CORE-MD

Coordinating Research and Evidence for Medical Devices

A publication on the essential principles of randomized registry trials

Deliverable 2.2

Deliverable factsheet

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Issue Date	Version	Involved	Comments
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Acronyms and abbreviations

BMS	Bare-metal stent
BVS	Bioresorbable vascular scaffold
CE	Conformité Européenne
CER	Clinical Evaluation Report
CORE – MD	Coordinating Research and Evidence for Medical Devices
COVID – 19	Coronavirus disease 2019
DES	Drug-eluting stent
DSMB	Data safety monitoring board
eCRF	Electronic case report form
EDC	Electronic data capture system
EES	Everolimus-eluting stent
EU	European Union
GCP	Good Clinical Practice
GCTC	Good Clinical Trials Collaborative
IABP	Intra-aortic balloon pump
ICH	International Council for Harmonization
ISIS-2	International Studies of Infarct Survival
MDR	Medical Device Regulation
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NHS	National Health Service
PCI	Percutaneous coronary intervention
PIN	Personal identification number
PMID	PubMed identifier
RCT	Ramdomized control trail
R – RCT	Registry-based randomized clinical trial
RECOVERY	Randomised Evaluation of COVID-19 Therapy

SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TASTE	Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia
TAVR	Transcatheter aortic valve replacement
TFL	Target lesion failure
TV – MI	Target vessel myocardial infarction
UK	United Kingdom

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Executive Summary

Randomized controlled trials (RCTs) are the cornerstone of modern evidence-based medicine. They are considered essential to establish definitive evidence for new drugs, and whenever possible they should also be the preferred method for investigating new high-risk medical devices. Well-designed studies robustly inform clinical practice guidelines and decision-making, but administrative obstacles have made it increasingly difficult to conduct informative RCTs. The obstacles are compounded for RCTs of high-risk medical devices by extra costs related to the device and procedure, challenges with willingness to randomize patients throughout a trial, and difficulties in ensuring proper blinding even with sham procedures. For many devices, too little high-quality clinical evidence is available. One strategy that may help to improve the evidence base is to promote the wider use of simpler and more streamlined RCTs. Recent large simple RCTs have successfully compared the performance both of drugs and of high-risk medical devices, against alternative treatments; they enrolled many patients in a short time, limited costs, and improved efficiency, while also achieving major impact. In this review conducted within the CORE-MD project, we report from our combined experience of designing and conducting large pharmaceutical trials during the COVID-19 pandemic, and of planning and coordinating large registry-based RCTs of cardiovascular devices. We summarize the essential principles and utility of large simple RCTs, relevant to all interventions but especially in order to promote their wider adoption to evaluate new medical devices.

1 Introduction

The Medical Device Regulation (MDR) that came into effect in the European Union (EU) in May 2021 provides a regulatory framework that aims to balance the efficient approval of new medical devices (or technical iterations of existing devices) with demonstration of their safety.[1] It requires evidence to be presented in a Clinical Evaluation Report (CER) that supports the intended use and safety of a medical device, before market approval, and then periodic reports on safety to be submitted thereafter.[1] The MDR imposes higher standards for generating and assessing evidence on the performance and safety of high-risk medical devices than was required under the previous medical device directives, and it specifies in particular that "clinical investigations shall be performed for implantable and other high-risk medical devices".[2] The CER is not made publicly available, however, and specific aspects regarding the design of clinical investigations are not addressed in detail in the MDR. This creates uncertainty about which questions clinical evidence should address and about which types of studies are appropriate – particularly for new high-risk devices, for which there is a dearth of information.([3],[4])

Randomized clinical trials (RCTs) provide the foundation of evidence-based medicine.[5] Randomly assigning participants to different therapeutic strategies minimizes sources of bias and allows inference of causality between interventions and their clinical outcomes.([6],[7]) Well-designed and accurately conducted RCTs robustly inform clinical practice guidelines and decision-making processes, but barriers to their conduct include high costs related to excessive complexity in the governance of trials, and limited generalizability when highly selected cohorts of patients are studied.[8] Large simple RCTs can address both problems.

The principles of simplifying the design and avoiding unnecessary distractions in the conduct of RCTs were developed many years ago.[9] They have been reconfirmed for 'streamlined' RCTs of drugs ([6],[7]) and demonstrated to be feasible for conducting large and simple RCTs of high-risk medical devices.([10],[11]) Now, the increasing availability of routinely collected healthcare data (for example in registries) and the continuing development of more powerful information and communication technologies, provide new opportunities for applying the concepts much more widely.

The objectives of the Coordinating Research and Evidence for Medical Devices (CORE-MD) project, led by the European Society of Cardiology and the European Federation of National Associations of Orthopaedics and Traumatology, are to review methodologies of clinical investigations and to advise on optimal study designs for high-risk medical devices.[12] Importantly, members of the consortium have pioneered the design and conduct of large, simple RCTs both of drugs and of medical devices. Sharing knowledge accumulated through that experience may be useful to apprise others of their unique value and to foster their wider adoption when obtaining evidence for regulatory approval. The objectives of this review are to identify the basic principles and to summarize the most important features of large simple RCTs.

2 Reducing obstacles to performing RCTs

Strict and inflexible (over-) interpretation of the International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines has placed ever-increasing demands on the conduct of RCTs.[8] Although ICH GCP recommendations are aimed primarily at drug trials, to acquire evidence for licensing, they have been considered relevant also for trials of medical devices. They were designed to safeguard patients while promoting the utility and transparency of RCTs, but now the bureaucratic burden imposed on institutions, clinicians, and research staff is perceived as overwhelming. ([13],[14]) Unnecessary and time-consuming hurdles can discourage patients from participating in trials. A lack of interest in reducing complexity, by actors involved in the conduct and oversight of RCTs such as Clinical Research Organizations, may also limit the design and conduct of new RCTs.[15] The GCP recommendations are being revised by ICH (for details see ICH E6 (R3) at https://www.ich.org/page/efficacy-guidelines), but it is unclear how much new guidance will reduce bureaucratic obstacles.

Streamlining the conduct of RCTs, without reducing their quality, is of paramount importance to increase the number of RCTs being performed and to reduce their costs.(8) Generating more high-quality clinical evidence will be useful for regulators, to increase the confidence and accuracy of their decisions to approve new drugs or medical devices. It will also benefit patients by upholding their right to receive treatments that are effective and safe. Essential principles have been summarized by the Good Clinical Trials Collaborative (GCTC, link at https://www.goodtrials.org/) (see Table 1), and are applicable to trials of devices as well as other interventions. They stress the importance of avoiding unnecessary distractions during the conduct of RCTs, such as excessive monitoring of data that are not of key relevance, unnecessarily complex procedures for reporting clinical information and adverse events, and needing investigators to accomplish redundant administrative processes.[16]

Table 1. Principles, implications and recommendations from the Good Clinical Trials Collaborative

Principles	Implications	Recommendations regarding:
Relevance and utility	Design characteristics of RCTs should aim to resolve important uncertainties about the effects of a health intervention	- Appropriate population - Robust intervention allocation - Adequate size - Blinding and masking of interventions - Adherence to allocated interventions - Completeness of follow-up - Relevant measures of outcomes - Proportionate, efficient and reliable capture of data - Ascertainment of outcomes - Statistical analysis

Principles	Implications	Recommendations regarding:
		- Assessing beneficial and harmful effects of the intervention - Monitoring emerging information on benefits and harms
Respect of participants	Ethical responsibilities regarding participants, future and current patients, and the public.	- - Appropriate communication - - Relevant consent - - Changing consent - - Implications of changing consent - - Managing the safety of individual participants - - Communication of new information relevant to the intervention
Collaboration and transparency	Practices that contribute to develop trust between all those involved in an RCT and generalize confidence in the RCT ecosystem.	- - Working in partnership with people and communities - - Collaboration among organizations - - Transparency
Appropriateness for their context	Ensuring that a trial is set up to be practicable and produce reliable, actionable results.	- - Setting and context - - Use of existing resources
Efficiency and management	Competent decision-making and coordinated execution based on good governance and good trial quality management	- Competent advice and decision-making - Protecting trial integrity - Planning for success and focusing on issues that matter - Monitoring, auditing and inspection of study quality

3 Landmark large simple RCTs of drugs and interventions

RCTs can be simplified by establishing easier processes for collecting information, using short case report forms and linking with data that are acquired routinely as part of the delivery of healthcare (including national databases, claims data, and disease-specific registries).([17],[18],[19],[20],[21],[22],[23],[24]) The feasibility of this approach has been demonstrated for large RCTs of drugs and medical devices([11],[25]) such as the RECOVERY trial in the United Kingdom[26] and the TASTE trial in Sweden.([10],[25])

3.1 The RECOVERY trial

During the COVID-19 pandemic there was an urgent need for reliable evidence about interventions to treat the effects of the SARS-CoV-2 virus, but little capacity within front-line hospitals to deliver research, so the 'Randomised Evaluation of COVID-19 Therapy' (RECOVERY) trial was initiated in March 2020 as a platform trial. It continues to assess the effects of potential therapies on all-cause mortality in patients hospitalized with COVID-19.

The trial was conceived as a large simple trial drawing heavily on the example of the second International Studies of Infarct Survival (ISIS-2) conducted in the 1980s.[27] A key factor in the success of ISIS-2 was the recognition that by keeping the workload associated with enrolling participants into the study to an absolute minimum, it was possible to embed the trial in the everyday work of busy hospitals where most heart attack patients are treated.

Using a similar approach, all aspects of the RECOVERY trial were streamlined by design (see Table 2 for an overview of its key design features).[28] Simple eligibility criteria include hospitalization with proven or suspected COVID-19, with the local investigator being allowed to assess suitability for each of the trial treatments according to local guidelines. The trial was open-label to enable rapid implementation, and it used a combination of parallel-group, sequential and factorial randomizations to assess potential therapies in an adaptive design. The primary outcome was all-cause mortality at 28 days, with secondary outcomes including the duration of hospital stay, and a composite end-point of death or need for invasive mechanical ventilation or extracorporeal membrane oxygenation among patients not on invasive mechanical ventilation at baseline. During maximum recruitment, 185 hospital sites across the UK were taking part, and since February 2021 non-UK sites have been included across seven countries.[29] By April 2023, over 48,000 participants had been randomized to one or more comparison and the trial had already delivered 13 practice-changing results (see https://www.recoverytrial.net/).

Table 2. Features of large simple randomized trials compared with more conventional designs

Features	Conventional design	RECOVERY	TASTE
Design	Sophisticated and controlled. Limited use of alternative strategies	Platform-based factorial design enabled multiple treatments to be assessed rapidly	Use of on an ongoing registry (SCAAR) for

Features	Conventional design	RECOVERY	TASTE
	(such as factorial and/or adaptive designs)		allowing a streamlined conduct of the study
Consent	Long and complex consent form, excessive training requirements for site staff	Short 3-page information leaflet, 20-minute self-directed training for site staff, a doctor independent of the study team could serve as the legal representative for patients unable to provide consent	Information provided by the treating physician at the time of primary percutaneous coronary intervention. Verbal consent accepted in the acute phase before the intervention. Simplified informed consent provided to the patient.
Eligibility criteria	Complex criteria requiring laboratory or other results and extensive exclusion criteria	Simple criteria that can be determined easily by the treating clinician	Simple criteria that can be determined easily by the treating clinician using the information collected routinely in the registry
Baseline assessments	Complex assessments including collection of biological samples, clinical measurements or disease severity scales	Minimal data collection by site staff (e.g. demographic characteristics, ventilation status, other COVID-19 therapies and major co-morbidities) supplemented by linkage to healthcare systems data	No extra activities for collecting baseline information. All information already collected in the registry.
Outcome data collection	Long follow-up eCRF, detailed data collection, adjudication of outcomes	Minimal data collection by site staff supplemented by linkage to healthcare systems data, no outcome adjudication	No extra activities for outcome collection. All events obtained using national registries.
Monitoring	Excessive source data verification	24-hour telephone support for site staff, central monitoring of recruitment and randomization balance, independent ascertainment of study	No monitoring and/or outcome adjudication.

Features	Conventional design	RECOVERY	TASTE
		outcomes by linkage to healthcare systems data, independent Data Monitoring Committee to make recommendations based on unblinded analyses of safety and efficacy data	
Long-term follow-up	Rarely possible	Low-cost long-term follow-up through linkage with healthcare systems data	Low-cost long-term follow-up through linkage with healthcare systems data

Data collection by local site staff was minimal. A one-page electronic Case Report Form (eCRF) is completed at randomization, and again at the earliest of 28 days later, hospital discharge, or death. In the UK, data collected by local sites are supplemented from National Health Service (NHS) datasets and national registries, using the NHS number which uniquely identifies each participant. The linkage of RECOVERY participants to more than 40 national datasets (predominantly coded data collected for health service planning and reimbursement and National Registries) aimed to:

1. Ensure complete follow-up information for the main trial outcomes, even when participants are transferred for care between hospitals,
2. Provide additional baseline characteristics (e.g. ethnicity), reducing on-site data collection,
3. Enable long-term follow-up of participants beyond 28 days,
4. Avoid the need for source data verification, by providing an independent source of information for the primary outcome, and
5. Allow assessment of additional outcomes not captured by the follow-up eCRF.

3.2 The TASTE trial

The 'Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies' (SWEDEHEART), which was launched in 2009, collects data consecutively on all patients with different cardiac conditions (such as acute or chronic coronary syndromes, heart valve disease, or cardiac rehabilitation) who require specialist medical management or interventional or surgical therapies.[30]

Patients are informed about their proposed inclusion in SWEDEHEART when they present to a cardiology service, and they are registered using their personal identification number (PIN), a unique 12-digit number that each Swedish inhabitant receives at birth or on immigration into Sweden, for taxation purposes. Written and verbal information is given but no specific informed consent is requested at the time of initial registration in SWEDEHEART, and patients can deny consent for registration as well as opt out at any time during follow-up. All information collected by caregivers is transferred directly to a central server located at the Uppsala Clinical Research Center. The PIN is used to collect follow-up data by merging SWEDEHEART with other national health care registries (for hospitalization, cause of death, etc.). SWEDEHEART is connected to the Swedish National Population Registry for obtaining information on vital status.

The limitations of using observational data for inferring causality have generated concerns and skepticism about the reliability of (adjusted) observational findings using data collected in the registry.([31],[32]) In an exceptional case related to the early evidence of outcomes from first-generation drug-eluting coronary stents, excessive reactions to adjusted observational findings from the registry significantly impacted routine clinical practice.[33] Initial concerns were not confirmed by long-term results from RCTs. The feasibility and value of using the web infrastructure of SWEDEHEART to overcome the limitations of observational data, by randomizing patients to different treatment strategies or interventions, was explored in the 'Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia' (TASTE) trial, which was the first (medical device) registry-based randomized clinical trial or 'R-RCT'.([25],[34])

TASTE compared the routine manual aspiration of intracoronary thrombus before percutaneous coronary intervention (PCI) *versus* standard PCI without thrombus aspiration in patients with acute myocardial infarction undergoing primary PCI.[35] Thus it investigated high-risk medical devices (all CE-marked manual aspiration catheters) used as part of a therapeutic strategy. The design of TASTE was kept very simple [35] by employing a minimal set of exclusion criteria, and by obtaining the primary endpoint of all-cause mortality by direct linkage with the Swedish Population Registry. A minimal administrative burden was imposed on investigators by using clinical and follow-up information that was already collected in the registry and by avoiding separate monitoring and adjudication of adverse events (see Table 2).

Pre-procedural data were registered as patients entered the PCI lab. The system helped investigators to check inclusion and exclusion criteria and then randomized eligible patients within a few seconds. In this acute clinical setting, randomizing patients directly at the time of the procedure was a necessary pre-requisite for the trial to be conducted successfully.

All hospitals performing PCI in Sweden, with one centre in Denmark and one in Iceland, contributed to the screening and randomization of 7,244 patients within less than three years. Routine thrombus aspiration had no impact on mortality at 30 days or at one year ([25],[36]), so the findings led to substantial de-implementation of thrombus aspiration in Sweden (Figure 1), even before a class III recommendation for its routine use during primary PCI was issued in European guidelines.[10]

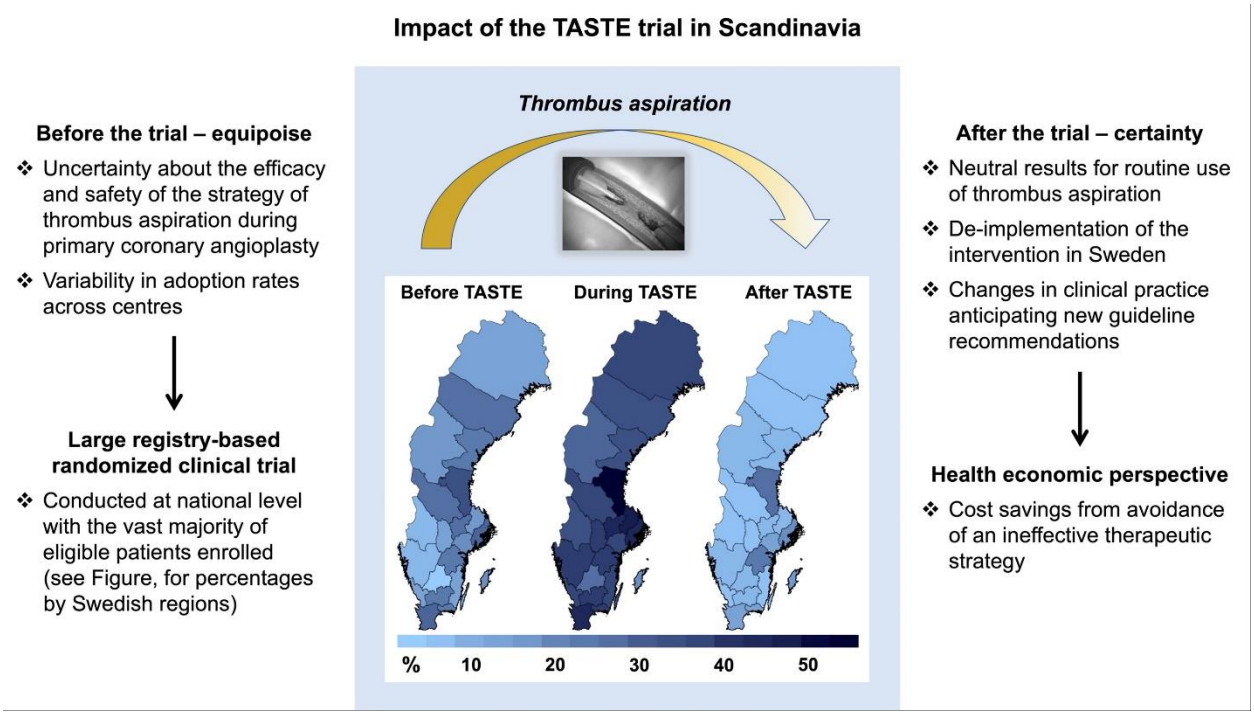

Figure 1. Illustration of the major impact that was achieved by the first registry-based randomized controlled trial (the TASTE study)[8]

4 Principles of large simple RCTs

The paradigm of using RCTs to assess the causal effect of an intervention on outcomes, and of using registries only later for post-market clinical follow-up, has now substantially shifted.[31] RCTs of drugs in acute emergency settings such as the ISIS-2 and RECOVERY trials have similarities with trials of therapeutic devices such as TASTE. Firstly, they are most likely to be successful in recruiting large numbers of participants if they are fully embedded in usual clinical care pathways, for which a streamlined approach to all aspects of trial design is essential. Secondly, in contrast to long-term drug trials in chronic conditions, they are less reliant on long-term engagement with participants themselves. Instead, high levels of adherence require effective engagement with healthcare professionals within the care pathway, and long-term capture of the occurrence (or, more challenging, the lack of occurrence) of relevant outcomes – which makes such trials suitable for remote, decentralized re-use of healthcare systems data.

4.1 A common definition of a large simple trial

Many different terms have been proposed to describe study designs and methodologies that share the key features of randomization, simplicity (leading to large sample sizes), and efficient management and data collection (achieved by exploiting existing electronic platforms and databases, see Figure 2). The single umbrella term "large simple trial" covers all these options, including platform trials (such as RECOVERY), registry trials (such as TASTE), and nested trials. The conceptual foundation of a large simple RCT is to make and keep its design and conduct as streamlined as possible. [37] It should be inclusive and affordable, and able to provide results that are widely generalizable to real-life clinical practice.([38],[39],[40])

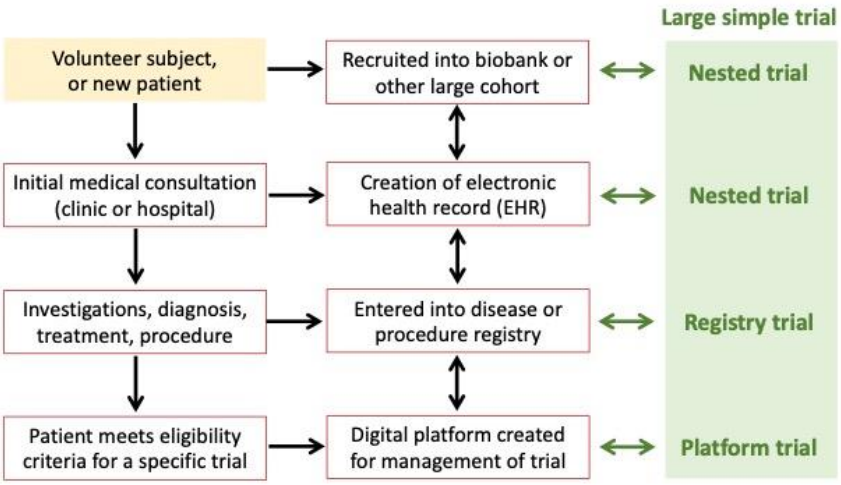

Figure 2. Variants of large simple trials

Legend: Whether a subject is a volunteer or a patient, and however he or she qualifies for a clinical study or trial, and irrespective of the electronic record or computerised database that is employed as the framework for a large clinical trial, then its essential principles are shared. Some of the most common terminologies that are used are shown in the right column.

The scope and definition of large simple RCTs overlap those of "pragmatic" RCTs, so that additional term may be redundant. Ideally, all clinical trials and certainly all large simple trials should be generalizable to standard clinical practice. Simplifying their designs makes it possible to conduct them in normal care settings.

4.2 Conduct of large simple trials

Data collected as part of routine healthcare delivery have been re-used successfully in registry trials, but few studies have employed this method in other settings. Barriers to the use of healthcare systems data for collecting outcomes in trials include:

- failure to collect sufficient consent to cover data linkage activities,
- lack of expertise within clinical trial teams for data engineering,
- challenges related to information governance (including reluctance to release participants' identifiers to the coordinating centre or sponsor, to allow linkage with national datasets),
- concerns from funders and healthcare regulators about the completeness and accuracy of outcomes ascertainment,
- lack of national healthcare datasets collated by organizations with mechanisms to undertake data linkage. Existing or possible cross-border collaborations (such as the European Health Data & Evidence Network, and the European Health Data Space) should ensure that linkage of healthcare data with national and international trial cohorts is prioritized.

Rather than any specific novel aspect of their streamlined design, the efficiency, quality, and chances of final success of any large simple trial are enhanced by applying general principles that guide the design and conduct of all RCTs. These include randomized allocation to an intervention without foreknowledge of the assigned treatment, adherence to the randomized intervention, complete follow-up, and unbiased collection and analysis of outcome data.

Large simple RCTs attempt to minimize unduly restrictive exclusion criteria, which simplifies, increases and speeds up enrolment [41]. By reducing the possibility of random errors, larger cohorts of patients provide more precise estimates of the treatment effect of an intervention (its internal validity). Broad inclusion criteria help to ensure that the risk profile of patients included in large simple RCTs will be similar to that expected in routine practice (providing external validity).[42] In comparison, RCTs that have been conducted only in well-defined and restricted cohorts of patients may lack sufficient power to provide compelling evidence on important clinical outcomes. There have been many prominent instances when the results of observational studies and smaller RCTs have deviated substantially from the findings of large RCTs (see Table 3).

Table 3. Examples of divergent outcomes observed in non-randomized and randomized cardiovascular studies

Type of device	Observational study	Smaller RCT	Larger RCT
First-generation drug-eluting stents versus bare metal stents	PMID: 17296822 Year: 2007	PMID: 12050336 Year: 2002	PMID: 14724301 Year: 2004
	- Propensity-score adjusted analysis (n=19,771) - Higher risk of death with DES versus BMS	- 1:1 randomization (n=238) - No in-stent restenosis with DES - No episodes of stent thrombosis - No differences in mortality	- 1:1 randomization (n=1,314) - Marked reduction in restenosis and repeat revascularization with DES - - No differences in mortality
Absorb Bioresorbable Vascular Scaffold versus everolimus-eluting metallic stent	PMID: 26875648 Year: 2016	PMID: 27806897 (ABSORB II) Year: 2016	PMID: 26457558 (ABSORB III) PMID: 30266412 (ABSORB IV) PMID: 31553222 (ABSORB III-LTFU) PMID: 37207924 (ABSORB IV-LTFU) Year: 2015 to 2023
	- Propensity-score matched (n=905 paired matches) - No differences in clinical outcomes	- 2:1 randomization (n=501) - No difference in vasoreactivity, and higher late luminal loss, with Absorb - Higher rate of TV-MI with Absorb	ABSORB III: - 2:1 randomization (n=2,008) - noninferiority of BVS versus EES for TLF met at 1 year - higher rates of TLF, TV-MI and scaffold thrombosis through 5 years ABSORB IV: - 1:1 randomization (n=2,604) - noninferiority of BVS versus EES for TLF met at 30 days and 1 year - - higher rates of TLF through 5 years
Manual thrombus aspiration versus standard PCI	PMID: 20550973 Year: 2010	PMID: 18256391 (TAPAS) PMID: 18539223 (TAPAS-FU) Year: 2008	PMID: 23991656 (TASTE) PMID: 25853743 (TOTAL) PMID: 25176395 (TASTE-FU) PMID: 26474811 (TOTAL-FU) Year: 2013 to 2016
	- Multivariable adjustment (n=22,632) - Increased risk of death with thrombus	- 1:1 randomization (n=1,071) - Better reperfusion and clinical outcomes with thrombus aspiration	TASTE: - 1:1 randomization (n=7,244) - No differences in mortality at 30 days and 1 year TOTAL:

Type of device	Observational study	Smaller RCT	Larger RCT
	aspiration (RR, 1.16, 95% CI 1.05 to 1.28)	- Reduced risk of cardiac death with thrombus aspiration	- 1:1 randomization (n=10,732) - No differences in the composite outcome of cardiovascular adverse events at 30 days and 1 year - Increased risk of stroke with thrombus aspiration
Intra-aortic balloon pump versus standard of care in patients with cardiogenic shock and AMI	PMID: 11376306 Year: 2001	PMID: 19770739 Year: 2010	PMID: 22920912 Year: 2012
	- Multivariable model in a large disease registry (n=23,180) - IABP in combination with thrombolytic therapy associated with reduced mortality	IABP-SHOCK: - 1:1 randomization (n=45) - No statistically significant effects on reduction of severity of disease, improvement of cardiac index, reduction of inflammatory state, or reduction of BNP biomarker	IABP-SHOCK II: - 1:1 randomization (n=600) - No differences in mortality at 30 days and 1 year
Embolic protection device during TAVI	PMID: 32972578 Year: 2020	PMID: 27815101 Year: 2017	PMID: 36121045 Year: 2022
	- Propensity-score matched (n=1,575 paired matches) - Use of embolic protection devices associated with a lower incidence of ischemic stroke and in-hospital mortality	- 1:1:1 randomization (n=363) - Embolic protection did not change neurocognitive function - No difference in new lesion volume on MRI	PROTECTED-TAVR: - 1:1 randomization (n=3,000) - No differences in stroke within 72 hours after TAVR

Small, focused trials can generate initial insights into the impact of an intervention on surrogate markers of efficacy or safety, and they may help to refine a hypothesis and inform the design of a subsequent large RCT. Studies of medical devices during their early development should ensure that evidence is collected concerning the stability of the design, protocols for implantation and use, variability in operator practice, and operator learning curves. Then, the appropriate type of RCT depends mainly on the stage of development of the drug or medical device. Initially, it is advisable to assess the value of a new intervention in small-sized, highly-controlled studies. If the safety and efficacy profile of a new

intervention or therapy is promising, then larger confirmatory RCTs should be used to established evidence for policy recommendations regarding its implementation. Large simple RCTs will be most efficient when the intervention is widely available and can be delivered to a large number of patients in a short time. That could be before regulatory approval of a new product entering an existing market, or for definitive evidence in a pivotal trial conducted as part of post-market clinical follow-up.

5 Large simple RCTs of medical devices: feasibility and challenges

The use of national quality registries has been instrumental in informing, standardizing, and improving the quality of cardiovascular care in Sweden, by reporting periodically on key quality measures across different hospitals and regions.([43],[44]) The SWEDEHEART registry has been much used for epidemiological research([33],[34],[35]) and as a unique source for clinical research.[36] In addition, experience has confirmed that national registries can be used successfully as a platform for screening, randomization, and follow-up of patients treated with high-risk medical devices.[25] As demonstrated in TASTE, registry-based RCTs embedded within an ongoing device or disease registry have been able to enroll large numbers of patients in a relatively short amount of time.([22],[34]) The streamlined design of TASTE was possible because it designated a relevant, unbiased and important clinical outcome as the primary endpoint (i.e., all-cause mortality). Moreover, no additional data beyond those routinely collected in the registry were captured. Finally, enthusiasm in the interventional community for the use of thrombus aspiration was counterbalanced by large remaining doubts about its efficacy, which resulted in substantial equipoise during the trial.

There are situations where more detailed information about baseline characteristics and technical details of the index procedure can be important and relevant, and sometimes more information has to be collected about adverse events during follow-up, to define a more granular composite primary endpoint. These issues have led to technical refinements of the infrastructure supporting the conduct of R-RCTs. The registry provides a direct link to a computerized R-RCT framework which is a web application developed by the Uppsala Clinical Research center. It provides a randomization module and a unique link between the patient's registry file and the trial electronic data capture system (EDC). The EDC can collect additional baeline, procedural and outcomes data from other sources or by direct data entry. Also, active monitoring and central adjudication of adverse events have been implemented in contemporary R-RCTs in Sweden. These iterations have not affected the conceptual framework of streamlining the conduct of large trials that remains central to the design of R-RCTs, but they have broadened the landscape of the types and nature of R-RCTs of medical devices that can be successfully conducted (see Table 4).

1

Table 4. Completed and ongoing R-RCTs of high-risk medical devices in Sweden

R-RCT name	Device investigated	Number of patients	Registry used for screening/ randomization	Primary endpoint	Type of monitoring/ adjudication	Funding for the trial	Status of completion
TASTE	Thrombus aspiration catheters	7,244	SWEDEHEART – SCAAR	All-cause death	None	- Swedish Heart Lung Foundation - Terumo Medical and Medtronic	Completed
iFR-SWEDEHEART	Pressure wire and software for coronary functional assessment	2,037	SWEDEHEART – SCAAR	Composite of all-cause death, non-fatal MI, and unplanned revascularization	Clinical event committee for non-fatal MI and unplanned revascularization	- - Volcano Corporation	Completed
SWEDEPAD	Drug-eluting technology (stents, balloons) in PAD	~2,500	Swedish Vascular Registry (SWEDVASC)	- Amputation rate in patients with critical limb ischaemia - - Health- related quality of life in patients with claudication	No adjudication DSMB in the trial.	- Swedish Research Council, Swedish Heart–Lung Foundation, and Region Västra Götaland - All companies selling drug-coated balloons and drug-coated stents	Ongoing (interim analysis on mortality published)
HipSTHeR	Arthroplasty implants	1,440	Swedish Fracture Registry	Composite all-cause death and re-operation	None	Swedish Research Council, Swedish Society of Medicine, Deltofs foundation, The Geriatric fund, Uppsala-Örebro Research Council, ALF funding	Ongoing

R-RCT name	Device investigated	Number of patients	Registry used for screening/ randomization	Primary endpoint	Type of monitoring/ adjudication	Funding for the trial	Status of completion
DUALITY	Dual mobility cups	1,600	Swedish Fracture Registry	Any dislocation of the index joint treated with closed or open reduction within 1 year after surgery	None	Research grant from the Swedish Research Council	Ongoing
INFINITY	Drug-eluting stents	2,400	SWEDEHEART – SCAAR	Composite of cardiovascular death, target vessel myocardial infarction, and ischemia-driven target lesion revascularization	Clinical event committee DSMB	Unrestricted research grant from Elixir Medical Corporation	Ongoing

2

5.1 Challenges for large simple RCTs of medical devices

The quality of all RCTs depends on avoiding bias [45] when allocating subjects to one of the investigational arms, when ascertaining, processing and analysing outcomes, and when ensuring adherence to the allocated intervention (minimising cross-over), along with obtaining complete follow-up data.[46] In RCTs of medical devices, randomization just before a procedure may help to reduce any risk of cross-overs or non-adherence to the assigned treatment. Bias may arise if patients or investigators are aware of the randomized assignment [45], which can occur if there are major differences between arms in the nature or intensity of how outcomes are ascertained. This is much less likely with hard clinical outcomes than those that are more subjective, but even a hard outcome such as all-cause mortality can be biased if there are differences in completeness of follow-up between the intervention and control arms. Follow-up through linkage with healthcare systems data can help to ensure complete ascertainment of outcomes, independently of any affect which knowledge of the treatment allocation might have on participant engagement with the trial.

5.2 Blinding using sham procedures

Double-blinding of both patients and investigators is the ideal approach to remove potential sources of bias arising from knowledge of the assigned treatment in RCTs.[35][47] It is usually easy in pharmacological trials, but often problematic in RCTs of non-pharmacological interventions.[48] Blinding of patients can be ensured by performing a sham procedure that mimics the active intervention in all aspects including the route of surgical access, the duration of the procedure, and any post-procedural diagnostic assessments ([49],[50]), but for obvious reasons operators cannot be blinded. To minimize biases, their roles should be limited in later RCT activities such as contacts with patients and the recording of outcomes. Examples of proper blinding using sham procedures in RCTs of cardiovascular interventions have been reported.[51]

It is not easy to implement blinding via sham procedures, however, either in large simple RCTs of high-risk medical devices or for other interventions. A sham procedure imposes extra costs and time, and it deviates from standard clinical practice. In head-to-head comparisons of different devices that are implanted using the same procedure (for example, comparing different drug-eluting stents during PCI), single-blinding of patients can be sufficient to reduce bias. Before the procedure and randomization, it should be stressed to the patient that he or she will not receive any information on the type of device that will be implanted, and afterwards blinding of patients can be maintained by training and instructing research staff and by avoiding any specific entry into the clinical records of the type of device that has been used. Sometimes information obtained by medical imaging or the nature of scars can be revealing.

Internationally accepted ethical principles for guiding the use of placebos in RCTs are presented below (Table 5).[52][53]

Table 5. International ethical guidance for the use of placebos in RCTs

Declaration of Helsinki [52]	
Principle n. 33	Statement
	The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
International Ethical Guidelines for Health-related Research Involving Humans - Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) [53]	
Guideline 5	Statement
	Placebo may be used as a comparator when there is no established effective intervention for the condition under study, or when placebo is added on to an established effective intervention. When there is an established effective intervention, placebo may be used as a comparator without providing the established effective intervention to participants only if: - there are compelling scientific reasons for using placebo; and - delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.

Overall, the concepts applied to a placebo in pharmacological trials can be generalized to sham procedures in RCTs of high-risk medical devices. Placebo or sham interventions that mimic the use of a device may be justified when there is equipoise, as long as the sham procedure is designed with minimum risk to individual patients who consent to the trial.[54] [54] Possible harms for future patients may be avoided if a procedure is abandoned because it has been shown to be ineffective compared with a sham

intervention, but that does not justify significant risk to the individual subject in a trial. An example of ethical practice would be RCTs of renal denervation for treating arterial hypertension, when the sham procedures were identical to the therapeutic renal denervation procedure in all aspects (e.g., preparation, puncture of the groin, catheter insertion, renal artery angiography, placement of the denervation catheter in the renal arteries), except for the final step of delivering energy to ablate the sympathetic nerves. [55][55]

Patients must be thoroughly informed about the possibility of not receiving the therapeutic intervention while still being exposed to the procedure's risks. Risks should be minimized by applying a careful benefit-risk analysis to guide the selection of patients for possible inclusion in RCTs using sham procedures. To justify any (small) additional risks to which control patients may be exposed, RCTs using sham procedures must be designed to yield reliable and conclusive results regarding the safety and efficacy of the device under investigation. Adaptive RCTs are particularly valuable in this context, allowing for re-estimation of sample size to maintain statistical power, or enabling early termination of the study for futility or efficacy. After primary endpoint data have been collected, patients who underwent a sham procedure should be offered the opportunity to cross over to the active treatment if the study results indicate favorable efficacy and safety for the therapeutic intervention.

Not accounting for a placebo effect in RCTs may exaggerate the relative efficacy of an intervention and, as a consequence, promote the use of interventions that are not truly beneficial. The ethical conundrum of sham-controlled RCTs is that of balancing the need for scientific validity of RCT findings versus the potential risks to which patients are exposed. [56][56]

Effective procedures to ensure single-blinding were implemented successfully in the INFINITY-SWEDEHEART registry based randomized trial (NCT 04562805). Blinding of investigators is less relevant in the context of R-RCTs using electronic health records, since follow-up data and information on adverse events are obtained via automated systems that are substantially independent of the inputs of individual investigators.

5.3 Operator experience and selective inclusion of centres

The technical skills of surgeons and other operators can be improved and refined through performing more interventions.([57],[58]) Learning curves for complex or new procedures are demonstrated when progressive improvements in efficacy and safety reach a plateau.[59] Ignoring the experience of individual operators during RCTs of medical devices may lead to inaccurate estimates of the outcomes of an intervention. Ideally, a device implanted via a complex procedure should be tested in an RCT once the technical proficiency of all operators in the study has reached the plateau phase. Investigations to understand and define learning curves should be encouraged, and virtual simulation of complex procedures may help in developing technical standards for operators who will participate in RCTs.([60],[61])

Large simple RCTs of medical devices should be conducted once their implantation techniques have matured and been standardized. Otherwise, starting a large RCT for a new and complex procedure could expose patients to unnecessary risks and could produce an unreliable assessment of the value of a new technology if compared to existing interventions with which the operators are familiar. The particular value and optimal role of large simple RCTs of medical devices, therefore, can be to investigate iterations of existing medical devices or to assess new devices that are delivered or implanted through established procedures (for example, comparing drug-eluting stents that are implanted using standard techniques).

In conventional industry-funded RCTs of medical devices, the intervention is generally delivered in a highly controlled setting in high-volume centres. Outcomes of a complex intervention using medical devices may be very different in specialized centres as compared to routine clinical care. By expanding the number of centres participating in a study, large simple RCTs mitigate the risk of overinterpreting the (proportional) effect of an intervention before it is transferred to standard clinical practice.

5.4 Willingness to randomize and be randomized

RCTs can be performed ethically when there is genuine uncertainty about the preferred treatment of a specific disease – namely a state of equipoise ([62],[63],[64]) – but strong beliefs among investigators about the value of an unproven intervention (novelty bias) may lead to the selective and unrepresentative inclusion of patients, for example from lower-risk categories.[65] Even worse, strong prior beliefs may make randomization impossible if no patients are screened for inclusion. This aspect is particularly important for RCTs of medical devices if there is eager anticipation about the value of an active intervention, leading to reluctance to enrol subjects or for patients to consent if the comparator arm involves no device implantation. For these reasons, it is crucial to share detailed information about the existing gaps in evidence that lie behind the need to conduct an RCT, with both investigators and eligible patients.

Where there is a perceived high risk of investigator bias, leading to a biased presentation of the evidence to patients, they should be protected from this by training investigators to present the facts in a neutral way [66] during the informed consent process, or by substituting them with trained nurses or computer decision-support programmes.[67]

6 Costs and funding of trials

Trials have substantial costs [68] and performing conventional RCTs has become prohibitively expensive. Data collection using existing platforms offers potential advantages in terms of cost, efficiency, and completeness, and critically it is not dependent on action from participants or site staff and therefore it is relatively unaffected by knowledge of the treatment allocation in open-label studies. Cost reduction has been substantial in RECOVERY; based on a final expenditure of £20 million for the trial (plus the cost of the drugs), it has been calculated that the cost per patient/per answer was less than £40 (about €45).

Despite TASTE being relatively inexpensive (entailing only the standard costs of maintaining the registry), its findings were consistent with the results of a conventional and significantly more expensive industry-funded RCT investigating the same research question.[69]

High costs are a particular disincentive for creating essential evidence for medical devices, since substantial investment is required for their development and testing as well as for accessing the market.[70] In Europe once a medical device has obtained the Conformité Européenne (CE) mark, there are limited incentives to raise the level of supporting evidence by demonstrating incremental benefit from a new device in a large pivotal RCT. Fear of negative results, alongside the need for more investment, can make it impossible or uninteresting for companies to strive for better clinical evidence.

The possibility of conducting large simple RCTs of high-risk medical devices should become less dependent on, but not uncoupled from, industry funding. Ideally, the infrastructure of registries required to evaluate medical devices should be paid for and maintained by public institutions or government, while research foundations and manufacturers should support individual trials. Regulatory incentives for conducting large RCTs would be crucial, and rigorous health economic assessments would be valuable. Demand from the medical community for reliable data from large RCTs could serve as a powerful incentive for conducting this type of studies.

In Sweden, many R-RCTs have been financed successfully by industry-independent research grants and public funding[25], while the costs of maintaining the national quality registries used in R-RCTs are met by the Swedish public health care providers and the government.[30] Economic support by industry partners has been also used in Swedish R-RCTs of medical devices, for example by the free donation of devices and through institutional research grants.

7 Summary and conclusions

More efficient methods of generating reliable clinical data on the safety and performance of drugs and high-risk medical devices are necessary. Adequate clinical evidence is crucial for supporting regulatory decisions and for ensuring that market approval is awarded to medical devices that provide benefits to patients. Whenever possible, and according to the stage of development of a medical device, the conduct of RCTs should be more strongly supported and in some cases required by regulatory guidance. Large simple RCTs can provide robust answers about the performance and safety of medical devices, so they should be encouraged whenever feasible.

Key points/Highlights

(a) Large simple RCTs of drugs and high-risk medical devices are feasible and may be streamlined using modern IT infrastructure and technology;
(b) RCTs need to be adequately large in order to get reliable answers to their clinical questions;
(c) RCTs need to be efficient by minimising additional work for patients and doctors in order to ensure that adequate numbers (and ideally, diversity) of patients are enrolled;
(d) RCTs need to focus information on important clinical outcomes; and
(e) use of registries, platform or other methods can help achieve these goals.

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