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Review

Current challenges for clinical trials of cardiovascular medical devices

Faiez Zannad [a,b,*], Wendy Gattis Stough [c], Ileana L. Piña [d], Roxana Mehran [e,f], William T. Abraham [g], Stefan D. Anker [h], Gaetano M. De Ferrari [i], Andrew Farb [j], Nancy L. Geller [k], Robert S. Kieval [l], Cecilia Linde [m], Rita F. Redberg [n], Kenneth Stein [o], Alphons Vincent [p], Holger Woehrle [q,r], Stuart J. Pocock [s]

[a] INSERM, Centre d'Investigation Clinique 9501 Unité 1116, Centre Hospitalier Universitaire, France
[b] Department of Cardiology, Université de Lorraine, Nancy, France
[c] Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, USA
[d] Department of Medicine, Division of Cardiology, Montefiore Medical Center, Bronx, NY, USA
[e] Cardiovascular Research Foundation, New York, NY, USA
[f] Mount Sinai Medical Center, New York, NY, USA
[g] Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA
[h] Applied Cachexia Research, Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany
[i] Department of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[j] U.S. Food and Drug Administration, Silver Spring, MD, USA
[k] National Heart Lung and Blood Institute, Bethesda, MD, USA
[l] CVRx, Inc., Minneapolis, MN, USA
[m] Department of Cardiology, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden
[n] University of California, San Francisco, CA, USA
[o] Boston Scientific Corporation, St. Paul, MN, USA
[p] Medtronic, Tolochenaz, Switzerland
[q] ResMed Science Center, ResMed, Martinsried, Germany
[r] Sleep and Ventilation Center Blaubeuren/Lung Center, Ulm, Germany
[s] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom

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ABSTRACT

Several features of cardiovascular devices raise considerations for clinical trial conduct. Prospective, randomized, controlled trials remain the highest quality evidence for safety and effectiveness assessments, but, for instance, blinding may be challenging. In order to avoid bias and not confound data interpretation, the use of objective endpoints and blinding patients, study staff, core labs, and clinical endpoint committees to treatment assignment are helpful approaches. Anticipation of potential bias should be considered and planned for prospectively in a cardiovascular device trial. Prospective, single-arm studies (often referred to as registry studies) can provide additional data in some cases. They are subject to selection bias even when carefully designed; thus, they are generally not acceptable as the sole basis for pre-market approval of high risk cardiovascular devices. However, they complement the evidence base and fill the gaps unanswered by randomized trials. Registry studies present device safety and effectiveness in day-to-day clinical practice settings and detect rare adverse events in the post-market period. No single research design will be appropriate for every cardiovascular device or target patient population. The type of trial, appropriate control group, and optimal length of follow-up will depend on the specific device, its potential clinical benefits, the target patient population and the existence (or lack) of effective therapies, and its anticipated risks. Continued efforts on the part of investigators, the device industry, and government regulators are needed to reach the optimal approach for evaluating the safety and performance of innovative devices for the treatment of cardiovascular disease.

Abbreviations: CE, Conformité Européenne; CEC, Clinical Events Committee; EMA, European Medicines Agency; E.U., European Union; FDA, Food and Drug Administration; HRQOL, health-related quality of life; IDE, investigational device exemption; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMT, optimal medical therapy; OPC, objective performance criteria; PRO, patient reported outcomes; PROBE, prospective open with blinded evaluation; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; STICH, Surgical Treatment for Ischemic Heart Failure; U.S., United STATES.

* Corresponding author at: Coordinateur Général, Centre d'Investigation Clinique Inserm, CHU, Université de LorraineCoordinateur Scientifique EU FP7 HOMAGECoordinateur Scientifique EU FP7 FIBROTARGETS UMR 1116 Chef de l'Unité HTA et Insuffisance Cardiaque Pôle de Cardiologie Président, Réseau Insuffisance Cardiaque ICALOR Institut Lorrain du Coeur et des Vaisseaux CHU de Nancy 4, rue du Morvan54500 VANDOEUVRE-LES-NANCY, France. Tel.: +33 383 15 73 22; fax: +33 383 15 73 24.
E-mail address: f.zannad@chu-nancy.fr (F. Zannad).

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1. Introduction

Numerous medical devices are available that prolong survival, decrease morbidity, reduce symptoms, and improve functional status and/or health-related quality of life (HRQOL) in patients across the spectrum of cardiovascular disease [1]. However, devices have different considerations than drugs, and the design of device clinical trials may not necessarily follow the patterns established for pharmacologic studies [2–4]. For example, in device clinical trials, blinding may be more challenging, making the use of subjective endpoints (e.g., quality of life or threshold for revascularization) less reliable, as they are more likely to show a powerful placebo effect, even from a sham procedure. Unlike drug studies, operator or procedural learning curves play an important role in device trials, which may result in poorer outcomes during the early phases of study. Patient selection, implant and surgical technique, and stratified follow-up are key elements for successful device therapy, but they may not be fully understood at the time a trial is designed. Fewer patients are usually enrolled in device trials than in drug trials; therefore, device trials are more prone to be underpowered for major morbid events and mortality. Conversely, inadequate patient adherence to the assigned intervention is not a problem in the evaluation of an implanted device, whereas it can be problematic in drug trials. As technology rapidly changes, new models of a device may be released during a trial, prior to the presentation of data for regulatory approval, or, in the case of devices already approved, new models can be approved via the pre-market approval (PMA) supplement process. Changes can also include updated software algorithms that dictate the response to certain measurements, which in reality, can significantly change the device function. There are no precise rules governing what degree of change is significant enough to require new clinical studies. Most approvals processed through the PMA supplement pathway follow a supplement category that does not require clinical data to support the approval [5]. This process is in contrast to the extensive pre-clinical and early phase trials that precede pivotal trials for pharmacologic therapies. Regulatory requirements for approval of medical devices in the United States are vastly different from those in Europe, causing difficulties in harmonizing research requirements globally. Finally, achieving reimbursement and ultimate adoption of a novel device may require data beyond that needed to assure safety and effectiveness. Given these factors, alternative trial designs and novel endpoints that accurately reflect safety and effectiveness are needed for the evaluation of cardiovascular devices. However, departure from the ideal randomized, double-blind, controlled trial to create a feasible environment for conducting trials and supporting innovation is associated with real concerns in terms of scientific validity and confidence in research results. The importance of these trade-offs should not be underemphasized.

During the 9th Global Cardiovascular Clinical Trialists Forum held in Paris, France, in December 2012, alternative approaches to randomized, double-blind, controlled trials of cardiovascular devices were discussed, highlighting the strengths and limitations of the regulatory environment, and considering methods to achieve quality science while ensuring feasibility, patient safety, and encouraging innovation. This paper summarizes the key challenges facing cardiovascular device research and development on the path to regulatory approval.

2. Pre-market clinical trial designs to support device approval

Approval of therapeutic innovations should be based on a reasonable assurance of safety and effectiveness ideally demonstrated by randomized, controlled study designs that provide unbiased data for clinical evaluation and regulatory decision-making. However, there are multiple challenges to utilizing this ideal approach for studies of cardiovascular devices.

2.1. Blinding considerations

Blinding reduces bias in clinical trials, and regulatory agencies encourage blinding to the fullest extent possible. Blinding a device trial may require a sham procedure (e.g., a procedure that simulates the device implantation, but no device is implanted), a sham device (which in most cases would violate ethical principles of research because of the lack of potential for individual benefit, although both sham procedures and devices can have a marked placebo effect which might restore the balance between potential risks and potential benefits), or implantation of a device without actuation. While sham approaches are possible for some device trials (e.g., renal artery nerve radiofrequency ablation to treat hypertension where all patients undergo renal angiography to determine anatomic eligibility and randomization and treatment is performed at the time of renal angiography [6] or cardiac resynchronization therapy), they are not for others (e.g., mechanical circulatory support). Sham procedures may be viewed by some as unethical because the risks associated with the procedure could outweigh any potential benefit gained from participating in the research. Additionally, devices are often linked to specific management or follow-up care that cannot be separated from the pure device effect.

Lack of blinding has the potential to bias outcome assessment by overestimating the treatment effect [7]. Truly large treatment effects can overwhelm such bias, but if treatment effects are more modest, the potential bias makes the results difficult to interpret. Therefore, when blinding is not possible, studies should be designed with hard objective endpoints (e.g., all-cause mortality versus cause-specific mortality; all hospitalizations versus heart failure hospitalizations; all revascularization versus urgent revascularization). Any cause-specific or subjective endpoints should be adjudicated by a clinical events committee (CEC) that is blinded as to each patient's allocated treatment (i.e., prospective open with blinded evaluation [PROBE] design) [8]. It is important to note that the CEC may be unblinded by diagnostic tests (e.g., computed tomography [CT] scans or chest X-rays) where devices are evident. Special efforts to avoid unblinding in these situations (e.g., redaction of progress notes, exclusion of imaging reports from documentation provided to CEC members unless absolutely required to classify events) need to be undertaken.

Open-label device trials can bias study subjects completing patient reported outcomes (PRO) or HRQOL questionnaires. Thus, such endpoints are usually inadequate as primary endpoints for pivotal trials. However, they are often important secondary or ancillary outcomes used by patients to make decisions about treatment preferences or by payers to support reimbursement decisions. Therefore, such endpoints should be rigorously collected and potential sources of bias acknowledged to facilitate data interpretation. Instruments that assess device-related burden independently from HRQOL may be more informative and reduce the influence of bias, since the assessment is more objectively determined. Instruments should be as device-specific as possible. Unfortunately, not many instruments have been developed or validated that capture specific device-related issues. Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have released specific documents to guide the development of PROs to support regulatory claims [9–11].

Bias can also originate from unblinded investigators who may adjust therapies and alter patient management during an ongoing study [12]. The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association (NYHA) class III Heart Failure Patients (CHAMPION) study is a good example of a recent trial in which regulators and FDA Advisory Panel members were initially uncertain about how to interpret the data in the context of the potential confounding influence of unblinded study staff who made treatment recommendations to study investigators [13]. Even in a blinded trial, accidental unblinding can occur, which may affect care differentially in the treatment arms. Investigators may tend to report adverse events more frequently in the investigational arm of open-label trials, or they may