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Authors

Jalloh, Mohamed
Averbuch, Tauben
Kulkarni, Prashanth
et al.

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Bridging Treatment Implementation Gaps in Patients with Heart Failure: JACC Focus Seminar

Mohamed B. Jalloh, MD, MSc[a], **Tauben Averbuch, MD**[b], **Prashanth Kulkarni, MD, DM**[a], **Christopher Granger, MD**[c], **James L. Januzzi, MD**[d,e], **Faiez Zannad, MD**[f], **Robert W Yeh, MD**[d,g], **Clyde Yancy, MD**[d,h], **Gregg Fonarow, MD**[i], **Khadijah Breathett, MD**[j], **C Michael Gibson, MD**[d], **Harriette G.C. Van Spall, MD, MPH**[a,d,k,l,*]

[a]Department of Medicine, McMaster University, Hamilton, ON, Canada

[b]Department of Cardiology, University of Calgary, Calgary AB, Canada

[c]Division of Cardiology, Duke University School of Medicine, NC, USA

[d]Baim Institute for Clinical Research, Boston, USA

[e]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, USA

[f]Université de Lorraine, INSERM Investigation Network Initiative–Cardiovascular and Renal Clinical Trialists, Centre Hospitalier Régional Universitaire, Nancy, France

[g]Smith Center for Outcomes Research, Beth Israel Deaconess Medical Center, Boston, USA

[h]Northwestern University, Chicago USA

[i]Ahmanson-UCLA Cardiomyopathy Center, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA

[j]Division of Cardiovascular Medicine, Indiana University, Indianapolis, IN, USA

[k]Research Institute of St. Joseph's, Hamilton, ON, Canada

[l]Population Health Research Institute, Hamilton, ON, Canada

Condensed Abstract

Heart failure (HF) is a leading cause of death and disability in older adults. Despite highest-quality evidence that supports the use of guideline-directed medical therapy (GDMT) to improve outcomes in HF, implementation of this evidence has been suboptimal. This review synthesizes implementation interventions that increase the uptake of GDMT, discusses barriers and facilitators of implementation, summarizes conceptual frameworks in implementation science that could improve knowledge uptake, and offers suggestions for trial design that could better facilitate long-term implementation. By adopting principles of implementation science, policy makers, researchers, and clinicians can reduce the burden of HF on patients and healthcare systems.

[*]**Correspondence:** Harriette GC Van Spall, MD, MPH; Population Health Research Institute, 20 Copeland Avenue, David Braley Research Building, Suite C3-117, Hamilton ON L8L 0A3. Harriette.VanSpall@phri.ca.

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Introduction

Heart failure (HF) is a leading cause of mortality and morbidity among older adults. Approximately 56.2 million people live with HF, mostly in low- and middle-income countries (LMICs).[1] With a substantial impact on health status, survival, and healthcare resource utilization, HF is a major burden on patients, clinicians, and healthcare systems.

Despite the highest quality evidence that guideline-directed medical therapies (GDMTs) decrease death or hospitalizations in persons with HF, the practical implementation of these treatments remains suboptimal. Less than 10% of patients with HF with reduced ejection fraction (HFrEF) receive all GDMT classes including beta-blockers; angiotensin-converting enzymes inhibitors, angiotensin receptor blockers, or angiotensin receptor neprilysin inhibitors; mineralocorticoid receptor antagonists; and sodium glucose cotransporter 2 inhibitors.[2,3] The uptake of other guideline recommendations in HF is also suboptimal.[4] The gaps in implementation appear to be amplified in women, minoritized racial and ethnic groups, and those who are socioeconomically deprived.[5-8]

Several implementation strategies have aimed to bridge gaps in the delivery of evidence-based care. While some strategies have improved GDMT uptake in clinical trials, the implementation of such interventions in clinical settings has lagged. There is an urgent need to disseminate and scale successful implementation strategies. This review synthesizes implementation strategies that increase the uptake of GDMT, presents barriers and facilitators of implementation, discusses how conceptual frameworks could guide implementation efforts, and offers suggestions for trial design that could better facilitate long-term implementation. Finally, it proposes an ‘Evidence to Care’ conceptual model that could foster simultaneous generation of evidence and long-term implementation to bridge the gap between evidence and care.

Barriers to the uptake of GDMT in HF

The uptake of GDMT in people with HF has multi-level barriers that must be considered when devising implementation solutions.[3] Healthcare system barriers include disparities in access to specialist care, restrictive drug policy and pricing, and inadequate funding for programs that integrate care.[3,7] Clinician-level barriers include knowledge gaps, therapeutic inertia or biases, and the workload associated with obtaining insurance approvals and monitoring patients during GDMT optimization. Patient-level barriers include limited health literacy and drug affordability, intolerable side-effects, and mistrust related to marginalization.[3] Structural disparities related to gender, race, and socioeconomic status are pervasive across healthcare systems, and compound the other barriers to GDMT uptake.[6]

Implementation strategies in HF

Several implementation strategies have aimed to bridge evidence-care gaps in HF, with varying effectiveness.

Financial incentives or disincentives

Financial rewards or penalties at the institution and clinician level are commonplace across jurisdictions, but have not been shown to improve HF care or clinical outcomes.[4] Policies that financially penalize institutions for readmissions may be associated with gaming or short-stay units to avoid penalties. They may also associated with increased death, particularly among patients not readmitted; the burden of such policies appears to disproportionately rest on patients who are socioeconomically deprived and on safety net hospitals.[9,10]

Audit-and-feedback

At least 2 cluster randomized controlled trials (RCTs) of hospitals [11,12] demonstrated that audit and feedback of HF performance measures coupled with clinician education programs and quality improvement initiatives did not improve GDMT implementation,[11] quality-of-care metrics,[12] or the primary clinical outcome that was measured in one of the trials (Table 1).[11] The lack of coordination between hospital and outpatient clinicians may have limited the post-discharge optimization of GDMT.

Transitional care interventions

Hospital-to-home transitional care interventions that improve clinical outcomes in small explanatory trials have demonstrated limited benefit in larger implementation trials.[13-15] In a cluster RCT that tested a transitional care program in patients hospitalized for HF, there was no improvement in the primary composite clinical endpoint or the uptake of GDMT compared to usual care (Table 2).[14,15] However, an RCT that evaluated algorithmic up-titration of GDMT in hospital and following discharge among patients on suboptimal GDMT demonstrated an improvement in the primary composite clinical outcome relative to usual care; in addition, a greater proportion in the intervention group achieved ≥50% of target GDMT doses.[16] Algorithm-driven GDMT titration appears to be an effective transitional care strategy.

Digital health technology (DHT) decision support

Decision support within electronic health records (EHRs) can improve GDMT uptake, at least in RCTs conducted within single healthcare systems. A cluster RCT that randomized clinicians to EHR-embedded GDMT alerts demonstrated an increase in GDMT (primarily beta-blockers) prescribed to patients with HF versus usual care.[17] In a 3-group cluster RCT in which cardiologists were randomized to EHR alerts during patient encounters, EHR messages about multiple patients between encounters, or usual care, the percentage of eligible patients prescribed mineralocorticoid receptor antagonists was greatest in the EHR alert group and least in the usual care group (Table 3).[18] It is unclear whether these results can be generalized to healthcare systems with different EHRs.

Prescription coverage

The uptake of newer GDMT classes may be limited by the cost-burden on individual patients,[7] and reducing out-of-pocket costs may increase medication uptake. Two cluster RCTs, one randomized at the hospital level [19] and the other at the insurer plan

level,[20] demonstrated that in the post-myocardial infarction setting, co-payments [19] or full prescription coverage [20] increased persistence [19] or adherence [20] to medications, although the primary composite clinical endpoints in each trial did not improve (Table 4). Such findings likely also apply to HF, although RCT evidence is lacking in HF.

Barriers to implementation

Despite the lack of supporting evidence, financial penalties and institutional audit programs remain in place; and effective strategies such as medication titration systems and digital tools await broad implementation. Thus, there remains a wide evidence-care gap even following implementation trials.

Barriers to implementation of interventions in research and clinical settings include misalignment with policy or healthcare system priorities, cost or complexity of the intervention, inadequate infrastructure or personnel to deliver the intervention, and inequities in resources across regions (Figure 1). Interventions that do not address local barriers or capitalize on local resources may fail, and strategies that may be effective in some healthcare systems and regions may be less so in others. The implementation of digital health technologies, which requires technical support, user-friendliness, and integration with institutional EHRs is particularly challenging.[21]

Implementation science

Implementation science (Table 5) can offer methodologies and frameworks designed to translate research evidence to clinical care, with the ultimate goal of improving health. Implementation science includes strategies that implement effective interventions and de-implement harmful ones.

Conceptual frameworks can provide a construct for designing, executing, and evaluating implementation interventions in research and clinical care. Conceptual frameworks can ensure that the preceding evidence, unmet needs of the target population, barriers and facilitators, and ethics are considered in implementation processes both, within a trial and in clinical settings. Examples of frameworks include the Knowledge-to-Action; Reach, Effectiveness, Adoption, Implementation, and Maintenance; Normalization Process Theory; and Consolidated Framework for Implementation Research (Table 6).[22,23]

Implementation trials

While implementation strategies and policies have clinical and cost implications and merit testing with robust methodology, they have often relied on observational data, mixed methods, or quasi-experimental designs. Implementation trials have not been subject to the same rigor or regulatory requirements as phase III efficacy trials. Suboptimal trial design, limited oversight, and selective reporting can lead to biased effect estimates. Additionally, many phase IV “implementation” trials do not test implementation interventions, but represent surveillance of patients for safety, tolerability, and mechanistic insights that may not have been evident in earlier phase drug or device trials.[24]

Implementation trials are different from other trials because they test the effect of strategies that aim to translate evidence to clinical care; it is the implementation strategy rather than the clinical intervention (e.g., drug, device) that is tested.[25] Implementation trials are similar, but distinct from quality improvement studies, which use iterative processes and cycles of change to improve care. Implementation trials are often pragmatic,[26] testing interventions within the complexities and variations of routine clinical care. Allocation is typically unblinded. The estimated treatment effect of interventions in pragmatic trials is often smaller than in explanatory trials, the latter of which deliver interventions with high fidelity, in controlled environments, and among selective patients most likely to benefit from the intervention.[26] Implementation trials may also be vulnerable to bias towards the null due to suboptimal fidelity to the intervention, which is often a complex health service intervention; thus, despite randomization, there may be a role for a secondary per-protocol analysis.

Approach to designing effective implementation trials

A thoughtful implementation trial should fulfill an unmet healthcare need and employ engage relevant stakeholders – healthcare system decision makers, clinicians, researchers, and patients - in the design of the intervention and trial (Figure 2). In selecting sites for the trial, organizational culture, operational environment, leadership commitment, resources, and competing programs must be considered. Clinicians' priorities and workflow should be considered, as should the patients' experience of care. The design of the intervention should incorporate stakeholder feedback and principles of health equity, sustainability, and scalability. The trial design must be matched to the aims of the study, with broad eligibility criteria [27] and culturally competent approaches to ensure that all those burdened by disease are represented in the trial.[28,29] Relevant and validated outcomes should be included, with careful selection of the primary outcome.[27]

Approaches to improving the uptake of implementation interventions may include embedding the delivery of the intervention in the healthcare system, engaging key stakeholders in the process, tailoring the intervention to regional needs, and generating high-quality evidence to guide future efforts (Figure 3). Healthcare systems best suited to embedded trials are those with a research-friendly policy, culture, infrastructure, data linkages, and skilled personnel to deliver the intervention (Figure 4). The challenges of embedding trials in healthcare systems may be offset by the gains in efficiency from the use of existing workforce and routinely collected data via electronic health records or administrative databases; the use of registries and administrative databases for randomization and data collection are critical assets that could move forward the design of implementation trials. A trade-off may be fidelity to the intervention and data accuracy, particularly when using endpoints that are disease-specific or that require adjudication.[26]

Hybrid effectiveness implementation trials

Instead of implementation being an afterthought when trial results are evident, it could be an early consideration in the design of pivotal phase III studies. For example, hybrid effectiveness-implementation trials can evaluate both the effect of an intervention and

implementation feasibility or success (Table 7). Both, health outcomes that reflect the effect of the intervention and implementation outcomes can be selected. One classification system categorizes hybrid trial designs into three types.[25] Hybrid Type 1 trials assess the effect of a clinical intervention on health outcomes and as a secondary aim, the context or feasibility of implementation. Hybrid Type 2 trials assess the effect of a clinical intervention on both health outcomes and implementation measures during the trial. Hybrid Type 3 trials assess the effect of implementation strategies on implementation outcomes, and as a secondary aim, on health outcomes.[25] Chosing the right hybrid effectiveness implementation design depends on various factors, especially the existing evidence for the drug or device intervention being implemented. For treatments with robust evidence of benefit based on large outcomes trials (e.g., GDMT), it is reasonable to adopt a type 3 design.

Randomization schemes used in implementation trials

Notwithstanding logistical complexities, randomization is essential for causal inferences to be reliably made. The cost and complexity of randomization can be balanced with efficiency in other aspects of the trial design. Several randomized designs can be adopted to test the effect of an implementation intervention (Figure 5).

Cluster randomized trials

Cluster randomized designs, often used in implementation trials, randomize clusters like regions, hospitals, or physicians. This design is ideal when the intervention is conducted at the level of the cluster, for example a clinic. Such designs avoid the risk of contamination bias that can occur with patient-level randomization when clinicians within a cluster share knowledge and practices. The correlation of outcomes within versus between clusters must be considered in the design and analysis to produce reliable conclusions.[30]

Parallel group cluster RCTs—Parallel group cluster RCTs randomize clusters to specific interventions that they receive through to the end of the intervention period. For example, the Care Optimization Through Patient and Hospital Engagement Clinical Trial for HF (CONNECT-HF) trial randomized 165 US hospitals to an intervention of audit and feedback of quality metrics and clinician education versus usual care; allocated groups received the same intervention until the end of the trial intervention period (Table 8).[12]

Cluster crossover RCTs—In cluster crossover RCTs, the clusters are randomized to treatments or interventions groups, but periodically crossover to the alternative within the study period, increasing statistical power. The Prevention of Arrhythmia Device Infection Trial (PADIT) cluster crossover trial randomized hospitals to different perioperative antibiotic regimens for cardiac implantable electronic device procedures, and hospitals crossed over between different strategies during the trial (Table 8).[31] This design is not recommended for interventions with long carry-over effects such that clinicians in the intervention group deliver aspects of the intervention when crossed over to a different group. This risk may be mitigated, at least partially, with a washout period after each crossover or with stepped wedge cluster randomization.

Stepped wedge cluster RCTs—The stepped wedge RCT is a crossover design involving a uni-directional crossover of clusters from comparator to intervention in a randomized sequence [14] until all clusters receive the intervention. The treatment effect is estimated via between and within-cluster comparisons at each crossover period, necessitating a longer study duration but fewer clusters to achieve statistical power relative to a parallel cluster trial.[32] This design is appropriate when all clusters wish to implement the intervention, when the intervention has anticipated benefits and minimal risk, and when routinely gathered data is available for outcome assessment to avoid the burden of repeated measurements. Because all clusters deliver the intervention by the end of the trial, processes for post-trial implementation are put in place across clusters should the intervention prove effective.[32]

Grounded in the Knowledge-to-Action conceptual framework, Patient-Centered Care Transitions in HF (PACT-HF) stepped wedge cluster RCT tested the effect of a transitional care model comprising services shown to be efficacious in explanatory trials. Participating hospitals crossed over from usual care to intervention at monthly intervals in a randomized sequence until all were delivering the intervention. Decision-makers, clinicians, and patients were involved in the trial design, and existing personnel in the healthcare system were used to deliver the intervention (Table 8).[14,15] This embedded trial utilized nationwide administrative databases for clinical outcomes and remote data collection for patient-reported outcomes, precluding the need for in-person study visits.

Improving implementation trial efficiency: Adaptive randomization schemes

Ideal for implementation interventions, adaptive trial designs provide flexibility and efficiency, allowing trial design modifications to be made in response to evolving circumstances during a study. These modifications may include randomizing patients to one of multiple alternative interventions against a single comparator group, adjusting the sample size based on observed event rates, and switching between noninferiority and superiority analyses, among others.[33]

The adaptive design has advantages related to efficiency, but limitations related to complexity. For example, an adaptive design can save time by halting recruitment to implementation interventions that have poor fidelity measures, and increasing recruitment to other interventions that are being delivered as designed. However, this requires interim analysis on an adequate sample of patients so that reliable conclusions are drawn.[33]

Sequential RCTs

A sequential multiple assignments randomized trial (SMART) is an adaptive design used that allows for greater flexibility and efficiency, with the ability to adjust the study as new information becomes available. For example, the results of the first phase can be used to determine whether the trial should be continued, terminated, or modified in some way. This increases the speed with which new strategies can be tested and decreases overall trial cost.[34]

The Quit SMART three-phase trial changes the level of randomization and intervention at each phase to increase patient enrollment in a tobacco cessation program.[34] In the first phase, clinics are randomized to two interventions to enhance referral of patients. In the second phase, unenrolled patients are randomized to one of two interventions aimed at enrolling them; and in the third phase, patients who are still unenrolled are randomized to one of two interventions (Table 8). Because of the relatively recent uptake of this design, the reliability of effect estimates in such complex schemes is not clear.

Platform RCTs

Platform trials allow for prespecified changes to key trial features as new information accumulates during the study. In addition to testing multiple interventions concurrently, platform trials use a common control group, streamlining enrollment. In the Novel Uses of Designs to Guide provider Engagement in Electronic Health Records platform implementation trial, physicians were randomly assigned to either usual care or one of 15 EHR-based tools to examine the effect on high-risk medication prescription for older adults.[35] The tools were ranked based on their effect on the primary outcome, and physicians initially assigned to usual care were then randomized to one of the top 5 EHR-based tools or continued usual care (Table 8).

Outcome selection and trial efficiency

Implementation trials often use surrogate endpoints as primary outcomes to reduce sample size, cost, and duration relative to clinical endpoints. This is a reasonable approach when there is high-quality evidence that demonstrates the effect of the intervention being implemented (e.g., GDMT) on clinical endpoints. Intermediate endpoints - those on the causal pathway to clinical outcomes – are ideal surrogate endpoints. In HF implementation trials, intermediate endpoints may include medication uptake and diagnostic markers of disease progression.[36] In contrast, the use of arbitrarily-derived endpoints that are not validated against clinical endpoints (e.g., medication titration or quality improvements scores) are not ideal.[37] Similarly, patient-reported outcomes, when used, should be adequately validated and demonstrate robust psychometric properties.[38]

Input from researchers, clinicians, decision-makers, and patients can ensure that outcomes are both relevant and valid. Large-scale implementation trials should ideally include clinical outcomes to assess cost effectiveness.

Future needs

There are few, if any, randomized trials that have been shown to improve implementation of GDMT on a broad scale, and even fewer that have tested de-implementation strategies. An important unmet need is to test the cost-effectiveness and widespread scaling of interventions that have been effective in select patients and with dedicated research staff. Health system leaders should play a major role in funding such trials if they are dedicated to improving the outcomes of their patients.

Few implementation interventions have been tested in LMICs and among marginalized populations.[28,29,39] Few trials have included measures of health equity among their process outcomes. Implementation science must explore novel strategies tailored to the socioeconomic and regional determinants of health. This unique space represents an ongoing unmet need in implementation trials.

A new conceptual framework

A minority of implementation trials are guided by conceptual frameworks, possibly due to complexity, and most conceptual frameworks for implementation do not consider health equity. We propose an 'Evidence-to-Care' conceptual framework to guide research and clinical implementation, with grounding in four pillars: high-quality evidence to support implementation of the therapy (e.g. drug, device, or health service); an equitable, scalable, and sustainable implementation strategy; a robust trial design to assess effect of implementation in healthcare settings; and measurement of relevant outcomes to guide scale-up of the implementation strategy. Anchoring these pillars within the healthcare system, with engagement of multi-level stakeholders and adaptation to regional and local context, can create better bridges between implementation research and clinical care (Central Illustration).

Conclusion

There remain gaps in the uptake of GDMT and also in the uptake of implementation strategies shown to close these gaps. We propose a conceptual framework that could bridge these evidence-care gaps and that is grounded in four pillars: high-quality evidence; equitable, scalable, and sustainable implementation interventions; robust embedded trials to assess effect of implementation in healthcare settings; and measurement of relevant outcomes to guide scale-up. Anchoring these four pillars in the healthcare system, with engagement of multi-level stakeholders and adaptation to regional and local context are important for implementation success, both in embedded trials and in healthcare settings themselves. Such efforts could facilitate broad end-of-trial implementation and definitively reduce the burden of HF.

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Abbreviations and Acronyms

CONNECT-HF	care optimization through patient and hospital engagement clinical trial for heart failure
DHT	digital health technology
HER	electronic health record
GDMT	guideline-directed medical therapies
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
LMICs	low- and middle-income countries
PACT-HF	patient-centered care transitions in heart failure
RCT	randomized controlled trial
SMART	sequential multiple assignments randomized trial

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Highlights:

- Implementation interventions that increase the uptake of guideline-directed medical therapy in randomized controlled trials - prescription subsidies, algorithmic titration schemes, and electronic health record-based decision support – remain to be broadly implemented.
- Implementation science provides a framework and methods to integrate research evidence into clinical care.
- Trials can better foster implementation of results by adopting implementation science principles and pragmatic design elements.
- We propose a four-pillar Evidence-to-Care framework anchored in the healthcare system: high-quality evidence; equity, sustainability, scalability; robust trial design; and relevant outcomes.

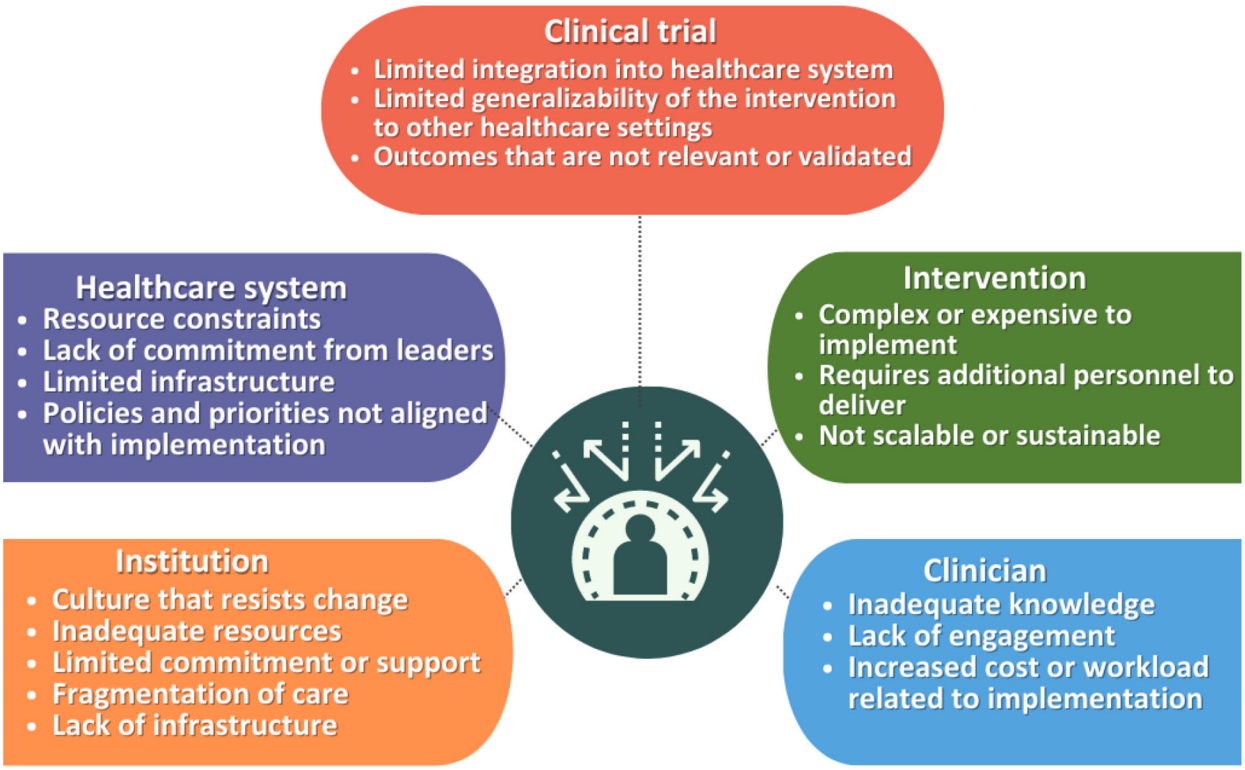


Figure 1. Barriers to implementation of evidence-based interventions in healthcare settings.
Barriers include misalignment with policy or healthcare system priorities, high cost or complexity, inadequate infrastructure or personnel to deliver the intervention, and regional disparities in resources.

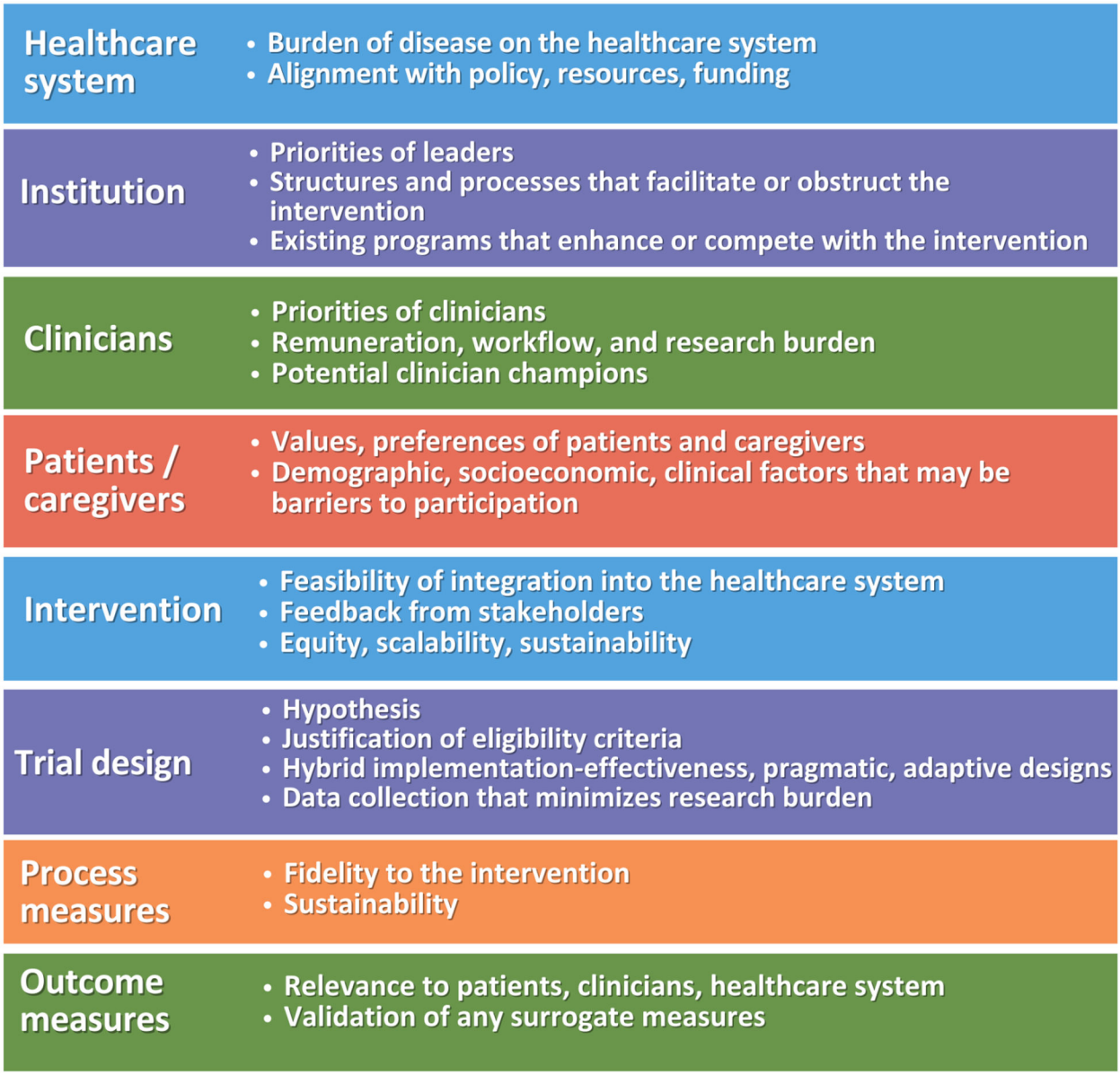


Figure 2. Considerations in the planning and design of implementation trials.

Once a clinically relevant evidence-care gap is identified, an implementation strategy should be designed with input from relevant stakeholders and consideration of health equity, sustainability, and scalability of the intervention. Site selection should consider operational culture and resources. The effect of the implementation should be tested using a robust design and relevant, valid outcomes.

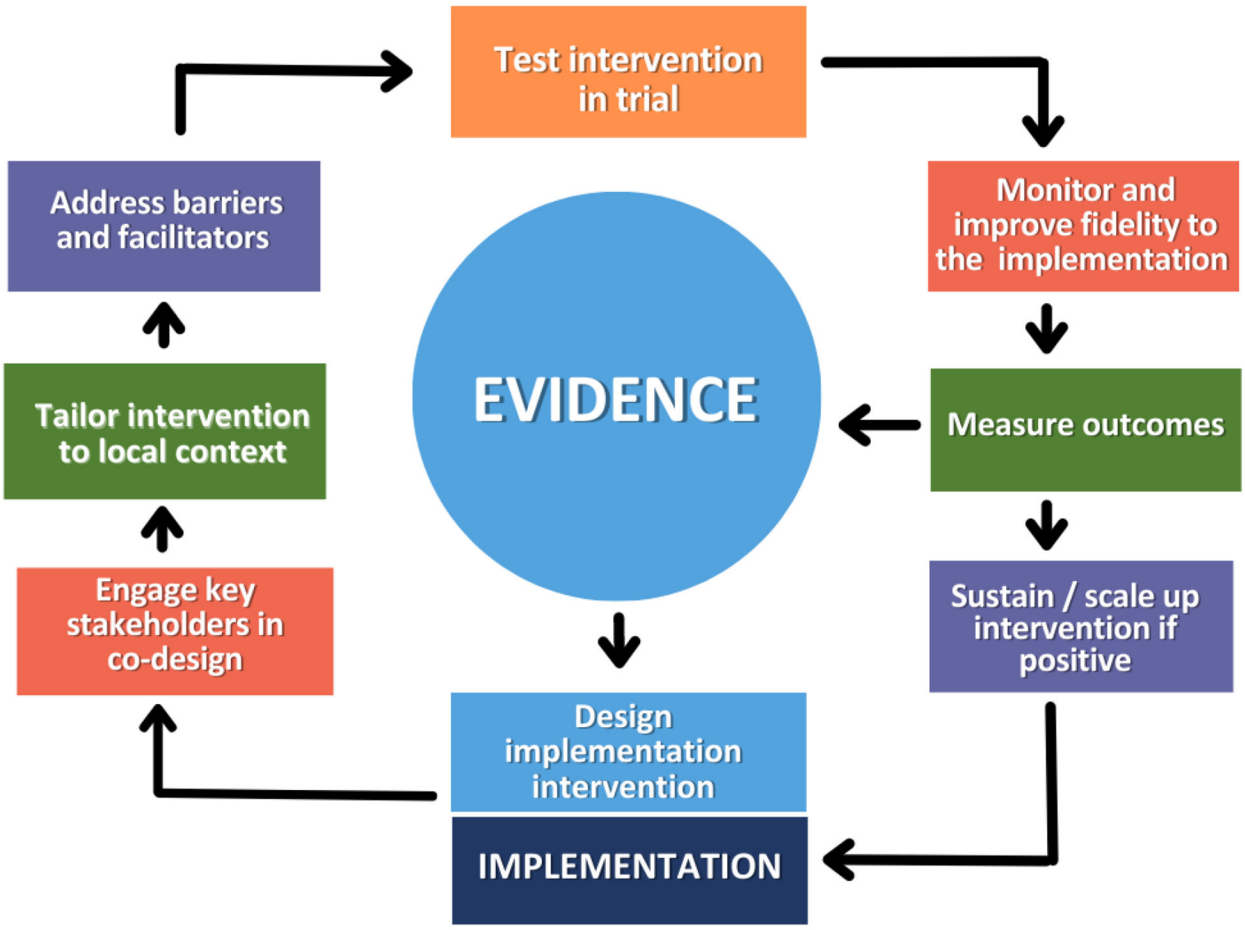


Figure 3. Steps to enhance implementation during and following a clinical trial.

High quality evidence can be implemented through the design of an intervention that is tailored to local context. A pilot phase can be used to assess feasibility and improve implementation processes during the trial. Knowledge generated from the full-scale trial can be used to drive further implementation efforts. This approach can also be used to improve implementation in clinical settings.

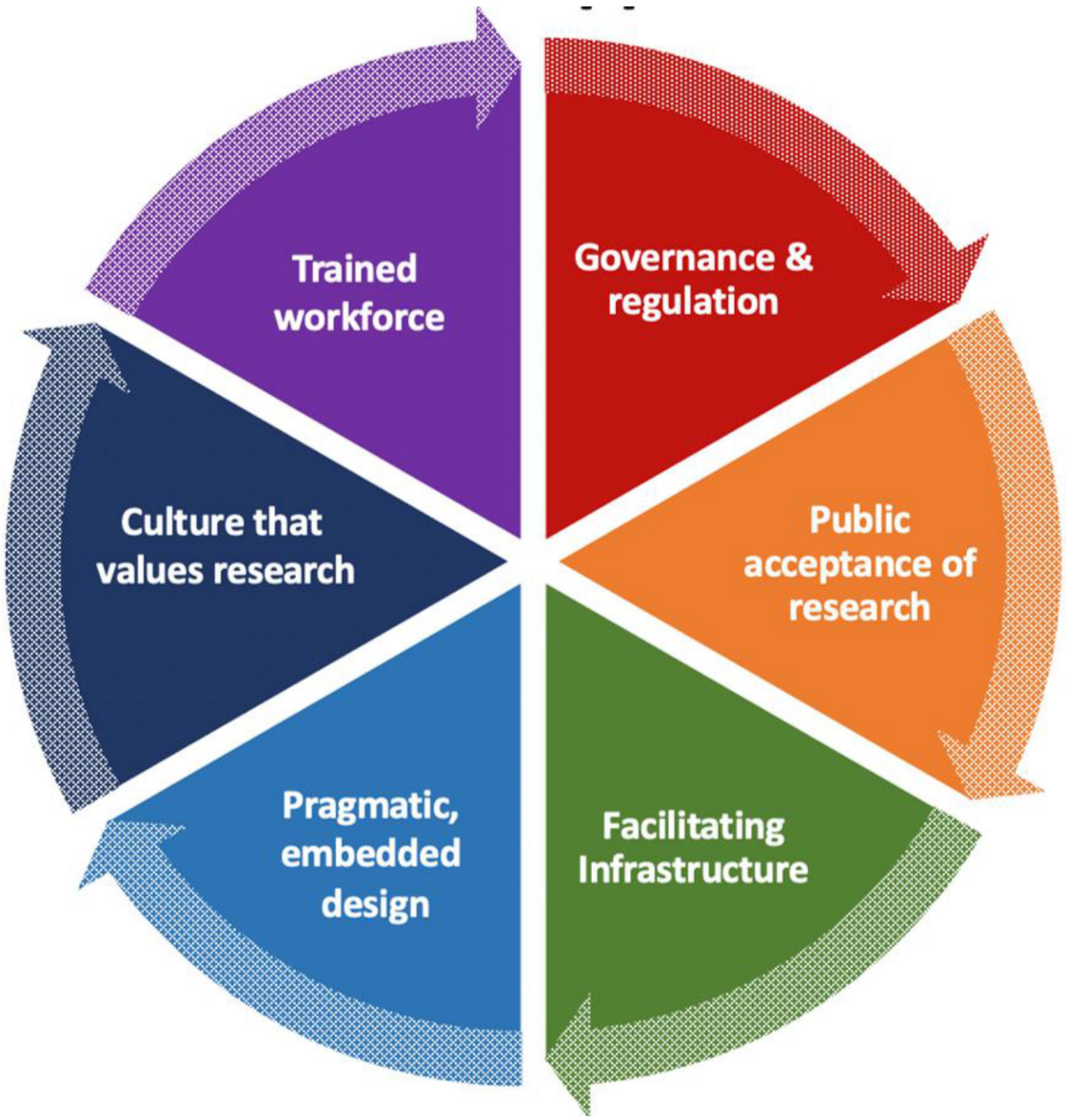


Figure 4. Factors that facilitate embedding of implementation trials in healthcare systems.
Effective embedding of trials in the healthcare system can facilitate long-term implementation, but require alignment of several important factors.

A.

PERIOD	1	2
CLUSTER 1	I	I
CLUSTER 2	I	I
CLUSTER 3	C	C
CLUSTER 4	C	C
CLUSTER 5	C	C

B.

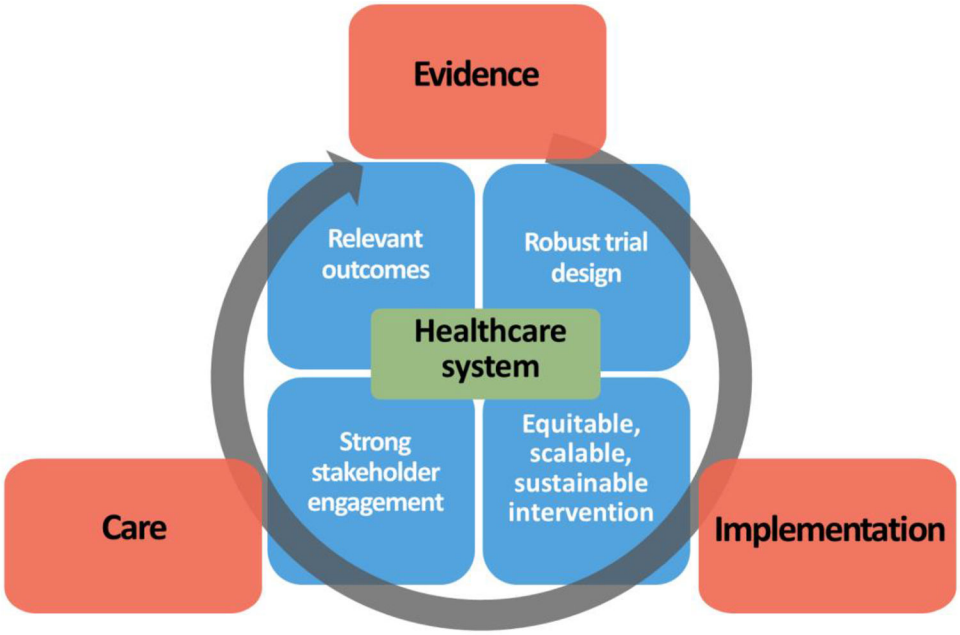
PERIOD	1	2	3	3
CLUSTER 1	C	I	C	I
CLUSTER 2	C	I	C	I
CLUSTER 3	I	C	I	C
CLUSTER 4	I	C	I	C

C.

PERIOD	1	2	3	4	5	6
CLUSTER 1	C	I	I	I	I	I
CLUSTER 2	C	C	I	I	I	I
CLUSTER 3	C	C	C	I	I	I
CLUSTER 4	C	C	C	C	I	I
CLUSTER 5	C	C	C	C	C	I

Figure 5. Randomization schemes in cluster trials.

Clusters are assigned to intervention (I) or control (C). **A. Parallel group cluster design.** Clusters receive their allocated treatment through to the end of the intervention period. **B. Cluster crossover design for a trial with four clusters and four periods.** Each row represents a treatment sequence. Cluster cross over between allocated treatments in each period. **C. Stepped wedge design.** In step 1, all clusters receive the control. At each subsequent step, a cluster crosses over to receive the intervention. The sequence of crossover is randomized.



Central illustration. Evidence-to-Care Conceptual Framework for Research and Clinical Implementation.

This framework is grounded in four pillars: high-quality evidence to support the therapy being implemented; an equitable, sustainable, and scalable implementation strategy; a robust trial design to test the effect of the implementation strategy; and measurement of relevant outcomes to guide scale-up of the implementation strategy. The four pillars are anchored in the healthcare system, with engagement of multi-level stakeholders and adaptation of the strategy to regional and local context.

Table 1.

Examples of trials that tested audit-and-feedback of hospitals to improve care among hospitalized HF patients

Intervention tested in trial	Trial Methods	Outcomes and main results
Personized Performance Feedback in Get With The Guidelines-Heart Failure (GWTG-HF) Participating Hospitals[11] **Design:** Parallel cluster RCT	**Population:** 165 hospitals randomized, 147 analyzed (71,829 patients hospitalized for HFrEF, median age 74.0 years, 48.6% female). **Setting:** United States. **Intervention:** Personalized quality improvement feedback, teleconferences, webinar invites, and specialized tool kits sent to hospitals every quarter, added to the standard GWTG-HF performance feedback information received by hospitals in the control group. **Control:** Access to standard GWTG-HF baseline and on-demand performance information, quality improvement resources, and open access webinars.	**Primary outcome:** Improvement in site composite quality of care score for participating hospitals. (Mean difference, −2.87 [95% CI: −7.32 – +1.58]). **Secondary outcomes:** In-hospital mortality; improvement in the defect-free composite score, defined as the percentage of eligible patients who received all achievement and quality measures.
Care Optimization Through Patient and Hospital Engagement Clinical Trial for HF (CONNECT-HF)[12] **Design:** Parallel cluster RCT	**Population:** 161 hospitals (5,746 patients with HFrEF, mean age 62.9 years, 33.3% female). **Setting:** United States. **Intervention:** Hospital and post-discharge quality improvement initiative, with regular education of clinicians by a trained group of HF & quality improvement experts and audit and feedback on HF process measures (e.g., use of GDMT). **Control:** Usual care.	**Primary outcomes:** Composite HF readmission or all-cause mortality (adjusted HR 0.92 (95% CI, 0.81-1.05); or composite HF care quality score (difference of 3.3% (95% CI, −0.8% to 7.3%]). **Secondary outcomes:** Total HF readmissions; all-cause mortality; and an opportunity-based quality score.

GDMT, Guideline-directed Medical Therapy; HF, Heart Failure; HFrEF, Heart Failure with Reduced Ejection Fraction; HR, Hazard Ratio; RCT, Randomized Controlled Trial

Table 2.

Examples of trials that tested transitional care interventions following hospitalization for HF

Intervention tested in trial	Trial Methods	Outcomes and main results
Patient-Centered Transitions in HF (PACT-HF)[15] **Design:** Stepped wedge cluster RCT; hybrid effectiveness-implementation trial.	**Population:** 10 hospitals (2,494 patients hospitalized for HFrEF, mean age 77.7 years, 50.4% female). **Setting:** Canada **Intervention:** In-hospital education, structured discharge summary, primary care visit within a week of discharge, and for high-risk patients, nurse-led home visits and heart function clinic visits. **Control:** Usual transitional care as per clinician's discretion.	**Primary outcomes:** Composite all-cause readmission, emergency department (ED) visit, or death at 3 months (HR 0.99 (95% CI, 0.83-1.19); or composite all-cause readmission or ED visit at 30 days (HR 0.93 (95% CI, 0.73-1.18). **Secondary outcomes:** B-PREPARED score for discharge readiness; 3-Item Care Transitions Measure (CTM-3) for quality of transition; 5-level EQ-5D version (EQ-5D-5L) for quality of life; and quality-adjusted life-years (QALY); and healthcare resource utilization.
The Safety, tolerability and efficacy of up-titration of GDMT for acute heart failure (STRONG-HF)[16] **Design:** Individual-level parallel design RCT	**Population:** 1,078 patients, mean age 63.0 years, 38.6% female. **Setting:** Argentina, Austria, Bulgaria, Columbia, France, Hungary, Israel, Mozambique, Nigeria, Russia, Serbia, Slovakia, South Africa, and Tunisia **Intervention:** Initiation of GDMT in hospital and post-discharge optimization of therapies, with the goal of achieving 100 % of the target GDMT doses within 2 weeks of discharge. Four outpatient appointments over the 2 post-discharge months to monitor clinical status, laboratory parameters, and NT-proBNP levels. **Control:** Usual care as per local physician follow-up.	**Primary outcome:** Composite of HF readmission or all-cause mortality by day 180 (adjusted RR 0·66 [95% Change from baseline to day 90 in EQ-5D visual analogue scale; All-cause mortality by day 180; HF readmission or all-cause mortality by day 90.

GDMT, Guideline-directed Medical Therapy; HF, Heart Failure; HFrEF, Heart Failure with Reduced Ejection Fraction; HR, Hazard Ratio; NT-proBNP, N-terminal -prohormone of Brain Natriuretic Peptide; RCT, Randomized Controlled Trial.

Table 3.

Examples of trials that tested digital health technology decision support interventions in ambulatory HF patients

Intervention tested in trial	Trial Methods	Outcomes and main results
PRagmatic Trial Of Messaging to Providers about outpatient Treatment of HF (PROMPT-HF)[17] **Design:** Parallel-group cluster RCT	**Population:** 93 providers (1,310 patients, median age 72.0 years, 30.7% female). **Setting:** United States **Intervention:** EHR based alerting system for outpatients with HFrEF for 30 days. The alert notified providers of personalized GDMT recommendations along with patient characteristics. **Control:** no alerts.	**Primary outcome:** Proportion of patients with HFrEF who had an increase in the number of prescribed GDMT classes at 30 days. (GDMT increase 25.7% in alert arm versus 18.7% in control arm [adjusted RR, 1.41; 95% CI, 1.03-1.93]). **Secondary outcome:** The percentage increase in each individual class of GDMT; dose of GDMT; length of stay; 30-day all-cause readmission; 30-day all-cause ED visits; 30-day all-cause mortality, 1-year all-cause mortality; percentage of GDMT prescriptions filled by patients, total cost of care.
Building Electronic Tools to Enhance and Reinforce CArdiovascular REcommendations for Heart Failure (BETTER CARE-HF).[18] **Design:** Multi-arm parallel-group cluster RCT	**Population:** 180 cardiologists (2,211 patients with HFrEF, mean age 72.2 years, 28.6% female) **Setting:** United States **Intervention**: Two intervention groups: EHR-based automated in-basket messages to physicians and EHR-based best practice alerts **Control:** Usual care, no alerts or message.	**Primary outcome:** Proportion of patients newly prescribed an MRA by the end of the study: EHR alert (29.6%), message (15.6%), usual care (11.7%); EHR alert vs usual care (RR: 2.53, 95% CI: 1.77-3.62); EHR alert vs message (RR: 1.67, 95% CI: 1.21-2.29). **Secondary outcomes:** ***Patient-level;*** Proportion of patients newly prescribed an MRA at 30-days, percentage of patients newly prescribed other GDMT by the end of the study (BB, ACEI/ARB/ARNI), prescribing rate by month of study. ***Provider-level;*** Prescribing rate for new MRA, prescribing rate for other GDMT (BB, ACEI/ARB/ARNI), engagement with clinical decision support intervention.

ACEIs, Angiotensin-converting Enzymes Inhibitors; ARBs, angiotensin receptor blockers; BBs, Beta Blockers; DHT, Digital Health Technology; EHR, Electronic Health Record; GDMT, Guideline-directed Medical Therapy; HF, Heart Failure; HFrEF, HF with Reduced Ejection Fraction; HR, Hazard Ratio; Left Ventricular Ejection Fraction; LVEF; MRA, mineralocorticoid receptor antagonist; RCT, Randomized Controlled Trial; RR, Risk Ratio.

Table 4.

Examples of trials that tested prescription coverage interventions following myocardial infarction

Intervention tested in trial	Trial Methods	Outcomes and main results
The Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study (ARTEMIS).[19] **Design:** Cluster randomized clinical trial.	**Population:** 301 hospitals (11,001 patients with MI. (median age 62.0 years, 31.4% female). **Setting:** United States **Intervention:** Co-payment voucher intervention for clopidogrel or ticagrelor. **Control:** usual care without vouchers for one year.	**Primary outcomes:** Coprimary endpoints were persistence of P_2Y_{12} inhibitor therapy at 1 year, defined as continued treatment with missed doses for ≥30 days (adjusted OR, 1.19 [95% CI: 1.02 – 1.40]); and MACE at 1 year, defined as the composite of death, recurrent MI, or stroke (adjusted HR, 1.07 [95% CI: 0.93 – 1.25]). **Secondary outcome:** Type of P_2Y_{12} inhibitor prescribed; Pharmacy fill–based P_2Y_{12} inhibitor persistence at 1 year; 1-year P_2Y_{12} use by serum drug levels; individual components of MACE at 1 year; bleeding
Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE).[20] **Design:** Cluster randomized clinical trial.	**Population:** 2,980 insurance-plan sponsors (5,855 patients post MI, mean age 53.7 years, 24.9% female). **Setting:** United States. **Intervention:** Full prescription coverage of insurance plan sponsors for any brand-name or generic statins, BBs, ACEIs, or ARBs. **Control:** Usual coverage paid out-of-pocket costs established by their insurance plan for prescribed medications.	**Primary outcome:** Composite of first major vascular event, defined as fatal or non-fatal acute myocardial infarction, unstable angina, stroke, or HF, or revascularization (HR, 0.93; 95% CI: 0.82 - 1.04). **Secondary outcome:** Rates of medication adherence; total major vascular events or revascularization; the first major vascular event, and health expenditures.

ACEIs, Angiotensin-converting Enzyme Inhibitors; BBs, Beta Blockers; DHT, Digital Health Technology; EHR, Electronic Health Record; GDMT, Guideline-directed Medical Therapy; HF, Heart Failure; HFrEF, Heart Failure with Reduced Ejection Fraction; HR, Hazard Ratio; Left Ventricular Ejection Fraction; LVEF; MACE, Major Adverse Cardiovascular Events; OR, Odds Ratio; RCT, Randomized Controlled Trial.

Table 5:

Key terminology in implementation science

Term	Definition
Adaptation	The extent of changes to the implementation intervention during the process of implementation.
Conceptual frameworks for implementation	Systematic methods to describe how interventions can be implemented and how barriers to implementation can be addressed.
Diffusion of innovation	The study of how ideas, theories, products, or innovations gain uptake over time within a given population.
Evidence-based intervention	A treatment with established efficacy for improving health outcomes in a randomized controlled trial.
Fidelity	Degree to which an intervention is delivered as intended.
Feasibility	The extent to which an intervention can be delivered as intended within a given environment. Feasibility trials are often small-scale trials performed prior to undertaking the main trial that evaluate the ability to provide the intervention in smaller, controlled settings.
Health equity	Fair and just opportunity for all individuals to achieve their full health potential, regardless of demographic, cultural, social, economic, or geographic attributes.
Hybrid-effectiveness trial	A trial that tests the effect of an intervention on both health-related and implementation outcomes.
Implementation outcome	An outcome that measures implementation success. Acceptability, feasibility, fidelity, cost, penetration, and sustainability are conceptually distinct implementation processes that can be used as implementation outcomes.
Implementation science	The study of methods for increasing the systematic uptake of evidence-based interventions in clinical practice.
Implementation strategy	A strategy or model of care designed to increase the uptake of a given evidence-based intervention.
Implementation trial	A trial that assesses the effect of an implementation strategy.
Knowledge translation	A process of knowledge synthesis, dissemination, and application to improve the health of people.
Penetration	The integration of an intervention or practice in a clinical setting.
Scalability	The ability of an intervention that is effective in a small population under somewhat controlled settings to be delivered to a larger, more representative population.
Sustainability	The degree to which an evidence-based intervention can be maintained over time after the termination of the study and external support.

Table 6:

Conceptual frameworks for implementation

Type	Description
Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM)[22]	• A 5-factor framework to assess the public health impact of an intervention: Reach, Effectiveness, Adoption, Implementation, and Maintenance. • Reach: Proportion of the target population participating in the intervention and their representativeness. • Effectiveness: Degree to which the intervention achieves its intended outcomes. • Adoption: Willingness of individuals, systems, or settings to adopt the intervention. • Implementation: Extent to which the intervention is delivered as intended, including associated costs. • Maintenance: Extent to which the intervention is incorporated into institutional practices and sustained over time in the usual care.
Knowledge-to-Action (KTA)[22]	• A process for translating knowledge into action and continuously testing the impact of that action in iterative cycles to generate more knowledge. • Knowledge generation and synthesis phase: – Identification of the knowledge that needs to be translated into action. – Review and synthesis of existing evidence and determination of the best approach to apply it in a specific context. – Adaptation of the application or intervention to the target audience's needs, accounting for to local / regional context. • Implementation phase: – Assessment of the multi-level factors that may impact the success of the intervention. – Development of strategies can address the specific barriers and facilitators to successful implementation. – Data collection to guide knowledge generation.
Normalization Process Theory[22]	• Utilizes sociological theory to create a framework that connects research, policy, and practice. It comprises four constructs: Coherence, Cognitive Participation, Collective Action, and Reflexive Monitoring. • Coherence: clarity and distinctiveness of the intervention. • Cognitive participation: individuals' likelihood of perceiving the intervention as beneficial. • Collective action: how the intervention impacts the work of its users. • Reflexive monitoring: how the intervention is perceived during use and identifying opportunities for improvement over time.
Consolidated Framework for Implementation Research (CFIR)[23]	• Guides complex intervention evaluation and implementation with 5 domains: intervention, outer and inner setting, individuals, and process. • Intervention characteristics domain covers design, complexity, adaptability, and evidence strength. • Outer setting domain relates to political, economic climate, patient needs, and community involvement. • Inner setting domain includes leadership, culture, and resources of the organization. • Individual characteristics domain includes knowledge, attitudes, and skills of those involved. • Process domain covers planning, executing, and evaluating the intervention. • Widely used to identify key factors affecting implementation success.

Table 7.

Type of effectiveness-implementation hybrid trials

Type of hybrid trial	I	II	III
Typical research aim	**Primary:** Evaluate the therapeutic effectiveness of a clinical or public health intervention on patient or population health outcomes. **Secondary:** Describe the implementation context or feasibility.	**Co-primary:** Simultaneously evaluate the therapeutic effectiveness of a clinical or public health intervention and the fidelity or adherence to the implementation.	**Primary:** Evaluate the effect of an implementation intervention on implementation outcomes. **Secondary:** Assess the health outcome of the implementation intervention.
Trial outcomes measures	**Primary:** Health-related outcomes. **Secondary:** Feasibility, acceptability and viability of the intervention with potential barriers and facilitators.	**Co-primary:** Health-related and process outcomes.	**Primary:** Process outcomes related to implementation. **Secondary:** Health-related outcomes.

Table 8.

Randomized trial designs used in implementation trials

Description	Considerations	Example
Cluster randomized trials		
Parallel group cluster RCT		
Clusters are randomly allocated to a treatment group, and remain in the allocated group till the end of the trial. No crossover between groups or clusters to alternative interventions or comparator group.	• Suitable when the intervention requires delivery at the cluster level (e.g., hospital penalties) or there is risk of contamination through delivery at the individual level (e.g., a quality improvement scheme delivered by a single clinician as part of intervention may influence the way they treat patients allocated to the comparator group).	To evaluate the effectiveness of audit and feedback of heart failure performance measures in the CONNECT-HF trial, 161 United States hospitals were cluster randomized to an intervention combining targeted quality metrics and clinician education programs.[12] The targeted quality metrics included GDMT prescription at discharge. **Primary outcome**: Enhancement of the composite quality of care score for the participating hospitals.
Cluster crossover RCT		
Clusters or groups (e.g., hospitals) are randomly allocated to a treatment or comparator group, and cross over to the other group at least once.	• Appropriate for limited sample sizes or limited trial resources. • Each cluster serves as its own control, minimizing imbalances in characteristics between clusters. • A washout period may be necessary to minimize contamination or carryover effects from previous interventions.	To evaluate the effectiveness of a hospital policy of incremental perioperative antibiotics in reducing device infection for cardiac implantable electronic device procedures, the PADIT trial[31], randomized 28 hospitals to different antibiotic strategies between which the clusters crossed. **Primary outcome:** One-year hospitalization for device infection within the high-risk group.
Stepped wedge cluster randomized trials		
After a baseline period, clusters cross over from usual care to intervention in a randomized sequence. Clusters then receive the intervention till the end of the trial.	• Suitable when a choice has been taken to deploy a strategy across an entire health system, when there is evidence that risks are low, and when there is preference for all clusters to receive the intervention. • Requires smaller number of clusters as treatment effect is established from within-group and between-group comparisons at each cross-over step, increasing statistical power.	In the PACT-HF trial that assessed the effectiveness of a transitional care strategy in patients hospitalized for HF, 10 hospitals were randomly assigned to receive an implementation intervention comprising services shown to be efficacious in explanatory trials.[14] Hospitals crossed over from delivering usual care to the intervention in a random sequence. **Primary outcome:** Composite emergency department visits for any cause, HF readmission or death at 3 months.
Adaptive trials		
Sequential trial design: sequential multiple assignment randomized trial		
Based on prespecified decision rules, the dose, nature, or delivery of an implementation strategy (or intervention) are adapted at multiple phases. The participant is randomly (re)assigned to one of multiple implementation strategy options at each step.	• Utilized for several pragmatic decisions to effectively facilitate implementation. Suitable when enough sample size is present for adaptive implementation strategies and there is good control over the implementation intervention in group. • Allows for early termination based on efficacy, futility, or harm.	In the ongoing 3-phase QuitSMART trial, clinics and then patients are randomized in a sequential fashion. Initially, clinics are randomized to two different EMR configurations to increase enrolment in tobacco cessation Quitlines, an evidence-based program where patients receive pharmacotherapy and behavioral interventions via telephone, text, or online platforms.[34] In the opt-in configuration, the clinician must opt in to initiate a referral to the Quitline, whereas in the opt-out configuration, tobacco users are automatically referred to the Quitline unless the clinician opts out. During phase 2, patients who are not enrolled in Quitline are then randomized to text messaging or eReferral through the EMR; patients who are still not enrolled are then randomized to receive either the text messaging or text messaging and phone counselling. **Primary outcome**: Enrolment in Quitline.

Description	Considerations	Example
Platform trials		
Examine the effects of at least two implementation interventions in comparison to a control or an alternative intervention concurrently. This study design allows for the intervention and the patient allocation ratio to change over the course of the trial.	• Ideally suited for situations with very large sample sizes, this design is beneficial when evaluating the comparative effects of different implementation strategies, either individually or combined, and when there is good control over the strategies applied to each group.	The NUDGE-EHR trial randomly allocated physicians 1:1 to usual care or one of 15 different EHR-based tools to assess the impact on prescribing of high-risk medications to older adults.[35] At 6 months of follow-up, the EHR-based tools were ranked based on the effect on the primary outcome; physicians initially in the usual care arm were then randomized 1:1 to one of the top 5 EHR-based tools or usual care; physicians who initially received an EHR-based tool that was not in the top 5 were then randomized 1:1 to one of the 5 top EHR-based tools or usual care. **Primary outcome**: Reduction in inappropriate prescribing, defined as discontinuation or tapering of the high-risk drug.

CONNECT-HF, Care Optimization Through Patient and Hospital Engagement Clinical Trial for Heart Failure; EHR, Electronic Health Record; EMR, Electronic Medical Record; GDMT, Guideline-directed Medical Therapy; NUDGE-HER, Novel Uses of Designs to Guide provider Engagement in Electronic Health Records; PACT-HF, Patient-Centered Care Transitions in Heart Failure; PADIT Prevention of Arrhythmia Device Infection Trial; QuitSMART, Quit Sequential Multiple Assignments Randomized Trial