is the 4th World Research Integrity Conference, to be held in Rio de Janeiro, Brazil, next year. The theme of that gathering will be "Research rewards and integrity: improving systems to promote responsible research", one of the key subjects of this Series.

Randy Schekman asked this question in his attack on "luxury journals" last year: "How do you think scientific journals should help advance science and careers?" That is a perfectly fair question to ask. But it does not go far enough. On the basis of the evidence we present in this Series, a far broader question should be posed: how should the entire scientific enterprise change to produce reliable and accessible evidence that addresses the challenges faced by society and the individuals who make up those societies?

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1 Schekman R. How journals like Nature, Cell, and Science are damaging science. *The Guardian* (London) Dec 9, 2013. http://www.theguardian.com/commentisfree/2013/dec/09/how-journals-nature-science-cell-damage-science (accessed Dec 16, 2013).
2 Aitkenhead D. Peter Higgs: I wouldn't be productive enough for today's academic system. *The Guardian* (London) Dec 6, 2013. http://www.theguardian.com/science/2013/dec/06/peter-higgs-boson-academic-system (accessed Dec 16, 2013).
3 Chalmers I, Glazsiou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009; **374:** 86–89.
4 Macleod MR, Michie S, Roberts I, et al. Biomedical research: increasing value, reducing waste. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62329-6.
5 Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62229-1.
6 Ioannidis JPA, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62227-8.
7 Al-Shahi Salman R, Beller E, Kagan J, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62297-7.
8 Chan A-W, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62296-5.
9 Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62228-X.

Biomedical research: increasing value, reducing waste

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Of 1575 reports about cancer prognostic markers published in 2005, 1509 (96%) detailed at least one significant prognostic variable.[1] However, few identified biomarkers have been confirmed by subsequent research and few have entered routine clinical practice.[2] This pattern—initially promising findings not leading to improvements in health care—has been recorded across biomedical research. So why is research that might transform health care and reduce health problems not being successfully produced?

Global biomedical and public health research involves billions of dollars and millions of people. In 2010, expenditure on life sciences (mostly biomedical) research was US$240 billion.[3] The USA is the largest funder, with about $70 billion in commercial and $40 billion in governmental and non-profit funding annually,[4] representing slightly more than 5% of US health-care expenditure. Although this vast enterprise has led to substantial health improvements, many more gains are possible if the waste and inefficiency in the ways that biomedical research is chosen, designed, done, analysed, regulated, managed, disseminated, and reported can be addressed.

In 2009, Chalmers and Glasziou[5] identified some key sources of avoidable waste in biomedical research. They estimated that the cumulative effect was that about 85% of research investment—equating to $200 billion of the investment in 2010—is wasted. This amount was calculated without consideration of the inefficiencies in the regulation and management of research. Although some real progress with the issues they identified has been made,[6–15] at the present rate, it will be many years before all the necessary improvements are in place.

The status quo in biomedical research is based on the complex and interdependent actions of diverse actors, each operating within their own systems of risks and incentives. These actions can be understood[7] as resulting from the interplay of capabilities (the individual's intellectual and physical abilities to engage with the activity in question), opportunities (factors external to the individual that make actions possible), and motivations (drivers that energise and direct behaviour). The actions of one set of actors affect others (table). Through consideration of these drivers, the economic, social, cultural, and political conditions that have shaped the research environment can be understood.[8]

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Economic forces are important. Industry seeks to maximise profit by bringing new products to market and by protecting and expanding market share. In industry-funded clinical research, commercial motives can control the study design and comparators, and so-called seeding trials (in which the purpose is to promote familiarity with a new drug rather than generate knowledge) can be done for marketing purposes.[9] The economic motivations of industry do much to characterise health as a commodity that can be bought, which informs and distorts the motivations of other actors. The profit motive is central to everything with which industry is involved, including its interactions with seemingly independent researchers and clinicians.[10]

Equally, advertising, publication charges, and charges for reprints make journal publication a highly profitable business, and attempts to maximise income are not always consistent with an ambition to publish only reports about research of the highest quality and relevance. Although peer review is supposed to uphold the quality of publications and grants awarded, the costs of the system are substantial,[11] raising questions about its cost-effectiveness.[12]

Governments and politicians have an important role. Funding is needed for research in areas important for the protection and restoration of human health even when the prospects for commercial profit are poor or non-existent. For example, the UK Health Technology Assessment Programme commissioned research assessing the effects of two low-cost drugs for Bell's palsy, which showed that corticosteroids were useful but acyclovir was not.[13] Additionally, six of a sample of 28 randomised trials in a programme funded by the US National Institute of Neurological Disorders and Stroke led to measurable improvements in health, and

	Researcher	Funder	Pharmaceutical company	Regulator	Institution
Motivation					
Good	Scientific discovery Develop treatments to improve human health Joy in moment of revelation Pleasure of collaboration	Fund high-quality research Show effectiveness of funding of decision making Develop treatments to improve human health	Generate shareholder value Pleasure of collaboration	Manage risks to study participants	Host high-quality research Build collaborative research capacity
Bad	Promotion Respect from peers Financial success Avoiding an unsuccessful hypothesis	Show that research that has been funded is of high quality Keep politicians and donors happy Avoid excessive risk	Generate shareholder value Protect existing income streams Markets could need short-term returns Fear that results of new research might undermine existing market share	Manage risks to regulators and politicians Little motivation to enable high-risk or high-gain research	Receive credit for continuing activity (fit activity to assessment, not vice versa) Generate institutional income University league tables Build in-house research capacity
Capability					
Good	Much training in some aspects of research approaches	Could influence behaviours of principal investigators through funding systems	Large research capacity Economies of scale Experience of negotiation of complex regulatory environments	Could influence behaviours of principal investigators through regulatory systems	Large research capacity Could influence behaviours of principal investigators through promotion and rewards systems Opportunity to influence skills of next generation as provider of undergraduate and postgraduate degrees
Bad	Poor knowledge of basic statistical and experimental design Diversionary training in fire safety, radiation protection, first aid, and other subjects	Insufficient knowledge of what is good research Underdeveloped metrics of valid research	Poor knowledge of empirical approaches to understanding weaknesses in the research methods they use Respect for venerableness and authority	Almost unrestricted power to introduce new regulations	Might have commitments to an existing workforce who do not have the necessary set of skills
Opportunity					
Good	Growing market (ie, funding and publication) for high-quality research	..	..	..	..
Bad	Little funding Funding and publication models not valuing validity and quality Few available skilled individuals to join research teams	Can only fund high-quality research if receive high-quality applications	System is not sufficiently rigorous, so short-term aims can be met in maladaptive way	Externalities are permissive for delay and caution rather than speed and pragmatism	External assessments value grants and publications more than the validity or relevance of research to patients and the public

Table: **Motivations, capabilities, and opportunities driving actions of different stakeholders in biomedical research**

four led to cost reductions; overall this public research programme was judged to be highly cost effective.[14]

Major non-commercial funders might not be driven by profit, but there are notable issues nonetheless. National funding agencies receive their money from governments, which are run, at least partly, by politicians. The success of funding policy, and the job security of the researchers thus funded, relies partly on the demonstration, every 4 or 5 years, that something useful has been done. Because results of strategic research decisions take many years to become clear,[15] individuals charged with disbursing government funds for research often rely on indirect measures of research quality. Unfortunately, these surrogates are often unduly affected by the quantity of grant funding secured and the impact factors of the journals in which research has been reported, neither of which are reliable measures of research quality.[16]

Regulators of research are motivated to protect research participants, mindful of the atrocities of the past that associate biomedical researchers with war criminals (eg, in the Nuremberg trials).[17] However, the result has been that regulatory burdens are often disproportionate to the plausible risks of the research,[18] which jeopardises the capacity and motivation of researchers to answer some important questions.

As with economic and political factors, social and cultural factors play an important part. Science is not done by paragons of virtue, but by individuals who are as prone to self-interest as anyone else. They can compromise their usually high standards of rigour when involved in commercial or otherwise conflicted relationships. When resources are scarce and competition is fierce they might seek the easiest and quickest—rather than the best—ways forward. They could judge that they would rather be first than be right. When their research hunch turns out to be wrong, many researchers move to the next one rather than going through the painstaking business of reporting negative findings. Finally, they could prefer research that they find interesting rather than research that addresses issues of importance to the users of research. These behaviours are compounded by the complacency and poor craftsmanship of some scientists. When grants are still coming in and reports published, why change? What could be better than this generation of scientists, standing on the shoulders of giants, and providing our own shoulders for future generations? And, if they are not really very good, careful, or precise, how would anyone know?

Funders and academic institutions do much to set the social and cultural context in which research occurs, and academia's reward and promotion systems shape the choices of scientists at all stages of their career. A focus on publication of reports in journals with high impact factors and success in securing of funding leads scientists to seek short-term success instead of cautious, deliberative, robust research that will take substantially longer to produce less exciting (but more valid) findings. Moreover, academia has failed to establish credible mechanisms to investigate and deal with research misconduct. This situation contrasts even with the pharmaceutical industry, in which one UK scientist was sent to prison in 2013, for falsification of laboratory research findings.[19]

Peer review and peer decision making in funding, publication, and promotion decisions give a false

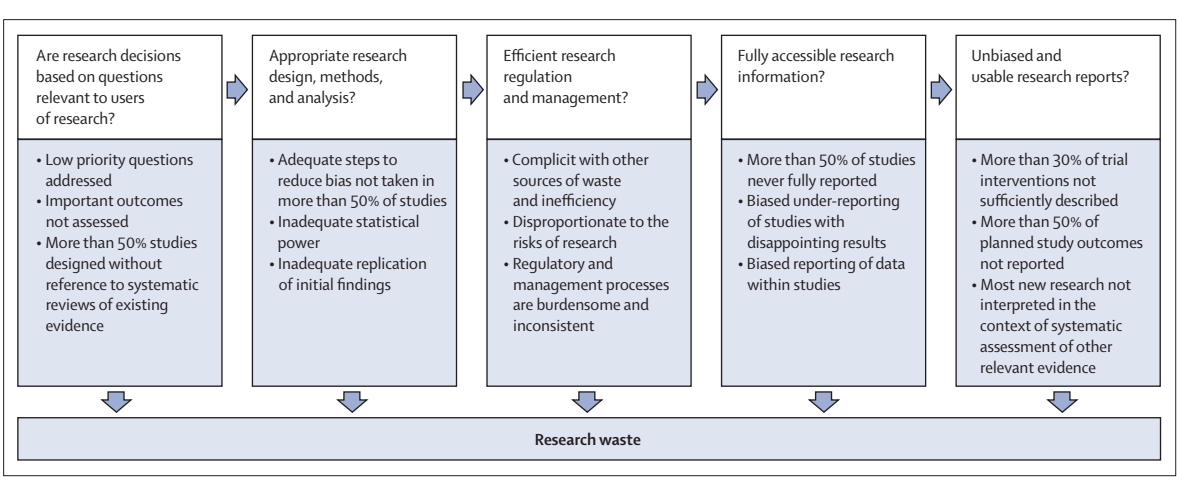

Figure: **Avoidable waste or inefficiency in biomedical research**

sense of independence. At every stage, every atomised individual in these processes is affected by the different drivers. Ambitious for success, advancement, and funding, it is easier to move with these forces than to challenge authority and the status quo. Because the community is led (as it should be) by individuals who have succeeded in the status quo ante, investigators at early stages of their careers might judge (perhaps wrongly) that the best chances of success (as defined by their peers) will come from working within and for the system, not by challenging it.

How might things be different? One protection from these distorting drivers would be the creation of a set of balancing counter-influences. So, instead of being judged on the basis of the impact factors of the journals in which their work is published, academics might be judged on the methodological rigour and full dissemination of their research, the quality of their reports, and the reproducibility of their findings. If these factors were to contribute substantially to promotion, funding, and publication decisions, institutions might even go so far as to audit the performance of their staff and, when substandard, pay more attention to continuation of professional development and appraisal of the research workforce.

All actors decide how best to proceed in their circumstances, which too often increase waste and reduce value in biomedical research. The scientific process needs to be reinvigorated and its guiding principles promulgated. Systems of oversight and regulation should be developed to promote rigour, protect the integrity of the scientific process, and protect scientists from some of the perverse influences. Fortunately, some institutional role models can be used as inspiration (appendix). By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste.

In *The Lancet*, we now present a Series of five papers about research (figure). In the first report, Iain Chalmers and colleagues[20] discuss how decisions about what research to fund might be based on questions that are relevant to users of research. Next, John Ioannidis and colleagues[21] consider improvements in the appropriateness of research design, methods, and analysis. Rustam Al-Shahi Salman and colleagues[22] then turn to issues of efficient research regulation and management. Next, An-Wen Chan and colleagues[23] examine the role of fully accessible research information. Finally, Paul Glasziou and colleagues[24] discuss the importance of unbiased and usable research reports. In these papers, we set out some of the most pressing issues, recommend how to increase value and reduce waste in biomedical research, and propose metrics for stakeholders to monitor the implementation of these recommendations.

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1 Kyzas PA, Denaxa-Kyza D, Ioannidis JP. Almost all articles on cancer prognostic markers report statistically significant results. *Eur J Cancer* 2007; **43:** 2559–79.
2 Anderson NL. The clinical plasma proteome: a survey of clinical assays for proteins in plasma and serum. *Clin Chem* 2010; **56:** 177–85.
3 Røttingen JA, Regmi S, Eide M, et al. Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? *Lancet* 2013; **382:** 1286–307.
4 Dorsey ER, de Roulet J, Thompson JP, et al. Funding of US biomedical research, 2003–2008. *JAMA* 2010; **303:** 137–43.
5 Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009; **374:** 86–89.
6 Petit-Zeman S, Firkins L, Scadding JW. The James Lind Alliance: tackling research mismatches. *Lancet* 2010; **376:** 667–69.
7 Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011; **6:** 42.
8 Marmot M. Social determinants of health inequalities. *Lancet* 2005; **365:** 1099–104.
9 Krumholz SD, Egilman DS, Ross JS. Study of neurontin: titrate to effect, profile of safety (STEPS) trial: a narrative account of a gabapentin seeding trial. *Arch Intern Med* 2011; **171:** 1100–07.

See **Online** for appendix

10 Stamatakis E, Weiler R, Ioannidis JP. Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review. *Eur J Clin Invest* 2013; **43:** 469–75.

11 Wessely S. Peer review of grant applications: what do we know? *Lancet* 1998; **352:** 301–05.

12 Jefferson T, Godlee F. Peer review in health sciences, 2nd edn. London: BMJ Books, 2003.

13 Sullivan FM, Swan IR, Donnan PT, et al. A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: the BELLS study. *Health Technol Assess* 2009; **13:** 1–130.

14 Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS. Effect of a US National Institutes of Health programme of clinical trials on public health and costs. *Lancet* 2006; **367:** 1319–27.

15 Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *J R Soc Med* 2011; **104:** 510–20.

16 Minnerup J, Wersching H, Diederich K, et al. Methodological quality of preclinical stroke studies is not required for publication in high-impact journals. *J Cereb Blood Flow Metab* 2010; **30:** 1619–24.

17 Shaw S, Barrett G. Research governance: regulating risk and reducing harm? *J R Soc Med* 2006; **99:** 14–19.

18 The Academy of Medical Sciences. A new pathway for the regulation of medical research. http://www.acmedsci.ac.uk/p47prid88.html (accessed Dec 4, 2013).

19 UK Medicines and Healthcare Products Regulatory Agency. Press release: man jailed in pre-clinical trial data scam case. April 17, 2013. http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON263951 (accessed Dec 4, 2013).

20 Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62229-1.

21 Ioannidis JPA, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62227-8.

22 Al-Shahi Salman R, Beller E, Kagan J, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62297-7.

23 Chan A-W, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62296-5.

24 Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* 2014; published online Jan 8. http://dx.doi.org/10.1016/S0140-6736(13)62228-X.