What can journals do to reduce research waste? View from The BMJ

Increasing value and reducing waste in biomedical research
Edinburgh, September 2015

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Competing interests

I'm editor in chief of BMJ Open and Head of Research at the BMJ, a wholly owned Subsidiary of the British Medical Association (BMA)

BMJ (the company) receives revenues from drug & device manufacturers through advertising, reprint sales, & sponsorship

I receive a bonus based partly on the financial performance of the BMJ. The BMJ is an open access journal that charges author fees for publication of research articles, as does BMJ Open

I'm currently working on a strategy to see how BMJ might help to build health research capabilities in emerging economies

Transparency policies to reduce selective reporting

For clinical trials:

- mandatory prospective registration + submission of protocols and CONSORT checklists + sharing of deidentified IPD on reasonable request
- RIAT

For all research articles:

- reporting checklists required
- open access, open peer review, patient review
- post publication peer review
- “negative” studies welcome
- transparency statement

BMJ transparency declaration

"The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

* The manuscript's guarantor.

Altman DG ,Moher D. Declaration of transparency for each research article. *BMJ* 2013;347:f4796

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BMJ 2013;347:f4796 doi: 10.1136/bmj.f4796 (Published 7 August 2013) Page 1 of 2

EDITORIALS

Declaration of transparency for each research article

OPEN ACCESS

An antidote to inadequate reporting of research

Douglas G Altman *director*[1], David Moher *senior scientist*[2]

[1]Centre for Statistics in Medicine, University of Oxford, Botnar Research Centre, Oxford, UK; [2]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa Hospital - General Campus, Ottawa, ON K1H 8L6, Canada

"It is the responsibility of everyone involved to ensure that the published record is an unbiased, accurate representation of research."[1]

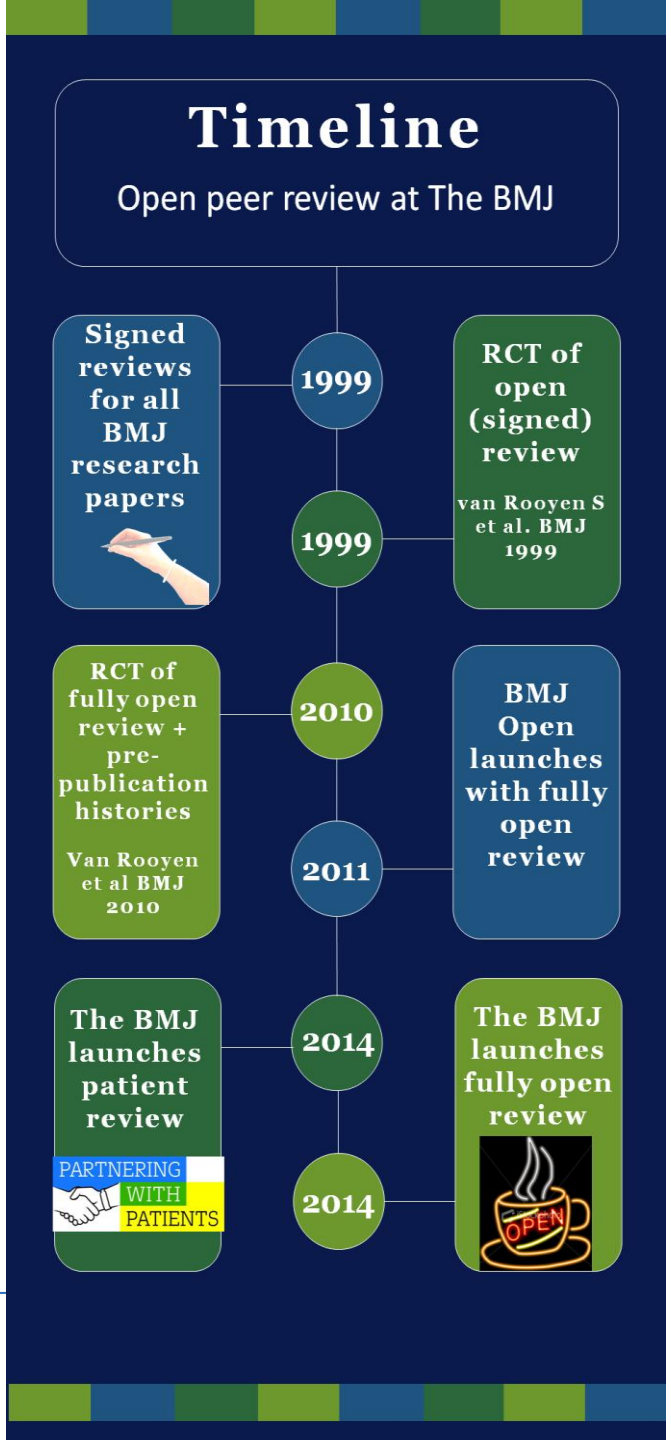
The research record is often manipulated for short term gain but at the risk of harm to patients. The medical research community needs to implement changes to ensure that readers obtain the truth about all research, especially reports of randomised trials, which hold a special place in answering what works best for patients.

Failure to publish the findings of all studies, especially randomised trials, seriously distorts the evidence base for clinical decision making. A recent systematic review of reboxetine for treating depression found that almost three quarters of included in relation to allocation. A 2006 study found that only a third of trial reports described how the randomisation sequence was generated and only a quarter described an adequate method of allocation concealment.[20] A review of 357 phase III oncology trials concluded that "numerous items remained unreported for many trials."[21] Harms too are poorly reported.[22 23]

The problems associated with publishing and reporting other types of research may be worse than for randomised trials. Although less intensively studied, similar concerns have been expressed in relation to epidemiology,[24 25] pharmacoepidemiology,[26] diagnosis research,[27] prognosis research,[28] and preclinical research.[29 30] Of course, good reporting is not the same as high quality research. But a full and clear report allows readers to judge a study's reliability and relevance.

The BMJ http://www.bmj.com/theBMJ publishes all research with open access and with a detailed prepublication history

This open peer review policy draws on evidence from two RCTs of open peer review, and on experience of mandatory open peer review for more than 3000 published papers at BMJ Open http://bmjopen.bmj.com/



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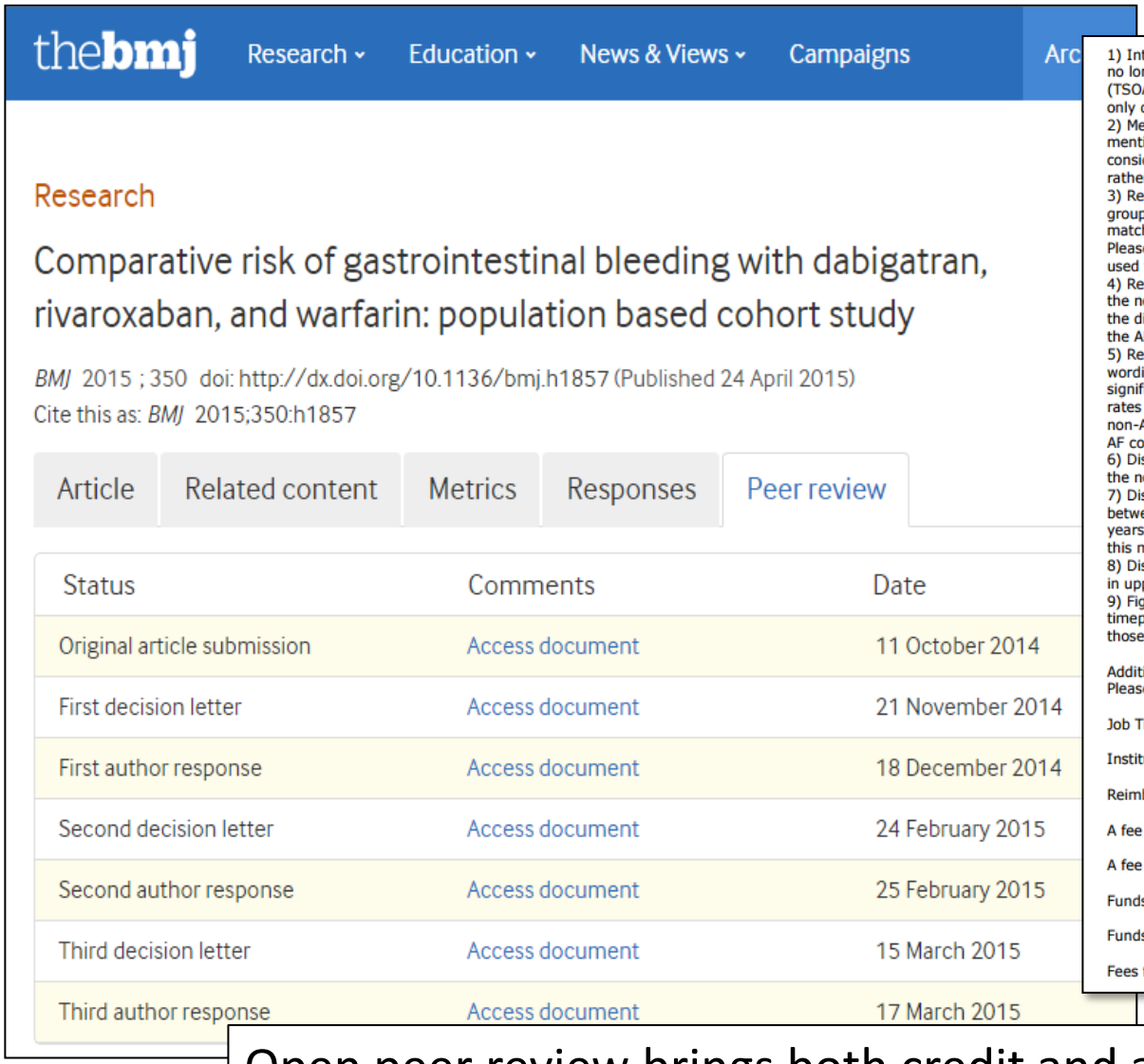

1) Introduction: Consider using an alternative term to NOAC, since these agents are no longer "novel". Perhaps something like "target-specific oral anticoagulants (TSOACs)". Also, either mention all of the available agents in the 1st paragraph (vs only dabi & riva), or just mention the drug classes as a whole.
2) Methods, Variables of Interest: Why were inducers/inhibitors of warfarin specifically mentioned, but not agents interacting with either dabigatran or rivaroxaban? Also, consider using the more universally recommended CHADS2-VASc stroke risk score rather than the outdated CHADS2.
3) Results: I am not clear on why so many differences remained different between groups (particularly in the rivaroxaban non-AF patients) following propensity-score matching. Did the model that was used for matching not fit the data appropriately? Please provide the model diagnostics to support/refute this. Were too few variables used to match?
4) Results, Table 3: How do you explain why the hazard of GI bleeds was higher in the non-AF group with dabigatran vs. warfarin? This was not addressed anywhere in the discussion. While not statistically significant, the results are trending opposite of the AF cohort. Why might this be?
5) Results: When discussing the results of the rivaroxaban analyses, please keep wording consistent. Stating that there were numerically, albeit not statistically significantly, fewer events with riva vs. warf in the AF-cohort, while saying "similar rates of GIB when compared to warfarin" in the non-AF cohort is inconsistent. The non-AF cohort had confidence intervals much closer to statistical significance than the AF cohort.
6) Discussion: In the first paragraph, why was only the AF findings mentioned, and the non-AF findings ignored?
7) Discussion, Interpretation of Findings: When discussing the differences in age between your cohort & the clinical trials, you seem to suggest that the difference of 4 years in mean age could explain the differences in GIB rates. Please substantiate how this magnitude of age difference relates to significant GIB rates.
8) Discussion: Is there a mechanistic rationale for why one might expect differences in upper vs. lower GIB rates with these agents?
9) Figures 2 & 3: Consider adding the p-value for each comparison at the various timepoints to allow for easier interpretation of the data within the figures (same for those in the appendix).

Additional Questions:
Please enter your name: William L. Baker

Job Title: Assistant Professor

Institution: University of Connecticut School of Pharmacy

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Open peer review brings both credit and accountability to reviewers, who have to declare their competing interests openly and may have to defend their comments. Several new initiatives aim to make this explicit: eg Rubriq, Publons, ORCID (soon)

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ANALYSIS

Restoring invisible and abandoned trials: a call for people to publish the findings

Unpublished and misreported studies make it difficult to determine the true value of a treatment. **Peter Doshi and colleagues** call for sponsors and investigators of abandoned studies to publish (or republish) and propose a system for independent publishing if sponsors fail to respond

Doshi P, Dickersin K, Healy D, Vedula SS, Jefferson T. BMJ 2013;346:f2865

"They challenge medical researchers and funding agencies associated with unpublished or misreported trials to swiftly signal their intent to publish or correct these "abandoned" trials and then to act on this within a year. If no such intention is declared, or if a corrective paper has not been published within a year, they propose offering the opportunity to become "restorative authors" to other responsible researchers, who would restore the integrity of the reporting of the trials involved."

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmj.h4320)

Cite this as: *BMJ* 2015;351:h4320
doi: 10.1136/bmj.h4320

Accepted: 03 August 2015

ABSTRACT

OBJECTIVES

To reanalyse SmithKline Beecham's Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The reanalysis under the restoring invisible and abandoned trials (RIAT) initiative was done to see whether access to and reanalysis of a full dataset from a randomised controlled trial would have clinically relevant implications for evidence based medicine.

DESIGN

Double blind randomised placebo controlled trial.

SETTING

12 North American academic psychiatry centres, from 20 April 1994 to 15 February 1998.

PARTICIPANTS

275 adolescents with major depression of at least eight weeks in duration. Exclusion criteria included a range of comorbid psychiatric and medical disorders and suicidality.

INTERVENTIONS

Participants were randomised to eight weeks double blind treatment with paroxetine (20-40 mg), imipramine (200-300 mg), or placebo.

MAIN OUTCOME MEASURES

The prespecified primary efficacy variables were change from baseline to the end of the eight week acute treatment phase in total Hamilton depression scale (HAM-D) score and the proportion of responders (HAM-D score ≤8 or ≥50% reduction in baseline HAM-D) at acute endpoint. Prespecified secondary outcomes were changes from baseline to endpoint in depression items in K-SADS-L, clinical global impression, autonomous functioning checklist, self-perception profile, and sickness impact scale; predictors of response; and number of patients who relapse during the maintenance phase. Adverse experiences were to be compared primarily by using descriptive statistics

WHAT IS ALREADY KNOWN ON THIS TOPIC

There is a lack of access to data from most clinical randomised controlled trials, making it difficult to detect biased reporting

BMJ Open

The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer

Tom Treasure,[1] Kathryn Monson,[2] Francesca Fiorentino,[3] Christopher Russell[4]

To cite: Treasure T, Monson K, Fiorentino F, *et al*. The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer. *BMJ Open* 2014;**4**:e004385. doi:10.1136/bmjopen-2013-004385

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2013-004385).

The following paper published in the *BMJ* relates

ABSTRACT

Objective: In patients who have undergone a potentially curative resection of colorectal cancer, does a 'second-look' operation to resect recurrence, prompted by monthly monitoring of carcinoembryonic antigen, confer a survival benefit?

Design: A randomised controlled trial recruiting patients from 1982 to 1993 was recovered under the Restoring Invisible and Abandoned Trials (RIAT) initiative.

Setting: 58 hospitals in the UK.

Participants: From 1982 to 1993, 1447 patients were enrolled. Of these 216 met the criteria for carcinoembryonic antigen (CEA) elevation and were randomised to 'Aggressive' or 'Conventional' arms.

Interventions: 'Second-look' surgery with intention to remove any recurrence discovered.

Primary outcome measure: Survival.

Results: By February 1993, 91/108 patients had died in the 'Aggressive arm' and 88/108 in the

Strengths and limitations of this study

- The carcinoembryonic antigen (CEA) Second-Look Trial was a well-planned and carefully executed study with a clear question and a well-defined outcome of interest.
- Second-look surgery prompted by the best available indicator of recurrence at the time conferred no survival advantage.
- A further strength, and a reason to publish this trial now, is that it shows that randomised trials in surgery can be carried out and that the result may be contrary to the beliefs and expectations of practitioners based on their uncontrolled observations.
- A limitation is that present day means of non-invasive detection of asymptomatic recurrence were not available at the time of the CEA Second-Look Trial. A recently reported randomised controlled trial (FACS) in which regular

Education to reduce research waste and build research capabilities

The BMJ's Research Methods and Reporting section publishes "how to" articles, with many on reducing research waste *

BMJ Research to Publication elearning programme (300hrs, aimed at integration into curricula) launches in early 2016, to help early career researchers to plan, conduct, and publish more relevant, less wasteful, more transparent research

thebmj

* meta-research and “journalology” studies too

RESEARCH TO PUBLICATION

http://http://rtop.bmj.com/

ABOUT FREE MODULE

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PROTOCOLS (FREE MODULE) −

How to Write & Publish a Study Protocol

BMJ FREE MODULE ►

- HOW TO WRITE A PAPER +
- WHAT EDITORS AND PEER REVIEWERS LOOK FOR +
- PUBLICATION ETHICS +
- DESIGNING CLINICAL RESEARCH +
- RESPONSIBLE CONDUCT OF RESEARCH +
- INTRODUCTION TO CLINICAL TRIALS +

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RESEARCH TO PUBLICATION

The importance of research protocols

Resume module

Written by:
Trish Groves

Reviews

BMJ Learning

The importance of research protocols - test yourself

1. Your department has had a strategy meeting where it decided it would start a prospectiv cohort study, in which patients with type II diabetes will be followed up over one year and have, every two months, digital photography of their retinas. This is specifically for the purposes of the study and these patients would not normally be examined so frequently have been asked to write the research protocol.

   Which is the most important reason for creating a research protocol?

   a. Having a protocol will make it easier to get funding for the study

   b. Making the protocol available to staff who will recruit patients into the study will ma patient enrolment quicker

   c. The protocol could be published

   d. Writing a protocol is an ethical requirement

   e. You will benefit from the academic exercise of writing a protocol

The ethical requirement to have a protocol

Learn more about how international standards on research ethics require a protocol for any human study.

International standards on research ethics require a protocol for any human study

WMA Declaration of Helsinki 2013 requires that:

the design and performance of each research study involving human subjects must be clearly described and justified in a research protocol

the protocol should state the ethical considerations involved

the protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study

0:29 / 1:16

Further study

Below we have presented a copy of clause 22 from the World Medical Association's Declaration of Helsinki. Read through this to understand why a protocol should describe and justify research involving human subjects.

You may also wish to read the full Declaration, last updated in 2013. [2]

Advocacy and campaigning

- The BMJ co-founded COPE and AllTrials and provides editorial support/staff to a wide range of groups, including EQUATOR and Open Trials

- editors from The BMJ have contributed to many reporting statements eg CONSORT 2010, SPIRIT 2013

- investigative journalism

AllTrials: rapid success

Since January 2013:

- 86292 people have signed the AllTrials petition
- 620 organisations have joined
- swayed vote on EU Clinical Trials Regulation
- helped make trial registration an ethics requirement in UK
- helped reverse proposed EMA restrictions on data sharing
- helped amend Canadian C-17 law on posting trial results
- convinced many pharma companies to share data
- audited pharma companies' transparency policies and actions
- built campaign across Europe and launched in U.S.

All Trials Registered | All Results Reported

Thank you

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