



Marie Skłodowska-Curie Actions Innovative Training Networks (ITN)

European Joint doctorate (EJD)

H2020-2015



MIROR Training Event

Practical session

Protocol writing

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What is a protocol?

- A document that provides sufficient details to enable understanding of the background, objectives, study design, outcomes, statistical analyses, ethical considerations, etc
- Not just a list of items but a cohesive document

Why is it necessary to write a protocol?

- Every study requires a protocol!
- Necessary for researchers
 - Rigorous scientific conduct
 - Avoid bias in planning and conduct
 - Allows for anticipating possible problems
- Necessary for ethical committees (participants involved)
 - Support for decision concerning approval
- Necessary even if no participants are involved (eg systematic review, etc)
- Necessary for researchers, editors, peer-reviewers
 - To judge the quality of the study

Why a protocol?

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

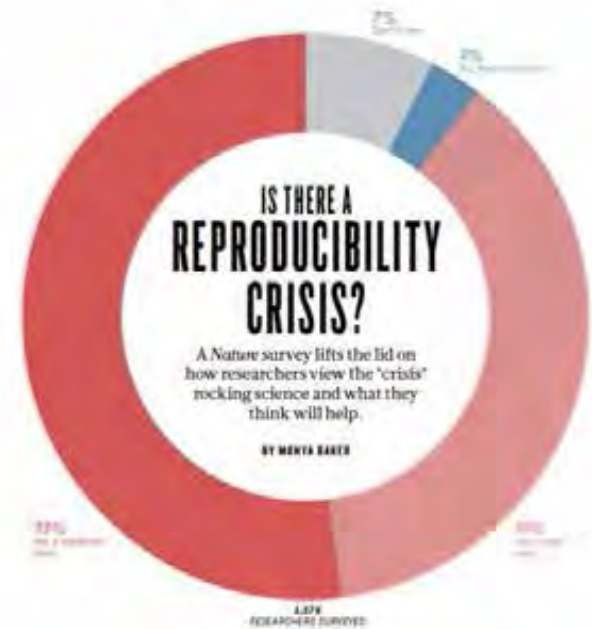
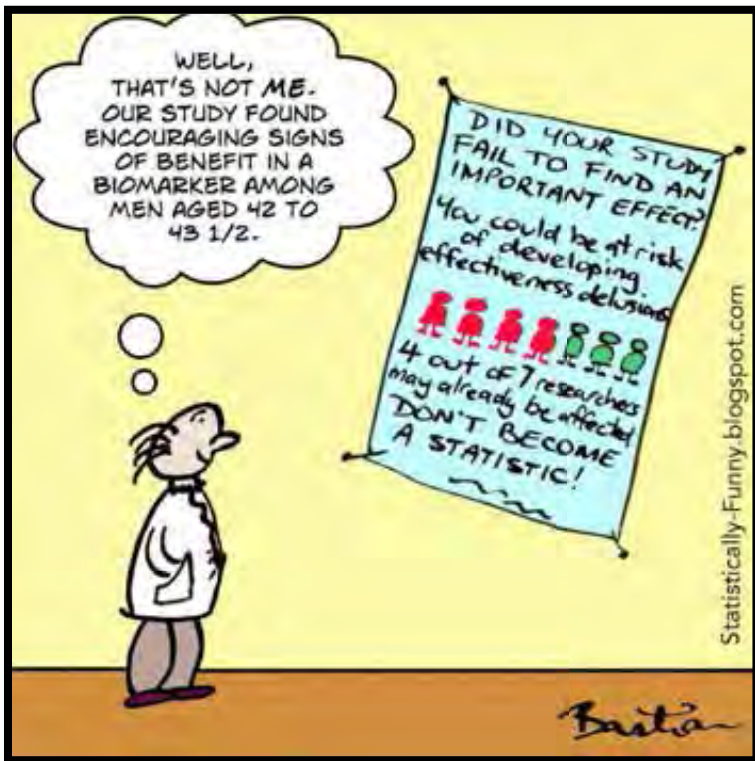
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Why a protocol?

- To reproduce the study
- To avoid cherry picking



When should we write the protocol?

- When planning the study
- Before the beginning of the study



A protocol is a « living » document

- A protocol can be modified
- Transparency must be the rule
 - List of all modifications
 - Date
 - Content
 - Keep all the versions of the protocol
 - Must be numbered
- Important modifications (amendments) in the protocol should be submitted to the ethical committee for validation

Research log

Date	Context	Decision	Justification
3/2/2016	Meeting with XX	Modification of the search strategy	Too many articles missed
3/3/2016	Conf call with XX	Validation of the protocol	
3/4/2016	Start of the study		
3/4/2016	Meeting with XX	Protocol amendment: Change in statistical analysis planned	Recent article with more relevant methods (ref)
.....			

What should be in the protocol?

- All the information needed to justify, conduct and reproduce the study



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

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.

News

- Spanish translation published (Feb 2016)

SPIRIT Checklist



Publications & Downloads



SEPTRE (SPIRIT Electronic Protocol Tool & Resource)

<http://www.spirit-statement.org/>

Protocol registration

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Protocol registration

International Clinical Trials Registry Platform (ICTRP)

Welcome to the WHO ICTRP

The mission of the WHO International Clinical Trials Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.



WHO/IP. Virat



The registration of all interventional trials is a scientific, ethical and moral responsibility.

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

New Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

[Find Studies](#) [About Clinical Studies](#) [Submit Studies](#) [Resources](#) [About This Site](#)

ClinicalTrials.gov currently lists 227,475 studies with locations in all 50 States and in 191 countries.

Text Size ▾

Search for Studies

Example: "Heart attack" AND "Los Angeles"

[Advanced Search](#) [See Studies by Topic](#)
[See Studies on Map](#)

Search Help

- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies



■ Non-U.S. only (56%)
■ U.S. only (39%)
■ Both U.S. and non-U.S. (5%)

Total N = 39,935 studies
(Data as of October 10, 2016)

• [See more trends, charts, and maps](#)

Protocol registration



The screenshot shows the top section of the EU Clinical Trials Register website. It features a blue header with the European Union flag and the text "EU Clinical Trials Register". Below the header is a navigation menu with four items: "Home & Search", "Joining a trial", "Contacts", and "About". The main content area is titled "Clinical trials" and contains the following text:

The European Union Clinical Trials Register allows you to search for protocol and results information on:

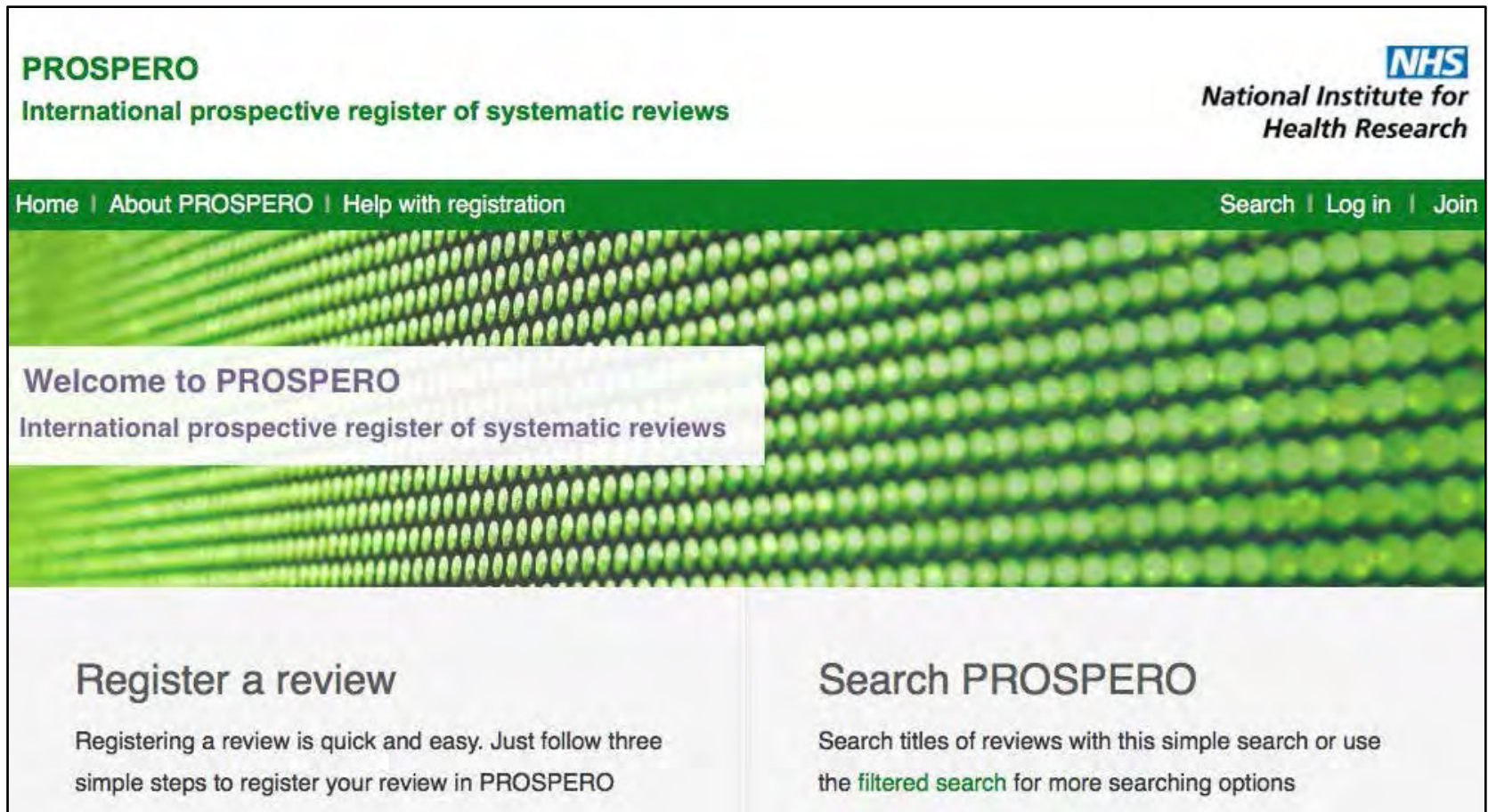
- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development.

Learn [more about the EU Clinical Trials Register](#) including the source of the information and the legal basis.

The EU Clinical Trials Register currently displays **28926** clinical trials with a EudraCT protocol, of which **4382** are clinical trials conducted with subjects less than 18 years old.

The register also displays information on **18612** older paediatric trials (in scope of Article 45 of the Paediatric Regulation (EC) No 1901/2006).

Protocol registration



The image shows the homepage of the PROSPERO website. At the top left, the text reads "PROSPERO International prospective register of systematic reviews". At the top right is the NHS logo and "National Institute for Health Research". A green navigation bar contains "Home | About PROSPERO | Help with registration" on the left and "Search | Log in | Join" on the right. The background features a green abstract pattern of overlapping circles. A white box in the center contains the text "Welcome to PROSPERO International prospective register of systematic reviews". Below this, there are two main sections: "Register a review" and "Search PROSPERO".

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

Home | About PROSPERO | Help with registration

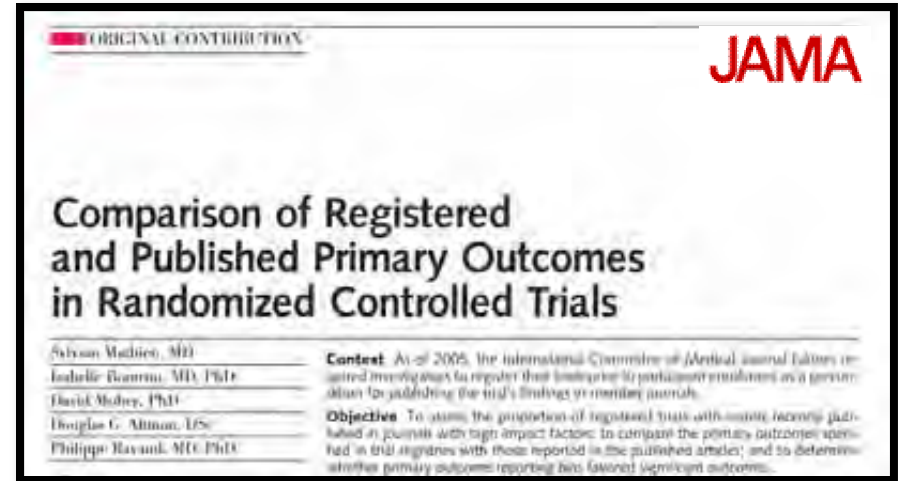
Search | Log in | Join

Welcome to PROSPERO
International prospective register of systematic reviews

Register a review
Registering a review is quick and easy. Just follow three simple steps to register your review in PROSPERO

Search PROSPERO
Search titles of reviews with this simple search or use the [filtered search](#) for more searching options

Use of Protocol in Research on Research



- 62% of the trials have at least 1 outcome that was changed omitted or added
- Positive outcomes were more likely to be published (OR=2.4[1.4-4.0])
- Discrepancies between the primary outcome registered and published for 31% trials

Comparison of protocols and registry entries to published reports for randomised controlled trials

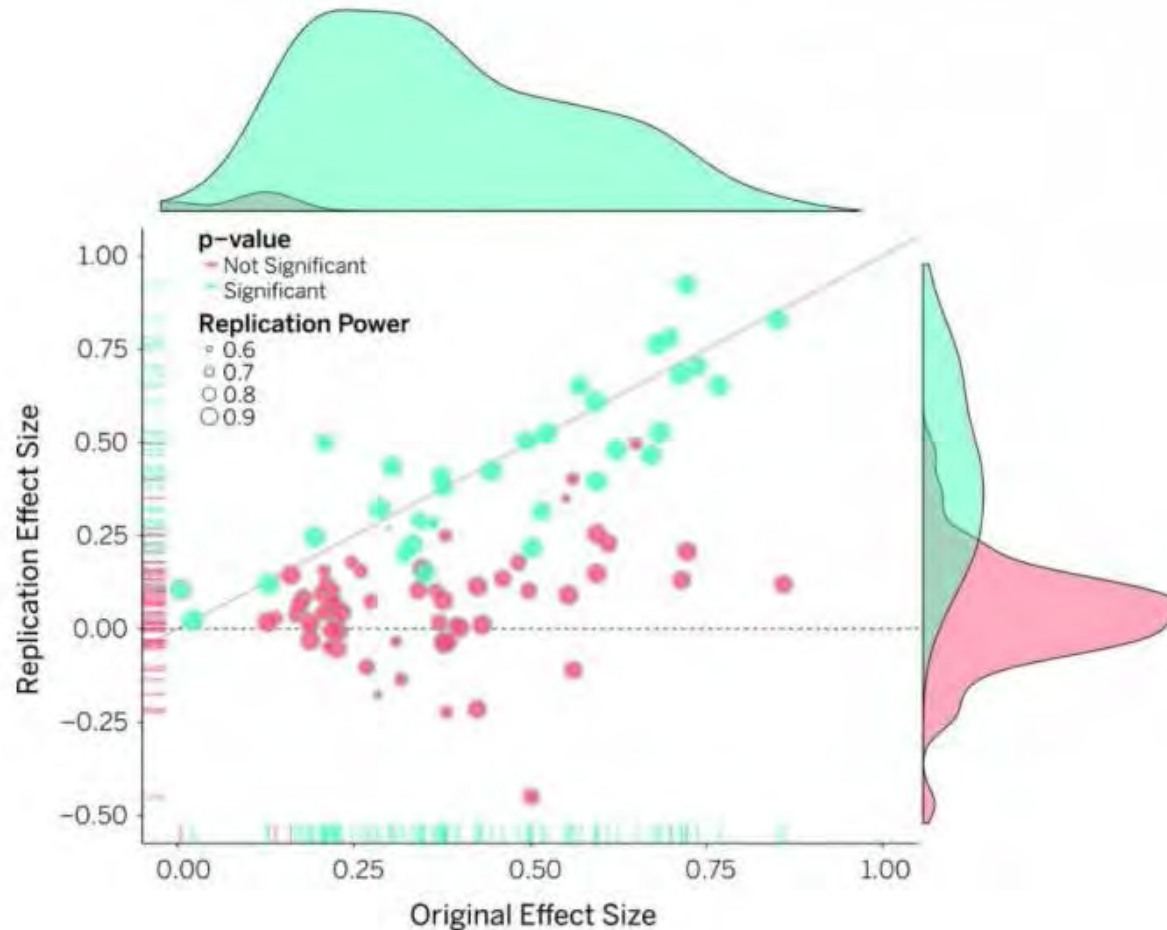


Kerry Dwan¹, Douglas G Altman², Lynne Cresswell³, Michaela Blundell³, Carrol L Gamble³, Paula R Williamson³

- **Authors' conclusions**
- Discrepancies between protocols or trial registry entries and trial reports were common, although reasons for these were not discussed in the reports.
- Full transparency will be possible only when protocols are made publicly available or the quality and extent of information included in trial registries is improved, and trialists explain substantial changes in their reports.

Replication

Replications of 100 experimental and correlational studies published in three psychology journals



Tracking switched outcomes in clinical trials

- Comparison of each clinical trial report with its protocol or registry entry for all trials published in the top 5 general Medical journal
 - NEJM, JAMA, The Lancet, Annals of Internal Medicine, BMJ
- In case of discrepancies, to determine
 - the number of outcomes pre-specified in the protocol or registry were never reported.
 - the number of new outcomes silently added.
- A letter to the editor is systematically sent in case of discrepancies.



Tracking switched outcomes in clinical trials

67

TRIALS
CHECKED

9

TRIALS WERE
PERFECT

300

OUTCOMES NOT
REPORTED

357

NEW
OUTCOMES
SILENTLY
ADDED

On average, each trial reported just 62.1% of its specified outcomes. And on average, each trial silently added 5.3 new outcomes.

58

LETTERS SENT

12

LETTERS
PUBLISHED

10

LETTERS
UNPUBLISHED
AFTER 4 WEEKS

33

LETTERS
REJECTED BY
EDITOR

On average

- each trial reported 62% of its specified outcomes
- each trial silently added 5 new outcomes.

JAMA reject correction letters on all trials they have misreported

March 24, 2016 - by [Ben Goldacre](#) — [Leave a Comment](#)

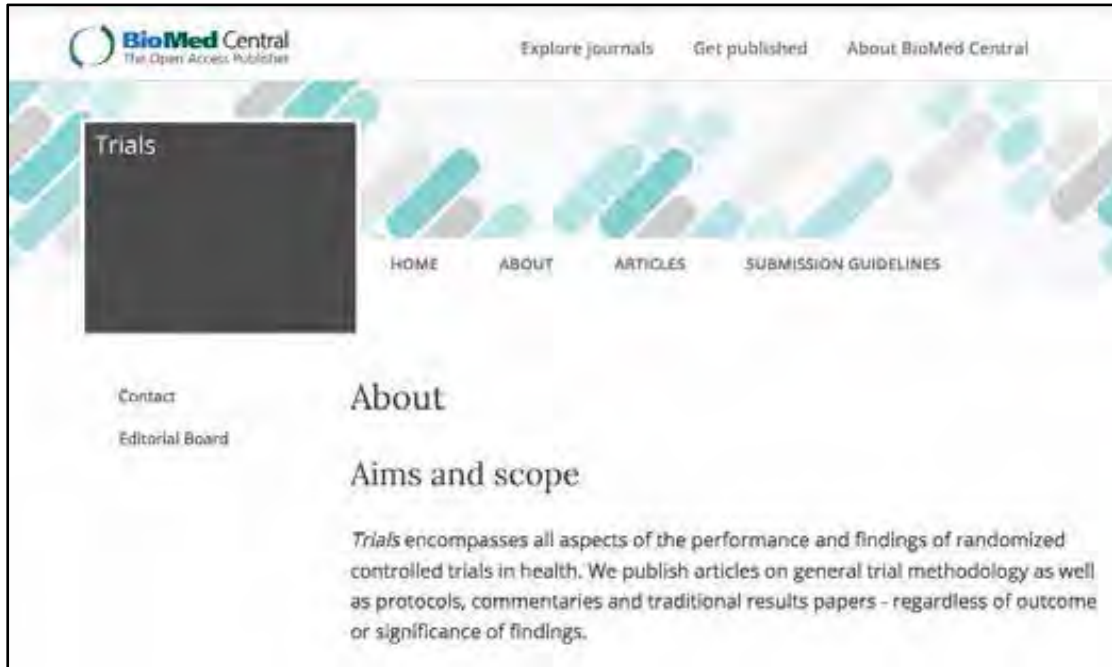
Here we publish some correspondence with JAMA, who have declined to correct the record on a series of trials that they have misreported in their pages.

First, one paragraph of background, for those unfamiliar with the problem of outcome switching, and COMPare's efforts to address it. It is well established that academic journals [routinely permit outcome switching](#) in the trial reports that they publish, despite public commitments to

Another ethical breach at Annals? Misleading transparency statements, and inaccessible protocols.

April 6, 2016 - by [Ben Goldacre](#) — [Leave a Comment](#)

Publication of protocols



The screenshot shows the BioMed Central website for the journal *Trials*. The BioMed Central logo is in the top left, with the tagline "The Open Access Publisher". Navigation links include "Explore journals", "Get published", and "About BioMed Central". A dark box labeled "Trials" is on the left. Below it are links for "Contact" and "Editorial Board". The main content area has a navigation bar with "HOME", "ABOUT", "ARTICLES", and "SUBMISSION GUIDELINES". The "About" section is active, with a sub-section "Aims and scope" containing the text: "Trials encompasses all aspects of the performance and findings of randomized controlled trials in health. We publish articles on general trial methodology as well as protocols, commentaries and traditional results papers - regardless of outcome or significance of findings."



The screenshot shows the BMJ Open journal website. The header features the "BMJ Open" logo and a search bar with "Search this site" and "Advanced search" options. Below the header is a navigation bar with links: "Latest content", "Archive", "Browse by topic", "About the journal", "Submit a paper", "Jobs", and "Help". The main content area highlights the journal's "Impact Factor 2.562" and provides a description: "BMJ Open is an online, open access journal, dedicated to publishing medical research from all disciplines and therapeutic areas. The journal publishes all research study types, from study protocols to phase I trials to meta-analyses, including small, specialist studies, and negative studies. Publishing procedures are built around fully open peer review and continuous publication, publishing research online as soon as the article is ready. BMJ Open aims to promote transparency in the publication process by publishing reviewer reports and previous versions of manuscripts as pre-publication histories. Authors are asked to pay article-publishing charges on acceptance; the ability to pay does not influence editorial decisions. All papers are included in MEDLINE/PubMed and Science Citation Index Expanded (Web of Science). Impact Factor: 2.562." At the bottom, there are three buttons: "About the Journal", "Submit", and "In the news".

Access to protocol



1997

Since the start of the year, *The Lancet* has been selecting and sending for peer review protocols from clinical trials and meta-analyses. For those that passed scrutiny, the journal has made a provisional commitment to publish the primary clinical manuscript.

VOLUME 29 - NUMBER 9 - MARCH 20 2011

JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L S

Providing Protocol Information for *Journal of Clinical Oncology* Readers: What Practicing Clinicians Need to Know

Daniel G. Haller, *Editor-in-Chief, Journal of Clinical Oncology*

Stephen A. Cannistra, *Editor-in-Chief-Designate, Journal of Clinical Oncology*

See accompanying articles on pages 1099 and 1204

Soon, readers of *Journal of Clinical Oncology (JCO)* will have access to information that has heretofore been available only to the editors and the reviewers. For those of you who have submitted manuscripts to *JCO*, you have noted the following requirement that has been in place since 2009: "JCO believes that, for the editors

potentially proprietary information. Given that such studies report on drugs or techniques not generally available to practitioners, the editors felt that this exclusion did not violate the spirit of redacted protocol submission for randomized phase II and III studies.



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Author Center Supplementary Appendix

PROTOCOL AND STATISTICAL ANALYSIS PLAN

The protocols of a clinical trial should be submitted as a separate PDF file, independent of the Supplementary Appendix. A statistical analysis plan may be included with the protocol, in the same PDF document.



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ORIGINAL ARTICLES

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

Maslakos A, Dimopoulos M, Alpert O, et al. *N Engl J Med* 2016; 375: 2018-2028. doi:10.1056/NEJMoa1601613

Comments open through October 12, 2018

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ORIGINAL ARTICLE

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

Supplementary Material

[Protocol](#) (PDF File, 654KB)

[Supplementary Appendix](#) (PDF File, 681KB)

[Disclosure Forms](#) (PDF File, 385KB)

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Fay Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H.,
and Sarah Carr, J.D.

Full Protocols and SAPs

After analyzing public comments in response to the NPRM as well as scientific discussions in the medical literature, HHS determined that having access to a copy of the full protocol and SAP is important to allow for the proper interpretation of a study's results. Therefore, the regulation requires the submission of a copy of the full protocol and SAP (if not included as part of the protocol) at the time of results information submission. These documents must include all amendments that have been approved by a human-subjects protection review board (if applicable) in a specified common electronic document format (e.g., Portable Document Format, or PDF). Although protocols and SAPs can be submitted at any time before the end of the study, an updated version would need to be submitted at the time of results information reporting. ClinicalTrials.gov will also accommodate the optional submission of informed consent forms at any time during the study life cycle (see Section III.D).