WRITING A RESEARCH PROTOCOL

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Introduction

The research protocol is a fundamental part of high quality medical research and radiological research is no exception. In terms of the "research pipeline", the detailed protocol writing usually follows the definition of the overall research question and must be informed by a detailed literature review to ensure all research procedures and interventions are up to date and the study methodology is relevant to answer the research question. Writing of the research protocol should precede application for ethical and regulatory approval; and the final protocol will be required upfront by ethical committees and research and development departments.

The length of the research protocol will be governed by the size and nature of the study – a multicenter drug trial will clearly have a much longer protocol than a single centre comparison of MRI and CT for rectal cancer staging. Nevertheless undertaking a "simple" project should not be an excuse for a short and inadequate protocol. The typical contents of the protocol are described below, but it is important to always bear in mind the need for *detail* – the protocol should explain exactly what will be done, to whom, by whom and when. A researcher from another hospital should be able to read your protocol and exactly reproduce the study at their site. If they can't, the protocol is ambiguous and the potential for protocol breeches is increased, leading to at best unreliable data collection or analysis, and at worse actual patient harm. A retrospective project requires a protocol just as much as a prospective study.

Research protocol contents

There is no single protocol template applicable to all studies – what is included will depend on the nature of the study. Most clinical trial units will have a protocol template and it may be worth obtaining a copy from your local unit. Such templates are usually applied to drug trials and include large sections on site selection, drug administration and handling, and pharmacovigilance such as adverse events. As such they may not be directly relevant for many radiological projects. Nevertheless, they are a good place to start it is better to have too much in a protocol (within reason) than too little!

A typical protocol would include:

1. **Study Title**.
   This should explain the study in full. Catchy titles and/or use of acronyms can be useful but it is important not to be too flippant when choosing a title. If in doubt keep it simple and factual. It is useful to also have a short title which can run as a footer throughout the protocol.

2. **Protocol number and date**.
   It is vital to assign your protocol a number and date. Ethical and R&D committees will rightly insist on this so that updates to the protocol can be tracked via an updated version number and date. Clearly it is inappropriate for researchers to be working form different protocols

versions. The date and version should also be added to the page footer throughout the protocol.

3. Regulatory data

It is useful to document who is the study sponsor (usually the NHS hospital in many single centre studies) who have given ethical permission, who has funded the study and where the research will take place. If your study has a clinical trials or Eudract number, it should be added here. Of course some of this data will not be available when submitting the protocol for ethical and regulatory review, but should be added as soon as it is known

4. List of researchers

The names, affiliations and contact details of all individuals involved in the project should be listed. One person must be identified as the principal or chief investigator – this person is ultimately responsible for the design and subsequent conduct of the study and is usually the senior researcher. Think carefully who to include at an early stage, as later additions require notification to the ethics committee which although a minor amendment, takes time and generates additional paper work. For example if radiographic or nursing staff will be actively involved in the project it may be appropriate to include them as study investigators. It is good practice for researchers to sign the protocol, although this is not always practical. However the chief investigator should sign and it may be appropriate for a representative of the sponsor (for example a university) to also sign.

5. Table of contents

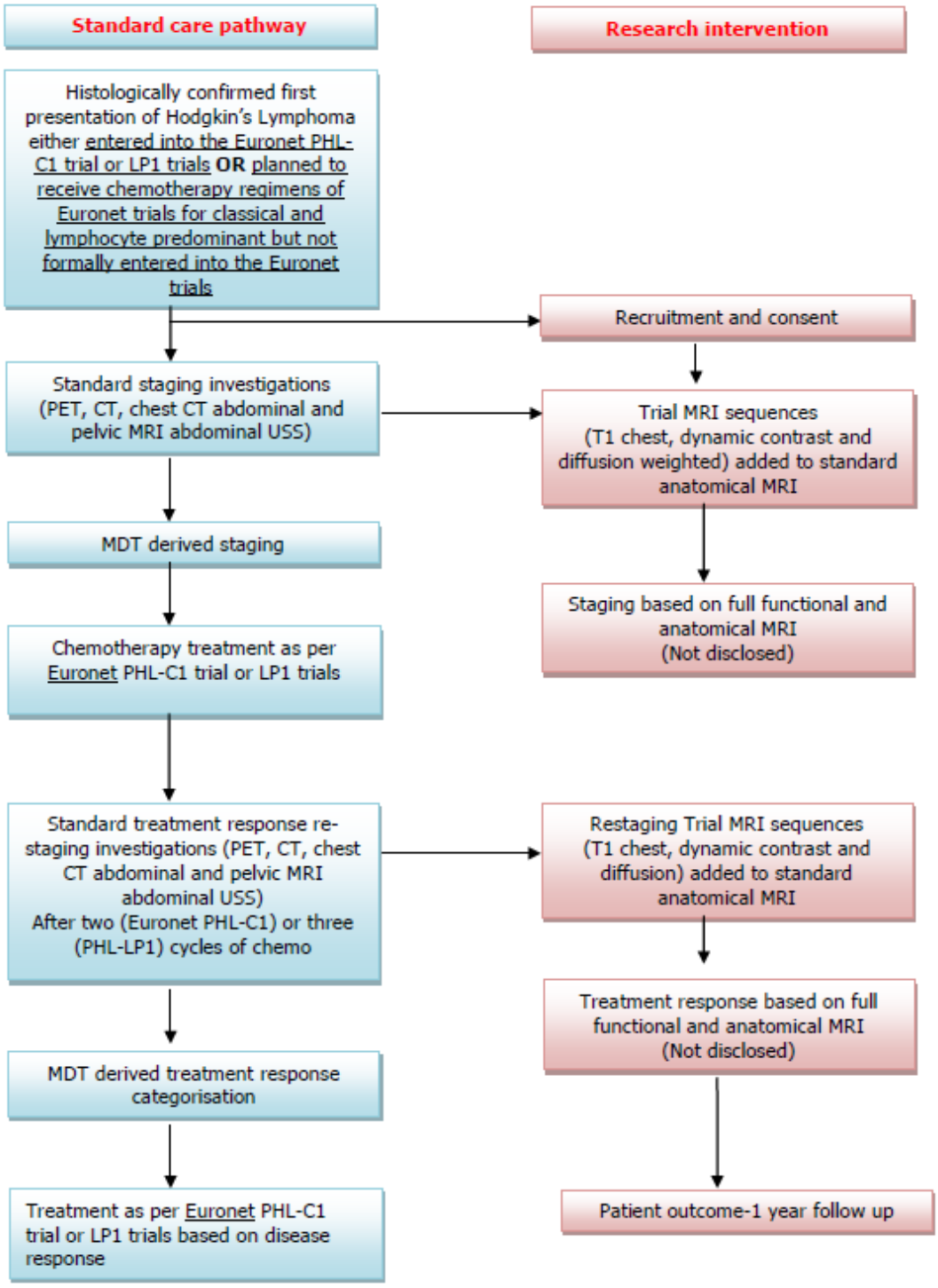
It is good practice to produce a formal table of contents for all the sections and subsections listed below so readers may easily access the required data from the protocol. Once done, this can be used as a template for future studies.

6. Study summary

A short summary of the study should be included either as free text or in a table format. The exact content will differ between projects, but in general the summary should include a brief background to the condition/intervention being researched, the overall aim of the study, a summary of the study design, the specific study endpoints, recruitment target and study duration. It is also useful to summarise the inclusion and exclusion criteria.

7. Trial schema/flow chart

The protocol should include a simple flow chart or schema summarising the patient pathway, and in particular what will be done to them and when, making a clear distinction between clinical and research activity. Simple retrospective studies may not require a flowchart, but one should be included in most prospective studies – if the study is simple so will be the flow chart! Include timing of interventions such as imaging, questionnaires etc and patient follow up (if applicable). An example study flow chart from a study investigating the use of whole body MRI in lymphoma staging is given below.



8. Background

This should explain the background to the research question and must be informed by a recent detailed literature review. Pertinent outcomes of this review and how they have informed the study question and protocol design should be included. For example if a study proposes to investigate the use of contrast enhanced ultrasound in assessment of small bowel crohn's disease activity, the background section should explain a little about the pathophysiology of crohn's disease and in particular the definition and importance of disease activity in patient management. The literature on imaging assessment of activity should then be summarised with emphasis on ultrasound and in particular contrast enhanced ultrasound. Finally it should be made clear what gaps there are in the literature which justify the new

research study and what question(s) the study is designed to address. At the end of the background section the reader should have an understanding of the condition or intervention being investigated, the current state of the literature and the rational for the study. Indeed when it comes to the final paper writing, the background section of the protocol usually makes a very good basis for the introduction section of the paper.

9. Pilot data

If there is pilot data available which has informed the final study design and endpoints, it is useful to include it just after the background section.

10. Trial hypothesis and endpoints

If the trial has a hypothesis, this should be stated up front. There may be more than one hypothesis, but a long list should be avoided. A list of trial endpoints should be provided. These must be succinct and unambiguous – there is no room for differing interpretations of trial endpoints. The statistical analysis (see below) should be specifically designed to derive the answers to the listed endpoints. Again, there may be more than one endpoint and it is conventional to divide this into the primary study endpoint (i.e. to address the bottom line research question) and secondary endpoints (which address ancillary research questions). Example endpoints derived from the lymphoma staging trial listed above would be:

2.2.1 Primary Endpoint

The per site sensitivity and specificity of MRI for both nodal and extranodal sites and concordance in final disease stage with the multi-modality reference standard

2.2.2 Secondary Endpoints

1. The number of correct patient classifications into therapy responders and non-responders by MRI compared to the multi modality reference
2. Inter observer agreement for MRI between reporting radiologists (on site and off site)
3. Sensitivity, specificity of qualitative assessment of Minimum intensity projection (MIP) inverted high B value datasets
4. Utility of apparent diffusion coefficient (ADC) histogram analysis for identifying responsive nodal disease
5. Simulated effect of MRI on clinical management

The study power (see below) is almost always derived from the primary endpoint.

11. Trial activation and selection of study sites

This section is mainly applicable to multicentre studies, where a mechanism for indentifying and opening recruitment sites is needed. This will include receipt of appropriate documentation such as ethical, sponsor and R&D approval, the level of training required by staff (such as Good clinical practice [GCP] etc), and the process of site initiation/activation (such as site visits, and site agreement documentation). This section may not be relevant for many single centre radiological studies, but nevertheless GCP training is advisable for all researchers and this requirement can be documented here.

12. Study design

This is the most important part of the protocol as it details exactly what will happen, how and when. The level of detail **must** be high-every procedure must be explained in full. If a researcher has a question it should be answerable after reading this section. The section is analogous to the methodology section of the later paper but must be more detailed! The exact structure and order of the components of this section can be flexible and modified according to the specific study, but all facets should be included somewhere. Contents include:

(i) Inclusion and exclusion criteria

Who is eligible? If they must be suffering from a specific disease state, what level of diagnostic certainty is required (e.g. if studying cancer patients with colorectal liver metastasis, is histological proof of the metastasis required or are characteristic imaging features acceptable? Can they have had previous chemotherapy or must they be chemotherapy naive? etc). Are there any age or sex restrictions (e.g. are patients under 18 eligible?). Is renal function important? (e.g. for contrast administration). If patients with renal impairment are excluded, how is this impairment defined? Are pregnant or breast feeding patients excluded, or those with contraindications to MRI? The list of inclusion and exclusion criteria must be sufficiently detailed such that it is clear which patients can and cannot be recruited.

(ii) Screening log

It is good practice to have a screening log so the basic demographics of patients approached and either ineligible or declining participation can be recorded. This is to later ensure the actual recruited cohort is representative of the overall patient population. If a screening log is to be kept, it is important to obtain appropriate ethical approval for the demographic data to be collected.

(iii) Patient recruitment

Exactly who will approach patients for recruitment, where (e.g. out patients) and when? If face to face, will it be a member of the patient's usual clinical care team or a researcher? Ethical committees focus very closely on how and when patients are approached and strongly discourage "cold calling" by researchers. Furthermore, a period of at least 24 hours is usually required for patients to consider participation (unless a shorter time is unavoidable, for example in trials in acute or emergency patient cohorts). Researchers must therefore think very carefully as to how patients are best approached and a clinical contact in the patient care team is often advantageous when undertaking radiological research. Sending an invite to patients in the post together with the patient information sheet is a valid method of recruitment but researchers should consider expected rates of recruitment if only this method is used. If a follow up phone call to patients is planned after postal invitation, appropriate ethical approval should be obtained. The protocol must make the recruitment procedure very clear, and ideally a list of individuals who will make the first approach should be provided. For retrospective studies (such as review of CT features of a particular disease), this section (combined with the eligibility section) should instead clearly describe how the scans are identified, using which database, over which time period and by whom.

(iv) Patient information

A high quality patient information sheet (PIS) must be provided in all prospective studies and this should be included as an appendix to the protocol (again with the relevant version number and date). The content of this PIS is beyond the scope of this article, but a good template is freely available from most R&D departments. The protocol must, however, detail how the patient information sheet is to be given to the patient, and how long they will have to consider participation. If patients are invited to contact researchers if interested in participation, the exact mechanism for this contact must be explained.

(v) Patient consent

The study consent form (with version number and date) should be provided as an appendix to the protocol. Again, the protocol should make it very clear how and when written consent is to be obtained, and by whom. In particular ethics committees expect those to obtain consent to be trained to do so, and a GCP certificate is increasingly expected. If the study involves volunteers, full consideration

should be given as to the handling of unexpected findings, and volunteers must be fully informed of the process used in the trial and appropriately consented.

(vi) *Detailed project description*
Again, what is included will depend on the actual project. Examples of things to include are:

- Definition of patient groups – is there one type of patient to be recruited or more than one?

- Exact detail of any radiological investigation – which machine, what are the precise patient preparation requirements (e.g. nil by mouth, oral contrast etc), how will the patients be positioned (e.g. supine or prone etc), what are the exact scan parameters, what drugs are administered (e.g. spasmolytics), what type and dose of contrast and injection rate. How long after contrast are patients imaged, etc?

- Data collection. Exactly what data will be collected and by whom (e.g. one radiologist or consensus of two). Will a scoring system be used (e.g. lesion conspicuity), and if so what are the ***exact*** definitions for each of the scores? If you are assessing relative parameters, e.g. bowel wall contrast enhancement, T2 signal, what is the structure against which you will compare, e.g. renal cortex or CSF, etc. Will length measurements be made? If so, how will they be done (e.g. on what sequence), in which axis (e.g. short or long axis of a lymph node). It is very useful to create a proforma or case report form which researchers will use to document their findings and include this as an appendix to the protocol. If questionnaires are to be administered, the exact mechanism should be described (e.g. by whom and where) and how patient response will be collected (by hand, by post, etc). The questionnaire should be included as an appendix to the protocol.

- Standard of reference. If your study evaluates the accuracy of a diagnostic test, what is the standard of reference and how will it be applied? For example will you use an established clinical score (this should be included in an appendix to the protocol), surgical findings or histopathology? Who will apply the standard of reference and will they be blinded to the patient details or imaging findings? Will the reference standard be scored (e.g. microvessel density) and if so what methods will be applied? If the outcome of an MDT is to be used, how will this outcome be recorded and by whom? If patient clinical data is to be collected, what are the data sources (e.g. patient notes, hospital databases) and is there a time limit as to when they must be done (e.g. should a blood test be undertaken within 1 day of the imaging to be valid?)?

As noted above, after reading the section on study design it should be possible for an individual not involved in the study to replicate it correctly at another site.

13. Data collection and storage

All research projects must comply with local and national data protection rules and ethical committees will scrutinise what data is collected and how it is stored. If proformas or case report forms are to be completed, where will they be collated and stored? How will corrections to case report forms be made (e.g. initialled and dated). The protocol should list where and how data will be stored (e.g. anonymised) and how it complies with data protection regulation. What is the process for missing data, e.g. is the patient excluded or is any data which is collected still usable?

14. Safety reporting

Most radiological research does not involve to administration of experimental drugs, and so a detailed description of adverse events and how they are handled may not be appropriate. However, even seemingly simple studies can lead to potential adverse events. For example, processes must be in place and clearly defined for handling of unexpected findings, particularly in studies of volunteers. Clearly, trials of interventional procedures such as vascular stenting will require detailed consideration of the definition and handling of expected and unexpected adverse events, and this should be clearly detailed in the protocol.

15. Trial monitoring

In general full descriptions of trial monitoring arrangements are required for therapeutic or interventional trials where the risk of patient adverse events can be high. In most cases a clinical trial unit will be involved in such studies and will have detailed monitoring protocols which can be copied into the protocol. Larger, more complex trials may also require the set up of steering and data monitoring committees and if so details should be included here.

However, monitoring also includes simple measures such as checking data completion, return of case reports forms, proformas and questionnaires, etc. In all but the simplest of studies it is good practice to appoint an independent individual to help monitor the conduct of the study, adherence to protocols, consent form completion, data collection, etc. It should be remembered that R&D departments often perform spot audits of approved projects and researchers are well advised to have mechanisms in place to detect errors and omissions before they are detected by somebody else!

16. Withdrawal of patients

The protocol should list how collated data is handled should a patient withdraw from the study.

17. End of trial

The protocol should clearly state when the trail or study will end. This is usually after the allotted numbers of patients have been recruited, or datasets analysed in the case of retrospective work, but sometimes there may be “time expiry” clauses when the study will cease after a certain time period regardless of recruitment.

18. Statistical analysis

The statistical section is a very important part of the protocol and although conventionally it comes towards the end, it should not be ignored! A thorough and clear analysis plan is vital and as noted above should be geared toward meeting the stated trial endpoints (it is good practice to repeat the primary endpoints in this statistical section to make it clear how each will be derived). The level of statistical analysis required will depend on the nature of the study, but it is always very useful to get the advice of a statistician for any project. Indeed, if the data collection protocol and subsequent analysis is complex, it is usual to include a medical statistician as a co-investigator on the protocol.

The first part of the section should deal with study power. Most prospective studies require a power calculation to justify recruitment numbers unless they are unequivocally a pilot study designed to gather preliminary data, in which case formal study powering may not be required. The advice of a statistician is essentially compulsory when generating a power calculation unless the researchers are themselves very experienced in medical statistics. Full details of the calculation should be included in the protocol so it can be reproduced by others. Clearly the number produced such match the recruitment target listed in the protocol, although it is often necessary for the recruitment target to be a little higher to account for patient drop out or loss to follow up.

The analysis plan should be comprehensive and include a description of how all the data collected in the study will be handled. Although it is not always possible to absolutely state the statistical tests which will be employed (for example it may not be known if the collected data will be parametric or non parametric which will influence how it is analysed), an indication of the planned statistical approach should be made.

It may be appropriate to list here how missing data will be handled in the analysis. It is also good practice to state up front if any interim statistical analysis will be performed and if so, justify why. There may be good reasons to perform an interim analysis, for example to check data collection protocols, test assumptions made in the power calculation, or for the purpose of patient safety in interventional trials. However, unless there are very good reasons, the principal researchers should be blinded to the outcome of this analysis so as not to potentially bias the conduct of the study going forward.

19. Regulatory approvals and Funding

The identity of the ethical and R&D authorities approving the study should be listed once known, together with details of the study sponsor and funding organisation if applicable.

20. Publication policy

Again, even with smaller studies it is good practice to outline the planned publication strategy. This may include the proposed authorship to avoid later disputes!

21. Reference list

22. Appendices

As noted above, appendices should include the proposed patient information sheet, consent form, data collection proformas/clinical report forms, scoring systems (research or as part of the reference standard), questionnaires to be administered, detail imaging protocols, summary of abbreviations and details of pilot data or additional background information.

Summary

The above suggested content can only be a guide – some sections may not be applicable in smaller projects while other studies may require additional information. Nevertheless, it remains important that any study, however small, has a formal agreed protocol. Clearly this is mandatory for projects requiring ethical approval, but even for smaller retrospective studies performed under an ethical waiver, it is still important to document exactly how and why things will be done in a formal protocol document.