Research: increasing value, reducing waste 3

Increasing value and reducing waste in biomedical research regulation and management

Rustam Al-Shahi Salman, Elaine Beller, Jonathan Kagan, Elina Hemminki, Robert S Phillips, Julian Savulescu, Malcolm Macleod, Janet Wisely, Iain Chalmers

After identification of an important research question and selection of an appropriate study design, waste can arise from the regulation, governance, and management of biomedical research. Obtaining regulatory and governance approval has become increasingly burdensome and disproportionate to the conceivable risks to research participants. Regulation and governance involve interventions that are assumed to be justified in the interests of patients and the public, but they can actually compromise these interests. Inefficient management of the procedural conduct of research is wasteful, especially if it results in poor recruitment and retention of participants in well designed studies addressing important questions. These sources of waste can be minimised if the following four recommendations are addressed. First, regulators should use their influence to reduce other causes of waste and inefficiency in research. Second, 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. Third, researchers and research managers should increase the efficiency of recruitment, retention, data monitoring, and data sharing in research through use of research designs known to reduce inefficiencies, and further research should be done to learn how efficiency can be increased. Finally, everyone, particularly those responsible for health-care systems, should promote integration of research into everyday clinical practice. Regulators and researchers should monitor adherence to each of these recommendations and publish metrics.

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This is the third in a **Series** of five papers about research

Division of Clinical Neurosciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK (Prof R Al-Shahi Salman PhD, Prof M Macleod PhD); **Centre for Research in Evidence-Based Practice, Bond University, Robina, QLD, Australia** (E Beller MAppStat); **Division of Clinical Research, National Institute of Allergy and**

Introduction

In 2009, Chalmers and Glasziou[1] identified many avoidable sources of waste and inefficiency in biomedical research, which are elaborated upon in this Series. After identification of an important research question and selection of an appropriate study design, waste can be noticeable and quantifiable from the way in which research is regulated and managed.[2] Furthermore, foreknowledge of regulatory and management requirements can affect researchers' choice of research question and study design, resulting in unnoticed and unquantifiable waste, such that important research is identified but never addressed. Ultimately, waste arises from questions being overlooked or unnecessarily addressed, research being underpowered or done too slowly, and research being too costly.

A consensus on the need to regulate biomedical research arose from Nazi research atrocities[3] and abuses of people in mainly non-therapeutic research,[4,5] such that by the 1980s, the need for ethics review and prelicensing regulation of biomedical research involving human beings was not controversial. Similarly, published revelations of maltreatment of experimental animals in preclinical research led to it becoming more regulated.[6] Nowadays, permission to do biomedical research (regulatory approval) is needed in accordance with requirements of national or regional laws or professional authorities. Research ethics committees are independent regulators of most types of biomedical clinical research, whereas additional specific regulators oversee research involving data, devices, drugs, embryos, radiation, and tissue, among others. Regulatory functions are also undertaken by institutional bodies concerned with biomedical research governance, which is

Recommendations

1 People regulating research should use their influence to reduce other causes of waste and inefficiency in research
   - Monitoring—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

2 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
   - Monitoring—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

3 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
   - Monitoring—researchers and methodologists should do research to identify ways to improve the efficiency of biomedical research

4 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
   - Monitoring—people responsible for management of health-care systems or research should measure the proportions of patients who are enrolled in research

Infectious Diseases, Bethesda, MD, USA (J Kagan PhD); **National Institute for Health and Welfare, Helsinki, Finland** (Prof E Hemminki MD); **Centre for Reviews and Dissemination, University of York, York, UK** (R S Phillips BM BCh); **Oxford Centre for Neuroethics, University of Oxford, Oxford, UK** (Prof J Savulescu PhD); **Health Research Authority, London, UK** (J Wisely PhD); **and James Lind Initiative, Oxford, UK** (Sir I Chalmers DSc)

Correspondence to:
Prof Rustam Al-Shahi Salman, Bramwell Dott Building, Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK
rustam.al-shahi@ed.ac.uk

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See Online for appendix

"…the system of administration and supervision through which research is managed, participants and staff are protected, and accountability is assured".[7] The procedural conduct (management) of biomedical research that has regulatory approval indicates not only the customs and habits of researchers, but also the regulatory requirements.

However, the increasing burden, inconsistency, and complexity of regulation in the past two decades, sometimes out of proportion to the risk of the research,[2] has attracted increasing criticism in many countries, including the UK, Canada, and the USA. Research ethics committees were the earliest regulators, and so account for most evaluations, but an increasing number of additional regulatory steps have also caused problems.[7,8]

In this report, we consider how both regulation (including governance) and management affect the wastefulness and value of biomedical research. First, we describe how regulation can contribute to the fundamental sources of waste and inefficiency in biomedical research, and cite one example from preclinical research. Second, we describe evidence for waste and inefficiency in clinical research arising from the burden and inconsistency of regulation (including governance), and how these permissions are often disproportionate to the conceivable risks of the research. Third, we describe sources of waste and inefficiency in the management of clinical research. Fourth, we make recommendations for increasing value and reducing waste, and list measures to monitor how successful these recommendations have been. Further reading for each section is provided in the appendix.

Regulation can be associated with other sources of waste and inefficiency

Regulation can miss the opportunity to minimise waste

In the conduct of their intended role, people who fund, regulate, or manage research might be complicit with the sources of waste and inefficiency described in other papers in this Series. Nearly two decades ago, evidence was presented that research ethics committees were behaving unethically: first, through failure to require researchers to show (by reference to systematic reviews of existing evidence) that proposed additional research was necessary and had been designed taking account of lessons from relevant previous research; and, second, through failure to ensure that clinical trials were registered at inception and reported when completed.[9] Because both failures can result in avoidable suffering and deaths, regulation can fail in its intended purpose to safeguard the rights, dignity, safety, and wellbeing of participants in clinical research.[10]

An example from preclinical research

Regulation of preclinical research focuses, rightly, on ensuring that investigators comply with national legislation.[11,12] This legislation is often based on the principles of the three Rs—ie, reduction (methods that reduce the number of animals used), replacement (use of non-animal methods), and refinement (methods that improve animal welfare)—as described by Russell and Burch in 1959.[13] In their discussion about the role of reduction, Russell and Burch contrasted hypothesis-testing experiments with what they called "trial and error on a grand scale", in which a "constant and huge stream of new chemical substances" were tested in many experiments involving animals to screen for biological activity.[13] Since most in-vivo research is now done for hypothesis testing rather than for screening, this issue, as it was originally conceived, is of little relevance.

There are many reasons for why experiments might be underpowered. Major funders, such as the Wellcome Trust and Medical Research Council, require applicants to show that they have considered the principles of the three Rs. This injunction operates alongside researchers' desire to do more experiments with few resources and a dearth of formal power calculations. This problem leads to a situation in which many in-vivo studies are underpowered to detect postulated effects. Systematic reviews have shown that investigators of fewer than 2% of reports of animal experiments describe the basis for their sample size calculations; had they done so, most calculations would have shown the need for the number of animals used in experiments to be substantially larger. Although this problem has several drivers, the finding that few ethics review panels require investigators to increase the number of animals used in a proposed research programme (even when proposed research is substantially underpowered) suggests that the principle of reduction takes precedence over the need for optimum experimental design.

Regulation of clinical biomedical research

Double standards for informed consent to treatment

Longstanding anomalies in regulatory requirements persist, such as those between requirements for research of novel treatments and research comparing standard treatments. Four decades ago, a British paediatrician noted that he needed permission to give a treatment to half his patients (to find out whether it did more good than it did harm), but that he did not need permission if he decided to give the treatment to all his patients (assuming, without good evidence, that it must be beneficial and safe).[14] 25 years ago, an Editorial in *The Lancet* noted that "the clinician who is convinced that a certain treatment works will almost never find an ethicist in his path, whereas his colleague who wonders and doubts and wants to learn will stumble over piles of them".[15] The disproportionate effort expended in the regulation and management of research comparing standard treatments remains the most formidable disincentive to health professionals, patients, and researchers who wish to collaborate to confront uncertainties about the effects of health-care interventions in everyday practice.[16–18]

Burden and inconsistencies in regulation

Many unpublished anecdotes (panel 1, figure 1) and much observational evidence (figure 2) indicate that

regulatory review is burdensome and too slow. These delays are additive when separate regulatory approvals have to be sought consecutively, rather than simultaneously. Dependent on its design, clinical research might need to be approved by several different regulators, each requiring amendments that, in turn, need to be considered by the other regulators who have already given approval. This duplication of effort for both researchers and regulators is inefficient. Not only do these delays result in wasted resources for research, they can also prevent research being rapidly responsive to unpredictable events, such as epidemics.[19] Burdensome requirements discriminate against regions where regulatory capacity is insufficient to oversee the regulations, especially low-income and middle-income countries.[20]

Regulatory approval for observational studies and clinical trials remains expensive and time-consuming in the USA, UK, and Australia.[21] Delays vary between countries, seemingly because of differences in national requirements, or governance steps applied by one country to another. Several hundred steps have been required to start up oncology clinical trials in the USA, accounting for roughly half of the total time for phase 3 trials from inception, and half these steps did not add value to trials. These inefficiencies are particularly inflated for multicentre studies in the UK, Australia, and the USA.[22] In these studies, repeated institutional governance review further increases the costs and complexity of such studies, and increases the time lag between research expenditure and health gain.

If centralised regulatory review is not available, multicentre clinical research can require as many applications for regulatory approval as there are institutions participating in the research, each sometimes requiring an individualised application. Despite the downsides of multiple ethics reviews of multicentre studies, proposals for multicentre studies in the USA rarely receive ethics review centrally, perhaps because of a conflation of ethics and institutional responsibilities. Decentralised ethics approval for a multicentre cancer trial in Australia led to delays which, after inclusion of the secular increase in cancer survival, resulted in about 60 avoidable cancer deaths in Australia per year.[23]

Inconsistency in decision making and processes has been noted between research ethics committees reviewing observational studies and clinical trials in Australia, Canada, the UK, and the USA; levels of inter-committee agreement were slight. Within a jurisdiction, inconsistency can arise from regulators' human judgment; different interpretations of laws, regulations, and guidelines; or amendments to study materials on the basis of subjective judgments, such as the wording of consent forms. In multinational research, inconsistency can also arise from discordance among countries' regulations, which are affected by their social, political, and cultural characteristics.[8,24]

***Panel 1:* An example from Sweden of the bureaucracy involved in applications for central research ethics committee approval**

In 2010, a group of researchers in Sweden wanted to pool data from several cohort studies to identify risk factors for subarachnoid haemorrhage. They identified about 20 studies, and spent about 300 h contacting all investigators and getting signed data-sharing agreements and data security processes agreed. Sweden has a central research ethics committee to approve projects. The team recorded the time taken for each step of the approval process. About 200 h of office time was spent on the ethics approval and resubmission process alone. The research ethics committee wanted to see all information that the participants of all cohorts had been given about the purpose of the study. These documents had to be provided as 18 copies and submitted manually. It took the team 6 months to collect all the information sheets from the 20 different cohorts, several of which began recruitment in the 1960s and for which little knowledge about what information was given by whom to whom in the recruitment phase was poor. The research ethics committee eventually had the team advertise in national newspapers about the pooling project, listing all original cohorts so that all individuals who did not want the team to use their data for this project could withdraw their consent for the study. Not one participant withdrew. It took more than 3 years to reach the stage of pooling data from the cohorts, ready for analysis.

Figure 1: **Paperwork required for regulatory review of the research described in panel 1**

Contradictions between separate regulations and guidelines result in confusion and a risk-averse culture among regulators, both for observational studies and for clinical trials. One result of changes in regulations and guidelines with time is inconsistency in the methods used in long-term research projects—eg, regulators might decline approval for record linkage to earlier recruits through the application of contemporary regulatory requirements, but a systematic review has shown that most patients consent to the use of secondary data for record linkage.[25]

Of course, researchers might contribute to slowing of regulatory approval. A survey of research ethics committee letters in the UK in 2005–06 showed that a quarter of researchers' applications had discrepancies and three-quarters had procedural violations. UK Health Research Authority management information indicates a small improvement—only a sixth of the 6000 applications to research ethics committees in the UK in 2012 were incomplete. The persistent problems related mainly to application quality, missing information, and researchers' inability to comply with a complex application process.

Disproportionate regulation

Although the conceivable risks of research vary, regulatory requirements do not seem to have been designed to be proportionate to the extent to which

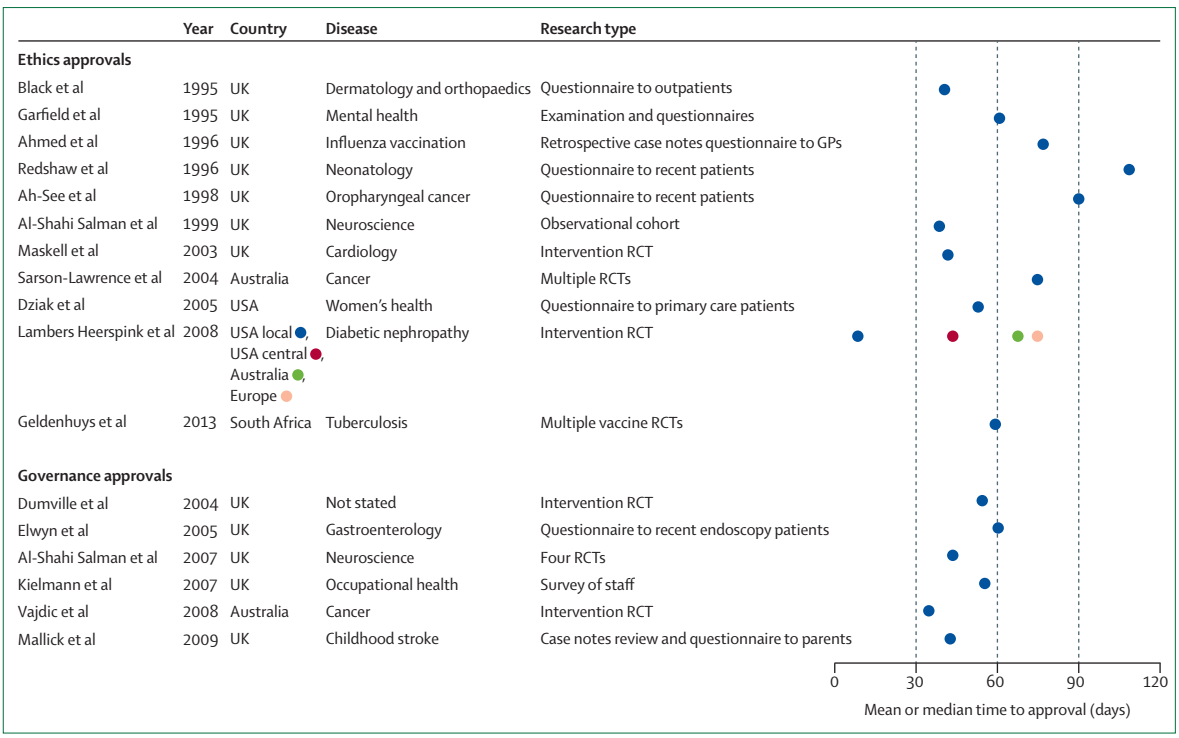

Figure 2: **Results of some observational studies describing average (mean or median) delays to ethics or governance approval of clinical research**
RCT=randomised controlled trial. References in the appendix.

safety of patients is likely to be jeopardised. Most patients do not support restrictive requirements for informed consent for low-risk epidemiological research and biobanking.[26–29] Furthermore, such requirements for consent introduce bias because people who do provide consent do so unpredictably and systematically differ from those who do not.[30] Some of the many barriers, in addition to research ethics review that investigators of clinical trials have to confront, are due to the requirements of drug and device regulatory agencies.[21,31,32] For example, the European Union's Clinical Trials Directive has been applied not only to prelicensing, industry-led trials of new drugs, but also to non-commercial trials assessing licensed treatments that have already been adopted in practice.[33,34] Although the directive might have standardised some aspects of the conduct of drug trials and improved trial quality, it has been variably interpreted and enforced.[35] This enforcement seems to have contributed to delays,[36] and increased administrative burdens—eg, between 2003 and 2007, the average time from protocol finalisation to initiation of recruitment increased from 144 days to 178 days.[37] Because requirements are disproportionate for low-risk trials of licensed drugs, the directive seems to have led to a decrease in non-commercial drug trials in some regions, such as Finland, the Netherlands, France, and the UK, although not in some others, such as Denmark and Germany. By contrast, the European and US regulatory standards for the licensing and approval of devices are far more permissive than are those for drugs, which, too, seems disproportionate in view of the risks and expense of many devices.

Management of clinical biomedical research

The design of clinical research affects its management and feasibility. Slow recruitment and poor retention are particularly inefficient because they delay the delivery of research and inflate its costs through increases in the number of staff and sites, extending the amount and duration of funding required. This problem is not small—systematic reviews show that the originally specified sample size is recruited in a little more than half of clinical trials.[38,39] Recruitment and retention are jeopardised by many factors,[40] including: insufficient funding;[41] unrealistic feasibility assessments;[41] exclusive eligibility criteria (such as age cutoffs[42]);[43] complex protocols arising, at least partly, from regulatory requirements (which increase the burden of administration, amendments, data collection, and adverse event reporting[44]); inefficient methods for approaching potential participants;[41] treatment protocols that make burdensome demands on participants;[45] problems with the delivery of interventions;[41] patient preferences for alternative treatments;[45] patients not understanding or liking the idea of randomisation, or of being so-called experimental subjects; and patients' fear of the unknown.[45] Delays in recruitment can be particularly

problematic in emergency settings, in which complex requirements for informed consent can result in avoidable deaths when they delay the start of treatments that are more effective the earlier they are given.[46]

Many processes that were intended to improve the quality and safety of clinical research are costly, time-consuming, and of unproven effectiveness. Systematic reviews have shown use of a range of onsite monitoring activities in trials, with little evidence to support them;[47,48] the only randomised controlled trial assessing onsite initiation visits did not show any benefits of this process.[47] Strategies that ensure data integrity, such as double-entry of data and source data queries, seem costly and inefficient. Onsite monitoring requirements are disproportionate in trials of low-risk treatments,[22] in which central statistical monitoring might be as accurate and more efficient.

Recommendations

Minimising waste and inefficiency in the regulation and management of research

In view of the extent of waste and inefficiency that we report in the regulation and management of research worldwide, we are surprised by the paucity of quantitative and qualitative research documenting and investigating solutions to it, as compared with other causes of waste and inefficiency. On the basis of what we have discussed, we propose the following steps to minimise waste and inefficiency in the regulation and management of research, and suggest measures to monitor compliance with these recommendations.

Recommendation 1

People regulating research should use their influence to reduce other causes of waste and inefficiency in research. People regulating, governing, and managing research should set and monitor standards that minimise known causes of waste and inefficiency for which funders, researchers in industry or academia, regulators, and health-service managers are responsible (panel 2). This recommendation could be addressed by making approval conditional on researchers referring to one or more systematic reviews of existing research (to minimise the number of unnecessary and poorly designed studies); providing potential participants with information from these reviews (to ensure that they realise studies are worthwhile); registering clinical trials (to help to avoid publication bias), as the UK Health Research Authority requires;[49] and making the results publicly accessible. Participants and potential participants could be encouraged to rate publicly the quality of ongoing trials;[50] and ratings would show studies that had adhered to these recommendations.[51]

Recommendation 2

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. Solutions to the burden and inconsistency of regulation for researchers include: standardisation of application processes (ideally use of a single standard application form and an information management system to seed data to populate multiple application forms) and decision making (through training, standard operating procedures, and accreditation); centralisation of reviews to smaller numbers of well resourced, qualified, and trained committees; and increases in regulators' accountability for decisions and delays.[52] Electronic approaches are likely to be less wasteful of natural resources and more sustainable than are paper-based approaches. Lean and quality-improvement approaches can more than halve clinical trial protocol development and approval times.[53] There are recent examples of progress with centralisation of review of multicentre trials in Ontario (Canada) and Italy, where delays in activation of academic trials seem to be shortening. In the UK, research ethics review of all multicentre projects is centralised (panel 3)—driven partly by the European Clinical Trials Directive and a 2011 Academy of Medical Sciences report[2]—although this centralisation is less pronounced in research governance approvals required by the UK National Health Service.[54,55]

The antidote to the proliferation of regulations is to streamline and harmonise them.[21] The recent revision of the Declaration of Helsinki made progress, but it remains

***Panel 2*: Features that research regulation and review should require**

- Show evidence, by reference to systematic reviews of relevant existing research evidence, that proposed additional research will address important continuing uncertainties
- Proportionate assessment of applications and comparison of potential benefits with any harm envisaged for research participants, additional to whatever would be expected during the health care that they would otherwise receive
- Potential research participants should be given, at the time of recruitment, a summary of existing evidence from systematic reviews (including, but not restricted to, evidence from clinical trials) about the possible risks and benefits of their participation, which is tailored to the nature and context of their illness
- Potential participants to be free to consent to research entailing reasonable, but more than minimal, risk (in some circumstances, even when consent cannot be obtained, such as in emergencies)
- Support for opt-out systems (or, in some rare circumstances, non-consensual systems) for collection of deidentified data from medical records, blood samples, and discarded tissue
- Registration of protocols for clinical trials in the public domain at trial inception
- Researchers, research funders, and research institutions to make their protocols and research results publicly accessible
- Provision, for every participant who wishes to receive them, of reports of results (including treatment received) and future available options
- Audit by research ethics services and other regulators of the conduct of research and reporting of results
- Appropriate randomised evaluations of research regulation and management strategies

***Panel 3*: Examples from the UK of solutions to some sources of waste and inefficiency in regulation of clinical research**

2004: Central Office for Research Ethics Committees (COREC)
- Standard operating procedures, applying the requirements of the European Clinical Trials Directive to trials and observational studies
- Single application form (including sections for local institution approval)
- Single UK-wide approval (except for research involving adults with mental incapacity in Scotland)

2007: National Research Ethics Service (NRES)
- Integrated Research Application System (IRAS), a single portal for applications to many regulatory bodies
- Generic approvals for research databases and tissue banks
- Local sites no longer required to be reviewed by a research ethics committee in addition to local research governance department

2011: Health Research Authority (HRA)
- Research ethics committees in England reduced from 200 in 2002, to 69 in 2013
- 6000 applications (1000 of which were clinical trials of investigational medicinal products) in 2012
- Number of applications reviewed at each research ethics committee meeting ranged from one to 70 in 2002, to five to six in 2013
- Observational research of health-care staff became exempt from ethics committee review
- Proportionate review service for low-risk studies, with shortened forms and timelines
- Reduced requirement for reporting safety to NRES and to the Medicines and Healthcare products Regulatory Agency (MHRA)
- Average time to approval 40 days in 2013
- Collaborative review of product safety with other regulators (eg, MHRA)

2013: Features of HRA strategic plan
- Reduce requirements of applicants
- Deduplicate review of applications by many agencies
- Extend the proportionate review service
- Reduce provisional opinions
- Shared ethics debate to identify whether further guidance is required to improve consistency
- Ethics officers to support applicants and research ethics committees
- Instruments to help decisions about whether regulatory approval is required
- Promotion of transparency in research conduct (ie, registration, publication, dissemination, access to data, access to tissue, and participants informed of study results)
- Greater coordination and less duplication of review by ethics committees and the National Health Service

For more on the **Integrated Research Application System** see http://www.myresearchproject.org.uk

For the **website of the Health Research Authority** see http://www.hra.nhs.uk

For the **Sensible Guidelines for the Conduct of Clinical Trials Forum** see http:/www.ctsu.ox.ac.uk/research/sensible-guidelines

too restrictive on waiver of consent, broad consent for multiple uses, research with reasonable net risks (panel 2), research in vulnerable groups, and comparators that are not regarded as the best proven interventions.[56] Another opportunity is the European Commission's revised proposal for clinical trial regulation, but this proposal needs more emphasis on the types of clinical studies to which it applies; the range of risk allowable in emergency situations; the risk-based (proportionate) approaches to application, monitoring, safety reporting, and amendment of trials; and the standards and openness needed to prevent regulators being complicit with some of the other sources of waste and inefficiency in clinical research.[9,57]

The main solution to disproportionality is to limit regulation to whatever is essential, both to protect the autonomy and wellbeing of research participants and to be proportionate to the plausible risks posed to them.[2,8] For clinical drug trials, the UK Medicines and Healthcare products Regulatory Agency and the Health Research Authority (panel 3) now take account of different amounts of estimated risk.[58] This proportionate approach is being considered elsewhere,[59] and progress such as this can be catalysed by an international forum, such as the Sensible Guidelines for the Conduct of Clinical Trials initiative.[21]

Risks should be minimised when possible (eg, through use of secure safe havens in which researchers can access identifiable and other data[60]), but regulations and regulators should also respect the preferences of mentally competent patients (if they are fully informed of the possible risks and benefits, and the alternatives) who might be prepared to participate in research of interventions that are of low likely benefit and of high likely risk.[61]

Recommendation 3

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. Use of opt-out consent procedures for observational clinical research and clinical trials of accepted treatment alternatives would help to improve recruitment.[62–64] Particularly, recruitment to clinical trials could be improved by involvement of patients in trial design and management;[65] design of simpler and more open clinical trials[66] with broad inclusion criteria;[43,67,68] use of routine electronic health records to identify and monitor participants;[69] and use of culturally sensitive materials,[66] shorter and more informative information leaflets,[70] monetary incentives,[66] and telephone reminders.[64,66] Much can be done to improve the quality and friendliness of information about continuing trials produced for patients.[50,71] A systematic review of controlled trials identified several strategies to improve responses to questionnaires (panel 4).[72] Involvement of patients, and better site capacity assessment in the design of studies, would also probably improve recruitment.

A systematic review showed that little research had assessed the effects of interventions intended to improve participation by clinicians in clinical research and that none of the research had included control groups.[73] A systematic review of interventions to improve clinicians' recruitment to clinical trials showed that the most promising individual intervention was the use of qualitative interviews of clinicians to identify and overcome barriers to recruitment.[74] Engagement of health-care professionals with clinical research can be fostered by their involvement in design and management of research, improvement of their training, and by fostering collaboration. For example,

Tognoni and colleagues at the Mario Negri Institute in Milan, Italy, described how nearly all coronary care units in Italy collaborated to establish the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI), and, between 1983 and 1993, recruited more than 43 000 patients to three randomised trials. The absence of reimbursement for recruitment meant that routine care within the Italian National Health Service was transformed into a controlled trial at very low cost. The training opportunity provided by participation, enthusiasm of the cardiologists and their professional body, and clinician involvement in the organisation and methods of the trial, increased clinicians' participation, and aligned the goals of the trial and those of the clinical specialty.

Methods of data management and analysis can also improve clinical trial efficiency. Use of comprehensive central monitoring and targeted onsite monitoring seems to identify most protocol and procedural compliance issues.[75] Central statistical monitoring in large trials is effective in the detection of fraud,[76] and seems cost effective, especially when risk assessment[77] does not mandate onsite monitoring.[78,79] Sharing of emerging data from similar trials among data monitoring committees can help to inform decisions about whether recruitment should continue.[80]

Recommendation 4

Everyone, particularly those responsible for health-care systems, should help to improve the efficiency of clinical research through promotion of the integration of research into everyday clinical practice. The disproportionate effort expended in the regulation and management of research comparing standard treatments, and the inefficiencies in the management of research into standard clinical practice, both provide arguments for seamless integration of evaluative research into everyday clinical practice.[68,81] This feat was achieved by the Italian GISSI collaboration, and was envisaged in the UK National Health Service's plan in 2000[82] and, subsequently, in its research strategy.[83] Consistent with these proposals, in 2006, the UK General Medical Council (GMC) advised British doctors that they "must work with colleagues and patients to help resolve uncertainties about the effects of treatment".[84] However, in their 2013 guidance,[85] the GMC has removed reference to this expectation as an element of good clinical practice, which is a major, ethically-flawed, and backward step that they have not defended in public at the time of writing.[86]

The medical specialty that has the longest established tradition of integrating research with clinical practice is paediatric oncology. About 70% of children with cancer enrol in one or more clinical trial,[87,88] which might partly explain the dramatic improvement in childhood cancer survival from 10% to almost 80% in the 50 year duration of the US Children's Oncology Group.[89] This situation arose because the assessment of treatments for rare diseases needs collaboration, and discovery of the first cure for one childhood cancer became a framework for evaluation of the treatment of other cancers.

Research networks embedded within health-care systems have streamlined research delivery, fostered a collaborative and constructively competitive environment (panel 5, figure 3), and incentivised recruitment of patients to observational studies and clinical trials in the UK, Canada, and the USA. There is no evidence that receiving treatments in research settings has greater risks than has receiving the same treatments outside research settings,[90] and there is some evidence that participation in research benefits participants.[87] Increases in participation in clinical trials in the context of specialist care have translated into better outcomes at the population level,[91] and research-active hospitals might have better treatment outcomes than have others.[92–94]

***Panel 4*: Methods to improve response to questionnaires[72]**

Questionnaire sent electronically

- Non-monetary incentives
- Shorter e-questionnaires
- Inclusion of a statement indicating that others had responded
- A more interesting topic
- Immediate notification or an offer of results
- Use of a white background
- Personalisation
- A simple header
- Textual representation of response categories
- Provision of a deadline
- Inclusion of a picture
- No mention of the word survey in the email subject line
- A female signatory

Sent by post

- Monetary incentives
- Sent by recorded delivery
- A teaser on the envelope
- A more interesting questionnaire topic
- Prenotification
- Follow-up contact
- Unconditional incentives
- Shorter questionnaires
- Provision of a second copy of the questionnaire at follow-up
- Mention of an obligation to respond
- University sponsorship
- Non-monetary incentives
- Personalised questionnaires
- Hand-written addresses
- Stamped return envelopes rather than franked return envelopes
- An assurance of confidentiality
- First-class outward mailing
- Questions that are not of a sensitive nature

For more on the **Clinical Research Network** see http://www.crncc.nihr.ac.uk

***Panel 5*: An example from England of how clinical research networks can catalyse recruitment**

2008

- Creation of the National Institute for Health Research Clinical Research Network in England

2012–13

- Recruitment increased by 40% between 2009–10 and 2012–13
- More than 600 000 National Health Service patients recruited in nearly 4000 studies in 2012–13 (figure 3)
- 99% of National Health Service trusts in England actively supporting clinical research in 2012–13

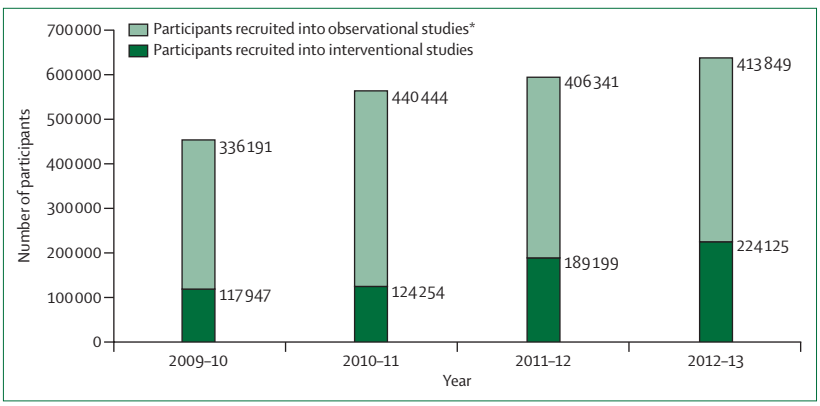

***Figure 3*: Number of participants recruited into National Institute Health Research Clinical Research Network portfolio studies in England by primary study design**

*Category includes studies that have not specified their primary study design.

Economic arguments also favour health-care systems embracing clinical research as the most parsimonious approach to the resolution of uncertainties about expensive, potentially beneficial, or harmful treatments.[95] For ethical and economic reasons, organisations representing the interests of third-party payers for health care (such as the National Institute for Health and Care Excellence in UK, and Medicare in the USA) have required inadequately assessed treatments to be made available only within the context of research to learn more about their effects.[95] Extended application of this policy would help to achieve greater integration of research within routine care. Inevitably, prioritisation of practice-oriented clinical research requires further shifts in the distribution of research funds.[96]

Conclusions

There are opportunity costs of wasteful regulation and management of research. Less research might be done. Research might be done too late to matter or be relevant. Participants might be retained in studies that do not recruit a sufficiently large sample to answer the questions being addressed. Independent research might be less sustainable than might commercially-sponsored research (with consequent sponsorship bias[97]). Professionals might be deterred from careers in research.

Ultimately, these problems are a threat to public health[98]—they cost people their lives through a failure to identify and introduce effective treatments and prevent harmful treatments from continuing; therefore, there is a strong moral imperative to do research. Everyone involved in research should be accountable for the efficiency and effectiveness of their research.[99] Because patients and the public have the most to gain from reductions in research waste and inefficiency, they should be involved in decisions about the need for, and extent of, the effects of regulation and management on clinical research.

Despite evidence for waste and inefficiency in the regulation and management of research, considering the likely effect of these factors, we feel that there is a disproportionate dearth of so-called protest research documenting waste and inefficiency and investigating solutions to it.[74] Such research is hard to fund and hard to do, but research regulation and management should be informed by empirical research (such as we have found in systematic reviews[22,25,30,38–40,45,47,48,64,66,70,72–74,90,93,94]) to assess whether processes and procedures serve the interests of research participants and the public.[100,101] Our recommendations make it clear that this goal is everyone's responsibility.[51]

Contributors

All authors contributed information to the article. RA-SS wrote the first draft of the manuscript, which was critically revised by all coauthors. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009; **374:** 86–89.
2 Academy of Medical Sciences. A new pathway for the regulation and governance of health research, 2011. http://www.acmedsci.ac.uk/p47prid88.html (accessed Dec 2, 2013).
3 Katz J. The Nuremberg Code and the Nuremberg Trial. A reappraisal. *JAMA* 1996; **276:** 1662–66.
4 Pappworth MH. Human guinea pigs: a warning. *Twentieth Century* 1962; **171:** 66–75.
5 Beecher HK. Ethics and clinical research. *N Engl J Med* 1966; **274:** 1354–60.
6 Guide for the Care and Use of Laboratory Animals. Institute for Laboratory Animal Research, Commission of Life Sciences, National Research Council. Washington, DC: National Academy Press, 1996.
7 Shaw S, Boynton PM, Greenhalgh T. Research governance: where did it come from, what does it mean? *J R Soc Med* 2005; **98:** 496–502.
8 Shaw S, Barrett G. Research governance: regulating risk and reducing harm? *J R Soc Med* 2006; **99:** 14–19.

9 Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996; **313:** 1390–93.

10 Califf RM. Clinical trials bureaucracy: unintended consequences of well-intentioned policy. *Clin Trials* 2006; **3:** 496–502.

11 Animals (Scientific Procedures) Act. London: Her Majesty's Stationery Office, 1986.

12 The European Parliament and the Council of the European Union. Directive 2010/63/EU on the protection of animals used for scientific purposes. *Official Journal of the European Union* 2010; **276:** 33–79.

13 Russell WMS, Burch RL. The principles of humane experimental technique. St Albans: Universities Federation for Animal Welfare, 1959.

14 Smithells RW. Iatrogenic hazards and their effects. *Postgrad Med J* 1975; **52** (suppl)**:** 39–52.

15 The Lancet. Medical ethics: should medicine turn the other cheek? *Lancet* 1990; **336:** 846–47.

16 Chalmers I, Lindley RI. Double standards on informed consent to treatment. In: Doyal L, Tobias JS, eds. Informed consent in medical research. London: BMJ Publications, 2001: 266–75.

17 Warlow C. A new NHS research strategy. *Lancet* 2006; **367:** 12–13.

18 Slowther A, Boynton P, Shaw S. Research governance: ethical issues. *J R Soc Med* 2006; **99:** 65–72.

19 Jester PM, Tilden SJ, Li Y, Whitley RJ, Sullender WM. Regulatory challenges: lessons from recent West Nile virus trials in the United States. *Contemp Clin Trials* 2006; **27:** 254–59.

20 Bollyky TJ, Cockburn IM, Berndt E. Bridging the gap: improving clinical development and the regulatory pathways for health products for neglected diseases. *Clin Trials* 2010; **7:** 719–34.

21 Reith C, Landray M, Devereaux PJ, et al. Randomized clinical trials–removing unnecessary obstacles. *N Engl J Med* 2013; **369:** 1061–65.

22 Duley L, Antman K, Arena J, et al. Specific barriers to the conduct of randomized trials. *Clin Trials* 2008; **5:** 40–48.

23 Christie DR, Gabriel GS, Dear K. Adverse effects of a multicentre system for ethics approval on the progress of a prospective multicentre trial of cancer treatment: how many patients die waiting? *Intern Med J* 2007; **37:** 680–86.

24 Neaton JD, Babiker A, Bohnhorst M, et al. Regulatory impediments jeopardizing the conduct of clinical trials in Europe funded by the National Institutes of Health. *Clin Trials* 2010; **7:** 705–18.

25 da Silva ME, Coeli CM, Ventura M, et al. Informed consent for record linkage: a systematic review. *J Med Ethics* 2012; **38:** 639–42.

26 Hansson MG. Need for a wider view of autonomy in epidemiological research. *BMJ* 2010; **340:** c2335.

27 Stjernschantz Forsberg J, Hansson MG, Eriksson S. Biobank research: who benefits from individual consent? *BMJ* 2011; **343:** d5647.

28 Barrett G, Cassell JA, Peacock JL, Coleman MP, for the National Cancer Registry. National survey of British public's views on use of identifiable medical data by the National Cancer Registry. *BMJ* 2006; **332:** 1068–72.

29 Tupasela A, Sihvo S, Snell K, Jallinoja P, Aro AR, Hemminki E. Attitudes towards biomedical use of tissue sample collections, consent, and biobanks among Finns. *Scand J Public Health* 2010; **38:** 46–52.

30 Kho ME, Duffett M, Willison DJ, Cook DJ, Brouwers MC. Written informed consent and selection bias in observational studies using medical records: systematic review. *BMJ* 2009; **338:** b866.

31 Dilts DM, Sandler AB. Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. *J Clin Oncol* 2006; **24:** 4545–52.

32 Kramer JM, Smith PB, Califf RM. Impediments to clinical research in the United States. *Clin Pharmacol Ther* 2012; **91:** 535–41.

33 McMahon AD, Conway DI, Macdonald TM, McInnes GT. The unintended consequences of clinical trials regulations. *PLoS Med* 2009; **3:** e1000131.

34 Frewer LJ, Coles D, van der Lans IA, Schroeder D, Champion K, Apperley JF. Impact of the European clinical trials directive on prospective academic clinical trials associated with BMT. *Bone Marrow Transplant* 2011; **46:** 443–47.

35 Hedgecoe A, Carvalho F, Lobmayer P, Raka F. Research ethics committees in Europe: implementing the directive, respecting diversity. *J Med Ethics* 2006; **32:** 483–86.

36 Lambers Heerspink HJ, Dobre D, Hillege HL, Grobbee DE, de Zeeuw D. Does the European clinical trials directive really improve clinical trial approval time? *Br J Clin Pharmacol* 2008; **66:** 546–50.

37 European Forum for Good Clinical Practice (EFGCP). Impact on clinical research of European legislation (ICREL). June 15, 2009. European Commission, Directorate Research. http://www.efgcp.be/ICREL/ (accessed Dec 2, 2013)

38 Campbell MK, Snowdon C, Francis D, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. *Health Technol Assess* 2007; **11:** ix–105.

39 Sully BG, Julious SA, Nicholl J. A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. *Trials* 2013; **14:** 166.

40 Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. *Cancer* 2008; **112:** 228–42.

41 McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006; **7:** 9.

42 Fern L, Davies S, Eden T, et al, for the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. *Br J Cancer* 2008; **99:** 1967–74.

43 Fonville AF, Samarasekera N, Hutchison A, Perry D, Roos YB, Al-Shahi Salman R. Eligibility for randomized trials of treatments specifically for intracerebral hemorrhage: community-based study. *Stroke* 2013; **44:** 2729–34.

44 Getz KA, Wenger J, Campo RA, Seguine ES, Kaitin KI. Assessing the impact of protocol design changes on clinical trial performance. *Am J Ther* 2008; **15:** 450–57.

45 Prescott RJ, Counsell CE, Gillespie WJ, et al. Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol Assess* 1999; **3:** 1–143.

46 Roberts I, Prieto-Merino D, Shakur H, Chalmers I, Nicholl J. Effect of consent rituals on mortality in emergency care research. *Lancet* 2011; **377:** 1071–72.

47 Bakobaki J, Joffe N, Burdett S, Tierney J, Meredith S, Stenning S. A systematic search for reports of site monitoring technique comparisons in clinical trials. *Clin Trials* 2012; **9:** 777–80.

48 Macefield RC, Beswick AD, Blazeby JM, Lane JA. A systematic review of on-site monitoring methods for health-care randomised controlled trials. *Clin Trials* 2013; **10:** 104–24.

49 Chalmers I. Health Research Authority's great leap forward on UK trial registration. *BMJ* 2013; **347:** f5776.

50 Chalmers I. A guide to patient-led good controlled trials. *Lancet* 2000; **356:** 774.

51 Evans I, Thornton H, Chalmers I, Glasziou P. Testing treatments: better research for better healthcare, 2nd edn. London: Pinter and Martin, 2011.

52 Blunt J, Savulescu J, Watson AJ. Meeting the challenges facing research ethics committees: some practical suggestions. *BMJ* 1998; **316:** 58–61.

53 McJoynt TA, Hirzallah MA, Satele DV, Pitzen JH, Alberts SR, Rajkumar SV. Building a protocol expressway: the case of Mayo Clinic Cancer Center. *J Clin Oncol* 2009; **27:** 3855–60.

54 Al-Shahi R. Research ethics committees in the UK–the pressure is now on research and development departments. *J R Soc Med* 2005; **98:** 444–47.

55 Fudge N, Redfern J, Wolfe C, McKevitt C. Streamlined research governance: are we there yet? *BMJ* 2010; **341:** c4625.

56 Millum J, Wendler D, Emanuel EJ. The 50th anniversary of the declaration of Helsinki: progress but many remaining challenges. *JAMA* 2013; published online Oct 23. DOI:10.1001/jama.2013.281632

57 Gøtzsche PC. Deficiencies in proposed new EU regulation of clinical trials. *BMJ* 2012; **345:** e8522.

58 Medicines and Healthcare Products Regulatory Agency. Risk-adapted approaches to the management of clinical trials of investigational medicinal products. Sept 7, 2012. http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/News/CON126145 (accessed Dec 2, 2013).

59 Smyth RL. A risk adapted approach to the governance of clinical trials. *BMJ* 2011; **343:** d6756.

60 Peddicord D, Waldo AB, Boutin M, Grande T, Gutierrez L Jr. A proposal to protect privacy of health information while accelerating comparative effectiveness research. *Health Aff (Millwood)* 2010; **29:** 2082–90.

61 Savulescu J, Hope T. Ethics of research. In: Skorupski J, ed. The Routledge Companion to Ethics. Abingdon: Routledge, 2010: 781–95.

62 Junghans C, Feder G, Hemingway H, Timmis A, Jones M. Recruiting patients to medical research: double blind randomised trial of "opt-in" versus "opt-out" strategies. *BMJ* 2005; **331:** 940.

63 Rogers CG, Tyson JE, Kennedy KA, Broyles RS, Hickman JF. Conventional consent with opting in versus simplified consent with opting out: an exploratory trial for studies that do not increase patient risk. *J Pediatr* 1998; **132:** 606–11.

64 Treweek S, Mitchell E, Pitkethly M, et al. Strategies to improve recruitment to randomised controlled trials. *Cochrane Database Syst Rev* 2010; **1:** MR000013.

65 Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. *Br J Psychiatry* 2013; **203:** 381–86.

66 Watson JM, Torgerson DJ. Increasing recruitment to randomised trials: a review of randomised controlled trials. *BMC Med Res Methodol* 2006; **6:** 34.

67 Sustainable Trials Study Group. Towards sustainable clinical trials. *BMJ* 2007; **334:** 671–73.

68 Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003; **290:** 1624–32.

69 Staa TP, Goldacre B, Gulliford M, et al. Pragmatic randomised trials using routine electronic health records: putting them to the test. *BMJ* 2012; **344:** e55.

70 Edwards SJ, Lilford RJ, Thornton J, Hewison J. Informed consent for clinical trials: in search of the "best" method. *Soc Sci Med* 1998; **47:** 1825–40.

71 Godlee F, Chalmers I. Publishing information about ongoing clinical trials for patients. *BMJ* 2010; **340:** c725.

72 Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev* 2009; **3:** MR000008.

73 Rendell JM, Merritt RD, Geddes JR. Incentives and disincentives to participation by clinicians in randomised controlled trials. *Cochrane Database Syst Rev* 2007; **2:** MR000021.

74 Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. *BMJ Open* 2012; **2:** e000496.

75 Bakobaki JM, Rauchenberger M, Joffe N, McCormack S, Stenning S, Meredith S. The potential for central monitoring techniques to replace on-site monitoring: findings from an international multi-centre clinical trial. *Clin Trials* 2012; **9:** 257–64.

76 Venet D, Doffagne E, Burzykowski T, et al. A statistical approach to central monitoring of data quality in clinical trials. *Clin Trials* 2012; **9:** 705–13.

77 Journot V, Pignon JP, Gaultier C, et al, for the Optimon Collaborative Group. Validation of a risk-assessment scale and a risk-adapted monitoring plan for academic clinical research studies–the Pre-Optimon study. *Contemp Clin Trials* 2011; **32:** 16–24.

78 Tudur Smith C, Stocken DD, Dunn J, et al. The value of source data verification in a cancer clinical trial. *PLoS One* 2012; **7:** e51623.

79 Baigent C, Harrell FE, Buyse M, Emberson JR, Altman DG. Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clin Trials* 2008; **5:** 49–55.

80 Chalmers I, Altman DG, McHaffie H, Owens N, Cooke RW. Data sharing among data monitoring committees and responsibilities to patients and science. *Trials* 2013; **14:** 102.

81 Weisfeld V, English RA, Claiborne AB. Public engagement and clinical trials. New models and disruptive technologies. Workshop summary. Washington, DC: The National Academies Press; 2011.

82 Chalmers I. It's official: evaluative research must become part of routine care in the NHS. *J R Soc Med* 2000; **93:** 555–56.

83 Department of Health (Research and Development Directorate). Best Research for Best Health: a new national health research strategy. Jan 25, 2006. London: Department of Health, 2006

84 GMC. Good Medical Practice. London: General Medical Council, 2006.

85 GMC. Good Medical Practice. London: General Medical Council, 2013.

86 Roberts I, Chaudhry B, Chalmers I. New GMC guidance takes a major, ethically flawed, backward step. *BMJ* 2013; **346:** f3879.

87 Stiller CA, Eatock EM. Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1994. *Arch Dis Child* 1999; **81:** 202–08.

88 Unguru Y. The successful integration of research and care: how pediatric oncology became the subspecialty in which research defines the standard of care. *Pediatr Blood Cancer* 2011; **56:** 1019–25.

89 O'Leary M, Krailo M, Anderson JR, Reaman GH, for the Children's Oncology Group. Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. *Semin Oncol* 2008; **35:** 484–93.

90 Vist GE, Bryant D, Somerville L, Birminghem T, Oxman AD. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database Syst Rev* 2008; **3:** MR000009.

91 Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978–2005 by eras of entry to clinical trials. *Ann Oncol* 2012; **23:** 2464–69.

92 Majumdar SR, Roe MT, Peterson ED, Chen AY, Gibler WB, Armstrong PW. Better outcomes for patients treated at hospitals that participate in clinical trials. *Arch Intern Med* 2008; **168:** 657–62.

93 Clarke M, Loudon K. Effects on patients of their healthcare practitioner's or institution's participation in clinical trials: a systematic review. *Trials* 2011; **12:** 16.

94 Papanikolaou PN, Christidi GD, Ioannidis JP. Patient outcomes with teaching versus nonteaching healthcare: a systematic review. *PLoS Med* 2006; **3:** e341.

95 Chalmers I. Addressing uncertainties about the effects of treatments offered to NHS patients: whose responsibility? *J R Soc Med* 2007; **100:** 440–41.

96 Rothwell PM. Funding for practice-oriented clinical research. *Lancet* 2006; **368:** 262–66.

97 Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2012; **12:** MR000033.

98 Warlow C. Over-regulation of clinical research: a threat to public health. *Clin Med* 2005; **5:** 33–38.

99 Whitney SN, Schneider CE. Viewpoint: a method to estimate the cost in lives of ethics board review of biomedical research. *J Intern Med* 2011; **269:** 396–402.

100 Califf RM, Morse MA, Wittes J, et al. Toward protecting the safety of participants in clinical trials. *Control Clin Trials* 2003; **24:** 256–71.

101 Chalmers I. Regulation of therapeutic research is compromising the interests of patients. *Int J Pharm Med* 2007; **21:** 395–404.