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# Increasing value and reducing waste: addressing inaccessible research

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The methods and results of health research are documented in study protocols, full study reports (detailing all analyses), journal reports, and participant-level datasets. However, protocols, full study reports, and participant-level datasets are rarely available, and journal reports are available for only half of all studies and are plagued by selective reporting of methods and results. Furthermore, information provided in study protocols and reports varies in quality and is often incomplete. When full information about studies is inaccessible, billions of dollars in investment are wasted, bias is introduced, and research and care of patients are detrimentally affected. To help to improve this situation at a systemic level, three main actions are warranted. First, academic institutions and funders should reward investigators who fully disseminate their research protocols, reports, and participant-level datasets. Second, standards for the content of protocols and full study reports and for data sharing practices should be rigorously developed and adopted for all types of health research. Finally, journals, funders, sponsors, research ethics committees, regulators, and legislators should endorse and enforce policies supporting study registration and wide availability of journal reports, full study reports, and participant-level datasets.

### Introduction

In 2010, Alessandro Liberati explained the difficulties he encountered when he had to make decisions about his treatment for multiple myeloma: “When I had to decide whether to have a second bone-marrow transplant, I found there were four trials that might have answered my questions, but I was forced to make my decision without knowing the results because, although the trials had been completed some time before, they had not been properly published....I believe that research results must be seen as a public good that belongs to the community—especially patients.”<sup>1</sup> The benefits of health research can only be realised when the study methods and results are fully disseminated in a timely and unbiased manner.<sup>2</sup> Availability of full information about study methods enables critical appraisal, interpretation of study results, and appropriate replication. Proper reporting of results can improve clinical practice and policy, prevent unnecessary duplication, and help to inform present and future research. Availability of participant-level data enables ancillary research and independent reanalysis of study results.

Despite advances in dissemination of study information, half of health-related studies remain unreported,<sup>3</sup> and few study protocols and participant-level datasets are accessible. Inaccessibility of research is detrimental to care of patients and wastes much of the US\$240 billion annual worldwide expenditure on health research.<sup>4</sup> In this report, we document the extent and effect of non-dissemination and selective reporting of health research, and examine the options to reduce the waste and harms arising from inaccessible study information.

### Access to primary reports

A published primary report is traditionally the main way by which research is communicated to the scientific community. Because unreported studies do not contribute to knowledge, they do not provide returns on the investment of research resources or the contributions of participants. For example, only half the health-related

### Recommendations

- 1 Institutions and funders should adopt performance metrics that recognise full dissemination of research and reuse of original datasets by external researchers
  - Monitoring—assessment of the proportion of institutional and funding-agency policies that explicitly reward dissemination of study protocols, reports, and participant-level data
- 2 Investigators, funders, sponsors, regulators, research ethics committees, and journals should systematically develop and adopt standards for the content of study protocols and full study reports, and for data sharing practices
  - Monitoring—surveys of how many stakeholders adopt international standards
- 3 Funders, sponsors, regulators, research ethics committees, journals, and legislators should endorse and enforce study registration policies, wide availability of full study information, and sharing of participant-level data for all health research
  - Monitoring—assessment of the proportion of stakeholder policies that endorse dissemination activities, and the proportion of studies that are registered and reported with available protocols, full study reports, and participant-level data

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See Online for appendix

studies funded by the European Union between 1998 and 2006—an expenditure of €6 billion—led to identifiable reports.<sup>5</sup> In the case of oseltamivir, unreported phase 3 clinical trials—including the largest known trial—accounted for 60% of patient data up to 2011 (table).<sup>6</sup>

Overall, only half of completed clinical and preclinical studies are reported, and this proportion has not changed substantially in the past 30 years (appendix pp 4–9). Studies approved by research ethics committees are often not reported (n=15 cohorts; pooled publication proportion 45%, 95% CI 40–50; appendix pp 4–9). The proportion reported is also low for studies defined by funding sources, trial registries, institutions, and research groups (n=16 cohorts; 54%, 44–63; appendix pp 4–9) and for those presented as abstracts at conferences (n=264 cohorts, 40%, 37–42).<sup>7</sup>

Studies with positive or significant results are more likely to be reported than are those with negative or non-significant results.<sup>3</sup> Selective publication has been recorded for cohorts of studies tracked from time of inception, abstract presentation, and regulatory submission (figure 1). This bias exists in both clinical and preclinical research, although selective reporting of animal experiments has not been widely assessed.<sup>3,9,10</sup> Other factors are not consistently associated with reporting of studies in journals (figure 2, appendix pp 4–9).

When reported, clinical trials with positive results appear in journals about 1 year earlier than do those with results that are not positive.<sup>12</sup> Reporting of trials that show no significant effect can be delayed for several years (table), even when the findings have substantial global implications. Although widely suspected, no empirical

	Type of biased dissemination	Effects
Oseltamivir	Trials with 60% of patient data not reported Full study reports inaccessible for 29% of trials Missing modules for 16 of 17 available full study reports Discrepancies between published articles and full study reports	Billions of dollars spent worldwide (US\$3.3 billion in 2009 alone) to stockpile a drug that did not necessarily reduce hospital admissions and pulmonary complications in patients with pandemic influenza, and that had unclear harms
Rosiglitazone	Unfavourable trials and sponsor's meta-analysis not reported Increased risk of myocardial infarction confirmed by independent meta-analysis of 56 rosiglitazone trials, which included 36 unreported trials for which data were obtained from the sponsor's trial registry	Number needed to harm of 37–52 for 5 years translates into 6000–8000 additional myocardial infarctions in 325 000 patients taking rosiglitazone in the USA and UK in 2010 About 83 000 additional myocardial infarctions potentially attributable to rosiglitazone in the USA from 1999 to 2006
Gabapentin	Negative trials for off-label indications not reported or reports delayed Selective reporting of positive primary outcomes for off-label uses in published reports, with suppression of negative outcomes	In 2002, \$2.1 billion (94% of total sales) spent in the USA alone on prescriptions for off-label uses promoted by sponsor despite poor evidence of efficacy
TGN1412	Phase 1 trial that showed serious adverse effects from a similar antibody in 1994 not reported	Serious adverse effects in a study of TGN1412 in 2006, with six previously healthy volunteers admitted to hospital
Paroxetine	Selective reporting of four positive post-hoc outcomes and suppression of four negative protocol-specified outcomes in highly cited published report of a trial of children with depression Two trials and two observational extension studies showing increased harms (eg, suicidal ideation) and poor efficacy in children not reported Systematic review showed that balance between risk and benefit no longer favoured the drug when unreported trials were included	In 2002, about 900 000 prescriptions (costing \$55 million) written for children with mood disorders in the USA for a drug with potential harms and poor evidence of efficacy
Lorcainide and class I antiarrhythmic drugs	Trial done in 1980 showing increased mortality with lorcainide (nine [19%] of 48) versus placebo (one [2%] of 47) not reported Mortality risk for this class of drugs remained unknown until subsequent trials with similar findings were reported in 1989 and 1992	20 000–70 000 preventable deaths every year in the 1980s in the USA alone because of widespread use of harmful antiarrhythmic drugs
Rofecoxib	Sponsor's internal meta-analysis of two trials showing increased mortality in Alzheimer's disease not reported; 2 year delay in reporting of the results to regulators Selective exclusion of placebo-controlled trials from three reported meta-analyses done by the sponsor, showing no overall increase in cardiovascular events, by contrast with a subsequent independent meta-analysis that included all trials (made available through litigation) Selective omission of cardiovascular harms from report of arthritis trial	88 000–144 000 additional myocardial infarctions for 107 million prescriptions filled in the USA from 1999 to 2004 About 400 000 users in the UK in 2004
Celecoxib	Selective reporting of favourable 6-month harms data in trial report, with suppression of unfavourable 12–15-month data (identified via publicly accessible regulatory documents) that no longer showed benefit for reduction of gastrointestinal ulcers Discrepant reporting of cardiovascular mortality data between regulatory report and two published reports of the same trial	In 2004, 600 000 users in the UK and more than 14 million prescriptions filled in the USA for an expensive drug with questionable benefit rather than cheaper alternatives
Ezetimibe-simvastatin	Report of randomised trial showing no benefit of ezetimibe-simvastatin versus simvastatin alone delayed by 2 years	Billions of dollars spent worldwide during publication delay (\$2.8 billion in 2007) for costly combination drug not known to be better than cheaper alternatives
Vitamin A and albendazole	Report of a clinical trial of 2 million children showing no benefit of vitamin A and deworming on mortality delayed for 5 years	Millions of children dewormed (>300 million in 2009) and given vitamin A supplementation (77% of preschool children in 103 countries) on the basis of global policies although benefits were unclear

See appendix pp 1–3 for references.

**Table: Examples of selective reporting for different drugs and the estimated effects**

evidence is available that journals preferentially publish reports showing positive results rather than those with non-positive results (figure 1),<sup>3</sup> indicating that investigators do not submit reports of studies with negative results. Investigators report that little time and low priority or importance of results are their most common reasons for not reporting findings—all factors that could be related to non-significance.<sup>3</sup>

Overall, the scientific literature represents an incomplete and biased subset of research findings. Selective reporting of studies means that fully informed decisions cannot be made about care of patients,<sup>1</sup> resource allocation, prioritisation of research questions,<sup>13</sup> and study design.<sup>14</sup> This ignorance can lead to the use of ineffective or harmful interventions and to wasting of scarce health-care resources (table).<sup>15-17</sup> For example, when unreported trials were included in a meta-analysis,<sup>18</sup> reboxetine was shown to be more harmful and no more efficacious than placebo for treatment of major depression—a different finding from that when only reported trials were included (figure 3).

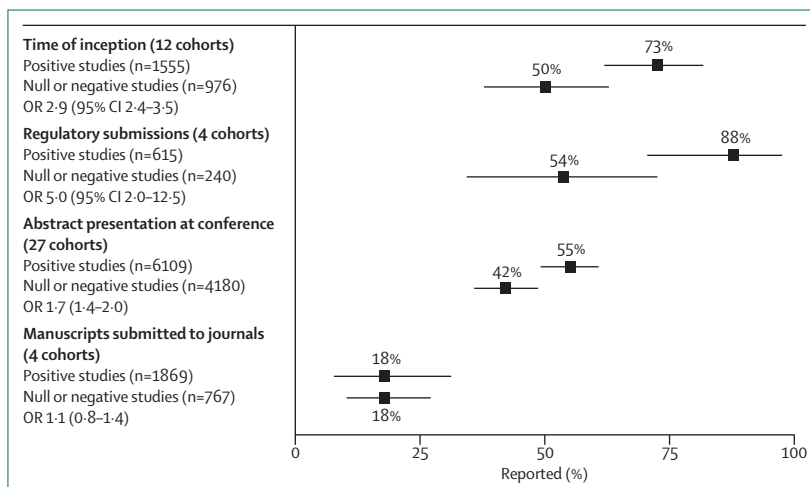
Selective reporting of positive preclinical or observational research is a potential explanation for why the reported results of only 11–25% of promising preclinical studies can be independently replicated for drug development,<sup>19,20</sup> why clinical trials often do not confirm the benefit shown in previous reports of animal or clinical studies,<sup>21,22</sup> and why many reported studies showing new epidemiological and genetic associations are subsequently refuted.<sup>23,24</sup> Inaccessible research can also lead to redundant, misguided, or potentially harmful research assessing similar interventions.

Even when studies are reported, access to research reports is restricted. Journal subscriptions are costly,<sup>25</sup> particularly in low-income settings, but even for leading private academic institutions.<sup>26,27</sup> Although the number of open-access reports has been increasing, access to 78% of reported medical research was restricted to journal subscribers in 2009.<sup>28</sup>

Language barriers are another obstacle. Most high-profile scientific journals are published in English, but much of the scientific literature is in other languages. More than 2500 biomedical journals are published in Chinese, fewer than 6% of which are indexed in Medline.<sup>29</sup> Publications in languages other than English are often excluded from systematic reviews because of inaccessibility or limited resources for translation and searching. Evidence about whether the quality and results of research differ systematically between studies reported in English versus other languages is conflicting,<sup>30,31</sup> and recent data are scarce. The impression and quality of studies reported in languages other than English is likely to be dependent on the context,<sup>30</sup> and the default exclusion of these studies from systematic reviews can lead to a substantial waste of research data.

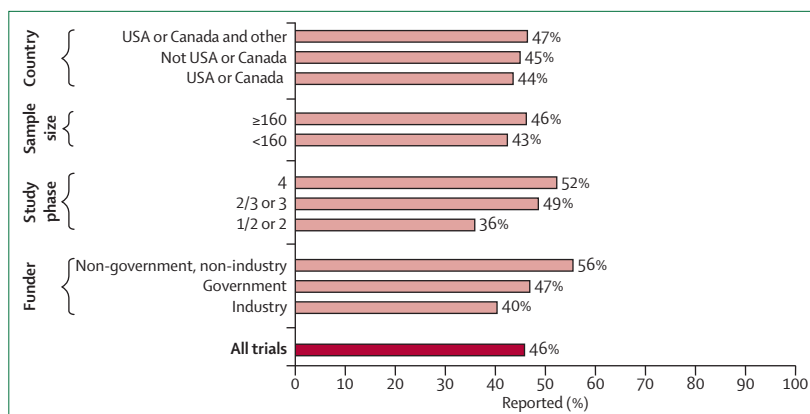
## Access to all study methods and results

Although the reporting of all studies has a major role in reductions in bias and improvements in transparency,



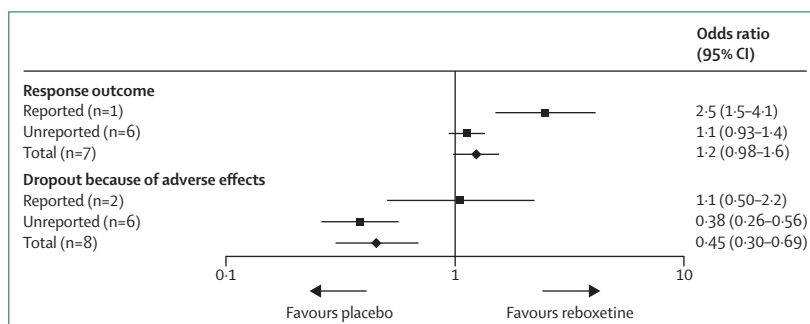
**Figure 1: Reporting of studies with positive results versus those with null or negative results tracked in cohorts from time of inception, regulatory submission, or abstract presentation, and for manuscripts submitted to journals<sup>3,8</sup>**

Horizontal bars show 95% CIs. Pooled proportions reported were estimated with the Freeman-Tukey transformation in random-effects meta-analysis. OR=pooled odds ratio.



**Figure 2: Reporting of completed trials, by study characteristic**

Data taken from Ross and colleagues' analysis<sup>14</sup> of a random sample of 677 completed trials registered with ClinicalTrials.gov between 2000 and 2007.



**Figure 3: Results of a meta-analysis of reported and unreported randomised trials of reboxetine versus placebo for acute treatment of major depression**

Data used to create this figure from Eyding et al.<sup>18</sup>

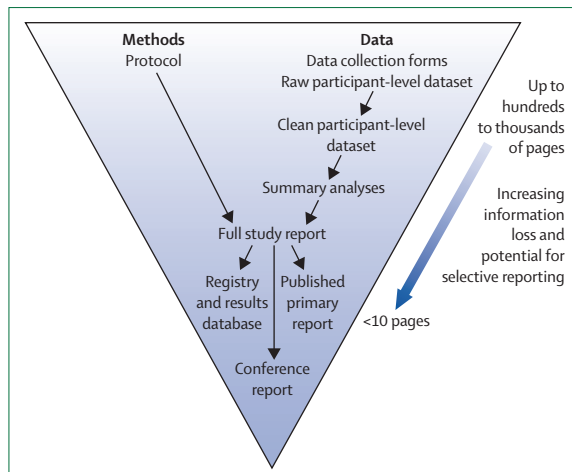


Figure 4: Key sources of information about study methods and results, with associated information loss and potential for selective reporting

journal publications alone are insufficient. Reporting of study methods and results is frequently incomplete and selective in journal articles, challenging their traditional role as the sole source of research information.<sup>32,33</sup> Produced by industry sponsors, a clinical study report is the most complete final report of study conduct and results, and contains the study protocol as an appendix.<sup>34,35</sup> Although clinical study reports are familiar to individuals involved in industry-sponsored drug or device trials, we use the general term full study report here to encompass unabridged final reports for all clinical and preclinical studies. The study protocol and full study report provide detailed information that is not included in the published primary reports.<sup>36,37</sup> They can help to clarify unclear information and identify selective reporting in primary reports, and inform clinical practice and future research. For example, eligibility criteria included in journal reports often differ from those listed in the protocol.<sup>38,39</sup> In trials done by two HIV research networks, the reported eligibility criteria implied 40% greater inclusivity when compared with the protocol-defined criteria,<sup>39</sup> meaning that journal readers could have an incorrect perception of a broader study population with greater generalisability.

Despite their importance, protocols and full study reports are generally not publicly accessible.<sup>40-42</sup> In a systematic review of oseltamivir,<sup>6</sup> discrepancies between the trial publications and full study reports prompted investigators from the Cochrane Collaboration to question the validity of the medical literature; only a subset of full study reports (with missing modules) could be obtained from the sponsor and European Medicines Agency (table).

Examination of full study reports of drug trials submitted to regulators provides insight into selective outcome reporting<sup>40,41</sup>—ie, the biased reporting of some results but not others within a published article.<sup>43</sup> Although the full study report can be thousands of pages long, this information must be compressed into a few journal pages (figure 4). The decisions about what to include in the

primary study report are rarely transparent and often lead to selective outcome reporting in journal reports of clinical trials,<sup>33</sup> systematic reviews,<sup>44</sup> and observational research.<sup>45</sup> On average, between a third and a half of efficacy outcomes are fully reported in the journal report of a randomised trial, with significant outcomes being more than twice as likely to be fully reported than non-significant ones.<sup>43,46,47</sup> Selective outcome reporting amplifies the bias arising from selective reporting of entire studies, and can have a substantial effect on the results of systematic reviews.<sup>17,48</sup> Additionally, selective outcome reporting can lead to substantial harm to patients and waste of resources (table).

Comparisons of protocols and registry records with journal reports have identified discrepancies in the definition of primary outcomes in between a third and two-thirds of reports of randomised trials and systematic reviews.<sup>33,44,49</sup> Similar issues have been noted when publications are compared with full study reports.<sup>37,50-52</sup> Frequent discrepancies have also been identified for important aspects of trial methods.<sup>33,53</sup> These changes are not transparently reported, precluding a full understanding of a trial's validity.

Critical appraisal is impaired when key methodological elements are not transparently described in a protocol,<sup>54</sup> and concerns can be raised about the quality of study design, conduct, and reporting.<sup>14</sup> If the analysis plan or primary outcome is not prespecified, investigators can select any result they wish to report. Although prespecification might not be needed for exploratory studies, the post-hoc nature of such analyses is often not transparently described in reports of clinical trials and systematic reviews.<sup>33,43,44</sup> In many randomised trial protocols, important aspects of study methods are not adequately addressed,<sup>33,54</sup> such as the primary outcomes, sample size calculations, allocation concealment mechanism, and blinding procedures. To our knowledge, the quality of study protocols for other types of clinical and preclinical research, and the quality of full study reports have not been examined.

### Access to participant-level data

Beyond the compelling rationale for dissemination of primary reports, protocols, and full study reports, sharing of participant-level data has many benefits. First, errors, selective reporting, and fraud can be identified and deterred when others can verify statistical properties and calculations using participant-level data. A substantial proportion of reported studies have statistical errors,<sup>55,56</sup> and willingness to share data has been positively correlated with methodological quality.<sup>57</sup> Reanalysis of participant-level data by independent researchers has previously raised serious questions about the validity of some high-profile reports.<sup>58,59</sup> In one case, promising results from gene expression microarray studies reported by one researcher led to the launch of three clinical trials,<sup>60</sup> but independent reanalyses did not reproduce the reported findings and identified concerns that prompted the retraction of at least ten articles.

Second, use of existing datasets to examine new questions broadens the effect of the original data and saves the costs of unnecessarily compiling new datasets.<sup>61</sup> For example, reanalysis of data from a radical prostatectomy trial showed substantial heterogeneity of treatment effect.<sup>62</sup> Additionally, reanalysis of data obtained through the US National Institutes of Health data sharing policy showed that women had significantly higher mortality with digoxin than did men.<sup>63</sup>

Third, pooled effect estimates can be calculated and more easily interpreted when the outcome definitions from the pooled studies are similar. For example, it can be difficult to combine data from trials for which absolute decreases in systolic blood pressure are reported with those from trials for which the proportion with a specific percentage reduction in blood pressure are reported. Access to participant-level data can harmonise such outcome definitions and yield more powerful meta-analyses.

Fourth, promotion of well annotated datasets would occur with sharing of participant-level data. In an empirical study,<sup>64</sup> investigators unwilling to share data often stated that doing so would be too much work, suggesting that researchers do not always develop a clean, well annotated dataset in a format that is easily understood by others. Along with enabling routine data sharing, proper annotation could help the researchers themselves to easily understand and use their datasets in the future.

Despite the benefits, participant-level data from health-related studies are rarely made available to external researchers.<sup>65</sup> Although public archiving of microarray datasets has been widely accepted, data remain unavailable for many gene expression studies.<sup>66</sup> Those of cancer or with human participants—arguably among the most valuable for their potential effect on health—are least likely to have archived data.<sup>67</sup> Additionally, investigators and sponsors too often deny requests for access to data.<sup>68</sup> In a typical study, data were made available on request for only one of 29 medical research reports.<sup>69</sup> Even when medical journals mandate data sharing, only 10–27% of authors provide their dataset on request from external academic researchers.<sup>64,70</sup>

Several practical barriers contribute to the widespread shortage of data sharing. The reality is that researchers are usually rewarded when they answer their main study questions, but are given little credit or funding for data sharing practices that in some instances can incur substantial time, effort, and costs. Additionally, no universal guidance for the practicalities of preparing datasets for reuse by others is available.

## Recommendations

### Recommendation 1

We propose three main recommendations to improve accessibility to full information from preclinical and clinical studies. First, institutions and funders should adopt performance metrics that recognise full dissemination of research. Incentives are needed to encourage investigators

to complete and submit primary reports. Rather than focusing on total numbers of published reports, reviews of academic performance should explicitly take into account the proportion of a researcher's initiated studies (eg, those receiving ethics approval or funding) that have been reported, for which protocols have been shared, and that have had their dataset reused by other researchers. Funding agencies should instruct review panels to strongly consider applicants' dissemination output from previously awarded funds. Journals can also encourage submissions by making an explicit statement that reports of studies with robust methods will be published irrespective of the magnitude or direction of their results, as done by 14 (12%) of a sample of 121 medical journals.<sup>71</sup>

To encourage data sharing, academic institutions and funders should make clear that they view dissemination of participant-level datasets and their reuse by other researchers as a metric of research impact. Efforts of the original investigators should be acknowledged in reports that arise from secondary analyses, along with citation of the datasets and the original report. In microarray research, data sharing is associated with increased citations.<sup>72</sup> Some journals now provide the opportunity to publish descriptions of datasets, producing a citable publication.<sup>73</sup>

### Recommendation 2

Investigators, funders, sponsors, regulators, research ethics committees, and journals should systematically develop and adopt standards for the content of key study documents and for data-sharing practices. Protocols and full study reports are most useful to researchers and external reviewers when they provide complete details of study methods and results. To address recorded deficiencies in protocol content, the SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials)<sup>54</sup> defines the key elements to address in the protocol of a clinical trial and the upcoming PRISMA-P statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols)<sup>74</sup> will define factors to address in the protocol of a systematic review. Protocol standards should also be systematically developed for other study designs. High-quality protocols can lead to transparency, rigorous study implementation, and efficiency of research and external review.<sup>75</sup>

Although protocols are standard for most types of studies,<sup>76–78</sup> full study reports are uncommon outside industry-sponsored trials. We encourage creation of a full study report that documents all analyses done and any modification to analysis plans and study methods. This report could serve as the basis for and, in the case of small studies with few analyses, could be the same document as the report submitted to journals.

For regulated drug trials, 1995 International Conference on Harmonisation E3 guidance outlines the key elements of a full study report.<sup>34</sup> This guidance, along with other relevant reporting guidelines for primary reports of specific study designs (eg, CONSORT, STROBE, STARD,



PRISMA, and ARRIVE),<sup>79</sup> could serve as the basis for guidelines for full study reports that are applicable to trials of non-drug interventions and to other types of clinical and preclinical research. To be widely used by investigators and sponsors, these standards for full study reports and protocols must be enforced by funders as a condition of grant payment, by research ethics committees as a condition of ethics approval, and by journal editors as a condition of publication.

Definition of best practices is also needed to enable researchers and sponsors to better prepare for and participate in data sharing. Consultation with researchers, patients, privacy experts, lawyers,<sup>80</sup> funders, sponsors, regulators,<sup>81</sup> journal editors, and data curators is needed to establish international standards and processes. An authoritative global body such as WHO should take the lead in this effort, as it did for trial registration. Six scientific, ethical, and technical considerations need to be clarified for implementation of routine data sharing:<sup>82,83</sup> privacy issues, scope, method of access, timing of access, academic input, and data format and archiving.

In most cases, privacy of patients can be protected with the use of guidelines for anonymisation that are neither technically complex nor time-consuming.<sup>84</sup> For clinical trials, European legislation already instructs industry sponsors to anonymise any participant-level data contained in the regulatory submission.<sup>85</sup> In some cases (eg, rare diseases), additional steps are needed to prevent the identification of individuals.<sup>82</sup> The low privacy risk of an anonymised dataset with appropriate safeguards is usually outweighed by the public interest of good research.

Exactly which participant-level data would be subject to a data-sharing policy—the original case report forms, a clean dataset that is ready for final analysis, or data from other intermediate stages—should be defined. Access to data from case report forms and other source documents can be important—eg, when there are concerns about adjudication of outcome events.<sup>86,87</sup>

Datasets could be accessed in several ways, ranging from full publication of anonymised participant-level data for unrestricted use to restricted access on the basis of some mechanism for assessment of the data request and the new study proposal.<sup>88</sup> In terms of when datasets should be released, researchers should be given sufficient time to explore their datasets, but the public interest of timely access has to be considered. The defined period should be as short as possible and could vary by type of research. For example, genomic data are usually subject to immediate release, with a period of exclusivity for publication by the original researchers.<sup>82</sup>

Datasets are often complex, and a good understanding of the conditions under which the data were collected or missed can be essential to ensure appropriate analysis. An investigator from the original research team who produced the dataset could be invited to join a new study, or, if independence is preferred, could be offered a commentary on reports that arise from secondary analyses.<sup>68</sup>

Formatting standards should be developed to define what constitutes a clean, well annotated dataset to allow researchers to prepare their datasets for sharing. Several options are available for the storing of participant-level data. Several journals now give authors the option to upload participant-level data as supplementary material. However, journal staff might have little expertise in data curation. Approved archives would seem to be a preferable solution, such as those developed for microarray data.<sup>89</sup> Datasets should be linked to the protocol, full study report, registry record, and journal report, creating a series of so-called threaded electronic documents that form the core components of a study (figure 4).<sup>90</sup>

### Recommendation 3

Funders, sponsors, regulators, research ethics committees, journals, and legislators should endorse and enforce study registration, wide availability of full study information, and sharing of participant-level data for all health research. Important progress has been made in the past decade to improve access to unreported studies.<sup>91</sup> Prospective, public registration of all studies at their inception is the key mechanism by which existing studies can be tracked. Since 2005, the International Committee of Medical Journal Editors has asked that clinical trials be registered prospectively in an approved registry as a condition of publication.<sup>92</sup> Subsequent legislation in several countries has extended the mandate for trials included in submissions to regulators,<sup>93</sup> and several government funders have registration of trials as a condition of grant approval.<sup>94,95</sup> Nevertheless, many reported trials remain unregistered, retrospectively registered, or registered with poor quality information, in violation of the journals' policies.<sup>49,96–98</sup> Therefore, research ethics committees, journals, funders, institutions, governments, regulators, and sponsors need to adopt and enforce comprehensive registration policies for all trials, including those that fall outside the present adherence mechanisms.

The compelling need to document existing studies is not limited to clinical trials. The registration of systematic reviews,<sup>77</sup> observational research,<sup>99</sup> and preclinical experiments<sup>10,22</sup> can be promoted through an expansion of registration requirements. The registry infrastructure for recording of systematic reviews and observational research already exists.<sup>99,100</sup> Registration of exploratory observational research and preclinical experiments has its challenges<sup>101</sup>—eg, if no formal protocol is prespecified—but a key benefit of registration would be to transparently distinguish between hypothesis-generating and confirmatory studies.

Ultimately, to encompass the greatest breadth of studies, registration requirements need to be firmly enforced by research ethics committees or institutional review boards.<sup>102,103</sup> Since October, 2013, the Health Research Authority has had registration of all clinical trials in the UK as a condition of ethics approval.<sup>104</sup> This important step should be taken in other countries so that the potential risks and costs of research are balanced by

its dissemination and contribution to knowledge.<sup>102</sup> The added workload on overburdened committees could be minimised through automatic withholding of final approval for any annual renewals or applications that do not provide a study registration number.

To increase access to published reports, a rising number of funding agencies, academic institutions, and legislators have adopted policies to support open-access journal publications, particularly for publicly funded research.<sup>27,105</sup> For example, grant submissions to the US National Institutes of Health have to include the PubMed Central open-access archive numbers for any reports arising from federally supported research. Public-private partnership programmes that provide free access to reports for low-income countries can be helpful if publishers maintain a long-term commitment to participate.<sup>26</sup>

To avoid potential waste due to exclusion of reports published in languages other than English, investigators doing systematic reviews should attempt to identify and screen these studies to establish their number and potential relevance. Further research is needed to assess the relevance of a recent cohort of these studies, weighed against the resources needed to identify and review them.

Enforceable solutions are needed to resolve the untenable status quo in which specific groups (eg, regulators and sponsors) have access to complete information, but individuals directly using, assessing, or paying for an intervention (eg, patients, clinicians, researchers, and policy makers) have access to only a potentially biased subset of information. To address this wasteful imbalance, detailed documents for all studies need to be made publicly accessible—including the study protocol with any amendments, and the full study report detailing all analyses and results.

The full protocol is inseparable from the study results, which in turn cannot be properly interpreted without a detailed understanding of the study methods.<sup>106</sup> Because study registries already include basic protocol information, they could serve as a logical repository for full protocols and full study reports. Several journals, such as *Trials* and *BMJ Open*, publish study protocols, serving as another important means of public access. Stakeholders with enforcement capacity—eg, regulators, legislators, journal editors, and funders—should promote access to protocols and full study reports.<sup>40,41,106</sup> The European Medicines Agency has committed to providing access to full study reports that are routinely submitted for market approval.<sup>41,107</sup> Individual companies have also committed to disclosing full study reports for their reported trials, with conditions.<sup>108</sup>

Since 2007, US legislation has necessitated the posting of main results of non-exploratory trials of licensed drugs and devices on ClinicalTrials.gov, and similar legislation is being implemented in Europe.<sup>93</sup> The ClinicalTrials.gov results database often contains valuable efficacy and safety data that are not reported in journal articles.<sup>109</sup> In 2012, additional US legislation was proposed to include

early phase 1 trials, trials without a US site, and trials of unapproved drugs or devices.<sup>110</sup> The proposed legislation also calls for availability of the full protocol, which has become increasingly accepted by some pharmaceutical companies.<sup>111,112</sup> Comprehensive legislation should also be introduced and enforced in other countries.

Because present legislative and regulatory policy efforts are limited to trials of regulated drugs and devices, additional measures by journals and funders are needed to encompass trials of unregulated interventions (eg, surgery) or other clinical and preclinical study designs. Half the highest-impact biomedical journals demand that authors make the study protocol available on request,<sup>65</sup> but the extent of adherence to and enforcement of this policy is unclear. Journals should routinely ask for submission of the protocol and full study report along with the manuscript, and provide links to them as a web supplement upon publication of the journal report. Peer reviewers and others who appraise studies should also be encouraged to routinely compare journal articles with protocols, full study reports, and study registries to identify any unacknowledged discrepancies. Only a third of journal peer reviewers routinely compare trial registry entries with manuscripts.<sup>113</sup>

To maximise the return on investment of public funds, funding agencies should promote rigorous reporting practices by adopting policies for public posting of the protocol and full study report for all funded studies. For example, the Health Technology Assessment Programme in England requires a detailed full study report to be submitted, peer reviewed, and published in its own journal (which has no space restrictions), with the ability to also publish abbreviated reports in other journals. The programme withholds 10% of funds until the full study report has been submitted, meaning that one is available for 98% of studies that it has funded.<sup>114</sup> This policy has now been extended to all research funded by the National Institute for Health Research.

With regard to data sharing, practices differ substantially between and within disciplines. Whereas it is commonly accepted that microarray data should be publicly deposited, clinical trial datasets are rarely available. A survey of trial investigators showed broad support for mandatory data sharing in principle, but also identified widespread concerns about sharing in practice.<sup>115</sup> A cultural shift that recognises the benefits and addresses the barriers is needed for data sharing to become a routine part of research practice.

Journals, industry, funders, regulators, and legislators should enable and enforce access to participant-level data for all research. Several journals—eg, *Science*, *Nature*, *BMJ*, and *PLOS Medicine*—make publication conditional on provision of access to participant-level data in an approved database or on request.<sup>16,65,116</sup> Industry efforts have committed to increase the availability of specific study datasets.<sup>117–119</sup> In 2010, a consortium of medical research funders made a commitment to increase the availability of data generated by the research they fund.<sup>120</sup>

Since 2003, the US National Institutes of Health has demanded that grant applications for more than \$500 000 per year include a plan for data sharing, although the extent of enforcement is unclear. The impact of datasets shared under this policy can be substantial, such as the data resources of the Women's Health Initiative that have been used for more than 200 studies.

Funders should demand that researchers make participant-level data from studies funded by previous grants available before they are eligible to receive new funds. Funders should also include sufficient funds in grant budgets to pay personnel for preparation of datasets and associated documentation for data sharing. This investment, which in some instances could be substantial in absolute terms, is usually small relative to the time and costs needed to gather new data.<sup>82,121</sup> To avoid datasets becoming redundant, funders should also ask grant applicants to explain why new proposed datasets are needed. For example, the UK Economic and Social Research Council will not fund any dataset creation unless applicants confirm that no appropriate dataset is already available for reuse.

Additionally, regulatory agencies could ask that participant-level data and protocols from drug or device trials be made publicly available once the market authorisation process has ended.<sup>81</sup> The public health benefit of provision of access to study data should outweigh any commercial interests.<sup>122</sup> Independent review by academic researchers will help regulators and could improve regulatory decision making.<sup>41</sup>

If publication, funding, and licensing were contingent on provision of access to participant-level data, data sharing would rapidly become a routine part of health research. Ultimately, legislation with substantial penalties for violation is the inevitable option when self-regulation fails.<sup>16</sup> However, legislation alone is not sufficient if its scope continues to be limited to clinical trials of regulated drugs and devices, rather than being broadly applicable.

The overwhelming evidence of substantial waste and harms caused by inaccessible research illustrates the need for urgent action. The time has come for all stakeholders to develop and implement policies that increase accessibility of health research, and promote its unbiased translation to the best possible care of patients.

#### Contributors

A-WC led the drafting of the report. A-WC, FS, AV, and TJ each produced the initial draft of various sections of the report. All authors contributed to substantial revisions and approved the final version.

#### Conflicts of interest

TJ receives royalties from books published by Blackwells and Il Pensiero Scientifico Editore; is occasionally paid for interviews by market research companies for anonymous interviews about phase 1 or 2 products; is corecipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors; was a paid consultant for Roche (1997–99), for GlaxoSmithKline (2001–02), and for Sanofi-Synthelabo for pleconaril (2003); acted as an expert witness in a litigation case related to oseltamivir (Roche; 2011–12); and was on a legal retainer for paid expert advice about litigation for influenza vaccines in health-care workers. HMK is the recipient of a research grant from Medtronic through Yale University to develop methods of clinical trial data sharing, and is chair of a cardiac

scientific advisory board for UnitedHealth. HBvdW has received speaker's fees from Sanofi-Aventis, GlaxoSmithKline, and Springer Media; and has served as a paid consultant to Bristol-Myers Squibb. The other authors declare that they have no conflicts of interest.

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