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Restoring invisible and abandoned trials

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Unpublished and misreported studies make it difficult to determine the true value of a treatment.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

Well designed and well performed randomised controlled trials are considered to provide the most reliable evidence on the effects of health related interventions. However, the credibility of findings from individual trials and from summaries of trials examining a similar research question (that is, systematic reviews and meta-analyses) has been undermined by numerous reporting biases in the published medical literature.[1-14] Reporting biases are often difficult to detect, but have the potential to discredit earnest efforts towards evidence based decision making.

Two basic problems of representation are driving growing concerns about relying on published research to reflect the truth.[10 15] The first is no representation (invisibility), which occurs when a trial remains unpublished years after completion. The second is distorted representation (distortion), which occurs when publications in medical journals present a biased or misleading description of the design, conduct, or results of a trial.[1 6 10 14] Both go against the fundamental scientific and ethical responsibility that all research on humans be used to advance knowledge and are symptomatic of a general culture of data secrecy. The end result is that the healthcare, biomedical research, and policy communities may, despite best intentions and best practices, end up drawing scientifically invalid conclusions based on only those parts of the evidence base they can see.

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CLINICAL STUDY REPORTS IN OUR POSSESSION

Amgen Epoetin Alfa study 930107

AstraZeneca quetiapine study 015, 041, 049, 135, 125, 127, 126

Bristol-Myers Squibb clopidogrel study CAPRIE, CURE, CLARITY, COMMIT, PICOLO

Bristol-Myers Squibb aripiprazole study CN138135

GSK H5N1 pandemic influenza vaccine studies H5N1-008, H5N1-011 EXT 008

GSK paroxetine study 329, 377, 453, 511, 701, 704, 715, 676, 716

GSK zanamivir study 167-101, 167T3-11, JNAI-01, JNAI-04, JNAI-07, NAI30008, NAI30009, NAI30010, NAI30011, NAI30012, NAI30015, NAI30020, NAI30028, NAI30031, NAI30034, NAIA2005, NAIA2006, NAIA2010, NAIA3002, NAIA3003, NAIA3004, NAIA3005, NAIAB2008, NAIAB2009, NAIB2005, NAIB2006, NAIB2007, NAIB3001, NAIB3002, PE-01

Merck rofecoxib study 078

Novartis Fluad studies V87P1, V87P6

Pfizer atorvastatin study 981080

Pfizer gabapentin study 879-201, 945-210, 945-209, 945-220, 945-217, 1032-001, 945-224, 945-306, 1035-001, 1032-004, 1032-002, 1035-002, 1032-003, 945-271, 945-411, 945-276, A945-1008, 945-291

A call to publish—or be published

Despite near universal agreement that reporting biases are harmful, efforts to correct the problem have largely focused on forward looking initiatives. Prospective registration of trials has made major strides in ensuring that the biomedical community is aware of trials at their inception, but at best only around half of registered trials on ClinicalTrials.gov were registered before they began enrolling patients.[16] Recent studies have also shown that even when disclosure of study findings is mandated by law, results often remain invisible.[17-19] In addition, trial registration does not address the problems of invisibility and distortion for trials that took place before registers were widely used. Most importantly, those demanding correcting action lacked the data required to actually correct the scientific record. However, with increasing amounts of data entering the public domain, it is now becoming possible to move from words to action and publish (or republish) abandoned trials.

We have access to around 178 000 pages of previously confidential company research documents (table 1 and box 1 on bmj.com). For drugs such as paroxetine, quetiapine, and gabapentin, litigation over illegal off-label marketing put thousands of pages of trial reports in the public domain. Other trial reports, such as for oseltamivir and clopidogrel, were obtained through new freedom of information policies at the European Medicines Agency (EMA) that have revolutionised the public's ability to access trial data.[20-23] The documents are a substantial resource of information about trials. We expect that other independent groups will also have access to many additional trial reports.

The documents we have obtained include trial reports for studies that remain unpublished years after completion (such as Roche's study M76001, the largest treatment trial of oseltamivir, and Pfizer's study A945-1008, the largest trial of gabapentin for painful diabetic neuropathy). We also have thousands of pages of clinical study reports associated with trials that have been published in scientific journals but shown to contain inaccuracies, such as Roche's oseltamivir study WV15671, GlaxoSmithKline's paroxetine study 329, and Pfizer's gabapentin study 945-291.[3 12 24 25] We consider these to be examples of abandoned trials: either unpublished trials for which sponsors are no longer actively working to publish or published trials that are documented as misreported but for which authors do not correct the record using established means such as a correction or retraction (which is an abandonment of responsibility) (box 1, bmj.com).[25] Because abandonment can lead to false conclusions about effectiveness and safety, we believe that it should be tackled through independent publication and republication of trials.

A call to action

We call on institutions that funded and investigators who conducted abandoned trials to publish (in the case of unpublished trials) or formally correct or republish (in the case of misreported trials) their studies within the next year. This should allow sufficient time for manuscript preparation, peer review, and publication. We will email a copy of this article to manufacturers of trials listed in table 1 (on bmj.com), asking them to signal their intent to publish by sending an electronic response to the article within 30

days. We propose that if anyone who declares an intention to publish or correct does not do so within one year, all available data for such trials should be considered "public access data" that others are allowed to publish.

We are committed to seeing the findings from abandoned trials published and describe here a minimum set of criteria for responsible publication and republication of abandoned studies (box 2). We call this concept restoring invisible and abandoned trials (RIAT). As the concept develops, interested individuals and organisations will ideally work together to develop detailed policies aimed at improving trial publication practices. We see RIAT as a collaborative, global effort, and over the next year we hope to discuss and debate our proposal at appropriate venues.

The concept of publishing trials that we neither participated in, nor paid for, is an extension of what, in certain cases, we currently have in place: public use of epidemiological and clinical trial datasets from government sources[30 31] and public access to summary trial results on ClinicalTrials.gov.[32] Thus the scientific community has already accepted that investigators not associated with the original trial will produce and publish additional or confirmatory analyses. Furthermore, there are precedents for both publishing unpublished studies and republishing distorted studies. Examples include the description of design and findings from unpublished studies on the effects of nicotine on hypothalamic functions by using previously confidential (but now publicly available) company documents,[33 34] and reports of case studies derived from the clinical observations of neurosurgeon Harvey Cushing.[35] More recently, an investigator unconnected to Amgen's epoetin alfa study 930107 republished this trial, documenting serious distortions in the original publication.[36 37]

Box 2 | Proposal for restoring invisible and abandoned trials (RIAT)

1. Obtain clinical study reports and any other study data

2. Collect documentation of trial abandonment

For unpublished trials—No primary publication detected by systematic search of the literature and/or confirmation from original trial sponsor or current responsible party that no publication exists

For misreported trials—Evidence of misreporting (ideally, published letters or other articles in the scientific literature or documentation of communication with the original trial publication author(s) detailing the misreporting) and a failure to correct the scientific record.

3. Issue a "call to action" by publicly registering your possession of data sufficient for publication

At least initially, this should be by an electronic response to this article and should include, as a minimum, trial identifiers, number of participants, date completed, publication status, pages in your holding, and level of access to trial data. This declaration offers original sponsors and trialists an opportunity to publish or formally correct their studies within the next 365 days. Send a copy of the rapid response by email to trial sponsors (and authors, for published trials), requesting confirmation of receipt.

4. Collect documentation of the need for restoration

Save time stamped copies of all rapid responses to this article (or other relevant websites) to document the time elapsed and consequent need for third party restoration.

5. Presubmission inquiry to RIAT friendly journal

Present editors with documentation from steps 1 to 4 and seek confirmation of editors' interest.

6. Prepare and submit manuscript according to RIAT procedures

- Include explanation (with references) in the Introduction of why this trial is being restored
- Provide auditable record of decisions (use RIATAR template), documenting which parts of the clinical study report (page number and paragraph) were used
- Report analyses specified in protocol
- Denote any analyses that were not prespecified
- Make all underlying data available electronically

Publishing trials, credibly

The major factor that makes publication of invisible and abandoned trials possible is the existence of clinical study reports (CSRs), documents produced by the pharmaceutical industry that include an unabridged and detailed summary of the planning, conduct, and results of a clinical trial.[38] The reports are rigidly structured according to guidelines that industry and regulators agreed to in 1995 (box 3, bmj.com) and are almost always hundreds, if not thousands, of pages long. Manufacturers submit clinical study reports to the US Food and Drug Administration as part of applications for new drugs. In addition, the FDA typically also requires submission of the protocol and individual participant data. The European Medicines Agency does not routinely request individual participant data or clinical study reports.[39] Although clinical study reports may be unfamiliar to the academic world, and in our experience are typically not produced for trials sponsored by non-commercial funders, when those in industry or the FDA want to know what occurred in an industry sponsored trial, they may refer to a clinical study report. When industry statisticians wish to carry out further analyses of the data, they can turn to their database of individual participant data. The rest of us, however—doctors, medical and public health researchers, patients, and non-regulatory government agencies including many health technology assessment groups—are left with only what is in the public domain (usually at best, synopses of the trials in the form of journal articles) (figure).

Although by definition no journal publication exists for "unpublished trials," clinical study reports for industry funded trials often do exist for these unpublished trials, but they have been traditionally treated as secret.[48 49] However, litigation and new freedom of information rules in Europe have helped many clinical study reports to emerge in the public domain, thereby making the restorative authorship possible. In addition, some drug companies have recently pledged to release their reports.[50 51] Not all of the clinical study reports and other materials we have obtained are complete. However, many contain sufficient detail to form a comprehensive understanding of the trials and would enable someone to produce a journal length manuscript for publication.

We believe it is important to publish unpublished and other abandoned studies, even though they will at best represent a brief synopsis of all the publicly available data. This is because we live in a research and practice environment based on publications, and unpublished trials remain largely invisible. There is still no PubMed-like indexing system for unpublished clinical study reports. Moreover, most researchers will not have the time to sift through hundreds or thousands of pages to understand what occurred in a single clinical trial. We therefore need a shorthand representation, and the best we know of is journal publication.

To avoid a continuation of journal papers with selective reporting, we propose that trial publications adhere to reporting standards that ensure accountability. With a compression factor in some cases well above 1000:1 (table 2 on bmj.com), summarising a clinical study report into a journal length manuscript inevitably requires value judgments about which information to include. These decisions should be transparent so that any bias can be identified and discussed. Responsible restorative authorship requires those publishing articles to also make the underlying trial data available simultaneously as an electronic appendix. In addition, there should be public access to an auditable record that documents which parts of the clinical study report (page numbers and paragraphs) were incorporated into the new publication, to help make restorative authors' value judgments about what to include in the summary explicit and transparent. We have designed the RIAT audit record (RIATAR), a tool to ensure this is done systematically, based on the CONSORT checklist for reporting randomised trials (see web appendix).[52]

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Providing public access to both source documents and an audit record gives readers a quick way to find (and cross check) the relevant and more detailed information within the original clinical study report. We think that it should apply to all trials published, irrespective of authorship, and follows on from previous calls by journal editors for improved research reporting standards.[53-57] It would enable independent verification of the accuracy of journal publications and permit better evidence synthesis and other forms of research.[49 58]

RIAT reports should also provide the context for the study to help the readers understand why the trial is being restored. This means including references to any previous publications of the trial and to details and evidence of the trial's abandonment. RIAT analyses should follow the analyses specified in the protocol (including any specified in amendments). Any other analyses are discouraged, but if done must be clearly noted as exploratory and not prespecified. At the same time, RIAT authors may wish to critically appraise the trials they report. This can be useful, but the critique should be clearly identifiable and placed in the discussion section.

Important details are still to be worked out (box 4 (bmj.com) lists some of them), and we welcome discussion on how to get it right.

Potentially controversial aspects of our proposal

The idea of restorative writing may be seen as taking on responsibility and credit for other people's actions, regardless of the trial's sponsor, but it takes on a slightly different cast when trials are funded by commercial sponsors rather than public money. Some people may think that publications based on clinical study reports with which the authors have no connection is equivalent to intellectual property theft, but you cannot steal what is already in the public domain (and only in the public domain because a drug regulator or judge had the documents unconditionally released or the sponsor waived their confidentiality claims over the documents). The considerable discussion about the need for public access to trial data and data ownership has not yet resolved how to handle the thorny but important question of proper scientific credit.[59-61] RIAT authorship will not usurp proper credit for a trial. Rather, it will show how problematic the concepts of authorship and results reporting are in the modern clinical trial. RIAT authors would be able to claim credit for bringing to light what was previously invisible or distorted but not for carrying out the trial.

In the case of the Roche sponsored oseltamivir trials, we have so far identified nine different layers of responsibility, perhaps partially overlapping: those who designed the trial, those who sponsored it, those who conducted it, those who analysed the data, those who wrote or assembled the clinical study report, those who decided the publication policy, those who decided which

parts to publish (and in some cases not to publish), those who presented results at meetings or conferences, and, lastly, those who put their names to the published manuscript. None of these roles has a clear thread of accountability and authors of the published trials have confirmed that they did not have access to the underlying study data.[45 62] In sum, in the context of the modern clinical trial research enterprise, the traditional journal article publication model obscures responsibility more than it illuminates.

Is restorative writing fundamentally different from professional medical writing and "ghost writing"? One important difference is that hired medical writers are paid for their services by those who stand to gain from the publication and restorative authors are not. Restorative authors are also likely to have access to more detailed trial records than medical writers. Another difference is that medical writers are often instructed to insert "key messages" in publication ready manuscripts.[11 63] Finally, medical writers are often unacknowledged in the publication and so are not accorded any responsibility for the work they produce. By contrast, RIAT authors will take full responsibility for publishing abandoned studies, although we will refer to RIAT to make it clear that the article is a work of restoration, not primary authorship. We are also contemplating how best to document RIAT authorship in our CVs: at a minimum, such publications need to be listed under a separate heading, identifying them as such.

Recently, a group of drug manufacturers and medical journal editors published "ten recommendations for closing the credibility gap in reporting industry-sponsored clinical research," aimed at eliminating reporting biases.[64] Their recommendations do not go far enough to address the problems. They do not mention publishing abandoned trials and ignore responsibility for correcting reporting biases persisting in existing trial publications. Furthermore, their recommendation to "make public all data" refers to publication of journal article length manuscripts rather than the full clinical study reports, individual participant data, investigators' brochures, case report forms, and many other of the semi-secret documents that would help people to understand a trial and its place in the research or regulatory approval programme—meaning the published results would have to be taken on trust without the possibility of verification.

Will the publication of detailed clinical study reports enable subsequent ill intentioned or otherwise misleading analyses by others (such as spurious findings from data dredging)? We challenge readers to provide an example of open clinical trial data sharing that has led to major public health harm. If RIAT evokes the spectre of data mining, it is important to remember that we currently have no way to judge the fidelity of the process of synthesising thousands of pages of a clinical study report into a journal publication. RIAT publication is important even for poorly conducted or unethical studies that many editors may not feel merit publication. Without public documentation that a trial was poorly done, researchers will be left guessing about the value of the study. A very brief trial report (without results if they would be misleading) may suffice.

Finally, some people may argue that RIAT republication of a misreported study is muddying the published record for dubious gain, especially with older trials. We believe that correcting the scientific record is preferable to ignoring inaccuracies. If the accompanying data support what is reported in the RIAT republication, doubts about which publication is correct should not be a problem.

Call for restorative authors and participating journals

The data we have obtained (table 1 on bmj.com) relate to only a small fraction of the masses of abandoned clinical trials. We call on others to join us, to contribute trial documents they have obtained from public sources that need publishing or republishing, and to help us with the writing. We need volunteers to act in place of those who should have but did not make trial reports visible and accessible.

Litigation and freedom of information promise to usher increasing amounts of clinical trial documents into the public domain. This reality necessitates an urgent discussion about what constitutes this new public commons and how it should function. Should there be a central repository for once secret trial documents and, if so, who should or can responsibly house, index, and maintain a public database of documents that span regulatory and legal boundaries? The tens of millions of pages of internal tobacco industry documents released in 1998 illustrate the enormity and importance of rising to the challenge.[65]

We challenge readers to provide an example of open clinical trial data sharing that has led to major public health harm

Endorsement of the concept of restorative authorship by medical journal editors will help the effort to complete and correct the scientific record. Journals can signal their willingness to accept RIAT publications by including details in their "instructions for authors." We suggest that journals ask restorative authors to provide documentation of a trial's status as abandoned; the provenance of data on which the RIAT publication is written (to ensure it is in the public domain), and to agree to submit the clinical study report and all other data used to write the manuscript as well as an audit record documenting what data were used. We suggest that to reduce wasted time on behalf of both authors and editors, authors submit a presubmission inquiry to discuss their case.

Our declaration to publish will be the first step towards public and open debate on an issue that affects everyone and has for too long been the preserve of people acting behind closed doors.

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References are in the version on bmj.com.
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● EDITORIAL, p 7, RESEARCH, p 12