Prospective Cohort Studies for Safety & Effectiveness

Recognizing Quality

Nancy A. Dreyer, PhD, FISPE

24 October, 2014

ICPE, Taipei

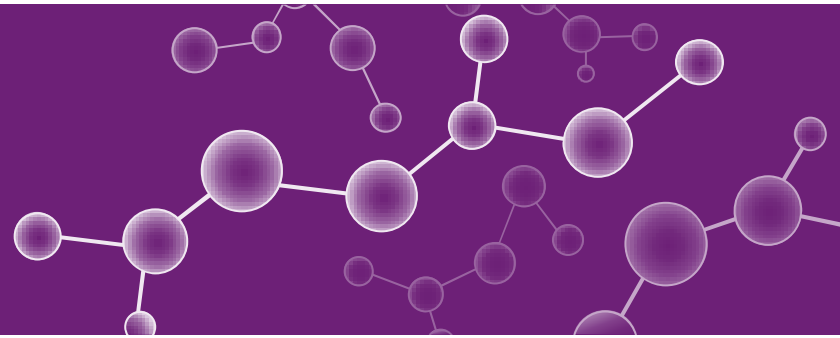
Improve your probability
of success™

Some guides to quality

—Guidelines for Prospective Studies and Registries

—Special Application for Comparative Effectiveness

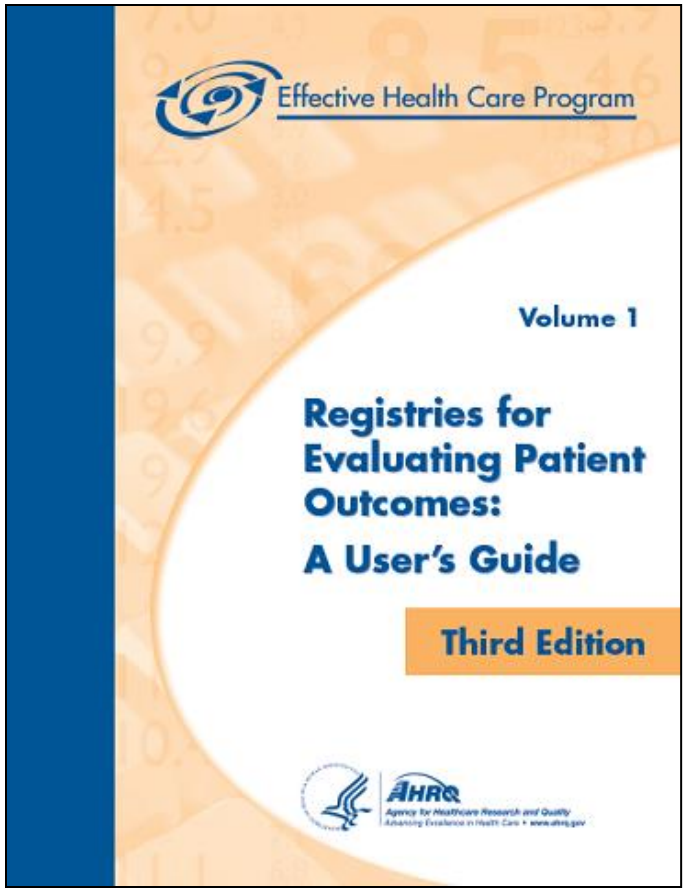
Registering Prospective Observational Studies



QUINTILES

2

Driving Consistency and Quality in Patient Registries



Gliklich RE, Dreyer NA, Leavy M, eds.

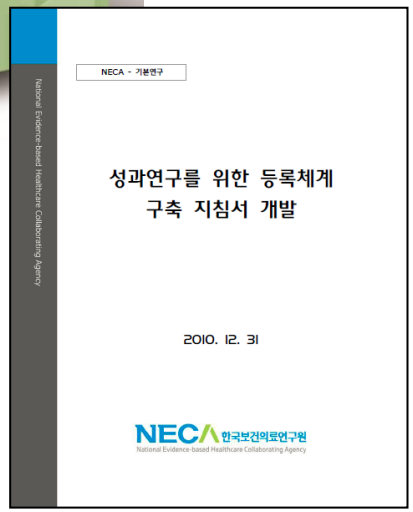
Registries for Evaluating Patient Outcomes: A User's Guide

3rd edition. Two volumes. AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014

- 100 contributors from industry, academia, health plans, physician societies, government, and patient advocacy groups
- 76 invited peer reviewers and public comment, including OCR, OHRP, IOM, FDA
- 64 case examples illustrate challenges and solutions

http://effectivehealthcare.ahrq.gov

Available in Chinese Adaptation in Korean



Gliklich RE, Dreyer NA, eds.

Registries for Evaluating Patient Outcomes: A User's Guide

Prepared by Outcome DEcIDE Center

AHRQ Publ. No. 07-EHC001-1. Rockville, MD:

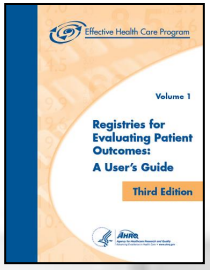
Agency for Healthcare Research and Quality, April 2007

2nd edition, September, 2010

- 55 contributors from industry, academia, health plans, physician societies and gov't
- 49 invited peer reviewers and public comment, including OCR, OHRP, IOM
- 38 case studies illustrate challenges and solutions

QUINTILES

Volume 1



Section I: Creating Registries

1. Patient Registries
2. Planning a Registry
3. Registry Design
4. Data Elements for Registries
5. Use of Patient Reported Outcomes in Registries
6. Data Sources for Registries

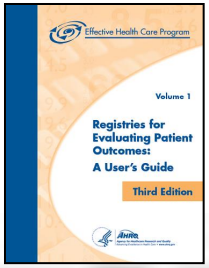
Section II: Legal and Ethical Considerations for Registries

7. Ethics, Data Ownership, and Privacy
8. Informed Consent for Registries
9. Data Confidentiality & Legal Concerns

Section III: Operating Registries

10. Recruiting and Retaining Participants in the Registry
11. Data Collection & Quality Assurance
12. Adverse Event Detection, Processing, and Reporting
13. Analysis & Interpretation
14. Modifying & Stopping Registries

Volume 2



Section IV: Technical, Legal and Analytic Considerations for Combining Registry Data With Other Data Sources

15. Interfacing Registries With Electronic Health Records
16. Linking Registry Data With Other Data Sources To Support New Studies
17. Managing Patient Identity Across Data Sources
18. Analysis of Linked Data Sets

Section V: Special Applications in Patient Registries

19. Use of Registries in Product Safety Assessment
20. Rare Disease Registries
21. Pregnancy Registries
22. Quality Improvement Registries
23. Registries for Medical Devices
24. Public-Private Partnership

Section VI: Evaluating Registries

25. Assessing Quality

Evaluating Quality

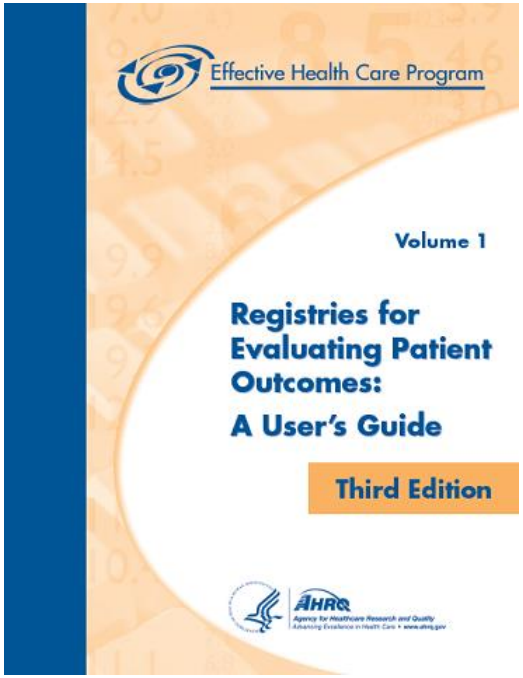
There are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions

Quality components

- Research quality (scientific process)
- Evidence quality (data/findings)

Components classified as

- Basic Good Registry Practice (Essential) or
- Potential Enhancements to Good Registry Practice (Further Indicators of Quality)



Gliklich RE, Dreyer NA, eds. *Registries for Evaluating Patient Outcomes: A User's Guide.* Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. dba Outcome] under Contract No. HHSA29020050035I TO1. AHRQ Publication No. 07-EHC001-1. Rockville, MD: Agency for Healthcare Research and Quality. 3nd Edition, April, 2014

European Network of Centers for Pharmacoepidemiology and Pharmacovigilance

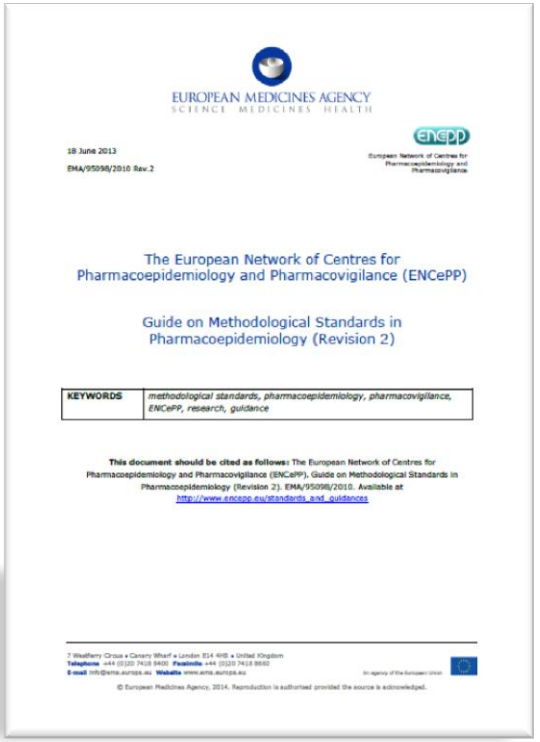
- Code of Conduct affirms many good practices, such as the right of the principal investigator to independently prepare study publications
- Methodological Guidance
- Checklist for Protocols
- Studies may be registered; offers an ENCePP Seal of Approval for registered studies
- ENCePP maintains a registry of studies

www.encepp.eu

QUINTILES

ENCePP Guide on Methodological Standards in Pharmacoepidemiology (Version 2)*

- First published 17 May 2011; last updated 18 June 2013
- Drives high scientific standards
- Contents:
  - > General aspects of study protocol
  - > Research question
  - > Approaches to data collection
  - > Study design and methods
  - > Statistical and epidemiological analysis plan
  - > Quality control and quality assurance
  - > Reporting of adverse events to regulatory authorities
  - > Communication


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2013
EMA/95098/2010 Rev.2

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

Guide on Methodological Standards in Pharmacoepidemiology (Revision 2)

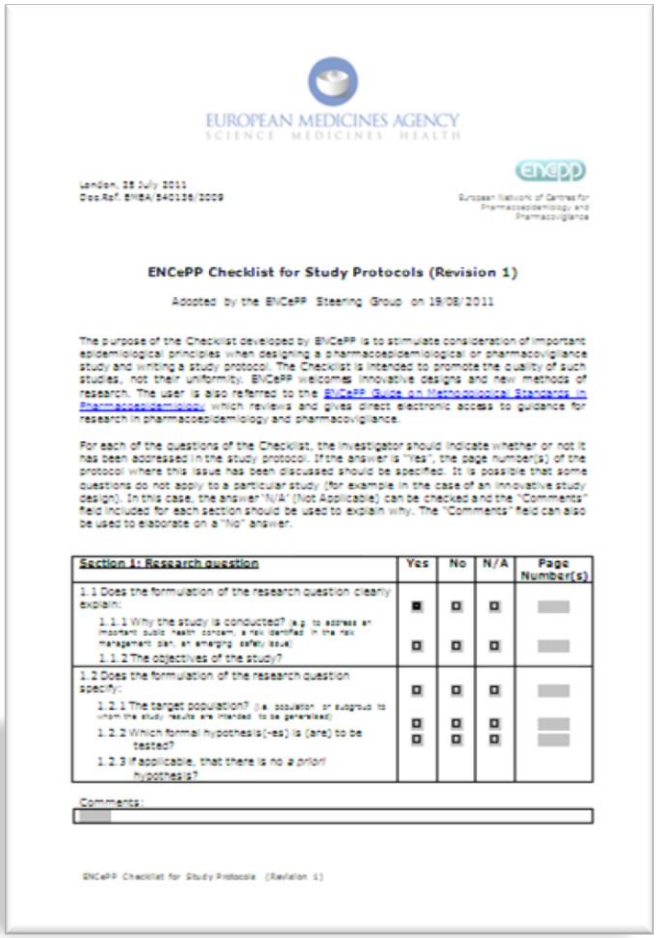
KEYWORDS	methodological standards, pharmacoepidemiology, pharmacovigilance, ENCePP, research, guidance

This document should be cited as follows: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 2). EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances

*European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 2). EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances.

ENCePP Checklist for Study Protocols

- Objectives:
  - > Stimulate researchers to consider important epidemiological principles when designing a pharmacoepidemiological study and writing a study protocol;
  - > Promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU;
  - > Increase awareness about developments in science and methodology in the field of pharmacoepidemiology.
- Checklist is intended to promote the quality of studies and not their uniformity



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

London, 28 July 2011
Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each of the questions of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer "N/A" (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

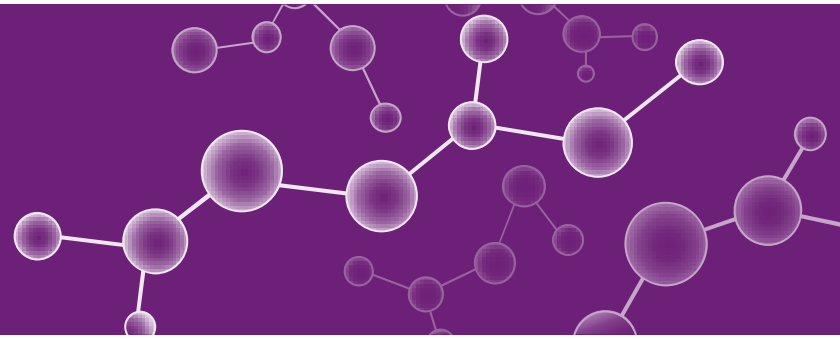
Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:	■	□	□	
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	□	□	□	
1.1.2 The objectives of the study?				
1.2 Does the formulation of the research question specify:	□	□	□	
1.2.1 The target population? (i.e. population or subgroup in whom the study results are intended to be generalised)	□	□	□	
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	□	□	□	
1.2.3 If applicable, that there is no *a priori* hypothesis?				

Comments:

ENCePP Checklist for Study Protocols (Revision 1)

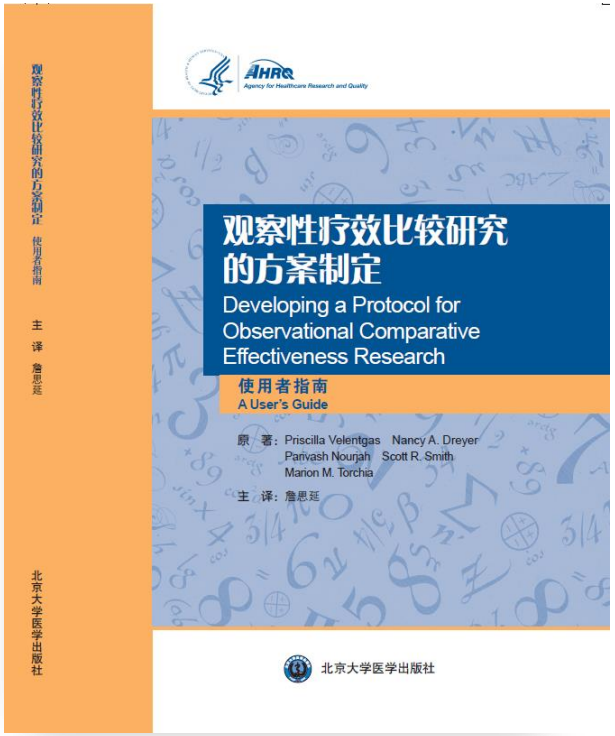
ENCePP Checklist for Study Protocols (Version 1). Available at http://www.encepp.eu/standards_and_guidances/index.html

Special applications for Comparative Effectiveness



QUINTILES®

Guide to Study Design for Observational Comparative Effectiveness Studies



Provides guidance and describes best practices for the design of observational CER studies

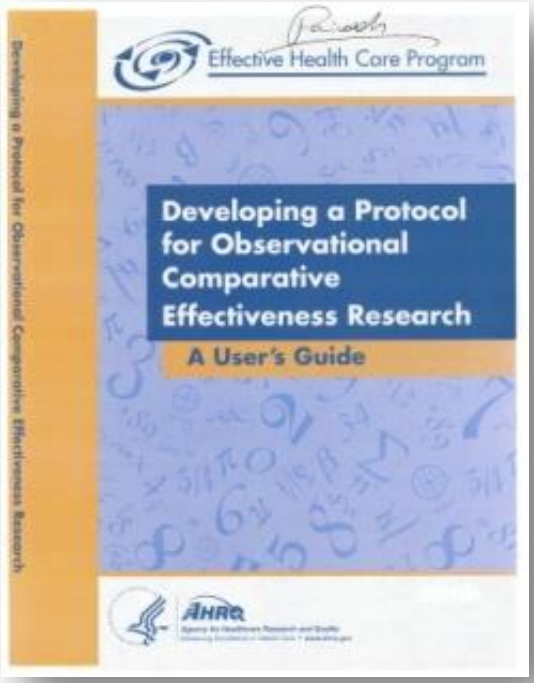
- Minimal standards and
- Best practices

>50 authors & reviewers -- all thought leaders in epidemiology, biostatistics, and/or medicine, from academia, government, and industry

Covers all aspects of study design, analysis, and causal inference

1st published in English January 2013. Available at http://effectivehealthcare.ahrq.gov
Chinese edition published August 2014

Guide to Study Design for Observational Comparative Effectiveness Studies



Provides guidance and describes best practices for the design of observational CER studies

- Minimal standards and
- Best practices

>50 authors & reviewers -- all thought leaders in epidemiology, biostatistics, and/or medicine, from academia, government, and industry

Covers all aspects of study design, analysis, and causal inference

1st published in English January 2013. Available at http://effectivehealthcare.ahrq.gov
Chinese edition published August 2014

www.graceprinciples.org

grace | Good ReseArch for Comparative Effectiveness

Home | the GRACE Initiative » | Publications & Citations | Contributors | Contact Us

The goal of the GRACE initiative is to enhance the quality of observational comparative effectiveness research (CER), and to facilitate its use for decision-making about therapeutic alternatives.

GRACE Principles

Designed as a set of high-level questions, the

GRACE Checklist

The GRACE Checklist is designed to guide the

News

The GRACE Initiative has been recently cited in the following publications. For a complete listing, see Publications & Citations:

A Format for Submission of Clinical and Economic Evidence of Pharmaceuticals in Support of Formulary Consideration

Academy of Managed Care Pharmacy: The AMCP Format for Formulary Submissions, Version 3.1, Dec 2012. See www.amcp.org/data/jmcp, p33.

Review of Quality Assessment Tools for the Evaluation of

GRACE

Good ReseArch for Comparative Effectiveness

The goal of the GRACE initiative is to enhance the quality of observational comparative effectiveness research (CER), and to facilitate its use for decision-making about therapeutic alternatives.

GRACE Principles

GRACE Checklist

http://www.graceprinciples.org/index.html

GRACE Principles

- A set of high-level questions, the GRACE Principles layout the elements of good practice for the design, conduct, analysis, and reporting of observational CER studies.

- The GRACE Principles are endorsed by the International Society for Pharmacoepidemiology and supported by a number of professionals and organizations.

GRACE Principles: Recognizing High-Quality Observational Studies of Comparative Effectiveness

Dreyer NA, Schneeweiss S, McNeil BJ, et al. Am J Manag Care. 2010:16(6):467-471

GRACE Validated Checklist & Scoring Guide

11 question: 6 about data & 5 about methods

Population

- New initiators or recipients of treatment

Treatment

- Adequate detail recorded

Comparators

- Concurrent are most desirable

Outcomes

- Adequate detail recorded
- Measured objectively
- Measured similarly in all arms
- Validated or adjudicated

Covariates

- Recorded
- Accounted for in analysis

Assessment of Bias

- Sensitivity analysis
- Check for immortal time bias

*See GRACE Checklist. J Managed Care Pharmacy 2014;20(3):301-8

GRACE Classification & Regression Tree (CART) For Studies of Drugs, Medical Devices & Procedures

If ≥1 comparison groups were used, were they concurrent comparators? If not, was the use of historical comparator groups justified? [Question M2]

If YES, was primary outcome(s) measured or identified in an equivalent manner between the treatment/ intervention group and the comparison group(s)? [Question D5]

If NO/ NOT ENOUGH INFORMATION is reported, the article is considered **insufficient quality.**

If YES, were important covariates that may be known confounders or effect modifiers available and recorded? [Question D6]

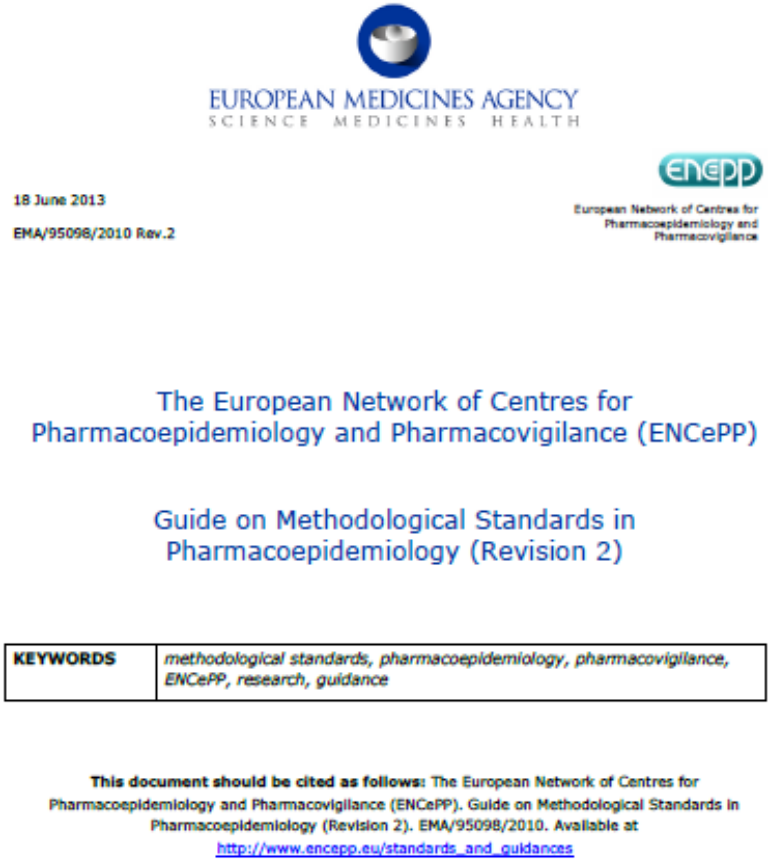
If NO/NOT ENOUGH INFORMATION is reported, the article is considered **insufficient quality.**

If YES, the article is considered sufficient quality for purpose.

If NO/NOT ENOUGH INFORMATION reported, were any meaningful analyses conducted to test key assumptions on which primary results are based? [Question M5]

QUINTILES

Cited by the EMA



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 June 2013
EMA/95098/2010 Rev.2

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

Guide on Methodological Standards in Pharmacoepidemiology (Revision 2)

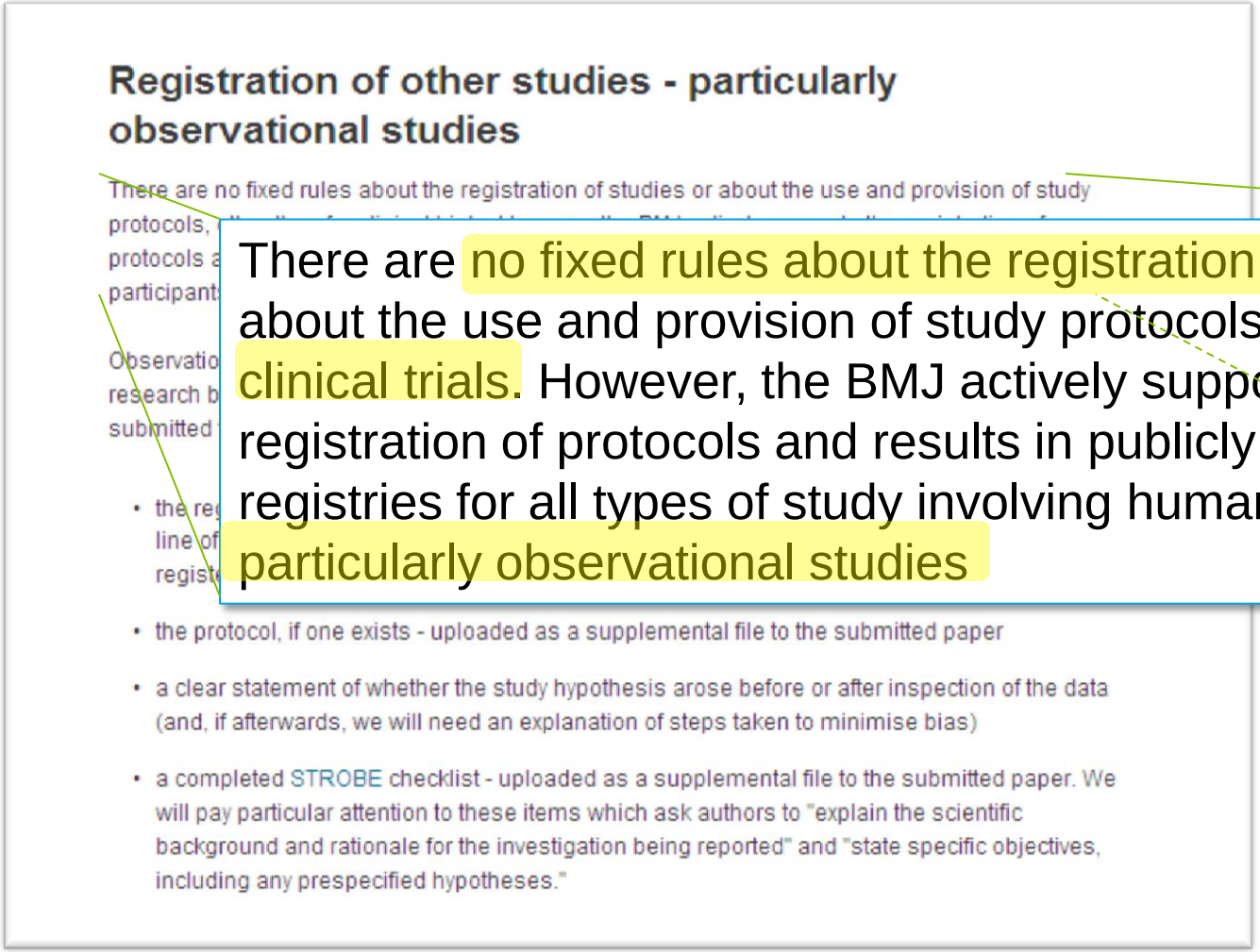
KEYWORDS	*methodological standards, pharmacoepidemiology, pharmacovigilance, ENCePP, research, guidance*

This document should be cited as follows: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 2). EMA/95098/2010. Available at http://www.encepp.eu/standards_and_guidances

AHRQ's Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide identifies minimal standards and best practices for observational CER. It provides principles on a wide range of topics for designing research and developing protocols, with relevant questions to be addressed and checklists of key elements to be considered. The GRACE Principles provide guidance on the evaluation of the quality of observational CER studies to help decision-makers in recognizing high-quality studies and researchers in study design and conduct. A checklist to evaluate the quality of observational CER studies is also provided.

QUINTILES

Registration of Observational Studies



Registration of other studies - particularly observational studies

There are no fixed rules about the registration of studies or about the use and provision of study protocols,

protocols a

participant

Observatio

research b

submitted

- the re
  line of
  regist
- the protocol, if one exists - uploaded as a supplemental file to the submitted paper
- a clear statement of whether the study hypothesis arose before or after inspection of the data (and, if afterwards, we will need an explanation of steps taken to minimise bias)
- a completed STROBE checklist - uploaded as a supplemental file to the submitted paper. We will pay particular attention to these items which ask authors to "explain the scientific background and rationale for the investigation being reported" and "state specific objectives, including any prespecified hypotheses."

There are no fixed rules about the registration of studies or about the use and provision of study protocols, other than for clinical trials. However, the BMJ actively supports the registration of protocols and results in publicly accessible registries for all types of study involving human participants, particularly observational studies

http://www.bmj.com/about-bmj/resources-authors/article-types/research

QUINTILES

Registration of Observational Studies in RoPR via clinicaltrials.gov

1. **Register the registry in ClinicalTrials.gov**
2. Select “patient registry” as the study type and enter initial data elements
3. Click to complete the registration in RoPR
4. Enter remaining data elements in RoPR and submit for posting

Note: Registry registration in RoPR is voluntary

Launched in September 2012

Question: which statement is true?

a) There is no acceptance guidance for good practice of prospective observational studies (patient registries).

b) Randomized controlled trials and prospective observational studies should use the same procedures for study design

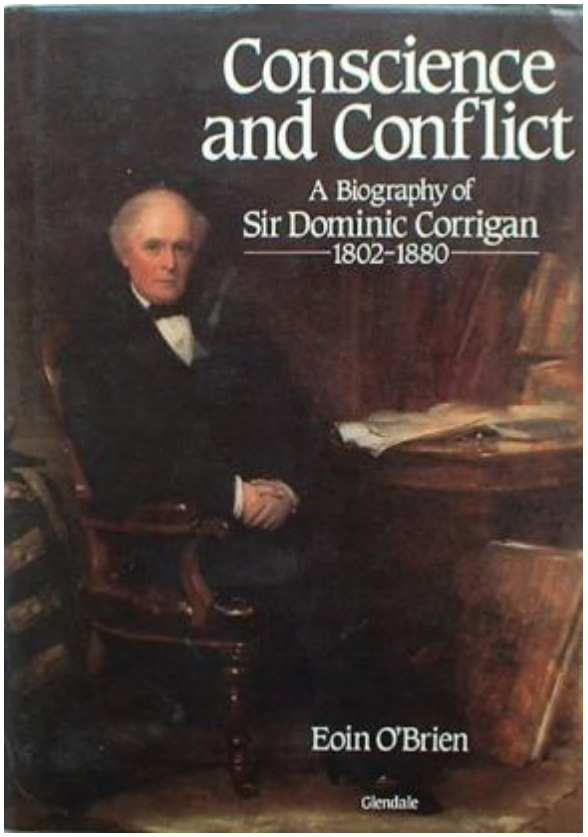
c) Prospective and retrospective observational studies are held to the same standards of quality

d) There are guidance documents for prospective observational studies (patient registries) that are used in the US, Europe and some Asian countries.

Closing Thought

"Whether my observations and opinions be disproved or supported, I shall be equally satisfied. Truth is the prize aimed for; and, in the contest, there is at least this consolation, that all the competitors may share equally the good attained."*

Sir Dominic Corrigan



*O'Brien E: Lancet 1980;2:1356-7

Contact Information

NANCY DREYER

QUINTILES GLOBAL CHIEF OF SCIENTIFIC AFFAIRS

Tel: +1 (617)715-6810

nancy.dreyer@quintiles.com