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SPECIAL ARTICLE

Improving clinical trials for cardiovascular diseases: a position paper from the Cardiovascular Round Table of the European Society of Cardiology

Neville Jackson[1], Dan Atar[2], Maria Borentain[3], Günter Breithardt[4,5], Martin van Eickels[6], Matthias Endres[7], Uwe Fraass[8], Tim Friede[9,10], Hakima Hannachi[11], Salim Janmohamed[12], Jörg Kreuzer[13], Martin Landray[14], Dominik Lautsch[11], Chantal Le Floch[15], Peter Mol[16,17], Huseyin Naci[18], Nilesh J. Samani[19], Anders Svensson[20], Cathrine Thorstensen[1], Jan Tijssen[21], Victoria Vandzhura[15], Andrew Zalewski[22], and Paulus Kirchhof[5,23]*

[1]Pfizer, Inc., Groton, CT, USA; [2]Oslo University Hospital Ulleval and University of Oslo, Oslo, Norway; [3]Bristol-Myers Squibb, Paris, France; [4]Department of Cardiovascular Medicine, Universitätsklinikum Münster, Münster, Germany; [5]Centre for Cardiovascular Sciences, School of Clinical and Experimental Medicine, University of Birmingham and Sandwell and West Birmingham Hospitals National Health Service Trust, Wolfson Drive, Birmingham B15 2TT, UK; [6]Bayer Healthcare, Berlin, Germany; [7]Charité-Universitätsmedizin, Berlin, Germany; [8]Amgen, Inc., Munich, Germany; [9]Department of Medical Statistics, University Medical Center, Göttingen, Germany; [10]DZHK (German Centre for Cardiovascular Research), Partner Site Göttingen, Göttingen, Germany; [11]Merck Inc., Cokesbury, NJ, USA; [12]GlaxoSmithKline, Heathrow, London, UK; [13]Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim, Germany; [14]University of Oxford, Oxford, UK; [15]Servier, Paris, France; [16]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [17]Dutch Medicines Evaluation Board, Utrecht, The Netherlands; [18]London School of Economics and Political Science, London, UK; [19]University of Leicester, Leicester, UK; [20]Roche, Inc., Basel, Switzerland; [21]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [22]GlaxoSmithKline, King of Prussia, PA, USA; and [23]Atrial Fibrillation Competence NETwork (AFNET) e.V., Münster, Germany

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Aims Cardiovascular disease is the most common cause of mortality and morbidity in the world, but the pharmaceutical industry's willingness to invest in this field has declined because of the many challenges involved with bringing new cardiovascular drugs to market, including late-stage failures, escalating regulatory requirements, bureaucracy of the clinical trial business enterprise, and limited patient access after approval. This contrasts with the remaining burden of cardiovascular disease in Europe and in the world. Thus, clinical cardiovascular research needs to adapt to address the impact of these challenges in order to ensure development of new cardiovascular medicines.

Methods and results The present paper is the outcome of a two-day workshop held by the Cardiovascular Round Table of the European Society of Cardiology. We propose strategies to improve development of effective new cardiovascular therapies. These can include (i) the use of biomarkers to describe patients who will benefit from new therapies more precisely, achieving better human target validation; (ii) targeted, mechanism-based approaches to drug development for defined populations; (iii) the use of information technology to simplify data collection and follow-up in clinical trials; (iv) streamlining adverse event collection and reducing monitoring; (v) extended patent protection or limited rapid approval of new agents to motivate investment in early phase development; and (vi) collecting data needed for health technology assessment continuously throughout the drug development process (before and after approval) to minimize delays in patient access. Collaboration across industry, academia, regulators, and payers will be necessary to enact change and to unlock the existing potential for cardiovascular clinical drug development.

Conclusions A coordinated effort involving academia, regulators, industry, and payors will help to foster better and more effective conduct of clinical cardiovascular trials, supporting earlier availability of innovative therapies and better management of cardiovascular diseases.

* Corresponding author. Tel: +44 1214147042, Email: p.kirchhof@bham.ac.uk

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Introduction

The systematic validation of new therapeutic concepts in controlled clinical trials has markedly improved the management of chronic cardiovascular diseases in the last four decades, as evidenced by prolonged survival of many patients with these conditions, and a longer average life span on a population level.[1] Despite this success, achieved by close collaboration between academia and industry,[2] cardiovascular diseases remain the most common cause of mortality and morbidity in the world.[3–5]

Given the large burden of cardiovascular diseases, it is in the public interest to encourage adequate levels of research and translation of research findings into new therapeutic or diagnostic strategies.[6] Recently, though, investment in this field has been negatively impacted by impediments to bringing new cardiovascular drugs to market, including late-stage failures, escalating regulatory requirements such as pediatric investigation plans, risk management plans, reluctance to consider certain trial endpoints as clinically meaningful, and bureaucracy created by the clinical trial business enterprise (e.g. complex interactions and operational procedures among stakeholders). While all of these governance structures have good reasons and well-intended motivations, the complexities and time requirements, especially when combined with health care systems that are justifiably concerned about cost effectiveness, have led to restricted or delayed patient access after approval of new medications.[7,8]

Are current structures designed to fail?

High-quality randomized, controlled clinical trials that produce scientifically robust evidence of efficacy and safety continue as a necessary standard path to drug approval. Data from these currently inform both clinical practice and health technology assessment. The randomized controlled trial has effectively transformed the practice of medicine, but the clinical trial enterprise has in many respects become a bloated and inefficient system that is hindering effective cardiovascular drug development[7] and failing to serve the best interests of patients with cardiovascular diseases.

The Cardiovascular Round Table (CRT) of the European Society of Cardiology (ESC) has long been concerned about the apparent declining interest in committing resources to develop innovative treatments for cardiovascular diseases. This paper is the outcome of a dedicated two-day workshop to explore new ways for clinical research, with the ultimate goal of reinvigorating investment in cardiovascular medicine and to decrease the timeline for patient access to new drugs after approval. Such investment is much needed to reduce the remaining burden of chronic cardiovascular diseases.

Impediments to investment in cardiovascular research

Cost of cardiovascular drug development

Cardiovascular drug development is generally more costly than in other therapeutic areas (Box 1). First, long-term treatment is required for many cardiovascular therapies to effectively modulate these chronic diseases. Secondly, many of these cardiovascular development programs involve event-driven studies where the annual incidence of events is small, but the population at risk is large, e.g. stroke prevention in atrial fibrillation where the majority of subjects will not suffer an event whether exposed to the new therapy or not. However, although difficult to do, event-driven studies generally produce clear results that lead to reliable estimates of efficacy and safety. Third, contemporary cardiovascular trials are conducted in patients receiving multiple evidence-based background treatments. Thus, cardiovascular mortality and other major clinical outcomes have steadily declined in study populations, such that demonstrating incremental risk reduction in ever larger study populations requires very large sample sizes.[8–11] Fourth, past drug development successes have spurred the build-up of an infrastructure designed to conduct 'large and complex' cardiovascular outcome trials. The practical conduct of trials has been hampered by added requirements such as event adjudication (when applied broadly rather than limited to relevant clinical situations, e.g. haemorrhagic vs. ischaemic stroke, or subtypes of myocardial infarction) and data protection, restrictions on the use of samples or data for exploratory analyses (e.g. when analyses for markers were not pre-specified or new, initially unplanned genetic analyses of previously collected samples), and by complex and at times contradicting national and regional regulations for clinical research. Finally, cardiovascular trials have historically been performed in large, unselected patient groups (e.g. 'heart failure', 'atrial fibrillation', or 'coronary artery disease'), in whom a diverse range of disease mechanisms may be active, not all of which are likely to be influenced by the agent being studied.

The ability to identify those who are likely to benefit from a new therapy is key to overcome these challenges, to the benefit of patients and drug developers. Although useful treatments have moderate benefits (i.e. proportional risk reductions in the order of 15–25%), they will help to avoid thousands of events each year in common cardiovascular conditions, like myocardial infarction, heart failure, atrial fibrillation, or hypertension. This approach, however,

Box 1 Reasons for the higher cost of drug development for cardiovascular as compared with other diseases

- Many cardiovascular therapies require long-term treatment to effectively modulate these chronic diseases.
- Many of these cardiovascular development programs involve event-driven studies where the annual incidence of events is small but the population at risk is large.
- Demonstrating incremental risk reduction often requires very large sample sizes.
- Cardiovascular disease encompasses a diverse range of mechanisms, not all of which are influenced by the agent studied making it difficult to identify patients likely to benefit.
- Complex infrastructure to conduct clinical trials.
- Regulatory burdens.

requires treatment of many patients who will not benefit including those who will not develop an event without treatment. Academia and drug developers have only recently begun to recognize the need for a better, refined classification of major cardiovascular disease syndromes.[12,13] Can we, by identifying more specific patient characteristics (i.e. those who are at higher risk of the cardiovascular outcomes we are trying to prevent or hazards that we are trying to avoid), develop and deliver better target therapy? This calls for the development of 'precision medicine' for cardiovascular diseases (i.e. more precise targeting of treatments to specific disease and patient characteristics, also commonly referred to as personalized or stratified medicine).[14]

The mission of the ESC is to reduce the burden of cardiovascular diseases in Europe and beyond. Thereby, the ESC supports a wider goal of governments and other stake holders in health care, and ultimately of the citizens of Europe. The discovery and use of new therapies that improve patient health is therefore a key component within the ESC remit. This mission is aligned with the larger societal need to improve health of populations. The ESC recognizes that the majority of major drug and interventional developments cannot be brought to the patient without efforts of the pharmaceutical and medical device industry, as well as the support of governments and acceptance by health care providers. A change from the current approach to drug development is needed to ensure that safe and effective new therapies are made available to patients in a timely fashion, supported by robust scientific data demonstrating safety and efficacy on health outcomes that are important to patients, health care providers, and other stakeholders. We need to generate these data efficiently and at lower cost so that cardiovascular disease research can regain its attractiveness.

Potential for return on investment

The cost of successfully bringing a single drug to market has been estimated at 1.2 billion euros (€) [1.5 billion dollars ($) in the USA].[15] The true cost, which also includes failures, has been estimated between $4–5 billion with some companies spending as much as $12 billion because of several drugs that failed in late-stage clinical trials.[16] While research and development (R&D) spending in both Europe and the USA has continued to rise over the past 20 years, the number of new drugs approved per billion dollars spent has shown a slow decline.[17]

Within the current 'working model' of major clinical outcome trials conducted in large populations, the timelines for market approval and patient access for new therapies are slow, often because of processes that do not add to the robustness or relevance of the data generated by the trial (e.g. extensive time required to obtain necessary start-up approvals, slow trial recruitment, and prolonged regulatory review or health technology assessment of results). Such delays often result in a short window for industry to recoup development and post-approval costs before patent expiration.[18] The impact of exclusivity loss should not be underestimated; it is increasingly considered a high-risk investment to fund outcome trials in cardiovascular medicine.

Late-stage drug failures

A reluctance to assume the risk of high cost failure is one factor contributing to the pharmaceutical industry's declining investment in cardiovascular drug development. Several examples can be given of compounds with promising pre-clinical, phase I, and phase II data that yielded disappointing results in phase III trials.[19–23] Studying a broad population of patients during product development and aiming for a 'broad indication' has been successful for manufacturers in the past, and contributed to reduced population-wide cardiovascular mortality. However, targeting those patients most likely to benefit from modification of receptor targets might be a more direct, efficient approach to generate robust scientific evidence and decrease the cost of failure in terms of resources and time. Currently, partly because of this 'mindset' within cardiovascular drug development aimed at large populations, development of promising compounds is often stopped at early stages rather than allocating resources to understand which (sub)populations may benefit. In the 'failed' dalcetrapib trial, a *post-hoc* genomic analysis identified genetic variants that were associated with effective therapy. If that drug had undergone the approach proposed here, it may now be available to such patients.[24]

Regulatory and health economic hurdles

Regulatory requirements often differ between countries, and regulatory agencies interpret identical data sets differently, which presents obvious challenges to global drug development programs. This complex process where the agreements with different regulatory agencies led to different registration trials in different regions may be especially difficult for new drugs that aim to improve existing therapeutic approaches. Greater use of joint scientific advice with key regulatory agencies [e.g. European Medicines Agency (EMA) and the US Food and Drug Administration (FDA)] is an important development to minimize the impact of this challenge.

Furthermore, the evaluation of newly approved cardiovascular therapies by national and regional health care systems, increasingly incorporating health technology assessment based on local data, can add significant uncertainty with respect to use and patient access for new cardiovascular medications. New agents are often highly scrutinized because the potential cost implications are substantial for these therapies intended for use as chronic therapies in common cardiovascular diseases.

Conclusive data to support economic evaluations are often not available from trials conducted within the clinical development program (e.g. quality-of-life benefits or utilization data representing real-world use); thus, additional studies are often required. It seems desirable to collect key economic measures in clinical trials to allow timely initiation of health economic evaluation of new therapies. In fact, health technology assessment analyses are best based on systematically collected 'real world' post-approval data sets. A limited access to market for a certain time combined with mandatory collection of health technology assessment-relevant data would enable collection of such data. Finally, the speed and willingness of professional societies—including ESC—to adopt new treatments into management guidelines has recently been publicly criticized as a potential unintentional contributor to further delays in the adoption of new, beneficial therapies.

Innovative approaches to cardiovascular drug development

Drug development and precision medicine

Incomplete understanding of disease mechanisms in defined patient groups is a major barrier to identifying novel, potentially effective therapies. New advances in scientific methods (e.g. genomics, proteomics, imaging, all of which have led to the existence of Big Data) may now allow more refined understanding of the underlying biology and identification of those patients likely to benefit from a novel treatment. New pre-clinical disease models may be needed to characterize disease mechanisms and to guide the identification of patients in whom such disease mechanisms are active. Furthermore, the integration of genetic predisposition, ambient stressors, and the complex interactions among multiple pathways common in human cardiovascular disease may be required to empower clinically relevant mechanism-driven cardiovascular research. Improved human target validation is needed to strengthen cardiovascular drug development. This could be accomplished by greater and earlier use of large genetic biobanks linked to phenotypes of interest using approaches such as Mendelian randomization to assess likely causality.[25–29] In addition, early investment in translational medicine studies potentially probing for responses in different phenotypes of the disease, possibly using suitable disease models to understand disease mechanisms, is worth considering. *We advocate support for research to develop better disease classifications, disease phenotypes, and biomarkers in cardiovascular diseases.*

Early testing in sub-populations that are likely to benefit, e.g. via testing and approving novel therapies in conjunction with a biomarker for the disease target, has been used in other disease entities with some success, although surrogate markers have been unreliable in many cardiovascular disease applications.[30,31] A similar approach of studying and approving a new therapy in a limited group of patients who are most likely to benefit from a new therapy (e.g. familial hypercholesterolaemia for new lipid-lowering medications) may overcome some of the challenges described earlier.

Although the concept of testing novel therapies in narrower subpopulations (defined by genetic, soluble, or other biomarkers, or by clinical disease phenotype) has been generally accepted in principle, there are several barriers preventing its full implementation. Specifically, current clinical disease segmentation is not always supported by robust evidence allowing for better target validation (e.g. heart failure segmentation beyond reduced ejection fraction and preserved ejection fraction, or atrial fibrillation beyond paroxysmal and chronic). Further, regulatory agencies are hesitant to accept plans for testing novel cardiovascular therapies in smaller groups (e.g. biomarker positive), sometimes requesting that lack of benefit be demonstrated in other phenotypes to avoid future inappropriate drug use (e.g. biomarker negative).

However, if successful, this more targeted drug development approach might allow smaller trials to be conducted more efficiently and quickly, and reduce the number of high-cost, late failures. Such an approach might prolong recruitment time and require expensive testing for patient selection, factors which might partially offset the efficiencies. Such development needs to be underpinned by new classifications providing phenotypic markers to identify relevant patient groups. Developing suitable tests, ranging from a simple electrocardiogram to blood-based markers derived from '-omics' analyses, should be of high priority. Such research is clearly in the interest of the general public. Approval would be initially restricted to a subpopulation, and safety evaluations will still be ongoing at the time of the initial (limited) approval. Initial experience with the new compound in clinical practice, further insights into disease mechanisms, and additional studies including investigator-initiated trials could support later evaluation and use of such therapeutics in broader populations (*Figure 1*). PCSK9 inhibitors may provide an example, as these have initially been evaluated in patients with familial hypercholesterolaemia,[32–36] while later and ongoing studies will test their value in larger populations in need for intensified cholesterol lowering.[37,38] A potential downside of this approach is the possible delay in expanding research and treatment to the broader population, particularly if disincentives exist, e.g. by patent expiration/loss of exclusivity. *We advocate a broader use of public–private early development partnerships, which may be initially driven by an academic research group or consortium, but will require industry partnership to develop new markers for targeted drug development.*

Furthermore, we advocate political solutions that motivate the industry to invest in early phase development, e.g. extended patent protection or earlier, limited approval of new agents.

Several assumptions are made in the planning phase of a clinical trial. In some cases, robust estimates of these variables can be made from recent literature or other clinical trial experiences. However, these measures can also be influenced by factors that are difficult to predict, such as wide variation of background therapy (particularly across geographic regions) or major shifts in clinical practice that may occur during a long-term clinical trial. If pre-trial decisions and planning assumptions are incorrect, a pivotal trial could fail for a variety of reasons unrelated to the effectiveness of the investigational drug. Such late-stage failures can halt further study of an otherwise useful compound. Many high-quality data sets have been collected and could support better planning of new cardiovascular trials if made generally available. Prospective implementation of procedures to address potential concerns or problems (e.g. including a period of exclusivity for analysis by trial investigators, development of data manuals to describe the database structure, data definitions, and methods of data collection) would be necessary to ensure the success of this approach. *We advocate the coordinated and open sharing of existing patient-level trial data sets among the research community to support precise planning of new clinical trials.*

Adaptive designs are one approach that can be used to reduce the uncertainty in clinical trials and to improve the chances of success in phase III. An adaptive design is defined as one where the statistical methodology allows a design element to be modified (e.g. sample size, randomization ratio, number of treatment arms) at an interim analysis with full control of the type I error.[39] Technically, any part of a clinical trial can be modified, but sample size adjustment based on blinded review of observed (versus anticipated) interim data is the most common adaptive design accepted by regulatory agencies, provided blinding is preserved and type 1 error is properly controlled.

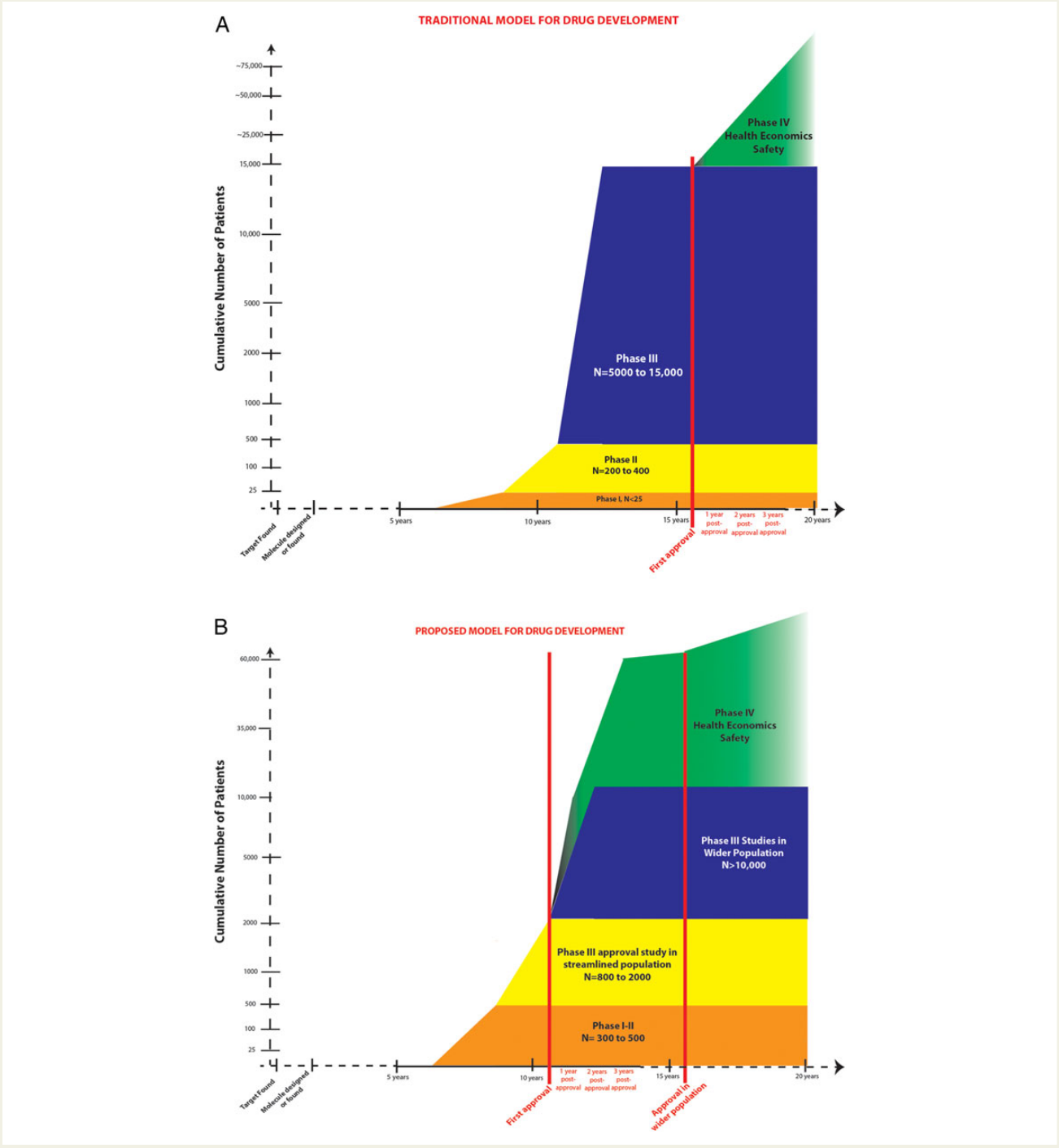

Figure 1 Comparison of current clinical drug development and proposed clinical drug development in target populations. Note, safety is assessed continuously. Safety is assessed continuously and integrates patients exposed to the novel therapy before and after first approval.

Seamless phase IIb/III designs are another approach currently being explored, but regulatory authorities have not issued a final position on their acceptability. This design combines trials of different phases into one study. Dropping the least and advancing the most effective treatment/dose into phase III, subgroup selection, or sample size re-estimations are areas that may be adapted based on interim data in seamless trials. Pre-specified criteria for the transition between phase IIb and III will build additional efficiency. This novel approach is currently being tested in a global study of patients with ACS treated with a novel anti-inflammatory intervention (ClinicalTrials.gov Identifier: NCT02145468).

Adaptive enrichment designs allow enrolment to target subpopulations most likely to respond to therapy (based on interim data), which may improve the power in a study.[40] This concept involves

more than targeting patients with high event rates; it also involves selecting patients with characteristics that predict therapeutic response.

Adaptive designs require specific statistical methods to control type I error and preserve the integrity of the study.[41] Although these designs may be more efficient, there is some uncertainty around whether adaptive designs really can achieve their intended advantage over traditional designs.[42–45] Communication with regulators is key before an adaptive design is implemented to ensure study results will be accepted, to ensure sufficient evidence will be generated to allow a thorough assessment of treatment effect, and to effectively convey complex design aspects (e.g. simulation reports). When used appropriately, these modern statistical techniques can manage risk in a clinical trial.[46–49] *We advocate scientific and regulatory evaluation of adaptive and 'seamless phase II/III' designs, an initiative that has already been adopted by several pharmaceutical companies.*

Simple, practical approaches to conducting large randomized trials

The critical components of large, simple trials have been well described in a recent publication of the ESC CRT.[8] Activities such as site-monitoring visits, source document verification, clinical endpoint adjudication, non-serious adverse event (AE) reporting, and extensive regular reporting have been implemented over time with the intent of reducing 'noise' and/or ensuring proper trial conduct, but these tasks are time consuming, costly, and do not necessarily improve the reliability of the study results or the safety of the participants. Simple techniques can effectively accomplish enrolment, treatment, and data collection goals with fewer resources. A Study of Cardiovascular Events in Diabetes (ASCEND), funded by the British Heart Foundation (www.clinicaltrials.gov, NCT00135226) used routine clinical data to identify potentially eligible patients and implemented a mail-based approach to invite, consent, enrol, randomize, and follow-up 15 000 patients at a fraction of the costs of traditional methods. This design achieved a broad representation of patients and accurately documented the screening denominator (number of patients invited to participate), which is often not possible when screening is performed at the individual site level.[50]

Indisputably, adequate data are needed for robust assessments of safety and efficacy; however, the temptation should be resisted to collect exhaustive data that are often never analysed or not informative. Intelligent information technology using real-time data can be used to promote protocol adherence, identify statistical outliers,[51] and perform targeted monitoring (i.e. risk-based monitoring[52]). Large cardiovascular trials should utilize to a greater extent step-down data collection strategies [e.g. collection of serious adverse events (SAE) and AE in the pre-registration phase in a subset of the study population, followed by collection of SAE and only selected AEs of interest]. In post-registration studies without post-market commitments to collect additional information, collection of SAEs only would greatly reduce trial complexity. Further, the rapid timelines required for reporting SAEs should be revisited, since informed decisions cannot be made on the basis of individual SAEs. Quarterly reports of all accumulated safety data would be more informative, with expedited reporting of the threatening events. Alternatively, reporting could be limited to genuinely severe events or unexpected only. Adjudication is another major cost driver in clinical trials, and its value has been debated.[53,54] It may be more efficient to redirect resources from adjudication towards enroling more patients, or only adjudicate a subset of the data where differentiating disease subtypes may be particularly important (e.g. cardiovascular vs. non-cardiovascular death, or haemorrhagic vs. ischaemic stroke in a trial of anticoagulants for atrial fibrillation).

Another approach worth consideration is the concept of time-to-first event vs. recurrent event analysis. For the majority of registration cardiovascular trials, time-to-first event has been an accepted method of data analysis. However, new therapies will less likely affect cardiovascular mortality (unless the trial size is enormous), and this approach does not fully capture the 'patient journey.'[55] Recurrent event analysis is particularly suitable for diseases where reductions in repeat hospitalizations are of interest (e.g. heart failure with preserved ejection fraction or acute decompensated heart failure).[56] Regulatory and statistical guidance in this respect will be helpful to industry and academia.

The viability of these proposed approaches to streamlining cardiovascular clinical trials ultimately depends on their acceptance by regulatory authorities. Some regulatory agencies are internally evaluating their processes and considering new approaches to drug approval.[57] For example, the EMA is considering adaptive licensing. Using this approach, fewer patients are studied pre-approval, prescribing restrictions are placed post-approval such that most treated patients are enrolled in observational studies or randomized controlled trials, then active surveillance decreases over time after full approval.[58] This approach is now formally supported by a pilot project,[59] which will initially involve drugs for small patient populations. Current experience with this approach is limited, and the EMA recognizes the many challenges. The FDA's approach to early drug approval before effects on clinical outcomes are demonstrated remains less clear, as exemplified by recent decisions,[60] although several approval pathways exist, such as breakthrough designation, fast-track, and accelerated approval for drugs targeting unmet medical needs. FDA also has processes where initial approvals can be based on surrogates with a subsequent outcome study required to verify clinical benefit. Both agencies agree that 'there is no surrogate for safety,'[61] and therefore large-scale enrolment and long-term follow-up are often required. Regulators encourage industry sponsors and investigators to engage in early dialogue with agencies to determine the optimal investigative path for a new product. Compliance with advice received from EMA's Scientific Advice Working Party is associated with regulatory approval.[62]

Electronic health records are now more widely used, creating a potential streamlined, efficient, and less costly data source for laboratory variables or health service utilization outcomes (e.g. hospitalizations) as well as for 'hard outcomes' in a clinical trial. Large differences between systems will require careful validation of which clinical endpoints are suitable for collection via this approach.[63] For pivotal studies that are intended to support a regulatory submission, assurance that the data collection methods are robust must be provided. Data protection and privacy are the major obstacles to using this type of information. Policies, procedures, and the scientific community's approach to data protection will need to evolve to match

Table 1 Proposed solutions to streamline cardiovascular drug development and reinvigorate industry investment

Unmet need	Proposed solution
Targeted development and evaluation in defined patient populations	• A concerted effort from regulators, academia, payers, and industry to allow targeted, mechanism-based, effective and rapid development of new compounds for use in defined 'precision' patient groups, complementing the present model of 'one size fits all' blockbuster development. • Efforts from academia and industry to better understand disease mechanisms and to develop new disease classifications reflecting such mechanisms. Integrated approaches for more effective human target validation using large biobanks and genetic collection is needed in the pre-competitive space. • Development of reliable public–private partnerships between academia and industry to make better use of the existing insights into disease mechanisms and their translation into targets for new medications.
Simple, practical approaches to conducting large randomized trials	• Careful revision of the current infrastructure and operating procedures for the conduct of clinical trials in cardiovascular medicine with a view to reducing administrative burden and focus on the regulatory and procedural requirements that add value in high-quality clinical trials. • Adoption of innovative statistical approaches for the design and analysis of clinical cardiovascular trials (e.g. adaptive designs, use of total events rather than time-to-first event).
Generating data to support health technology assessment	• Systematic collection of key data elements in pivotal clinical trials of new agents for performing cost-effectiveness analyses required by health technology assessments. • Implementation of existing information technology for long-term follow-up of patients enrolled in clinical trials, requiring adaptation and harmonization of data protection rules.

the current environment such that patients are protected but data can still be accessible. The European Union has a pivotal role in evaluating the societal benefits of this information, i.e. comparing the potential benefits of long-term follow-up of trial participants to the potential risks in an increasingly digital, transparent world. *We advocate the evaluation and implementation of simple follow-up strategies for outcome trials with a proportionate and coordinated European trials framework, support for transparent and monitored access to digital health care data sets for research, and the formation of alliances between industry partners and academic research organizations to facilitate the conduct of meaningful, lean outcome trials.*

Generating data to support health technology assessment

Regulatory approval is not the last step in the process of making effective drugs available to patients. Often termed the 'fourth hurdle', health technology assessments are a key component of the decision process used by payers to determine if a therapy will be reimbursed or, in some cases, even offered to patients. Both economic and quality of life data (to calculate quality adjusted life years) are needed to support the health technology assessment. Collecting data on 'procedures saved' might also be considered to characterize the effect of a therapy beyond direct monetary value.

Economic evaluations should be performed using simple, practical, unobtrusive, large randomized clinical trials, ideally using data collection systems that are already in place.[64,65] This simplified approach increases the practicality of the data gathered, since they better reflect the population which will use the therapy as opposed to a complex trial with restrictive eligibility criteria. Electronic medical records may be potential sources of data because they are linked to health service utilization (i.e. hospitalizations, length of stay, number and type of clinician visits), which are the true drivers of cost. However, potential bias may be introduced (e.g. confounding by indication, channelling phenomenon where new drugs are preferentially used in more seriously ill patients) by using electronic medical records, which may make them impractical for use with some drugs. These biases should be recognized and efforts made to minimize their influence to the extent possible. Further discussion on the practical implementation of using electronic medical records for this purpose is needed. In addition to service utilization parameters, systematically capturing quality-of-life information and other patient reported outcomes using standard metrics is key. Further, incorporating these assessments into pivotal simple trials prevents delays that will occur if separate studies to inform health technology assessments are required after marketing authorization is received. *We advocate health technology assessment of new cardiovascular therapeutics based on the collection of key economic measures in clinical trials and data collected in the early post-approval period, based on transparent, robust processes.*

Evidence gaps and limitations

If implemented, the approaches outlined in this document have the potential to improve the efficiency of cardiovascular clinical trials. However, their impact cannot fully be known until more experience with these strategies has been gained. Some of the 'unknowns' include the importance of clinical and statistical uncertainty in smaller 'precision'-driven trials, bias in adaptive designs where the results are 'unblinded' in an ongoing manner, and whether alternative approaches to clinical trial conduct will actually translate into improved efficiency. Future research efforts will need to focus on achieving more comprehensive knowledge regarding these issues.

Conclusion

There is a large, increasingly unmet need for novel approaches to the development of new therapies to reduce the unacceptable global burden of cardiovascular diseases (*Table 1*). The ESC has

identified several key areas in need of further improvement. Collaboration among industry sponsors, academic investigators, regulators, governments, payers, and society as a whole will be necessary to enact change in the current state of cardiovascular clinical drug development.

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References

1. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980–2009. *Eur Heart J* 2013;**34**:3017–3027.
2. Braunwald E. Cardiovascular pharmacology: a look back and a glimpse into the future. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:7–9.
3. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe: epidemiological update. *Eur Heart J* 2013;**34**:3028–3034.
4. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. *Int J Cardiol* 2013;**168**:934–945.
5. Murphy S, Xu J. Deaths: Final data for 2010. National Vital Statistics Reports. Hyattsville, Maryland: National Center for Health Statistics, 2013. p. 61.
6. Sipido KR, Tedgui A, Kristensen SD, Pasterkamp G, Schunkert H, Wehling M, Steg PG, Eisert W, Rademakers F, Casadei B, Fuster V, Cerbai E, Hasenfuss G, Fernandez-Aviles F, Garcia-Dorado D, Vidal M, Hallen M, Dambrauskaite V. Identifying needs and opportunities for advancing translational research in cardiovascular disease. *Cardiovasc Res* 2009;**83**:425–435.
7. Reith C, Landray M, Devereaux PJ, Bosch J, Granger CB, Baigent C, Califf RM, Collins R, Yusuf S. Randomized clinical trials--removing unnecessary obstacles. *N Engl J Med* 2013;**369**:1061–1065.
8. Calvo G, McMurray JJ, Granger CB, Alonso-Garcia A, Armstrong P, Flather M, Gomez-Outes A, Pocock S, Stockbridge N, Svensson A, Van de Werf F. Large streamlined trials in cardiovascular disease. *Eur Heart J* 2014;**35**:544–548.
9. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
10. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**2**:349–360.
11. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *Lancet* 2001;**357**:373–380.
12. Kirchhof P, Breithardt G, Aliot E, Al KS, Apostolakis S, Auricchio A, Bailleul C, Bax J, Benninger G, Blomstrom-Lundqvist C, Boersma L, Boriani G, Brandes A, Brown H, Brueckmann M, Calkins H, Casadei B, Clemens A, Crijns H, Derwand R, Dobrev D, Ezekowitz M, Fetsch T, Gerth A, Gillis A, Gulizia M, Hack G, Haegeli L, Hatem S, Georg HK, Heidbuchel H, Hernandez-Brichis J, Jais P, Kappenberger L, Kautzner J, Kim S, Kuck KH, Lane D, Leute A, Lewalter T, Meyer R, Mont L, Moses G, Mueller M, Munzel F, Nabauer M, Nielsen JC, Oeff M, Oto A, Pieske B, Pisters R, Potpara T, Rasmussen L, Ravens U, Reiffel J, Richard-Lordereau I, Schafer H, Schotten U, Stegink W, Stein K, Steinbeck G, Szumowski L, Tavazzi L, Themistoclakis S, Thomitzek K, Van Gelder IC, von SB, Vincent A, Werring D, Willems S, Lip GY, Camm AJ. Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2013;**15**:1540–1556.
13. Kirchhof P, Sipido K, Cowie M, Eschenhagen T, Fox K, Katus H, Schroeder S, Schunkert H, Priori S. The continuum of personalized cardiovascular medicine: a report from a joint workshop of the Cardiovascular Round Table and the European Affairs Committee of the European Society of Cardiology. *Eur Heart J* 2014; in press.
14. Kirchhof P, Sipido KR, Cowie MR, Eschenhagen T, Fox KA, Katus H, Schroeder S, Schunkert H, Priori S. The continuum of personalized cardiovascular medicine: a position paper of the European Society of Cardiology. *Eur Heart J* 2014.
15. Mestre-Ferrandiz J, Sussex J, Towse A. The R&D cost of a new medicine. Office of Health Economics, 2012.
16. Hersher R. The price of failure: new estimate puts drug R&D in the billions per agent. **http://blogs.nature.com/spoonful/2012/02/the-price-of-failure-new-estimate-puts-drug-rd-in-the-billions-per-agent.html** (4 January 2014). Last updated 2 October 2012.
17. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov* 2012;**11**:191–200.
18. Komajda M, Coats A, Cowie MR, Jackson N, Svensson A, Vardas P. Championing cardiovascular health innovation in Europe. *Eur Heart J* 2013;**34**:2630–2635.
19. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010;**363**:1419–1428.
20. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the

Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002;**106**:920–926.
21. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.
22. O'Donoghue ML, Braunwald E, White HD, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP, Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA* 2014;**312**:1006–1015.
23. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;**371**:203–212.
24. Tardif JC, Rheaume E, Lemieux Perreault LP, Gregoire JC, Feroz ZY, Asselin G, Provost S, Barhdadi A, Rhainds D, L'Allier PL, Ibrahim R, Upmanyu R, Niesor EJ, Benghozi R, Suchankova G, Laghrissi-Thode F, Guertin MC, Olsson AG, Mongrain I, Schwartz GG, Dube MP. Pharmacogenomic Determinants of the Cardiovascular Effects of Dalcetrapib. *Circ Cardiovasc Genet* 2015.
25. Jansen H, Samani NJ, Schunkert H. Mendelian randomization studies in coronary artery disease. *Eur Heart J* 2014.
26. Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN, Gao P, Saleheen D, Rendon A, Nelson CP, Braund PS, Hall AS, Chasman DI, Tybjaerg-Hansen A, Chambers JC, Benjamin EJ, Franks PW, Clarke R, Wilde AA, Trip MD, Steri M, Witteman JC, Qi L, van der Schoot CE, de FU, Erdmann J, Stringham HM, Koenig W, Rader DJ, Melzer D, Reich D, Psaty BM, Kleber ME, Panagiotakos DB, Willeit J, Wennberg P, Woodward M, Adamovic S, Rimm EB, Meade TW, Gillum RF, Shaffer JA, Hofman A, Onat A, Sundstrom J, Wassertheil-Smoller S, Mellstrom D, Gallacher J, Cushman M, Tracy RP, Kauhanen J, Karlsson M, Salonen JT, Wilhelmsen L, Amouyel P, Cantin B, Best LG, Ben-Shlomo Y, Manson JE, Davey-Smith G, de Bakker PI, O'donnell CJ, Wilson JF, Wilson AG, Assimes TL, Jansson JO, Ohlsson C, Tivesten A, Ljunggren O, Reilly MP, Hamsten A, Ingelsson E, Cambien F, Hung J, Thomas GN, Boehnke M, Schunkert H, Asselbergs FW, Kastelein JJ, Gudnason V, Salomaa V, Harris TB, Kooner JS, Allin KH, Nordestgaard BG, Hopewell JC, Goodall AH, Ridker PM, Holm H, Watkins H, Ouwehand WH, Samani NJ, Kaptoge S, Di AE, Harari O, Danesh J. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet* 2012;**379**:1205–1213.
27. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de FU, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de BA, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012;**380**:572–580.
28. Wensley F, Gao P, Burgess S, Kaptoge S, Di AE, Shah T, Engert JC, Clarke R, Davey-Smith G, Nordestgaard BG, Saleheen D, Samani NJ, Sandhu M, Anand S, Pepys MB, Smeeth L, Whittaker J, Casas JP, Thompson SG, Hingorani AD, Danesh J. Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data. *BMJ* 2011;**342**:d548.
29. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med* 2008;**359**:1897–1908.
30. Dunn BK, Wagner PD, Anderson D, Greenwald P. Molecular markers for early detection. *Semin Oncol* 2010;**37**:224–242.
31. Sethi S, Ali S, Philip PA, Sarkar FH. Clinical advances in molecular biomarkers for cancer diagnosis and therapy. *Int J Mol Sci* 2013;**14**:14771–14784.
32. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, Liu T, Mohanavelu S, Hoffman EB, McDonald ST, Abrahamsen TE, Wasserman SM, Scott R, Sabatine MS. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet* 2012;**380**:2007–2017.
33. Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, Bolognese M, Wasserman SM. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2012;**380**:1995–2006.
34. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:341–350.
35. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, Langslet G, Scott R, Olsson AG, Sullivan D, Hovingh GK, Cariou B, Gouni-Berthold I, Somaratne R, Bridges I, Scott R, Wasserman SM, Gaudet D. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**385**:331–340.
36. Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, Wu R, Pordy R. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet* 2012;**380**:29–36.
37. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, Ceska R, Roth E, Koren MJ, Ballantyne CM, Monsalvo ML, Tsirtsonis K, Kim JB, Scott R, Wasserman SM, Stein EA. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014;**370**:1809–1819.
38. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, Somaratne R, Legg JC, Nelson P, Scott R, Wasserman SM, Weiss R. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* 2014;**311**:1870–1882.
39. Committee for Medicinal Products for Human Use (CHMP). Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. **http://wwwemeaeuropaeu/pdfs/human/ewp/245902enadoptedpdf** 2007.
40. Friede T, Parsons N, Stallard N. A conditional error function approach for subgroup selection in adaptive clinical trials. *Stat Med* 2012;**31**:4309–4320.
41. Friede T, Parsons N, Stallard N, Todd S, Valdes ME, Chataway J, Nicholas R. Designing a seamless phase II/III clinical trial using early outcomes for treatment selection: an application in multiple sclerosis. *Stat Med* 2011;**30**:1528–1540.
42. Bornkamp B, Bretz F, Dmitrienko A, Enas G, Gaydos B, Hsu CH, Konig F, Krams M, Liu Q, Neuenschwander B, Parke T, Pinheiro J, Roy A, Sax R, Shen F. Innovative approaches for designing and analyzing adaptive dose-ranging trials. *J Biopharm Stat* 2007;**17**:965–995.
43. Coffey CS, Levin B, Clark C, Timmerman C, Wittes J, Gilbert P, Harris S. Overview, hurdles, and future work in adaptive designs: perspectives from a National Institutes of Health-funded workshop. *Clin Trials* 2012;**9**:671–680.
44. Emerson SS, Fleming TR. Adaptive methods: telling "the rest of the story". *J Biopharm Stat* 2010;**20**:1150–1165.
45. Wittes J. Comments on the FDA draft guidance on adaptive designs. *J Biopharm Stat* 2010;**20**:1166–1170.
46. Barnes PJ, Pocock SJ, Magnussen H, Iqbal A, Kramer B, Higgins M, Lawrence D. Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. *Pulm Pharmacol Ther* 2010;**23**:165–171.
47. Cohen AT, Boyd RA, Mandema JW, DiCarlo L, Pak R. An adaptive-design dose-ranging study of PD 0348292, an oral factor Xa inhibitor, for thromboprophylaxis after total knee replacement surgery. *J Thromb Haemost* 2013;**11**:1503–1510.
48. Chaturvedi P, Antonijevic Z, Mehta C. Practical considerations for a two-stage confirmatory adaptive clinical trial design and its implementation: ADVENT trial. In: He W, Pinheiro J, Kuznetsova O (eds), *Practical Considerations for Adaptive Trial Design and Implementation*. Springer; 2014.
49. Lawrence D, Bretz F. Approaches for optimal dose selection for adaptive design trials. In: He W, Pinheiro J, Kuznetsova O (eds), *Practical Considerations for Adaptive Trial Design and Implementation*. Springer; 2014.
50. Aung T, Cowan H, Haynes R, Bowman L, Armitage J. Recruiting patients cost-effectively by mail [abstract]. *Trials* 2014;**12**:A117.
51. Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E, Becker U, Bee V, Wilson V, Legrand C, Buyse M. A statistical approach to central monitoring of data quality in clinical trials. *Clin Trials* 2012;**9**:705–713.
52. U. S. Department of Health and Human Services and Food and Drug Administration. Guidance for Industry. Oversight of clinical investigations—a risk-based approach to monitoring. **http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf**. Last updated 2013.

53. Pogue J, Walter SD, Yusuf S. Evaluating the benefit of event adjudication of cardiovascular outcomes in large simple RCTs. *Clin Trials* 2009;**6**:239–251.
54. Granger CB, Vogel V, Cummings SR, Held P, Fiedorek F, Lawrence M, Neal B, Reidies H, Santarelli L, Schroyer R, Stockbridge NL, Feng Z. Do we need to adjudicate major clinical events? *Clin Trials* 2008;**5**:56–60.
55. Cleland JG, Charlesworth A, Lubsen J, Swedberg K, Remme WJ, Erhardt L, Di LA, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson PA. A comparison of the effects of carvedilol and metoprolol on well-being, morbidity, and mortality (the "patient journey") in patients with heart failure: a report from the Carvedilol Or Metoprolol European Trial (COMET). *J Am Coll Cardiol* 2006;**47**:1603–1611.
56. Rogers JK, Pocock SJ, McMurray JJ, Granger CB, Michelson EL, Ostergren J, Pfeffer MA, Solomon SD, Swedberg K, Yusuf S. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail* 2014;**16**:33–40.
57. Ehmann F, Papaluca AM, Salmonson T, Posch M, Vamvakas S, Hemmings R, Eichler HG, Schneider CK. Gatekeepers and enablers: how drug regulators respond to a challenging and changing environment by moving toward a proactive attitude. *Clin Pharmacol Ther* 2013;**93**:425–432.
58. Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, Ferguson J, Garner S, Honig P, Hukkelhoven M, Lim JC, Lim R, Lumpkin MM, Neil G, O'Rourke B, Pezalla E, Shoda D, Seyfert-Margolis V, Sigal EV, Sobotka J, Tan D, Unger TF, Hirsch G. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;**91**:426–437.
59. European Medicines Agency. Pilot project on adaptive licensing. **http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163409.pdf** (26 June 2014). Last updated 19 March 2014.
60. Hiatt WR, Smith RJ. Assessing the clinical benefits of lipid-disorder drugs. *N Engl J Med* 2014;**370**:396–399.
61. Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? *JAMA* 1999;**282**:790–795.
62. Regnstrom J, Koenig F, Aronsson B, Reimer T, Svendsen K, Tsigkos S, Flamion B, Eichler HG, Vamvakas S. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. *Eur J Clin Pharmacol* 2010;**66**:39–48.
63. Barry SJ, Dinnett E, Kean S, Gaw A, Ford I. Are routinely collected NHS administrative records suitable for endpoint identification in clinical trials? Evidence from the West of Scotland Coronary Prevention Study. *PLoS One* 2013;**8**:e75379.
64. McNamara RL, Brass LM, Drozda JP Jr., Go AS, Halperin JL, Kerr CR, Levy S, Malenka DJ, Mittal S, Pelosi F Jr., Rosenberg Y, Stryer D, Wyse DG, Radford MJ, Goff DC Jr, Grover FL, Heidenreich PA, Malenka DJ, Peterson ED, Redberg RF. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Data Standards on Atrial Fibrillation). *Circulation* 2004;**109**:3223–3243.
65. Weintraub WS, Karlsberg RP, Tcheng JE, Boris JR, Buxton AE, Dove JT, Fonarow GC, Goldberg LR, Heidenreich P, Hendel RC, Jacobs AK, Lewis W, Mirro MJ, Shahian DM, Hendel RC, Bozkurt B, Jacobs JP, Peterson PN, Roger VL, Smith EE, Tcheng JE, Wang T. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards. *Circulation* 2011;**124**:103–123.