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 cohersive 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 ancipating 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.

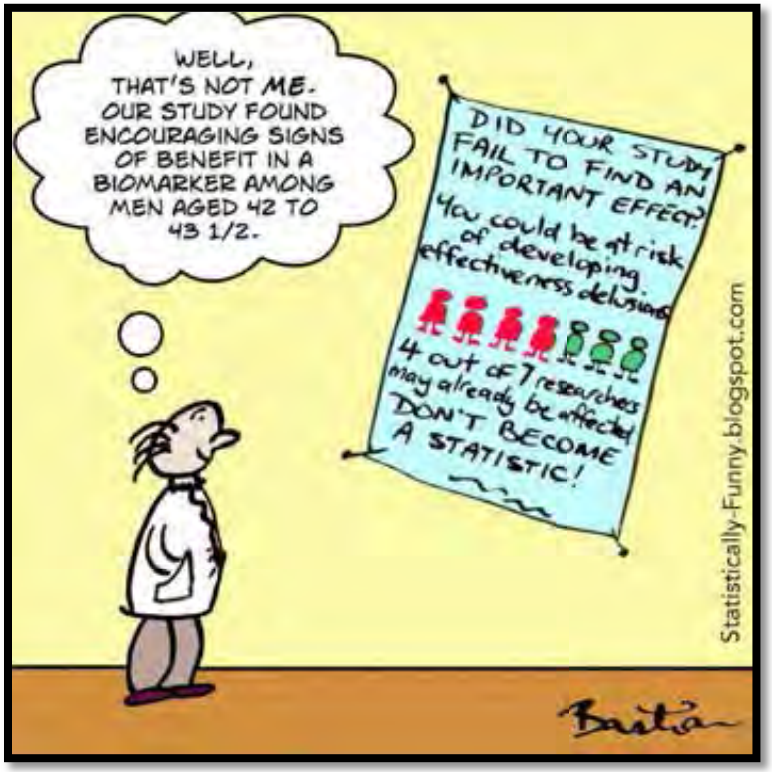
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for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

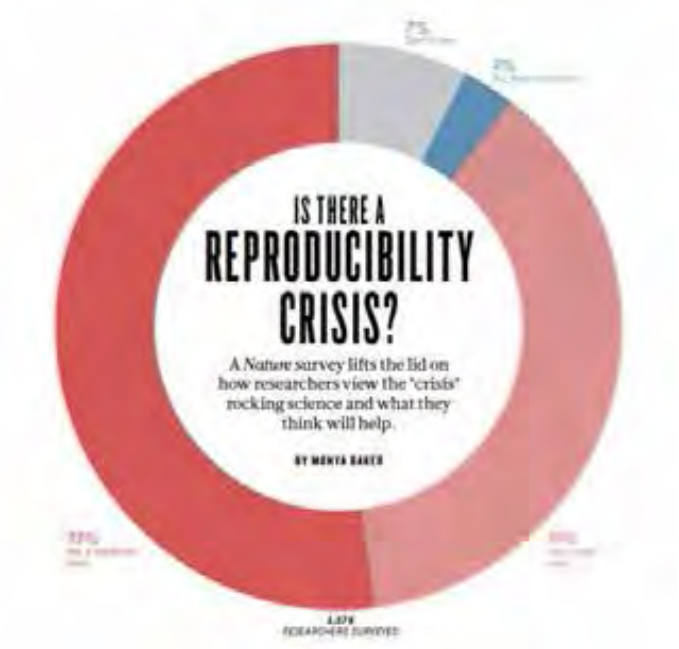
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Why a protocol?

- To reproduce the study

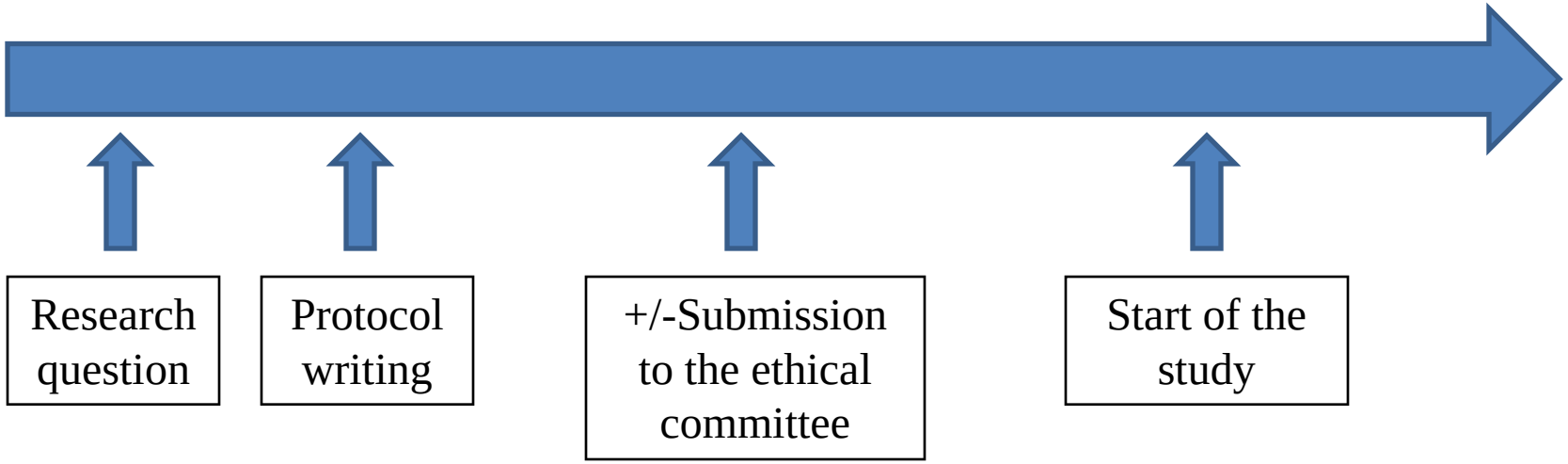
- To avoid cherry picking





When should we write the protocol?

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



A protocol is a « living » document

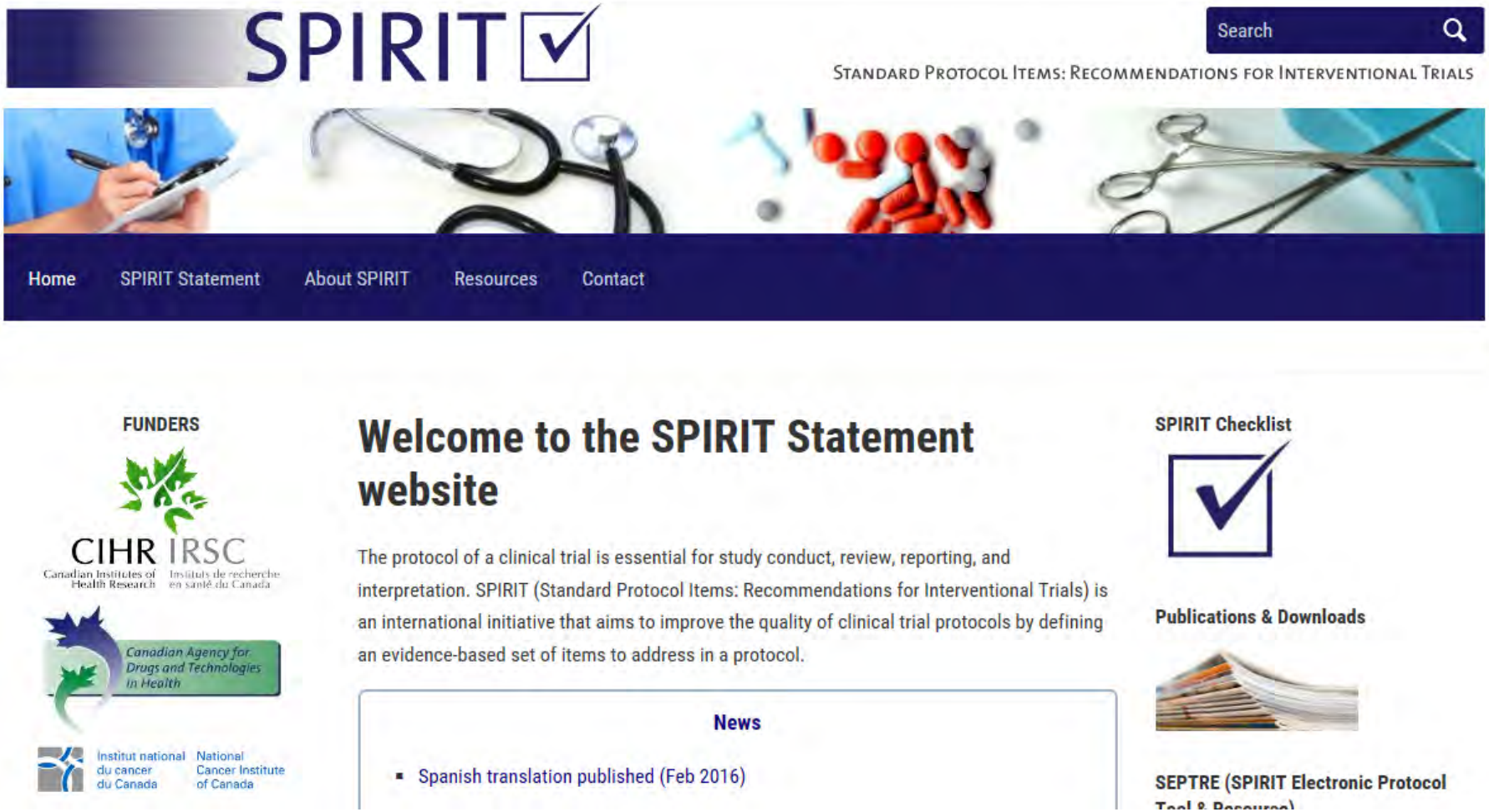
- A protocol can be modified
- Transparency must be the rule
  - List of all modifications
    - Date
    - Content
  - Keep all the versions of the protocol
    - Must be numbered
- Important modifications (amendments) in the protocol should be submitted to the ethical committee for validation

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



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/P. Virot

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.

Now 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"

Search

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

EU Clinical Trials Register

Home & Search | Joining a trial | Contacts | About

Clinical trials

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

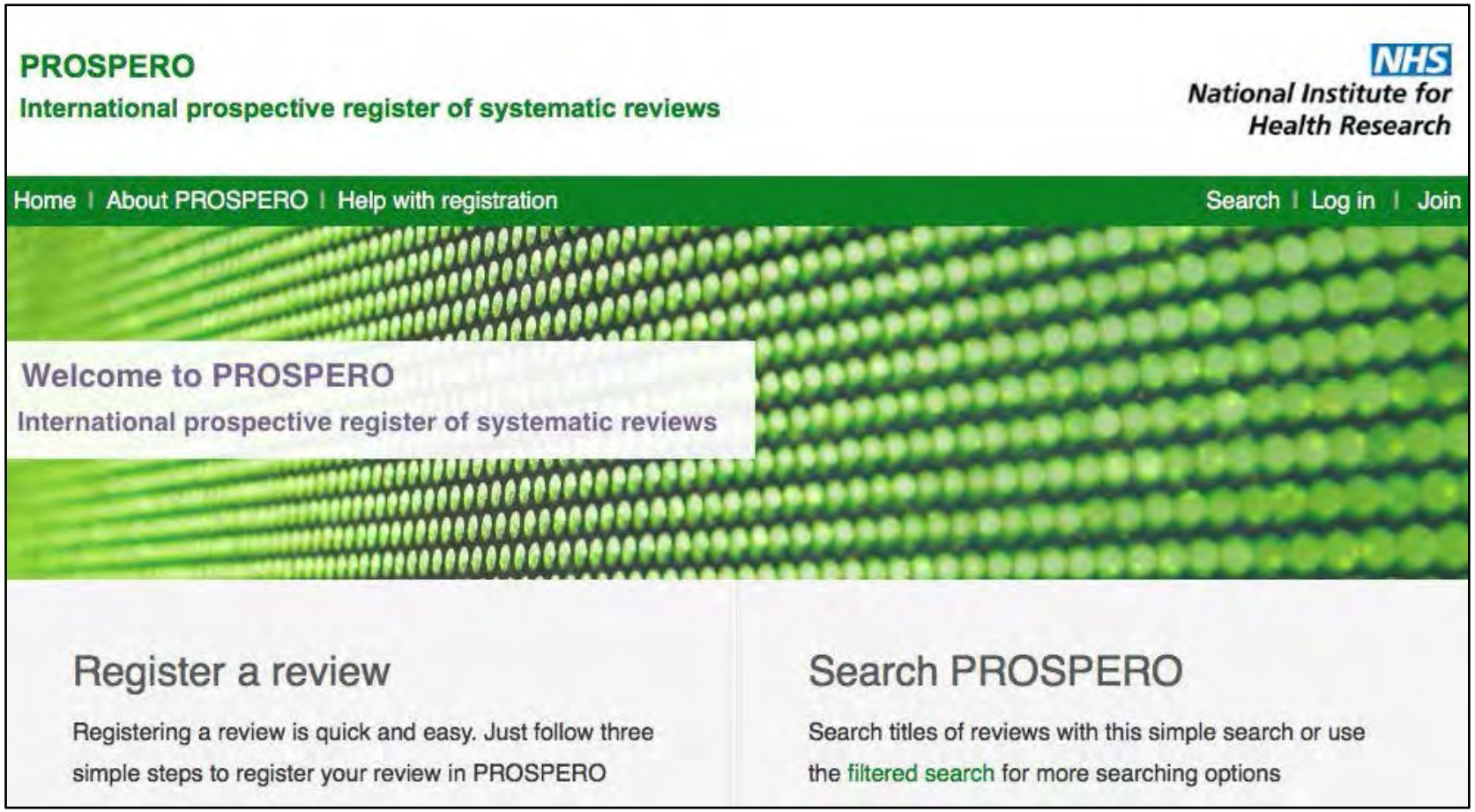
- interventional clinical trials that are conducted in the European Union (EU) and the European Economic Area (EEA);
- clinical trials conducted outside the EU / EEA that are linked to European paediatric-medicine development.

Learn more about the EU Clinical Trials Register including the source of the information and the legal basis.

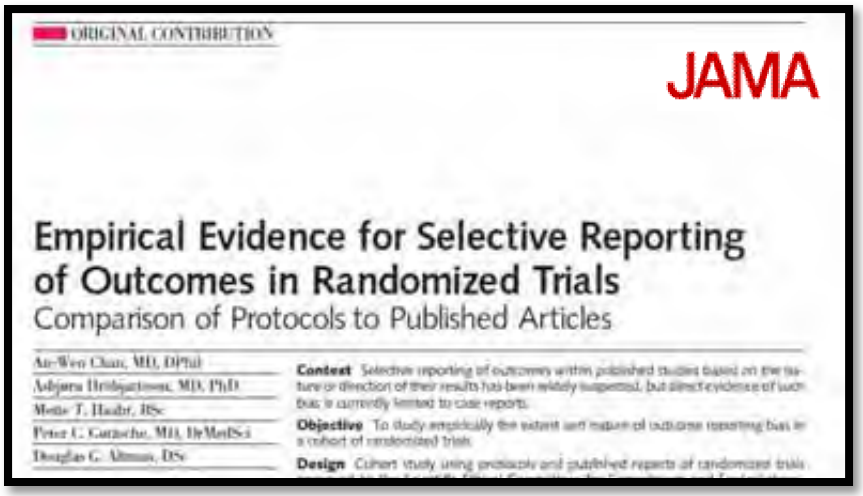
The EU Clinical Trials Register currently displays **28926** clinical trials with a EudraCT protocol, of which **4382** are clinical trials conducted with subjects less than 18 years old.

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



Use of Protocol in Research on Research



ORIGINAL CONTRIBUTION

JAMA

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil
Asbjørn Hróbjartsson, MD, PhD
Mette T. Haahr, BSc
Peter C. Gøtzsche, MD, DrMedSci
Douglas G. Altman, DSc

Context Selective reporting of outcomes within published studies based on the nature or direction of their results has been widely suspected, but direct evidence of such bias is currently limited to case reports.

Objective To study empirically the extent and nature of outcome reporting bias in a cohort of randomized trials.

Design Cohort study using protocols and published reports of randomized trials.

ORIGINAL CONTRIBUTION

JAMA

Comparison of Registered and Published Primary Outcomes in Randomized Controlled Trials

Sylvain Mathieu, MD
Isabelle Boutron, MD, PhD
David Moher, PhD
Douglas G. Altman, DSc
Philippe Ravaud, MD, PhD

Context As of 2005, the International Committee of Medical Journal Editors required investigators to register their trials prior to patient enrollment as a precondition for publishing the trial's findings in member journals.

Objective To assess the proportion of registered trials with results recently published in journals with high impact factors, to compare the primary outcomes specified in trial registries with those reported in the published articles, and to determine whether primary outcome reporting bias favored significant outcomes.

- 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

Chan, JAMA, 2004
Mathieu, JAMA, 2009

[Methodology Review]

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

Kerry Dwan[1], Douglas G Altman[2], Lynne Cresswell[3], Michaela Blundell[3], Carrol L Gamble[3], Paula R Williamson[3]

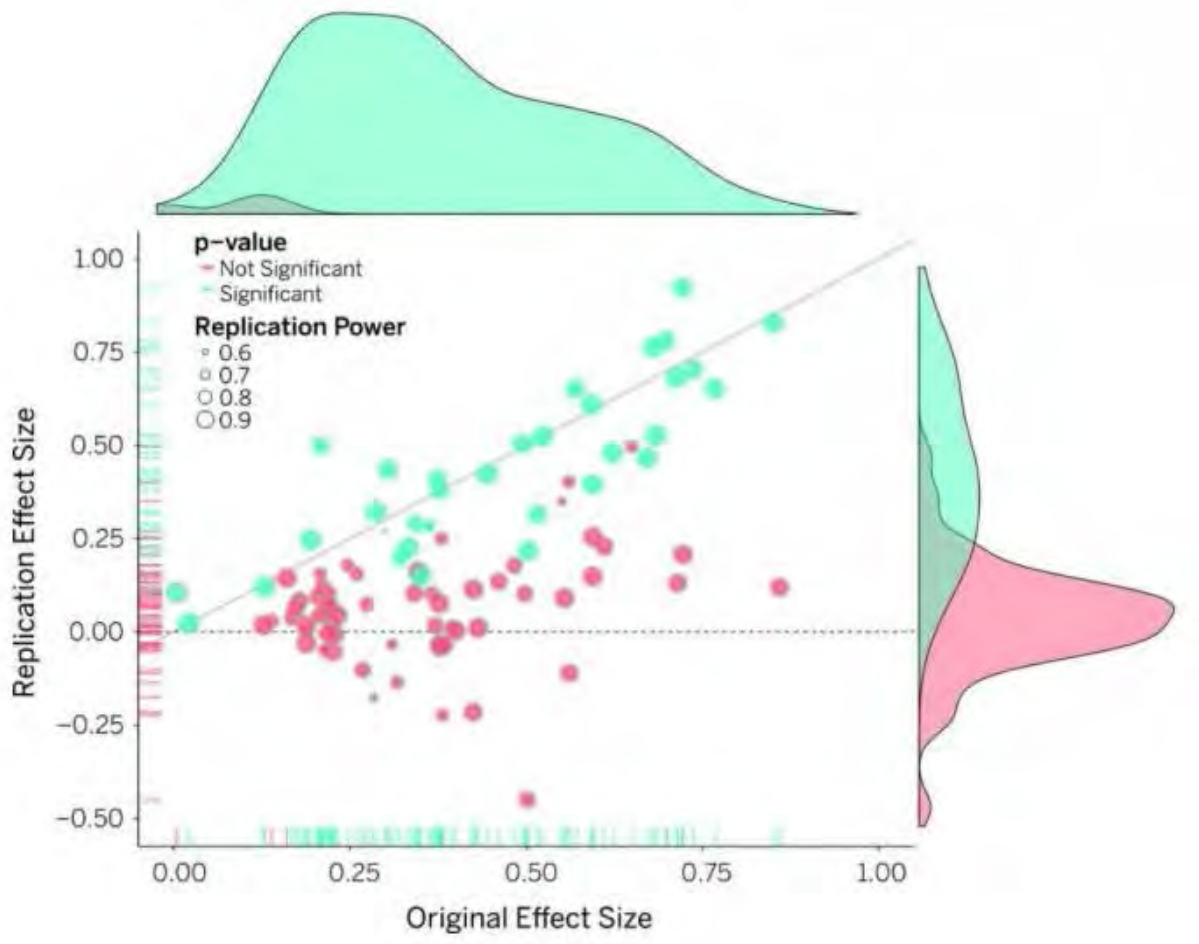
THE COCHRANE COLLABORATION

- **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.

2011

Replication

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



Science 2015

- 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.

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

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.

http://compare-trials.org/

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

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

EDITORIALS

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

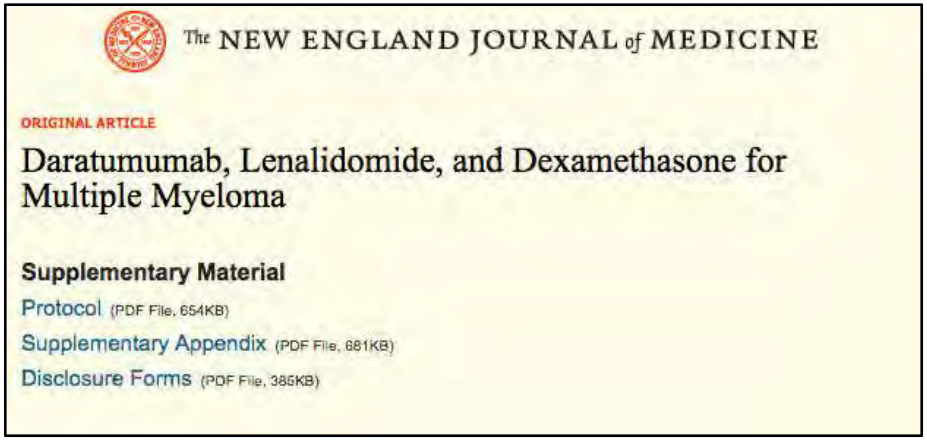
See accompanying articles on pages 1099 and 1204

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.

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.



THE NEW ENGLAND JOURNAL OF MEDICINE

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

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

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).