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Editor’s Perspective: Publishing Results of Your RCT

EQUATOR Network Seminar – Getting Your Trial Published

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Why do journal editors care about good reporting – and what can we do about it?
Harms caused by mis-representation of trial findings in published papers (aka, bad reporting)

- Rofecoxib – omission of cardiovascular harms data from key company trial report in *NEJM*
- Rosiglitazone – FDA reanalysis of harms data, outcomes misclassified in *Lancet* postmarketing paper
- Paroxetine – systematic under-reporting of harms outcomes (suicidality, withdrawal problems) in trials
- Gabapentin – use of clinical trials in off-label marketing

...the list goes on, and on, and on...
An example

- Tsai et al in *PLoS Medicine* – what’s the evidence base for aripiprazole in maintenance treatment for bipolar disorder?
- Initially approved for treatment of schizophrenia, subsequently approved and increasingly prescribed for use in bipolar disorder
- Tsai et al found a single manufacturer-sponsored trial supporting use in bipolar maintenance
- Problems extracting sufficient data from the published report to understand whether claims for efficacy were supported
- Report four key problems with the trial design which limit relevance for clinical practice – only one acknowledged in the report
The Bigger Picture: What Reporting-Related Biases are Out There?

- Nonpublication of entire studies – some estimates gauge perhaps ~50% of trials aren’t published in full

- Outcome level reporting bias – may include any / all of the below
  - Selective reporting of analyses
  - Selective reporting on specific endpoints
  - Selective reporting on specific timepoints
  - Selective reporting of harms data

- Narrative Spin

- Studies of these phenomena suggest these forms of reporting bias are incredibly common...

  *Dissemination and publication of research findings: an updated review of related biases. Song et al, Health Technol Assess. 2010 Feb;14, 1-193*
Are journals still relevant?

- Once, journals were (pretty much) the only mechanism for publishing results of trials and other studies.

- Now - increasing focus on web registries – eg clinicaltrials.gov, company websites.

- But journals still provide the main method of disseminating full details of trial design and results.

- Investigators still want peer-reviewed journal publication as credit for what has been done.

- Peer review and editorial process provides an important opportunity for achieving good quality reporting.
What about journals’ conflicts?

- Editors can act in ways which promote bias
- Want to publish new and “exciting” papers
- (Some) journals need to sell copies / reprints
- Most journals want to get (and maintain) a high impact factor so they can attract good papers

“It is important for the industry to publish reports of large trials in prestigious journals, as such reports are essential for clinical decision making and for the sales of drugs and devices [2],[3]. However, journals not only stand to gain financially through the sales of reprints, but also publication of such trials may increase their impact factors, as a large number of reprints distributed to key clinicians by drug companies will likely increase citation rates.”

The life cycle of a research article

- Research
- Submission
- Peer review
- Publication

2-3 Experts
Is it rigorous?
Good enough?
Right audience?
Takes months/years

Journal name is key
What goes on in the black box called “peer review”? At PLoS Medicine:

• Papers handled by in-house editor
• Additional advice from external academic editor (researcher / clinician)
• Around 90% papers rejected before peer review based on scope, quality, importance
• Typically 2-3 subject reviewers (eg in the clinical specialty)
• 1 statistical reviewer
• Around further 50% papers rejected after peer review
How *PLoS Medicine* uses CONSORT during the editorial process

- RCT submissions **must** include CONSORT flowchart and checklist to get through to editorial assessment
- These items also made available to academic editor, peer reviewers (including statistician)
- We encourage authors reporting non-randomized trials (eg single-arm) to use applicable parts of CONSORT guidance
- Editors and peer reviewers consider how well specific items in CONSORT have been reported
- Editors give further guidance / advice to authors on improving writeup if a revision is invited

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PLoS journals – additional standards for trials reporting

• Trial registration: require prospective registration in WHO ICTRP approved registry
• Authors must also provide a copy of the original trial protocol
• Editors and peer reviewers check protocol and registry record for key items
• If there are differences between paper and protocol in outcomes reported, ask authors to add those data during a revision
• Encourage authors to be more upfront in describing changes from protocol in their paper

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What is outcome reporting bias ("ORB")?

- An area addressed by CONSORT that’s receiving greater attention from journals and researchers
- ORB is a form of publication bias
- Occurs when statistically significant findings are more likely to be included in report
- Authors, reviewers and editors can all contribute to the problem (and help address it)
- Some journals – including PLoS journals – now ask for full protocols for submitted RCTs
- On PLoS Medicine – check outcomes reported in the paper against those in the protocol
- Frequently ask authors to add results for these outcomes to the paper and / or add explanations about outcome changes

Applying CONSORT guidance to real papers

• Many researchers think that once they have ticked the boxes in the checklist and filled out the numbers in the flowchart, salvation is theirs – they are “CONSORT compliant”

• I hope CONSORT group would agree: this is not true

• For reader (and those who want to use the findings) the devil is in the details!
In the real world – how should we decide which CONSORT to use?

- Lots of flavours of CONSORT...
- “Vanilla” (2-arm parallel design RCT)
- 8 extensions:
  - Cluster RCT
  - Non-inferiority / equivalence
  - Pragmatic trials
  - Herbal medicines
  - Non-pharmacological
  - Acupuncture
  - Harms
  - Abstracts
Using CONSORT and its extensions

- If multiple “flavours” of CONSORT apply to a study, we’d advocate trying to identify the one that is most relevant to your situation.
Using CONSORT and its extensions

Example – cluster trial with non-pharmacological intervention (and pragmatic aspects!)

4 CONSORT’s apply

Many of the complexities of this trial centre on the nature of the intervention and whether it can be replicated elsewhere

So we advised the authors to use CONSORT for non-pharmacological extension as their main tool in reporting

But also to make sure they considered CONSORT for cluster advice in the statistical components
Using CONSORT and its extensions

- Example – cluster trial of diagnostic regimens, non-inferiority framework, also fairly pragmatic!
- 3-4 CONSORT’s apply, plus STARD (reporting guideline for diagnostics)
- We thought the diagnostics issues were really important here, so advised authors to use vanilla CONSORT, and also refer to STARD
Using CONSORT in publication

- Optional template for authors, using CONSORT items as headings for structured writeup of the paper

- Available for authors on all PLoS journals but most heavily used on *PLoS Medicine, PLoS ONE*

- Sent to authors when a revision is invited

- Authors can use components that work for them – in addition to the CONSORT checklist and flowchart

- Works best for primary papers (ie reporting main results of RCT); less so for exploratory / ancillary papers

- For published papers, CONSORT flowchart, checklist and protocol all included alongside as figures / supporting information

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Where are CONSORT items reported?

- Trial registration (item 23)
- Funding (item 25)
Where are CONSORT items reported?

- Study setting (item 4b)
- Participants (item 4a)
- Interventions (item 5)
- Outcomes (item 6a)
Journal experiences of CONSORT

• *PLoS Medicine* is a CONSORT endorser (and we try hard to be an implementer!)

• But making sure that every paper we publish fully adheres to CONSORT is another matter

• Despite the simplicity and usability of CONSORT, substantial work – from authors, peer reviewers and editors - is often needed to promote full adherence to CONSORT during the peer review and revision process

• CONSORT instruments (checklist, flowchart) now well accepted and used by authors

• Some reluctance to report that “not all went as planned” eg conduct, outcome changes during the trial

• We want to encourage researchers that this is OK, and we won’t reject a paper just because it didn’t all go to plan

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Using CONSORT: what are the advantages and opportunities?

For **authors**:

- Adhering to CONSORT upfront means your paper will go straight through to the editor’s desk

  - (Anecdotally) - clearly reported papers go through peer review faster and with fewer revisions. Quicker, easier trip through copyediting

- We can’t guarantee the decision will be different (as this may well hinge on the importance of the question and quality of the study)

For **editors / guideline developers**:

- How do we encourage better reporting of exploratory or ancillary sub-studies?

- How do we encourage better reporting for non-randomized trials?
How are things changing? Beyond published papers

Analysis

Ensuring safe and effective drugs: who can do what it takes?

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Drawing on their experience in producing a Cochrane review of neuraminidase inhibitors for influenza, Tom Jefferson and colleagues discuss how to improve the reliability of systematic reviews.

In the midst of the H1N1 flu "pandemic," the Australian and UK governments commissioned an update of our longstanding Cochrane review on neuraminidase inhibitors for influenza in (otherwise) healthy adults. The review had first been published in 1999 with updates in 2006 and 2008. While preparing the 2009 update, we received a comment from a Japanese paediatrician. He questioned our conclusion that oseltamivir (Tamiflu) reduces the risk of complications (such as pneumonia) and pointed out that the evidence underlying this conclusion in our 2006 review was based on a single paper—a manufacturer funded meta-analysis¹ of 10 manufacturer trials, of which only two had been published in the peer reviewed literature.² ³ To verify the quality and reliability of our previous conclusions, we wrote to the lead author of the

• Jefferson et al:

• To get a full picture of all the evidence on a particular drug, we need access to:
  • Full clinical study reports
  • Regulatory documents
  • Full datasets for individual trials
  • Original protocols
  • Emphasis on understanding entire trial programme, not just individual trials

"We do not yet know whether sound scrutiny is feasible with a journal’s resources..."