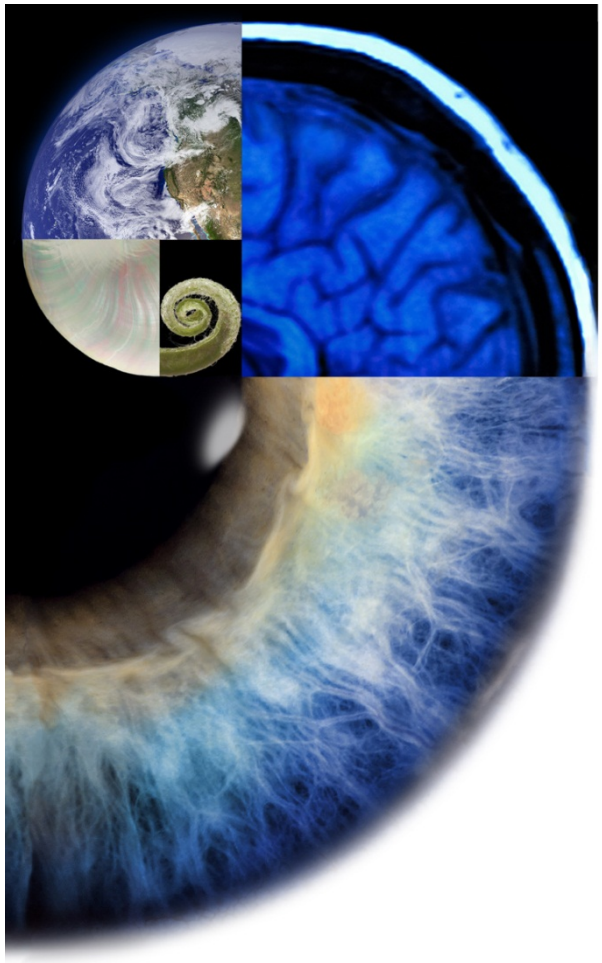
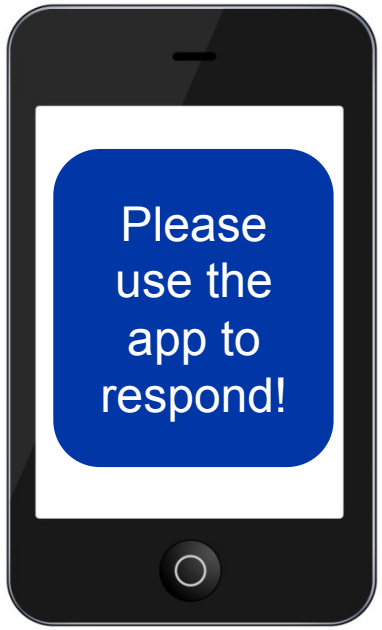


What are the specific issues for RWE study publications?

Stephen Sweet, Gary Male

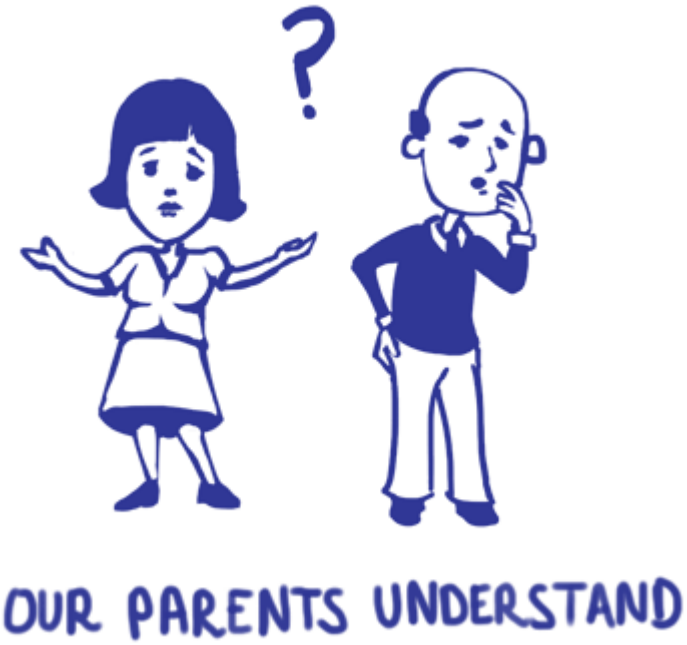
A question for you

- Why are you here?
  1. I work with RWE all the time
  2. RWE is becoming more important and I need to know about it
  3. Tea and biscuits



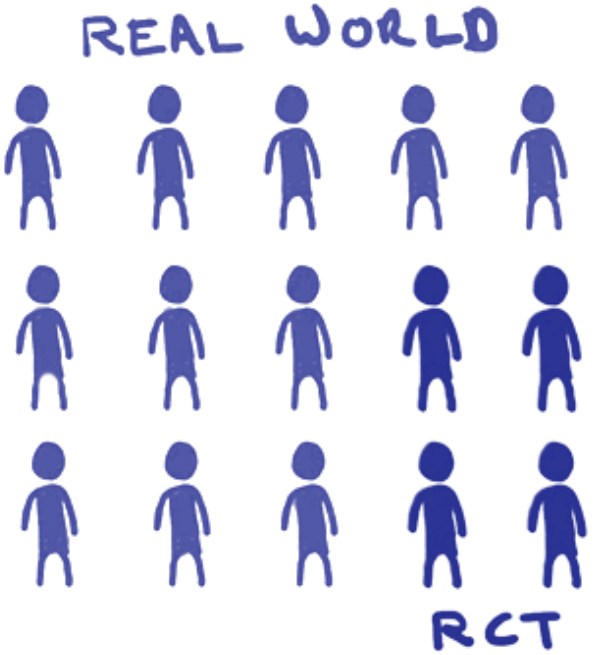
Clear and effective communications are essential for RWE studies

- Research question



Clear and effective communications are essential for RWE studies

- Research question
- Explore in the real world



Clear and effective communications are essential for RWE studies

- Research question
- Explore in the real world
- Understand the data source

Clear and effective communications are essential for RWE studies

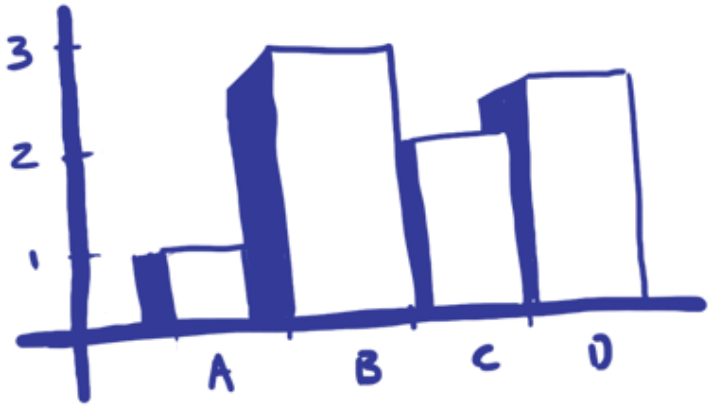
- Research question
- Explore in the real world
- Understand the data source
- How many patients?

Clear and effective communications are essential for RWE studies

- Research question
- Explore in the real world
- Understand the data source
- How many patients?
- Duration of follow-up

Clear and effective communications are essential for RWE studies

- Research question
- Explore in the real world
- Understand the data source
- How many patients?
- Duration of follow-up
- Results



Clear and effective communications are essential for RWE studies

- Research question
- Explore in the real world
- Understand the data source
- How many patients?
- Duration of follow-up
- Results
- Conclusion

Writing up the studies – STROBE

- Guidance on the reporting of observational studies in epidemiology (cohort studies, case–control studies, cross-sectional studies)
- Specialized versions
  - STROBE – conference abstracts
  - STROME-ID – molecular epidemiology in infectious diseases
  - STROBE – EULAR version for biologics RWE studies
  - STROBE-ME – epidemiology/molecular epidemiology studies
  - STREGA – genetic association studies

http://www.strobe-statement.org/index.php?id=strobe-home/

STROBE guidance can be at least as challenging as CONSORT

- How can I address all 22 points of the STROBE core checklist within a 3000-word manuscript?
  - **Publish in advance** as much of the RWE study methodology as you can (e.g. data source characterization, algorithms to identify patient populations and outcomes)
  - Make use of **supplementary tables/figures/methods**

- How can I convey the meaning to a non-RWE specialist among all this technical detail?
  - **Use the abstract** to place the study in a clinical context
  - **Preface each section** with one sentence that tells the non-specialist what it means (e.g. what is propensity scoring)
  - **Use the conclusion** to convey how the results might affect healthcare decision-making

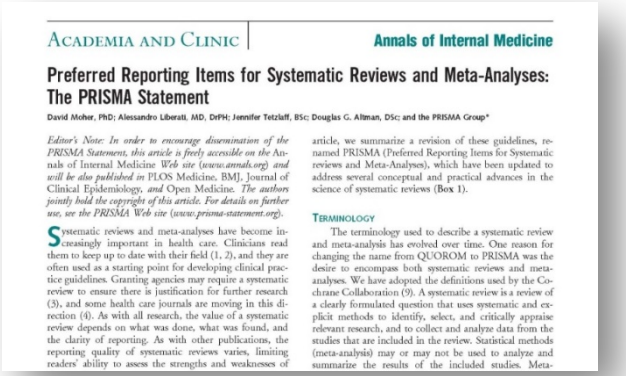
Writing up the studies – RECORD

- Guidance for studies conducted using routinely-collected health data (e.g. health administrative data, electronic medical records)
- An extension of the STROBE guidelines

RECORD
REporting of studies Conducted using Observational Routinely-collected Data

Writing up the studies: other guidelines

- **PRISMA**: Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and for study protocols (PRISMA-P)
- **MOOSE Group**: Meta-analysis Of Observational Studies in Epidemiology
- **CARE** guidelines: consensus-based clinical case reporting guideline development



ACADEMIA AND CLINIC | Annals of Internal Medicine

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher, PhD; Alessandro Liberati, MD, DrPH; Jennifer Tetzlaff, BSc; Douglas G. Altman, DSc; and the PRISMA Group*

Editor's Note: In order to encourage dissemination of the PRISMA Statement, this article is freely accessible on the Annals of Internal Medicine Web site (www.annals.org) and will be also published in PLOS Medicine, BMJ, Journal of Clinical Epidemiology, *and* Open Medicine. *The authors jointly hold the copyright of this article. For details on further use, see the PRISMA Web site (www.prisma-statement.org).*

Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field (1, 2), and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research (3), and some health care journals are moving in this direction (4). As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of

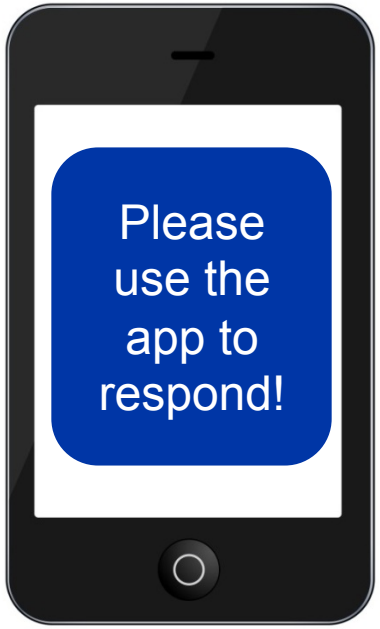
article, we summarize a revision of these guidelines, renamed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses), which have been updated to address several conceptual and practical advances in the science of systematic reviews (**Box 1**).

TERMINOLOGY

The terminology used to describe a systematic review and meta-analysis has evolved over time. One reason for changing the name from QUOROM to PRISMA was the desire to encompass both systematic reviews and meta-analyses. We have adopted the definitions used by the Cochrane Collaboration (9). A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-

A question for you

- Do you/does your organization use STROBE and similar guidelines when writing up RWE studies for publication?
  1. Always
  2. Sometimes
  3. Never
  4. It's all new to me



When to target mainstream clinical versus specialist journals and meetings

- Specialist journals and meetings for RWE studies are important for advancing methodology and expert understanding
  - However, most of your key audiences are not outcomes research specialists
- Effective publication planning is essential

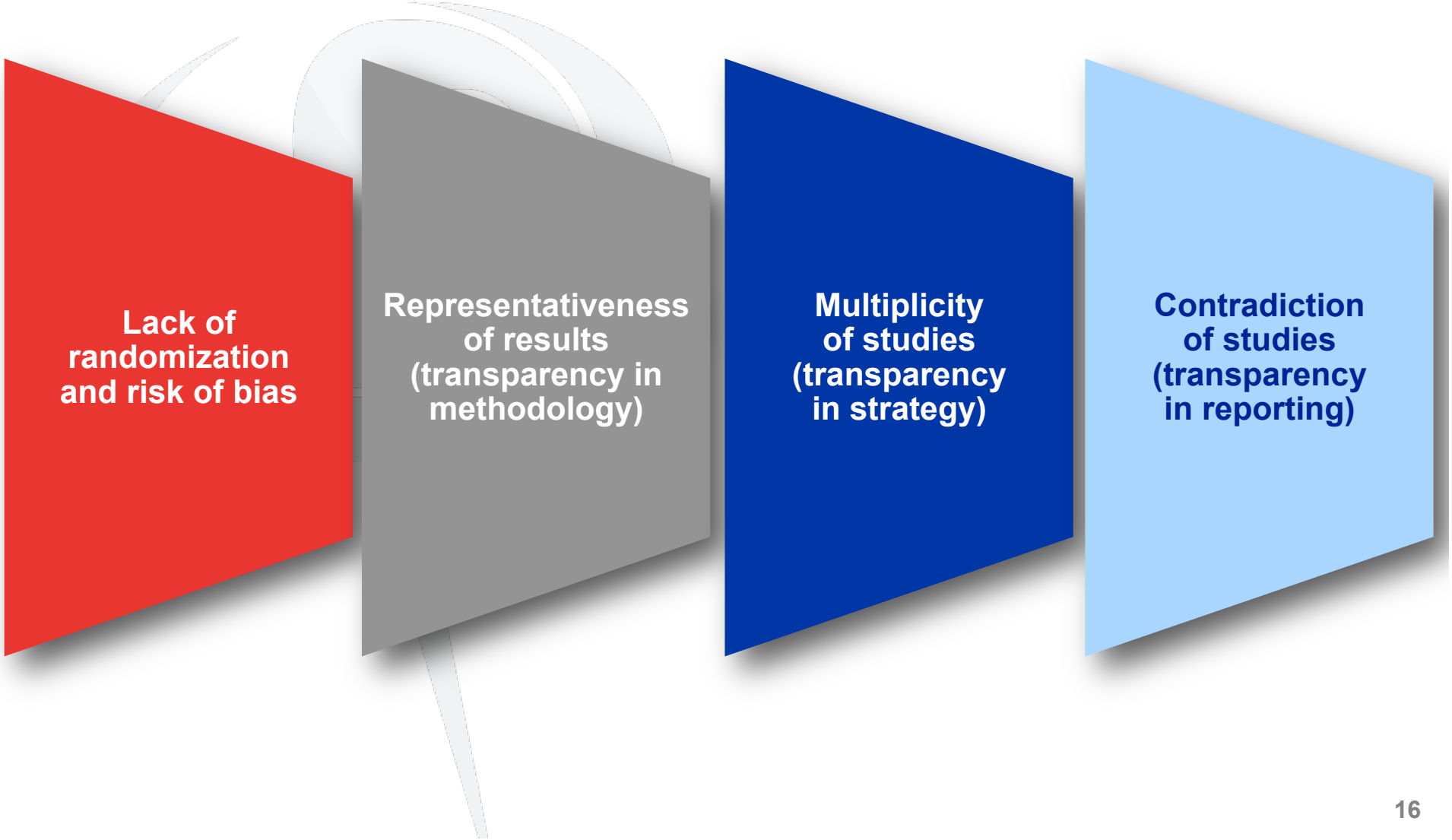
Mainstream clinical journals and meetings

- Core RWE outcomes papers (can be published in top-tier journals, e.g. *BMJ*, *Circulation*)

Specialist journals and meetings

- Technical and methodology papers (e.g. disease and outcome algorithms)

Major barriers to credibility of RWE



Efficacy versus effectiveness: an analogy

Standing quarter mile:
12.5 seconds

Standing quarter mile:
> 12.5 seconds!

RWE issue 1: lack of randomization and risk of bias

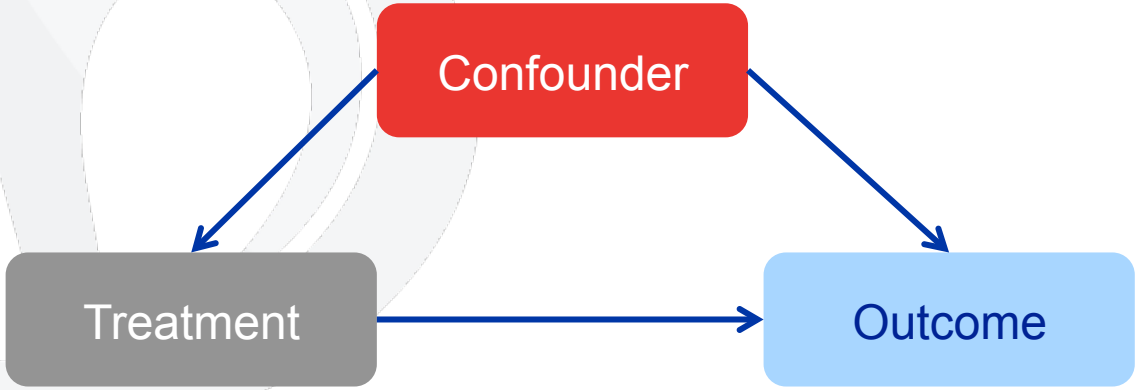
Standing quarter mile:
16.2 seconds

Standing quarter mile:
21.6 seconds

Standing quarter mile:
12.5 seconds

What is a confounder?

Confounding is the bias that arises when the treatment and outcome share a common cause



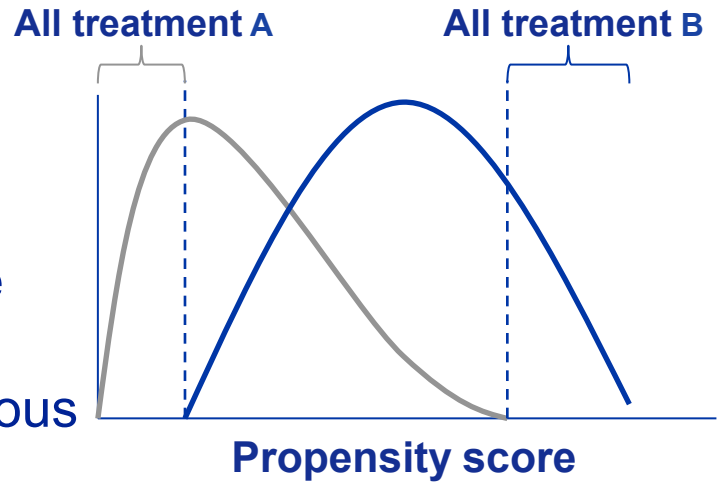
A lack of randomization of patients in a study is likely to lead to baseline differences between the treatment groups that will effect the outcome

As a result, if we do not adjust for all of these baseline differences, we cannot be sure that the effect we observe is due to treatment

Hernan MA and Robins. JM 2015

RWE publications must explain methods used to minimize bias/confounding

- Simple comparison of real world outcomes for patients receiving drug A versus drug B risks bias, because treatment allocation in clinical practice depends on patient characteristics
- Statistical methods (e.g. propensity score matching) allow comparable cohorts of patients to be created from a heterogeneous RWE data set



Regression analysis is used to determine the likelihood of patients receiving a particular therapy as a function of characteristics such as age, sex, and disease duration and severity

Rosenbaum, Rubin. *Biometrika* 1983;70:41–55

RWE publications must explain methods used to minimize bias/confounding

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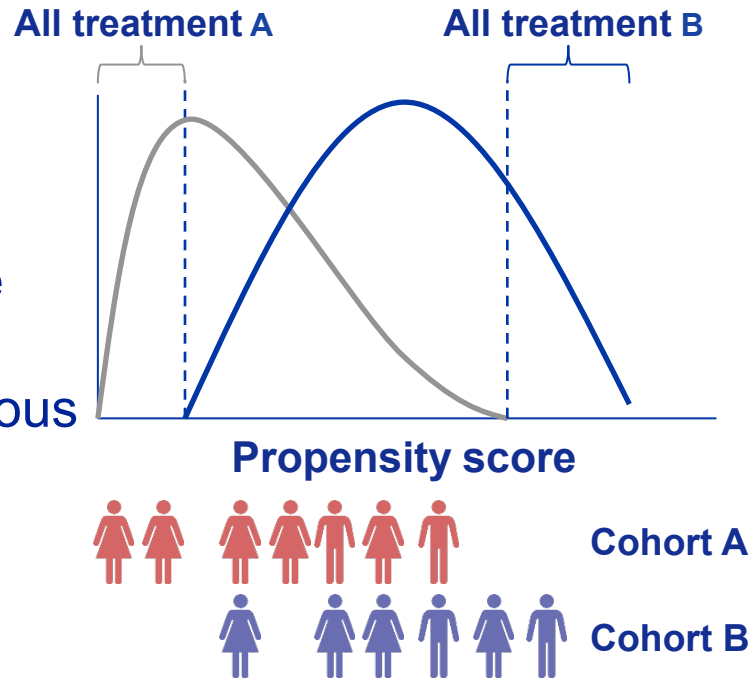

Patients in different treatment groups are matched according to their propensity score

Rosenbaum, Rubin. *Biometrika* 1983;70:41–55

RWE publications must explain methods used to minimize bias/confounding

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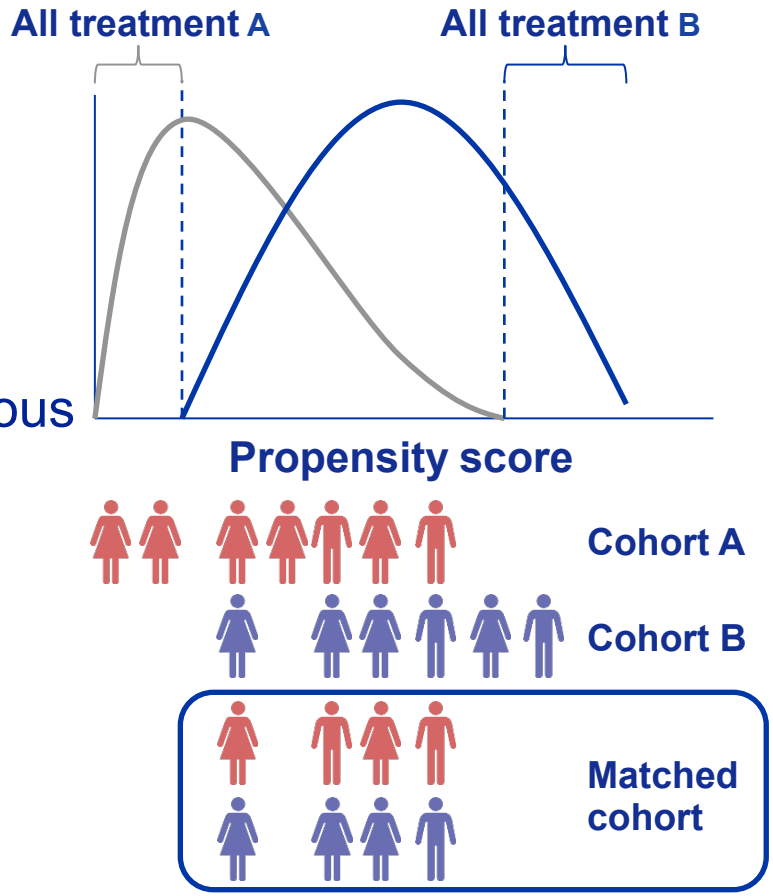
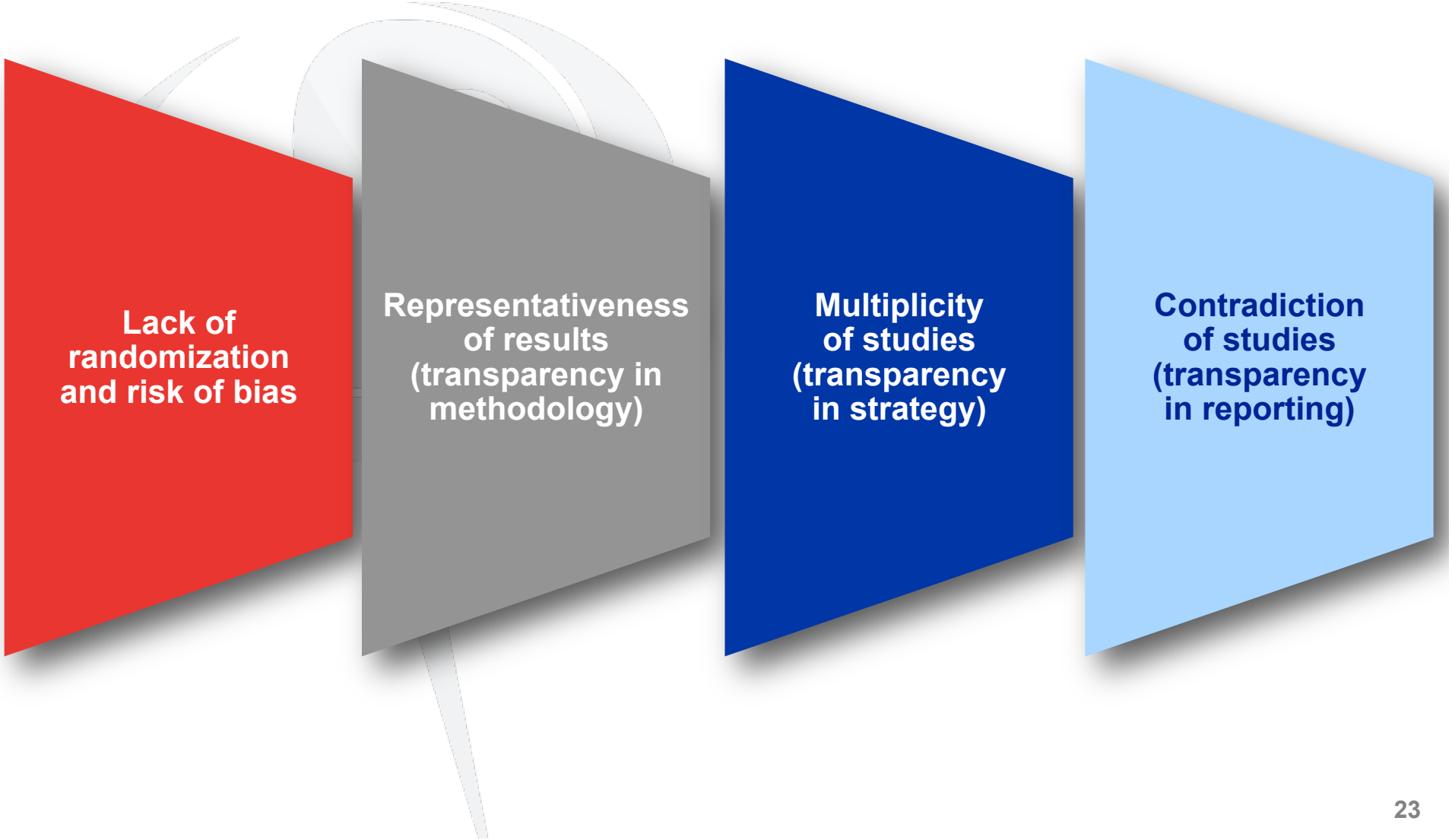


The resulting matched cohort is balanced with regard to patient characteristics that influence treatment allocation

Rosenbaum, Rubin. *Biometrika* 1983;70:41–55

Major barriers to credibility of RWE



RWE issue 2: representativeness of results (transparency in methodology)

Standing quarter mile:
19.5 seconds

Standing quarter mile:
21.6 seconds

Finding the right RWE data sources, rather than any available data source

- RWE studies commonly face one of two major issues

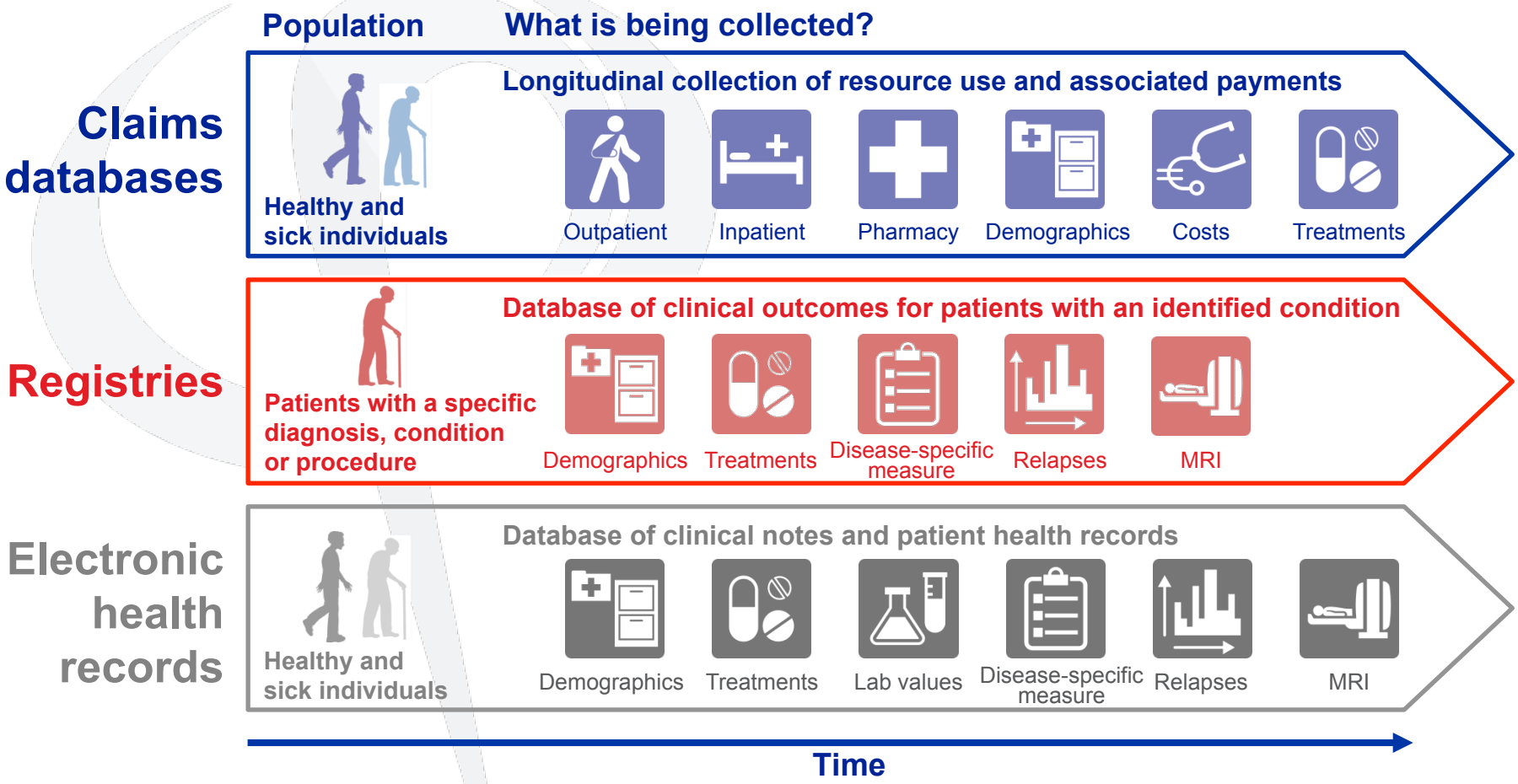
‘Data deluge’

Often encountered for common therapeutic areas (e.g. diabetes, cardiovascular diseases)

‘Data desert’

Often encountered for orphan indications, specialized information (e.g. laboratory data) or rare events

Different types of RWE data sources provide different information



MRI, magnetic resonance imaging

RWE issue 3: multiplicity of studies (transparency in strategy)

Multiplicity of studies: issues for internal RWE publications policy

- Need clear internal RWE study and publications policies
  - Adopt the same rigour as for RCTs
- Commit to publishing protocols
  - RWE study protocols can be posted on the Internet (e.g. www.clinicaltrials.gov)
  - Predefine outcomes and analyses
- Follow guidance on the design and validation of RWE studies
  - GRACE, AHRQ, EMA, ISPE

AHRQ, Agency for Healthcare Research and Quality; EMA, European Medicines Agency; GRACE, Good ReseArch for Comparative Effectiveness; ISPE, International Society for Pharmacoepidemiology

Multiplicity of studies: issues for internal RWE publications policy

- What is the definition of an RWE according to the policy?
  - Does it include safety studies (e.g. PASS)? PRO and utility studies? Pragmatic (or 'large simple trials')?
- How is authorship defined (compliant with ICMJE criteria)?
- Who owns and who controls access to study data?
  - Freedom to analyse/re-analyse? Secondary publications?
- Will the policy commit to publication of data?
  - Same approach as RCTs (i.e. regardless of findings)?
- Will the policy assure compliance with standard publication plan requirements?
  - Disclosure of author affiliations and financial relationships, acknowledgement of non-author contributions, documentation of payments and TOV

Berger *et al*. *Value Health* 2009;12:1044–52; Association of the British Pharmaceutical Industry, 2012. http://www.abpi.org.uk/our-work/library/guidelines/Pages/real-world-data.aspx; Academy of Medical Sciences and the Association of the British Pharmaceutical Industry, 2016. http://www.abpi.org.uk/media-centre/newsreleases/2016/Documents/Real_world_evidence_event_report.pdf

RWE issue 4: contradiction of studies (transparency in reporting)

Standing quarter mile:
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Standing quarter mile:
16.2 seconds

Standing quarter mile:
19.5 seconds

Standing quarter mile:
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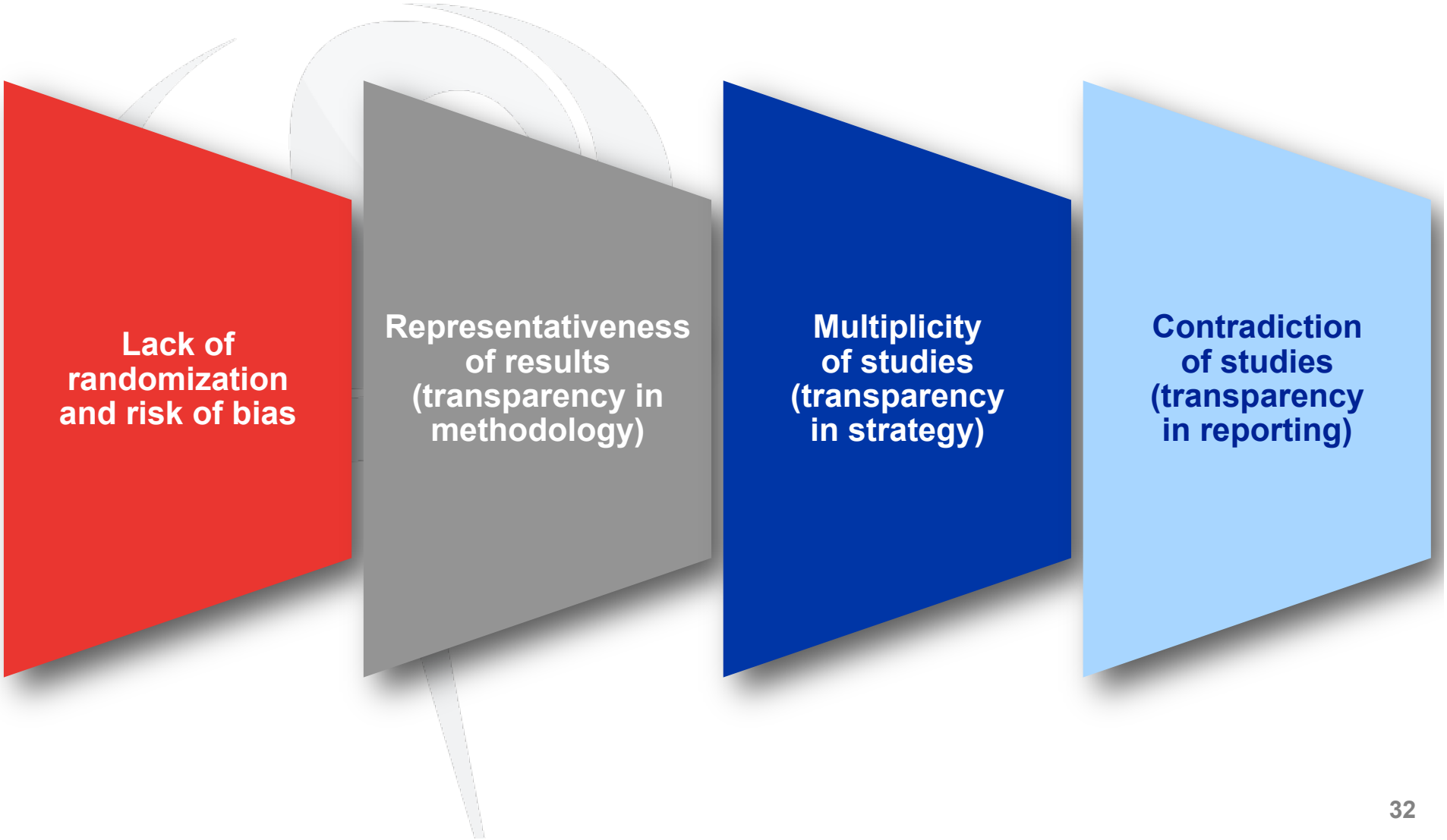
Reporting guidelines

Major barriers to credibility of RWE



We need to talk about RWE

- The Academy of Medical Sciences, in partnership with the ABPI held a workshop on RWE in September 2015
  - Involved over 50 stakeholders from industry, policy, academia and regulatory sectors
- Discussions focused on the approaches to RWE from various stakeholders and the aspirations and challenges associated with the use of RWE, particularly in a regulatory context

http://www.acmedsci.ac.uk/more/news/real-world-evidence-workshop-report-published/