Increasing value and reducing waste in stroke research

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Summary

Stroke represents a major burden to patients and society, and resources spent on stroke research must be used efficiently and produce good value in terms of improvements in human health. However, there are many examples of poor value from stroke research funding, which result from the way in which stroke research has been chosen, designed, conducted, analysed, regulated, managed, disseminated, or reported. In a project including a survey and a symposium and involving stroke researchers in the European Stroke Organisation we have sought to identify sources of inefficiency and waste, recommended approaches to increase value, and highlighted examples of best practice in stroke research. Recent evidence suggests that progress has been made, but there is room for much improvement, and stroke researchers, funders and other stakeholders might consider our recommendations when planning new research.

Introduction

The World Health Organisation has reported that stroke is the leading cause of disability among adults, and the second leading cause of death worldwide(1). More than 33 million people worldwide have a stroke each year(2), and in 2010 the estimated annual cost of stroke was $53.9 billion in the US and €64.1 billion in Europe(3;4). Demographic changes caused by increase in longevity and changes in lifestyle will lead to a further increase in the burden of stroke(1;2), and research into prevention and treatment of stroke should therefore be a priority(5). Several notable successes in stroke research have delivered substantial health benefits in the past, with associated costs savings for society, for treatments such as antithrombotic or blood pressure lowering treatment for stroke prevention, and thrombolytic drugs, intra-arterial interventions, and multidisciplinary care in stroke units for treatment in the acute phase(6-10). However, despite recent modest increases in funding(5;11), stroke research remains underfunded compared to research in other major disease areas, such as cardiac disease and cancer(11;12).

Given the limitations of resources it is all the more important that funding allocated to stroke research is used efficiently, and produces good value for money in terms of advances in knowledge or improvement in human health. A key challenge for funders of research is that much research does not lead to notable changes(13). It is to be expected that some projects will yield neutral or negative results, and some studies must be done with the sole intention of replicating previous research findings, but much research is wasteful or produces very little value for the financial, human or animal resources used. Waste and inefficiency may occur in the ways that biomedical research is chosen, designed, conducted, analysed, regulated, managed, disseminated or reported(13), and stroke research is no exception. Biomedical research typically involves many stakeholders, and researchers must navigate a complex environment of funders, regulators, academic research governance bodies, commercial clinical research organisations, industry, insurers, patient groups, publishers, and others. In stroke research, this complexity is

increased by the specific requirements of studies in prevention, acute care, and rehabilitation, with potential for waste and inefficiency.

The Reduce research Waste And Reward Diligence (REWARD) Alliance(14), supported by a campaign launched by *The Lancet*(15), and a series of five papers(16-20), aims to increase value and reduce waste in biomedical research. The five papers produced specific recommendations and gave suggestions for monitoring of progress, aimed at funders, regulators, publishers, academic institutions, and researchers(16-20). In a satellite symposium at the ESO Conference in May 2016, arranged jointly by the ESO Trials Network Committee and *The Lancet Neurology*, stroke researchers, representatives from industry and publishers gathered with the aims to identify sources of waste, recommend approaches to increase the value of stroke research, and highlight examples of best practice (Panel 1). The symposium, which focussed on randomised-controlled trials of treatments in clinical practice, was accompanied by a short survey among participants to inform the discussion, and used the structure of *The Lancet* series: research prioritisation; design, conduct and analysis; regulation and management; accessibility; and reporting(16-20). This Policy View summarises the symposium and survey conclusions.

Panel 1. Aims of this Policy View

- To identify sources of waste in the way stroke research is chosen, designed, conducted, analysed, regulated, managed, disseminated and reported
- To suggest methods to reduce waste and increase value in each of these areas
- To reinforce and encourage good practice and methodological research, by providing examples of best practice in stroke research
- To encourage other disease-specific communities to seek evidence of waste in their own research and to seek ways to reduce it

Research prioritisation

The financial and human resources available to undertake human health research are ~~finite~~limited. Therefore, to ensure best use of resources, regulators, funders, researchers and potential research participants should work collaboratively to identify priority areas for research(16). Many projects do not lead to notable benefits, either because they contribute little to knowledge about basic mechanisms that have relevance for human health (basic research), or to practice and policy (applied clinical research), or both (the "waste quadrant")(16;21). Other projects contribute little because of unnecessary duplication of existing knowledge(16;21).

An accepted criterion for prioritisation is that the research should address a health problem that causes a significant burden to society(21). However, resources allocated to stroke research are often not directed at yielding the greatest health benefits on a population level. For example, strategies for improved primary or secondary prevention (e.g. blood pressure lowering) are likely to yield large benefits at a population level, but are often not prioritised. Similarly, research into stroke recovery is consistently highly valued by patients and may have a large impact on stroke-related disability, but few large rehabilitation trials have been performed. Several recent initiatives have sought to improve prioritisation of health research studies. The National Institutes of Neurological Disorders and Stroke (NINDS) are leading an effort to make trial selection more explicit and rationale in its Immediate Practice-Altering Clinical Trials (ImPACT) pilot program(22), and metrics for the public health impact of clinical trials have been developed(23). The James Lind Alliance(24) seeks to establish priority setting partnerships for a wide range of health problems, by bringing together stakeholders to identify the most important uncertainties. Of relevance to neurology, such partnerships have been established to set research priorities for cavernous malformations, dementia, multiple sclerosis, neuro-oncology, Parkinson's disease, spinal cord injury, and stroke(25).

Another frequently cited criterion for priority setting is that the research should be patient-centred, focussing on the aspects of the problem that people with the condition under study consider important. However, different stakeholders in research may have different priorities. For example, funding agencies may have selected a broad thematic area (e.g. cognitive decline after stroke), yet researchers may have a very narrow scientific question (e.g. whether a particular agent prevents cognitive decline), and potential research users may value studies that addresses clinical services rather than a specific drug therapy. Care givers may have yet another view(26), and, ~~I~~importantly, even among patient sub-groups different priorities may exist. For example, patients with stroke-related disability may be more interested in research into rehabilitation, while people who have not had a stroke, or a non-disabling stroke, may be more interested in research into prevention or acute treatment. Patients may also have different views on which outcomes are important. For example, while some will value the effect of a new treatment on cognitive function, others will prioritise social and emotional function, outcomes over the longer term, and risk of adverse reactions(27-29). To fulfil the criteria that research should address major health problems and the needs of patients, it seems clear that priority topics must be agreed through an alliance between stakeholders, including regulators, funders, researchers, care givers and patients(16).

While some research aim at changing practice and policy (applied clinical research), other research can contribute to knowledge about basic mechanisms that have relevance for human health (basic research)(16;21), such as genetic mechanisms of stroke(30). There should also be a scientific basis for evaluating a specific clinical intervention. For example, it is possible that many of the neutral or negative trials of neuroprotective agents could have been avoided, had there been a better understanding of basic mechanisms, experimental bias, and the disparities between pre-clinical models and clinical studies(31-33), and a closer collaboration between pre-clinical and clinical researchers. ~~It is also~~Finally, it is a fundamental criterion for effective

research prioritisation that the question under study should not have been answered by prior research. It is therefore important that all research is preceded by a systematic review of what has already been done, to avoid unnecessary duplication, to identify what should be replicated, and to identify questions from previous work which could lead to new research(34).

Research prioritisation exercises can themselves be wasteful of researcher time and effort. For example, although a specific EU "Horizon 2020" funding call will disburse half a dozen millions of Euros, only a few of the many applications will be funded(35). When the total cost in research time in preparing the applications is considered, a significant amount of non-productive resource is expended by those groups whose proposals were not funded. This raises the question whether projects should be triaged at an earlier stage, or whether there can be other ways of allocating funding, for example more sustained core funding over a defined period of time to particularly skilful research groups, to allow maximum freedom of research(36).

Panel 2 gives examples of best prioritisation practice in stroke research.

Panel 2. Examples of best prioritisation practice in stroke research

1. ***Accessibility of information about completed, on-going and planned research.*** The Database of Research in Stroke (DORIS)(37) contains over 23,000 references to completed, ongoing and planned controlled clinical trials and systematic reviews collected by the Cochrane Stroke Group(38). It provides a rich source of information and can be used to identify research questions and to assess whether new research on a particular topic is called for or not.
2. ***Use of systematic reviews to identify an important research topic.*** A Cochrane systematic review of trials of selective serotonin reuptake inhibitor after stroke showed that a large number of small trials had been conducted, which, in aggregate, suggested that a large scale trial was needed(39). It was not feasible to obtain funding for a multinational trial, so a

"federation" of three parallel trials has been established(40), with an agreed core dataset to address mutually agreed questions.

3. ***Involvement by stroke organisations.*** The World Stroke Organization recently collated publications on research prioritisation efforts in stroke. It highlighted the wide range of approaches that have been employed and how priorities differ(41). National and international stroke organisations can clearly play a facilitatory role in defining and setting priorities.

Research design, conduct, and analysis

Without appropriate design, conduct and analysis research is of reduced value, no matter how relevant the research question is, how efficiently the research is regulated, how widely the findings are disseminated, or how well they are reported(17). It is therefore important that research teams are able to draw on expertise appropriate to their tasks, at every stage of the research cycle. As Ronald Fisher said, "to call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination: he can perhaps say what the experiment died of". Because current incentives for biomedical researchers prioritise novelty and quantity over replication and quality, it is not enough simply to do work which is important and relevant. One must also be able to demonstrate that the work is of high quality.

Poor experimental design, conduct and analysis are important causes of waste in stroke research. Pre-clinical research may be planned without input from clinical research, and clinical researchers may not have a proper understanding of what can be translated and what is lost in translation from pre-clinical studies(31-33). Eligibility criteria may be overly complex, for example relying on invasive or complex imaging studies, restricting the pool of available patients and centres and reducing generalisability. Data collection forms may also be complex, burdening centres with a requirement to collect data items which are subsequently never analysed or reported. Overly-optimistic assumptions may be made for sample size calculations,

leading to underpowered trials with inconclusive results. Important outcome measures may not be included at design phase, missing the opportunities to capture valuable information about quality of life, cognition, or costs of treatment.

Institutions, funders and stroke organisations share the responsibility for education and training of stroke researchers, to enable them to design and conduct high-quality stroke research, including pre-clinical studies, translation research, and clinical trials specific for prevention, acute treatment, and recovery of stroke. Openly accessible resources could be developed (including, for example, standard contracts, outcome assessment instruments, trial insurance information). Investment should also be made into developing and maintaining stroke research networks, to facilitate and standardise stroke research within health care systems(42).

Research institutions should also provide core methodological expertise. To ensure high quality, researchers need to have not only content expertise (e.g. a theoretical understanding of the statistical methods used), but also experience of the practical application of this knowledge in stroke studies. Problems may arise at the design phase if such expertise is not available, and recruiting individuals with such expertise after a grant has been awarded is challenging, since by that stage much of the study design is already established. Many research groups are funded largely through income from time-limited grants, so it is only possible to retain such experienced individuals if the lead researcher repeatedly applies for grants to sustain the group. This may divert effort from addressing the most relevant research questions, and so another perverse incentive is born. An alternative model would be that research institutions on a local or regional level provide funding for individuals with core research methodological expertise, either embedded within, or accessible to, the research groups that they serve.

Finally, it is important that publishers, funders, institutions and stroke organisations reward not only researchers who produce research outputs in large quantity or on novel topics, but also those who do research to replicate key research findings, or high quality studies of treatments in clinical practice with large impact on human health. While publishers and funding agencies have an important role (by limiting access to publications and grants), it is also critical that institutions adopt a more nuanced approach to selecting candidates for promotion or tenure, with emphasis on delivery of high quality, well-designed research (following for instance the Leiden Manifesto(43)), and that national research assessment exercises take greater account of the rigour with which research was conducted(44). There is also insufficient academic recognition of some key aspects of clinical research. For example, Data Monitoring Committees provide vital oversight of clinical trials, the members of such committees require a unique set of skills and experience and carry a great burden of responsibility, but such work does not attract academic recognition or reward(45).

Panel 3 gives examples of good design, conduct, and analysis in stroke research.

Panel 3. Examples of good design, conduct, and analysis in stroke research

1. ***Quality of pre-clinical research.*** There has been greater attention to the rigour with which preclinical research is conducted and reported, mediated through the Stroke Therapy Academic Industry Roundtable (STAIR) initiative(31) and the publication of the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines(46), with subsequent changes in editorial policy at *Stroke*, *Journal of Cerebral Blood Flow and Metabolism* and *International Journal of Stroke*. Analysis of risk of bias in in-vivo research published in *Stroke* shows substantial improvements in the rates of reporting of, for instance, randomisation and blinding(47).
2. ***Trial registration.*** There has been an increase in registration of stroke trials. Allowing a two year lag between study completion and publication, and looking only at stroke trials

registered at clinical trials.gov and only at studies indexed in PubMed, since 2000 there has been a 20-fold increase in the proportion of clinical trials registered (Malcolm R. Macleod, personal communication).

3. ***Standardisation of conduct and analysis of stroke trials.*** The creation of clinical stroke research networks such as the National Institute for Health Research (NIHR) Stroke Research Network in the UK and StrokeNET in the US has led to standardisation and improvement in delivery of stroke trials (Gary A. Ford, personal communication). Progress has also been made in determining the most relevant outcome measures after stroke(48), including measures of cognitive function(49), and the best ways of analysing data from stroke trials(50).

Regulation and management

Research regulation (including governance) and management is essential to ensure that trials are performed ethically for the best interest and protection of participants, and to high scientific standards, but waste can arise from excessive and complex regulation and from poor management. Overburden of regulation and governance can lead to the failure of trials to recruit to time or target, or to researchers avoiding addressing important questions because of concerns that it will not be feasible to meet regulatory requirements, resulting in unnoticed and unquantifiable waste(18;51).

Regulations for approval and conduct of research involving medical devices or drugs are complex, variably interpreted and enforced in different countries, and often out of proportion to the risk to participants(52). For instance, the EuroHYP-1 study of therapeutic hypothermia for acute ischaemic stroke(53) has been subject to extensive delay in receiving regulatory approval, due to being inconsistently classified as a drug trial, a device trial, neither or both, across different competent authorities in Europe. Some of the regulations for drug trials, such as

expedited reporting of suspected unexpected serious adverse reactions, and on-site monitoring, were developed for the testing of new agents in industry-led studies, and may not be appropriate for low-risk investigator-led trials testing licensed agents that have been in everyday clinical use for many years.

Regulations for recruitment of patients with reduced consent capacity represent a particular problem in acute stroke trials, in some cases leading to delays in recruitment because of burdensome consent processes. There is a need to find alternative and simpler ways of patient recruitment to low-risk acute stroke trials. For example, some trials have developed emergency consent processes, with brief(54) or verbal consent(55;56), or even waiver of consent(57), after approval by ethics committees. The European Commission's revised proposal for clinical trial regulation opens for a more flexible approach to consent in emergency settings(58), and this should probably be used more often in stroke research.

Reduction in waste can also be expected from recent initiatives aiming at simplifying, centralising and harmonising regulation, and at making it proportionate to the degree of risk posed by the intervention under study. For example, the revised Declaration of Helsinki and the revised proposal for clinical trial regulation in the EU(58) state that the level of trial monitoring should be proportionate to the potential harms to research participants, and the Voluntary Harmonisation Procedure makes it possible to seek national approval simultaneously from several EU member states(59). Centralisation of research ethics committees has also taken place in many countries, but other initiatives have had less impact, such as the European Network of Research Ethics Committees (EUREC)(60), which was formed to foster a coordinated ethics review infrastructure in Europe. The MoreTrials campaign(61) represents a group of trialists lobbying for a revision of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines which will make trials simpler, quicker and cheaper to run. For example, risk

adaptive monitoring and data verification processes can reduce monitoring costs without impacting on patient safety(62). The most recent addendum has gone some way to achieving this(63).

Waste can be further reduced if regulators, policy makers and health care funders can play an active role in supporting research, for example by facilitating the integration of research into everyday clinical practice. Funding can be used as an incentive for institutions to take part in research, and re-imbursement of new, expensive treatments can be reserved for treatment that are given within a trial, as was done in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial of intra-arterial treatment for acute ischaemic stroke(64). Integration of research in clinical practice can also be facilitated through establishment of research networks within the health care system, although this has not been scientifically evaluated. The NIHR Stroke Research Network has streamlined research delivery and fostered a collaborative and constructively competitive environment in the UK(18), and in the US the establishment of StrokeNet was seen as a step in improving both research and clinical stroke care(65). Recruitment into randomised-controlled trials may also be increased by allowing co-enrolment to take place under special circumstances(66), or by allowing randomisation of patients who have already been included in stroke registries, as is planned in the TIMING study of the optimal timing of anticoagulation after stroke among patients with atrial fibrillation(67).

Inefficient trial management is another source of waste, which can lead to slow recruitment and poor retention of patients in clinical trials(68), as well as low data quality. There is some evidence from methodological research for the effect of interventions aiming at increasing patient recruitment and retention in trials(68), and the Trial Forge(69) and Prioritising Recruitment in Randomised Controlled Trials (PRioRiTy)(70) initiatives aim at increasing

efficiency of trial management. Other initiatives are advocating methodological research to find better ways of recruiting and retaining patients, for example by conducting randomised-controlled trials embedded within an on-going trial (host trial), a so-called Study Within A Trial (SWAT)(71-73). The SWAT Store is a central repository of ongoing SWATs, which allows investigators to see what methods are currently being tested(74).

Panel 4 shows examples of best practice in regulation and management of stroke research.

Panel 4. Examples of best practice in regulation and management of stroke research

1. ***Integration of research in clinical practice: Trials within registries, and reimbursement of cost of new, unproven treatments only within a trial.*** Patients with stroke and atrial fibrillation included in the Swedish Stroke Registry are simultaneously included into the randomised-controlled TIMING trial of early vs. deferred start of anticoagulant therapy(67). During most of the course of the MR CLEAN trial of intra-arterial treatment for acute ischaemic stroke, the costs of treatment were only reimbursed for patients included into the trial(64), which was important for the trial's ability to deliver to time and target.
2. ***Use of alternative information and consent procedures, and alternative methods for site initiation and management.*** The Tranexamic acid for IntraCerebral Haemorrhage (TICH-2) trial uses a simple abbreviated one-page patient information sheet in order to effectively gain consent in an emergency situation(54). The Paramedic Initiated Lisinopril For Acute Stroke Treatment (PILFAST) trial(55) and the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial 2 (RIGHT-2)(56) used verbal consent in the pre-hospital setting. The Ultra-early Tranexamic Acid After Subarachnoid Hemorrhage (ULTRA) trial of tranexamic acid for subarachnoid haemorrhage allows waiver of consent(57), as did some of the trials of intra-arterial treatment. Remote site initiation and monitoring has been used in many stroke trials(54;75-77) as a more cost-effective alternative to face-to-face visits.

3. ***Research on methods to improve recruitment and retention in stroke studies: Study-Within-A-Trial (SWAT).*** The ESO Trials Network Committee has addressed regulation and management in previous workshops(52;68), and the REstart or STop Antithrombotics Randomised Trial (RESTART)(78) is delivering on these workshops by testing an alternative method for patient recruitment in a SWAT(79).

Accessibility of information

Much research never gets published(20;80), and access is restricted to subscribing institutions for many of the journal reports that are published. Furthermore, journal reports represent only a fraction of the information from a study, and the selection of which studies to report, and what information to share from each study, is often biased. Valuable information is also contained in research protocols, and more detailed analysis of participant-level data can be of great value, to verify the original findings, to answer new questions, or to plan new research. Accessibility of research protocols, primary journal reports, full study reports and availability of individual participant data will therefore increase value of research, and can reduce waste by avoiding redundant, misguided or even harmful research being done(19).

Investigators report that limited time and low priority or importance of results are the most common reasons for not reporting studies(81). At the same time there is no empirical evidence that journals preferentially publish reports showing positive results(81), so there are reasons to believe that publication bias is mostly due to investigators' selective reporting. It was therefore an important step in the right direction when the International Committee of Medical Journal Editors (ICMJE) in 2005 required prospective registration of all trials as a condition for publication of a primary study report. This year the US Department of Health and Human Services and the US National Institutes of Health have gone further by issuing rules for registering of clinical trials and submission of summary results to ClinicalTrials.gov(82). A next,

natural step could be for funders to withhold a part of the grant until the research is published, as practiced by the NIHR Health Technology Assessment programme in the UK. At the same time, research institutions could develop methods for rewarding full dissemination of research.

Trials produce many more data than presented in a single article, and data selected for presentation in the primary report can be biased. For example, the study protocol and the statistical analysis plan contain data that are essential to the correct interpretation of the trial's results. Unexpected challenges can arise, and plans often need to be changed for good reasons (e.g. change in inclusion criteria, change in sample size requirements due to unexpected outcome event rates, change in analysis method), but such changes need to be apparent rather than hidden. However, study protocols and statistical analysis plans are often not generally accessible, and when these can be accessed, even items as critical as eligibility criteria for inclusion into the trial were found to differ frequently between the study protocol and the published article(83;84). Such selective reporting can amplify the bias arising from selective reporting of entire studies(19), and is a possible explanation why the results often cannot be independently replicated. Suspicion of selective reporting can also be a reason for distrust in trial results, even for treatments of which benefits are considered beyond reasonable doubt by the majority of clinicians, such as thrombolysis for acute ischaemic stroke(85). One solution could be to require the publication of the study protocol after registration(83;84) or, if this is not feasible, through registration at for example the Open Science Framework(86).

Even when studies are reported, access to research is restricted, due to costs of journal subscriptions, or language barriers. "Open access" publishing represents a step forward, but is still not widely used(87), probably because of the extra costs for research institutions and individual researchers, and because most open access journals do not yet have comparably high impact factors.

The problem of reporting bias can perhaps be reduced by mandating the sharing of individual participant data from clinical trials, as proposed by the ICMJE and increasingly demanded by research funders and publishers(19;88;89). Data sharing will allow verification of the published results and detection of errors(19), which can increase confidence in results. It can also be used to examine new research questions, particularly if data from different trials can be pooled, and to plan new trials, for example in sample size calculations.

Obviously, specific conditions must be met to support the widespread sharing of individual participant data(88;90). Participants' anonymity must be preserved, and investigators should receive academic credit for sharing their data, from funders, publishers and institutions. They should also have the opportunity to publish any pre-specified analyses before giving access to others, and they should be included in publications arising from analysis of data that they have collected(91). It is also important that data is collected in standard formats to allow their integration, and that data are accompanied by clear metadata to avoid misinterpretation. There is also a need for standardised repositories where data can be uploaded and curated, such as the Virtual International Stroke Trials Archive (VISTA)(92;93).

There are several initiatives aiming at making research information available. The AllTrials campaign has proposed that "all trials past and present should be registered, and the full methods and the results reported"(94). The Linked Clinical Trial project(95) is an independent membership association, founded and directed by publishers, that connects users to all published material related to an individual clinical trial. ClinicalTrials.gov also allows for links to protocols and full study reports, including data that were not included in the published report(96). Center for Open Science allows researchers to organise and archive research material and data, and later make these publicly available(97). Finally, the Academic Research Organization Consortium for

Continuing Evaluation of Scientific Studies — Cardiovascular (ACCESS CV) aims to provide avenues for sharing data from cardiovascular clinical trials(98).

Panel 5 shows examples of best data sharing practice in stroke research.

Panel 5. Examples of best data sharing practice in stroke research

1. ***Repository for individual participant data.*** The Virtual International Stroke Trials Archive (VISTA)(92) has collated anonymous data from clinical trials and provided access to researchers for novel exploratory analyses for more than 10 years, and currently contains data from more than 82,000 patients.
2. ***Pooling of individual participant data.*** Pooled analyses of individual participant data from trials of carotid endarterectomy for symptomatic carotid artery stenosis(99;100), carotid endarterectomy versus stenting(101), surgical decompression of space-occupying hemispheric infarction(102), thrombolytic treatment(103), and intra-arterial treatment for acute ischaemic stroke(104) have been able to estimate treatment effects in specific subsets of patients. The sharing of individual participant data before the publication of the results of the individual trials has allowed much earlier identification of benefit of surgical decompression in patients with space-occupying hemispheric infarction than would have been possible with each of the trials alone(102).
3. ***"Threaded publications" and publication of full datasets.*** The Third International Stroke Trial (IST-3)(105) was given the BioMed Central Open Data Award in 2012 for excellence in sharing, standardisation, publication and re-use of biomedical research data, by linking "threaded publications" to create a "thread of evidence"(106). The NINDS trial(107) and the First IST(108) datasets are made freely available on-line, and the IST-3 dataset is now also available to bona fide researchers.

Reporting

Few would dispute that reports of research should describe the question, its importance, the experimental method, the results, and the meaning of the results(109). Research will be wasteful if information is inadequate to be able to interpret the results correctly, to plan new research based on what has already been done, and to replicate research. Reporting guidelines aim to improve the quality of research reports, but they are often not adhered to. Many studies have found substantial evidence of poor research reporting, for all objectives listed above, regardless of disease, type of study, and type of publication(20).

Adequate reports of research should clearly describe which questions were addressed and why, what was done, what was shown, and what the findings mean. Although the investigation of the quality of reporting in stroke research has not been extensive, there is evidence of: publication bias among pre-clinical stroke studies(110), clinical randomised-controlled trials(20;111) and observational studies(112); inadequate adherence to reporting criteria among randomised-controlled trials(113); and insufficient descriptions of interventions in trials included in systematic reviews(114). However, it has yet to be establish the extent of adherence to reporting guidelines, the adequacy of reporting of pharmacological interventions, the selectiveness of outcome reporting(115), and the reproducibility of findings in stroke research.

Reporting guidelines exists for protocols for some research designs (including the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline for clinical trial protocols(116)), but reporting guidelines for stroke trial protocols may also need to be specific to trials of prevention, acute treatment and rehabilitation. Stroke organisations could take on the task of writing guidelines for stroke trial protocols, or for elements of such protocols, for example outcome definitions.

A major initiative that arose to address some of the systemic problems with reporting in biomedical research was the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network(20;117). EQUATOR includes a comprehensive searchable library of reporting guidelines (e.g. CONSORT, PRISMA, STROBE, STARD, ARRIVE), toolkits to facilitate good reporting, and training courses. These reporting guidelines are not just a resource for researchers, but also for teachers, peer reviewers, and journal editors. For example, the Consolidated Standards of Reporting Trials (CONSORT)(118) and most other reporting guidelines recommend that research reports should set their findings in the context of an updated systematic review of all the available evidence. However, journals can still do more to endorse and enforce the use of reporting guidelines, such as CONSORT(119), including the recommendation to include updated systematic reviews.

The Lancet has set an example by requiring, since 2005, clinical trials to be reported in the context of all the available evidence(120), requiring a Research in Context panel in which the authors report any research in the context of an up-to-date systematic review since 2010(121), and requiring the added value of the research to be described in a more prominent panel since 2014(122). *The Lancet*'s series also recommended several actions to resolve and monitor the problems with research reporting(20): Funders and research institutions were encouraged to take responsibility for providing an infrastructure that facilitates good reporting, as well as to regulate and reward research so that it is well reported, and publishers should join funders and institutions in improving the capability and capacity of authors and reviewers to support good reporting.

Some examples of best practice in research reporting exist in stroke research (Panel 6). We hope that these examples will motivate good practice as well as systematic evaluations of the adequacy of reporting of stroke research.

Panel 6. Examples of good reporting practice in stroke research

1. ***Reporting guidelines for rehabilitation journals.*** A collaborative initiative between 28 rehabilitation and disability journals has arisen to adopt reporting guidelines(123).
2. ***Adherence to reporting guidelines in stroke journals.*** The *European Stroke Journal* requires authors to submit a checklist to demonstrate adherence to the relevant reporting guideline(124).
3. ***Use of the Template for Intervention Description and Replication (TIDieR) checklist.*** The TIDieR checklist, intended to improve the reporting of interventions(125), has already been used in a trial of functional strength straining after stroke(126).

Conclusions and future perspectives

In this Policy View we have identified sources of waste in stroke research, and recommended approaches to reduce waste and increase value for each of the areas covered by *The Lancet's* series (Panel 7). Our examples of best practice illustrate that some progress has been made, but there is room for much improvement, and stroke researchers, funders and other stakeholders might consider our recommendations when planning new research.

For some of the areas (e.g. research design, accessibility and reporting) there is consensus on what constitutes best practice, and what changes to practice and policy that might reduce waste. However, little empirical evidence exists about adherence to these practices. For example, although reporting guidelines have been made, we have no data on whether they are used for reporting of stroke studies. For other areas (e.g. research regulation, management and analysis) there is uncertainty about what is best practice, and consensus has yet to be reached. For example, there is still many questions about the best ways to increase patient recruitment and retention(68), and to analyse data from stroke trials(50). In order to understand what is best practice in these areas, and to learn whether best practices are followed, we need more methodological research.

~~Approaches to reduce waste and increase value in stroke research must therefore include changes to practice as well as methodological research.~~

For the areas in which there is consensus, waste must be reduced by changes to practice, for example, stronger adherence to reporting guidelines. Just as integration of research findings into clinical practice is often slow (e.g. proven treatments), adherence to best practices in stroke research can be inadequate. Information about adherence is important, but may not be sufficient, and stroke research may benefit from the results of implementation science to foster this last, important step from consensus to change in research practice.

We have highlighted examples of best practice in stroke research in the hope that they will encourage stroke researchers to seek collaboration with each other, with other stakeholders, and with researchers in other disease-specific areas. The REWARD Alliance brings together researchers and other stakeholders in all areas of biomedical research, and can be one way of reducing waste. The REWARD Alliance and *The Lancet* series have already had many impacts(127), the first REWARD Alliance conference took place together with the EQUATOR Network in 2015, and REWARD symposia have taken place at the Clinical Trials in Alzheimer's Disease (CTAD) conference in 2015 and now at the ESO Conference in 2016. Stroke researchers and clinicians can join by signing up to the REWARD statement(128), encouraging their organisations to add their name to the other partners of *The Lancet*'s REWARD campaign(15), conducting research to investigate the existence, causes, and solutions to waste, and – most of all – scrutinising their own practice.

Panel 7. Take-home messages

- There is waste and reduced efficiency in the way stroke research is chosen, designed, conducted, analysed, regulated, managed, disseminated and reported. There is need for

change in practice, as well as for methodological research to investigate methods of reducing waste and to monitor whether known methods of reducing waste are being followed.

- ***Prioritisation:*** Criteria for prioritisation and priority topics for stroke research should be agreed through an alliance between stakeholders, including professional and patient/carer stroke organisations. All projects should be able to demonstrate that they have considered the needs of users of research, and that they build on knowledge from previous research.
- ***Design, conduct and analysis:*** Institutions should provide education and training in research methods, and core methodological expertise. Funders should consider investing in stroke research networks, and funders, publishers and institutions should reward replication and quality of stroke research (instead of quantity alone). Stroke researchers might consider developing specific recommendations for the conduct of clinical trials in prevention, acute treatment, and recovery of stroke. Metrics could be used to check compliance with recommendations. Methodological research should be done to monitor the degree to which recommendations are followed, and to find the best research methods.
- ***Regulation and management:*** Regulators and researchers should work together to simplify, centralise and harmonise regulations, and make them proportionate to the potential harms to participants. Researchers and regulators should consider simpler consent procedures and waiver of consent in the acute phase of stroke, and work together with health service funders to facilitate the integration of research in everyday clinical practice. Researchers should perform methodological research, for example to find the best methods for increasing patient recruitment and retention.
- ***Dissemination:*** All research protocols and statistical analysis plans should be published or at least registered. Funders and institutions should support stroke researchers to publish their research with open access, and might consider allocating a part of the grant for publication and wider dissemination. Institutions and researchers should be willing to share individual participant data, and studies should be planned in advance to combine data. Researchers and

regulators should work together to solve issues relating to protection of participant anonymity and rights of investigators.

- ***Reporting:*** Researchers and publishers might consider developing reporting recommendations for stroke trials that are specific to trials of prevention, acute treatment and rehabilitation. Metrics could be used to assess adherence to recommendations. Institutions and funders should reward adherence to reporting recommendations, as well as full and prompt reporting. Publishers should do more to endorse and enforce the use of reporting guidelines, including the recommendation to include updated literature reviews

Search strategy and selection criteria

References for this Policy View were suggested by members of the ESO Trials Network Committee. Further references were identified through searches on PubMed with the terms "waste", "inefficiency", "prioritisation", "design", "conduct", "analysis", "regulation", "management", "accessibility" OR "reporting", each in combination with "stroke" AND "research". Only papers published in the period January 2010 to August 2016 were considered. The symposium was based on *The Lancet* series(16-20), and topics and speakers were agreed between the ESO Trials Network Committee and *The Lancet Neurology* editors. The survey was designed by members of the ESO Trials Network Committee.

Contributors

EB led the writing of the report and made the first draft. PS, MRM, NS, HBvdW, RA-SS and CS each wrote the first draft of various sections of the report. CS was responsible for the survey. All authors contributed to the survey and the symposium and commented on the report.

Declarations of interest

HBvdW, MRM and RA-SS were co-authors of *The Lancet* series "Research: increasing value, reducing waste". EB, NS and RA-SS are members of the MoreTrials campaign. All other authors did not declare competing interests.

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