring timeous completion of each stage of the project.

b. *Study team, contributors and authorship.* From the outset it should be clear who is responsible for each component of the study and who should be acknowledged and who should be an author on any papers published from the research. This not only clarifies everybody's role in the project but also avoids possible future embarrassment or acrimony. Also, naming individuals responsible for each part of the research project can ensure that everything gets done. For example, any laboratory analysis requires identification of the individual responsible for the analysis additional to permission to use the laboratory facilities for the project.

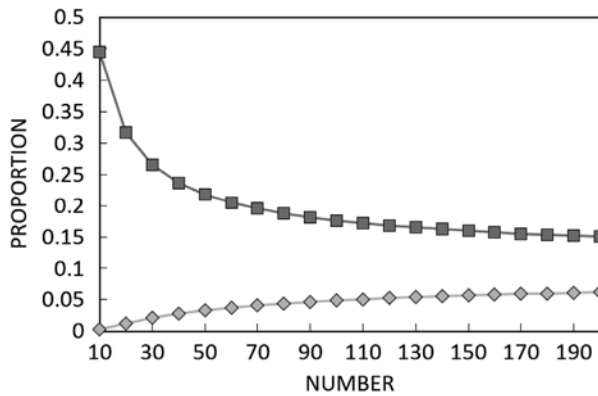


Figure 2: 95% confidence limits on a proportion of 0.1 at sample sizes from 10 to 200.

Regarding authorship, guidelines from the International Committee of Medical Journal Editors (ICMJE) should be followed.²³ Criteria for authorship are:

- substantial contributions to: the conception or design of the work (individual study); OR the acquisition, analysis, OR interpretation of data for the work; AND
- drafting the work or revising it critically for important intellectual content (comment during writing the paper); AND
- final approval of the version to be published (email approval acceptable); AND
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions not complying with all the criteria merit a detailed 'Acknowledgement' at the end of the paper.

Proposed authorship need not be cast in stone, as required roles may change during the course of the study but changes to the study personnel may require notification to the Ethics Committee.

c. *Participating centres.* If the study is to be conducted in more than one centre, all centres should have the requisite resources (time, personnel, equipment and expertise) to fulfil study requirements.

d. *Study funding and progress.* Protocol submission for a study without adequate funding will never bear fruit and is a waste of everybody's time. However, it is acceptable to submit a realistic budget with the protocol before a grant has been awarded, as most grants will be subject to ethical (and in the case of a degree, postgraduate committee) approval, and grant application will require your protocol. This section of the protocol must be completed even if there are no direct costs (e.g. a historical chart review) or the stationery etc. can be covered by departmental resources. Costs must match funds. Reasons should be given why grants are delayed or deferred if that is the case.

Ethical considerations

While the underlying principles of autonomy, beneficence, non-maleficence and justice form the basis of research ethics, ethical review has to be more extensive. Notably, the participants in the study have to be protected from inexperienced and unqualified

researchers. Thus scientific content is and always has been within the purview of Health Research Ethics Committees. Also the underlying principles must be applied to the individual participants, so when 'beneficence' is discussed it must apply to the benefit for the participant in addition to societal value.

Ethical issues arise from (*inter alia*) the following:

- direct participant contact (requiring a full explanation of what is to be done using simple language and an appropriately worded consent document);
- the inclusion of vulnerable groups (children, prisoners, mentally disabled, those in pain);
- anonymity and confidentiality;
- data protection and storage;
- participant reimbursement;
- insurance against study-related injury;
- potential risks or discomfort;
- storage and/or export of tissue samples (including blood);
- use of health care resources;
- potential benefits to the patient and society;
- post-trial access to any demonstrated benefits;
- the means of dissemination of the results of the study;
- conflicts of interest.

Remember that research towards a degree is automatically a conflict of interests (particularly so when associated with career advancement) and should be included in the participant information document and consent form. Also research cannot proceed without the requisite gatekeeper (site and provincial healthcare) permissions.

Study significance

Include a brief concluding paragraph as to the expectations of the study in terms of improving knowledge and how the results can be applied to the underlying clinical problem addressed by the study.

Example:

'The significance of this study into the factors underlying the pharmacogenetic basis of mitochondrial disorders uncovered by HIV infection or initiation of NRTI drugs will result in more effective design of NRTI drugs with enhanced activity and minimal toxicity, leading to improved patient outcome.'

Appendices

These should include your research instrument (i.e. questionnaire or data-collection tool), patient information sheet and consent form, letters of approval, certificates of ethical and clinical good standing and brief curriculum vitae of the principal investigator, any co-investigators, supervisors and co-supervisors etc. Ensure that all required documentation is included with your protocol and HREC submission, using any checklist provided.

Conclusion

Following this format should, it is hoped, result in a smooth passage through review committees. The format can be converted into a template design that can be used to complete a draft protocol *within a day*, provided that the initial literature review and conceptualisation have been completed beforehand.

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