

A Guide to Implementation Science for Phase 3 Clinical Trialists: Designing Trials for Evidence Uptake

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Highlights

- Cardiovascular disease remains inadequately treated, highlighting the need for greater attention to implementation science.
- Trialists and clinicians could harness key principles of implementation science to foster better end-of-trial uptake.
- Phase 3 trials could use less restrictive eligibility criteria, engage broad stakeholders in trial design, use existing health care systems to execute the trial, evaluate barriers and facilitators to implementation, and improve workflow processes within the trial.
- When trial results are positive, trial sites could be engaged in early implementation research and deployment of the intervention.

Abstract

The delayed and modest uptake of evidence-based treatments following cardiovascular clinical trials highlights the need for greater attention to implementation early in the development and testing of treatments. However, implementation science is not well understood and is often an afterthought following phase 3 trials. In this review, we describe the goals, frameworks, and methods of implementation science, along with common

multilevel barriers and facilitators of implementation. We propose that some of the approaches used for implementation well after a trial has ended can be incorporated into the design of phase 3 trials to foster early post-trial implementation. Approaches include, but are not limited to, engaging broad stakeholders including patients, clinicians, and decision-makers in trial advisory boards; using less restrictive eligibility criteria that ensure both internal validity and generalizability; having trial protocols reviewed by regulators; integrating trial execution with the health care system; evaluating and addressing barriers and facilitators to deployment of the intervention; and undertaking cost-effectiveness and cost utility analyses across jurisdictions. We provide case examples to highlight concepts and to guide end-of-trial implementation.

Key Words: clinical trials; conceptual frameworks; de-implementation; implementation science; trial design

Abbreviations and Acronyms

CVCT - Cardiovascular Clinical Trialists

HF - heart failure

RCT - randomized controlled trial

STEMI - ST-segment elevation myocardial infarction

Knowledge generation has far exceeded knowledge translation in cardiovascular sciences,¹ with suboptimal uptake of evidence-based and guideline-recommended interventions. For example, <10% of patients with heart failure with reduced ejection fraction receive target doses of guideline-directed medical treatments that can prolong their lifespan.^{2, 3, 4} Similarly, only about 20% of adults at high- and very-high cardiovascular risk achieve guideline-recommended low-density lipoprotein cholesterol goals to prevent adverse cardiovascular events.^{5, 6} Across cardiovascular conditions and geographic jurisdictions, implementation gaps are wider among women, ethnic minorities, and those in socioeconomically deprived regions.^{7, 8, 9, 10}

Barriers to the implementation of evidence-based treatments are often multilevel, related to the health care system (eg, health care economics, drug reimbursement, infrastructure), clinician (eg, knowledge gaps, clinical inertia, change fatigue, biases, uncertainty about the generalizability of trial evidence), patient (eg, low awareness, socioeconomic barriers, side effects, preference), or intervention itself (eg, access, cost, complexity, or mode of delivery).^{3, 11} Phase 3 trials themselves could serve as barriers to implementation.¹² Phase 3 trials, designed to optimize estimates of efficacy and safety, are often highly restrictive and delivered in silos outside of the health care system.¹³ Trials do not consider known barriers and facilitators of implementation in their design, missing the opportunity to expedite the translation of evidence to clinical care.

Implementation science evaluates strategies that systematically translate research evidence into clinical practice.¹⁴ It offers an organized way to foster the uptake of evidence-based treatments.^{15, 16} Principles of implementation science could be applied to the design of phase 3 trials to pave the way for end-of-trial implementation. The infrastructure and resources of

phase 3 trials could be harnessed to generate evidence that meet the needs of multilevel stakeholders in health care systems.

This paper aims to discuss the principles of implementation science and how these principles can be adopted in the design of phase 3 cardiovascular clinical trials. It is partly based on discussions held in December 2023, at the 20th Global Cardiovascular Clinical Trialists (CVCT) forum, involving clinical trialists, implementation scientists, patients, and clinicians, as well as regulatory, government, and industry representatives.

Implementation Science Principles

Implementation science is the study of methods to promote the systematic uptake of evidence-based interventions or processes into routine practice, with the goal of improving the quality of care.¹⁴ In focusing not only on the patient but also on the clinician, organization, network or system, and policy, its scope is broader than traditional clinical research. Effective implementation research requires transdisciplinary collaboration among behavioral, health service, health economy, and clinical researchers, and effective engagement of decision-makers, front-line clinicians, and patients. Implementation research differs from efficacy research, both in focus and approach. Efficacy research examines the effect of a treatment in highly controlled environments on patient-level outcomes, with great emphasis on internal validity.^{17,18} Implementation research assesses strategies aimed at health care systems, organizations, clinicians, or patients to foster the uptake of effective treatments¹⁹; it operationalizes the evidence and focuses on treatment uptake, with study outcomes typically centered not only on individual outcomes but also on clinician or system-level processes.^{19,20} In implementation science, attention is (ideally) paid to acceptability, adoption, appropriateness, feasibility, fidelity, cost, penetration, sustainability, and health equity.^{16,20,21} Figure 1 provides an overview of the research approach in implementation science.

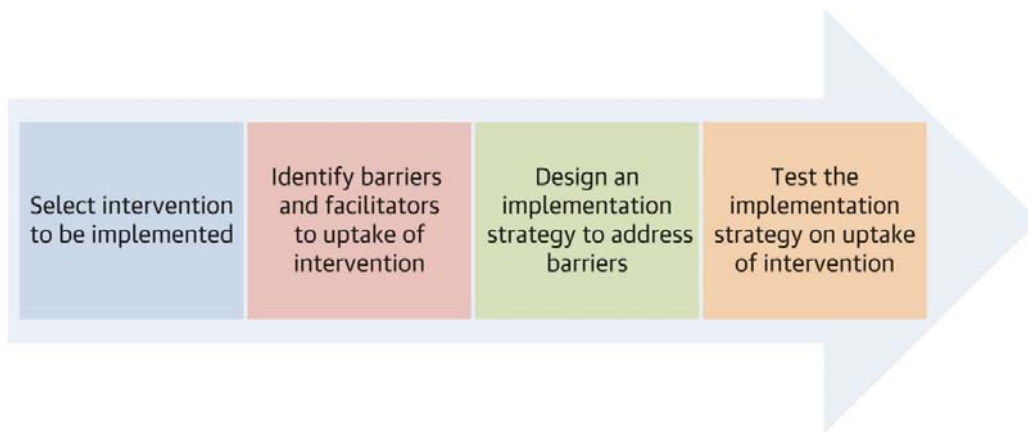


Figure 1. Research Approach in Implementation Science

A thoughtful implementation strategy should address barriers to the uptake of a desired intervention. The implementation strategy should then be tested to ensure effectiveness prior to scale-up and spread.

Implementation Strategies

Implementation strategies refer to the techniques used to enhance the adoption, delivery, and uptake of a treatment.²² Implementation strategies can be aimed at any of the stakeholders whose engagement is required for the deployment or uptake of a treatment.^{23,24} There are now well over 100 discrete implementation strategies with classification schemes (Figure 2),^{23, 24, 25} and many have been tested in randomized controlled trials (RCTs), with varying degrees of effectiveness.^{4,26, 27, 28}

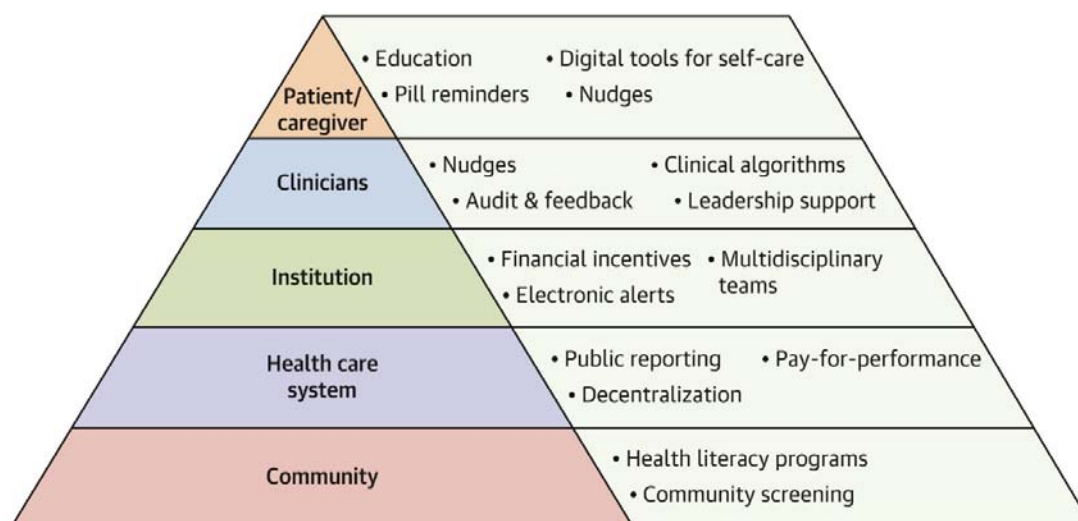


Figure 2. Examples of Implementation Strategies Aimed at Different Health Care Stakeholders

Implementation strategies can be aimed at any of the stakeholders whose engagement is required for the deployment or uptake of the treatment. A few of the implementation strategies shown in the figure have demonstrated utility in randomized controlled trials. These are examples, not an exhaustive list, and strategies may be targeted to more than one stakeholder. Based on Powell et al²³ and Waltz et al.²⁴

Implementation strategies work best when tailored to address specific regional or local barriers and facilitators.²⁹ Barriers and facilitators can be identified through prior research and by inviting input from relevant implementation partners, including patients, clinicians, payers, and administrators. Tailoring involves choosing implementation strategies to navigate barriers and leverage facilitators, and sometimes, adjusting strategies as needs change over time.^{23,29, 30, 31, 32} For example, a paper-based decision support tool for clinicians to increase the prescription of evidence-based therapies may be incorporated into electronic health records to integrate decision support at the point of care. There are some data to suggest that tailoring implementation strategies to context can improve the uptake of the intended intervention.³³ A meta-analysis of 15 studies found a 56% improvement in the uptake of clinical guideline recommendations when implementation strategies were tailored vs not tailored to context.³³ Figure 3 provides an example of tailoring implementation strategies for delivery of transitional care services involving home nurse visits and heart function clinic visits following hospitalization for heart failure in the PACT-HF (Patient-Centered Care Transitions in Heart Failure) stepped wedge cluster randomized trial.³⁴ Although this was a pragmatic

implementation trial, the same process of tailoring interventions can be adopted in phase 3 trials, particularly those testing invasive or device interventions.

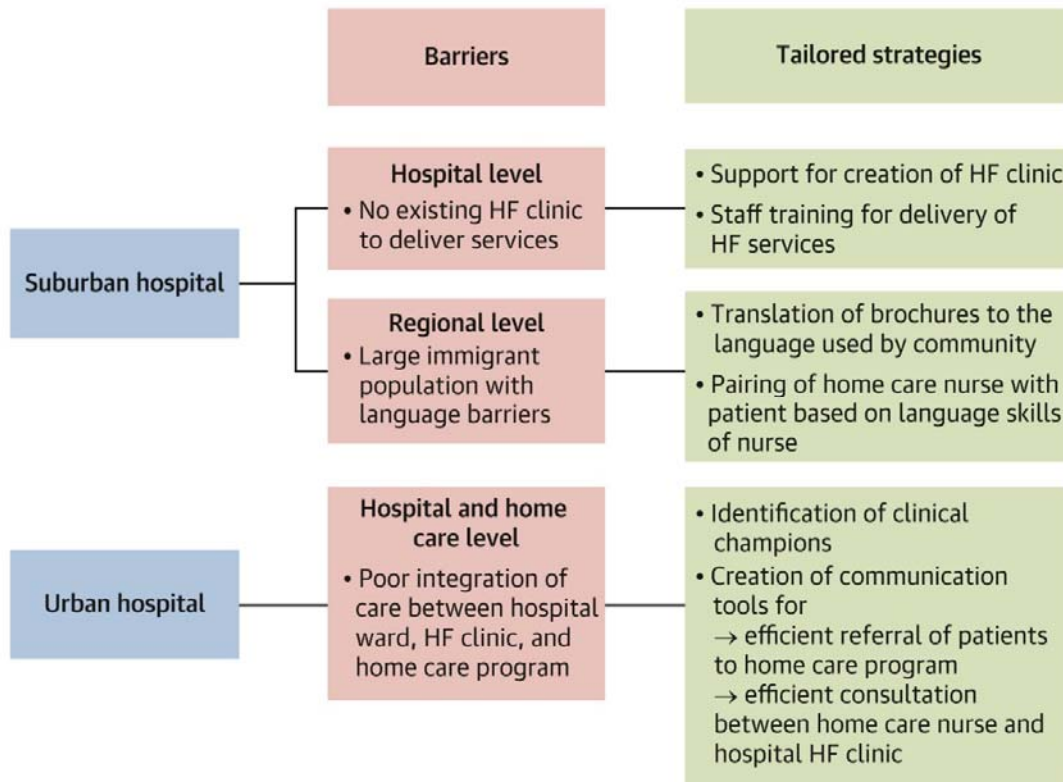


Figure 3. Implementation Strategies Tailored to Barriers Across Primary Care Settings for the Adoption of a Transitional Care Service in the PACT-HF Randomized Trial

In this example, the implementation of a transitional care service involving home nurse visits and heart function clinic visits following hospitalization for heart failure in the PACT-HF (Patient-Centered Care Transitions in Heart Failure) trial has been tailored to address barriers in a suburban vs an urban hospital. Based on Van Spall et al.³⁴ HF = heart failure.

Frameworks for implementation research

Conceptual frameworks provide structured ways to define an implementation question and to find appropriate answers or solutions. Several frameworks have been developed to guide implementation in research or clinical settings. The choice of framework depends on the implementation challenge and the level of focus (eg, individual, organization, system). Frameworks can be used to translate research evidence to health care delivery (process frameworks), to describe factors that influence implementation outcomes (determinant frameworks), or to assess implementation outcomes such as cost, feasibility, and acceptability (evaluation frameworks).^{12,22,35, 36, 37} Selection of a framework can be guided by tools such as the Theory Comparison and Selection Tool.³⁸

De-implementation Science

Some of the conceptual frameworks and strategies that guide implementation can also guide de-implementation, the systematic discontinuation of low-value health care practices.^{39,40} Not only does de-implementation discontinue ineffective practices, it simplifies care and allows for resources to shift to more effective strategies.^{39,40} Examples include reducing or discontinuing an ineffective or low-value practice such as inappropriate antimicrobial use for cardiac device implantation, or substituting a practice with another, more effective one such as changing practice from femoral to radial access for coronary angiography. Removing proven-ineffective drugs from hospital formularies and individual patient regimens minimizes low-value care, risk from drug-drug interactions, and burden of polypharmacy, allowing for evidence-based drugs to be introduced instead.

Implementation Research Methods

Implementation science can involve qualitative (in-depth interviews and focus groups), quantitative (observational, quasi-experimental, single-arm, and randomized clinical trial designs), and mixed (concurrent use of quantitative and qualitative) methods.¹⁸ Artificial Intelligence algorithms can be used to identify social acceptability of treatments and contextual reasons for implementation gaps, analyze data to identify gaps in implementation, suggest tailored approaches to organization or patient characteristics, and mobilize knowledge in culturally competent ways.^{41,42}

Process Evaluation in Implementation Research

An implementation strategy should not be deemed ineffective if fidelity to the strategy was poor. A process evaluation can assess whether the strategy was deployed, what was delivered, how it was delivered, and how many people received it^{43,44}; these measurements would reflect fidelity, the degree to which the intervention was implemented as intended.⁴⁴ Process evaluation also looks at the *mechanisms of impact* (ie, how and why the intervention led to changes in practice), and at *contextual factors* influencing implementation success. For example, a process evaluation may uncover the need to streamline the workflow associated with implementation. Process evaluation is essential when implementation requires complex coordination between groups for an aim to be achieved. For example, a strategy to shorten time from symptoms to reperfusion in ST-segment elevation myocardial infarction may involve electrocardiogram transmission and direct activation of regional cardiac catheterization laboratories by emergency medical services (EMS). However, a process evaluation should confirm uptake of or fidelity to this strategy before outcomes are attributed to it.

Adopting Principles of Implementation Science Into the Design of Phase 3 Trials

Phase 3 trial design itself can be a barrier to implementation.¹² Phase 3 trials are designed to demonstrate efficacy and are typically conducted in very narrowly defined populations, which can limit the generalizability of the results.¹³ The exclusion of some groups—pediatric and older adults, peripartum women, and those with common comorbidities—creates

uncertainty about safety and efficacy in these groups.¹³ Despite regulatory agencies highlighting the importance of representativeness in phase 3 pharmaceutical and device trials, new interventions continue to be tested in highly homogenous populations.^{45, 46, 47} Trials conducted in research units outside of the health care system miss the opportunity to engage clinicians and organizations in delivery of the investigational treatment. Some interventions may not receive regulatory approval because the trial design did not meet regulatory requirements.

Implementation research frameworks and principles (Figure 4) could be applied to the design of Phase 3 trials to foster end-of-trial implementation of the treatment under investigation.¹²

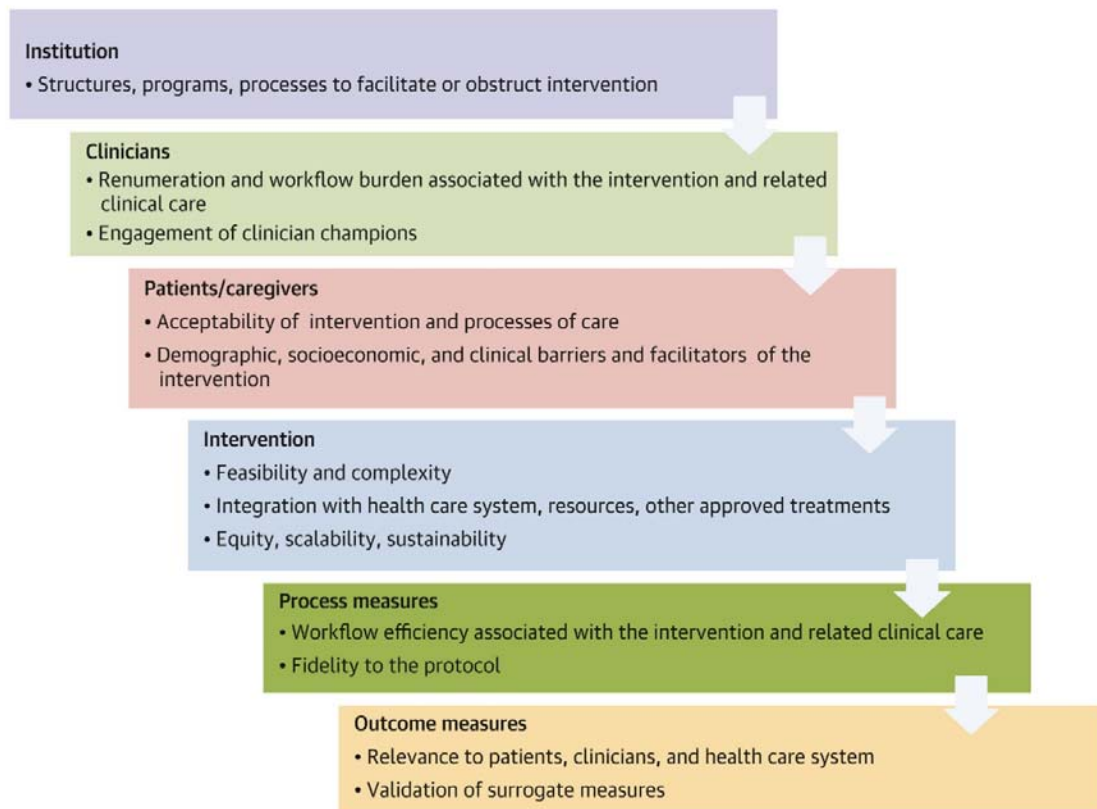


Figure 4. Considerations in Designing a Phase 3 Trial to Foster End-of-Trial Implementation

Multilevel stakeholder engagement and input can help align the intervention for uptake once the trial demonstrates efficacy and safety of the intervention. Based on Jalloh et al.¹²

Eligibility criteria

Less restrictive eligibility criteria generate more generalizable treatment effect estimates that could foster broader uptake. Published justification schemes for exclusion criteria can be used to ensure that trial eligibility criteria are justified in the context of the specific trial.⁴⁸ The perception that highly restrictive eligibility criteria enhance the internal validity of a trial is misguided; in fact, limiting trial eligibility criteria to those that are justified in the context of the trial decreases selection bias, thereby increasing trial validity.

Engagement of relevant knowledge users

Early engagement of broad knowledge users and decision-makers (including patients, clinicians, payers, and policy-makers) in trial advisory boards could add insights about treatment acceptability and could guide selection of outcomes relevant to patients, clinicians, and the health care system. Regulatory agencies offer protocol support to ensure that trial designs are rigorous enough to facilitate regulatory approval should a treatment be proven efficacious; this can be an important resource to investigators. Decision-makers and clinicians can add important insights about foreseeable barriers to implementation of an intervention in clinical environments. Patients are the ultimate stakeholders in implementation. The inclusion of patients on trial advisory boards could foster trust and obtain valuable perspectives on treatment acceptability, preferred mode of treatment delivery, selection of meaningful trial outcomes, and strategies for implementation. Patients are increasingly included in advisory boards to explore the acceptability of interventions and endpoints in drug and device trials sponsored by industry and federal funding agencies. Beyond patient engagement, direct-to-patient trials take research directly to patients, and now include phase 2 RCTs of drug interventions.⁴⁹

The PACT-HF trial tested the effect of transitional care services across hospital and home settings following hospitalization for heart failure.^{34,50,51} The trial was embedded in the health care system and utilized publicly funded personnel to deliver services. Clinicians, patients, and decision-makers were engaged in the design of services and selection of outcomes. This engagement fostered the integration of services between hospital, clinic, and home during and following the trial.

In an era of new innovations and escalating costs, payers rely on cost effectiveness and cost utility analysis; drug and device trials should include these analyses for markets across jurisdictions. The estimation of cost utility—an outcome relevant to payers and health care systems—requires collection of quality-of-life and survival measures during the trial so that cost relative to quality of life or cost per quality-adjusted life year can be estimated. Generic quality of life scales such as the EQ5D5L are useful in this regard, and can be collected remotely to facilitate efficient data collection.⁵²

Delivery of the intervention

Although drug, health service, and remote monitoring interventions are commonly delivered in research units, using existing health care processes and personnel could better engage clinicians and sites in the trial and leave processes in place for post-trial implementation. Interventional and device trials have highlighted the feasibility of delivering high-quality interventions within health care systems and quickly transforming practice and policy. Pivotal primary percutaneous coronary intervention trials in ST-segment elevation myocardial infarction (STEMI) are an example.

Anticipated barriers and facilitators to the delivery of new treatments could be addressed in the trial design; these may be identified through engagement of relevant knowledge users including clinicians, patients, and communities.¹² For example, reimbursement schemes for delivery of interventions could influence the uptake of interventions. The AEGIS-II (ApoA-I

Event Reducing in Ischemic Syndromes II) trial tested the efficacy of intravenous infusions of CSL112 following acute MI.⁵³ The initial dose was delivered in hospital and subsequent doses in ambulatory settings. During the trial, a systematic review along with a survey of trial sites across countries were conducted to understand the models of care, settings, and reimbursement schemes that would be required to deliver intravenous therapies in ambulatory patients.⁵⁴

Process evaluation—typically used in implementation projects—could be adopted during phase 3 trials to help improve workflow efficiency during and following the trial. For a device trial, process measures may include procedural time, proportion of failed attempts, reason for procedural failure, resource limitations, and other feedback from the proceduralist. Process mapping, with steps to optimize both workflow and procedural success in the trial, could be published following the trial to optimize implementation success. Phase 3 trials could publish details on pathways or guidance adopted across trial sites to optimize care. For example, greater clarity around the processes adopted to deploy and demonstrate success of a device or invasive intervention such as mechanical circulatory support could make it easier for clinicians to optimally implement it following the trial. Process measures are particularly important in phase 3 trials that require complex care in addition to the device itself. These process measurements could also help interpret subgroup differences in efficacy and safety. For example, in subgroup analysis of the DanGer (Danish-German) Shock trial, Impella (Abiomed) reduced mortality in male but not female patients with STEMI and cardiogenic shock; this difference may be related to biological differences in response to the device or to gender disparities in care processes (longer time to presentation, delayed initiation of Impella) in women.⁵⁵ Data collection and clear reporting on these processes could highlight underlying factors relevant to treatment effect and provide important context to guide implementation efforts.

Trials are often conducted in disease silos, without considering the common comorbidities and cointerventions that people require for optimal health. For example, antiretroviral therapy has rapidly returned people with HIV to near-normal life expectancy.⁵⁶ However, successful treatment with modern antiretroviral therapy is strongly associated with progressive obesity, especially in Black women, and is possibly associated with hypertension.^{57,58} This is especially concerning because these patients have a preexisting doubling of cardiovascular risk by virtue of their HIV status. A preventative RCT within this group demonstrated that pitavastatin decreased cardiovascular events in low- to moderate-risk participants with HIV.⁵⁹ Taking pitavastatin to scale, along with antiretroviral therapy, antihypertensive medications, the new wave of antiobesity agents, as well as a host of other required interventions such as tuberculosis prevention poses a formidable challenge to implementation scientists.

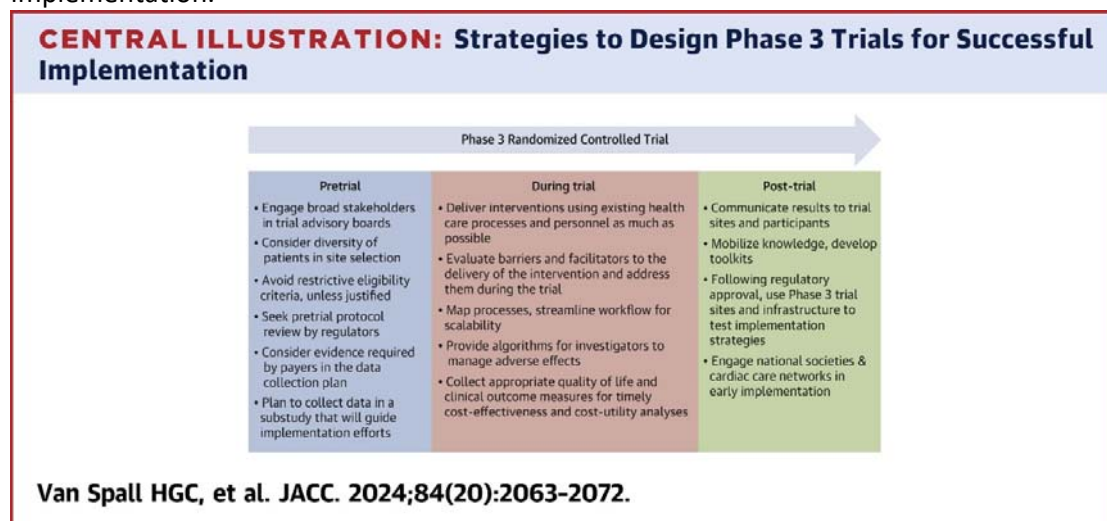
Similarly, patients with heart failure commonly live with atrial fibrillation, hypertension, diabetes, kidney disease, and lung disease, requiring evidence-based groups of therapies for each of these conditions. The complexity of background polypharmacy, the risk of drug-drug interactions, and associated barriers to implementing new therapies could be considered, with efforts made by site investigators to de-implement ineffective therapies before trial enrollment. An informal phase to deprescribe minimally effective baseline treatments before randomization in a phase 3 trial may be another way to foster post-trial implementation. The

ELEVATE-HFpEF (ELEVATED cardiac pacing rate for personalized treatment of Heart Failure with preserved Ejection Fraction) trial will randomize patients with HFpEF to a personalized elevated pacing rate vs a device control. Site clinicians will be encouraged to de-prescribe beta-blockers—the use of which is not evidence-based and may exacerbate chronotropic incompetence in HFpEF⁶⁰—before enrolling patients unless other indications for beta-blockers are present. This is to avoid the perception that any demonstrated benefits of pacing could have been obtained by stopping beta-blockers instead. Additional strategies to foster implementation will include broad stakeholder engagement in trial advisory boards, justification of eligibility criteria, barrier and facilitator analysis, and efforts to streamline workflow.

When side effects to an intervention are expected based on prior data, algorithms of care could be provided to site investigators so that patients can persist with the intervention in the trial; this guidance, if published, can also be useful during post-trial implementation.

Post-trial implementation

After trial results are read out, trial sites could be engaged in early implementation efforts. Existing trial infrastructure can be leveraged to conduct a barrier-facilitator survey, and decision-makers, clinicians, and patients may be engaged to test strategies for long-term implementation (Central Illustration). The UMPIRE (Use of a Multidrug Pill In Reducing Cardiovascular Events) trial showed that simplifying a medication regimen using a once-daily polypill improved adherence as well as the clinical outcomes of blood pressure and cholesterol lowering.⁶¹ The INPUT (Interpreting Processes of the UMPIRE Trial) included qualitative interviews of clinicians and participants in the UMPIRE trial to uncover factors relevant to treatment adherence.⁶² Such implementation studies could be embedded within phase 3 trials to understand contextual factors and inform post-trial implementation.^{62,63}



Central Illustration. Strategies to Design Phase 3 Trials for Successful Implementation

Phase 3 trials should be designed with implementation as an up-front priority. Thoughtful steps before, during, and after the trial can help foster implementation.

In the early and mid-1990s, pivotal trials demonstrated the superiority of primary percutaneous coronary intervention aiming for a door-to-balloon time of 90 minutes or less over lytic therapy in STEMI.^{64, 65, 66} The translation of these trial results into national strategies for reperfusion across countries—with combined efforts from cardiac care networks and regional centers—occurred a decade or later following publication of at least 2 of the RCTs.^{67,68} Routine cardiovascular care processes across regions—from initial call to emergency medical services to percutaneous coronary intervention—were discordant with achieving timely reperfusion. Process mapping and process redesign allowed programs such as the Mission: Lifeline Program to decrease emergency medical services-to-balloon and door-to-balloon time (Table 1).^{69, 70, 71, 72} Such process mapping techniques could be accomplished to improve delivery of an intervention within a phase 3 trial itself. For practice changing trials, early knowledge mobilization and engagement of national societies, national guideline committees, and cardiac care networks could expedite the translation from research to practice. Strategies to better design phase 3 trials for end-of-trial implementation are presented in the Central Illustration.

Table 1. Process Evaluation, Mapping, and Improvement of Systems of Care to Improve Timely Primary PCI in STEMI

| Processes of Care | Intended Process Outcomes |
|---|--|
| Coordination of STEMI care between EMS and receiving center | <ol style="list-style-type: none"> 1. Preplanned EMS destination protocols 2. Early notification by EMS to the receiving center of suspected or confirmed STEMI patient 3. Early activation of the catheterization laboratory (STEMI alert) by the receiving center before the arrival of patient with STEMI identified in the field by EMS 4. Immediate, 24-48 h, and quarterly feedback to EMS by the receiving center |
| Throughput processes at receiving centers | <ol style="list-style-type: none"> 1. Decreased door to 12-lead ECG times for patients transported by EMS without a diagnostic 12-lead ECG 2. Decreased ED dwell time for STEMI patients |
| Coordination of care between EMS and referring hospital | <ol style="list-style-type: none"> 1. Preplanned EMS destination protocols that may include bypass of the closest referring hospital when EMS to PCI can be achieved ≤ 90 or ≤ 120 min when EMS transport >45 min 2. Preplanned transfer plans with EMS for the STEMI patient |
| Throughput processes at referring hospitals | <ol style="list-style-type: none"> 1. Protocols to ensure timely identification of the STEMI patient, timely acquisition and interpretation of the 12-lead ECG 2. Decreased length of stay in ED (door in-door out) |
| Coordination of care between referring hospital and receiving centers | <ol style="list-style-type: none"> 1. Automatic acceptance of STEMI patients by receiving centers 2. 1-call STEMI activation process in place 3. Immediate, 24-48 h, and quarterly feedback to referring hospital by the receiving center |

From the American Heart Association⁶⁹ and Jacobs et al.⁷⁰

ECG = electrocardiogram; ED = emergency department; EMS = emergency medical services; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Summary

The suboptimal uptake of evidence-based cardiovascular therapies emphasizes the need for greater attention to implementation science in cardiovascular research and clinical care. Phase 3 cardiovascular trials could be better designed to foster post-trial implementation of proven-effective treatments. Trial design considerations include less restrictive eligibility criteria, early engagement of implementation stakeholders in trial advisory boards, delivery of the intervention using existing health care processes and personnel, in-trial assessment of barriers and facilitators in delivery of the intervention, and assessment of cost effectiveness and cost utility across jurisdictions. Implementation strategies should be informed by prior evidence, tailored to local context, and tested for effect on clinical or implementation outcomes using robust methods. Conceptual frameworks can guide the processes, measurements, and process evaluation required for optimal delivery of the intervention, both during the trial and in the post-trial implementation phase.

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understood or quoted as being made on behalf of or reflecting the position of the organizations with which the authors are employed/affiliated.

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