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

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Abstract

The biomedical research complex has been estimated to consume almost a quarter of a trillion dollars every year. Unfortunately, there is evidence that a high proportion of this sum is avoidably wasted. Last year the *Lancet* published a series of 5 papers 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. Seventeen recommendations were addressed to five main stakeholders - funders, regulators, journals, academic institutions, and researchers. This paper provides some initial observations on the possible impacts of the series. It appears to have provoked several important discussions and has appeared on the agendas of several key players. There are also examples of individual initiatives illustrating ways of reducing waste and increasing value in biomedical research. This momentum is likely to move more strongly across stakeholder groups, if more collaborative relationships evolve among key players; more important work is required to increase research value. A forthcoming meeting in Edinburgh will provide a forum within which to foster the collaboration needed.

Introduction

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

Non-publication was one of four contributors to the estimated 85% of current research funding that Chalmers and Glasziou suggested in 2009 were being avoidably "wasted"[13] across the entire biomedical research spectrum (e.g., clinical, health services, and basic science). Evidence of the degree and avoidability of waste in research production at each of their 4-stage model (see Figure 1) has strengthened: imbalenced research question selection, poor study design[14,15] and execution, non-publication[16] and poor reporting[17]. In addition to 295 citations, the 2009 paper led the 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. Their "Adding Value in Research" programme added an additional stage aiming to ensure that NIHR funded research: 1. addresses questions relevant to clinicians, patients and the public; 2. uses appropriate design and methods; 3. is delivered efficiently; 4. results in accessible full publication; and 5. produces unbiased and usable reports. They developed a quality improvement tool[18] for these 5 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 should reference an existing systematic

review " as well as including reference to any relevant literature published subsequent to that systematic review" or where no such systematic review exists applicants should undertake to review the relevant evidence (using a methodology that systematically identifies, critically appraises and then synthesises the available evidence) which "must also include reference to relevant on-going studies, e.g. from trial registries".[19]

Last year the *Lancet* published a series of articles ("Increasing value: reducing waste") extending the 2009 analysis to 50 journal pages, with over 40 authors[20-24] focused on the 5 NIHR stages (see Figure 1). 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.".[25]

The series, and an accompanying symposium[26], provided a voluminous body of evidence of the problems in biomedical research, along with 17 recommendations (see Table 1) to help increase its value, covering funders, regulators, journals, academic institutions, and researchers. The problems include (although they are not limited to) whether planned research met the needs of end users.[27-29]

Initial media attention included coverage by several newspapers including the leading German paper Der Spiegel[30], although there has been almost no response from German researchers or organizations.[31] Several research funders responded through meetings, working parties, and some changes of processes (see Funders section below). In the year since their publication the five articles have been downloaded 46,596 times from the Lancet.com and Science Direct.com websites. The five articles have already been cited 113 times (Scopus); were all in the top 5% of all articles indexed by Scopus; and their Altmetric scores (social media) all ranked above the 98th percentile (of more

than 3 million articles scored) including 589 tweets (about 20% of which were by healthcare professionals).

This follow-up paper offers an overview of the initial influence of the series. Prior to conducting the assessment a protocol was developed outlining the key players, the methods of our investigation, including sampling frames (see Panel 1 with more detail in Appendix 1). The primary focus was to examine what funders, regulators, journals, academic institutions, and researchers are doing, and plan to do, to address waste in biomedical research.

Funders

A few funders have already responded to the series. In May 2014, The French Institute of Health and Medical Research INSERM (Institut National de la Santé et de la Recherche Médicale), in conjunction with the EQ

UATOR network, organised a 1-day conference in Paris on "Improving reporting to decrease the waste of research" with the head of the Wellcome Trust and NIHR's HTA programme among the speakers (video of all sessions is available on the EQUATOR website.[32] The series was included in recent discussions of INSERM's strategic plan for 2016-2020, and was presented at the annual meeting of INSERM team leaders.[33] In Australia, the National Health and Medical Research Council (NHMRC) set up a working party to review all the recommendations in the series[34], updating and modifying their procedures, and also featured an opening session on "Adding Value, Reducing Waste" at their 2014 annual scientific meeting[35] The series was also on the agenda of the Heads of International Research Organizations (HIRO) group's meeting in 2014.

We are also heartened that concern about poor replicability and quality of much animal and other preclinical research[36] 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 (www.nc3rs.org.uk) has supported three international meetings (in Nijmegen, Edinburgh and Washington DC) on systematic reviews of animal research, and this year held an international meeting on biased under-reporting of animal research[37], bringing together several relevant groups targeted in the series. Whether or not the Lancet series had any role in these initiatives, they are very welcome.

The examination of the funder's websites (see Methods panel) indicates that most funders are not explicit about many of the key issues, making it challenging to evaluate them. The NIHR had a number of innovative and exemplary features, such as requirements for systematic reviews before embarking on additional primary studies, active monitoring of ongoing studies, and its own journal. For other funders, the picture was more mixed (see Table 2). Most required trial registration, but few required systematic reviews prior to additional primary studies, or mentioned reporting guidelines, such as CONSORT, or the EQUATOR Network. Regarding conduct of systematic reviews before additional primary research, most funding organisations only required systematic reviews before considering funding future clinical trials. NIHR was an exception in that they ask for a systematic review for any research projects being submitted to them (see Table 1; 3rd recommendation from series). 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 program, and the Patient-Centered Outcomes Research Institute (PCORI) in the United States.

To maximize research value funders may want to consider ways to enhance their funding priorities in line with existing (regional, national, and international) priority setting initiatives (See Table 1; 2nd recommendation). Similarly, funders may want to enhance efforts to ensure that wherever possible protocols are developed using relevant guidance, such as SPIRIT for randomized trials and PRISMA-P for systematic reviews (see: www.equator-network.org/), and that the research they fund is registered in a relevant repository (e.g., World Health Organization's International Clinical Trials Registry Platform - http://www.who.int/ictrp/en/, and PROSPERO) (See Table 1; 4th recommendation). For example, a review of 75 recently funded randomized trial protocols at one granting agency showed they often did not provide adequate information about allocation sequence generation (13% missing) and concealment (19% missing): important characteristics of well conducted randomized trials.[38] Funders could also consider stronger policies to support (guidance, education, and infrastructure) and enforce (incentives and penalties) publication of all research, open access, and data sharing.

Regulators

Regulators can help here by not providing ethics approval of protocols that are scientifically inadequate. Research proposals that are scientifically poor are, by definition, ethically inadequate. For example, the guidance for researchers issued by the newly established Health Research Authority (HRA) [39] 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."

On the other hand, research regulators can reduce waste resulting from inefficiencies in research regulation. Some of these result from hyper-regulation of low risk non-interventionist research, such as many descriptive surveys. Following a report[40] from the Academy of Medical

158 Sciences in the UK, the HRA is now addressing this problem. As a result, proportionate measures of
159 assessing research proposals have been introduced that take account of the plausible risks associated
160 with the research proposals being considered.

161 Some research regulators have also taken steps to reduce the problem of biased under-
162 reporting of research (see Table 1; 14th recommendation). In the UK, a favourable ethics opinion
163 for proposed clinical trials will not now be granted unless the proposed trial has been registered
164 publicly.[41] Following pressure from the Alltrials campaign, the European Medicines Agency has
165 now committed to make available all clinical study reports (see Table 1; 5th and 13th
166 recommendations) of research leading to marketing licences for new drugs.[42]

167 **Journals**

168 Given that more than half of the reports of clinical trials do not set their results in the
169 context of the totality of evidence[24], journals have much work to do to improve this situation. They
170 can achieve this by providing specific guidance on their websites about this crucial feature and
171 providing similar guidance to peer reviewers. In response to the series, the Lancet strengthened its
172 requirement to put research into context (see Table 1; 3rd recommendation).[43] From the beginning of
173 this year, all research papers submitted to any journal in the Lancet family must include a 'Research
174 in context' panel. The editors expressed their "hope that increasing the prominence of putting
175 research into context in the submission and publication stages will help researchers, institutions and
176 funders make decisions earlier in the process on which research questions to address and fund.".
177 Other journals have made similar efforts, such as panels asking authors 'what this paper adds'.
178 Something more explicit, such as the research in context panel might be more helpful.

Based on our interviews with journals editors (see Methods panel) the Lancet series has been an impetus for reflection and change among some editors. It has been discussed internally during in-house editorial meetings, at an editorial board retreat of one journal and is on the agenda for discussions with other editorial boards. The series has also been on the agenda of the influential editorial groups, such as ICMJE, along with other ongoing initiatives, such as the Institute of Medicine's recent report on data sharing.[12] Some journals have already acted on the series. For example, PLoS Medicine commissioned an editorial on how open access can reduce waste.[44] Other concurrent initiatives focused on reducing 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.[45] This policy is likely to introduce a strong incentive to prospective authors across this content area to use reporting guidelines. Other fields are starting to implement similar strong guidance.[46]

The results of examining the journals websites (see Methods panel) indicates there is wide variability of information contained on journal websites and the language used across journals (see Figure 2). This is likely to confuse prospective authors, particularly those early on in their research careers and those whose first language is not English. While journals want to maintain their uniqueness, and emphasize particular issues important to them, it might be useful to consider some items, perhaps particularly those related to the recommendations in the series, as core information, and unambiguous language that could be included across all journal websites. This might help improve matters for journals, prospective authors, and readers.

One immediate goal could be for every journal to explicitly support use of reporting guidelines (see Table 1; 17th recommendation). The evidence indicates that their use is associated with increases in the completeness of reporting clinical trials.[48] Approximately half of the websites

mentioned reporting guidelines which is a similar proportion to that reported by Hirst and Altman in 2012.[49] Far fewer journal websites explicitly mentioned the EQUATOR Network and few mentioned the use of systematic reviews in the context of reporting the main results of their research (see Table 1; 3rd recommendation).

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, few (11%) reports from a sample of 255 cancer trials provided sufficient information about the interventions studied[50] to allow clinicians to use the results in practice.[51] Across the 10 questions used to assess the websites the results did not vary substantially by journal impact factor (< 5; ≥ 5).

Academic Institutions

We are aware of very little explicit attention by academic institutions to the Lancet series. One 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 50 Medical Universities of Iran.[52]

Based on our e-mail survey (see Methods panel) we received complete responses from only 26 of the 100 invited universities. We found that most (n=20) schools have a policy to register clinical trials in a publically 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 the 26 universities indicated not having an institutional policy for any of these five elements (see Table 1; e.g., 12th and 14th recommendations).

Only five medical schools reported having a policy to make all study protocols publically available. At Duke University, for example, "all approved study protocols are available through the School of Medicine's electronic IRB [*Institutional Review Board*] pathway", but such a repository for study protocols seems rare elsewhere. In contrast, prospective registration of clinical trials in a publically accessible trial register is enforced by almost all institutions we surveyed. Although registration appears common among 'top' institutions, the extent to which this policy happens across less prestigious academic institutions is unclear. Trial registration has been required by the ICMJE since 2005[7], and also some governmental institutions, such as FDA in the US, require registration of all clinical trials.[7] Despite these policies, only about half of all published trials are currently being registered.[54] At Duke University "registration at ClinicalTrials.gov is required before IRB approval, and registration record completion is required before IRB close-out". These examples highlight the importance of regulation to help maximize best research practice.

Up to half of all initiated clinical trials remain unpublished.[55] The Food and Drug Administration (FDA), in the United States, requires posting of clinical trial results in ClinicalTrials.gov within one year after study completion, but this is done for less than a quarter of trials falling within FDA's mandatory reporting rules[56], possibly due to lack of enforcement. This indicates the important role of universities in further enforcing the publication of all trial results. The majority of the responding deans said they have a policy to make publically available full publications of studies performed at their institution (see Table 1; 17th recommendation). The University of Sydney is currently in the final stages of establishing an open access policy which "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, "full publications

248 are typically published in its final version in the University Repository and thus largely publically
249 available".

250 Policies to make raw data and analytical algorithms publically available seem much rarer,
251 although individual universities show promising initiatives (see Table 1; 5th and 14th
252 recommendations). The University of Sydney has a "research data registry and Electronic Lab
253 Notebook platform, both of which enable the publication of metadata (i.e., data about data - data
254 that describes and gives information about other data) and data sets". It states that "Researchers
255 should make completed research data sets openly available for re-use by other researchers, unless
256 this is prevented by the requirements of legislation or University policy, or ethical, contractual or
257 confidentially obligations. If open access is not possible due to legal or policy reasons, researchers
258 should make metadata openly available".

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

266 The slow uptake of some of the recommendations by academic instructions is unfortunate,
267 as a considerable proportion of all biomedical research resources go to universities[57]. One
268 explanation may be the fact that university policies on these issues are rarely defined on a nationwide
269 or even global level, making it difficult to coordinate policies. This can be illustrated by the large
270 variety in the surveyed universities' policies to make study materials publically available.

Researchers

Motivated by the principle that it is unethical, unscientific, and wasteful to embark on research without systematically reviewing evidence of what is already known, particularly when the research involves people or animals, three Scandinavian researchers[58] convened and inaugurated an international Evidence-Based Research (EBR) Network at the end of 2014. The EBR 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[59], and the Clinical Trials Transformation Initiative[60] both aiming to improve the efficiencies of trial conduct, should also help researchers maximize the efficiencies when conducting clinical trials (see Table 1; 10th recommendation).

To gauge further the researcher community about the series we surveyed them (see Methods panel). 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 believe waste was less important in their field (e.g., "[…] 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 were concerned by the risk of a negative impact of the series on the societal view of the value of research, which could result in decreased funding. The reluctance of basic researchers to face waste in research in their field contrasts with the evidence of the lack of reproducibility of basic and pre-clinical research.[5,62]

Most researchers endorsed the series recommendations. Nevertheless, they identified some barriers to increasing research value (see Table 3). 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 having their ideas stolen by others. Some also

considered that adherence to these recommendations could decrease researchers' autonomy and be an obstacle to scientific discovery (e.g., "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").

Lack of expertise and appropriate support were also important barriers to performing systematic reviews before planning additional studies. Some researchers expressed some concern about the emergence of several quality constraints adding many discrete tasks (e.g., protocol registration, adherence to reporting guidelines, data sharing etc.) that would create a cumulative and discouraging burden for researchers (e.g., "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 impact for patients and researchers, perhaps researchers should be rewarded for implementing them. Finally, researchers identified important structural factors involved in waste in research such as the top-down funding system with an inappropriate identification of priorities, a questionable peer-review and selection process, the ever-growing "red tape" in research, and a reward system based on quantity of publications and journal impact factor rather than on quality. It is important to take into consideration these barriers and provide appropriate education, incentives, and support to improve researchers' compliance with these guidelines and increase research value. Nevertheless several researchers in the field of basic science have taken the lack of reproducibility and waste in research very seriously and initiatives are already underway to facilitate the implementation of these guidelines.[63]

Looking to the Future

The overall response to the 2014 series might be summed up as – some gratifying actions, but much, much more to be done. From a bibliometric and social media perspective, the series has

317 gained some traction, which is encouraging. Recognition of the problems described in the series, and
318 dialogue about the recommendations, and possible ways to monitor progress are important first
319 steps. However, if we are to avoid the well known problem of failing to implement research
320 knowledge into practice[64], we will need to use systematically planned knowledge translation strategies
321 including the use of theory-based strategies[65] to influence research practice, programs, and policies
322 of the five included groups, and others. A good starting point may be to re-visit the series'
323 recommendations and consider ways of monitoring of increased research value (see Table 1).

324 Across the five groups our investigation has revealed nuggets of innovation and leadership,
325 and indications of potential change, all of which need to be harnessed and sustained. Historically,
326 the stakeholders have venues to talk and act within their own silos, such as the ICMJE for editors
327 and HIRO for funders. However, we are unaware of any venue in which these groups collectively
328 engage to discuss and cross pollinate ideas, or promote better research practice. The paradox is that
329 the problems outlined in the series are large and complex (e.g., there are likely large systemic and
330 cultural differences between preclinical and clinical researchers, and others, such as health services
331 and populations health researchers, in how problematic they see waste or how they think it should
332 be reduced) and no one group is responsible for addressing them. Harnessing research value may be
333 optimized through more collaborative efforts. One immediate venue to help begin the dialogue is
334 the forthcoming REWARD/EQUATOR conference (http://researchwaste.net/research-
335 wasteequator-conference/), envisaged as an annual forum to monitor progress and exchange ideas
336 on improving the entire research system. The structure of the meeting has been set up deliberately to
337 help promote and harness collaboration between all of the sectorial groups, and others, and will
338 specifically include a meeting of several networks interested in improvement of at least one of the 5
339 stages.

All five targeted groups have a role to play in increasing research value. Some argue that the most effective strategy for maximizing research value may 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 minimize waste. For example, the National Institutes of Health offers training in 'Responsible Conduct of Research' (http://grants.nih.gov/training/responsibleconduct.htm), an emphasis reflected in initiatives of some professional bodies, such as the American Psychological Association (http://apa.org/research/responsible/index.aspx). Funders can also hold back a proportion of grant funding for research that has not yet been made publically available, to bring about better value. Regulators have the authority and enforce change in keeping with the series recommendations.[42] Research ethics boards, for example, could play a greater role in checking that it has been demonstrated that more research in an area is needed and helping to ensure that all relevant studies are appropriately registered (see Table 1; 14th recommendation). Funders can employ strong financial incentives, such as holding back a proportion of grant funding for research that is not published or made publically available, to bring about better value. They can also use funding policies to support the series recommendations and provide guidance to researchers on how to minimize waste.

Others argue that academic institutions are ideally placed to lead the movement to enhance research value. They 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.[66] Publication officers could also help researchers adhere to policies of funders and journals, such as registering their studies at inception and using reporting guidelines to

363 report their research. Other innovations could also be integrated into the role of publications
364 officers, including helping researchers when developing research protocols.[67]

365 Another strategy that might be considered is setting adherence targets for each of the series'
366 17 recommendations and monitoring progress towards achieving the targets. Would it be
367 unreasonable to consider annual increases in research value, say by 10% over the next decade? For
368 example, a 2012 survey[49] of journals' instructions to peer reviewers shows that reference to or
369 recommendations to use reporting guidelines during peer review was rare (19 of 116 journals
370 assessed; 16%). Positive incremental change could be observing at least a 10% improvement in
371 guidance to peer reviewers in the 116 journals initially surveyed. More active dissemination, in
372 keeping with the series recommendations, might involve journal organizations, such as ICMJE and
373 the World Association of Medical Editors, promoting use of reporting guidelines by peer reviewers
374 and authors. This might constitute part of a toolkit for groups affected by reporting research. More
375 generally, increases in research value can cut across stakeholders and dimensions of research (see
376 Table 1). These issues along with a general discussion about infrastructure needed to facilitate and
377 monitor change in research value, and ways to fund it, will be discussed during the forthcoming
378 REWARD/EQUATOR meeting in Edinburgh (http://researchwaste.net/research-wasteequator-
379 conference/) which is planned as a series of meetings to bring together funders, editors, and
380 research organisations together with groups working on methods to reduce research waste..

381 Perhaps it is also time to reconsider how the entire research awards system works? It has
382 been in place for a considerable time and the current state of biomedical research suggests a
383 different set of metrics and currencies may be needed to increase the value of research investment
384 (see Table 1; 12th, 15th, and 17th recommendations). During the waste launch symposium some
385 argued that the current reward system is conservative and not open to new ideas. Alternatives could

be discussed, piloted, evaluated, and, implemented if they bring better research value.[68,69] The need for a paradigm shift in the research reward system is also something else that could be discussed at the forthcoming REWARD/EQUATOR meeting.

Our initial observations are based, in part, on examining websites which were often difficult to navigate. Similarly, it is possible that we missed information or that some of the content has been modified since we examined it. 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 requiring more cautious interpretation.

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

Contributorship

DM coordinated the project, wrote the first draft of the introduction and discussion, and with IG 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; and IB and PR completed the researchers (authors) assessment and draft. All authors provided feedback on subsequent drafts of the paper.

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Table 1

The Lancet series recommendations and examples of groups who can take action to discuss, endorse, and implement the recommendations and monitor progress.

#	Recommendation	Monitoring	Examples of groups who can take action
	Research priorities		
1	More research on 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, HIRO
2	Research funders should make information available about how they decide what research to support, and fund investigations of 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, 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 required 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 research that is in progress, ensure that they are 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, 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, WHO platform
6	Maximise the effect-to-bias ratio in research through defensible design and conduct standards, a well trained	Proportion of publications without conflicts of interest, as attested by declaration statements and then	Trial Forge, CTTI, HIRO, COMET, OMERACT,

	methodological research workforce, continuing professional development, and involvement of non-conflicted stakeholders	checked by reviewers; the proportion of publications with involvement of scientists who are methodologically well qualified is also important, but difficult to document	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, 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	Trial Forge, CTTI, Health Research Authorities, 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 they 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, Research Ethics Boards
10	Researchers and research managers should increase the efficiency of recruitment, retention, 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 ways to improve the efficiency of biomedical research	Trial Forge, 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 CEOs, Trial Forge, CTTI
	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, U15 (Canada),
13	Investigators, funders, sponsors, regulators, research ethics committees, and journals should systematically develop and adopt standards for the content of	surveys of how many stakeholders adopt international standards	Alltrials, HIRO, clinicaltrials.gov, ISRCTN, WHO platform

	study protocols and full study reports, and for data sharing practices		
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 available protocols, full study reports, and participant-level data	HIRO, COPE, IRBs, ICMJE, WAME,
	Reporting		
15	Funders and research institutions must shift research regulations and rewards to align with better and more complete reporting	when assessing research (or researchers), funders and research institutions should consider the accessibility of research protocols, study materials, study data, and their use by others	HIRO, 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, individual funding agencies
17	Funders, institutions, and publishers should improve the capability and capacity of authors and reviewers in high-quality and complete reporting	researchers should use reporting guidelines, registries, archives, etc; and take up training opportunities	HIRO, CSE, EASE, EQUATOR, ICMJE, WAME, COPE CONSORT, PRISMA, STaR Child Health

Alltrials -
Altmetrics – Alternative metrics
CONSORT – Consolidated Standards of Reporting Trials
COPE – Committee on Publication Ethics
CSE - Council of Science Editors
CTTI – Clinical Trials Transformation Initiative
EASE - European Association of Medical Editors
EBRN – Evidence Based Research Network
HIRO – Heads of Research Organizations
ICMJE – International Committee of Medical Journal Editors
ISRCTN - International Standard Randomised Controlled Trial Number
JLA – James Lind Alliance
NIH – National Institutes of Health
PRISMA – Preferred reporting items for systematic reviews and meta-analyses
StarChild Health -
U15 (Canada) – Leading research intensive universities in Canada
WAME - World Association of Medical Editors

617
618 Table 2
619
620 Information available on the websites of selected funding agencies with regard to some dimensions of "reducing waste of research" framework
621

Funders (Country)	Is there engagement with users of research in prioritizing funding for future research (R2)	Are systematic reviews a key part of the information to inform future (basic or applied) research priorities? (R3)	Does the funder require prior registration of research? If so, which types? (R4)	What is the funder's policy on public access to data from completed research? (R13, R14)	What is the funder's policy on public access to protocols for completed or ongoing research? (R13)	What is the overall process to set a research agenda? (R2)
National Institute for Health Research – NIHR (England)	They involve researchers, policy makers and patient's representative. Active patient involvement is key in the process. Outline and/or full applications (depending on specific research programme and/or funding stream) are peer reviewed – this includes **a Public and patient involvement (PPI) reviews**. This relates to research applications. In terms of the decisions to fund applications, Programme Boards have PPI members who will consider applications from a **PPI perspective and**	**Yes, for any type of research** The funder provides funding for systematic reviews. For Health Technology Assessment (HTA) applications, any relevant and ongoing clinical trials have to be also included. There is a specific system for monitoring the conduct of clinical trials. Reviews are carried out internally by NETSCC Programmes to ensure research not duplicated within NIHR Programme portfolios (and to identify, in certain cases, where research may feed into other NIHR calls for research in commissioned areas/themed calls – the	**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 regarding registration (for research application, contracting, start-up processes – this is available on website). NETSCC-funded projects which include	The rules for publishing completed research are here http://www.nihr.ac.uk/policy-and-standards/publishing-research-findings.htm • the principal award holder submits an end-of-project report within 14 days study close. This is managed through NIHR monitoring processes • to meet NIHR's open access commitment a copy of the final manuscript is deposited with UK PubMed Central upon acceptance for publication, to be made freely available as soon as possible and in any event within six months of the journal publisher's official date of final publication.	All of protocols are published on the programme website.	NIHR Evaluation, Trials and Studies (NETSCC), part of NIHR programme, works with external organisations and individuals, including a public website for suggestions, to identify research questions likely to make the greatest difference in people's health. An advisory board prioritises proposals along with checks that there is 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

	patient need.	latter is perhaps not completely clear on the website)	systematic review as part of their protocol, must register protocols on the PROSPERO database.			
Medical Research Council – MRC (United Kingdom)	For setting the research agenda stakeholder involvement is very important (includes department of health, department of international development, devolved administrations) but they don't get involved in individual funding decisions. In individual funding decisions, strong involvement of researchers and the private sector (pharma industry); very limited and selective involvement of the public and patients. Public and patients are only involved 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. The latter requires clear rationale based on an analysis of previous work but not a systematic review per se The only proposals requiring 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 (EME) Programme so their requirements which include clinical trial registration are followed.	MRC has policies for data sharing although it emphasizes 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 there is flexibility.	There is no policy on protocols, only a policy for completed research beyond the requirements of sharing information as part of registering clinical trials.	There is an overall strategic plan to guide decisions about research priorities and there are specific goals and objectives 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 involved in setting the research agenda and identifying priorities.
National Health and Medical Research Council - NHMRC (Australia)	Researchers are strongly involved. The degree of involvement of other stakeholders is unclear.	**No,** Expert opinion seems to be the key. No explicit mention of the need for systematic reviews prior to new primary research.	**Yes. For Clinical trials only**	Yes. Publication from NHMRC supported research must be deposited into an open access institutional repository within a twelve months of publication but	No. We were unable to identify a policy for access for protocols beyond the requirement to	There is an overall strategic vision and they have health care, preventive and community health and genetic committees to advise them along with clear principles:

				don't specifically mention databases.	share information as part of the registration of clinical trials.	Fairness, Transparency. Independence, Appropriateness and balance, Research community participation, Confidentiality, Impartiality, Quality and excellence.
National Institute of Health – NIH (USA)	NIH Institutes receives data and information on the burden of disease and disability from patient and advocacy groups, professional societies, and voluntary organizations. Clinicians and basic and clinical scientists provide input on scientific opportunities. NIH Institutes and Centre's advisory councils/boards made up of scientific expert and members of the public make recommendations to ICs. In the first stage of peer review, fellow researchers evaluate 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	**No –**NIH uses a variety of reports and data to inform these decisions but systematic reviews is not a required piece of information 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, as well as commercialization 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 upon acceptance for publication 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	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 U.S. congress sets NIH and its institute and centers (IC) 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. Trans-NIH planning for the Common Fund involves broad stakeholder input from multiple scientific and public inputs. The mission of each NIH institute and center generally focus on a different disease, organ, or stage of life. The individual ICs set their own research priorities considering the following factors, IC 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

	the IC.			research to the public by linking information on publications and patents arising from NIH funded projects to project abstracts and administrative information, including budget		investigator initiated proposals.
Canadian Institute for Health Research – CIHR (Canada)	Strong involvement of researchers, moderate involvement of policy makers, selective or limited involvement of members of public and industry. The Investigator Initiated program uses peer reviewers to evaluate and rank which proposals should be funded. These are primarily academics/healthcare providers, however, depending on the expertise required to review the proposal can also include knowledge users (e.g., policy makers, industry representatives). The priority-driven research program also uses peer reviewers but each peer review	**No,** Expert opinion seems to be the key. They do encourage a systematic review for clinical trials. The specific requirements for proposals can vary between funding opportunities but the criteria for assess evidence and justification for research can include completeness of the literature review and relevance to study design/research plan.	**Yes, for clinical trials**	Yes. The Tri-Agency Open Access Policy on Publications [1](Tri-Agency or Tri-Council refers to Canada's three Federal Research Granting Councils, CIHR, the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC))requires that any publication arising from agency supported research must be deposited into an institutional or disciplinary repository that makes the manuscript freely accessible within 12 months of publication, and/or published in a journal that offers immediate open access or that offers open access on its website within 12 months. CIHR researchers are also required to deposit some	No, The Tri-Agency Open Access Policy on Publications provides policy guidance related to public access for all completed research. There is no separate policy on protocols (except for the requirements for clinical trials as specified in Chapter 11 of the TCPS-2. All fields outlined in the WHO Trial Registration Data Set (TRDS) must be completed in order for a trial to be considered fully registered. A registration with missing	CIHR is a health research funding organization. CIHR does not commission research of any kind for its own use. 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 prioritized 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. Strategic priorities are developed by CIHR's Governing and Science Council, by evaluating government priorities, emerging needs,

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	committee is tailored to the specific strategic initiative competition. Depending on the scope and nature of the program these reviewers can include some 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, provider and private sector reviewers.			specific types of data in appropriate public databases immediately upon publication of research results.	information or uninformative fields in the TRDS is unacceptable0	trends and important knowledge deficits in the Canadian health research landscape. More specifically, in order to determine how to allocate its strategic funding, CIHR develops a five-year Strategic Plan based on a number of important inputs and involving many stakeholders. Inputs include the Government of Canada Science & Technology (S&T) Strategy, Ministerial priorities and key stakeholders including patients, industry, policy makers and provincial health ministries. In addition 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 recently approved by CIHR's Governing Council and is posted on CIHR's website. CIHR's Institutes and their Scientific Directors are also involved, along with their communities, in helping to inform the directions of CIHR's Priority-Driven programs

						through the design of initiatives that service the priorities of their research communities. This process often includes consultations with researchers, partners, patients, etc. Each CIHR institute also has their own strategic plan that aligns with CIHR's strategic plan (as mentioned above) and is available on CIHR's website. CIHR's Governing Council is comprised of 18 women and men who are able to contribute to the achievement of CIHR's objectives in the overall interests of Canadians; each come from a unique background and possess an outstanding skill set; reflect a range of relevant backgrounds and disciplines.
Deutsche Forschungsgemeinschaft –DFG (Germany)	Researchers are involved in reviewing and making decisions. For some proposals, it goes to the joint committee that involves policy makers too. n the decision making process, the proposal is evaluated by voluntary reviewers (scientists) exclusively according to scientific criteria; on the basis of this expert review, it is	**Yes for clinical trials** The current state of the research field and evidence is to be presented 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	**Yes for clinical trials only**	There are suggestions and examples for researchers on reusing 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 it isn't compulsory.	All clinical trials funded after the 1.6.2014 have to deposit the study protocol at the clinical trials registry prior to trial start but not for other study designs.	The DFG is the self-governing organisation for science and research in Germany. It serves all branches of science and the humanities. The chief task of the DFG is to select the best research projects by scientists and academics at universities and research institutions on a competitive basis and to finance these projects. Projects are presented by scientists and academics or by universities in a proposal dealing with their chosen topics from a particular discipline or taking an

	assessed by chosen members of the Review Board (scientists), and the final decision is taken by the Grants Committee. There are different Grants Committees involved for the different programmes of DFG funding. They consist of researchers, representatives of the federal and the state governments as well as from the Donors' Association for the Promotion of Sciences and the Humanities in Germany. Members of the standing review boards all elected by the scientific communities every four years.	be funded in the individual grants programmes.				interdisciplinary approach. In a multi-layered decision making process, the proposal is evaluated by voluntary reviewers exclusively according to scientific criteria; on the basis of this expert review, it is assessed by chosen members of the Review Board, and the final decision is taken by the Grants Committee. In this way, DFG funding guarantees quality-based differentiation in the German research system. In keeping with the DFG's concept of its role as a self-governing organisation, any eligible researcher may submit a funding proposal at any time and on any research topic. As the DFG does not specify a topic for proposals, but, instead, reacts to proposals on any topic, it promotes research primarily in what is known as "response mode", thereby complementing the agenda driven and programme oriented funding by the ministry of research and education. (BMBF) in Germany.

Table 3
Barriers to reducing waste in research identified by researchers and facilitators to increasing research value

#	Recommendations	Barriers identified	Facilitators
3	Perform a systematic review of all available evidence before planning a study	Basic Researchers (BR): "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." BR: "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 (CR): "Very expensive and time consuming to do full systematic reviews and most researchers aren't good at it."	Funders to make systematic review a condition for grant submission; Funders and journals to collaborate on developing educational toolkits for "research in context"; Institutions to provide methodological and logistical support to researcher to perform systematic reviews
14	Systematically register study protocol at inception	BR:"A registry will add extra work and a collection of information that will not correspond to the actual experiment." CR: Lack of knowledge in how and when to register.	Develop appropriate register for basic scientists; Develop researcher toolkits for use of the World Health Organization's International Clinical Trials Registry Platform, PROSPERO, and other relevant repositories.
5	Make the full protocol publicly available	BR: This demand would make it impossible for smaller groups to come to new break throughs even though it is their idea CR: Takes time and innovative ideas might be hard to publish once it's on the public domain	To develop appropriate repository for basic scientists; to provide specific funding and logistical support to researchers to make these documents and data available; funders, institutions,
5	Make the analysis plan publicly available	BR: Obviously these questions are not for basic research but for applied clinical research CR: I would love to do this, but usually there is too little time to complete the analysis plan	
15	Systematically	BR: Time waste, need lot of time to write negative	

	make their results publicly available	experiments. CR: Negative results are less likely to have enthusiasm for publication.	editors to reward researchers making the protocol, analysis plan, results, raw data publicly available.
5	Make raw data publicly available	BR: Lack of suitable repositories-lack of funding to establish these. CR: This would create many problems of confidentiality etc. that would require redacting and involve a lot of "wasted" time. There is also probably reluctance to give access to such data because others may use them for their own purposes. CR: massively sharing data could lead to inappropriate use, as the context of data collection, the objective of the study, are necessary to understand their meaning.	

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628 Figure 1: Stages in research production (stage 3 – dashed box – added to 2009 model by NIHR).
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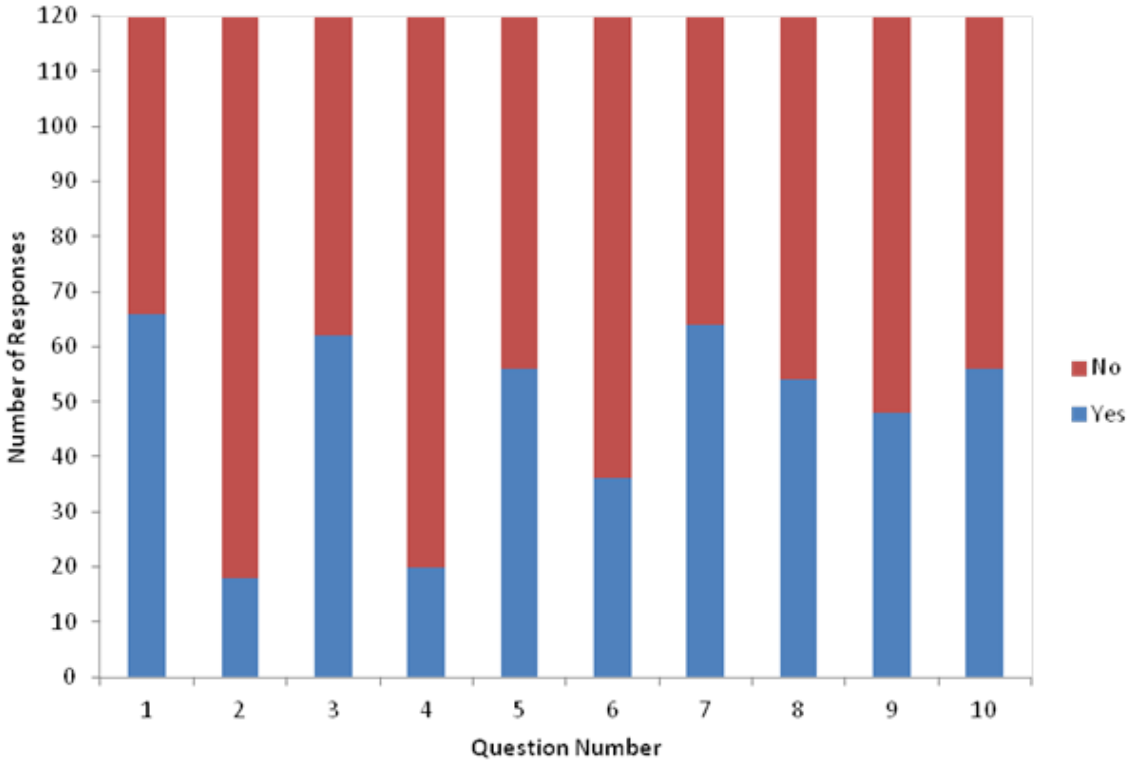
630 Please see PowerPoint slide (Waste initial observations figure 1).

Figure 2

Frequency of responses to 10 questions from websites of 119 core clinical journals included in Medline's Abridged Index Medicus (http://www.nlm.nih.gov/bsd/aim.html).



Q1 – Does journal ITA explicitly mention reporting guidelines (such as CONSORT)?
Q2 – Does journal ITAs explicitly mention the EQUATOR Network?
Q3 – Does journal ITA explicitly mention clinical trial, systematic review, or other registration (such as PROSPERO; indicate which one(s) specifically)?
Q4 – Does the journal ITA mention use of systematic reviews as part of reporting main study results (e.g., item 23 of CONSORT**)?
Q5 – Does the journal's Instruction to Authors recommend authors to go to the ICMJE Website for guidance?
Q6 – Does the journal support publishing "research on research", such as a "methods and reporting section"?
Q7 – Has the journal published editorials highlighting the series, other pieces on waste, duplication, reporting guidelines, registration, other topics related to increasing value?
Q8 – Does the journal provide support for good reporting infrastructure? Ex: study registries, data repositories, other
Q9 – Does the journal mention open access?
Q10 – Does the journal have a policy on public access to data from completed research?