Prospective Cohort Studies for Safety & Effectiveness
Recognizing Quality

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24 October, 2014
ICPE, Taipei
Some guides to quality

– Guidelines for Prospective Studies and Registries
– Special Application for Comparative Effectiveness

Registering Prospective Observational Studies
Driving Consistency and Quality in Patient Registries

Gliklich RE, Dreyer NA, Leavy M, eds.


- 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.


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
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

Section III: Operating Registries
8. Informed Consent for Registries
9. Data Confidentiality & Legal Concerns
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)

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
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

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

Special applications for Comparative Effectiveness
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
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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.
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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
<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New initiators or recipients of treatment</td>
<td>• Adequate detail recorded</td>
<td>• Concurrent are most desirable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Covariates</th>
<th>Assessment of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adequate detail recorded</td>
<td>• Recorded</td>
<td>• Sensitivity analysis</td>
</tr>
<tr>
<td>• Measured objectively</td>
<td>• Accounted for in analysis</td>
<td>• Check for immortal time bias</td>
</tr>
<tr>
<td>• Measured similarly in all arms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Validated or adjudicated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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]
Cited by the EMA

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.
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.
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
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