Large simple trials: really, it can't be that simple!

Robert M. Califf^{1,2*}

¹Duke Translational Medicine Institute, Durham, NC, USA; and ²Division of Cardiology, Department of Medicine, Duke University School of Medicine, DUMC 3701, 200 Trent Drive, 1117 Davison Building, Durham, NC 27710, USA

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In this issue of the *European Heart Journal*, Calvo *et al.*¹ present another plea for simplified approaches to clinical trials evaluating cardiovascular therapies. In the interest of disclosure, I note that I work closely with many of the authors of this article. Dr Christopher Granger, in particular, is a long-time collaborator and senior investigator in my own institution.

The thesis advanced by Calvo *et al.* could be called the 'large simple trial (LST) mantra'. Although I agree with most of the concepts expressed in their paper—and indeed, I co-chair the Clinical Trials Transformation Initiative (<http://www.ctti-clinicaltrials.org/>), a public-private partnership with the US Food and Drug Administration (FDA), and more than 60 other organizations that champion similar ideas—this mantra nonetheless omits important aspects that should be considered if LSTs are to be understood within a larger context. To clarify the role that LSTs can play in informing the cardiovascular evidence base, I believe that the following issues deserve consideration.

The LST mantra is pertinent to only a tiny fraction of the total clinical trials portfolio

A recent analysis of data from the ClinicalTrials.gov registry showed that only 3–4% of interventional trials enrol more than 5000 participants, while the vast majority—over 90%—enrol fewer than 100 participants² and therefore could not possibly apply LST methods. Numerous articles published in the nearly three decades since Yusuf, Collins, and Peto first advocated this approach³ have touted LST methods, including the streamlining of trial designs and focusing on outcomes that matter to patients, but these key details have largely gone unheeded. LSTs are vastly outnumbered by complex trials, both large and small. Accordingly, the overwhelming majority of trials do not inform the decisions that patients, healthcare providers, and health systems must make every day, and the overall cost of trials continues to escalate while proliferating bureaucracies absorb ever-increasing shares of research budgets. Thus, a reasonable goal would be to increase the number of large trials that

would fit within the LST construct, but that would leave the majority of trials within a different fundamental framework.

We are in serious need of a new understanding of cardiovascular physiology

Despite the fact that vascular disease (coronary, cerebral, and peripheral) continues to rank as the world's leading cause of death and disability, there is increasing concern that industry is retreating from investment in new therapies for cardiovascular disease.⁴ Although such retrenchment may be due in part to the extraordinary costs of the large complex trials that have dominated the cardiovascular research landscape (as opposed to LSTs), the evidentiary hurdles for approval of new cardiovascular therapies are tougher than in many other fields, and a number of recent, seemingly promising approaches have ultimately failed more stringent tests. It is interesting to note, for example, that despite the enrolment of thousands of volunteers in Roche-sponsored clinical trials examining the peroxisome proliferator-activated receptor- α/γ agonist aleglitazar,⁵ it took a large complex trial to demonstrate that aleglitazar did not reduce cardiovascular events despite favourable effects on classical risk factors, a result that led to the discontinuation of the entire programme.⁶ Reliance upon putative surrogate endpoints such as high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, and blood pressure would have put this medicine on the market, with clearly negative consequences for patients—consequences that might never have been discovered.

Until we develop a mature approach to combining intensive knowledge generated by genetics, gene expression, proteomics, and metabolomics with integrated physiological measures and imaging, we will continue to be duped by nature as we pursue simplistic target concepts and find off-target effects late in expensive development programmes. The technologies and informatics capabilities that could usher in this new paradigm in human research now exist in our major academic medical centres, but they are being applied to non-human models, where they are frequently yielding the disappointing but familiar finding that human beings differ in many

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* Corresponding author. Tel: +1 919 668 8820; Fax: +1 919 668 7103, Email: robert.califf@duke.edu

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important ways from preclinical models. There is hope that the reconfigured Clinical and Translational Science Awards funded by the US National Institutes of Health (NIH) will be able to assemble technologies and methods in a coherent way to rewrite the textbook of physiology. Perturbation of the human system by drug or behavioural intervention should enable us to use modern informatics to assess integrative physiology and on- and off-target effects in ways that were not imaginable just a few years ago.

One research trend running directly counter to the LST is the small, intense, biomarker-driven trial intended to find a large treatment effect via the ability to target a specific causal biological pathway

The biomarker-targeted approach is currently the rage in cancer trials and accounts for a major portion of investment in translational research and drug development in oncology. This approach is predicated on the hypothesis that an increasingly accurate understanding of biology will enable 'personalized' therapy that optimizes the balance of risk and benefit and permits radical reductions in the size of clinical trials.

Unfortunately, despite the promise of this approach, there have been few such breakthroughs in cardiovascular disease thus far⁷ and most treatments have had a modest effect (actually, the same is true for cancer to date). To reliably detect a small effect and differentiate it from random noise, large sample sizes are needed. The saving grace (such as it is) for the cardiovascular specialty is the ubiquitous nature of cardiovascular disease, so that a small benefit applied to a very large population translates into a major effect on the public health.

The focus on 'hard outcomes' typical of LSTs is appropriate in many circumstances, but ignores the movement toward patient-reported outcomes

When there is no major difference in hard outcomes, differences in symptoms, adverse events (AEs), and quality of life are critically important to patients and their families. In addition to validated formal patient-reported outcome (PRO) measures, such as those available through the NIH's PROMIS system (<http://www.nihpromis.org>), a variety of disruptive approaches are gaining momentum, including research efforts spearheaded by patient advocacy groups (e.g. PatientsLikeMe [<http://www.patientslikeme.com/>]), the use of mobile devices as biosensors, and the leveraging of social media applications to capture health data. Although LSTs will continue to be needed, thoughtful attention to PROs and the integration of person-centred ambient physiological measures will be an increasingly critical element of the clinical trials portfolio.

Academic medicine is doing a poor job of preparing the workforce for the informatics-intensive era of LSTs

We currently face a shortage of expertise regarding the theory and operations of LSTs. This problem is exacerbated by the fact that members of academic executive committees offering input into the design of many trials often have little operational responsibility and can make suggestions that result in greater complexity, without considering the impact such changes would have on trial operations or budgets. An LST is an elegant construct, and it is often the academics who spoil it by adding complex procedures to produce fodder for publications. The authors in this issue of the *European Heart Journal* might better spend their time focusing on capacity building within academia to train and educate the researchers of the future rather than focusing only on the shortcomings of industry and regulators.

Even after these other hurdles are passed, industry and government sponsors still face profound international regulatory disharmony

For example, following recent US regulatory changes, the FDA has given clear guidance⁸ to investigators, assuring them that they may reduce the expedited reporting of AEs once the safety profile of a drug is known, or when the AE is part of a measured outcome for the trial. Yet, within Europe, some countries still require expedited reporting of all serious AEs and collection of routine AEs, even when there is no plausible rationale for using the reports to improve trial safety. Given the many arguments for globalization of LSTs, research sponsors are obliged to conform to the most labour intensive and burdensome regulatory regime.

Finally, the best methods to support implementation of LSTs are undergoing radical and disruptive change

Beginning with the fax machine, technological advances have enabled the automation of clinical trial data collection and communications; these advances have progressed to the internet and are now spreading outward to include networks comprising a myriad of different personal electronic devices. But despite these advances, clinical trials remain in a 'parallel universe' of data collection alongside patient care. In countries where labour costs are low, this approach has remained feasible, but in countries where labour costs are higher, even simplified research designs suffer from hypertrophied trial budgets.

However, the broad adoption of increasingly interoperable electronic health records (EHRs), disease registries, and PROs is creating a new, continuous data fabric for health and healthcare. Data

generated as part of routine patient care are readily available in the electronic form and are being used now for institutional and health system quality improvement. The key issues are how to develop effective approaches for the secondary use of clinical data and how best to involve administrators, patients, and clinicians in the research mission. Indeed, recent ethics discussions⁹ have stressed that, in a learning health system, learning from patient care occurs across a continuum that stretches from pure data analysis to interventions applied by random assignment at the group (cluster) or the individual level. Ultimately, this data fabric should allow harvesting of baseline and outcomes data with insertion of randomization into the clinical care record, as has already been accomplished by the TASTE Trial in Europe¹⁰ and the SAFE-PCI Trial in the USA.¹¹ Major efforts are currently underway in the USA through the NIH's Health Care Systems Research Collaboratory (<https://www.nihcollaboratory.org>) and the Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network (www.pcornet.org) to hasten this much-needed change.

In summary, although I agree with Calvo *et al.* on the points that they do raise, I also think it is past time to evaluate the cardiovascular clinical trials portfolio with fresh eyes. We do, indeed, need LSTs. Moreover, we also need small, detailed trials that can reinvigorate systems physiology and provide a more compelling set of therapeutic targets. We need targeted trials that make a 'personalized approach' possible (these will likely be rare for the time being). Finally, we also need a paradigmatic shift in larger trials to incorporate new data and operational platforms that can unite rich streams of information from EHRs, registries, PROs, and mass enrolment from integrated health systems to enable rapid, efficient, and high-quality research that informs decision-making for patients, providers, and healthcare systems.

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