Research: increasing value, reducing waste 1

How to increase value and reduce waste when research priorities are set

Iain Chalmers, Michael B Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A Metin Gülmezoglu, David W Howells, John P A Ioannidis, Sandy Oliver

The increase in annual global investment in biomedical research—reaching US$240 billion in 2010—has resulted in important health dividends for patients and the public. However, much research does not lead to worthwhile achievements, partly because some studies are done to improve understanding of basic mechanisms that might not have relevance for human health. Additionally, good research ideas often do not yield the anticipated results. As long as the way in which these ideas are prioritised for research is transparent and warranted, these disappointments should not be deemed wasteful; they are simply an inevitable feature of the way science works. However, some sources of waste cannot be justified. In this report, we discuss how avoidable waste can be considered when research priorities are set. We have four recommendations. First, ways to improve the yield from basic research should be investigated. Second, the transparency of processes by which funders prioritise important uncertainties should be increased, making clear how they take account of the needs of potential users of research. Third, investment in additional research should always be preceded by systematic assessment of existing evidence. Fourth, sources of information about research that is in progress should be strengthened and developed and used by researchers. Research funders have primary responsibility for reductions in waste resulting from decisions about what research to do.

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James Lind Initiative, Oxford, UK (Sir I Chalmers DSc); **School of Public Health and School of Medicine, Yale University, New Haven, CT, USA** (Prof M B Bracken PhD); **Center for Evidence-Based Medicine and Health Outcomes Research, Division of Internal Medicine, University of South Florida, Tampa, FL, USA** (Prof B Djulbegovic PhD); **Department of Hematology and Department of Health Outcomes and Behavior, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA** (Prof B Djulbegovic); **Istituto di Ricovero e Cura a Carattere Scientifico Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy** (S Garattini MD); **RAND Europe, Cambridge, UK** (J Grant PhD); **UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), WHO, Geneva, Switzerland** (A M Gülmezoglu PhD); **Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia** (D W Howells PhD); **Stanford Prevention Research Center, Department of Medicine** (Prof J P A Ioannidis MD), **and Division of Epidemiology, Department of Health Research and Policy** (Prof J P A Ioannidis), **School of Medicine, Stanford University, Stanford, CA, USA; Department of Statistics, School of Humanities and Sciences, Stanford University, Stanford, CA, USA** (Prof J P A Ioannidis); **and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA, USA** (Prof J P A Ioannidis); **and Institute of Education, London, UK** (S Oliver PhD)

Introduction

This report will be focused on the waste of resources resulting from decisions about what research to do. After exploring investment patterns, we consider waste that ensues when the needs of potential users of research evidence (ie, policy makers, patients, professionals making practice or personal decisions, and researchers and research funders deciding which additional research should be done) are ignored and what is already known or already being researched is overlooked. We conclude with recommendations for how to reduce waste when research priorities are set.

We have approached our task using the research categories suggested by Stokes:[1] pure basic research (to advance knowledge), pure applied research (to increase immediate applicability of research results in practice and policy decisions), and use-inspired basic research (to both advance knowledge and increase applicability). Stokes created a schema to represent categories, which we have adapted (figure 1). He named the quadrant representing use-inspired basic research after Louis Pasteur, because Pasteur's basic research had been motivated by the need to generate evidence relevant to reductions in morbidity, mortality, and economic costs of infections in people and animals. In our adapted schema, we have retained Pasteur in his original quadrant, but replaced Nils Bohr (the nuclear physicist) with Marie Curie in the quadrant for pure basic research, because of the medical importance of her studies of radiation. We also replaced Charles Edison (inventor of the light bulb) with Richard Doll in the quadrant for pure applied research, because of Doll's work with Bradford Hill to identify smoking as a cause of lung cancer. We have

Recommendations

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
   - Monitoring—periodic surveys of the distribution of funding for research and analyses of yields from basic research
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
   - Monitoring—periodic surveys of information on research funders' websites about their principles and methods used to decide what research to support
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
   - Monitoring—audit proposals for and reports of new primary research
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
   - Monitoring—periodic surveys of progress in publishing protocols and analyses to expose redundant research

Correspondence to:
Sir Iain Chalmers, James Lind Initiative, Oxford OX2 7LG, UK
ichalmers@jameslind.net

named Stokes' previously unnamed quadrant the waste quadrant to take account of the many research projects that contribute nothing or very little to knowledge or to practice and policy. As Altman lamented in a much cited 1994 report,[2] we need less research, better research, and research done for the right reasons—an issue that has since been revisited several times.[3,4]

Relative investment in basic and applied research

Global investment in biomedical research is increasing, reaching US$240 billion (adjusted for purchasing power parity) in 2010.[5] Basic research is the principal beneficiary of this investment.[6] More than half of the £1·6 billion in public and charitable investment in research in the UK in 2009–10 was allocated to basic research (table 1),[7] a pattern that was also reported in the USA in 2012.[8] This longstanding funding pattern is partly a result of assertions made many years ago by two scientists—Julius Comroe and Robert Dripps—who claimed that 62% of all reports judged to be essential for subsequent clinical advances were the result of basic research.[9] However, the rigour and objectivity of their analysis was questioned,[10] and an attempt by bibliometricians to replicate the findings showed not only that Comroe and Dripps' analysis was "not repeatable, reliable or valid", but also that only 2–21% of research underpinning clinical advances could be described as basic.[11]

Basic research has led to some notable and often serendipitous advances in the protection and promotion of human health. For example, discovery of a high-temperature polymerase in an extremophile bacterium[12] led to the development of PCR, which is now an essential instrument in genetics and diagnostics. A spin-off from research into the effect of electric fields on bacterial growth was the discovery that platinum inhibits cell division,[13] which thus led to the introduction of potent anticancer compounds, such as cisplatin. Additionally, research into fungi and cholesterol led to the development of statin drugs, which are now widely used to reduce cholesterol in people at increased risk of cardiovascular disease.[14] Examples such as those are often used in arguments that more than half the total resources invested in biomedical research should be allocated to basic research.[8]

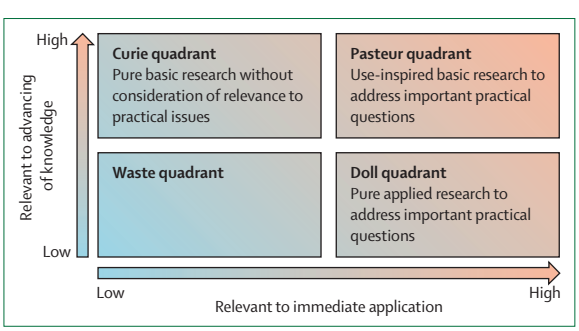

Figure 1: **Classification of different categories of research**

	Pure basic research		Pure applied research		Use-led basic research	
	2004–05	2009–10	2004–05	2009–10	2004–05	2009–10
Proportion of funds allocated	68·3%	59·4%	21·2%	27·2%	10·7%	13·3%

Percentages calculated with data from UK health research analysis 2009/2010.[7] Pure basic research is concerned with understanding of biological, psychological, and socioeconomic processes and functioning (underpinning research), and aetiology. Pure applied research is concerned with prevention, detection and diagnosis (but not the discovery and preclinical testing of markers and technologies), treatment assessment, disease management, and health services. Use-led basic research is concerned with development of detection, diagnosis, and treatment (including the discovery, development, and preclinical testing of biological markers, imaging technologies, and diagnostic and predictive tests).

Table 1: **Distribution of public and charitable funds for medical research in 2004–05 and 2009–10, by category of investment**

Formal evidence for the value of basic research is not strong, and understanding about what would represent realistic yield targets (eg, number of discoveries that result in substantial translational impact) is poor. Most initially promising findings are subsequently identified as false positives or exaggerations. Of more than 25 000 reports published in six leading basic-science journals between 1979 and 1983, 101 included confident claims that the new discoveries had clear clinical potential, yet only five had resulted in interventions with licensed clinical use by 2003, and only one led to the development of an intervention used widely.[15]

In a series of projects assessing the translation of research from bench to bedside,[16–18] applied clinical research—not basic research—has been consistently shown to have large health, social, and economic effects. The finding that clinical research has greater impact than does preclinical basic research was observed over a period of 10–15 years in arthritis research,[16] over 15–20 years in cardiovascular research,[17] and over 20–25 years in mental health research.[18] These findings suggest that the time needed for translation of basic research into practice is long (>20–25 years), and longer than previous estimates of 10–20 years.[19] Indeed, between 2004 and 2011, the development time for three classes of drugs actually increased in both clinical and approval phases.[20]

The slight proportional increases in charitable and public funding for pure applied research and use-led basic research in the UK between 2006 and 2010 (table 1), were partly a result of recognition that the numbers of non-commercial clinical trials had been decreasing,[21] and that the capacity and infrastructure for applied research was inadequate.[22] Promising ideas developed in basic research were not being translated into applied research; they were meeting a bottleneck in assessments of whether they could lead to advances in prevention and treatment. Because this bottleneck was threatening national wealth and health, in 2006, the UK Government decided that research funding ratios should be altered to foster increased capacity for applied research.[22] Similar developments have occurred in some other countries—eg, the USA[23] and Italy.[24]

Because basic research accounts for such a high proportion of the overall expenditure on biomedical

research, credible scientific methods need to be used to assess its yields relative to those of applied research. Opportunities to improve the yield from basic research might not have been realised, but they will probably not be confidently identified without additional so-called research on research done by investigators whose interests do not depend on the findings.[25]

Ways to decide priorities for research

Funding decisions vary depending on whether priorities are set by researchers or funders solicit proposals addressing questions that they believe are important.[21] Different models have been proposed for decisions about which high-risk basic research to support. They typically focus on funding of scientists rather than projects to allow maximum freedom of thinking and action.[26] However, most research funding organisations do not follow this path—eg, of 35 944 awards made by the US National Institutes of Health in 2011, only 50 were in the three new innovator categories that focus more on funding of individual scientists rather than on detailed projects with specific end results.[27] As Horrobin forcefully pointed out three decades ago,[28] the kind of creative lateral thinking that has led to important advances in understanding has had to survive peer-review systems that tend to be innately conservative, subject to fashion, and often inimical to ideas that do not conform with mainstream thinking. Experimental evidence suggests that a strong bias against novelty does exist in traditional peer-review systems.[29] Moreover, peers tend to support proposals that have similar fingerprints to their own interests, not those that are really novel.[30]

Nasser and colleagues[31] examined six critical reviews of varied approaches to deciding which research to support. Despite limitations of the data and analyses included in the critical reviews, some common themes emerged; they identified several steps that could improve strategies used to set research priorities (panel 1).

Decisions about what research to do can be informed by the burden of disease.[32] Analyses often identify mismatches between disease burden and research funding,[21,33–36] and could help to increase attention to neglected tropical diseases—eg, schistosomiasis and dengue virus infection—and to worldwide problems—eg, mental health, dementia, and stroke. However, analyses of the burden of disease have limitations. The reality that many patients experience burdens from multiple diseases can be overlooked, and orphan treatments and diseases are missed, despite the large numbers of people who are affected. Furthermore, analyses of the burden of disease offer little insight into the research needs of health systems, and research funding decisions need to take account of costs and whether investigation of research questions is feasible.[37]

Use-inspired basic research receives proportionately less funding than either pure basic research or pure applied research (table 1). It results when there is creative interaction involving basic researchers, applied researchers, and the users of research. For example, a systematic review[38] of the effects of drugs tested in experimental autoimmune encephalitis in rodents identified three off-patent drugs worthy of assessment in people with primary progressive multiple sclerosis. Because these potentially useful agents are of no commercial interest, their effects in patients with multiple sclerosis are being assessed in publicly funded trials.[39]

Development of so-called needs-led research agendas is dependent on the expertise of individuals who are well placed to use the findings as well as that of researchers. In some exercises in research priority setting, specific attention has been paid to interpersonal communication, with consideration of aspects of collaborative working, such as mutual respect and mutual learning.[40] Discussions about research prioritisation can benefit from the inclusion of someone with the skills to unite different groups, translating between different languages or spheres of expertise, and enabling interactions.[41] As long as the processes used to prioritise proposals for research are transparent and justifiable, disappointing subsequent results should not be thought of as wasteful, let alone as failures; they are an inevitable feature of the way science works. Indeed, new treatments assessed in randomised trials are only slightly more likely, on average, to turn out better than existing (standard) treatments.[42]

Whichever methods are used to decide what research to support, decision makers should endeavour to avoid wasting resources. They should not ignore the needs of potential users of research evidence or what is already known or being researched.

Waste caused when potential users' needs are ignored

Waste results when the needs of users of research evidence are ignored. In 2011, Liberati said: "I have had the opportunity to consider from more than one

Panel 1: **Steps for research groups to improve setting of priorities[31]**

1. Include objectives in research groups' strategic plans and define the stakeholders whose opinions and priorities will be considered
2. Draw on an existing summary of previous priority-setting exercises in the specialty before undertaking own exercise
3. Use available methodological reviews of research priority setting as guidance about how to meet priority-setting objectives
4. Ensure that the priority-setting team has the necessary data, information about context, and skill set for their exercise
5. Pilot, assess, revise, and update the priority-setting exercise at intervals
6. Participate in discussions within the community of interest to share findings and experiences

Reproduced from Nasser et al,[31] by permission of Elsevier.

perspective the mismatch between what clinical researchers do and what patients need. I am a researcher; I have responsibility for allocating funding for research; and I have had multiple myeloma for the past decade."[33] He emphasised the need for a new research governance strategy, adding that "Left to themselves, researchers cannot be expected to address the current mismatch".[33] Users of preclinical research need reliable information to inform research priorities, both for additional preclinical research and for clinical research. Furthermore, users of the results of animal research need assurance that disease models developed in animals are actually relevant to human disease.[43]

Industry is showing signs of concern that basic research done in academic centres does not provide a sufficiently reliable basis for drug development.[44] Researchers at Amgen were unable to replicate 47 of 53 reports of important basic science studies of cancer that had originated in academia.[45] In view of such concerns and the unknown translational potential of basic research done in academia, it is unsurprising that some hedge funds are having doubts about the value of investment in basic research.[46] Additionally, the available evidence has not validated the previously confident predictions of basic researchers about the promise of new areas such as genomics and personalised and individualised medicine.[47]

When promising early findings are not replicated—indeed, they are often contradicted[48]—it is hard to know whether the differences are recorded because designs of the original studies have been based on incomplete assessments of what is already known, the quality of data is poor,[43] or basic understanding of the relevant biology and other factors is incomplete. Whatever the reasons, users of research want reliable evidence that can be replicated. Yet researchers often struggle to obtain funding to repeat what has been done previously and to publish the results of replications.[49] Without attempts to replicate positive initial findings, judgment of their validity will remain difficult, if not impossible. Until recently, tests were done of one gene at a time in most studies of human genome epidemiology, with selective reporting of results and spurious conclusions, and no replication in subsequent large consortia-based, genome-wide efforts. The misleading results have been perpetuated in meta-analyses that are based on selectively presented information.

If researchers do not meet the needs of the users of research, evidence will have less of an effect on clinical and public health practice than it should. The principal users of clinical and epidemiological research are clinicians and the patients who look to them for help.[50] Both are often frustrated by mismatches between the uncertainties that they wish to see addressed in research and the questions that researchers choose to investigate.[33–36] They express concern about clinical trials having little relevance in real-world settings[51] and complain that researchers often do not assess the effects of interventions in terms of functional, social, and emotional wellbeing, or adverse reactions and long-term outcomes.[52–54] Evidence suggests that the end users of research are much less interested in drug research than are the institutions and investigators who fund and do research (figure 2).

What might account for mismatches between what researchers do and what potential users of research want? Apart from the effect of commercial, political, and academic interests in decisions about what is researched,[4] one obvious reason is that users of research evidence are only rarely involved in the setting of research agendas.[55] As a result, some research questions rated important by patients and clinicians might never occur to researchers. But so-called methodological disincentives might have a role: the design, running, and interpretation of trials of drugs will usually be methodologically straightforward compared with assessments of psychological or physical therapies, service delivery, and the other non-drug interventions that feature so prominently in the priorities identified by patients and clinicians.

Waste caused when what is already known or being researched is ignored

In 2001, a major funder of research in the UK—the English Department of Health—emphasised that systematic assessment of what is already known or being researched is essential when decisions are made about what further research to do.[56] Such assessment will identify what should be replicated, avoid unnecessary duplication, and result in research that addresses deficiencies in previous work.[57] Although the point at which necessary replication becomes wasteful duplication can almost always be disputed, decisions should be informed by as high a proportion as possible of the relevant existing evidence.[50,58]

Surveys of citation patterns in reports of clinical trials provide worrying evidence that previous research is being ignored.[59,60] An analysis[61] of clinical trials reported over four decades showed that, irrespective of the number of relevant previous trials, fewer than a quarter of previous studies (and a median of only two) had been cited in reports. A survey[62] of investigators of clinical trials generating data that others had used to update systematic reviews showed that less than half were even aware that relevant reviews of existing evidence were available when they designed their studies.

Matters might be improving,[63] but the present situation is ethically, scientifically, and economically indefensible.[57] In reports published in five highly cited general medical journals, only rarely did investigators state that they had used up-to-date systematic reviews when designing their new clinical trials (table 2).[64] Similarly, of 446 protocols for clinical research submitted to British research ethics committees, in only four (1%) had meta-analyses of data from relevant previous studies been used to plan target sample sizes.[65] The resulting optimism bias[66] leads to studies with inadequate statistical power and inconclusive

results: Djulbegovic and colleagues[67] showed that trial results match expected size of treatment effects in only 12% of studies.

Undercitation of previous research is a particularly egregious problem when the selection of previous studies is biased.[68] In a citation network analysis of research on β-amyloid accumulation in Alzheimer's disease, non-supportive references were ignored in grant applications and in published reports, even when the evidence came from the laboratory submitting the grant application.[69]

A systematic review of animal and human research before additional primary research is undertaken is of great importance (panel 2).[75,76] Cumulative meta-analyses of clinical trials clearly show why systematic reviews need to be done—eg, trials of whether a short course of corticosteroids in pregnant women expected to give birth prematurely improved neonatal mortality were repeatedly undertaken even after a clear reduction in risk of death had been shown.[77] Additionally, cumulative meta-analyses showed that the effects of tranexamic acid on the use of blood transfusion were established a decade ago (figure 3). However, the results also showed that questions about the effects of the drug on myocardial infarction and death were unresolved, because studies had been much too small to provide definitive answers (figure 3).[60]

How common is an absence of a systematic review in clinical research? An analysis of 50 reports including more than 1500 cumulative meta-analyses of clinical intervention studies (appendix) shows that, had researchers systematically assessed what was already known, some beneficial and harmful effects of treatments (eg, thrombolytic and antiarrhythmic drugs in myocardial infarction) could have been identified earlier than they were. Not only would systematic reviews in these cases have reduced waste resulting from unjustified research, they would also have shown how to reduce morbidity and sometimes mortality, both in patients allocated to relatively less effective or actually harmful treatments in unnecessary trials, and in patients generally. Similar issues arise in some epidemiological studies—eg, had investigators researching possible aetiological factors in sudden infant death syndrome taken proper account of what was already known, the lethal effect of babies lying on their front would have been recognised at least a decade earlier than it was, and tens of thousands of infant deaths could have been avoided.[78] Similarly, a cumulative meta-analysis[79] of 55 studies done in a 24 year period showed that the research had repeatedly confirmed that never-smoking women who had been exposed to smoking via their husbands were more likely than others were to develop lung cancer.

Recognition of how unreliable initial evidence can be is important.[80,81] Some cumulative meta-analyses have shown how replications have challenged initially favourable or unfavourable results (appendix). An analysis[82] of data from 85 002 meta-analysis forest plots with binary outcomes published by the Cochrane Collaboration showed that early trials in a series tend to show overestimated treatment effects. This overestimation might result from selection of unrepresentative subgroups of patients known to have responded favourably to similar drugs previously, or from exclusion of other patients who have not responded.[83] The overestimation in single trials and even meta-analyses could be a result of biased under-reporting of early trials with disappointing results,[84] or time-lag bias in the reporting of trials.[85] As a result, early studies and meta-analyses could tend to yield inflated estimates of effects, which needs to be taken into account during consideration of proposals for additional studies.[86]

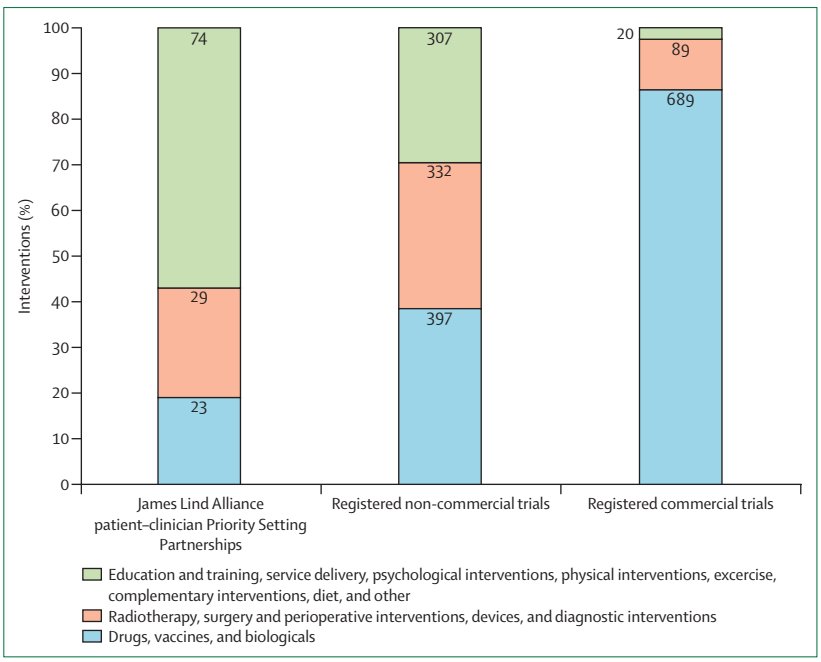

Figure 2: **Interventions mentioned in research priorities identified by James Lind Alliance patient–clinician Priority Setting Partnerships[90] and in registered trials, 2003–12**

	May, 2009 (n=29)	May, 2012 (n=35)
Claims that clinical trial is the first to address the question	5	5
Contains an updated systematic review that was used to inform trial design	1	1
Previous systematic review* discussed that was not used in trial design	10	13
Contains references to other randomised trials	4	10
Does not contain references to other randomised trials or claim to be the first trial	9	6

Analysis of reports published in *The Lancet*, *New England Journal of Medicine*, *British Medical Journal*, *Journal of the American Medical Association*, and *Annals of Internal Medicine*.[64] *Systematic review in the topic area of the trial cited.

Table 2: **Analysis of Introduction sections of reports of controlled trials published in five medical journals in May, 2009, and May, 2012**

See **Online** for appendix

Recommendations

Research funders and research regulators have the primary responsibility to address sources of avoidable waste when research priorities are set. We recommend four important

Panel 2: **Examples of what can happen when no systematic review of existing animal or human evidence is done before new research begins**

- Animal experiments are unnecessarily replicated—eg, experiments to confirm the efficacy of tissue plasminogen activator would not have continued for almost a decade after its benefit had been shown in stroke models.[70]
- Unnecessary deaths and life-threatening side-effects—eg, a healthy volunteer recruited to help with assessments of the effects of inhaled hexamethonium on lung function would not have died from the toxic effects of the drug on her lungs,[71] and life-threatening cytokine storms would have been avoided in six healthy volunteers paid to participate in a phase 1 trial of the monoclonal antibody TGN1412.[72]
- Patients are enrolled into clinical trials that do not need to be done—eg, more than 7000 individuals who had had a stroke would not have been enrolled in clinical trials of nimodipine because systematic reviews of the effects of the drug in animal studies of stroke did not identify any protective effects,[73] and had animal studies been reviewed systematically, the large ENABLE study of endothelin receptor blockers would probably not have been done.[74]

ways to reduce this waste. First, more so-called research on research is needed to identify the 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. Ideas worthy of further examination are whether the pace at which basic research is translated into useful application could be accelerated, whether duplication in this type of research is excessive, and whether the emphasis is on conforming rather than innovative efforts.

Ways are needed to fund the best scientists and allow them to pursue innovative, high-risk ideas without obstacles, as in the Howard Hughes Medical Institutes model. Experimental studies should assess whether processes through which scientists are funded on the basis of merit and record of excellence (rather than by convincing peers about high-risk ideas) could liberate creativity and lead to major discoveries.[26] Filley[87] suggested that career success in research should rest on the validity of findings as established by whether they can be replicated, rather than whether the research has been published in popular journals.

Encouragement to work across traditional academic boundaries can lead to creative sharing of ideas—eg, natural scientists and computer scientists collaborated to imagine the creative possibilities of combining DNA nanotechnology with cutting-edge polymer chemistry.[88] In the future, useful basic research will probably be increasingly multidisciplinary. The dividing boundaries of funding agencies could be managed to avoid the funding of overly narrow projects and resulting silo effects of researchers from different backgrounds independently addressing the same issue from different perspectives. If more basic researchers encountered major problems of health and disease, they might be inspired to think in new directions, producing new ideas and new solutions, as Pasteur was. Use-inspired basic research might result from continuous communication between scientists working at the later stages of the translational process and health-care practitioners and patients who can contribute potentially relevant findings.

Mapping of the entire research portfolios of major agencies could establish whether some basic research specialties are too large and have unnecessary duplication of effort, meaning that thousands of scientists and their projects make incremental, iterative contributions within basic research bubbles. Investments could be shifted to newer, higher-risk, but possibly also higher-yield ideas. Scientometric research could identify clusters of generally conforming research output versus more innovative counterparts.

Our second recommendation is that 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. Members of the public are beginning to identify novel research topics and are helping to shift the focus of research programmes.[89,90] These trends have meant that researchers have had to clarify and justify their research plans; have changed how problems have been approached; have initiated or accelerated research;[91] and have led to the identification of shared priority topics and questions[90] (panel 3). Such discussions with users of research also provide opportunities to abort unpromising efforts early. For example, an idea that health professionals studying stroke were keen to turn into a funding bid was abandoned when individuals who had had strokes and their carers were consulted about whether it was worth pursuing.[97] Similarly, other potential research briefs have been discarded when consultation showed that patients were sceptical or had alternative preferences.[98]

What motivates some research funders and researchers to respect the needs of potential users of research? Researchers' intentions to engage the public seem to depend less on the time and funds available than on whether they are positively inclined to try to apply the principle of consulting research users, feel capable of implementing it, and see their colleagues doing so.[99] Intrinsic motivation to involve potential users of research comes from the satisfaction of addressing and delivering solutions to problems that research users deem important. The needs-led approach is sometimes taken when public or charitable funds are being used to commission research.[95,98] For researcher-initiated studies, funders could give additional extrinsic motivation by asking applicants to

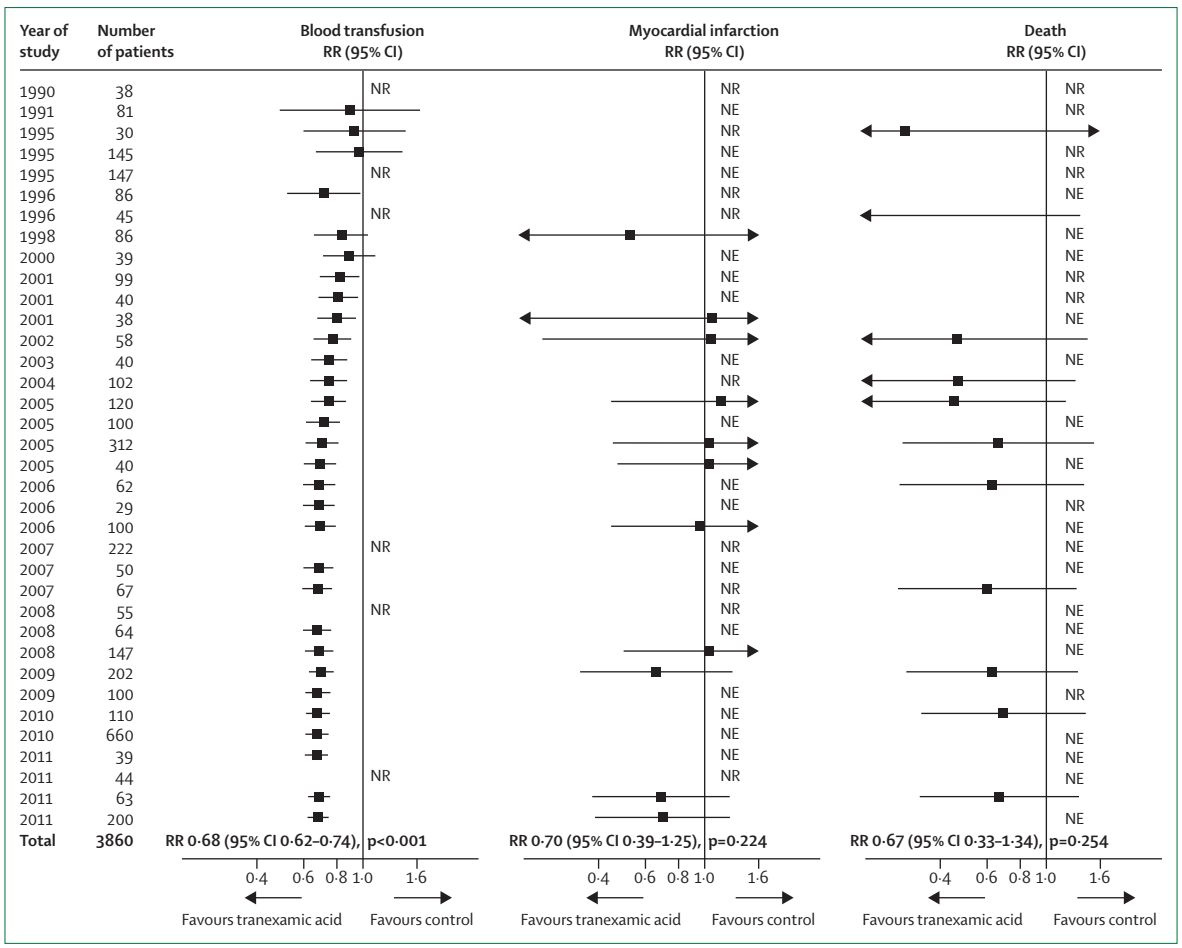

Figure 3: **Cumulative meta-analyses of 36 trials of tranexamic acid during surgery**
Data taken from Ker et al.[60] The effects of tranexamic acid on risk of bleeding and subsequent blood transfusion were clearly established a decade ago, but the effects of the drug on risk of myocardial infarction and death were still unknown in 2011. RR=risk ratio. NR=not reported. NE=no events.

describe how they have involved potential users of research in their plans.[55]

The numbers of reports about how research priorities are being set by some research users, particularly by clinicians and patients, are growing.[100] Some of the mismatches between research agendas and the needs of the users of research can be reduced by inviting research users to help to shape research agendas. In the past 10 years, the James Lind Alliance has developed a formal process through which patients and clinicians identify their shared research priorities to address uncertainties about the effects of treatments.[90]

Our third recommendation is that research funders and regulators should demand that proposals for additional primary research are justified by systematic reviews of what is already known and increase funding for the necessary syntheses of existing evidence. Two decades ago, Bausell invited the readers of *Evaluation and the Health Professions* to consider a moratorium on all proposals for new investigations until the results of existing research had been incorporated in scientifically defensible reviews.[101] In the light of the evidence of waste that we have presented here, Bausell's proposal and its potential benefits should not seem far-fetched.

Nevertheless, encouraging progress has been made in the enhancement of the capability and opportunities to

Panel 3: **Examples of patients' and clinicians' shared research priority topics**

- Are the beneficial effects of ibudilast, riluzole, and amiloride reported in experimental autoimmune encephalitis in rodents replicated in people with primary progressive multiple sclerosis?[38,39]
- How can sexual dysfunction due to antipsychotic drugs be managed?[92]
- Can a group-based cognitive rehabilitation programme after acute traumatic brain injury retrain an individual's memory and other cognitive functions?[93]
- What are the effects of breathing exercises as a form of physical therapy for asthma?[94]
- How can itching and oedema on scars and skin donor sites be reduced?[95]
- What genetic, environmental, and lifestyle factors cause or affect the onset of asthma or chronic obstructive pulmonary disease?[40]
- How can overtreatment for prostate cancer be prevented with identification and exclusion of the treatment of harmless tumours?[96]

apply this principle in practice. Indeed, in specialties such as human genome epidemiology, primary research and meta-analyses have become practically tautologous. Additionally, helpful methodological developments have been made—eg, network meta-analyses have been described when few head-to-head studies have compared the effects of similar treatments.[102] Although systematic reviews of animal studies remain rarer than are those of clinical research,[103] they can identify previously unappreciated lines of investigation and so provide the basis for evidence-informed translational medicine. Despite this progress, it will often be the case that no relevant systematic reviews are available to inform plans for additional research.

Increased recognition of the need to assess systematically what is already known will mean that researchers need to be trained in research synthesis methods. The high expected standards for systematic reviews are undoubtedly challenging. If systematic reviews of relevant existing evidence are to inform proposals for additional primary research, work is needed to identify how trustworthy results can be generated with methods that are less resource intensive than are those expected now,[104] and how computers can be used to increase the efficiency of the preparation of systematic reviews.[105,106]

Our final recommendation is that 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. Systematic assessments of what is already being investigated can help to reduce redundant research and encourage the collaboration that is often needed to achieve studies of sufficient size to provide reliable results. All research funders should be motivated to pursue these objectives so that they can be seen to be using the resources entrusted to them efficiently and responsibly.

The means to assess what is already being researched are gradually becoming increasingly available with prospective registration of protocols for clinical trials and systematic reviews.[107] There have also been calls for protocol registration of non-experimental human studies,[108] although some have challenged its desirability,[109] and there is probably a greater consensus about registration of proposals for observational datasets. Recognition of publication bias and inadequate sample sizes of many animal experiments has also prompted calls for registration[110] and multilaboratory collaboration in studies with animals.

Researchers can decide not to embark on a study on the basis of information about similar investigations that are in progress—whether primary studies or systematic reviews. Alternatively, the information can prompt researchers to contribute to an existing study or to plan collaborative analyses of similar, but independently organised research, with an agreed core dataset to address mutually agreed questions. Such prospectively planned meta-analyses seem likely to offer an important way to generate precise and generalisable estimates of effects and associations, and a way of confronting some of the practical and political difficulties encountered during organisation of large international studies.[111] Efficient exploitation of these opportunities will need increased international collaboration and coordination among research funders.

For more on **prospective registration of protocols of clinical trials** see http://www.who.int/ictrp/en/

For more on **prospective registration of systematic reviews** see http://www.crd.york.ac.uk/prospero/

For more on **review of animal data** see http://www.camarades.info

Contributors
All authors prepared sections of the report. The complete first draft was prepared by IC. All authors contributed to revision and preparation of the final report.

Conflicts of interest
We declare that we have no conflicts of interest.

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