Investigating the impact of randomized clinical trial reports

Oh! what a tangled web we weave
When first we practise to deceive!
Sir Walter Scott, *Marmion*

Fiona Stewart, University of Aberdeen
Alison Avenell*, University of Aberdeen
Andrew Grey, University of Auckland
Mark Bolland, University of Auckland
Greg Gamble, University of Auckland
Our presentation in three acts

I  Novel statistical investigation methods examining data integrity for 33 randomized trials in 18 journals from one research group

II  Investigating the impact of retracted randomized clinical trial reports

III  Reporting concerns about data integrity for 33 randomized trials in 18 journals from one research group: a narrative review
Conflict of interest statements

• None of the authors has a conflict to disclose
• All authors wish to improve the integrity of the research literature – more promptly
Appendix e-1:

Table e-1A: 33 Randomized controlled trials carried out by the researchers.

<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Institutions</th>
</tr>
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Timeline

• Our investigations started at the end of 2012
• May 2017 – only 11/33 trial reports retracted
• Misconceptions persist, e.g. 2015 JBMR

modest effects of calcium and vitamin D which were provided to the control groups in each of these studies. Pharmacologic treatment is also more effective in reducing hip fracture risk in elderly patients with a history of Alzheimer’s disease or with Parkinson’s disease than is vitamin D alone.⁹⁻¹¹ In contrast to Järvinen and colleagues’ interpretation that the effect of therapy with osteoporosis. N Engl J Med. 2009 Aug 20;361(8):756–63.


Aims

• To investigate the extent of citation of trial reports from this group in secondary publications, including:
  – clinical trials
  – systematic reviews
  – guidelines
• To examine the impact of the trial reports in these publications
• To discuss the issues raised by our investigation and how best to correct the evidence base
Methods (1)

- We examined the impact of potentially the most influential trial reports of
  - Potent oral bisphosphonates, e.g. alendronate
  - Vitamin K
  - Vitamin D analogues
  - Vitamin B12 and/or folate

- Had to report hip fracture as an outcome

- Reports also had to be in higher impact journals
  - (ISI Web of Knowledge impact factor ≥ 4)

12/33 RCT reports to investigate
6/12 retracted so far......
Methods (2)

- Excluded from our analysis reviews and meta-analyses by the two main authors under investigation, where they cited their own work
  - 24 reviews
    - Sato = 5
    - Iwamoto = 19
  
  - Meta-analyses
    - Iwamoto = 7 (3 retracted)
Methods (3)

• August 2016
  – Citation searching in Scopus for total numbers of citations
  – Citation searching in Google Scholar, PubMED, ISI Web of Science for
    • clinical trials
    • systematic reviews
    • guidelines

• Assessing impact on publications
  – Findings likely to change
  – Unclear if findings would change
  – Findings unlikely to change
Methods (4)

- Rerun meta-analyses (rarely possible)
- One researcher assessed, checked by a second
  - Discussed differences
  - Reference to a third researcher if still uncertain about impact
- With a view to alerting affected publications
Results

- 12/33 RCT reports
  - 2956 participants
  - 703 citations, excluding self-citations
  - Median number of citations 40 (range 6 to 208)
    - All reported a significant reduction in hip fractures
    - 6/6 reported a reduction in non-vertebral fractures
    - 11/11 reported significant improvements in BMD
    - 9/9 reported no significant effect on falls

- Highest cited trial report
  - JAMA 2005;293:1082-8
Permeation of 12 RCT reports in secondary publications

RCT reports (n = 81)
  - Sato RCT reports (n = 33)

  Sato reports with characteristics of interest (n = 12)

  Included in fracture reviews and meta-analyses: (n = 9)

  Findings likely to change (n = 4):
  - Cockayne 2006
  - Zhang 2014
  - Zhao 2012
  - Dai 2015

  Unclear if findings would change (n = 4):
  - Richy 2004
  - Richy 2005
  - Myrad 2012
  - Yang 2012

  Findings unlikely to change (n = 1):
  - McCarus 2008
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      McCarus 2008
    Included in falls reviews and meta-analyses: (n= 2)
      Findings unlikely to change (n = 2):
      Gillespie 2012
      Batchelor 2010
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  - Gillespie 2012
  - Batchelor 2010
- Findings unlikely to change (n = 2):
  - Binks 2016
  - Hermann 2007
  - Peterson 2014
- Unclear if findings would change (n = 4):
  - Alibhai 2006
  - Carda 2009
  - Simpson 2011
  - Zhao 2013
- Findings unlikely to change (n = 5):
  - Bjelakovic 2014
  - Lv 2014
  - Marsden 2008
  - Rucklidge 2013
  - Salari 2008

Cited in other reviews and meta-analyses: (n = 12)
- Findings likely to change (n = 3):
  - Binks 2016
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  - Bjelakovic 2014
  - Lv 2014
  - Marsden 2008
  - Rucklidge 2013

Excluded from SRs (n = 4)
- Reasons for exclusion uncertainties with data (n = 4):
  - Avenell 2014
  - Cameron 2012
  - Lathan 2003
  - Verheyden 2013
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Sato RCT reports (n = 33)
Sato reports with characteristics of interest (n = 12)

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- Findings likely to change (n = 3): Binks 2016, Hermann 2007, Peterson 2014
- Unclear if findings would change (n = 4): Alibhai 2006, Carda 2009, Simpson 2011, Zhao 2013

Excluded from SRs (n = 4)

Cited in guidelines (n = 5)
- Findings likely to change (n = 1): Kernan 2014
- Unclear if findings would change (n = 1): Qaseem 2008
- Findings unlikely to change (n = 3): Crandall 2012, MacLean 2007, SIGN 2015
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Gillespie 2012
Batchelor 2010

Cited in guidelines (n = 5)
Findings likely to change (n = 1):
Kernan 2014

Findings unlikely to change (n = 3):
Crandall 2012
MacLean 2007
SIGN 2015

Cited in trials & cohorts (n = 33)
Sato trial reports contributed to the rationale for the trial (n = 8 RCTs):
Baumann 2004
Berendsen 2013
Binkley 2009
Emaus 2013
Greiger 2009
Hermann 2007
Rucklidge 2012
Van Wijngaarden 2014
RCTs citing Sato trial reports in rationale

- 5107 participants in 8 RCTs citing Sato trial reports in rationale
- Size ranged from $n = 40$ to $n = 2919$
- B-PROOF trial (van Wijngaarden 2014):
  - B-vitamins for the prevention of fractures (Am J Clin Nutr 2014;100:1578-6)
  - 2919 participants
  - Recruitment 2008 – 2011
  - Follow-up for 2 years
prevalent in 30–50% of persons aged >65 y (15, 16). Treatment with vitamin B-12 and folic acid, which both play a central role in homocysteine metabolism (17), is effective in normalizing homocysteine concentrations (18, 19). Three randomized controlled trials investigated the effect of B-vitamin supplementation on fracture risk (20–22). Among stroke survivors (mean age: 71 y), a large protective effect of 2-y supplementation of 1.5 mg vitamin B-12 and 5 mg folic acid was observed on hip fracture risk in the trial by Sato et al (21). However, in the Heart Outcomes Prevention Evaluation-2 (HOPE-2) trial, no effect of 5-y supplementation of 1 mg vitamin B-12, 2.5 mg folic acid, and 50 mg vitamin B-6 was observed on fracture incidence in persons with high cardiovascular disease risk (mean age: 69 y) (22). In the VITAmins TO Prevent Stroke (VITATOPS) study, there was also no effect of treatment with 2 mg folic acid, 25 mg vitamin B-6, and 500 μg vitamin B-12 during a mean of 2.8 y on osteoporotic fracture incidence observed in patients with cerebrovascular disease (mean age: 63 y) (20). Given the conflicting results and low generalizability to the general older population, further investigation is needed.
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Howard Bauchner, MD; Phil B. Fontanarosa, MD, MBA

In reaffirming our previous Expression of Concern, the article “Effect of Folate and Mecobalamin on Hip Fractures in Patients With Stroke: A Randomized Controlled Trial” by Sato et al has been retracted due to acknowledgment of scientific misconduct resulting in concerns regarding data integrity and inappropriate assignment of authorship.

ARTICLE INFORMATION
Author Affiliations: Dr Bauchner is Editor in Chief and Dr Fontanarosa is Executive Deputy Editor, JAMA.
Corresponding Author: Howard Bauchner, MD (howard.bauchner@jamanetwork.org).

Published Online: June 3, 2016. doi:10.1001/jama.2016.7190.

REFERENCES
Citation Map from Web of Science for Sato et al 2005, (red is 2007, purple is 2016, green 2015)
>220 Publications

81 Human and animal RCTs
For discussion

1. Authors and editors of secondary affected publications
   • At what stage should they be alerted – EoC, retraction?
   • How should this happen – via editors, learned societies, institutions, database alerts?

2. What about wider influences outside affected publications?
   • Tertiary affected publications…?
   • Influences beyond publications, e.g. media?

3. Who is there to advise on this?

4. Who should coordinate this?

5. Who should fund all of this?

6. What consequences for the researchers investigated?
Acknowledgements

Bill Gillespie (Hull York Medical School, UK)

Lesley Gillespie (University of Otago, New Zealand)

David Torgerson (University of York, UK)

Mari Imamura, Research Fellow and native Japanese speaker (University of Aberdeen, UK)

Doug Altman and anonymous referees for their comments

Numerous colleagues who listened and advised