Increasing value and reducing waste in biomedical research: who's listening?

David Moher, Paul Glasziou, Iain Chalmers, Mona Nasser, Patrick M M Bossuyt, Daniël A Korevaar, Ian D Graham, Philippe Ravaud, Isabelle Boutron

The biomedical research complex has been estimated to consume almost a quarter of a trillion US dollars every year. Unfortunately, evidence suggests that a high proportion of this sum is avoidably wasted. In 2014, *The Lancet* published a series of five reviews showing how dividends from the investment in research might be increased from the relevance and priorities of the questions being asked, to how the research is designed, conducted, and reported. 17 recommendations were addressed to five main stakeholders—funders, regulators, journals, academic institutions, and researchers. This Review provides some initial observations on the possible effects of the Series, which seems to have provoked several important discussions and is on the agendas of several key players. Some examples of individual initiatives show ways to reduce waste and increase value in biomedical research. This momentum will probably move strongly across stakeholder groups, if collaborative relationships evolve between key players; further important work is needed to increase research value. A forthcoming meeting in Edinburgh, UK, will provide an initial forum within which to foster the collaboration needed.

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Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada (D Moher PhD, Prof I D Graham PhD)**; School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, ON, Ottawa, Canada** (D Moher, Prof I D Graham)**; Centre for Research in Evidence Based Practice, Bond University, Robina, QLD, Australia** (P Glasziou FRACGP)**; James Lind Initiative, Oxford, UK** (I Chalmers DSc)**; Peninsula Dental School, Plymouth University, Plymouth, UK** (M Nasser DDS)**; Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands** (P M M Bossuyt PhD, D A Korevaar MD)**, METHODS Team, Centre of Research in Epidemiology and Statistics Sorbonne Paris Cité, UMR 1153, Institut National de la Santé et de la Recherche Médicale, University Paris Descartes, Paris, France** (Prof P Ravaud MD, Prof I Boutron MD)

Correspondence to:
Dr David Moher, Clinical Epidemiology Program, Ottawa Hospital Research Institute, The Ottawa Hospital, General Campus, Ottawa, ON K1H 8L6, Canada
dmoher@ohri.ca

For the **Alltrials initiative** see http://www.alltrials.net

Introduction

More than 30 years ago, the adverse clinical consequences of biased under-reporting of research were clearly documented[1] and non-publication of research remains hugely problematic.[2–5] Non-publication is bad value for funders, who could double research output by ensuring all the funded studies are published, and this situation puts patients and clinicians at a substantial disadvantage in making informed decisions about health care.[6] Trial registration, supported by the International Committee of Medical Journal Editors (ICMJE),[7] has helped to address this problem[8,9] although this solution is clearly not a panacea.[10,11] Other related initiatives, such as the Alltrials initiative and the Institute of Medicine's report on data sharing[12] are working to ensure that the results of all trials are reported and that their data are made available.

Chalmers and Glasziou[13] estimated in 2009 that 85% of research funding was being avoidably wasted across the entire biomedical research range (eg, clinical, health services, and basic science). Evidence of the extent and avoidability of waste in research production at each stage of the authors' four stage model has grown, and has confirmed imbalanced research question selection,[14] poor study design[15,16] and execution, non-publication,[17] and poor reporting[18] and some have suggested that a more fundamental reassessment is needed in how research priorities are developed and pursued.[19,20] In addition to 228 citations as of Sept 11, 2015, the 2009 paper[13] led National Institute of Health Research (NIHR) in England to establish a working group to monitor and plan actions, with regular meetings and an annual closed conference. The NIHR's Adding Value in Research programme had an additional stage (figure 1) aiming to ensure that NIHR funded research: addresses questions relevant to clinicians, patients, and the public; uses appropriate design and methods; is delivered efficiently; results in accessible full publication; and produces unbiased and useable reports. NIHR developed a quality improvement method[21] for these five stages to identify common themes and examples of good practice across their programmes. For example, since 2013, NIHR has required applicants for support of new primary research to reference an existing systematic review "as well as including reference to any relevant literature published subsequent to that systematic review" or when no such systematic review exists, applicants should review the relevant evidence (with a method that systematically identifies, critically appraises, and combines the evidence), which "must also include reference to relevant on-going studies, eg, from trial registries".[22]

In 2014 *The Lancet* published a Series ("Increasing value: reducing waste")[23–27] extending the 2009 analysis from 4 to 50 journal pages, with more than 40 authors focused on the five NIHR stages. As the Commissioning Editors noted: "Our belief is that research funders, scientific societies, school and university teachers, professional medical associations, and scientific publishers (and their editors) can use this Series as an opportunity to examine more forensically why they are doing what they do...and whether they are getting the most value for the time and money invested in science."[28]

The Series, and an accompanying symposium,[29] provided a voluminous body of evidence for the issues in biomedical research, along with 17 recommendations (table 1) to help to increase value, covering funders, regulators, journals, academic institutions, and researchers. These issues include (although they are not limited to) whether planned research met the needs of end users.[30–32]

Initial media attention included coverage by several newspapers including the leading German paper, *Der Spiegel*,[33] although almost no response has been made from German researchers or organisations (Antes G, German Cochrane Centre, personal communication). Several research funders responded through meetings, working parties, and some changes of processes. In the year since their publication, the five articles have been downloaded 46 596 times from *The Lancet* and

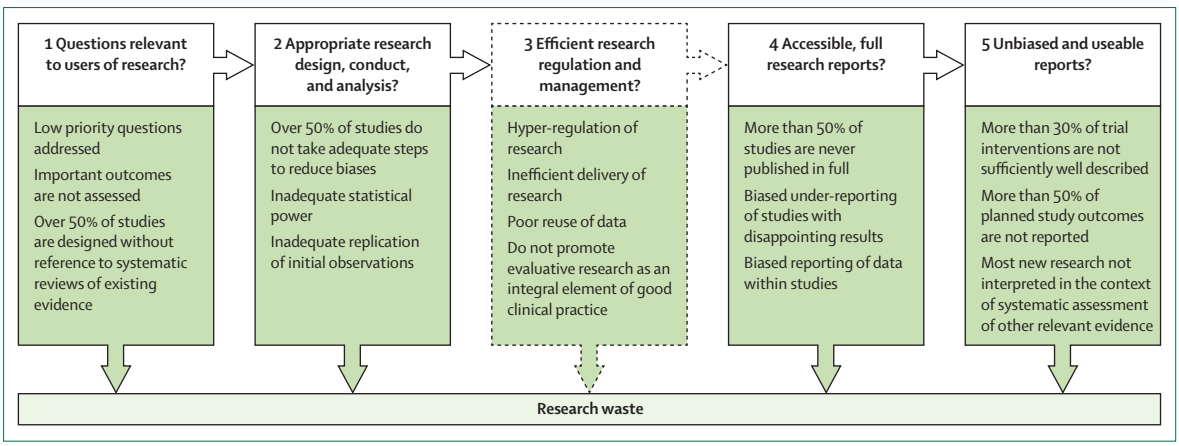

Figure 1: **Stages in research production that lead to waste**
Dashed box represents an addition to the 2009 model by National Institute for Health Research.

ScienceDirect websites. The five Series papers have already been cited 113 times (Scopus); were all in the top 5% of all articles indexed by Scopus; and their alternative metric scores (used to measure social media) all ranked more than the 98th percentile (of more than 3 million articles scored) including 589 tweets (about 20% of which were by health-care professionals).

This follow-up Review offers an overview of the initial stimulus of the Series. Before the assessment, a protocol was developed outlining the key players and the methods of our investigation, including sampling frames (panel 1). The primary focus was to assess what funders, regulators, journals, academic institutions, and researchers are doing, and plan to do, to address waste in biomedical research.

For the **National Centre for the Replacement, Refinement and Reduction of Animals in Research** see http://www.nc3rs.org.uk

Funders

A few funders have already responded to the Series. In May, 2014, the French Institute of Health and Medical Research, Institut National de la Santé et de la Recherche Médicale (INSERM), in conjunction with the Enhancing the Quality and Transparency of Health Research (EQUATOR) network, organised a 1-day conference in Paris on "Improving reporting to decrease the waste of research" with the director of the Wellcome Trust and NIHR's Health Technology Assessment programme among the speakers (video of all sessions is available on the EQUATOR website).[37] The Series was included in discussions of INSERM's strategic plan for 2016–20, and was presented at the annual meeting of INSERM team leaders.[38] In Australia, the National Health and Medical Research Council set up a working party to review all the recommendations in the Series (Ghersi D. National Health and Medical Research Council, personal communication), updating and modifying their procedures, and featured an opening session entitled Adding value, reducing waste at their 2014 annual scientific meeting.[39] The Series was discussed at the Heads of International Research Organizations group's meeting in 2014 in Ottawa, Canada.

We are also heartened that concern about poor replicability and quality of animal and other preclinical research[40] has prompted some influential organisations to draw attention to and address these concerns. For example, a meeting on reproducibility and reliability of biomedical research was convened jointly by the UK Academy of Medical Sciences, the UK Medical Research Council, the Wellcome Trust, and the Biotechnology and Biological Sciences Research Council. The National Centre for the Replacement, Refinement and Reduction of Animals in Research has supported three international meetings (in Nijmegen, Netherlands; Edinburgh, UK; and Washington DC, USA) about systematic reviews of animal research, and in 2015 held an international meeting in London, UK on biased under-reporting of animal research,[41] bringing together several relevant groups targeted in the Series. Some important papers drawing attention to issues with the reproducibility of research have also been published.[42–44] Whether or not the *Lancet* Series had any role in these initiatives, they are very welcome.

The investigation of the funders' websites (panel 1) suggests that most funders are not explicit about many of the key issues of research policies, which made this assessment challenging. The NIHR's website had several innovative and exemplary features, such as the requirements for systematic reviews before the initiation of additional primary studies, active monitoring of in progress studies, and NIHR's own journals. For other funders, the picture was more mixed than NIHR's website (table 2).[45–47] Most organisations required trial registration, but few needed systematic reviews before beginning additional primary studies, or mentioned reporting guidelines, such as Consolidated Standards of Reporting Trials, or the EQUATOR network. NIHR is an exception, compared with the other organisations studied, in that systematic reviews are needed for any research project submissions (table 1). Only two of these funders had a substantial targeted research scheme that

addressed priority questions for clinicians and patients: the NIHR's Health Technology Assessment programme, and the Patient-Centered Outcomes Research Institute in the USA.

To maximise research value, funders might want to consider ways to enhance their funding priorities in line with existing (regional, national, and international) priority setting initiatives (table 1). Similarly, funders might want to ensure that, wherever possible, protocols are developed with relevant guidance, such as Standard Protocol Items: Recommendations for Interventional Trials for randomised trials and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols for systematic reviews available on the EQUATOR website, and that the research they fund is registered in a relevant repository (eg, World Health

For the **EQUATOR website** see http://www.equator-network.org

For the **World Health Organization's International Clinical Trials Registry Platform** see http://www.who.int/ictrp/en

	Monitoring	Examples of groups who can take action
Research priorities		
1. More investigations into research should be done to identify factors associated with successful replication of basic research and translation to application in health care, and how to achieve the most productive ratio of basic to applied research	Periodic surveys of the distribution of funding for research and analyses of yields from basic research	EBRN, NIH, and HIRO
2. Research funders should make information available about how decisions are made about what research to support and fund investigations into the effects of initiatives to engage potential users of research in research prioritisation	Periodic surveys of information on research funders' websites about their principles and methods used to decide what research to support	HIRO, JLA, EBRN, and Cochrane
3. Research funders and regulators should demand that proposals for additional primary research are justified by systematic reviews, showing what is already known, and increase funding for the syntheses of existing evidence	Audit proposals for and reports of new primary research	HIRO
4. Research funders and research regulators should strengthen and develop sources of information about in progress research, ensure that this information is used by researchers, insist on publication of protocols at study inception, and encourage collaboration to reduce waste	Periodic surveys of progress in publishing protocols and analyses to expose redundant research	EBRN and HIRO
Research design, conduct, and analysis		
5. Make publicly available the full protocols, analysis plans or sequence of analytical choices, and raw data for all designed and undertaken biomedical research	Proportion of reported studies with publicly available (ideally preregistered) protocol and analysis plans, and proportion with raw data and analytical algorithms publicly available within 6 months after publication of a study report	HIRO, PROSPERO, PRISMA-P, SPIRIT, ClinicalTrials.gov, ISRCTN, and WHO platform
6. Maximise the effect-to-bias ratio in research through: defensible design and conduct standards, a well-trained methodological research workforce, continuing professional development, and involvement of non-conflicted stakeholders	Proportion of publications without conflicts of interest, as attested by declaration statements and then checked by reviewers; the proportion of publications with associated scientists who are methodologically well qualified (eg, people who are formally trained in areas such as epidemiology or statistics) is also important, but difficult to document	Trial Forge, CTTI, HIRO, COMET, OMERACT, and STaRChild Health
7. Reward (with funding and academic or other recognition) reproducibility practices and reproducible research and enable an efficient culture for replication of research	Proportion of research studies undergoing rigorous independent replication and reproducibility checks, and proportion replicated and reproduced	HIRO, ICMJE, WAME, and NIH
Research regulation and management		
8. People regulating research should use their influence to reduce other causes of waste and inefficiency in research	People regulating, governing, and managing research should measure the extent to which the research they approve and manage complies with the other recommendations in this Series[20–24]	Trial Forge, CTTI, Health Research Authorities, and Research Ethics Boards
9. Regulators and policy makers should work with researchers, patients, and health professionals to streamline and harmonise the laws, regulations, guidelines, and processes that govern whether and how research can be done, and ensure that these factors are proportionate to the plausible risks associated with the research	Regulators, individuals who govern and manage research, and researchers should measure and report delays and inconsistencies that result from failures to streamline and harmonise regulations	PCORI, SPOR, Patients Canada, JLA, and Research Ethics Boards
10. Researchers and research managers should increase the efficiency of recruitment and retention of participants, data monitoring, and data sharing in research through the use of research designs known to reduce inefficiencies, and do additional research to learn how efficiency can be increased	Researchers and methodologists should do research to identify various ways to improve the efficiency of biomedical research	Trial Forge and CTTI
11. Everyone, particularly individuals responsible for health-care systems, can help to improve the efficiency of clinical research by promoting integration of research in everyday clinical practice	People responsible for management of health-care systems or research should measure the proportions of patients who are enrolled in research	Government ministries of health, hospital chief executive officers, Trial Forge, and CTTI

(Table 1 continues on next page)

	Monitoring	Examples of groups who can take action
(Continued from previous page)		
Accessibility		
12. Institutions and funders should adopt performance metrics that recognise full dissemination of research and reuse of original datasets by external researchers	Assessment of the proportion of institutional and funding-agency policies that explicitly reward dissemination of study protocols, reports, and participant-level data	HIRO, Altmetric, and U15 (Canada)
13. 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	Surveys of how many stakeholders adopt international standards	Alltrials, HIRO, clinicaltrials.gov, ISRCTN, and WHO platform
14. 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	Assessment of the proportion of stakeholder policies that endorse dissemination activities, and the proportion of studies that are registered and reported with protocols, full study reports, and participant-level data	HIRO, COPE, IRBs, ICMJE, and WAME
Reporting		
15. Funders and research institutions must shift research regulations and rewards to align with better and more complete reporting	Funders and research institutions should assess research (or researchers) and consider the accessibility and use of research protocols, study materials, study data	HIRO and individual funding agencies
16. Research funders should take responsibility for reporting infrastructure that supports good reporting and archiving	Funders and research institutions should regularly report expenditures for reporting infrastructure and archiving	HIRO and individual funding agencies
17. Funders, institutions, and publishers should improve for authors and reviewers the capability and capacity for high-quality and complete reporting	Researchers should use reporting guidelines, registries, archives, and take up training opportunities on these topics	HIRO, CSE, EASE, EQUATOR, ICMJE, WAME, COPE CONSORT, PRISMA, and STaR Child Health

EBRN=Evidence Based Research Network. NIH=National Institutes of Health. HIRO=Heads of Research Organizations. JLA=James Lind Alliance. PRISMA-P=Preferred Reporting Items For Systematic Review And Meta-Analysis Protocols. SPIRIT=Standard Protocol Items: Recommendations for Interventional Trials. ISRCTN=International Standard Randomised Controlled Trial Number. CTTI=Clinical Trials Transformation Initiative. COMET=Communications, Media and Electronic Technologies. OMERACT=Outcome Measures in Rheumatology. STaRChild Health=Standards for Research in Child Health. ICMJE=International Committee of Medical Journal Editors. WAME=World Association of Medical Editors. PCORI=Patient-Centered Outcomes Research Institute. SPOR=Strategy for Patient-Oriented Research. Altmetrics=Alternative metrics. COPE=Committee on Publication Ethics. IRBs=Institutional review board. CSE=Council of Science Editors. EASE=European Association of Medical Editors. EQUATOR=Enhancing the quality and transparency of health research. CONSORT=Consolidated Standards of Reporting Trials.

Table 1: **The *Lancet* Series recommendations by number and examples of groups who can take action to discuss, endorse, and implement the recommendations and monitor progress**

Panel 1: Methods

Funders

To further investigate how funders address the issues and recommendations in the Series, we searched the websites of six funders. These were selected purposively to gauge activities of some large funders and those in proximity to the authors. We assessed documents such as instructions to funding applicants then checked our findings with the funder.

Journals

To further explore how journals are dealing with the seven recommendations from the Series most relevant to them, we assessed the websites of the 120 core clinical journals included in MEDLINE's Abridged Index Medicus,[34] particularly their instructions to authors. Journal websites had similar responses across most of the questions; about half of them had information we were seeking (figure 1). We also interviewed two editors from general medical journals (*BMJ*, *The Lancet*), an editor from a specialty journal (*Archives of Physical Medicine and Rehabilitation*), an editor from a predominantly methods-based journal (*Journal of Clinical Epidemiology*), and an editorial director (*PLoS* journals) with a structured interview guide of ten questions.

Academic institutions

We assessed the extent to which academic institutions have policies to make study materials publically available, a recommendation from the Series. Deans and directors of research of the medical schools of the top 100 universities from the *Times Higher Education*[35] World University Rankings 2013–14 (ordered by clinical, preclinical, and health) were invited to participate in a five-question email survey.

Researchers

To identify the extent of support among researchers for the recommendations in the Series, and the perceived barriers to adherence, we did a qualitative online survey as we did not aim to have a representative sample but to emphasise different perceptions of clinical and preclinical researchers. We surveyed basic scientists (n=59) and clinical researchers (n=70) who published in high impact factor journals or were listed as highly influential researchers.[36]

Organization's International Clinical Trials Registry Platform and PROSPERO; table 1). For example, a review[48] of 75 randomised trial protocols funded at NIHR's Health Technology Assessment programme, Southampton, UK, showed these protocols often did not provide adequate information about allocation sequence generation (13% missing) and concealment (19% missing): important characteristics of well conducted randomised trials. Funders could also consider stronger policies than at present to support (guidance, education, and infrastructure) and enforce (incentives and penalties) publication of all research, open access, and data sharing.

Regulators

Regulators can help with this goal by not providing ethics approval of protocols that are scientifically poor, which would mean that these protocols are also ethically inadequate. For example, the guidance for researchers issued by the newly established Health Research Authority (HRA)[49] in the UK now states: "Any project should build on a review of current knowledge. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical."

Conversely, research regulators can reduce waste resulting from inefficiencies in research regulation. Some of these inefficiencies result from hyper-regulation

	Are users of research engaged in prioritising funding for future research? (Recommendation 2)	Are systematic reviews a key part of the information to inform future (basic or applied) research priorities? (Recommendation 3)	Does the funder need previous registration of research? If so, which types? (Recommendation 4)	What is the funder's policy on public access to data from completed research? (Recommendations 13 and 14)	What is the funder's policy on public access to protocols for completed or in progress research? (Recommendation 13)	What is the overall process to set a research agenda? (Recommendation 2)
NIHR (England)	Involvement for researchers, policy makers, and patient's representative; active patient involvement is key in the process; outline or full applications (depending on specific research programme or funding stream) are peer reviewed, including a PPI review; in terms of the decisions to fund applications, programme boards have PPI members who will consider applications from a PPI perspective and patient need	Yes, for any type of research; the funder provides funding for systematic reviews; for health technology assessment applications, any relevant and in progress clinical trials have to be also included; a specific system is available for monitoring the conduct of clinical trials; reviews are done internally by NETSCC programmes to ensure research is not duplicated within NIHR programme portfolios (and to identify, in certain cases, where research might feed into other NIHR calls for research in commissioned areas or themed calls, however these are perhaps not completely clear on the website	Yes, clinical trials and some other studies; NETSCC-funded, patient relevant projects must register through www.controlled-trials.com onto the ISRCTN; programme-specific advice is provided on the website regarding registration (for research application, contracting, start-up processes; NETSCC-funded projects, which include a systematic review as part of their protocol, must register protocols on the PROSPERO database	For publishing completed research:[45] the principal award holder submits an end-of-project report within 14 days study close, which is managed through NIHR monitoring processes; to meet NIHR's open access commitment, a copy of the final manuscript is deposited with PubMed Central on acceptance for publication, to be made freely available as soon as possible and within 6 months of the journal publisher's official date of final publication	All of protocols are published on the website	NETSCC, part of NIHR programme, works with external organisations and individuals, including a public website for suggestions, to identify research questions that will probably make the greatest difference to people's health; an advisory board prioritises proposals and checks for no inadvertent duplication; NETSCC is now responsible for the James Lind Alliance programme of Priority Setting Partnerships, which engages clinicians and patients in setting research priorities
MRC (UK)	For setting the research agenda, stakeholder involvement is very important (includes department of health, department of international development, and devolved administrations) but stakeholders do not get implicated in individual funding decisions; in individual funding decisions, strong involvement of researchers and the private sector (pharmaceutical industry); very restricted and selective involvement of the public and patients, who are only implicated in selective projects if deemed appropriate	No, expert opinion seems to be the key factor; a lot of MRC funding goes to basic laboratory work, which needs clear rationale based on an analysis of previous work but not a systematic review in itself; the only proposals that need systematic assessment of existing evidence are global health clinical trials	Yes for clinical trials; the funding of large-scale clinical trials is done through NIHR Efficacy and Mechanism Evaluation Programme so MRC's requirements, which include clinical trial registration, are followed	MRC has policies for data sharing, although it emphasises access for scientists, not the public; the research councils in UK have an overall open access policy and give universities budgets to publish completed research in an open access format, although flexibility is available	MRC do not have a policy on protocols, only a policy for completed research beyond the requirements of sharing information as part of registering clinical trials	An overall strategic plan guides decisions about research priorities and specific goals and objectives are made for each funding panel; the strategy board, the research boards and the four overview groups (public health, global health, translation, and research careers) are heavily implicated in setting the research agenda and identifying priorities in research

(Table 2 continues on next page)

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NHMRC (Australia)	Researchers are strongly involved; the extent of the association of other stakeholders is unclear	No, expert opinion seems to be the key; no explicit mention of the need for systematic reviews before new primary research	Yes, for clinical trials only	Yes, publication from NHMRC supported research must be deposited into an open access institutional repository within 12 months of publication but NHMRC do not specifically mention databases	No, we were unable to identify a policy for access for protocols beyond the requirement to share information as part of the registration of clinical trials	An overall strategic vision is available and NHMRC have health care, preventive and community health, and genetic committees to advise them along with clear principles: fairness, transparency, independence, appropriateness and balance, research community participation, confidentiality, impartiality, and quality and excellence
NIH (USA)	NIH receives data and information on the burden of disease and disability from patient and advocacy groups, professional societies, and voluntary organisations; clinicians and basic and clinical scientists provide input on scientific opportunities; NIH and Centre's advisory councils or boards, made up of scientific experts and members of the public, make recommendations to institutes and centres. In the first stage of peer review, fellow researchers assess the scientific merit of grant applications; in the second stage, advisory councils made up of science experts and members of the public make funding recommendations to the institutes and centres	No, NIH uses various reports and data to inform these decisions but systematic reviews are not needed for future research	Yes, for clinical trials only	Yes, the NIH grants policy statement sets the expectation that grantees make the results and accomplishments of their activities available to the research community and to the public at large, including sharing of publications, research data, unique research resources, and commercialisation of federally funded inventions; the NIH public access policy requires NIH funded scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to PubMed Central immediately on acceptance for publication and no later than 123 months after the official date of publication; NIH has clear data sharing policies that are part of terms and conditions of the grant; NIH's RePORTer database provides information on the results of NIH funded research to the public by linking information on publications and patents arising from NIH funded projects to project abstracts and administrative information, including the budget	No, we were unable to identify a policy for access for protocols beyond the requirement to share information as part of the registration of clinical trials	The US congress sets NIH funding levels and directs NIH attention to particular areas of research interest or emphasis; the NIH Division of Coordination, Planning and Strategic Initiatives in the NIH Office of the Director identifies important areas of scientific opportunity, rising public health challenges, and gaps in knowledge that deserve special emphasis; TransNIH planning for the Common Fund is associated with broad stakeholder input from many scientific and public inputs; the mission of each NIH institute and centre generally focus on a different disease, organ, or stage of life; the individual ICs set their own research priorities considering the following factors, institutes and centres mission, available funding, scientific needs and opportunities, gaps in funded research, burden of disease, and public health need, such as an emerging threat; priorities are partially driven by the research community with their investigator initiated proposals

(Table 2 continues on next page)

of low risk non-interventionist research, such as many descriptive surveys. After a report[50] from the Academy of Medical Sciences, UK, HRA is now addressing this issue. As a result, proportionate measures for assessments of research proposals have been introduced that take into account the plausible risks associated with the research proposals being considered.

Some research regulators have also taken steps to reduce the problem of biased under-reporting of research (table 1). In the UK, a favourable ethics opinion for proposed clinical trials will not be granted unless the proposed trial has been registered publicly.[51] After pressure from the Alltrials campaign, the European Medicines Agency has now committed to make available all clinical study reports of research leading to marketing licences for new drugs (table 1).[52]

Journals

In view of the fact that more than half of the reports of clinical trials do not set their results in the context of the

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CIHR (Canada)	Strong involvement of researchers, moderate involvement of policy makers, selective or little involvement of members of public and industry; the investigator initiated programme uses peer reviewers to assess and rank which proposals should be funded; these proposals are primarily academics or health-care providers, however, depending on the expertise needed to review the proposal, this process can also include knowledge users (eg, policy makers and industry representatives); the priority-driven research programme also uses peer reviewers but each peer review committee is tailored to the specific strategic initiative competition; depending on the scope and nature of the programme, these reviewers can include a combination of patients, public, academics, press, private sector representatives, or health-care providers; with the Strategy for Patient-Oriented Research, for example, CIHR is gaining experience developing peer review committees with public, academic, patient, and provider and private sector reviewers	No, expert opinion is the key; CIHR do encourage a systematic review for clinical trials; the specific requirements for proposals can vary between funding opportunities but the criteria to assess evidence and justification for research can include completeness of the scientific literature review and relevance to study design or research plan	Yes, for clinical trials	Yes, the Tri-Agency* Open Access Policy on Publications[46] requires that any publication from research supported by the agency must be deposited into an institutional or a subject-based repository that makes the manuscript freely accessible within 12 months of publication, or published in a journal that offers immediate open access or that offers open access on its website within 12 months; CIHR researchers must also deposit some specific types of data such as bioinformatics, atomic, and molecular coordinate data in appropriate public databases immediately on publication of research results	No, the Tri-Agency open access policy on publications provides policy guidance related to public access for all completed research; no separate policy exists on protocols (except for the requirements for clinical trials) as specified in chapter 11[47] of the tri-council policy statement-2; the TRDS must be completed for a trial to be fully registered and any missing information or uninformative fields in the TRDS is unacceptable	CIHR does not commission research; CIHR has two streams of funding: investigator initiated and priority driven; investigator-initiated research is researcher driven in that researchers submit proposals on subjects of their choice and not on subjects prioritised or targeted by CIHR, these proposals are peer reviewed and weighted against similar proposals and subsequently funded in order of ranking within the available budget; priority-driven health research is designed to respond to Canada's strategic health-related research priorities, developed by CIHR's Governing and Science Council by assessing government priorities, emerging needs, trends, and important knowledge deficits in the Canadian health research landscape; to determine how to allocate its strategic funding, CIHR develops a 5-year strategic plan on the basis of several important inputs with many stakeholders; inputs include the Government of Canada Science & Technology Strategy, Ministerial priorities, and key stakeholders including patients, industry, policy makers and provincial health ministries; during the strategic planning exercise, input from the public is invited through various electronic means; the latest strategic plan (Health Research Roadmap II: Capturing Innovation to Produce Better Health and Health Care for Canadians 2014–2015–2018–2019), was approved by CIHR's Governing Council (CIHR's institutes, Scientific Directors, and communities) help to inform the directions of CIHR's priority-driven programmes through the design of initiatives that service the priorities of their research communities; this process often includes consultations with researchers, partners, patients, among others; each CIHR institute also has their own strategic plan that aligns with CIHR's strategic plan; CIHR's Governing Council comprises 18 members who are able to contribute to the achievement of CIHR's objectives in the overall interests of Canadians—each member comes from a unique relevant background, possess an outstanding skill set, and are from various disciplines

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	Are users of research engaged in prioritising funding for future research? (Recommendation 2)	Are systematic reviews a key part of the information to inform future (basic or applied) research priorities? (Recommendation 3)	Does the funder need previous registration of research? If so, which types? (Recommendation 4)	What is the funder's policy on public access to data from completed research? (Recommendations 13 and 14)	What is the funder's policy on public access to protocols for completed or in progress research? (Recommendation 13)	What is the overall process to set a research agenda? (Recommendation 2)
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DFG (Germany)	Researchers are involved in reviewing and making decisions; some proposals go to the joint committee, which involves policy makers too; the proposal is assessed by voluntary reviewers (scientists) exclusively according to scientific criteria; on the basis of this expert review, proposals are assessed by members of the review board and the final decision is made by one of the grants committees; the committees consist of researchers, representatives of the federal and the state governments, and members from the Donors' Association for the Promotion of Sciences and the Humanities in Germany; members of the standing review boards are all elected by the scientific communities every 4 years	Yes for clinical trials, the state of the research specialty and evidence is to be included in the proposals; for clinical trials, the structured search for evidence has to be described or systematic reviews to be referenced; the comprehensive description of the existing evidence is a key reviewing criterion; systematic reviews can be funded in the individual grants programmes	Yes for clinical trials only	Suggestions and examples for researchers are available for the reuse of research data; DFG strongly encourages researchers to have strategies to reuse data "In order to enhance the long-term archiving and curation of research data, the DFG funds projects that seek to achieve an efficient reuse of research data" but this inclusion is not compulsory	All clinical trials funded after June 1, 2014, have to deposit the study protocol at the clinical trials registry before trial start but not for other study designs	DFG is the self-governing organisation for science and research in Germany, serving science and the humanities; the main task of the DFG is to select and finance the best research projects on a competitive basis; projects by scientists and academics or by universities deal with topics from a particular discipline or from an interdisciplinary approach; in a multilayered decision making process, the proposal is assessed by voluntary reviewers exclusively according to scientific criteria and then assessed by chosen members of the review board, and the final decision is made by the Grants Committee; as a result, DFG funding guarantees quality-based differentiation in the German research system; any eligible researcher can submit a funding proposal at any time and on any research topic; because the DFG does not specify a topic for proposals, but, instead, reacts to proposals on any topic, the organisation promotes research mainly in what is known as response mode, therefore complementing the agenda driven and programme oriented funding by the ministry of research and education (BMBF) in Germany

NIHR=National Institute for Health Research. PPI=public and patient involvement. NETSCC=NIHR Evaluation, Trials and Studies Coordinating Centre. ISRCTN=International Standard Randomised Controlled Trial Number. MRC=Medical Research Council. NHMRC=National Health and Medical Research Council. NIH=National Institutes of Health. CIHR=Canadian Institute for Health Research. TRDS=WHO Trial Registration Data Set. DFG=Deutsche Forschungsgemeinschaft. BMBF=Bundesministerium für Bildung und Forschung. *Tri-Agency refers to Canada's three Federal Research Granting Councils: CIHR, the Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council.

***Table 2*: Information available on the websites of selected funding agencies with regard to some dimensions of reducing waste of research framework**

totality of evidence,[27] journals have much work to do to improve this situation. Journals can progress by providing specific guidance on their websites about this crucial feature and by providing similar guidance to peer reviewers. In response to the Series, *The Lancet* strengthened the journal's requirement to put research into context (table 1).[53] From the beginning of this year, all research papers submitted to any journal in *The Lancet* family must include a research in context panel. The Editors expressed their "hope that increasing the prominence of putting research into context in the submission and publication stages will help researchers, institutions, and funders to make decisions earlier in the process on which research questions to address and fund". Other journals have made similar efforts, such as the addition of panels asking authors what this paper adds. However, something more explicit, such as the research in context panel, might be more helpful. To complement these initiatives, the Transparency and Openness Publications committee has proposed journal guidance to increase author transparency, openness, and reproducibility.[54]

On the basis of our interviews with journals editors (panels 1, 2), the *Lancet* Series has been an impetus for consideration and change in some editors. The papers have been discussed internally during in-house editorial meetings, at an editorial board retreat for a journal, and is on the agenda for discussions with other editorial boards. The Series has also been on the agenda of influential editorial groups, such as ICMJE, and other continuing initiatives, such as the Institute of Medicine's report on data sharing.[12] Some journals have already acted in response to the Series. For example, *PLoS Medicine* commissioned an editorial on how open access can reduce waste.[55] Other concurrent initiatives focused on the reduction of research waste, not directly attributable to the Series, are also underway. For example, a large group of

rehabilitation medicine Editors signed up collectively to mandate the use of reporting guidelines in their journals.[56] This policy is likely to introduce a strong incentive to prospective authors across this content area to use reporting guidelines. Other specialties, such as surgery, are starting to implement similar strong guidance.[57]

The results of investigating the journals' websites (panels 1, 2) show the wide variability of information contained on journal websites and the language used across journals (figure 2). This variability will probably confuse prospective authors, particularly those early on in their research careers and those whose first language is not English. Although journals want to maintain their uniqueness, and emphasise particular issues that are important to them, some items, perhaps particularly those related to the recommendations in the Series, might be considered as core information and unambiguous language could be included across all journal websites. This approach might help to improve matters for journals, prospective authors, and readers.

One immediate goal could be for every journal to explicitly support the use of reporting guidelines (table 1). The evidence suggests that guideline use is associated with increases in the completeness of reporting of clinical trials.[58] Roughly half of the websites we investigated mentioned reporting guidelines, which is a similar proportion to that reported by Hirst and Altman[59] in 2012. Far fewer journal websites (18 of 120) explicitly mentioned the EQUATOR Network and few (11 of 20) mentioned the use of systematic reviews in the context of reporting the main results of their research (table 1).

Journals can also add value to their websites by explicitly asking authors to provide more information about their methods, particularly the interventions used or details of participants. For example, 30 (12%) reports from a sample of 255 cancer trials provided sufficient information about the interventions studied[60] to allow clinicians to use the results in practice.[61] Across the ten questions used to assess the websites, the results did not vary substantially by journal impact factor (<5 *vs* ≥5).

Academic institutions

We are aware of very little explicit attention by academic institutions to the *Lancet* Series. An exception has been in Iran, where a group of academics are running a series of workshops on the *Lancet* series. Two workshops on "Biomedical research: increasing value, reducing waste" were run in February, 2015, for Directors of Clinical Research Centers, research vice chancellors, and Director Generals of Research Affairs of Medical Universities of North West Universities of Iran. A final national workshop is planned for the research deputies of all 55 medical universities of Medical Sciences in Iran is planned to be launched in December, 2015 (Pezeshki MZ, Tabriz Medical Sciences, Tabriz, Iran, personal communication).

Based on our email survey (panel 1), we received complete responses from only 26 of the 100 invited universities. We noted that most of these schools (n=20) have a policy to register clinical trials in a publicly accessible trial registry and to make full study reports available (n=19), but such policies are rare for protocols (n=5), analytical algorithms (n=5), and raw data (n=5). Two of 26 universities did not have an institutional policy for any of these five elements (table 1).

Only five medical schools reported having a policy to make all study protocols publicly available. At Duke University in the USA, for example, "all approved study protocols are available through the School of Medicine's

***Panel 2:* Questions asked to the 119 journals of MEDLINE Abridged Index Medicus[34]**

1. Does the journal's instructions to authors explicitly mention reporting guidelines?
2. Does the journal's instructions to authors explicitly mention the Enhancing the Quality and Transparency of Health Research Network?
3. Does the journal's instructions to authors explicitly mention clinical trial, systematic review, or other registration?
4. Does the journal's instructions to authors mention use of systematic reviews as part of reporting main study results?
5. Does the journal's instructions to authors recommend authors to go to the website of the International Committee of Medical Journal Editors for guidance?
6. Does the journal support publishing research on research, such as methods and reporting section?
7. Has the journal published editorials about the Series, other pieces on waste, duplication, reporting guidelines, registration, or other topics related to increasing research value?
8. Does the journal provide support for good reporting infrastructure?
9. Does the journal mention anything or have policies about open access?
10. Does the journal have a policy on public access to data from completed research?

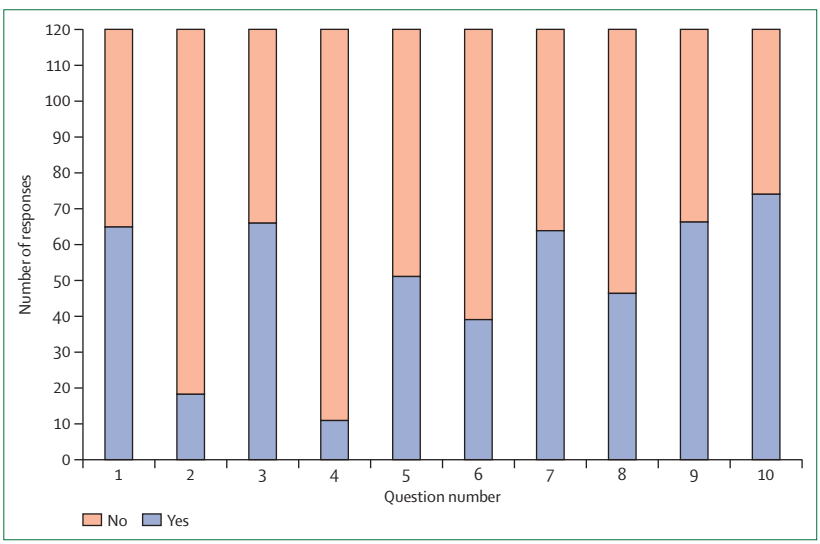

***Figure 2:* Frequency of responses from websites of 120 core clinical journals that are included in MEDLINE's Abridged Index Medicus[34]**
For the specific questions relating to each question number, see panel 2.

electronic IRB [Institutional Review Board] pathway", but such a repository for study protocols seems rare in other universities. By contrast, prospective registration of clinical trials in a publicly accessible trial register is enforced by almost all institutions we surveyed. Although registration seems common in highly respected research institutions, the extent to which this policy is adhered to in less prestigious academic institutions is unclear. Trial registration has been required by the ICMJE since 2005,[7] and some governmental institutions, such as the US Food and Drug Administration (FDA), require registration of all clinical trials.[7] Despite these policies, only about half of all published trials are currently being registered.[62] At Duke University, "registration at ClinicalTrials.gov is required before IRB approval, and registration record completion is required before IRB close-out". These examples emphasise the importance of regulation to help to maximise best research practice.

Up to half of all initiated clinical trials are unpublished.[63] The FDA requires posting of clinical trial results in ClinicalTrials.gov within a year after study completion, but this posting is done for less than a quarter of trials that are within the FDA's mandatory reporting rules,[64] possibly because of no enforcement. This situation shows the important role of universities in further enforcing the publication of all trial results. Most of the responding deans said they have a policy to make publicly available full publications of studies done at their institution (table 1). The University of Sydney, Australia, is in the final stages of establishing an open access policy that "will make publications available whenever copyright/archiving policies allow through its external access repository, no later than 12 months after the date of publication. Where access to the full text of collected scholarly works is not permitted by the publisher, publication of metadata and a link to the published work will be made openly available". At the University of Groningen, Netherlands, "full publications are typically published in its final version in the University Repository and thus largely publicly available".

Policies to make raw data and analytical algorithms publicly available seem much rarer than clinical trial results, although individual universities show promising initiatives (table 1). The University of Sydney has a "research data registry and Electronic Lab Notebook platform, both of which enable the publication of metadata (ie, data about data; data that describes and gives information about other data) and data sets". The University states that "Researchers should make completed research data sets openly available for re-use by other researchers, unless this is prevented by the requirements of legislation or University policy, or ethical, contractual or confidentially obligations. If open access is not possible due to legal or policy reasons, researchers should make metadata openly available."

Other universities have less explicit policies. Cambridge University, UK, for example, explicitly "encourages researchers to be as open as possible in discussing work with other researchers and with the public. Once results have been published, the University expects researchers to make available relevant data and materials to other researchers, on request". At the University of Bristol, UK, "researchers can make study protocols, raw data and analytical algorithms publicly available at the institutional data repository". Beyond the stated policies, no data are available for whether and how the universities monitor the implementation of any of these policies.

The slow uptake of some of the recommendations by academic institutions is unfortunate, since a large proportion of all biomedical research resources go to universities.[65] An explanation might be because university policies on these issues are rarely defined at a nationwide or even a global level, making coordination of policies difficult. This situation can be shown by the large diversity in the policies of the surveyed universities to make study materials publicly available.

Researchers

Motivated by the principle that initiation of research without a systematic review of already known evidence is unethical, unscientific, and wasteful, particularly when the research involves people or animals, three Scandinavian researchers[66] convened and inaugurated an international Evidence-Based Research Network at the end of 2014. This network will urge funders, regulators, researchers, academic institutions, and journals to implement the changes needed to promote evidence-based research. Initiatives such as Trial Forge,[67] and the Clinical Trials Transformation Initiative[68] aiming to improve trial undertaking, should also help researchers to maximise the efficiencies in clinical trials (table 1). To help to promote greater efficiencies in the research process several US Governmental agencies have released regulations that streamline and simplify the conduct of research involving human beings.[69] Additionally, in May 2015, the PRECIS-2 was published to help researchers during the design phase of their studies.[70]

Most researchers agreed that the Series was important to increase research value. However, basic scientists and clinical researchers had notably different perceptions of the concept of waste in research. For example, some basic scientists disagreed with the concept and believed that waste was less important in their specialty (eg, "[...] to state that 85% of research funding is wasted is an insult to current research efforts"; "There is no [...] waste in pure, basic science"). Some of these individuals were concerned by the risk of a negative effect of the Series on the societal view of the value of research, which could result in decreased funding. The reluctance of basic researchers to acknowledge waste in research in their specialty contrasts with the scarcity of reproducibility of basic and preclinical research.[5,71]

Most researchers endorsed the Series recommendations. Nevertheless, these individuals identified some barriers to increasing of research value (table 3).

	Barriers identified	Facilitators
Perform a systematic review of all available evidence before planning a study	Basic researchers: "The primary barrier is the vast amount of information that has to be surveyed combined with reduced time to linger and concentrate on a given project in university institutions in general." Additionally: "There is no such thing as all available evidence. What constitutes evidence for a particular study is integral part of the conceptualization of the study. Different people have legitimately different methods in using evidence. Too much evidence, some of which is just bad data, can be paralyzing and prevent innovation" Clinical researchers: "Very expensive and time consuming to do full systematic reviews and most researchers aren't good at it"	Funders to make a systematic review a condition for grant submission; funders and journals to collaborate on developing educational instruments for research in context; institutions to provide methodological and logistical support to researchers to do systematic reviews
Systematically register study protocol at inception	Basic researchers: "A registry will add extra work and a collection of information that will not correspond to the actual experiment" Clinical researchers: "…little knowledge of how and when to register"	Develop an appropriate register for basic scientists; develop researcher guides for use of the WHO's International Clinical Trials Registry Platform, PROSPERO, and other relevant repositories
Make the full protocol publicly available	Basic researchers: "…this demand would make new break-throughs impossible for smaller groups, even though the idea was theirs" Clinical researchers: "…takes time and innovative ideas might be hard to publish once in the public domain"	Develop an appropriate repository for basic scientists; provide specific funding and logistical support to researchers to make these documents and data available; funders, institutions, and editors to reward researchers making the protocol, analysis plan, results, and raw data publicly available
Make the analysis plan publicly available	Basic researchers: "Obviously these questions are not for basic research but for applied clinical research" Clinical researchers: "I would love to do this, but usually time to complete the analysis plan is too short"	Develop appropriate repository for basic scientists; provide specific funding and logistical support to researchers to make these documents and data available; funders, institutions, and editors to reward researchers making the protocol, analysis plan, results, and raw data publicly available
Systematically make their results publicly available	Basic researchers: "…time waste, need lot of time to write negative experiments" Clinical researchers: "…negative results are less likely to have enthusiasm for publication"	Develop appropriate repository for basic scientists; provide specific funding and logistical support to researchers to make these documents and data available; funders, institutions, and editors to reward researchers making the protocol, analysis plan, results, and raw data publicly available
Make raw data publicly available	Basic researchers: "…scarcity of suitable repositories and little funding to establish these" Clinical researchers: "…this would create many issues such as confidentiality, which would need to be redacted and would waste time; probably reluctance to give access to such data exists because others could use them for their own purposes; and mass sharing of data could lead to inappropriate use, as the context of data collection and the objective of the study are necessary to understand their meaning"	Develop appropriate repository for basic scientists; provide specific funding and logistical support to researchers to make these data available; funders, institutions, and editors to reward researchers making the protocol, analysis plan, results, and raw data publicly available

Table 3: **Recommendations for the barriers to reducing waste in research identified by researchers and facilitators to increasing research value**

Barriers to protocol registration and data sharing included the fear of inappropriate use of data, issues related to patient confidentiality, the protection of original researchers' efforts, and the risk of researchers having ideas stolen by others. Some individuals also thought that adherence to these recommendations could decrease researchers' autonomy and might be an obstacle to scientific discovery (eg, "In basic science, there is a great need for flexibility to modify the protocol in response to the latest finding. Too rigorous control on the planning of experiments would simply kill the last nerve in basic research"; "Research is not a car factory").

A shortage of expertise and appropriate support were also important barriers to systematic reviews being done before plans of additional studies. Some researchers expressed some concern about the emergence of several quality constraints, adding many discrete tasks (eg, protocol registration, adherence to reporting guidelines, and data sharing) that would create a cumulative and discouraging burden for researchers (eg, "We can't overly restrain creative scientists with organizational rules without burdening their work"). In fact, although adherence to these recommendations should have a positive collective effect for patients and researchers, perhaps researchers should be rewarded for implementing them. Finally, researchers identified important structural factors associated with waste in research, such as the top-down funding system with an inappropriate identification of priorities from funders rather than the bottom-up approach from researchers, a questionable peer-review and selection process, the ever-growing restrictions in research, and a reward system based on quantity of publications and journal impact factor rather than on research quality. These barriers should be taken into consideration and provide appropriate education, incentives, and support to improve researchers' compliance

with these guidelines and increase research value. Nevertheless, several researchers in basic science have taken the dearth of reproducibility and waste in research very seriously and initiatives are already underway to enable the implementation of these guidelines.[40]

Looking to the future

The overall response to the 2014 Series might be summed up as some gratifying actions, but much more needs to be done to reduce research waste than at present. From a bibliometric and social media perspective, the Series has gained some traction, which is encouraging. Recognition of the problems described in the Series, and dialogue about the recommendations and possible ways to monitor progress are important first steps. However, if researchers are to avoid the well known issue of not implementing research knowledge into practice,[72] scientists will need to use systematically planned knowledge translation strategies, including the use of theory-based strategies,[73] to affect research practice, programmes, and policies of groups such as funders, regulators, journals, academic institutions, and researchers. A good starting point might be to revisit the Series' recommendations and consider ways to monitor increased research value (table 1).

Across funders, regulators, journals, academic institutions, and researchers our investigation has shown some innovation and leadership, and suggestions of potential change, all of which need to be harnessed and sustained. Historically, the stakeholders have their own venues to talk and act within, such as the ICMJE for editors and Heads of International Research Organizations for funders. However, we are unaware of any venue in which these groups collectively engage to discuss and exchange ideas, or promote better research practice than at present. The paradox is that the issues outlined in the Series are large and complex (eg, large systemic and cultural differences probably exist between groups, such as preclinical and clinical researchers, and health services and populations health researchers, in how much of an issue these groups perceive research waste to be or how they think waste should be reduced) and no one group is responsible for addressing these concerns. Research value might be optimised through more collaborative efforts. An immediate venue to help to begin the dialogue is the forthcoming REduce Waste And Reward Diligence (REWARD, and EQUATOR conference in Edinburgh, UK, on Sept 28–30, 2015. This collaboration was envisaged as an annual forum to monitor progress and exchange ideas for the improvement of the entire research system. The structure of the meeting has been set up to help to promote and harness collaboration between all of the sectorial groups and will specifically include a meeting of several networks interested in improvement of at least one of NIHR's five stages.

For the **EQUATOR conference** see http://researchwaste.net/research-wasteequator-conference/

All five targeted groups have a part to play in increasing research value. Some argue that the most effective strategy for maximising research value might be through the leadership of funders and regulators. Funders can use funding policies to support recommendations in the Series and provide guidance to researchers on how to minimise waste. For example, the National Institutes of Health offers training in Responsible Conduct of Research,[74] an emphasis shown in initiatives of some professional bodies, such as the American Psychological Association.[75] Funders can use strong financial incentives such as withholding a proportion of grant funding for research that has not yet been made publicly available to encourage public distribution. Regulators also have the authority to enforce change in keeping with the Series recommendations.[52] Additionally, research ethics boards, for example, could have a greater role than at present in checking that research in an area has been shown to be needed and helping to ensure that all relevant studies are appropriately registered (table 1).

Some argue that academic institutions are ideally placed to lead the movement to enhance research value. These universities are training subsequent generations of researchers, some of whom migrate to other places of employment, such as journals, funders, and academic institutions. For example, perhaps universities could employ a new professional publications officer to help researchers, their staff, and trainees to adhere to policies of funders and journals, such as registering their studies at inception and using reporting guidelines to report their research.[76] Other innovations could also be integrated into the role of publications officers, including helping researchers in the development of research protocols.[77]

Another strategy that might be considered is setting adherence targets for each of the Series' 17 recommendations and monitoring progress towards achieving the targets. Would it be unreasonable to consider annual increases in research value, say by 10% over the next decade? For example, a 2012 survey[59] of journals' instructions to peer reviewers showed that reference to or recommendations to use of reporting guidelines during peer review was rare (19 [16%] of 116 journals assessed). Positive annual incremental change could be an improvement of at least 10% from 2012 in guidance to peer reviewers in the 116 journals initially surveyed. More active dissemination of recommendations, in keeping with the Series recommendations, might include journal organisations, such as ICMJE and the World Association of Medical Editors, promoting use of reporting guidelines by peer reviewers and authors. This distribution might constitute part of a instrument for groups affected by reporting research. More generally, increases in research value can cut across stakeholders and dimensions of research (table 1). These issues along with a general discussion about infrastructure needed to enable and monitor change in research value, and ways to fund it, will be discussed in the REWARD/EQUATOR meeting, which is planned as a series of meetings to bring funders, editors, and research organisations together with groups working on methods to reduce research waste.

Perhaps it is also time to reconsider how the entire research awards system works? This system has been in place for a long time and the state of biomedical research suggests a different set of metrics and currencies might be needed to increase the value of research investment (table 1). During the waste launch symposium,[29] some argued that the reward system is conservative and closed to new ideas. Alternative systems could be discussed, piloted, assessed, and implemented if they improve research value.[78,79] The need for a change in the research reward system is also something that could be discussed at the REWARD/EQUATOR meeting.

Our initial observations are based, in part, on assessing websites, which were often difficult to navigate. Similarly, we could have missed information or some of the content might have been modified since our investigation. For example, on some journal websites instructions to authors are modified at the beginning of the calendar year. The survey response rates were also lower than we would have liked, therefore needing more cautious interpretation.

This overview is a starting point. The plan is to publish more in-depth assessments of several of the stakeholder groups assessed and encourage others to do likewise. Several of the issues reported here will be part of the deliberations at the REWARD/EQUATOR meeting. The meeting will be a central point for groups such as funders, regulators, journals, academic institutions, and researchers, to help to increase the value of the enormous investments made in biomedical research. Everyone is responsible for helping to ensure that all research is planned, conducted, and reported to such high standards that the findings are of value to all. Everyone deserves a guarantee of reliable evidence resulting from the global research endeavours.

Contributors

DM coordinated the project, wrote the first draft of the introduction and discussion, and with IDG, completed the assessment of the journals, including the editor interviews and initial draft. PG, MN, and IC completed the funders assessment and initial draft. PMMB and DAK completed the academic institutions assessment and draft. IB and PR completed the researchers assessment and draft. All authors provided feedback on subsequent drafts of the paper.

Declaration of interests

We declare no competing interests.

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