The HRA Guidance on Clinical Study Design Considerations

Ludwig-Maximilians-University Munich

HRA / RSS Workshop

London, 27th November 2014

Agenda

- Background to HRA collaboration
- Research project:
  - Objectives / Methods
  - Results
  - Limitations
  - Conclusions
  - Recommendations
- Overview of the HRA Guidance
- Discussion

Guidance for researchers

Essay

Doing New Research? Don't Forget the Old

Nobody should do a trial without reviewing what is known

Mike Clarke

On May 2, 1898, George Gould used his address to the founding meeting of the Association of Medical Librarians in Philadelphia to present a vision of the future of health information. 'I look forward,' he said, 'to such an organisation of the literary records of medicine that a puzzled worker in any part of the civilised world shall in an hour be able to gain a knowledge pertaining to a subject of the experience of every other man in the world' [1]. Has his vision been realised?

good quality, but some of it is not. Thus, anyone wishing to use the health literature to make well-informed decisions must both identify the relevant research from amidst this vast amount of information and then appraise it. This is an impossible task for many. Even though making access to the literature easier and cheaper will increase the ability of people to find research, it will also reveal just how much information there is out there and how daunting is the task of making sense of it.

with one or more search engines? Almost certainly, as the speed of the search increased through these four

Citation: Clarke M (2004) Doing new research? Don't forget the old. PLoS Med 1(2): e35.

Mike Clarke is director of the United Kingdom Cochrane Centre, Oxford, United Kingdom. E-mail: mclarke@cochrane.co.uk

Background to HRA Collaboration

- Reviews of published literature suggest:
  - Hypothesis frequently based on limited data
  - Study design often fails to take account of successes and failures of previous studies
  - Sample size parameter estimates often retrofitted to the available participants (sample size samba)
  - Optimism bias is common
- No extensive review of unpublished protocols:
  - Publication less detailed than the research protocol
  - Publication bias
  - Discrepancies between protocol and the publication

BMJ

BMJ 2013;346:f1135 doi: 10.1136/bmj.f1135 (Published 21 March 2013)

RESEARCH

Sample size determinations in original research protocols for randomised clinical trials submitted to UK research ethics committees: review

Timothy Clark *research scientist*, Ursula Berger *senior statistician*, Ulrich Mansmann *director, and chair of biostatistics and bioinformatics*

Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, Faculty of Medicine, Ludwig-Maximilians University, Munich, Germany

Project objectives

- Review unpublished protocols
- Assess the scientific underpinning of the research question and hypothesis
- Evaluate how the assumptions used in the sample size calculation were determined
- Assess reporting of sample size calculations
- Develop simple user friendly guidance for Research Ethics Committees

Methods: Filter criteria

Randomised Clinical Trial
Submitted to the NRES during the period January to December 2009
Clinical trial of an investigational medicinal product
Commercial or non-commercial Phase IIb, III or IV randomised clinical trial
Valid applications with a favourable or unfavourable REC opinion

Results: study characteristics

Study characteristic	Number of protocols (%) N=446
Commercial status:	
-Commercial	314 (70.4%)
-Non-commercial	132 (29.6)
Clinical Phase:	
-Phase IIb	102 (22.9%)
-Phase II / III	5 (1.1%)
-Phase III	251 (56.3%)
-Phase IV	88 (19.7%)

Results: study characteristics

Study characteristic	Number of protocols (%) N=446
Primary endpoint (Data type):	
-Continuous	202 (45.3%)
-Binary	116 (26.0%)
-Time-to-event	114 (25.6%)
-Other	14 (3.1%)
Trial design:	
-Parallel group	319 (71.5%)
-Group sequential	88 (19.7%)
-Crossover	18 (4.0%)
-Factorial	13 (2.9%)
-Adaptive	6 (1.4%)
-Withdrawal	2 (0.5%)

Results: study characteristics

Study characteristic	Number of protocols (%) N=446
Test hypothesis:	
Superiority	375 (84.1%)
Non-inferiority and equivalence	58 (13.0%)
Superiority & non-inferiority	11 (2.5%)
Not stated	2 (0.4%)
Allocation ratio:	
Equal	375 (84.1%)
Unequal	71 (15.9%)
Number of treatment arms:	
Two	339 (76.0%)
More than two	107 (24.0%)

Results: sample size reporting

Parameter / Analysis	Outcome	Number of protocols (%) N=446
Basis of treatment difference sought (or margin) reported	Yes	190 (42.6%)
	No	256 (57.4%)
Explained why the treatment difference (or margin) reasonable choice for planned study	Yes	13 (2.9%)
	No	433 (97.1%)
Clinical importance discussed	Yes	55 (12.3%)
	No	391 (87.7%)
Basis of estimated HR / Median Survival / Event or responder rate / Standard deviation reported	Yes	213 (47.7%)
	No	236 (50.7%)

Results: sample size reporting

Parameter	Outcome	Number of protocols (%) N=446
Explained why the HR / Median Survival / Event or responder rate / Standard deviation reasonable choice for the planned study	Yes	17 (3.8%)
	No	429 (96.2%)
Sensitivity analysis reported	Yes	11 (2.5%)
	No	435 (97.5%)
Withdrawal / drop-out rate	Yes	269 (60.3%)
	No	177 (39.7%)
Reproducible (n=416)	Under-estimated	51 (11.4%)
	Reproduced	262 (58.7%)
	Over-estimated	103 (23.1%)

Results: sample size reporting

Parameter	Outcome	Number of protocols (%) N=446
Multiple Comparisons and control Type I error (n=144)	Yes	81 (56.3%)
	No	63 (43.7%)
Interim Analysis and control Type I error (n=95)	Yes	56 (58.3%)
	No	39 (41.1%)
Reproducible (complete reporting, n=188)	Under-estimated	20 (10.6%)
	Reproduced	134 (71.3%)
	Over-estimated	34 (18.1%)

Results: sample size reporting

- 188 protocols (42.2%) reported all requisite information to re-calculate sample size
- Withdrawal / drop-out rate was the most frequently unreported parameter
- Very limited justification of design assumptions
- < 5% of the protocols explained the reasoning behind the assumptions used in calculation
- Meta-analyses rarely reported
- 11 (2.5%) protocols reported sensitivity analyses

Results: reproduction of the sample size

- 262 / 446 (58.7%) calculations reproduced
- 134 / 188 (71.3%) calculations from protocols with complete reporting reproduced
- 20 / 188 (10.6%) under-estimated and 34 / 188 (18.1%) over-estimated
- 134 / 446 (30.0%) original sample size calculations could be accurately reproduced

Results: commercial vs. non-commercial

- Commercial sponsors less likely to report the basis of design assumptions
- Non-commercial protocols were less likely to provide “complete reporting”
- Sample sizes from non-commercial sponsors were less likely to be reproduced
- Non-commercial sponsors were less likely to report adjustments for multiplicity

Limitations

- No direct contact with sponsors
- Only UK studies
- Results for commercial studies can be generalised to other countries and regions
- Non-commercial studies will depend on the investigators experience

Conclusions

- Scientific validity of the clinical study could not be properly assessed
- Systematic reviews of the existing data not performed / reported
- Sample size reporting requirements not met
- Validity of the calculation could not be judged
- New methodologies such as adaptive clinical trial designs not used

Recommendations

- Research protocol should include a detailed scientific rationale for the study design
- Facilitate the early detection of deficiencies in the study design

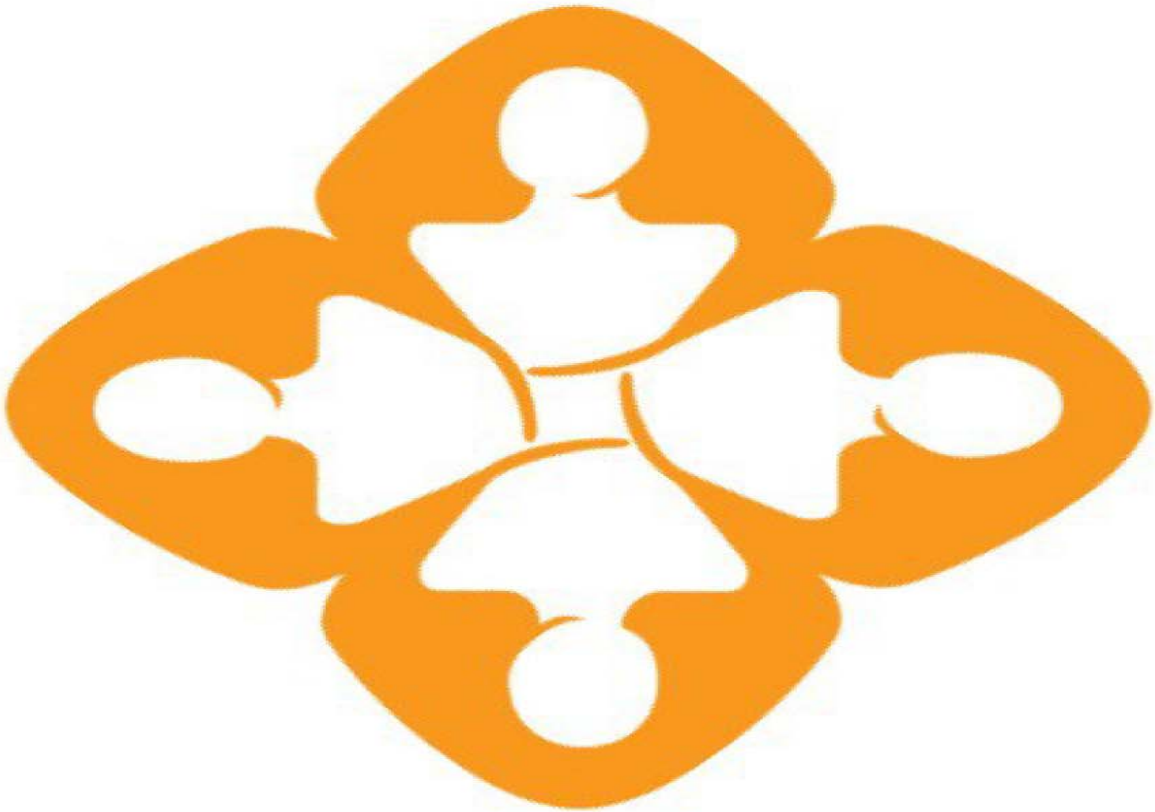
“if you get your design wrong….you are scuppered”

Steven Julious

NHS
Health Research Authority

Guidance

Specific questions that need answering when considering the design of clinical trials



Clark et al. Trials 2014, 15:286
http://www.trialsjournal.com/content/15/1/286

TRIALS

COMMENTARY Open Access

Five questions that need answering when considering the design of clinical trials

Timothy Clark[1], Hugh Davies[2*] and Ulrich Mansmann[1]

Abstract

Evidence suggests that research protocols often lack important information on study design, which hinders external review. The study protocol should provide an adequate explanation for why the proposed study methodology is appropriate for the question posed, why the study design is likely to answer the research question, and why it is the best approach. It is especially important that researchers explain why the treatment difference sought is worthwhile to patients, and they should reference consultations with the public and patient groups and existing literature. Moreover, the study design should be underpinned by a systematic review of the existing evidence, which should be included in the research protocol. The Health Research Authority in collaboration with partners has published guidance entitled 'Specific questions that need answering when considering the design of clinical trials'. The guidance will help those designing research and those reviewing it to address key issues.

Keywords: Research protocol, Research question, Ethical research, Systematic review, Sample size, Design assumptions, Justification, Monitoring, Study registration, Publication

HRA guidance

- Simple accessible guidance
- Questions that:
  - researchers,
  - sponsors,
  - peer reviewers, and
  - ethics committees

  should ask when planning or reviewing clinical studies

HRA guidance

Provenance

In developing this guidance we have combined material initially developed for National Research Ethics Service training workshops, papers arising from a collaboration between the Health Research Authority (HRA) and the University of Munich, Institute for Medical Informatics, Biometry and Epidemiology and advice provided by reviewers from the National Institute for Health Research's research programmes including the Health Services & Delivery Research Programme (NIHR HS&DR programme) which funds research focusing on improving outcomes for health and social care[1, 6].

We are particularly grateful to Tim Clark who led the collaboration and drafted the subsequent guidance. We are also grateful to Charles Beck, Steph Garfield-Birkbeck, Sue Bourne, Iain Chalmers, Clive Collett, Gary Collins, David Dickinson, Ron Driver, Ulrich Mansmann, Victoria Owen, Margaret Stoddart, Matthew Sydes, Nick Taub, and Gordon Taylor who contributed to our initial training days and an HRA workshop on this topic, and commented on earlier drafts of this guidance. David Dickinson also helped with the design and editing of this guidance.

HRA guidance

The structure of this document and how to use it.

This document is "layered", providing increasing detail if needed. It is not designed to be read from beginning to end. The reader should first consider the questions in **Layer I** and then **click** over the term or phrase if more information is required.

Layer I sets out in tabular form the "**Questions**" and "**Considerations**" that researchers, sponsors, peer reviewers, and RECs should ask

⇓

By **clicking** over the question or specific words or phrases in the table in **Layer I** the reader will be able to navigate to a more detailed discussion in **Layer II**

⇓

By **clicking** over specific terms or phrases in **Layer II** the reader will be able to navigate to more detailed explanations of individual components of the sample size in **Layer III**

⇓

By **clicking** over specific terms or phrases in **Layer III** the reader will be able to navigate to explanatory notes on some underlying statistical principles in **Layer IV**

⇓

Click on the link at the end of each section to get back to the first layer.

HRA guidance

HRA guidance poses five questions:

1) Is there a clear research question?
2) Will the proposed study design answer the research question?
3) Are the assumptions used in the sample size calculation appropriate?
4) How will safety and efficacy be monitored during the trial?
5) How will the trial be registered and subsequently published?

HRA guidance

1. Is there a clear research question?

Is the research question clearly and consistently stated?

Is there a satisfactory review of current knowledge?

Is this question of potential importance to patients and health care practitioners?

A clear research question is the cornerstone of good research practice.

Any project should build on a review of current knowledge. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical.

Researchers should explain why the question is worth asking.

HRA guidance

2. Will the proposed study design answer the research question?

What is the primary outcome measure of the research?

What is the treatment difference?

Researchers should be able to explain how the proposed research method is appropriate for the question posed, demonstrate that the design will answer the research question, and why it is the best approach.

The primary outcome measure should be a clear, quantitative measure of effect which, along with the time it will be measured, should be plainly and consistently described in the study protocol.

Researchers should present the evidence that any treatment difference they are seeking to detect is clinically important to patients and realistic.

HRA guidance

3. Are the assumptions used in the sample size calculation appropriate? Is there evidence and reasoning behind the design assumptions used in the calculations? Can the calculation be reproduced?	*Researchers must report all the information needed to allow any reader to understand the rationale for the assumptions that have been made and reproduce the sample size.* *The sample size should always be justified.*
4. How will safety and efficacy be monitored during the trial? Is the safety of participants adequately protected?	*Researchers have a responsibility to the study participants to monitor safety and clinical benefit during the trial.* *The sample size normally needs adjustment for planned interim analyses.*

HRA guidance

5. How will the trial be registered and subsequently published?

Are there plans to place the project in the public domain by registration and publication?

How and when will these results be shared with the participants?

Ethical research is open. Trials should be registered and results published. The HRA has made registration a condition of the favourable REC opinion and is leading further work.

Thanks for listening!