



abstract Journal publications of randomised controlled trials (“literature”) have so far formed the basis for evidence of the effects of pharmaceuticals and biologics. In the last decade, progressively accumulating evidence has shown that literature is affected by reporting bias with evident implications for the reliability of any decision based on literature or its derivatives such as research synthesis. Instead of trying to reform the fields of research, industry, government, regulation and publishing, I propose basing public health decisions and reimbursement of any important intervention on independent trials and studies following the model pioneered by the Mario Negri Institute of Pharmacological Research.

Facing the unreliability of clinical trials literature

TOM JEFFERSON
Honorary Research Fellow
Centre for Evidence Based Medicine, Oxford OX2 6GG

Introduction

The ISDB General Assembly organisers asked me to write some reflections after my presentation, when I discussed the RIAT declaration, of which I am co-author. RIAT stands for Restoring Invisible and Abandoned Trials: a call for people to publish the findings.¹ RIAT is an initiative that had almost gone unnoticed, although backed by some powerful sponsors (Box 1) until the restoration of GSK's paroxetine trial 329 was published.²

The basic concept of RIAT involves the restoration of clinical trials hitherto abandoned by sponsors and authors or suspected of being distorted. Abandonment and restoration are elegant terms to indicate that the trials either remain invisible, sometimes decades after completion (Figure 1), or are journal-published but suspected or known to have been biased in their reporting. The RIAT procedures include serving notice on sponsors and authors of the original trial that there is a group of researchers who are interested in restoring the trial and have evidence of its abandonment or distortion. The message is simple: "do it, or we will do it for you".

As the RIAT conceptual and procedural aspects are publicly available and are now becoming better-known,^{1,2} I have concentrated in this article on the context which made RIAT possible and will analyse its implications for the evolving evidence paradigm.

Contemporary context

RIAT came about from the increasing realisation of the shortcomings of contemporary clinical trial journal publications (henceforth "literature").

Since the beginning of the millennium, there has been rapid accumulation of evidence on the unreliability of literature on pharmaceuticals, biologics and medical devices. This is slowly leading to a rethink of the value of considering literature as "evidence".³⁻⁶ The work was made possible by a series of connected events. I will mention what I think are the main factors, but a good chronology of the evolution of our understanding and the efforts to address the situation is available.⁷

The first factor was the gradual discovery that sources of evidence considered to be reliable in the past (such as trial registers and literature) were affected by reporting bias.⁸⁻¹⁰ Reporting bias is the systematic selection of information and data reported in literature on the basis of unclear criteria. Reporting bias includes the well-documented

Box 1. RIAT-friendly journals.

- BMJ
- PLOS Medicine
- Antivir Ther
- Cephalalgia
- Circulation
- Clinical Diabetes
- Diabetes
- Diabetes Care
- Diabetes Spectrum
- Headache
- J Affect Disord
- J Infect
- JAMA
- JAMA Internal Medicine
- Journal of the American Medical Directors Association (JAMDA)
- Lancet
- Pediatrics
- PLOS ONE
- Trials
- Journal of Negative Results in BioMedicine

publication bias¹¹⁻¹⁵ and other, more insidious forms of bias.⁹ Trials have not been registered,^{4,16,17} or the registry entries for some of those that have been registered are not updated^{17,18} or have been changed without explanation.^{18,19}

Reporting bias includes trials (and their meta-analyses) with conclusions and take home messages exceeding the evidence presented,²⁰⁻²² reporting only selected outcomes,²³ and ignoring or misreporting harms.^{8,24-27} This can lead to inflated positive findings (sometimes based on surrogate outcomes, such as antibody responses) grabbing the headlines.²⁸ In some specific topic areas the literature is dominated by a small number of authors whose output is in direct relation with their standing with a pharmaceutical sponsor.^{29,30}

Reporting bias is present consistently across topics and disciplines,³¹⁻³⁵ both for drugs and non-pharmacological interventions.^{36,37}

The second factor was the obstinacy of the Nordic Cochrane Centre who, by appealing to the European Ombudsman, forced the regulator European Medicines Agency (EMA) to lift the veil of secrecy surrounding the documents used as evidence to make decision on pharmaceuticals.³⁸

The trial reports (called clinical study reports or CSRs) that have become available from EMA since 2010 (and the few released before 2010 through litigation) form the basis of the comparison between published evidence and evidence submitted to regulators. These comparisons

Figure 1. The RIAT iceberg of visible and invisible trials and their components (from Doshi 2013).⁴¹



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.

have so far shown important discrepancies.^{4,39,40} CSRs are very detailed and very long documents including the "core report", the trial protocol, its amendments and analyses plans and provide an exhaustive record of the trial, its design development and its bureaucracy.⁴¹ The structure of the core report is similar to a journal article with a synopsis, introduction, methods, results and discussion but it is hundreds of pages long.

The sheer size of CSRs means that whoever is writing a manuscript of a trial for journal submission must synthesize thousands of pages' worth of information into very few pages. We called this the compression factor: the highest we could calculate was 8805, meaning data in over 95,000 pages for the clopidogrel study, CAPRIE, were condensed into an 11 page journal article.^{41,42}

With compression, the choice of what goes into the submission, and most importantly what is left out, is made by unknown people. The rationale and judgement that go into compression are unknown variables, representing a likely but inscrutable source of reporting bias.

Literature (and register entries) do not fare well for completeness, relevance and reliability even compared with publicly available regulator's reviews, which are a critique of and not supposed to be a full description of studies.⁴³

The third connected factor is the growing body of evidence of the fragility of editorial quality control mechanisms in biomedicine and their easy exploitation for commercial purposes in the dangerous symbiosis between publishing and the pharmaceutical industry.⁴⁴

While nobody is certain how many journals there are, biomedical publishing is big business in the hands of very few publishers.⁴⁵ Some journals derive up to 40% of their income from the reprint business⁴⁶ and spin offs such as conferences and sales of training aids in the face of a decline in subscriptions.⁴⁷ In 2008 Drazen, Editor in Chief of the New England Journal of Medicine, reported to the journal's owners that "The results in recruitment advertising and bulk reprints were outstanding this year; they went a long way to offset declines in print-based revenue that all publishers are experiencing".⁴⁸

Editorial peer review, the vaunted process to assess the quality of a submission is a requirement for journal indexing in the main databases, but has never been tested fairly and its objectives and outcomes remain unclear.⁴⁹⁻⁵¹ Short training packages for peer reviewers have a very small impact.⁵²

Ghost writing, ghost management, guessting, plagiarism and fraud are of unknown prevalence in literature but the impact of even a few cases has been devastating for its credibility.⁵³⁻⁵⁷ Literature has become a dangerous environment with a proliferation of [predatory publishers](#) and agencies offering placements for researchers' articles on a fee basis, [so-called article brokering](#).

RIAT focuses on restoring the published record, as it recognises that literature is still the basis for evidence. However, in an environment in which science and commerce blur and with such inadequate quality control tools, it is not surprising that some are beginning to question the very basis of the concept of "evidence" as the basis for the EBM paradigm for decision-making.^{1,4,6}

I will argue that the fruits of the recent transparency drive are at best temporary, and that because of the fundamental difference in aims and perspectives between industry and public health research, we need a longer term solution in which public support for important interventions is tied to availability of independently designed and executed, accessible and reproducible research.

Using regulatory documents as evidence

Clinical study reports and other regulatory documents provide an alternative evidence source to address the biases of contemporary literature. Regulators' comments are contained in publicly accessible EMA European Public Assessment Reports – EPARs and FDA Drug Approval Packages – DAPs. Clinical study reports allow full exploration of the history and design development of a trial, from protocol to completion and cross-referencing all the different components (also see the RIAT declaration for a nomenclature and content of clinical study reports).¹

Parts of a manufacturer's submission (such as the so-called Module 2.5 or Clinical Overview), form the container and context for clinical study reports of the trial

The basis of the "E" in Evidence Based Medicine mostly consists of randomised trials published in journals.

Increasing proof of the unreliability of published trials and a move to liberalise access to regulatory reports has led to calls for the use of regulatory data for clinical decision-making.

Regulatory documents provide a far more detailed and auditable record of clinical trials but their scope is limited to pharmaceuticals and their market access process.

supporting the submission and provide a detailed overview of the trials in the evidence development programme. For a systematic reviewer, Module 2.5 is possibly the most important part as it provides a complete and accurate overview of all trials, planned, underway or completed. Module 2.5 includes details of trials that may have not been registered (and sometimes not published) and allows instant identification of trials on sponsors' websites and registers as a coherent whole. If you have access to such a document, a literature search becomes redundant.

In some cases EMA will be making available pooled or meta-analysed effectiveness and safety data used to support a Marketing Authorisation Application (MAA) in integrated summaries of effectiveness and safety (ISE and ISS) (see Table 1 for an overview).

Table 1. Typology of regulatory documents and their availability.

Item	Acronym	Length (pages)	Content	Source
Clinical Study Reports	CSR	1000s	Core report, protocol, amendments, Statistical Analysis Plan (SAP), listings, consent form, blank case report forms	EMA**
Integrated Summary of Effectiveness or Safety	ISE ISS	100s?	Pooled or meta-analysed summaries of data	EMA*
Drug Approval Packages	DAP	100s	Reviewers' reports and correspondence	FDA
European Public Assessment Reports	EPAR	10s	Summary of Committee for Medicinal Products for Human Use conclusions	EMA
Common Technical Document	CTD	100s	Overviews (Modules 2.5 & 2.7)	EMA**

(*) Available prospectively from mid-2016 (under EMA policy 0070).

(**) Available now retrospectively on application (under EMA policy 0043) and prospectively from mid-2016 (under EMA policy 0070).

In brief, regulatory documents are probably far more reliable than currently accessible other sources. Our Cochrane review on Neuraminidase Inhibitors, which included only regulatory material and ignored any published trial data proved this is a feasible, if somewhat complex, undertaking.

This was especially so for a team at their first experience of handling and synthesising huge regulatory documents.²⁴ DAPs provided early important background information for the review and their content included in the review. Clinical study reports and portions of submission Modules have been available on request from EMA since 2010 and from mid-2016 will be available on the EMA website without need for a request.⁵⁸

Availability of regulatory documents probably provides an alternative to any pharmaceutical trial publication as a basis for research and decision-making and should enhance reproducibility. This represents an evidence paradigm shift. Pioneering editors are making availability of data a prerequisite for trial publication in their journals but it is not practical to ask unpaid peer reviewers, no matter how dedicated, to assess huge alien clinical study reports especially in the short timeframe required by editorial systems.

In addition, compression into a few pages persists as a problem although in this case readers have the possibility of comparing source with article, an unlikely event outside a formal study setting.

The laboriousness of obtaining clinical study reports and their complexity are possible reasons why up to now they have not been included in research synthesis and interest in their use is muted.⁵⁹ In addition, most tools commonly used in synthesis (such as the Cochrane Risk of Bias tool) need adaptation for use on regulatory material and reviewing methods and practices need changing.⁶⁰

At a first glance, EPARs and DAPs could provide a simpler alternative. They are publicly available, shorter and easier

to read. FDA medical officers' reports provide an authoritative appraisal of the manufacturer's submission and even report re-analysis of trial data conducted by FDA on a limited set of trials in the programme.

However they are reviews of something that is invisible, as the FDA do not release clinical study reports and their standalone use in research synthesis is conceptually the same as conducting a systematic review of clinical trials based only on journal peer reviewers' reports. Exclusive use of DAPs contravenes the basic rules of research synthesis, as it does not allow first hand appraisal of trial methods.

There are other severe limitations to the long-term use of regulatory documents for research synthesis and decision-making; they are only available at present for compounds on which EMA has reached a decision, but are not available for those that have not been through the EMA procedure and are not available for non-pharmaceuticals.

Finally, pharmaceutical trials are carried out to register and market products, not to answer public health questions or to help manage health systems. The design and reporting of pharmaceutical trials is influenced by commercial factors, their populations are usually selected and comparators are often of questionable clinical significance. Access to regulatory documents and their use for decision-making is not going to change any of this. It is, at best, a temporary improvement.

Good Pharma

In a world of rapidly escalating healthcare costs, we still need a long-term solution to produce solid research relevant to everyday care. Access to regulatory documents will not provide such a solution. A good summary of the crisis brought about by use of commercially generated evidence is provided by the much-studied field of oncology drugs.⁶¹

The costs of new oncology drugs and biologicals are so high that oncologists have coined the term “financial toxicity”. This is a proposed grim but realistic system to grade the impact of privately acquiring such new drugs. The grades go from 1 (change of lifestyle and cessation of holidays) to 4 (personal bankruptcy and contemplation of suicide).⁶²

However, evidence of benefits of new oncology drugs is not overwhelming, unlike their impact on oncology departmental budgets.⁶³ Society must contrast the slide into “promissory medicine” and its potentially dangerous regulatory counterpart adaptive licensing (AL).

Promissory medicine is a term I have adapted from the seminal work of Davis and Abraham who coined the phrase “promissory science”.^{64,65} The concept of promissory medicine is based on the assumption that early marketing of new drugs (which are usually more costly than existing ones) is beneficial to users (See Box 2).

To open the door to early marketing, regulators have proposed AL as layered licensing levels leading to market access and then accrual of post-market evidence to build a body of evidence upon which to make further decisions.

In 2012 adaptive licensing (AL) was defined as “a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made”.⁶⁶

Other possible benefits of AL are the containing of off label use and greater reliance on observational evidence, which is supposed to reflect the reality at point of delivery more closely than trials.

Given the potential for changing regulation and clinical medicine, what evidence is there that the assumptions behind AL are correct? Not much. A Cochrane review found that just over half of new treatment can be expected to be better than existing treatments and these conclusions are only valid for publicly funded trials with few or no commercial incentives.⁶⁷

In 2011 the French independent drug bulletin *Prescrire* rated 58/97 (60%) of new drugs or indications introduced in 2010 as providing “nothing new” or “unacceptable”.⁶⁸ In 2013 out of 90 rated products, the proportions were similar.

This fits with evidence from a review of the increasing trends of expedited development and registration of new drugs by the FDA in the last two decades. The authors observe that: “Though expedited programs should be

Health systems should reimburse those important interventions for which independently generated evidence accessible is available.

The 50-year old Mario Negri Pharmacological Research Institute model shows that this is feasible.

strictly limited to drugs providing noticeable clinical advances, this trend is being driven by drugs that are not first in class and thus potentially less innovative”.⁷⁰

Most of the other assumptions are wrong or simply not proven. There is good evidence of the reluctance or tardiness of regulators to re-visit bad decisions,⁶⁵ of holding trial sponsors to their post-marketing commitments⁷¹ and of acting in cases of research misconduct identified during site inspections.⁷² Perhaps the most bizarre in this list of regulatory failings is the lack of policing of the US Federal law of 2007 requiring full disclosure of results within 12 months of trial completion.

Box 2. The evidence-free principles of promissory medicine .

- 1 New drugs are more effective and safer than existing ones [Corollary: new=innovative]
- 2 Whatever their price, new drugs are more cost-effective than existing ones
- 3 Patients who have been on new fast drug X are going to be happy to switch back to old drug Y if X fails regulatory or post-market hurdles.
- 4 Physicians are neutral in their approach.
- 5 Early market entry (whether with rapid procedures or with the proposed adaptive licensing - like routes) is beneficial to society
- 6 Current or proposed mechanisms for market and post market regulation are up to making such decisions
- 7 Current or proposed mechanisms for market and post market regulation are up to reversing or limiting initial bad decisions
- 8 Our information systems can support the process with unbiased (or minimally biased) up to date information.

Table 2. Pharmaceutical vs pharmacological research in the Mario Negri model (Table adapted from Light and Maturro 2015).⁶⁵

Pharmaceutical research maximizes patents & profits (The Big Pharma Model)	Pharmacological research maximizes health of individuals and populations (The Mario Negri Public Health Model)
Goal is to maximize number of new patented products and profits from them in government protected markets. clinical benefits to patients or populations secondary.	Goal is to develop clinically beneficial new ways to address health problems of patients or populations without considering their profitability.
Consider no promising agent that cannot be patented.	Consider all possibly helpful agents, regardless of patentability – past breakthroughs, ingredients in nature, traditional cures –.
Research directed by executives to maximize profits. Less profitable projects or teams or whole disease areas are not funded, or abandoned when profit projections fall. Priorities shift as markets or priorities shift.	Research self-directed by researchers, supported by brain-storming with colleagues.
Research funded out of high profits from protected prices as an investment in future profits. Patent everything.	Research paid in classic ways – grants, contracts – by a range of public & private funders. No patenting
Short-term research focused on patentable minor drug variations. Little basic research.	Relentless pursuit for years or decades to figure out how to solve a clinical problem.
“Innovation” measured by new molecules, best in class, or first in class, even if clinically no better or worse.	“Innovation” measured by improved clinical or population health status or reduced suffering.
Closed-science secrecy. guard info on projects, progress, failures, successes, budgets, patenting strategies, to ward off competitors and poachers. Closely manage disclosures. sculpt research findings.	Open-science transparency, sharing, network-building. Publish all results and learn from failures. Share new solutions, methods, strategies to find effective interventions.
Ghost management or ghost writing of publications. distorts medical knowledge.	All results published. Researchers write their own papers and publications.
Develop slightly different new drugs for large-profit conditions already treated. occasional superior meds occur.	Focus on finding clinically superior drugs for serious, often untreated medical conditions.
Trials designed to minimize evidence of harms & maximize evidence of benefits in artificial populations that are likely to exclude those whomight experience adverse reactions and include those likely to have a positive reaction. Often exclude elderly, women and people with co-morbidities.	Trials designed to test clinical outcomes on the populations that will take the medicine. Test for superiority over current treatments, regardless of patent status. Include the natural diversity of the practice population.
Trials undertaken and designed to generate better market information and recruit doctors. Very costly, measure everything to find something.	Trials undertaken only after careful review of what is known and careful work to identify a strong end point. Clean, simple & cheap, about 1/10th the cost per patient.
Trials pay doctors and patients so well that doing or being in them is a profit stream. distorts design, data, and results.	Patients volunteer for no pay, doctors for no or modest pay for their time. Trials part of a national health care system.
Goal to maximize the number of people on as many patented drugs as possible, with few benefits to offset risks of harm. Costs to taxpayers & others about US\$1 trillion.	Goal to maximize the number of superior drugs, at low prices, while minimizing drug consumption. Would cost taxpayers & others 1/5th as much.

Competing interests: TJ was a co-recipient of a UK National Institute for Health Research grant (HTA – 10/80/01 Update and amalgamation of two [Cochrane Reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children](#)).

TJ receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. TJ is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013, TJ acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu [Roche] and in a labour case on influenza vaccines in healthcare workers in Canada. In 1997-99 TJ acted as a consultant for Roche, in 2001-2 for GSK, and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral, which did not get approval from the Food and Drug Administration). TJ was a consultant for IMS Health in 2013, and in 2014 was retained as a scientific adviser to a legal team acting on the drug Tamiflu (oseltamivir, Roche). In 2014-15 TJ was a member of two advisory boards for Boehringer and is in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ has a potential financial conflict of interest in the investigation of the drug oseltamivir. TJ is acting as an expert witness in a legal case involving the drug oseltamivir (Roche). TJ is a member of an Independent Data Monitoring Committee for a Sanofi Pasteur clinical trial

Apart from the ethical aspects of not reporting data of experiments on humans, failure to impose the law results in a considerable loss of federal income.^{73,74}

A systematic review of withdrawals of modern pharmaceuticals reports a delay of 1-2 years after the first attributable deaths were reported.⁷⁵ Although the authors did not calculate the death burden attributable to regulators' tardiness, the findings contradict the public acceptability of AL and promissory medicine.

Donald Light and Antonio Maturo provide what seems a well-tested alternative solution in their book *Good Pharma*.⁶⁵ *Good Pharma* tells the story from 1961 to present of the origins and development of the Istituto di Ricerche Farmacologiche Mario Negri, named after its endower, a Milanese jeweller-philanthropist.

The Mario Negri Institute for Pharmacological Research has a distinctive model of trial conception and delivery. The corner stones are open science (no patenting of compounds in development and data sharing), nesting trial questions and design in an up-to-date systematic review of the topic, clinically oriented study questions and absence of surrogate outcomes of unclear link to the hard outcome.

Table 2 compares the industry and Mario Negri models, which Light and Maturo call pharmaceutical and pharmacological respectively. What is striking about the comparison is the complete difference in aims and consequent viewpoints and implementation of the two concepts.

This difference undermines attempts at criticising the pharmaceutical industry's behaviour along ethical lines (except of course in cases of fraud and misconduct). The aims of industry and healthcare are simply fundamentally different and not reconcilable. Light and Maturo remind us that promissory medicine is based on serious risk management, whereas regulation was introduced in the 1960s to minimise such a risk appearing in the first place.

As a physician, I do not understand brinkmanship with other people's lives in search for what is often a minimal benefit. *Good Pharma* is worth reading and digesting as it documents how the Negri model has produced some outstanding successes, such as the GISSI trials, and makes a strong case for viewing pharmacological research as a long-term risky investment, rather than the generator of everyday miracle breakthroughs, so lovingly portrayed by media and grant-hungry researchers.

Once the difference between the pharmaceutical and pharmacological approaches are understood, the solution to the next phase of evidence evolution is conceptually relatively simple, provided society has the will to adopt and benefit from public health research. The evidence shows that the current regime of pharmaceutical regulation and licensing with its ingrained symbiosis (each benefiting from the other) is simply not amenable to reformation or change without a complete revolution, which I believe is unlikely.

Hence, the regulatory system should carry on with ever-increasing transparency. However, publicly-funded reimbursement decisions of any important intervention used by the health services (such as pharmaceuticals, imaging, diagnostics and invasive devices from which users may derive benefit) should be based only on independently-produced and analysed robust evidence. In the EU with its publicly funded national universal healthcare coverage, this principle is coherent with Beveridge philosophy.

Several obvious objections may be raised to such a proposal. "Time to market" is an essential component of promissory medicine with its vision of swift, real benefit. Even allowing for the early commencement of public health research on promising interventions, there may be some delay in completion of trials and consequent decisions. However, Light and Maturo⁶⁵ and Davis and Abrahamson⁶⁴ again remind us that there is no evidence of societal benefit from rapid access to new interventions.

Funding of an international network of independent researchers could also be an obstacle, but as with the Mario Negri model, public and private funds in quotas could be levied to build a common pooled source of funds, thus avoiding any direct funding. Furthermore, the Negri model provides a guide on how to train and develop the minds of independent researchers. Topics for research must not be restricted to drugs and must be set publicly, not influenced by private interests.

What is certain in all this is that the paradigm for the "E" in EBM is changing, probably for the better.

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Conclusions

Trial literature is affected by reporting bias. It is probably no longer ethical to use it as a basis for evidence-based decision-making.

Although access to regulatory documents is likely to provide a short-term decrease in the impact of reporting bias, a final settlement requires reform of the fields of government and regulation, research, industry and publishing.

As this is unlikely to come about, I propose basing public health decisions and reimbursement of any important intervention on independent trials and studies following the model pioneered by the Mario Negri Institute for Pharmacological Research.

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INFORMATION AND SUSCRIPTION

Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail

farmacia.atprimaria@cfnavarra.es

Web site

www.dtb.navarra.es

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