

We Need a Useful Clinical Research: What Should Change to Make it Valuable?

*"If you always do what you always did,
you will always get what you always got" (1)*

ALBERT EINSTEIN

INTRODUCTION

It seems that the last Nobel laureates refute the system used to publish articles in the most prestigious journals and also disagree with the academic criteria used to assess researchers. (2) Randy Schekman who received the Nobel Prize on December 9, 2013 for his discovery, together with James Rothman and Thomas Südhof, of the cellular machinery regulating the traffic of vesicles, wrote in the Guardian an article entitled: "How journals as Nature, Cell and Science are damaging science". And he declares: "These luxury journals are supposed to be the epitome of quality, publishing only the best research. Because funding and appointment panels often use place of publication as a proxy for quality of science, appearing in these titles often leads to grants and professorships. But the big journals' reputations are only partly warranted. While they publish many outstanding papers, they do not publish only outstanding papers. Neither are they the only publishers of outstanding research." (3) Schekman and his laboratory are now boycotting "luxury" journals and he is encouraging other scientists to do the same.

Another 2013 Nobel laureate, Peter Higgs, the publicized winner of the Physics award (together with Francois Englert) for the theoretical discovery of the mechanism that helps to understand the origin of mass, describes himself, in an article also in The Guardian, as "an embarrassment" to his department at the University of Edinburgh, because he published so little: "Today -he says- I wouldn't get an academic job. It's as simple as that. I don't think I would be regarded as productive enough." (4)

Perhaps, issues and discussions raised by the last Nobel laureates should be expanded to the world of basic and clinical researchers and even physicians who provide and consume the information published in journals.

In recent years, global investment in biomedical research has consistently increased, reaching U\$S 240 billion dollars (adjusted by purchasing power parity)

in 2010. From this huge investment, the main beneficiary is basic research, receiving approximately 60% to 70% of public and private funds. (5) However, new discoveries have come to a standstill or have even decreased in medicine, especially in cardiology. In truth, we do not need more investigations to appear in the curricula vitae but less and better quality research, with great team participation of physicians and researchers and made for the right reasons to answer well formulated questions.

Already 17 years ago, in 1997, E. D. Stokes outlined three different categories of research: Pure Basic Research (to develop knowledge itself), Pure Applied Research (to increase the immediate applicability of research results in medical practice and health policy decisions), and Use-Inspired Basic Research (to simultaneously expand knowledge and increase its applicability). Stokes represented this in a four-quadrant scheme, according to the high or low relevance for expanding the frontiers of understanding in a vertical sense, or to the high or low relevance for its immediate application in a horizontal sense (Figure 1).

Although we preserved from Stokes the Louis Pasteur quadrant representing "use-inspired basic research", as basic research was performed to develop relevant evidence to decrease infectious diseases both in men and animals, the "pure basic research" quadrant was changed, as suggested by Ian Chalmers, (5) by the Marie Curie quadrant for her radiation studies, which by serendipity, later had clinical importance. And we chose to give the name Sir Bradford Hill, among other candidates, to the "pure applied research" quadrant, for performing the first modern randomized clinical trial with a pharmaceutical agent, streptomycin, for pulmonary tuberculosis. And lastly, the nameless quadrant, with low relevance both to expand knowledge as for its immediate application, remains as a pointless, useless quadrant.

RELATIONSHIP BETWEEN BASIC AND APPLIED RESEARCH FUNDING

The financial pattern favouring basic research has remained unaltered for a long time. More than 40 years ago, two scientists, Jules Comroe and Robert Dripps, declared and defended in Science that 62% of all communications deemed essential for subsequent clinical progress resulted from basic research. (5) However,

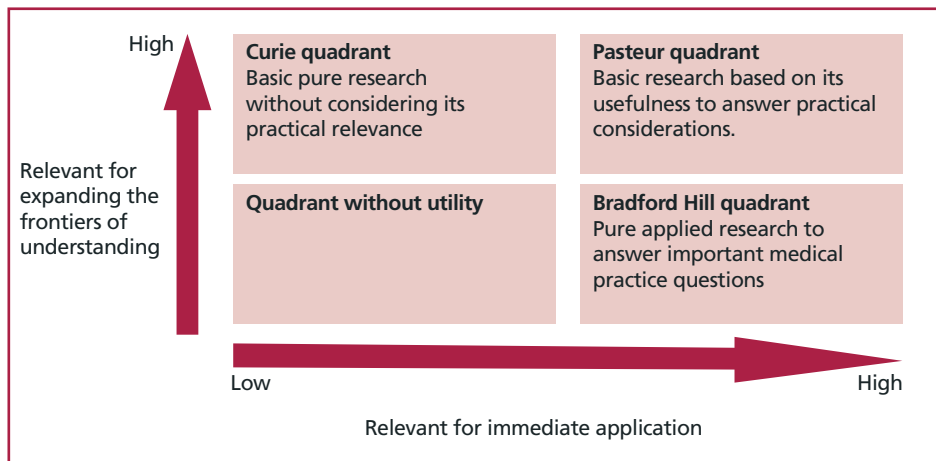


Fig. 1. Classification of the different research categories.

bibliometrist attempts to faithfully and objectively replicate these findings showed not only that Comroe and Dripps's analysis was not "reproducible, trustworthy or valid", but only that 2 to 21% of investigations supporting clinical progress could be described as basic research. (5)

Even though we all know some basic researches which led to remarkable progress in human health, they were often serendipity findings, as the one that occurred in Cardiology, published in an infectology journal, showing that the *Penicillium citrinum* fungus produced a new cholesterologenesis inhibitor, (6) a discovery that gave rise to the well known statins, widely used by clinicians to reduce the risk of cardiovascular disease.

Therefore, the formal evidence of the value of basic research is poorly consistent, since many promising findings are later shown to be exaggerated or simply false. Chalmers claims: "From over 25,000 publications in 6 leading basic research journals between 1979 and 1983, 101 allegedly claimed that the new discoveries had a clear clinical potential, though until 2003, only 5 resulted in interventions with licence for clinical use, and only one led to the development of a widely used intervention.

In a series of projects evaluating translation from bench to bedside, applied clinical research –not basic research– has consistently shown to have great health, social and economic effect. The awareness that clinical research has greater impact than preclinical basic research was observed over a period of 10 to 15 years in arthritis research, more than 15-20 years in cardiovascular research and over 20-25 years in mental health research." (5)

The promises of basic research led us to a bottleneck in the progress of prevention and treatment, jeopardizing not only national health but economy, due to the ever increasing cost of medical care. Therefore, in 2006, the British government decided to alter the proportion of fund allocation in order to promote a growing capacity for applied research, and similar

policies have been developed in other countries, as Italy, Sweden and the USA.

ASSESSMENT TO FINANCE RESEARCH PROJECTS

The current system to finance research based on the classical assessment of a specific project has failed, since the time scientists need to investigate is dedicated to write protocols to obtain grants and scholarships, and control and administer these funds for which they will be judged at their own institutions. New models are timidly arising to decide which research should be supported. Although it seems that greater system reviews would be necessary, making some scientists justifiably nervous, small pilot efforts would allow us to know how they work before adopting them.

If it is decided that the institutions assigning funds are not operative and hence that they should be abolished, there would be two solutions. One would be to share equal funds for all investigators, so that each scientist would receive a small part and great multicentric investigations could not be supported. The other would be random financing, that is, the lottery for a few fortunate researchers, not detecting deserving scientists, though the current adjudication system by peer review does not seem to do it either, as one out of three grants is randomly assigned.

Another way would be to finance scientists taking into account their merit as a research team instead of considering isolated projects, providing time for the complete development of their project (that could be extended to 5 years) without auditing their expenses but assessing their results. Of course, their merit should not be valued as simply as it is commonly done by the number of publications in peer-review journals or the journal impact factor, but by assessing the value of the individual article, considering the average number of citations it has received –instead of the number of published articles–, which is also a measure capturing quality rather than quantity. (7)

Only 0.13% of grants approved by the USA National

Institutes of Health in 2011 were in the three innovative categories focussing in financing individual scientists rather than detailed projects with a specific final result.

WHO DECIDES WHAT TO INVESTIGATE?

In addition to not knowing whether the relationship with basic research is correct and that in medical research evaluation the presence of multiple communications (real or not real investigations) seems more important than each specific research, we should also pose the following question: who decides what to investigate?

Despite strong support from the state in developed countries, business interests rather than the population's real needs set the agenda of what is to be investigated.

If those who should use the information developed by medical research, the real patients, sought information for their ailments in medical publications, they would express their concern on the fact that the reported clinical trials generally have little relevance in the real world scenario, and would rightfully complain that researchers do not often appreciate the effects of interventions in terms of functional, social and emotional wellbeing.

Evidence from organizations as the "James Lind Alliance" (where patients participate in setting research priorities), suggests that research end users are much less interested in research with drugs than the funding institutions and the researchers performing the investigations. (5)

Why is this discrepancy between what researchers do and what potential users want them to do not evident at first glance? Obviously, the reason is that those who use research evidence are rarely involved in the setting of research agendas, decided as all physicians know, according to commercial, academic and political interest, in that order of importance.

As a result, some research questions classified as important for patients and clinicians may never cross the mind of those who design research projects.

There is also a problem and a disincentive due to the methodology of clinical research we are accustomed to use. Performance and interpretation of clinical trials with drugs are more standardized; therefore, they are more direct and easier to perform than other therapies without drugs, psychological interventions, analyses of the best way of providing services, and others of interest to patients and to public health.

BIAS IN DESIGN, CONDUCT AND ANALYSIS

There is often a misguided use of statistical methods, which is magnified by inadequate training. Ioannidis et al. mention, "for example, a study performed in 2001 showed that p values did not correspond to those of statistical tests in 38% of articles published in *Nature* and 25% in the *British Medical Journal*. Prevalent conflicts of interest can also affect the design, analy-

sis, and interpretation of results. Problems in study design go beyond statistical analysis, as shown by the poor reproducibility of research results. Researchers at Bayer could not replicate 43 of 67 oncological and cardiovascular findings reported in academic publications. Researchers at Amgen could not reproduce 47 of 53 landmark oncological findings for potential drug targets." (8)

We do not know whether the research is made on the basis of a rudimentary protocol or poor design or even with the absence of the whole protocol, because even though the protocol is written, it is often publicly unavailable. Nevertheless, this issue improved when leading journals began requesting protocol publication in advance in clinical trial registries which keep detailed records of all the sequences of change. The relevance of the findings prospectively specified in the protocol should be clearly distinguished from those made post-hoc.

Studies are often designed without proper consideration of the usefulness or value of the information they will produce. This happens when substitute endpoints are posed instead of selecting pragmatic, patient-centered results, which would be important for those who eventually use the research.

The need for adequate statistical power may lead researchers to choose outcomes that are clinically trivial or scientifically irrelevant, such as Alzheimer trials with small variations in cognitive scales that have little or no clinical value. Or even use composite endpoint results in an attempt to achieve statistical power, though the components of the composite endpoint may not show the same underlying disease process or may be tied to very subjective clinical decisions. For example, in the composite endpoint of death, myocardial infarction or repeat revascularization, the latter component does not possess the clinical hierarchy of the two former ones; however, it may be the one that gives the endpoint statistical significance.

Most research designs do not take into account similar studies which are being done simultaneously. Therefore, those who design new randomized trials should take into consideration the review of all published research or that still in progress and perform a complete cumulative meta-analysis placing the new work in the global context, in the introduction or discussion.

It is necessary for a member of the research team to have advanced statistical knowledge or for a statistician to be part of the design team. While reviewing the use of Fisher's exact test in 71 articles in 6 important medical journals, the test was more appropriately used when a statistician was part of the research team. (8) These problems with statistical analysis may not be identified in a peer review, especially when they are not evaluated by physician reviewers with adequate statistical and methodological knowledge.

It is necessary to have public access to raw data (open data) and the complete statistical analysis man-

uscripts, which should be required by the journals or published in open ad-hoc repositories; furthermore, funding agencies should request them to sponsor further investigations by the same researcher or research team.

CAN WE AFFORD MUCH OF THE INFORMATION TO BE INACCESSIBLE?

When a physician acts as a patient he may find that his problem was barely studied, but also that the limited information is inaccessible. This happened to Alejandro Liberati in 2010, who explained the difficulties he found to make a rational decision about a new treatment when the initial treatment for multiple myeloma had failed. He declares: "When I had to decide whether to make a second bone marrow transplant I found that there were 4 clinical trials that could have answered my question, but I was forced to make my decision without knowing the results because although the clinical trials had been completed sometime before, they had not been conveniently published... I think that research results should be viewed as a public good that belongs to the community, especially patients."(9)

We must be clear in stating that the benefits of clinical research are only fulfilled in clinical practice when the methods and results of the study are fully and timely reported in an unbiased manner. Therefore "all" research should be easily accessible.

Although we are at a moment of great digital communication and information display, half of the studies related to health are still unreported, and in addition, only a few protocols and database studies are accessible. All inaccessible information, of course, is detrimental to patient care and wastes part of the USD 240 billion spent annually on health research, worldwide.

For example, the Lancet reports that only half of the studies related to health, financed by the European Union between 1998 and 2006 -an expenditure of 6000 million euros-, resulted in identifiable publications (10). In the case of oseltamivir, all unreported clinical trials, including the largest known trial, turned inaccessible 60% of the total patient data at 2011. (11)

Very recently, a review of all studies with neuraminidase inhibitors for influenza was achieved after ending a 4 and a half year battle with the Roche Laboratory to gain access to clinical trials with oseltamivir, all financed by the pharmaceutical industry. After a struggle initiated in 2009 by principal researcher Tom Jefferson, a Cochrane and BMJ reviewer, it was possible to gain access to the clinical trial reports (CTR) which are sent to regulatory agencies with detailed and structured information involving hundreds of sheets and raw data, very different to the abbreviated information published in a medical journal article. These CTR are available in full in a data repository called Dryad (<http://datadryad.org/>), making this one

of the most transparent, if not the most transparent, systematic review ever made.

Reviewers believe that most clinical trials with oseltamivir have a high risk of bias, with poor definition of important endpoints such as pneumonia, all compared against placebo rather than against standard drugs to relieve symptoms, and with test performed during the pandemic. In addition, in some cases publications were written by ghost writers and no trial was independent of drug producers. A few weeks ago the European Union adopted a new regulation that will request registering all clinical trials, publishing all results, and making public all available CTR. (12)

With the new review covering all data, the former perspective has changed substantially. While the finding remains that symptoms can be shortened by half a day from the week's duration with placebo, it has become clear, in all available prophylaxis and treatment studies, that there is no convincing evidence to claim that it decreases the risk of hospitalizations or complications and even death. Moreover, reviewers found that oseltamivir causes nausea and vomiting and increases the risk of headache, kidney disorders and psychiatric syndromes.

Patients would not request active treatment if they had this information, where the small benefit of shortening symptoms (without using any treatment, such as paracetamol) is counterbalanced by treatment damage. (13)

At the same time, 20,000 million dollars were spent since the beginning to supply and store a drug that possibly does not reduce hospitalizations and pulmonary complications in patients who have suffered annual epidemics and pandemic influenza, and that may actually produce damage.

The fact that half of the completed preclinical and clinical studies remain unpublished has not changed in the last 30 years

Not only positive studies are less published, but on average, they are also published a year earlier than negative studies, which tend to get published several years after their conclusion.

Therefore, published scientific literature represents only a subgroup of the conducted research findings, and as a result the information is incomplete and biased. This means that, unfortunately, we cannot be sure we are taking informed decisions together with our patients and that these are complete.

For example, another selective serotonin re uptake inhibitor such as reboxetine was being used in major depression based on published successful results. But when clinical trials that had not been communicated were included in a meta-analysis they actually revealed that reboxetine is more harmful and not more effective than a simple placebo, a finding completely different from that included in published trials. (14)

Moreover, even if the studies were published, access to research communication is restricted, because journal subscriptions are expensive, particularly for

low-income countries, and even for leading private academic institutions. Although in recent years there is open access, 78 % of medical research communication is restricted to paid subscription publications. (9)

Another difficulty is that publications in languages other than English are frequently excluded from systematic review due to lack of language knowledge and access difficulty; for example, more than 2500 biomedical journals are published in Chinese, of which less than 6% are indexed in Medline.

THE NEED FOR UNIVERSAL RECORDS AND LARGE AND SIMPLE CLINICAL TRIALS

Although treatment efficacies, such as in acute myocardial infarction, have been extensively studied in randomized clinical trials, much less is known of how the incorporation and use of these proven treatments vary over time within and between countries.

The comparative intra and international effectiveness research related to the way comprehensive health systems provide care can produce important information to guide the development of public policies and clinical practice.

But such research of national and international comparative effectiveness has three main limitations: 1) although there are voluntary records of selected hospitals or short time cross-sectional surveys, all these studies are based on a part of the population which is already known to differ in treatments and outcomes from the whole population; therefore, the registry and comprehensive comparison of complete health systems would be needed; 2) national and international comparative studies which have been conducted using administrative databases only report some results without knowing the conditions and the individual treatments; 3) there should also be an attempt to standardize mortality according to different patient characteristics (case mix).

A comparison of short-term survival (30 days) of acute myocardial infarction, using national comprehensive records of Sweden and the United Kingdom has been recently published fulfilling all these requirements. (15) A crucial feature to make this work is that health systems in Sweden and the United Kingdom are the only ones in the world who have an ongoing national clinical registry of acute coronary syndrome, involving mandatory participation of all hospitals for many years. (16, 17)

Data from 119,786 patients in Sweden and 391,077 in the United Kingdom between 2004 and 2010 were evaluated. Thirty-day mortality was 7.6 % (95% CI 7.4-7.7) in Sweden and 10.5 % (10.4-10.6) in the United Kingdom. Mortality was higher in clinically relevant subgroups of the United Kingdom defined by the concentration of troponin, ST-segment elevation, age, gender, heart rate, systolic blood pressure, diabetes and smoking. In Sweden, compared to the United Kingdom, there was an earlier and more extensive use of primary angioplasty (59% vs. 22 %) and beta-

blockers at discharge (89% vs. 78%). The standardized 30-day mortality was 1.37 (95% CI 1.30 -1.45) times higher in the United Kingdom than in Sweden, but decreased with time, from 1.47 in 2004 to 1.20 in 2010.

Gale and Fox commented that "The authors reveal large international disparities in the management and outcome of these patients. Despite substantial reductions in early mortality after acute myocardial infarction, cardiovascular disease remains one of the greatest killers". (18)

In conjunction with large national registries, simple and inexpensive randomized clinical trials are needed to provide reliable estimates with numerous events (narrow confidence intervals) of the risk-benefit balance in representative populations; i.e. simpler, with fewer administrative regulations and limited data collection during the test, and without restrictive inclusion criteria to allow extrapolation of results to broader and more heterogeneous populations (19).

Platforms which collect data in registries represent a new opportunity to facilitate patient enrolment in large and simple clinical trials. The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) is an example of a randomized clinical trial, which enrolled patients from the Swedish Coronary Angiography and Angioplasty Registry (SACAR) and obtained the all-cause mortality end point at 30 days from another national registry. (20)

In the TASTE study 7244 STEMI patients were randomized to manual thrombus aspiration followed by PCI or to conventional PCI. Overall mortality was 2.8 % (103/3621) in the thrombus aspiration group and 3.0 % (110/3623) in the group with conventional PCI (HR 0.94, 95% CI 0.72-1.22, $p = 0.63$). This result ended the controversy by demonstrating that routine thrombus aspiration before PCI compared with conventional PCI does not reduce 30-day mortality in patients with STEMI.

Another example is mentioned by Salman et al.: "The medical specialty that has the longest established tradition of integrating research with clinical practice is paediatric oncology. Approximately 70 % of children with cancer are enrolled in one or more clinical trials, which may partially explain the dramatic improvement in childhood cancer survival from 10% to almost 80 % in the 50 years of the U.S Children Oncology Group." (21)

CONCLUSIONS

Most of those involved in basic biomedical and clinical research (funders, researchers, clinicians and patients) are not satisfied with the current status quo based on various complex and interdependent actions of the different actors, each operating within its own set of risks and incentives. These actions can be understood as the result of reciprocal interactions between the individual capacity committed with the activity, opportunities external to the individual that enable action and motivations that produce energy

and direct the actions. Only by considering the economic, social, cultural and political conditions can we understand how the environment of current investigation is shaped.

Economic forces in the industry look for the maximum benefit of new products brought into the market. Since the economic motivations of the industry, as could not be otherwise, characterize health as a commodity that must be purchased, this concept shapes and distorts other actors, even independent researchers and clinicians.

Medical research journals have also become a highly profitable business for the few existing companies, and efforts to maximize income are not always consistent with the ambition to publish research of the highest quality and relevance, even with peer review, which has obvious defects.

Non commercial funders, although not influenced by profit but by political interests, may have to prove, in a few years, that something useful has been done, when we know that the results of strategic decisions in research can take many years to be clear and evident. Grants are awarded based on the amount of work published and where it is published without the specific assessment of the research project value.

The regulatory burden is often disproportionate to the possible research risks and threatens the ability and motivation of researchers to answer some important questions. (22)

How can we do things differently? Given these distorting influences, a protection would be to create an environment with opposing influences that attempt to counterbalance the situation. For example, academics should be judged on their methodological rigor, the quality of their publications, the reproducibility of their findings, and the times they are cited in other papers, and not by the impact factor of the journal in which the work is published.

The scientific process needs to be invigorated and guided by principles promulgated by researchers and academic institutions, to promote rigor, to protect the integrity of the scientific process and to shield scientists from some bad influences. The scientific community must defend itself from the sophistry of politicians, untangle the conflicting motivations of capital and science, and ensure that the tax money of the citizens is transformed into useful results for the practice of medicine. (22)

Dr. Hernán C. Doval^{MTSAC}

Director of the Argentine Journal of Cardiology

REFERENCES

1. <http://wouterdeheij.wordpress.com/2013/04/27/famous-innovation-quotes-from-steve-jobs-gunter-pauli-einstein-henry-ford-abnd-many-others>
2. Kleinert S, Horton R. How should medical science change? *Lancet* 2014;383:197-8. <http://doi.org/f2pk89>
3. Schekman R. How journals like Nature, Cell, and Science are damaging science. *The Guardian* (London) Dec 9, 2013. <http://www.theguardian.com/commentisfree/2013/dec/09/how-journals-nature-science-cell-damage-science>
4. Aitkenhead D. Peter Higgs: I wouldn't be productive enough for today's academic system. *The Guardian* (London) Dec 6, 2013. <http://www.theguardian.com/science/2013/dec/06/peter-higgs-boson-academic-system>
5. Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gülmezoglu AM, et al. How to increase value and reduce waste when research priorities are set? *Lancet* 2014;383:156-65. <http://doi.org/f2pgj5>
6. Endo A, Kuroda M, Tsujita Y. ML-236^a, ML-236B, and ML-236C new inhibitors of cholesterologenesis produced by Penicillium citrinum. *J Antibiot* (Tokyo) 1976;29:1346-8. <http://doi.org/sfv>
7. Ioannidis JP. More time for research: fund people not projects. *Nature* 2011;477:529-31. <http://doi.org/bffx87>
8. Ioannidis JP, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014;383:166-75. <http://doi.org/f2pgj6>
9. Chan AW, Song F, Vickers A, Jefferson T, Dickersin K, Gøtzsche PC, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet* 2014;383:257-66. <http://doi.org/f2pmbc>
10. Galsworthy MJ, Hristovski D, Lusa L, Ernst K, Irwin R, Charlesworth K, et al. Academic output of 9 years of EU investment into health research. *Lancet* 2012;380:971-2. <http://doi.org/f2fssq>
11. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965.
12. Loder E, Tovey D, Godlee F. The tamiflu trials. Progress toward data sharing but many battles still to fight. *BMJ* 2014;348:g2630. <http://doi.org/sfw>
13. Krumholz HM. Neuraminidase inhibitors for influenza. The whole truth and nothing but the truth. *BMJ* 2014;348:8-9. <http://doi.org/sfv>
14. Eyding E, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010;341:c4737. <http://doi.org/c4v8k8>
15. Chung SC, Gedeberg R, Nicholas O, James S, Jeppsson A, Wolfe C, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014;383:1305-12. <http://doi.org/f2rcn8>
16. Herret E, Smeeth L, Walker L, Weston C; MINAP Academic Group. The Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2010;96:1264-7. <http://doi.org/d75ksp>
17. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart* 2010;96:1617-21. <http://doi.org/cc2hhk>
18. Gale CP, Fox KA. International comparisons of acute myocardial infarction. *Lancet* 2014;383:1274-6. <http://doi.org/f2rcnd>
19. Eapen ZJ, Lauer MS, Temple RJ. The imperative of overcoming barriers to the conduct of large, simple trials. *JAMA* 2014;311:1397-8. <http://doi.org/sfz>
20. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. TASTE Trial. Thrombus aspiration during ST segment elevation myocardial infarction. *N Engl J Med* 2013;369:1587-97. <http://doi.org/pzm>
21. Al-Shahi Salman R, Beller E, Kagan J, Hemminki E, Phillips RS, Savulescu J, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet* 2014;383:176-85. <http://doi.org/f2pgj7>
22. Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JP, et al. Biomedical research: increasing value, reducing waste. *Lancet* 2014;383:101-4. <http://doi.org/f2pgj7>