Improving the quality and value of clinical trials: the role of reporting guidelines

Doug Altman

Centre for Statistics in Medicine
and EQUATOR Network, Oxford

"Poorly conducted trials are a waste of time, effort, and money. The most dangerous risk associated with poor-quality reporting is an overestimate of the advantages of a given treatment … Whatever the outcome of a study, it is really hard for the average reader to interpret and verify the reliability of a poorly reported RCT. In turn, this problem could result in changes in clinical practice that are based on false evidence and that may harm patients.

Zonta and De Martino. Standard requirements for randomized controlled trials in surgery. *Surgery* 2008

Transparency and value

- **Research only has value if**
  - Study methods have validity
  - Research findings are published in a usable form

Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou

Lancet 2009; 374: 86–89
Published Online

Without accessible and usable reports, research cannot help patients and their clinicians. In a published research involving patients have be disincentives for those who might otl

Research article

- **Scientific manuscripts should present sufficient data so that the reader can fully evaluate the information and reach his or her own conclusions about results**
  - to assess reliability and relevance
- **Readers need a clear understanding of exactly what was done**
  - Clinicians, Researchers, Systematic reviewers, Policy makers, …
- **The goal should be transparency**
  - Should not mislead
  - Should allow replication (in principle)
  - Can be included in systematic review and meta-analysis

Evidence of poor reporting

- **There is considerable evidence that many published articles omit vital information**
  - Hundreds of reviews of published research articles
- **We often cannot tell exactly how the research was done**
- **These problems are generic**
  - not specific to randomised trials
  - not specific to studies of medicines
  - not specific to research by pharmaceutical companies

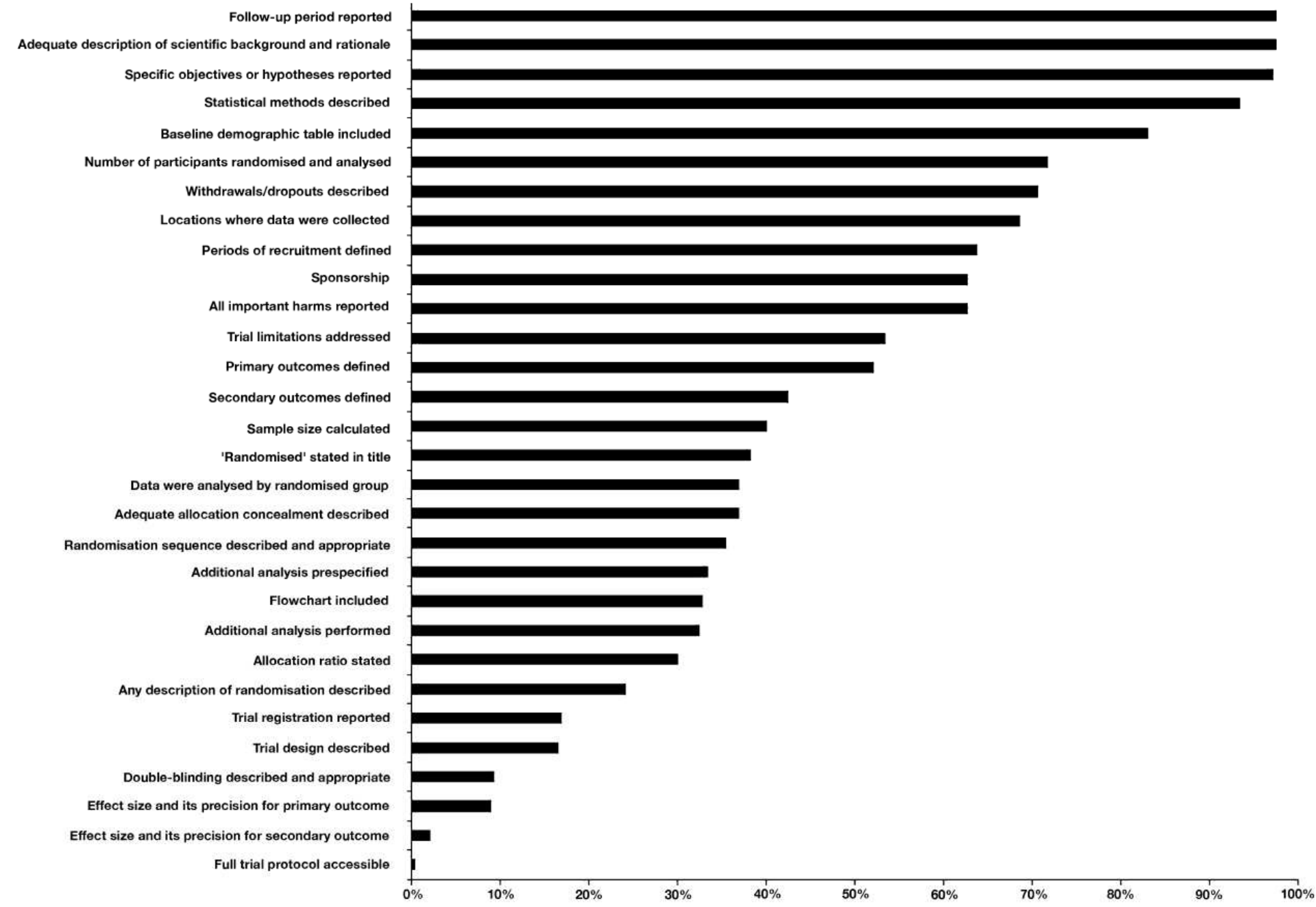


Figure 1 Compliance to the 30 items of the CONSORT statement (n = 290 trials).

Liu et al., *Transplant Int* 2013

Consequences of inadequate reporting

- **Assessing the reliability of published articles is seriously impeded by inadequate reporting**
  - Clinicians cannot judge whether to use a treatment
  - Data cannot be included in a systematic review

- **Serious consequences for clinical practice, research, policy making, and ultimately for patients**

"A basic principle can be set up that … it is at least as important to describe the techniques employed and the conditions in which the experiment was conducted, as to give the detailed statistical analysis of results."

"If cases are allotted to a control group or to a treatment group … what method of random selection is used?"

[Daniels M. Scientific appraisement of new drugs in tuberculosis. *Am Rev Tuberc* 1950;61:751-6.]

Reporting guidelines

- **A minimum set of items required for a clear and transparent account of what was done and what was found in a research study**
  - Reflect in particular issues that might introduce bias into the research
  - Evidence-based & reflect consensus opinion

- **Benefits of using reporting guidelines**
  - Improved accuracy and transparency of publications
  - Easier appraisal of reports for research quality and relevance
  - Improved efficiency of literature searching

A Proposal for Structured Reporting of Randomized Controlled Trials

SORT, *JAMA* 1994

Checklist of Information for Inclusion in Reports of Clinical Trials

The Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature*

Asilomar, *Annals Intern Med* 1994, 1996

Improving the Quality of Reporting of Randomized Controlled Trials

The CONSORT Statement

Colin Begg, PhD; Mildred Cho, PhD; Susan Eastwood, ELS(D); Richard Horton, MB;

CONSORT, *JAMA* 1996

The CONSORT statement: revised recommendations for improvin the quality of reports of parallel-group randomised trials

*David Moher, Kenneth F Schulz, Douglas G Altman, for the CONSORT Group**

CONSORT 2001 *Lancet*, *Annals*, *JAMA*

CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials

Kenneth F. Schulz[1]*, Douglas G. Altman[2], David Moher[3], for the CONSORT Group[¶]

CONSORT 2010 *Lancet*, *Annals*, *JAMA* etc

Major changes in 2010

- **Added 3 new items**
  - Registration, Protocol, Funding
- **Added several sub-items**
  - e.g. any important changes to methods after trial commencement, with a discussion of reasons
- **Made some items more specific**
  - e.g. allocation concealment mechanism, blinding
- **We simplified and clarified the wording throughout**

- NB Changes are documented in paper

Evolution of the CONSORT Statement

Outcomes

- **CONSORT 1996**
  - "Primary and secondary outcome measure(s) …"
- **CONSORT 2001**
  - "Clearly defined primary and secondary outcome measures …"
- **CONSORT 2010**
  - "Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed"

The "explanation and elaboration" document

- **To enhance the use and dissemination of CONSORT**
- **For each checklist item: examples of good reporting and explanation, with relevant empirical evidence**

Ann Intern Med. 2001;134:663-694.

The Revised CONSORT Statement for Reporting Randomized Trials: Explanation and Elaboration

Douglas G. Altman, DSc; Kenneth F. Schulz, PhD; David Moher, MSc; Matthias Egger, MD; Frank Davidoff, MD; Diana Elbourne, PhD; Peter C. Gøtzsche, MD; and Thomas Lang, MA, for the CONSORT Group

CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials

David Moher,[1] Sally Hopewell,[2] Kenneth F Schulz,[3] Victor Montori,[4] Peter C Gøtzsche,[5] P J Devereaux,[6] Diana Elbourne,[7] Matthias Egger,[8] Douglas G Altman[2]

BMJ 2010;340:c869

Many extensions

- Nonpharmacological treatments
- Harms
- Abstracts
- Cluster trials
- Non-inferiority and equivalence trials
- Acupuncture
- Patient reported outcomes
- …

"My question is: Are we making an impact?"

History
The CONSORT Group
CONSORT Endorsement
Endorse CONSORT
CONSORT Endorsers - Journals
CONSORT Endorsers - Organizations
Uptake of CONSORT by journals
Endorsement of CONSORT
CONSORT Funders
CONSORT Translation Policy
Impact of CONSORT

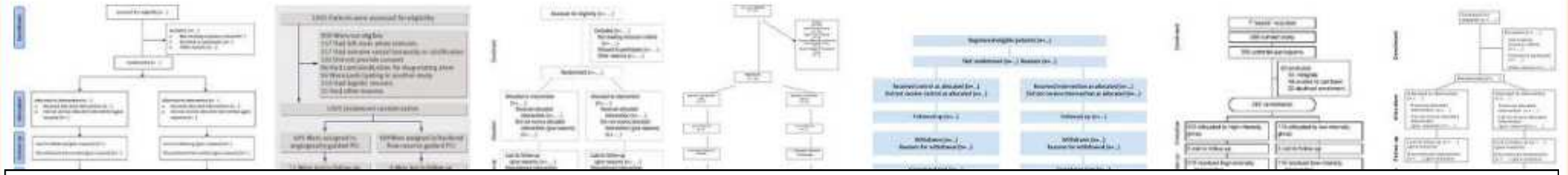
CONSORT Endorsers - Journals

The following journals have endorsed CONSORT.

CONSORT is endorsed by over 50% of the core medical journals listed in the *Abridged Index Medicus* on PubMed.

- A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Academic Emergency Medicine
Acta Neurologica Scandinavia
Advances in Neonatal Care
African Journal of Medicine
AIDS
AIDS Research and Therapy
Alcohol and Alcoholism
Allergy
Alternative Therapies in Health and Medicine
American Journal of Audiology
American Journal of Clinical Nutrition
American Journal of Denistry
American Journal of Gastroenterology
American Journal of Kidney Diseases
American Journal of Obstetrics & Gynecology
American Journal of Occupational Therapy
American Journal of Ophthalmology
American Journal of Psychiatry
American Journal of Public Health
American Journal of Respiratory and Critical Care Medicine
American Journal of Speech Language Pathology
American Journal of Sports Medicine
American Journal of Transplantation
Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders
Anesthesia and Analgesia
Anesthesiology



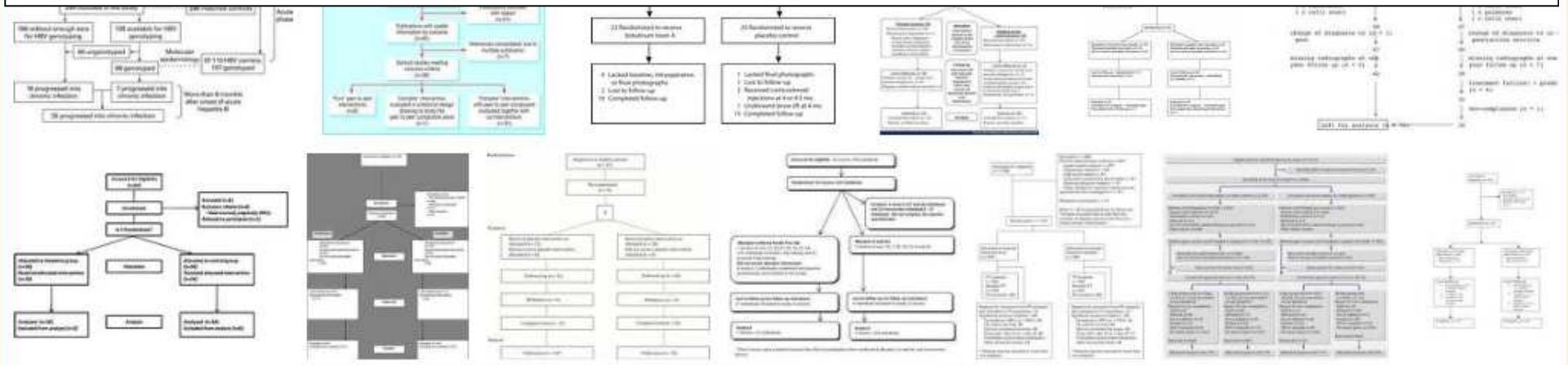
Hopewell *et al. Trials* 2011, **12**:253
http://www.trialsjournal.com/content/12/1/253

TRIALS

RESEARCH Open Access

Reporting of participant flow diagrams in published reports of randomized trials

Sally Hopewell*, Allison Hirst, Gary S Collins, Sue Mallett, Ly-Mee Yu and Douglas G Altman



Reporting of adverse events in randomised controlled trials of antiepileptic drugs using the CONSORT criteria for reporting harms

Arif A. Shukralla[a,*], Catrin Tudur-Smith[b], Graham A. Powell[a], Paula R. Williamson[b], Anthony G. Marson[a]

Reporting of AEs in RCTs … is poor and has not improved since the publication of the CONSORT guidelines on the reporting of harms. Commercially funded trials were better reported than non-commercially funded trials and trials recruiting adults were better reported than trials recruiting children. **These findings have serious implications as poor reporting precludes bias being detected and hinders adequate risk benefit analyses.**

Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals (Review)

Turner L, Sham

"The results of this review suggest that journal endorsement of CONSORT may benefit the completeness of reporting of RCTs they publish ... However, despite relative improvements when CONSORT is endorsed by journals, the completeness of reporting of trials remains suboptimal. Journals are not sending a clear message about endorsement to authors submitting manuscripts for publication."

d Central
ess Publisher

formatted

Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane reviewa

Systematic Reviews 2012, 1:60 doi:10.1186/2046-4053-1-60

Lucy Turner (lturner@ohri.ca)
Larissa Shamseer (lshamseer@ohri.ca)
Douglas G Altman (doug.altman@csm.ox.ac.uk)
Kenneth F Schulz (kshulz@ohri.ca)
David Moher (dmoher@ohri.ca)

Importance of trial protocol

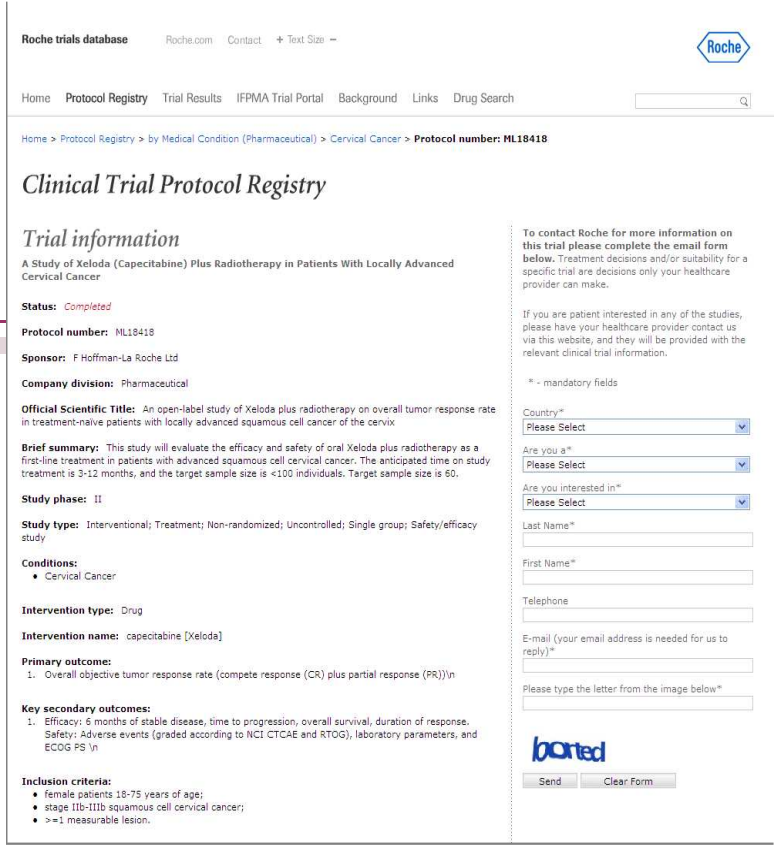
- **Trial 'roadmap'**
  - Detailed blueprint
- **Informs scientific & ethics review**
- **Origin for all subsequent reporting**

- **Transparency**

Need for public access to full protocols

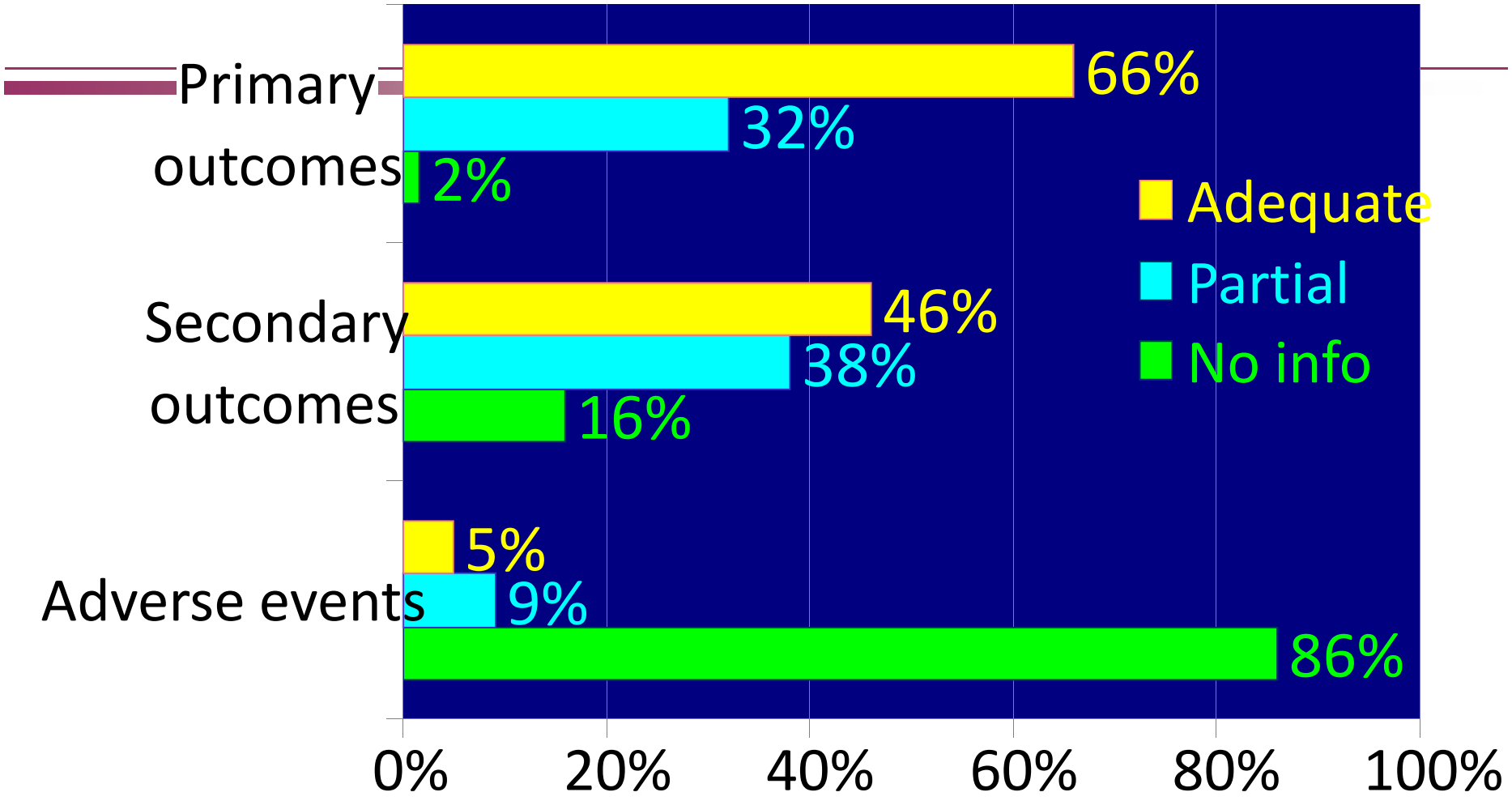
- **Critical appraisal of study methods**
- **Identification of selective reporting of results**
- **Venues:**
  - Registries
  - Websites
  - Journals

Limitations of trial registration



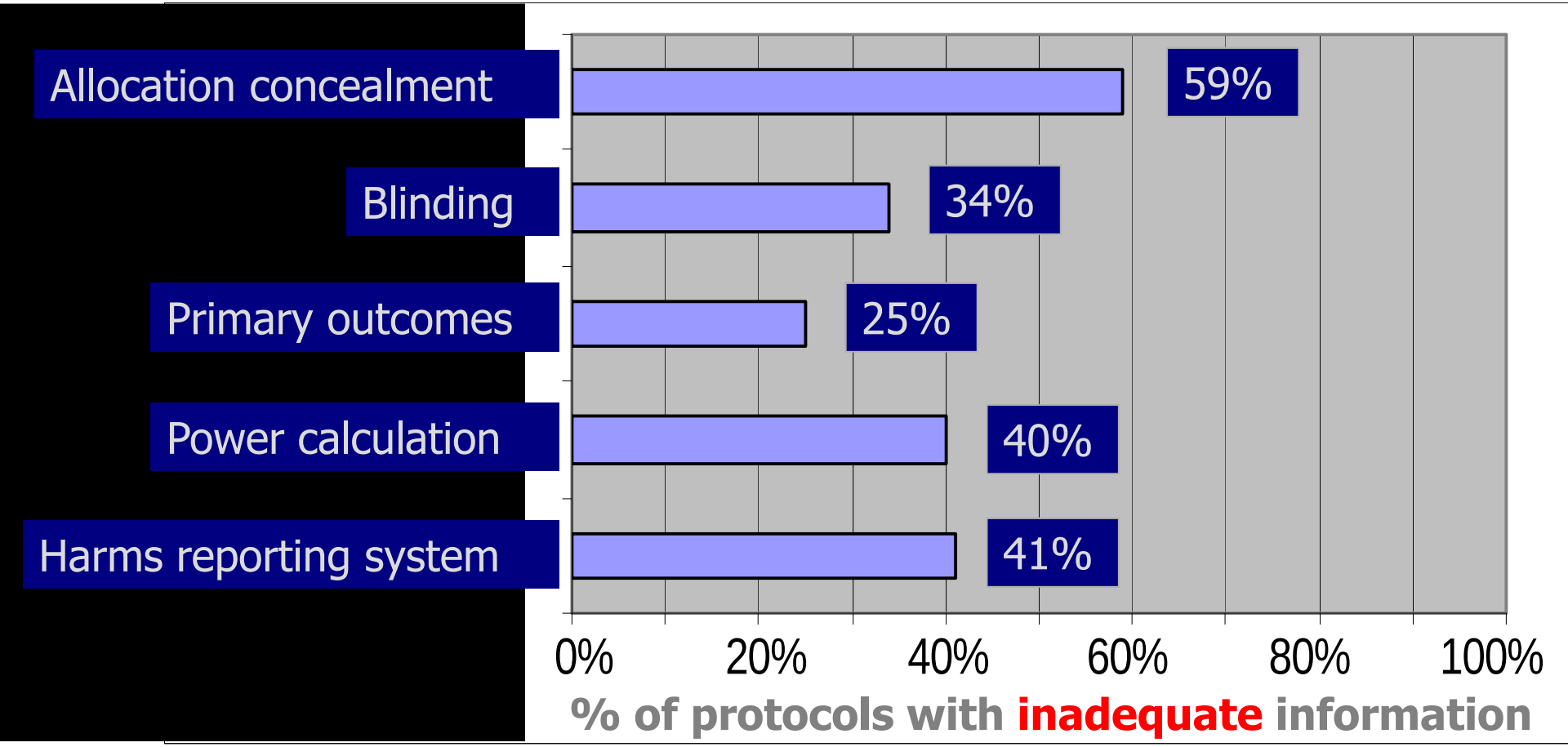
- **Only limited methodological information:**
  - basic trial design (controlled/randomised)
  - interventions
  - target sample size
  - primary and key secondary outcomes
- **No mechanism to ensure registration**
- **Variable quality of registered information**
- **Can't help critical appraisal of methods**
- **Rarely helps to identify selective reporting**

Registration of outcomes (N = 265 trials)



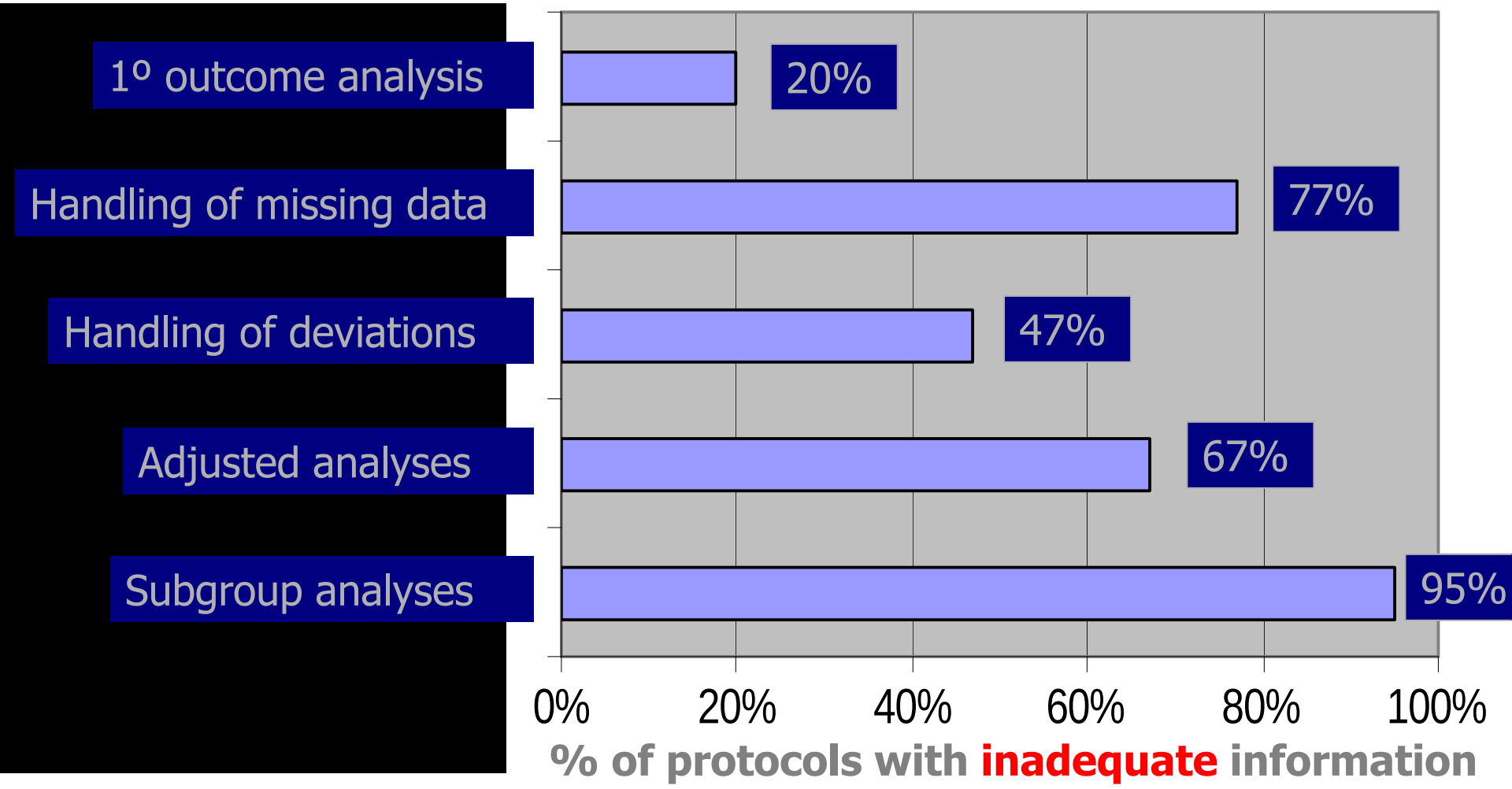
Reveiz *et al, PLoS One* 2010

Protocols lack important information



Hróbjartsson A *et al, J Clin Epid* 2009; Chan AW *et al*, *BMJ* 2008, *JAMA* 2004; Scharf O, *J Clin Oncol* 2006; Pildal J *et al*, *BMJ* 2005; Soares HP *et al*, *BMJ* 2004.

Protocols lack important information



Chan AW *et al*, *BMJ* 2008; Al-Marzouki S *et al*, *Lancet* 2008

Open Access Protocol

BMJ open
accessible medical research

Protocol: inspiratory muscle training for promoting recovery and outcomes in ventilated patients (IMPROVe): a randomised controlled trial

Bernie M Bissett,[1,2] I Anne Leditschke,[3,4] Jennifer D Paratz,[5,6] Robert J Boots[5,6]

To cite: Bissett BM, Leditschke IA, Paratz JD, *et al*. Protocol: inspiratory muscle training for promoting recovery and outcomes in ventilated patients (IMPROVe):

ABSTRACT

Introduction: Inspiratory muscle weakness is a known consequence of mechanical ventilation and a potential contributor to difficulty in weaning from ventilatory support. Inspiratory muscle training (IMT) reduces the weaning period and increases the likelihood of

it is not
piratory
g nor

ARTICLE SUMMARY

Article focus

- Mechanical ventilation (MV) is known to cause inspiratory muscle weakness, which may contribute to both difficulty weaning and poor recovery.
- Can IMT hasten weaning and enhance recovery from MV if commenced while still ventilated?

Study protocol

Open access

Efficacy of two educational interventions about inhalation techniques in patients with chronic obstructive pulmonary disease (COPD). TECEPOC: study protocol for a partially randomized controlled trial (preference trial)

Francisca Leiva-Fernández, José Leiva-Fernández, Fernando Zubeldia-Santoyo, Antonio García-Ruiz, Daniel Prados-Torres and **Pilar Barnestein-Fonseca**

For all author emails, please log on.

Trials 2012, **13**:64 doi:10.1186/1745-6215-13-64
Published: 21 May 2012

Abstract (provisional)

Background

Drugs for inhalation are the cornerstone of therapy in obstructive lung disease. We have observed that up to 75% of patients do not perform a correct inhalation technique. The inability of patients to correctly use their inhaler device may be a direct consequence of insufficient or poor inhaler technique instruction. The objective of this study is to test the efficacy of two educational interventions to improve the inhalation techniques in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods

This study uses both a multicenter patients' preference trial and a comprehensive cohort design with 495 COPD-diagnosed patients selected by a non-probabilistic method of sampling from seven Primary Care Centers. The participants will be divided into two groups and five arms. The two groups are: 1) the patients' preference group with two arms and 2) the randomized group with three arms. In the preference group, the two arms correspond to the two educational interventions (Intervention A and Intervention B) designed for this study. In the randomized group the three arms comprise: intervention A, intervention B and a control arm. Intervention A is written information (a leaflet describing the correct inhalation techniques). Intervention B is written information about inhalation techniques plus training by an instructor. Every patient in each group will be visited six times during the year of the study at health care center.

Discussion

Our hypothesis is that the application of two educational interventions in patients with COPD who are treated with inhaled therapy will increase the number of patients who perform a correct inhalation technique by at least 25%. We will evaluate the effectiveness of these interventions on patient inhalation technique improvement, considering that it will be adequate and feasible within the context of clinical practice. Trial registration Current Controlled Trials ISRTCTN15106246

The complete article is available as a provisional PDF. The fully formatted PDF and HTML versions are in production.

Trials
Volume 13

Viewing options
Abstract

Associated material
About this article
Readers' comments
Pre-publication history

Related literature
Cited by
on Google blog search
Other articles by authors
on Google Scholar
on PubMed
Related articles/pages
on Google
on Google Scholar

Tools
Download references
Email to a friend
Order reprints
Post a comment

Share this article
Recommend
Tweet 0
More options...

A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Summary

Background Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intesive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation could be reduced with a protocol of no sedation versus daily interruption of sedation.

Methods Of 428 patients assessed for eligibility, we enrolled 140 critically ill adult patients who were undergoing mechanical ventilation and were expected to need ventilation for more than 24 h. Patients were randomly assigned in a 1:1 ratio (unblinded) to receive: no sedation (n=70 patients); or sedation (20 mg/mL propofol for 48 h, 1 mg/mL midazolam thereafter) with daily interruption until awake (n=70, control group). Both groups were treated with bolus doses of morphine (2·5 or 5 mg). The primary outcome was the number of days without mechanical ventilation in a 28-day period, and we also recorded the length of stay in the intensive care unit (from admission to 28 days) and in hospital (from admission to 90 days). Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00466492.

Findings 27 patients died or were successfully extubated within 48 h, and, as per our study design, were excluded from the study and statistical analysis. Patients receiving no sedation had significantly more days without ventilation (n=55; mean 13·8 days, SD 11·0) than did those receiving interrupted sedation (n=58; mean 9·6 days, SD 10·0; mean difference 4·2 days, 95% CI 0·3–8·1; p=0·0191). No sedation was also associated with a shorter stay in the intensive care unit (HR 1·86, 95% CI 1·05–3·23; p=0·0316), and, for the first 30 days studied, in hospital (3·57, 1·52–9·09; p=0·0039), than was interrupted sedation. No difference was recorded in the occurrences of accidental extubations, the need for CT or MRI brain scans, or ventilator-associated pneumonia. Agitated delirium was more frequent in the intervention group than in the control group (n=11, 20% *vs* n=4, 7%; p=0·0400).

Lancet 2010; 375: 475–80
Published Online January 29, 2010 DOI:10.1016/S0140-6736(09)62072-9

See Comment page 436

Department of Anesthesia and Intensive Care Medicine, Odense University Hospital (T Strøm MD, Prof P Toft DMSc), **and Department of Biostatistics, Faculty of Health Sciences** (Prof T Martinussen PhD), **University of Southern Denmark, Denmark**

Correspondence to: Dr Thomas Strøm, Department of Anesthesia and Intensive Care Medicine, Odense University Hospital, Unit 26, 5000 Odense C, Denmark
t.s@dadlnet.dk

Current landscape of protocols

- **Generally not publicly available**
- **Incomplete information**
- **Variable standard**

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Objective

- **To improve content and quality of clinical trial protocols through evidence-based guidance**

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

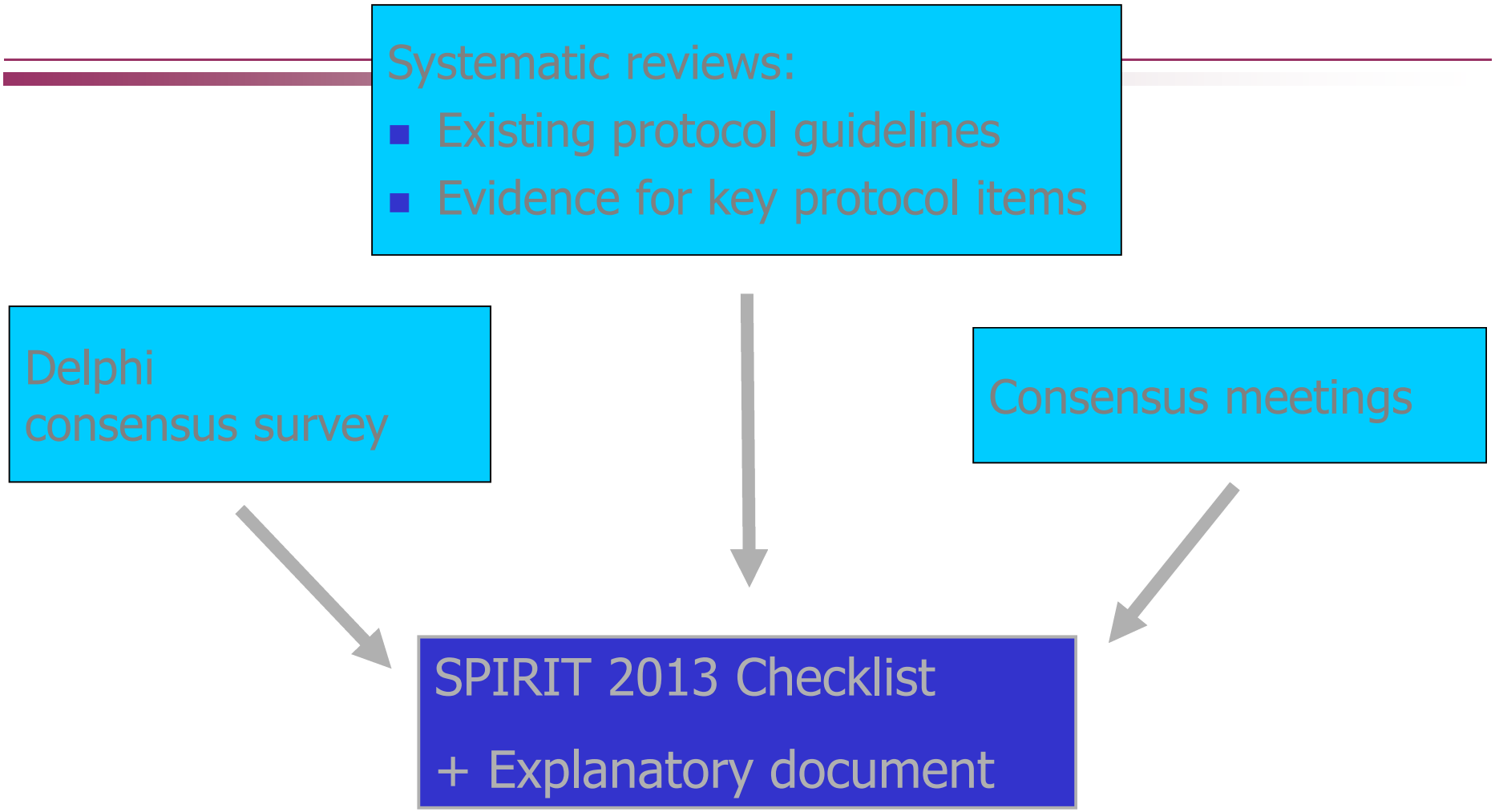
Canadian Agency for Drugs and Technologies in Health
Agence canadienne des médicaments et des technologies de la santé

National Cancer Institute of Canada
Institut national du cancer du Canada

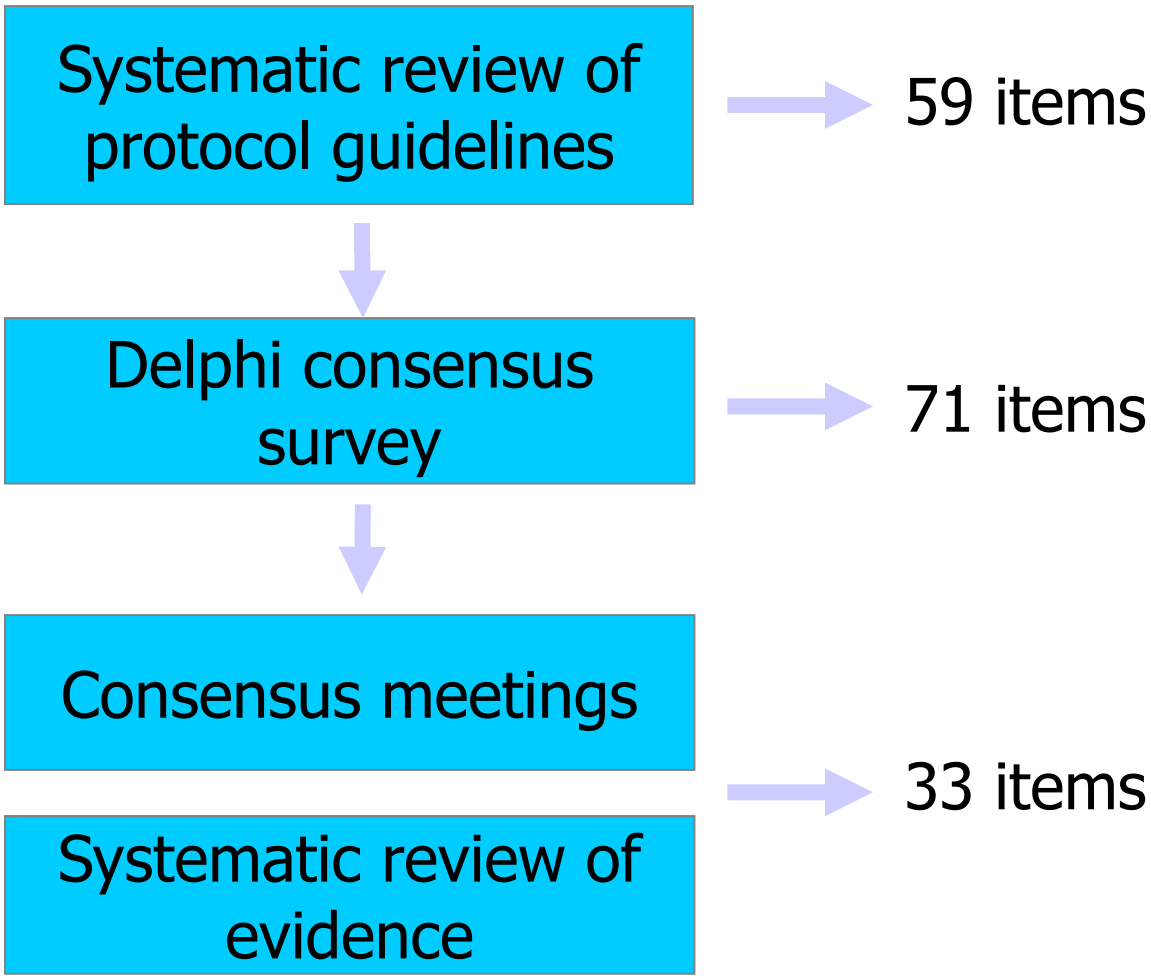
Definition of protocol

- **Pre-trial document submitted for ethics approval**
  - Background & objectives
  - Population & interventions
  - Methods & statistical analyses
  - Ethical and administrative aspects
- **Evolving document**
  - Transparent audit trail
- **Related documents (SAP, contracts)**

Methods


Systematic reviews:
Existing protocol guidelines
Evidence for key protocol items
Delphi consensus survey
Consensus meetings
SPIRIT 2013 Checklist
+ Explanatory document

Evolution of SPIRIT Checklist



Annals of Internal Medicine | Research and Reporting Methods

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.

For author affiliations, see end of text.

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

SPIRIT 2013 Checklist

- **33 items in five categories**
  - Administrative information
  - Introduction
  - Study methods
  - Ethical considerations & dissemination
  - Appendices

Similarities to CONSORT

- **Format and content**
  - Consistent wording and structure for items common to both checklists
  - Aids transition from SPIRIT to CONSORT
  - Systematic approach informed by evidence

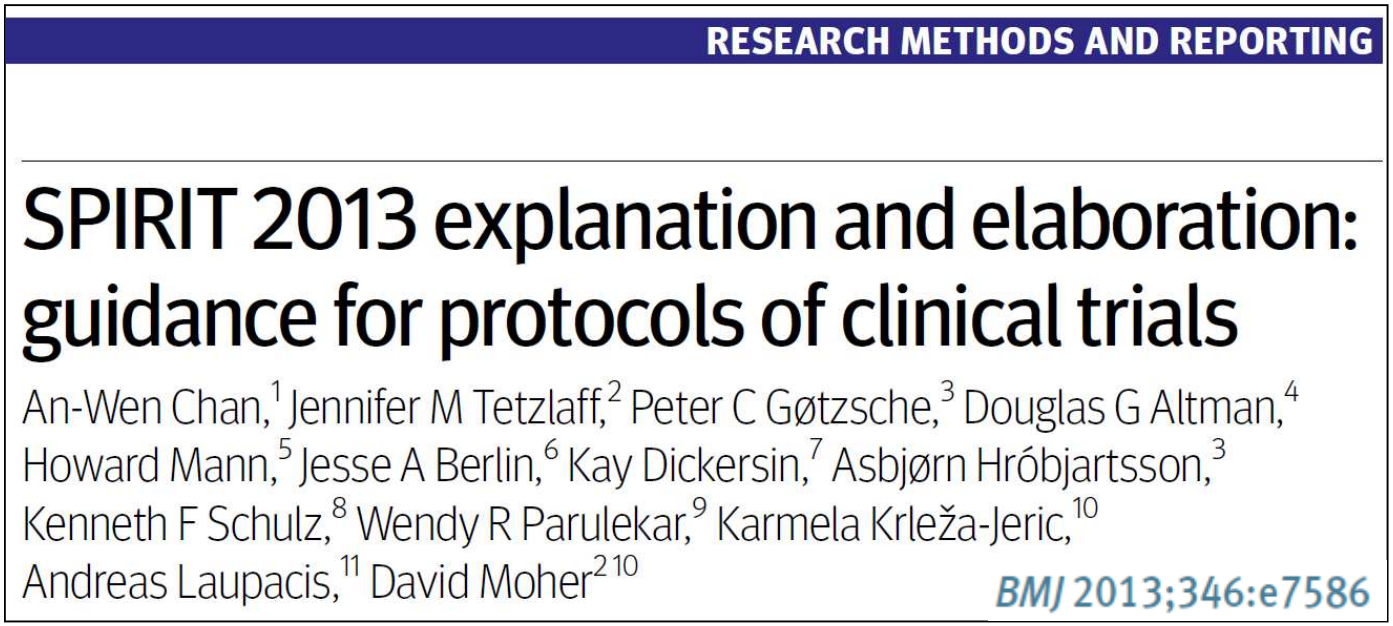
- **Planned implementation strategy**

Scope of SPIRIT

- **All clinical trials**
- **Minimum content**
- **Relevant information from contracts & operations manuals**

SPIRIT Explanation & Elaboration

- **For each item:**
  - Model example
  - Rationale and explanation
  - References to empirical evidence and further reading



RESEARCH METHODS AND REPORTING

SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials

An-Wen Chan,[1] Jennifer M Tetzlaff,[2] Peter C Gøtzsche,[3] Douglas G Altman,[4] Howard Mann,[5] Jesse A Berlin,[6] Kay Dickersin,[7] Asbjørn Hróbjartsson,[3] Kenneth F Schulz,[8] Wendy R Parulekar,[9] Karmela Krleža-Jeric,[10] Andreas Laupacis,[11] David Moher[2 10]

BMJ 2013;346:e7586

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT*	$-t_1$	0	t_1	t_2	t_3	t_4	*etc*	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
(List other procedures)	X							
Allocation		X						
INTERVENTIONS:								
(Intervention A)			←	—	→			
(Intervention B)			X		X			
(List other study groups)			←	—	—	→		
ASSESSMENTS:								
(List baseline variables)	X	X						
(List outcome variables)				X		X	etc	X
(List other data variables)			X	X	X	X	etc	X

* List specific timepoints in this row

Fig 1 | Example template for the schedule of enrolment, interventions, and assessments (recommended content can be displayed using other schematic formats)

Implementation strategy

- **Dissemination**
- **Endorsement and enforcement**
  - Journals, funders, etc
- **Implementation tools**
- **Evaluation of impact**

SPIRIT

Search Search

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Welcome to the SPIRIT Statement website

The protocol of a clinical trial is essential for study conduct, review, reporting, and interpretation. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) is an international initiative that aims to improve the quality of clinical trial protocols by defining an evidence-based set of items to address in a protocol.

Page last updated: January 30, 2013 @ 3:32 am

FUNDERS:

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Canadian Agency for Drugs and Technologies in Health

Institut national du cancer du Canada | National Cancer Institute of Canada

WOMEN'S COLLEGE RESEARCH INSTITUTE
Health care for women REVOLUTIONIZED

SPIRIT CHECKLIST

PUBLICATIONS & DOWNLOADS

SPIRIT ELECTRONIC PROTOCOL TOOL

Conclusions

- **Trial protocols are central to transparency, scientific validity, and ethical rigour**
- **SPIRIT checklist aims to improve protocol quality**
- **Impact requires broad adoption**

"Poorly conducted trials are a waste of time, effort, and money. The most dangerous risk associated with poor-quality reporting is an overestimate of the advantages of a given treatment … Whatever the outcome of a study, it is really hard for the average reader to interpret and verify the reliability of a poorly reported RCT. In turn, this problem could result in changes in clinical practice that are based on false evidence and that may harm patients.

Zonta and De Martino. Standard requirements for randomized controlled trials in surgery. *Surgery* 2008

"Poorly conducted trials are a waste of time, effort, and money. The most dangerous risk associated with poor-quality reporting is an overestimate of the advantages of a given treatment … Whatever the outcome of a study, it is really hard for the average reader to interpret and verify the reliability of a poorly reported RCT. In turn, this problem could result in changes in clinical practice that are based on false evidence and that may harm patients. **The only way to avoid this risk and to be sure that the final message of a RCT can be correctly interpreted is to fulfill the items listed in the CONSORT statement."**

Zonta and De Martino. Standard requirements for randomized controlled trials in surgery. *Surgery* 2008