



Protocols

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**EQUATOR – OUCAGS training course
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Session outline

- **What is a study protocol?**
- **Why is a protocol important?**
- **Considerations for writing a research protocol**



What is a study protocol

- **Study 'roadmap'**
 - Provides a detailed plan of the study
 - Every research study **should** have a protocol
- **Informs scientific and ethics review**
 - Regulatory bodies (e.g. MHRA) require a protocol for clinical trials
- **Origin for all subsequent dissemination & reporting**
 - Try and prevent selective reporting
 - **'Should'** match any registry information
 - E.g. clinicaltrials.gov, controlled-trials.com, crd.york.ac.uk/PROSPERO/

=> **Transparency**



Why is a protocol important?

- **Forces the investigator(s) to clarify their thoughts about all aspects of the study**
- **Essential for scientific and ethical approval**
- **Requirement for funding and often for publishing clinical trials (particularly the 'big' journals, e.g. BMJ)**
- **Guide the study team working on the research**
- **Critical appraisal of study methods**
- **Transparency**

Typical research process:
Key steps

Conception

Design

Execution

Analysis

Publication and reporting



Poor protocols

Ioannidis et al, *Lancet* 2014

“The extent to which research is done on the basis of a rudimentary protocol or no protocol at all is unknown, because even when protocols are written, they are often not publicly available. Consequently, researchers might improvise during the conduct of their studies, and place undue emphasis on chance findings. Although some improvisation is unavoidable because of unanticipated events during a study (eg, an unexpectedly high dropout rate, or unpredicted adverse events), changes in the research plan are often poorly documented and not present in formal data analyses (eg, non-response and refusal data might be neither reported nor used to adjust formal uncertainty measures).”



All studies should have a protocol

- **Randomized clinical trials**
 - Mandatory for funding and scientific review
 - usually required for publication (often needed to include the protocol when submitting the manuscript)



Lancet, 2008

Panel: Lancet editors' checklist for randomised trials: protocol versus submitted manuscript

- Does the trial registration number match the trial and report?
- Is the aim the same in the protocol and the report?
- Is this the main report (not preliminary or substudy)?
- Do the primary and secondary endpoints match in the protocol and report?
- Was the sample size achieved?
- Is the population in the report the same as in the protocol?
- Are the interventions and follow-up as per protocol?
- Are the main and any subgroup analyses as specified in the protocol?
- Are adverse events collected and reported?
- Does the role of the funder preclude publication (according to the journal's requirements)?



All studies should have a protocol

- **Randomized clinical trials**

- Mandatory for funding and scientific review
 - usually required for publication (often needed to include the protocol when submitting the manuscript)

- **Observational studies**

- Required for funding
- Not mandatory (yet) for publication
- Having pre-defined objectives/analysis strategy will reduce the risk of being accused of 'data-dredging', enhance scientific integrity of the study

- **Systematic reviews**

- Good practice
- Required for those conducting Cochrane systematic reviews



Protocol structure

- **Scientific content will differ across studies, but the general elements of the study protocol will be similar**
 - What is the research question and how will it be answered
 - **Summary, administrative information, background & objectives**
 - **Participants, *interventions* & outcomes**
 - **Data management & statistical analysis**
 - **Ethical, logistical aspects, dissemination**
 - **Related documents**
 - Statistical analysis plan (SAP), contracts
- } Methods



Protocol structure

- **Summary & administrative information**
- **Background & objectives**
- **Participants, interventions & outcomes**
- **Data management & statistical analysis**
- **Ethical & logistical aspects**



Summary & administrative information

- **Title**
 - Informative, helps identification in databases / registries
- **Protocol (lay) summary**
- **Study team**
 - who is the principal investigator
 - who is the statistician
 - who contributed to the design of the study
 - steering committee / data monitoring committee
- **Protocol version**
- **Funding**
- **Study registration**
 - e.g. clinicaltrials.gov, controlled-trials.com, crd.york.ac.uk/PROSPERO



Protocol structure

- **Summary & administrative information**
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Background & objectives

- **Clear description of the research question**
 - Why is it important
- **Rationale**
 - summary of existing evidence/studies
- **Specific (explicit) objectives and hypotheses**
- **Study design**
 - e.g. trial design, case-control, systematic review



Protocol structure

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Participants, interventions & outcomes

- **Defining the study population**
 - Inclusion & exclusion criteria



Example

Muller *et al.* *BMC Musculoskeletal Disorders* 2012, **13**:102
<http://www.biomedcentral.com/1471-2474/13/102>



STUDY PROTOCOL

Open Access

The epidemiology of polymyalgia rheumatica in primary care: a research protocol

Sara Muller^{1*}, Samantha Hider¹, Toby Helliwell¹, Joanne Bailey¹, Kevin Barradough², Louise Cope¹, Bhaskar Dasgupta³, Rebecca Foskett⁴, Rhian Hughes¹, Zoe Mayson¹, Charlotte Purcell¹, Edward Roddy¹, Simon Wathall¹, Irena Zwierska¹ and Christian D Mallen¹



Example

Design

Prospective observational inception cohort recruited in UK primary care.

Sampling frame

All adults (aged ≥ 18 years) registered with approximately 200 general practices, presenting at the practice and receiving a new Read-coded diagnosis of PMR between June 2012 and June 2014.

Patient eligibility

Inclusion criteria

- Aged 18 years and over.
- Registered with a participating general practice during the study period.
- First Read-coded consultation for PMR in the last three years occurred during the study period.
- Provided written informed consent to primary care medical record review.

Exclusion criteria

- Less than 18 years of age.
- Vulnerable groups, e.g. significant cognitive impairment, dementia, severe/terminal illness.
- Previous PMR diagnostic code in the last three years.



Participants, interventions & outcomes

- **Defining the study population**
 - Inclusion & exclusion criteria
- **Explain any interventions (for each group) to allow replication (including how and when administered)**
 - TIDieR checklist – reporting of interventions (Hoffmann et al, BMJ, 2014)
- **Outcomes should be clearly specified, related to the objectives / hypothesis of the study**
 - Primary & secondary outcomes should be clear
 - Any exploratory analyses should be pre-specified
- **Sample size (including any assumptions & feasibility)**
 - this will be discussed in more detail in the next OUCAGS session



Example

Kennedy *et al.* *BMC Cancer* 2012, **12**:181
<http://www.biomedcentral.com/1471-2407/12/181>



STUDY PROTOCOL

Open Access

EnROL: A multicentre randomised trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme

Robin H Kennedy^{1*}, Anne Francis², Susan Dutton³, Sharon Love³, Sarah Pearson², Jane M Blazeby⁴, Philip Quirke⁵, Peter J Franks⁶ and David J Kerr⁷



Example

Measurement of outcomes

Primary endpoint

The primary endpoint is physical fatigue 4 weeks after surgery as measured using the physical fatigue domain of the multidimensional fatigue inventory 20 (MFI-20). The MFI-20 is a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue.

Secondary endpoints

Postoperative hospital stay

Postoperative hospital stay will be reported, counting the day of operation as day zero.

Complications, re-admission, re-operation and mortality rates

30 day morbidity will be assessed at 30 days post-operatively by the centre's Research Nurse using a standardised definition of complications which have been modified from Lang et al. (2001) who reported a doubling of cost and hospital stay associated with postoperative complications [27]. The standard definitions of complications are detailed in Table 2. 30 day re-admission and re-operation rates, along with 30 day and in-hospital mortality will also be recorded.



Protocol structure

- **Summary & administrative information**
- **Background & objectives**
- **Participants, interventions & outcomes**
- **Data management & statistical analysis**
- **Ethical & logistical aspects**



Data management & statistical analysis

- **Data collection**

- what data is required
- how will the outcome data be collected

- **Data management**

- how to code the data, data entry/cleaning

- **Statistical Methods**

- specify the statistical methods to analyse the primary (and any secondary) outcomes
- any additional (exploratory analyses)
- availability of a statistical analysis plan (SAP)
- how will missing data be handled?

For studies using existing data, provide some information on how the data was collected, how it is coded, any data cleaning etc...



Protocol structure

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Ethical & administrative / logistical aspects

- **Ethics approval (REC/IRB numbers)**
- **Quality assurance**
 - Compliance with protocol
- **Independent data monitoring committee**
- **Gantt chart (milestones)**
- **Protocol amendments (date-stamped, version)**
- **Informed consent procedures**
- **Confidentiality**
- **Access to data**
- **Publication policy**
 - How will the results be communicate, authorship eligibility



Example

The EnROL trial has been approved by the National Research Ethics Service Committee South Central - Oxford B (REC reference: 07/H0605/150). The trial is co-ordinated by the Oncology Clinical Trials Office (OCTO) at the University of Oxford, with statistical support from the Centre for Statistics in Medicine, which together form Oxford Clinical Trials Research Unit (OCTRU). OCTRU is a UKCRN Registered Clinical Trials Unit. The trial is sponsored by the University of Oxford and North West London Hospitals NHS Trust. The Data Safety and Monitoring Committee and Trial Steering Committee, which includes a patient representative, will meet regularly in order to oversee the trial appropriately. Funding has come principally from the Bobby Moore Fund, Cancer Research UK (CR-UK) (Ref number: CRUK/07/019). Ethicon Endo-surgery have provided additional funding to facilitate provision of wound dressings and collection of pathology material.



SPIRIT 2013 Statement

RESEARCH AND REPORTING METHODS | **Annals of Internal Medicine**

SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials

An-Wen Chan, MD, DPhil; Jennifer M. Tetzlaff, MSc; Douglas G. Altman, DSc; Andreas Laupacis, MD; Peter C. Gøtzsche, MD, DrMedSci; Karmela Krleža-Jerić, MD, DSc; Asbjørn Hróbjartsson, PhD; Howard Mann, MD; Kay Dickersin, PhD; Jesse A. Berlin, ScD; Caroline J. Doré, BSc; Wendy R. Parulekar, MD; William S.M. Summerskill, MBBS; Trish Groves, MBBS; Kenneth F. Schulz, PhD; Harold C. Sox, MD; Frank W. Rockhold, PhD; Drummond Rennie, MD; and David Moher, PhD

The protocol of a clinical trial serves as the foundation for study planning, conduct, reporting, and appraisal. However, trial protocols and existing protocol guidelines vary greatly in content and quality. This article describes the systematic development and scope of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013, a guideline for the minimum content of a clinical trial protocol.

The 33-item SPIRIT checklist applies to protocols for all clinical trials and focuses on content rather than format. The checklist recommends a full description of what is planned; it does not prescribe how to design or conduct a trial. By providing guidance

for key content, the SPIRIT recommendations aim to facilitate the drafting of high-quality protocols. Adherence to SPIRIT would also enhance the transparency and completeness of trial protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders.

Ann Intern Med. 2013;158:200-207.

For author affiliations, see end of text.

This article was published at www.annals.org on 8 January 2013.

www.annals.org

Standard Protocol Items: Recommendations for
Interventional Trials



Specific issues for clinical trials

- **Details on assignment of intervention**
 - who generated the allocation sequence and how?
 - how was the allocation concealed? (opaque envelopes)
 - how and who will assign participants to the intervention?
 - who will be blinded to the intervention after assignment?
- **How will harms be collected, reported, assessed and managed?**
- **What are the plans to monitor the progress of the study?**
- **What is the remit of the data monitoring committee? Is there a charter?**



Example

Randomisation

Following consent, eligible patients will be randomised in a 1:1 ratio to open or laparoscopic resection using a central computer system at the Oncology Clinical Trials Office. Simple randomisation will be used for the first 50 patients then minimization with a random element (0.8) [25]. The stratification factors used in the minimization are hospital, cancer site (colon/rectum) and age (<66 years, 66–75 years, >75 years). To facilitate blinding of outcome observers the randomisation allocation will be sent directly to the patient's surgeon via email and will not be made available to the site staff member completing the randomisation process.



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Example

Blinding

Patients and outcome observers are to be blinded to the randomisation allocation until 7 days after surgery or the day of discharge if earlier. To facilitate this large Allevyn™ adhesive dressings will be provided for all trial patients. In addition, centres should ensure that all patient records which detail the randomisation allocation are stored in a sealed envelope within the patient's notes until after the patient is unblinded.



Published study protocol

Lemiale *et al. Trials* 2014, **15**:372
<http://www.trialsjournal.com/content/15/1/372>



STUDY PROTOCOL

Open Access

Early non-invasive ventilation for acute respiratory failure in immunocompromised patients (IVNIctus): study protocol for a multicenter randomized controlled trial

Virginie Lemiale^{1*}, Matthieu Resche-Rigon^{2,3}, Elie Azoulay^{1,3} and Study Group for Respiratory Intensive Care in Malignancies (Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie, GRRR-OH)¹

Registration number: clinicaltrials.gov NCT01915719



Trial record 1 of 1 for: NCT01915719.

[Previous Study](#) | [Return to List](#) | [Next Study](#)

Early Non Invasive Ventilation in Immuno-compromized Patients With Acute Respiratory Failure. (IVNICTUS)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified April 2014 by Assistance Publique - Hôpitaux de Paris

Sponsor:

Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):

Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:

NCT01915719

First received: July 26, 2013

Last updated: April 22, 2014

Last verified: April 2014

[History of Changes](#)

[Full Text View](#)

[Tabular View](#)

[No Study Results Posted](#)

[Disclaimer](#)

[How to Read a Study Record](#)

▶ Purpose

Assess the superiority of early non invasive ventilation in comparison to Oxygen therapy only, for immuno-compromized patients with acute respiratory failure

Condition	Intervention
Adult Acute Respiratory Failure Admitted in ICU Immuno Compromized	Procedure: Early non invasive ventilation Procedure: Oxygen therapy only

Study Type: Interventional

Study Design: Allocation: Randomized

Endpoint Classification: Efficacy Study

Intervention Model: Parallel Assignment

Masking: Open Label

Primary Purpose: Treatment

Official Title: Early Non Invasive Ventilation in Immuno-compromized Patients With Acute Respiratory Failure. A Prospective Randomized Clinical Trial.



Observational Studies: Getting Clear about Transparency

The *PLOS Medicine* Editors*

Protocol Publication

PLOS Medicine already requires that study protocols be submitted with reports of clinical trials, and publishes these alongside the accepted paper. Accordingly, for observational studies,

- (4) **Going forward, if a prospective analysis plan (from the study's funding proposal, IRB or other ethics committee submission, study protocol, or other planning document written before analyzing the data) was used in designing an observational study, authors must include the relevant prospectively written document with the manuscript submission for access by editors and reviewers and eventual publication alongside the accepted paper.**



Observational Studies: Getting Clear about Transparency

The *PLOS Medicine* Editors*

As with studies of any design, in some cases the final analysis of an observational study will necessarily differ from the analysis plan (as a result of unforeseen practical circumstances, changes requested by peer reviewers, etc.). Under such conditions, authors should explain why analyses could not be completed as planned, or why they had to be revised, and thereby address potential concerns over selective non-publication. If no prospectively written document exists, authors should explain how and when they determined the analyses being reported.



Systematic Reviews

"All research should be carried out according to a pre-defined plan. Cochrane researchers use the protocol to describe the proposed approach for a systematic review. It outlines the question that the review authors are addressing, detailing the criteria against which studies will be assessed for inclusion in the review, and describing how the authors will manage the review process. Protocols contain information that defines the health problem and the intervention under investigation, how benefits and harms will be measured, and the type of appropriate study design. The protocol also outlines the process for identifying, assessing, and summarizing studies in the review. By making this information available the protocol is a public record of how the review authors intend to answer their research question"

www.thecochranelibrary.com/view/0/AboutCochraneSystematicReviews.html



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www.thecochranelibrary.com/view/0/AboutCochraneSystematicReviews.html



Protocol for Systematic Reviews

- Background/rationale
 - why is a review and synthesis required
 - what existing evidence is there
- Methods
 - Population
 - who are you interested in
 - Study eligibility
 - Intervention, comparator & outcome(s)
 - Search strategy, study selection, data extraction
 - Data synthesis
 - Quantitative, qualitative



Published Systematic Reviews

Keir *et al.* *Systematic Reviews* 2014, **3**:92
<http://www.systematicreviewsjournal.com/content/3/1/92>



PROTOCOL

Open Access

Adverse effects of small-volume red blood cell transfusions in the neonatal population

Amy Keir^{1,2*}, Sanchita Pal³, Marialena Trivella⁴, Lani Lieberman^{5,6}, Jeannie Callum^{7,8}, Nadine Shehata^{8,9} and Simon Stanworth¹⁰



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Welcome to PROSPERO
International prospective register of systematic reviews

Latest news

Statement of founding principles

The PROSPERO Advisory Group have updated the [Statement of Founding Principles](#). The statement centres on both registration and access to search the database being free of charge. Planning and development decisions aim to make PROSPERO as inclusive as possible while ensuring we achieve the key aims of avoiding duplication and minimising bias in systematic reviews.

[More news...](#)

Latest new and updated records

[Blood-based biomarkers for the diagnosis, characterization and outcome prediction of traumatic brain injuries in adults: a living systematic review](#)

[A pill to save bleeding mothers: a systematic review and network meta-analysis of misoprostol's effectiveness, safety, and dosage for the prevention of postpartum haemorrhage in resource-poor communities.](#)

[Passive smoking as a risk factor for cognitive impairment and dementia](#)

[Prognostic role of microRNA-155 in non-small cell lung cancer](#)

[Effects of orthognathic surgery on the upper airway: a systematic review](#)



Summary (I)

A protocol consists of

- **Background / rationale / existing evidence**
- **Aims, objectives, study population, outcomes**
- **Methods (how to achieve the study objectives)**

Generally regardless of study design



Summary (II)

- **All studies require a protocol**
- **Having a protocol clarifies thought**
- **Vital for others involved in the study so that common procedures are being followed**
- **Transparency**
- **Can be used to draft any manuscripts**



Summary (III)

- **How to start?**
 - Don't reinvent the wheel
 - Try and get good examples
 - Search for published protocols

 - Use checklists (such as SPIRIT)
 - SPIRIT Explanation & Elaboration document for additional information (Chan et al, BMJ 2013 [see further reading])

 - Funders often have pre-specified formatted structure

 - Share with colleagues
 - Consult with a statistician



Useful reading

1. Chan et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; 158: 200—207.
2. Chan et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.
3. Ott MG. Importance of the study protocol in epidemiological research. *J Occup Med* 1991; 33: 1236—1239.
4. Enarson et al. Getting started in research: the research protocol. *Int J Tuberc Lung Dis* 2004; 8: 1036—1040.
5. Fronteira I. How to design a (good) epidemiological observational study: epidemiological research protocol at a glance. *Acta Med Port* 2013; 26: 731—736.
6. Ioannidis et al. Increasing value and reducing waste in research design, conduct and analysis. *Lancet* 2014; 383: 166-175.
7. Silverman R, Kwiatkowski T. Research fundamentals: III. Elements of a research protocol for clinical trials. *Acad Emerg Med* 1998; 5: 1218-1223.

