



Use of registries and observational data in the benefit assessment of medical interventions



Ralf Bender



Institute for Quality and Efficiency in
Health Care (IQWiG), Germany

- **Introduction**
- **Value of registries and observational data**
 - Definition
 - Problems
 - Use in benefit assessment
- **Registry-based randomized trials**
- **Conclusion**
- **References**

Editorial

Real world data: Additional source for making clinical decisions

International Journal of Applied and Basic Medical Research, May-Aug 2015, Vol 5, Issue 2



The Official News & Technical Journal Of The International Society For Pharmacoeconomics And Outcomes Research

POLICY ANALYSIS

Real-Life Data: A Growing Need

Lieven Annemans PhD, MSc, Principal HEOR, IMS Health, Miesse, Belgium, Michael Aristides MSc, BA, Principal HEOR, IMS Health, London, UK, and Maria Kubin MD, MSc, Director, Global Health Economics and Reimbursement, Bayer Healthcare AG, Wuppertal, Germany

It is increasingly recognized that conclusions drawn from classical clinical trials are not always a useful aid for decision-making - assessing the value of a drug or technology requires an understanding of its impact on current management in a practical, real-life setting. But as the benefits of real-world data become more apparent so, too, do issues around its appropriate collection and reliability. Lieven Annemans, Principal HEOR, IMS Health, Michael Aristides, Principal HEOR, IMS Health, and Maria Kubin, Director, Global Health Economics and Reimbursement, Bayer Healthcare AG, consider some of the issues.



[Home](#) [News](#) [Intelligence](#) [Thought leadership](#) [Appointments](#) [Awards](#) [Blogs](#) [Clinical](#)

[Thought Leadership](#) [Research](#) [Sales](#) [Marketing](#) [Regulatory](#) [Healthcare](#)

[Trending](#) | [Snapchat comes to congresses](#) | [Imbruvica filed for non-cancer use](#) | [Pfizer gains new Ibrance approval](#) | [Opdivo cl](#)

The importance of real-world data to the pharma industry

It is a crucial time for pharma and other stakeholders to demonstrate medicines' value

For years, randomised controlled trials (RCTs) were considered the gold standard for generating clinical data on efficacy and safety to support product registration and subsequent prescribing. Recently, analysts and academics have discussed the promise of real-world data (RWD), signalling its potential to contribute to improved health outcomes. Data's role in normal clinical practices, or in settings that reflect the reality of healthcare delivery, is likely to become increasingly important in ensuring that medicines are accepted by national policymakers and are adopted into practice.



Geneviève Bonnellye, MsC,
Divisional President - Real
World Evidence, Kantar
Health. **Andrew Miniuks**,



Workshop

„Real world data“ und Registerdaten in der klinischen und epidemiologischen Forschung: Chancen und Herausforderungen

17./18. November 2016



Herbst-Symposium 2015

***Real World Data –
ein Gewinn für die Nutzenbewertung?***
**Welchen Beitrag können Register und Routinedaten
liefern?**

Real world data (RWD):

- "Everything that goes beyond what is normally collected in phase III clinical trials ..." (ISPOR)
- "Collected from sources outside of traditional clinical trials" (FDA)
- "In most cases data from non-randomized trials" (NICE)

Sources for real world data:

- **Registries**
- **Health insurance data**
- **Electronic health records**
- **Observational studies**
 - Single-arm trials
 - Cohort studies
 - Case-control studies
 - Case series, case reports
- **Pragmatic clinical trials**
 - RCTs with pragmatic elements
 - Non-randomized trials (?)

Some thoughts:

- **RWD $\approx$ Data from non-randomized trials**
- **Is evidence from RCTs "unreal" ???**
- **Frequently made claim:**
 - **RCT = high internal but low external validity**
 - **RWD = low internal but high external validity**
- **What is the value of high external validity without internal validity?**
- **In other words:**
What is the value of generalizing an effect estimate to a broader population, when this estimate is highly biased?

Topic of the talk:

What is the value of registries and observational data in the benefit assessment of medical interventions?

IQWiG Autumn Symposium 2015

Real-world data for benefit assessments: How can registries and routine data contribute?

<https://www.iqwig.de/en/events/autumn-symposium/symposium-2015.6883.html>

PATIENTENREGISTER FÜR DIE NUTZENBEWERTUNG

Kein Ersatz für randomisierte Studien

Patientenregister-Daten sind für die Klärung von Ursache-Wirkungs-Zusammenhängen und somit für die Nutzenbewertung ungeeignet. Ihre sonst unstrittigen Potenziale erfüllen sich nur bei Ausschöpfung anspruchsvoller Qualitätsanforderungen.

Jürgen Windeler, Jörg Lauterberg, Beate Wieseler, Stefan Sauerland, Stefan Lange

Deutsches Ärzteblatt | Jg. 114 | Heft 16 | 21. April 2017

Registries:

- "... a patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease ..." (AHRQ)
- "... but there is no consistent definition in current use." (AHRQ)

Observational studies:

- "... in which conditions are not under the control of the investigator ..."
(Wiley Statistics Reference Online)

Problems with observational data:

- Potential for large bias
- Confounding
- Recall bias
- Detection bias
- ...
- Remember:
"... conditions are not under control ..."

Approaches to reduce bias:

- Adjustment methods
- Multiple regression
- Instrumental variables
- Propensity scores
- Matching
- Stratification
- ...
- **BUT:**
These methods do **NOT** provide assurance that all known and unknown sources of bias are sufficiently under control!

Review

Reliable assessment of the effects of treatment on mortality and major morbidity, II: observational studies

Stephen MacMahon, Rory Collins

Observational studies and randomised trials can contribute complementary evidence about the effects of treatment on mortality and on major non-fatal outcomes. In particular, observational studies have an important role in the identification of large adverse effects of treatment on infrequent outcomes (ie, rare, but serious, side-effects) that are not likely to be related to the indications for (or contraindications to) the treatment of interest. Such studies can also provide useful information about the risks of death and disability in particular circumstances that can help to generalise from clinical trials to clinical practice. But, due to their inherent potential for moderate or large biases, observational studies have little role in the direct assessment of any moderate effects of treatment on major outcomes that might exist. Instead, sufficiently large-scale evidence from randomised trials is needed to assess such treatment effects appropriately reliably. Wider appreciation of the different strengths and weaknesses of these two types of epidemiological study should increase the likelihood that the most reliable evidence available informs decisions about the treatments doctors use—and patients receive—for the management of a wide range of life-threatening conditions.

Lancet 2001; **357**: 455–62

Special Articles

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

Conclusions We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

Conclusions The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic. (N Engl J Med 2000;342:1887-92.)

Pocock & Elbourne (Editorial, *NEJM* 2000):

"It is likely that the studies used in both reports are a highly selected sample, since it is rarely sensible for a therapeutic question to be equally and simultaneously addressed by both experimentation and observation."

Comparison of Evidence of Treatment Effects in Randomized and Nonrandomized Studies

John P. A. Ioannidis, MD

Anna-Bettina Haidich, MSc

Maroudia Pappa, MSc

Nikos Pantazis, MSc

Styliani I. Kokori, MD

Maria G. Tektonidou, MD

Despina G. Contopoulos-Ioannidis, MD

Joseph Lau, MD

Context There is substantial debate about whether the results of nonrandomized studies are consistent with the results of randomized controlled trials on the same topic.

Objectives To compare results of randomized and nonrandomized studies that evaluated medical interventions and to examine characteristics that may explain discrepancies between randomized and nonrandomized studies.

Data Sources MEDLINE (1966–March 2000), the Cochrane Library (Issue 3, 2000), and major journals were searched.

Study Selection Forty-five diverse topics were identified for which both randomized trials (n=240) and nonrandomized studies (n=168) had been performed and had been considered in meta-analyses of binary outcomes.

Conclusions Despite good correlation between randomized trials and nonrandomized studies—in particular, prospective studies—discrepancies beyond chance do occur and differences in estimated magnitude of treatment effect are very common.

JAMA. 2001;286:821-830

www.jama.com

Results of a systematic evaluation of data from a large number of therapeutic or preventive interventions:

"Randomized trials and nonrandomized studies often disagree substantially on how much a treatment works."

Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: meta-epidemiological survey

Lars G Hemkens,^{1,2} Despina G Contopoulos-Ioannidis,^{3,4} John P A Ioannidis^{1,4-6}

CONCLUSIONS

Studies of routinely collected health data could give different answers from subsequent randomized controlled trials on the same clinical questions, and may substantially overestimate treatment effects. Caution is needed to prevent misguided clinical decision making.

BMJ 2016;352:i493

Results of recent meta-epidemiological research:

"Despite the wide and increasing use of RCHD in CER, the reliability of this approach needs to be questioned."

"... decisions for ... reimbursement of expensive interventions with evidence based entirely on RCHD may be best withheld until trial evidence becomes available."

IQWiG makes use of nRCT data:

- **In drug dossier assessments, e.g.**
 - to assess how many patients are affected
 - to assess costs of therapies
- **In assessments of "potential" (not benefit)**
 - to select "promising" non-drug treatments, for which an RCT should be performed for benefit assessment (§ 137e/h)
- **In general:**
For questions which can be answered by nRCT data.

IQWiG makes use of RCT data:

- **For the benefit assessment of medical interventions, because**
 - data from studies with low risk of bias are needed
 - high internal validity is required
 - RCTs are (almost) always possible
- **There are exceptions:**
>> Dramatic effects <<
- **But exceptions are exceptions and not a regular option**

Advantages:

- Rapid participant enrollment
- Low costs
- Enhanced generalizability of results
- Potential completeness of follow-up

Li et al. (*JCE* 2016)

Challenges and limitations:

- Registry data quality
- New ethical issues (e.g., patient consent)
- New methodological issues
 - No standardized implementation procedures
 - Different follow-up patterns
 - Different recruitment procedures

Li et al. (*JCE* 2016):

"... trials requiring comprehensive safety monitoring, ..., strict inclusion criteria and well-defined endpoints, r-bRCTs are not an adequate choice."

- **Registries and observational data are useful for questions which can be answered by nRCT data**
 - Epidemiological issues
 - Assessment of potential
- **For the benefit assessment of medical interventions RCT data are required (in general)**
- **Dramatic effects represent exceptions**
- **Registry-based RCTs represent an option but application areas are limited**

- Hemkens, L.G., Contopoulos-Ioannidis, D.G. & Ioannidis, J.P. (2016): Agreement of treatment effects for mortality from routinely collected data and subsequent randomized trials: Meta-epidemiological survey. *BMJ* **352**, i493.
- Ioannidis, J.P., Haidich, A.B., Pappa, M., Pantazis, N., Kokori, S.I., Tektonidou, M.G., Contopoulos-Ioannidis, D.G. & Lau, J. (2001): Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA* **286**, 821-830.
- Li, G., Sajobi, T.T., Menon, B.K., Korngut, L., Lowerison, M., James, M., Wilton, S.B., Williamson, T., Gill, S., Drogos, L.L., Smith, E.E., Vohra, S., Hill, M.D. & Thabane, L. on behalf of the 2016 Symposium on Registry-Based Randomized Controlled Trials in Calgary (2016): Registry-based randomized controlled trials – what are the advantages, challenges, and areas for future research? *J. Clin. Epidemiol.* **80**, 16-24.
- MacMahon, S. & Collins, R. (2001): Reliable assessment of the effects of treatment on mortality and major morbidity, II: Observational studies. *Lancet* **357**, 455-462.
- Windeler, J., Lauterberg, J., Wieseler, B., Sauerland, S. & Lange, S. (2017): Patientenregister für die Nutzenbewertung: Kein Ersatz für randomisierte Studien. *Dtsch. Ärztebl.* **114**, A783-786.