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

SO OUR PARENTS UNDERSTAND
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
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- How many patients?
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- 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

One statement that people can understand and remember.
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

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

STROBE guidance can be at least as challenging as CONSORT
Guidance for studies conducted using routinely-collected health data (e.g. health administrative data, electronic medical records)

An extension of the STROBE guidelines
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
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

Please use the app to respond!
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.

<table>
<thead>
<tr>
<th>Mainstream clinical journals and meetings</th>
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<tr>
<td>• Core RWE outcomes papers (can be published in top-tier journals, e.g. BMJ, Circulation)</td>
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<td>• Technical and methodology papers (e.g. disease and outcome algorithms)</td>
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Major barriers to credibility of RWE

- Lack of randomization and risk of bias
- Representativeness of results (transparency in methodology)
- Multiplicity of studies (transparency in strategy)
- Contradiction of studies (transparency in reporting)
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.

RWE publications must explain methods used to minimize bias/confounding

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- Statistical methods (e.g. propensity score matching) allow comparable cohorts of patients to be created from a heterogeneous RWE data set.

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

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.

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

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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

**Claims databases**
- **Population**: Healthy and sick individuals
- **What is being collected?**: Longitudinal collection of resource use and associated payments
- **Outpatient**
- **Inpatient**
- **Pharmacy**
- **Demographics**
- **Costs**
- **Treatments**

**Registries**
- **Population**: Patients with a specific diagnosis, condition or procedure
- **What is being collected?**: Disease-specific measure, Relapses, MRI
- **Demographics**
- **Treatments**
- **Disease-specific measure**
- **Relapses**
- **MRI**

**Electronic health records**
- **Population**: Healthy and sick individuals
- **What is being collected?**: Disease-specific measure, Relapses, MRI
- **Demographics**
- **Treatments**
- **Lab values**
- **Disease-specific measure**
- **Relapses**
- **MRI**

Time

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, acknowledgment of non-author contributions, documentation of payments and TOV

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

Standing quarter mile: 12.5 seconds

Standing quarter mile: 16.2 seconds

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Standing quarter mile: 21.6 seconds
Reporting guidelines

STROBE Statement
Strengthening the reporting of observational studies in epidemiology

RECORD
Reporting of studies Conducted using Observational Routinely-collected Data

equator network
Major barriers to credibility of RWE

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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/