Large streamlined trials in cardiovascular disease

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Received 8 August 2013; revised 26 September 2013; accepted 21 November 2013; online publish-ahead-of-print 2 January 2014

Introduction

In the search for new and better therapies, reliable evidence of efficacy and safety—usually provided from large-scale randomized trials—is essential to support licensing, inform guidelines, and change clinical practice. However, the size, duration, complexity, and costs of conducting contemporary clinical trials have risen steadily. This coupled with an apparently diminishing likelihood of a positive trial has raised concerns about return on investment to the point of restricting drug development in cardiovascular diseases (CVD).1

More efficient ways to conduct randomized trials need to be developed with engagement by the various stakeholders.

Root-cause analysis

There is a widespread perception that complex clinical trials designs and exhaustive data collection are associated with an improved quality of clinical research. Emphasis on eliminating any potential source of error has made trials more complex and bureaucratic, resulting in increased cost. Greater complexity and cost have restricted the size of trials and investigator and patient willingness and ability to participate. These challenges are multifactorial; they include risk aversion from industry and regulators with an attendant bureaucracy. Commercial stakeholders who benefit financially from over-regulation and increasingly complex trial design and overzealous data collection further exacerbate these issues (Table 1). It is estimated that costs could be reduced by between 30 and 80% through a variety of simple measures to streamline trials.2 The current position where we have many potentially promising new treatments but the requirement to spend hundreds of millions of euros to bring them to market is untenable. There is an urgent need to reverse the trend of increasing trial complexity and cost such that more clinically relevant questions can be answered quickly and efficiently, ultimately to improve patient outcomes.

Streamlining randomized controlled trials

In our view, the design and conduct of clinical trials should focus on the most relevant clinical outcomes, the safety of the participants, and the efficient use of resources. Ideally a large simple trial (LST) should minimize bias through randomization and, preferably, blinding, have streamlined data collection and focus on objectively measured outcomes (Table 2).

Simplification and quality can be well aligned in many trials with a greater focus on conduct of the trial in a typical care setting to improve generalizability and capture of only the most important clinical outcomes and accrual of adequate numbers of these outcomes to assure a reliable estimate of treatment effect. A more streamlined approach is possible at a number of levels.3

Design features

Streamlining begins with design, tailored to the individual needs of each trial particularly in relation to risk management. Research question should be pertinent, focussed, and specific with matching objectives and outcomes. Each outcome measured increases trial complexity and cost. Mechanistic trials are essential to establish the biologic activity of new treatments and to begin to define safety. However, based on an analysis of clinicaltrials.gov, registered clinical trials are dominated by single centre, small studies with questionable methodology, and many are never published.4

Another consequence of the increasing cost and complexity of trials is that because many treatments are developed in restricted populations they do not represent the broad cross section of patients with the disease of interest. Often this reflects an attempt to minimize trial size (while maximizing the likelihood of detecting a treatment effect and minimize risk) or defining such a specific population that it will comprise a unique indication for the treatment in a highly
The more complex the efficacy competitive environment. Study design is strongly influenced by regulatory guidelines and advice.\textsuperscript{5,6} The era where major advances emanating from modest sized studies of interventions with large treatment benefits may be over.\textsuperscript{7–9} While most large cardiovascular trials focus on hard clinical outcomes like death and events that cause hospitalization, patient-centred outcomes are also important targets for treatment of cardiovascular disease, including, for example, heart failure. Symptom relief and quality of life may be the most important goals of some therapies, costs through the need for costly screening tests and payment for ‘screen failures’.

Large simple trials are event-driven studies and may use composite endpoints that integrate the effect of treatment across different outcomes reflecting disease activity. This approach increases the total number of events and the power to discriminate differences. The use of composite endpoints is discussed in more detail elsewhere but it should be remembered that the result of a trial will be difficult to interpret and potentially controversial if the composite if driven by a single ‘soft’ component or when directionally different treatment effects occur amongst different components. Moreover, using composite endpoints in a time to event design mandates using only the first event in the primary analysis. Since this may not represent the most important event (e.g. death), it may lead to a substantial loss of information because subsequent events are ignored, or at least under emphasized. There is a growing enthusiasm for methods that reflect the weight, i.e. relative importance of individual components and account for the total number of events patients experience, not just the first one. This is particularly germane for long-term therapies in chronic diseases characterized by recurrent non-fatal events. These approaches should improve the power and efficiency of studies in diseases where patients have multiple events.\textsuperscript{7–9}

### Table 1 Factors contributing to the increased complexity and cost of clinical trials

<table>
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<th>Scientific reasons</th>
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| Advances in the management of cardiovascular diseases | • Both the quality and life expectancy have dramatically improved over the last three decades.  
• The era where major advances emanating from modest sized studies of interventions with large treatment benefits may be over.  
• Seeking for ‘niche indications’  
• Eagerness for data collection (hypothesis generating, publication production)  |
| Academia                                                                           |• Excessive risk aversion  
• Obsession for data collection  
• Obsession with GCP  
• Intensive monitoring  
• Financial incentive to propagate status quo that generates work |
| Industrial reasons                                                                 |
| Sponsor’s needs                                                                   |• Excessive risk aversion  
• Obsession for data collection  
| CROs                                                                              |• Obsession with GCP  
• Intensive monitoring  
• Financial incentive to propagate status quo that generates work |
| Regulatory and legal requirements                                                  |
| Regulatory                                                                        |• Excessive risk aversion  
• Regulatory recommendations tend to give priority to explanatory trials with high internal consistency and extensive data rather than incentivizing more pragmatic approaches.  
• Impression that mid-level reviewers do not follow philosophy of regulatory leaders who write guidance and codes to promote streamlining  
| Legal framework                                                                    |
| Regulatory                                                                        |• Good Clinical Practice rules  
• The original intention has been greatly over-interpreted, impairing feasibility, increasing cost and dramatically decreasing efficiency.  
• The expansion of GCP implementation can be misused as a way to justify and fund the clinical trial industry and infrastructure (CROs, ethic committees, regulatory review structures).  |
| Legal framework                                                                    |• Heterogeneous and complex clinical trials regulations across the world  
• Complex and resource-demanding AE reporting requirements |

### Table 2 Key quality elements of large simple trials

| Design                  | Clearly formulated hypothesis  
|                        | Clinically meaningful objectives  
|                        | Objectively measured endpoints  
|                        | Avoid unnecessarily restrictive selection criteria  |
| Conduction             | Patients receive/maintain assigned treatment  
|                        | Follow-up is complete with ascertainment of primary outcome(s)  
|                        | Bias is avoided (with randomization and blinding)  
|                        | Quality is assured by on-going measurement and feedback during trial conduct  |
| Ethics                 | The rights and safety of enrolled patients are protected  |

The expansion of GCP implementation can be misused as a way to justify and fund the clinical trial industry and infrastructure (CROs, ethic committees, regulatory review structures).
but assuring the treatment has a neutral or beneficial effect on hard clinical outcomes is usually necessary.

The main aims of adjudication are to reduce bias and enhance accurate ascertainment, thereby acting as a quality control system. The need for adjudication depends on a number of factors, including the level of masking, nature of the endpoint in question (all-cause death does not need to be adjudicated), objectivity of the definition, and level of expertise and engagement of the investigators. Adjudication, however, is a time-consuming and costly activity, and usually does not materially alter the effect of treatment in a trial. While accepting that adjudication may be sometimes advisable (e.g. in an unblinded trial, or where the primary endpoint does not pertain to the area of expertise of the investigators), there are strategies to minimize the amount of adjudication needed (Table 3).

Experienced trialists can help identify opportunities to collect data in an efficient and targeted way, pinpointing the key elements, and avoiding unnecessary distractions that have the potential to consume resources. Strong and enlightened leadership from sponsors and contract/academic research organizations (CRO/AROs) is also necessary if this is to be achieved.

The extent of data collection requirements in a trial will vary depending upon the nature of the drug, the indication, and whether the profile of the drug is already well established (e.g. early vs. late phases of clinical development or pre-approval vs. post-approval trials). Current pivotal studies in cardiovascular diseases tend to collect an immense amount of data from individual patients, most of which is unnecessary for the evaluation of drug efficacy and safety. Excessive data collection increases cost and may have the paradoxical effect of reducing the overall quality and integrity of the trial data, as it increases the complexity and the amount of work of the investigators. The reasons behind this inefficient practice are multifactorial. On the one hand, drug development is frequently more prone to risk aversion rather than to risk management. For both industry and regulators, detection of safety signals has sometimes become an obsession rather than a scientifically guided activity. Also, academic participants in studies tend to advocate collection of ‘nice to have’ data to satisfy scientific curiosity, without appreciating the incremental costs and the risk of false-positive findings. A useful exercise is to limit data collection, focussing on the primary study objective and the specific safety aspects related to the treatment in question. A recent example of over exuberant data collection leading to a delay in regulatory approval was recently reported by the ARISTOTLE investigators. Collection of the study drug bottle numbers that were returned to the study sites, and sometimes transcribed incorrectly, led to an erroneous estimate of improper drug allocation, when the true problem was the transcription of thousands of extra data points rather than actual allocation error. This would never have been a problem if this unnecessary variable was never collected.

### Study conduct

Data and investigator site monitoring have the ultimate goal of assuring that the protocol is being followed and that patient data collected are reliable and accurate. Monitoring visits to study centres may also be used for motivation and training purposes. Clinical trials are most widely monitored through frequent on-site visits, sometimes verifying virtually all data collected from all patients. This means that a vast amount of money is currently spent on site-monitoring. There are on-going initiatives on both sides of the Atlantic to rationalise monitoring requirements, adapting them to the study setting.

Large outcome trials are the most important example where risk-based monitoring approaches are needed. Reduced monitoring strategies (where both random and targeted samples of centres, patients and outcomes are monitored) are needed in clinical studies involving hundreds of centres and thousands of patients. This approach can ensure that a predefined rate of errors is not exceeded and thereby also ensure the credibility of the study results. A small amount of random errors is unavoidable and acceptable. Their impact on the study results in large studies is minimal, if any. Central statistical monitoring as a powerful tool to minimize systematic errors, and importantly, fabricated data should be routinely considered in LSTs. A proper statistical monitoring plan should foresee the creation of key indicators leading to targeted on-site monitoring strategies.

There are recent examples where withdrawal of consent for follow-up was so common that it undermined interpretation of the study results by regulators. Having complete follow-up data on as many patients as possible is crucial. It is important to obtain as much follow-up information on each patient as possible, even if a patient stops taking the study drug, whether due to choice or an adverse event. There should be efforts to minimize patients withdrawing from follow-up and anticipatory agreement between trial subjects and investigators to permit passive follow-up for important outcome events and vital status in such patients. The original informed consent can include the statement that patients may withdraw from study procedures but that attempts will be made, nevertheless, to obtain follow-up for major events and vital status. Even when a patient does refuse any follow-up to occur, efforts should be made to obtain vital status at the end of the trial. Not doing so reduces the value of participation of every other patient. It also particularly jeopardizes the collection of data on safety with which to guide the treatment of all future patients. Thus there is arguably as much or more of an ethical mandate to obtain information on outcomes, involving minimal or no inconvenience to patient, as there is to allow patients to withdraw completely from even passive follow-up in a trial.

Education on the importance of continued follow-up is of overriding importance. This should be aimed at everybody involved in the trial, including CRO/AROs, sponsors, coordinators, investigators, clinicians (including those not directly involved in the study, but

### Table 3  Strategies aimed to avoid/minimize the need for central adjudication

<table>
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<tr>
<th>Strategy</th>
<th>Expected impact</th>
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<tr>
<td>Using objectively defined primary endpoints</td>
<td>Avoiding subjective interpretation of data</td>
</tr>
<tr>
<td>Optimizing the design of the clinical report form</td>
<td>Collect the elements that comprise the definition of the events in a systematic way</td>
</tr>
<tr>
<td>Using adaptive adjudication</td>
<td>Adjudication dropped if felt not needed at predefined time points</td>
</tr>
<tr>
<td>Using selective adjudication</td>
<td>For more subjective endpoints</td>
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<tr>
<td></td>
<td>In a random subset of patients</td>
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who may treat patients (if they have an event), nurses (especially those involved in collecting follow-up information), and patients and their families. Proactive contact with sites that have an unusually high number of withdrawals can help identifying problems and improving long-term follow-up. Patient education is particularly important. Patients need to understand the significance of their role in the trial, and the benefits of their continuation in the trial. In addition to the value of the statement at the time of consent that some follow-up will be conducted in all circumstances, patients should be made fully aware of the level of commitment required and the importance to all other patients in the trial and in future care guided by the trial. This can be coupled with a personal letter to each patient enrolled, not only thanking them for their participation in the trial, but also highlighting the importance of their involvement and commitment. Although it is not possible to stop patients from withdrawing their consent for trial treatments and procedures, it is reasonable to request the collection of some critical data for the study completion, either directly from them (follow-up visits or calls), from healthcare providers or from public medical records. Most patients are agreeable for data to be collected ‘from afar’ even if they do not want to participate in the study any longer. At the very least, their vital status should be assessed. It is notable that when the FDA did not grant approval for the treatment in part based on a high level of loss to follow-up, the ATLAS-2 study team was able to go back and collect vital status on most patients who lacked it. This suggests that the high degree of loss to follow-up, even with current barriers, is modifiable.

Therefore, maximizing follow-up information should be of paramount importance to the trial executive and the sponsors, but requires support and endorsement from regulators. This is an area where regulatory, societal (including governmental), and ethical guidance is urgently needed.

Final reflections
The spirit of good clinical practice recommendations was to protect patients’ rights and guarantee the integrity and reliability of the results of clinical studies. However, it is clear that these original intentions have resulted in unnecessary complexity and diversion of limited resources to activities that do not improve trial quality and in fact undermine the impact of clinical trials. Strategies for streamlining study design and conduction have to be tailored to the individual clinical trial, but can be applied to a large majority of phase III/IV cardiovascular clinical trials. Attempts to contain costs by constraining trial size may also have led to ‘false-negatives’ and failure to proceed to phase 3 of development. The expansion of the clinical trial enterprise, including regulatory departments in pharmaceutical companies and CROs, propagates trial complexity and cost. Lack of clear, consistent, and harmonized regulatory directives around the specific needs of clinical trials has also been a barrier to conduct trials more efficiently.

Initiatives from both sides of the Atlantic have now started, more prominently in the USA than in the European Union. In the USA, the Clinical Trials Transformation Initiative (CTTI) has been established by the Food and Drug Administration (FDA) and the Duke University as a public–private partnership to identify practices aimed at increasing the quality and efficiency of clinical trials. In the EU a regulation intended to replace the Clinical Trials Directive is under discussion by the EU Council. The regulation is expected to fix some fundamental deficiencies of the current EU regulatory environment. There is a unique opportunity to fundamentally reform regulations and standards for clinical trials. A joint venture of all stakeholders (patients, trialists and academia, pharma and regulators) sharing the responsibility of assuring the sustainability of clinical research will be required. We not only have to improve the situation, but we must do it quickly. The alternative will be to both forgo our responsibility to conduct the trials necessary to improve public health and to be left out of global trials that will shift to environments where more efficient approaches are possible.

Acknowledgements
This article is the result of a Regulatory Workshop organized by the Cardiovascular Round Table and the European Affairs Committee of the European Society of Cardiology (ESC) on 14–15 June 2012. The Cardiovascular Round Table is a strategic forum for high-level dialogue between industry and ESC leadership to identify and discuss key strategic issues for the future of cardiovascular health in Europe.

The authors acknowledge the following meeting participants for their contributions to this paper: Caroline Atkenny (GlaxoSmithKline), Caroline Boulton (Novartis), Colin Baigent (Department of Clinical Medicine. University of Oxford) Christian Bourguignon (Servier), Adam Crisp (GlaxoSmithKline), Amany El-Gazayerly (Medicines Evaluation Board, The Netherlands), Neville Jackson (Pfizer), Patricia Maille`re (Servier), Luc Sagnard (Sanofi), Stefan Schroeder (Bayer Healthcare), Cathrine Thorstensen (Pfizer), Michael van der Laan (Hoffmann-La Roche), Patrice Verpillat (Sanofi).

Conflict of interest: The views expressed in this article represent a consensus of the authors and do not necessarily reflect the views of the organizations that employ, retain, or contract with the authors.

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A 53-year-old patient called the emergency due to persistent thoracic pain and dizziness. The medical history of the patient and that of his family were inconspicuous. The initial ECG showed a ventricular tachycardia of 210 b.p.m., which was terminated by external cardioversion. The patient was thereafter referred to our hospital. After conversion to sinus rhythm, the ECG showed peripheral low voltage with negative T-waves in V2–V6 (Panels A and B). Blood testing revealed a six-fold increase in CK (10% CK-MB), highly elevated GOT, LDH, and Troponin, and a mild increase in C-reactive protein. Atypical hypertrophic cardiomyopathy of the left lateral wall leading to ventricular tachycardia

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A 53-year-old patient called the emergency due to persistent thoracic pain and dizziness. The medical history of the patient and that of his family were inconspicuous. The initial ECG showed a ventricular tachycardia of 210 b.p.m., which was terminated by external cardioversion. The patient was thereafter referred to our hospital. After conversion to sinus rhythm, the ECG showed peripheral low voltage with negative T-waves in V2–V6 (Panels A and B). Blood testing revealed a six-fold increase in CK (10% CK-MB), highly elevated GOT, LDH, and Troponin, and a mild increase in C-reactive protein. Chest X-ray showed an enlarged heart (C), and bedside echocardiography suggested an impairment of left lateral wall movement, and mild, haemodynamically not relevant circular pericardial effusion. After exclusion of coronary artery disease by cardiac angiography, laevocardiography showed only mild reduction of systolic function but suggested diaphragmatic enlargement of the myocardium with denoted mid-ventricular constriction of the apex (Panels D and E). A second echocardiography confirmed a confined swelling of the left lateral wall, suggesting a cardiac tumour (Panels F and G). Cardiac magnetic resonance imaging was then performed, showing isolated thickening (4 cm maximum) of the left ventricular free/lateral wall (Panels H and I). Myocardial tissue characterization showed no infiltration, oedema, or necrosis, but revealed a smoothly delineated mass with almost homogeneous high signal intensities in the late enhancement imaging in this area, suggesting an atypical form of hypertrophic cardiomyopathy (Panels J and K). This preliminary diagnosis was soon validated comparing the current findings with previous examinations of the patient >10 years ago that also showed isolated left ventricular free wall hypertrophy. In this first clinical manifestation, myocardial biopsy and investigation of pericardial effusion had shown massive hypertrophy but no malignant cells or inflammation. Therefore, no further diagnostics were conducted, and the patient received an implantable cardiac defibrillator for secondary prevention of ventricular tachycardia. The patient could be dismissed from the hospital in good physical health, and until then encountered no further ventricular tachycardia.