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Original article

A framework for designing hybrid effectiveness-implementation trials for digital health interventions

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ABSTRACT

This article proposes methods for designing randomized controlled trials studying the implementation and effectiveness of digital interventions, meaning websites or applications ("apps") that patients use in healthcare. Deploying digital interventions for behavioral health differs from implementing traditional interventions such as medications or human-delivered therapy. Prior trial design guidance has ignored the existence of international governmental evidence standards, has paid insufficient attention to implementation reporting guidelines, and has not described methods for empirically testing the approach for organizing the delivery of digital interventions. This framework for designing hybrid effectiveness-implementation trials of digital behavioral health interventions helps researchers articulate research questions that matter to decision-makers and meaningfully contribute to implementation. The framework outlines three phases: 1) frame effectiveness and implementation questions in terms of the digital intervention components, types of clinical support for the digital intervention, and specific strategies for implementing the digital intervention; 2) define and delineate actors, activities, action targets, dose, temporality, and outcomes to maximize inference and reproducibility; and 3) specify trial design features used for hybrid classification. We illustrate the utility of this framework with two effectiveness-implementation studies of digital interventions for substance use. This framework can help researchers decide on appropriate methodology and help decision-makers apply findings.

Introduction

Digital interventions include websites, mobile apps, and other health software. Some are "digital therapeutics," that seek regulatory body clearance for claims to prevent, manage, or treat disease [1,2]. This article focuses specifically on digital interventions used by patients as part of behavioral healthcare, including treatment for mental health and substance use. For simplicity, we use the term digital interventions. Meta-analyses suggest that these interventions may improve outcomes for many conditions [3–9] and effectiveness trials support their use by healthcare systems [10–13]. However, translation of this evidence into practice is hindered by the unique implementation challenges of digital interventions [14–22].

Digital interventions may require healthcare teams to learn new software outside of their organization's system so they can assist patients in using it, monitor their use, and follow up. Staffing models may not support use of digital interventions [22]. Patients may not have devices or internet access to engage with digital interventions. Given the

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; DIGITS, Digital Therapeutics for Opioids and Other SUD trial; FDA, Food and Drug Administration; NICE, National Institute for Health and Care Excellence; PICOTS, Population Intervention Comparator Outcome Timing Setting; US, United States.

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novelty and rapid innovation of digital interventions, existing evidence on digital interventions is rarely sufficient to inform decisions relevant to their implementation in healthcare settings, including which products will be impactful, what type of clinical support services are needed to deliver it, and how to design implementation strategies—the methods or techniques used to support intervention adoption, implementation, and sustained engagement [23]. The lack of evidence on how to deploy digital interventions in real-world care has resulted in effectiveness study failures or null results [16,24], and may inadvertently exacerbate health disparities for under-resourced populations [25]. For these reasons, evidence on digital intervention effectiveness and implementation must be obtained concurrently.

Clinical research trials with dual focus on effectiveness and implementation are called hybrid studies [26]. Hybrid studies are particularly suitable for digital interventions, which may have limited evidence, indirect evidence obtained from human-delivered forms of the newly digitized intervention, or evidence limited to particular settings or populations. Even when evidence is limited, health systems may have interest in implementing a digital intervention to meet a treatment need [26,27]. This article offers methods for designing hybrid randomized controlled trials for digital interventions based on a synthesis of current approaches and recommendations in the field.

These methods meet broader calls for studying both digital interventions and approaches for integrating them into practice. A recent White House Report on Mental Health Research Priorities called for "research that evaluates and improves the safety, effectiveness, usability, accessibility, and scalability" of digital interventions [28]. The National Institute for Health and Care Excellence (NICE) evidence standards for digital interventions was recently updated to include deployment considerations [29]. However, researchers have little practical guidance on how to meet these evidence standards. This article offers preliminary guidance by presenting a framework for designing randomized controlled trials that aim to provide evidence on the effectiveness of digital interventions for behavioral health and how to integrate them into real-world care.

Development

This trial design framework was iteratively developed by implementation science and digital intervention experts (coauthors) with first-hand knowledge of considerations that arise when designing hybrid effectiveness-implementation trials of digital interventions in healthcare settings. This framework reflects our own experiences using and studying digital interventions for behavioral health conditions [18–21,24,30–37] and integrates trial design [26,38–42], digital intervention evidence standards [29], and implementation frameworks that enhance clinical applicability [22,23,25,27,43–49]. To identify these sources, we consulted the references of seminal training programs [38] and design papers [30]. We scanned reporting guidelines (www.equator-network.org) and evidence standards [29] to ensure reporting requirements are considered early in the design phase. Our goal was not to systematically review the literature on digital health trials (several reviews already exist) [3–9], but to synthesize trial design considerations and frameworks from different disciplines with our own lessons learned. This synthesis occurred over approximately one year of coauthor discussions and drafts and is summarized in Additional File 1. Early versions of the framework were presented at local and international forums [50–52] to elicit external feedback and discussion for further refinement.

The resulting framework outlines three major phases for designing hybrid effectiveness-implementation trials of digital interventions: 1) framing the research question in terms of domains critical to the effectiveness and implementation of digital interventions; 2) delineating dimensions of those domains; and 3) specifying the experiment and other elements of trial design (Fig. 1). At each phase, the researcher must consider three domains critical to the effectiveness and implementation of the digital intervention: 1) the digital intervention itself [9]. 2) the level of clinical support (e.g., "human touch") necessary for digital intervention delivery [21]; and 3) the implementation strategies that support adoption and sustainment in the practice setting (Table 1) [44,46]. This trial design framework is novel in that it encourages researchers to distinguish between three, rather than two, things. While prior implementation evaluation frameworks differentiate between the intervention and the implementation strategies, we propose that trials of digital interventions must also consider a conceptually distinct domain (clinical support services, described below), and that researchers must explicitly identify which of these domains are to be evaluated in the trial. This distinction has been previously recognized (i.e., categories or continuums of the extent to which digital interventions had provider-involvement), but no framework has yet been made available to guide the design and evaluation of trials along these domains [21,49].

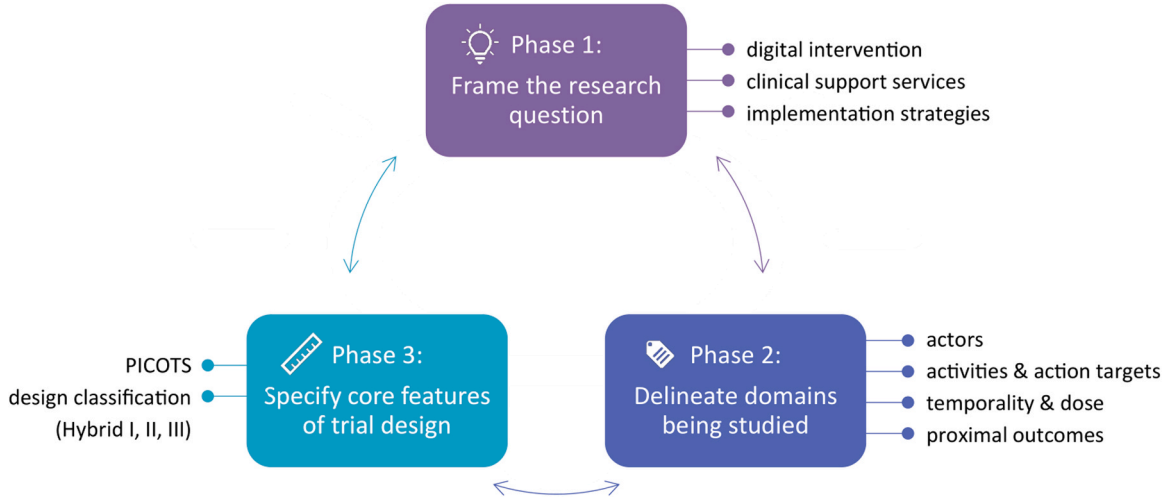

Fig. 1. Digital intervention effectiveness-implementation trial design phases. In Phase 1, the researcher frames the critical questions the study will answer in terms of the digital intervention domains under study, including: 1) the digital intervention; 2) the clinical support services used to enhance intervention delivery, implementation, and/or effectiveness; and 3) the implementation strategies used to promote adoption, implementation, and sustainment. In Phase 2, the researcher defines and delineates the domains under study based on six dimensions (actors, activities, action target, temporality, dose, and proximal outcomes). In Phase 3, the researcher addresses core features of trial design such as setup of the main experiment (Population, Intervention, Comparator, Outcome selection with added Timing and Setting considerations [PICOTS]) and classification of trial design. The double-headed arrows represent the iterative nature of trial design.

Table 1
Domains critical to the implementation and effectiveness of digital interventions.

Domain	Definition	Example Research Questions
Digital Intervention	Software such as websites or mobile apps used by patients as part of healthcare to improve health outcomes. This includes products that have sought FDA clearance as well as products that have not made explicit claims to prevent, manage, or treat disease. These patient-focused digital interventions may be packaged with software that includes clinician-facing features. Diagnostic products, telecommunication devices, and health information technology such as electronic health records are beyond this article's scope.	• What is the cost-effectiveness of the digital intervention compared to usual care[90]? • Will the digital intervention improve patient outcomes in this setting, with this patient population [27]? • Will the digital intervention result in inequitable benefit across patient subgroups[86,91]?
Clinical Support Services	Clinical services that support digital intervention delivery and enhance implementation and/or effectiveness. Services operationalize the approach used in a specific setting or context to assist patients in using digital interventions. This may include how a system will introduce, distribute, and provide enrollment assistance to patients, and subsequently monitor and follow-up with patients to ensure successful digital intervention delivery. A protocolized clinical support service might articulate patient communication and follow-up procedures and clinical workflows, and describe the "who, what, when, where, and how" of digital intervention delivery. A system's ongoing delivery of the digital treatment is entirely dependent on the clinical support strategy.	• What approaches for supporting patient use of digital interventions are feasible [20]? • How much navigation is needed for the digital intervention to be effective [32]? • Are existing clinical staff able to support patient use of a digital intervention, or does the digital intervention require a dedicated clinician and/or outside expertise [31,80]?
Implementation Strategies	Methods or techniques that enhance the adoption, integration, and sustainment of a clinical program or practice [23]. We emphasize that implementation strategies are not clinical programs or practices but influence people or systems to use a practice. Compilations of implementation strategies [45,46] describe activities that influence the adoption, implementation, and sustainment of digital interventions in healthcare. While almost all these implementation strategies target healthcare professionals or systems, literature is emerging on patient-facing implementation strategies to increase patients' roles as active contributors to their own health care.	• How might health systems maximize adoption of a digital intervention in clinics [44]? • What strategies work best to facilitate spread of a digital intervention across a health system[31,44]? • How might health systems encourage sustainment of a digital intervention in clinics and long-term institutionalization within the healthcare setting [92]?

Abbreviations: FDA, U.S. Food and Drug Administration

While we draw from implementation concepts, this is not a new implementation framework [53] but rather a trial design framework intended to help researchers plan for, execute, and communicate about trial design. The framework intends to improve the quality of evidence for digital interventions by ensuring trials are designed in ways that match how they will be eventually deployed. The framework is not intended to be linear: each step requires iteration as design develops. For example, researchers may consider re-framing the research question (Phase 1) after delineating intervention domains (Phase 2) or they may repeat the process for a secondary research question. After outlining the framework, we applied it to two protocol papers to demonstrate its potential utility for designing trials with conceptual and operational clarity.

Framework

Phase 1: frame the research Question(s)

Phase 1 identifies a research question that is timely, relevant to healthcare constituents who will make implementation decisions, and considers the complexity of digital interventions. Reviewing evidence standards against the literature can help researchers understand gaps in the evidence base [29]. It may be necessary to review data produced by treatment developers because digital interventions often undergo updates and adaptation, outpacing the speed of peer-review. People with a vested interested such as health system leaders, clinicians, and digital intervention consumers are another source of information about needed evidence and should be engaged during this process [54]. A systematic review summarized factors important for implementing digital interventions and could guide data collection among constituents prior to trial design [22]. In developing questions, researchers are encouraged to attend to the unique features of digital interventions, which heavily reflect the intersection of technology, patient needs, and accessibility.

Domain 1: digital interventions

Rationale and considerations. Given an abundance of digital interventions and general lack of regulatory oversight [55] constituents need help to know whether to adopt a digital intervention or how to select one digital intervention over another. Several groups have articulated evidence standards around which research questions may be framed. Questions evaluating the impact of digital interventions generally map to NICE evidence standards 13 and 18 (costs, including cost-effectiveness, cost-benefit, or return on investment); 10 and 14 (effectiveness, including patient uptake and outcomes); and 15 (real--world evidence, including equivalence of clinical benefit across patient subgroups) [29]. If developing a new digital intervention, researchers should additionally reference NICE evidence standards 1–9 for design factors, the U.S. Food and Drug Administration (FDA) for disease-specific guidelines, and the digital therapeutic alliance standards [29,56,57]. Research questions about the digital interventions themselves (Table 1) typically reflect traditional effectiveness science (what outcomes can digital interventions improve in a given setting?), although some questions may reflect novel ways in which safety and effectiveness pertain to digital interventions (how will consumer privacy be protected?) [55].

Several factors should be considered when developing the evidence base about the effectiveness of digital interventions. Findings of studies conducted in researcher-controlled settings may not generalize into real-world clinical care where digital intervention delivery neither fits traditional processes for prescribing, payment, nor reimbursement. Studies evaluating the effectiveness of digital interventions in pragmatic settings with interventions delivered by clinical staff, not researchers, are still emerging [31,39,58,59]. While efficacy trials traditionally precede effectiveness trials [26], the ever-evolving technology industry coupled with clinical urgency to meet a treatment need and indirect evidence supporting therapeutic techniques contained in the digital intervention may motivate treatment developers or researchers to skip the efficacy phase.

Domain 2: clinical support services for digital interventions

Rationale and considerations. Clinical support services facilitate digital intervention delivery and enhance effectiveness (Table 1). Examples

include clinical workflows for incorporating the intervention (e.g., processes for introducing, setting up, and monitoring app use), talking points for explaining an intervention to patients, or delivering therapeutic support in conjunction with the app. Research questions about clinical support services (Table 1) yield results that guide health systems in determining approaches for offering a digital intervention to patients and providing support for its use on an ongoing basis. Questions evaluating clinical support services map to NICE evidence standards 6 (defining the level of professional oversight needed for digital intervention); 11 (mapping existing care pathways and system processes with health system representatives); 12 (identifying whether the digital intervention replaces or complements existing care and documenting changes needed in infrastructure, service provision and workforce); and 20 (developing appropriate communication so the digital intervention is understood by clinicians and patients).

Clinical support services are ways of organizing care, similar to how organizing and delivering psychosocial and/or pharmacologic interventions may use care management or collaborative care models [60]. For digital interventions, research questions about clinical support services will yield findings that help systems decide whether to reorganize staffing resources, hire new staff, or contract out services to a third party. Clinical support services can address common problems including logistical failures (e.g., problems with installation and setup of apps); patient unfamiliarity with digital interventions as a care method; and waning patient engagement over time. Researchers may frame research questions in this domain around who can and will provide support (e.g., clinicians, healthcare staff, outside experts), how a system will introduce, distribute, provide enrollment assistance to patients, and subsequently monitor and follow up with patients, and what activities they will use to promote engagement and ensure successful digital intervention delivery. The nature and amount of support provided to patients will depend on the digital intervention and health system. For instance, Hermes et al. defined a "continuum of support" as how delivery systems provide minimal or extensive support to patients in using digital interventions and consider apps as a primary or secondary component of treatment [21].

Clinical support services must be studied with the same rigor used to study digital interventions themselves. Digital interventions are unique because their clinical benefits occur when patients interact with software. Theoretically, they offer benefits without support from a healthcare system because patients can use them on their own. However, evidence supports that human facilitation maximizes patient engagement and clinical effectiveness [11,49,61,62].

Domain 3: implementation strategies

Rationale and considerations. Research questions about implementation strategies (Table 1) provide information about the processes and activities that health systems can use to encourage adoption, implementation and sustainment of digital interventions into real-world care [45]. These questions are particularly relevant when researchers have institutional buy-in for a digital intervention, but leaders are not sure how to best implement in their setting. Questions evaluating implementation strategies map to NICE evidence standard 12 (training that helps clinical teams and patients effectively implement and use the digital intervention while addressing barriers to implementation); 16 and 19 (performance measurement and feedback); and 21 (ensuring the intervention can scale to meet anticipated uptake) [29].

Although prototypical implementation strategies may apply to technology, little evidence shows which strategies are most effective for digital interventions. Graham and colleagues proposed a compilation of implementation strategies, mapping them to specific barriers and facilitators relevant to digital intervention implementation [44]. However, the impact of these strategies on adoption, implementation, and sustainment of a digital interventions has been untested experimentally. Ross and colleagues identified determinants to digital intervention implementation that may be important targets of implementation strategies [22]. Sustainment is a particularly salient concern when implementing technology because software updates over time could impair their fit within the implementation context [30,47].

Research questions about implementation strategies should be framed to clearly distinguish between the implementation strategy, the clinical support services, and the digital intervention itself (Phase 2, below). Clinical support services and implementation strategies may both involve a human-delivered component. To distinguish between them, consider the potential impact of their removal [21]. Clinical support services are a critical part of delivering the digital intervention regardless of implementation phase; removing them results in self-guided use without health system support. In contrast, implementation strategies may intentionally be used for a finite period, for instance to increase adoption by clinicians. Some researchers conceptualize the digitization of an evidence-based practice as an implementation strategy, so distinguishing between the processes of that adaptation and the digital intervention itself may be helpful.

Phase 2: delineate domains

In Phase 2, researchers delineate trial domains (Table 1) by creating a clear a priori representation of boundaries between them. This clarity is critical for specifying core features of trial design in Phase 3. It supports reproducibility and the ability to make collective inferences about digital intervention implementation across studies. Clear, accurate delineation of trial domains helps regulatory bodies and constituents understand digital intervention content and requirements before endorsing, funding, or implementing them.

Delineation procedure

For each domain, we recommend delineation based on dimensions from the Proctor et al. implementation strategy specification process (Table 2): actors, activities, action target, temporality, dose, and proximal outcomes [23]. Researchers should also select and provide justification for the digital interventions, clinical support services, and implementation strategies in the trial, which may be articulated in Phase 1. Researchers identify actors, which could be identified as healthcare consumers, providers, individuals providing clinical support services, or other healthcare staff performing implementation activities. Researchers then specify activities under the broadest definition of each domain, not restricting to activities within specific randomization groups. Activities may include consumer interactions with the digital intervention, provider actions to support activities directed by the intervention, and facilitator actions that support intervention implementation. To maximize transparency, researchers should consider specific and standardized communication about digital intervention characteristics [63]. Next, action targets (ways in which individuals or organizations are affected by the activities), temporality (time and duration of activities), and dose (frequency and intensity of activities) are specified. Finally, proximal outcomes that are immediately affected by hypothesized activity mechanisms are specified [48]. Each of these dimensions could further be characterized on the pragmatic-explanatory continuum to ensure alignment with the research question specified in Phase 1 and to better guide trial design in Phase 3 [39].

Considerations

The delineation process may be difficult because the literature provides few examples of this process [31]. Researchers do not uniformly agree about the presence and characteristics of digital intervention trial domains, especially clinical support services that organize and deliver digital interventions and their implementation strategies. Boundaries between domains are often unclear and may be interpreted differently by researchers, intervention developers, and other constituents. Domains are often context dependent, varying among trials in different

Table 2
Dimensions[1,2] of digital intervention trial domains.

Trial Domain	Example Hybrid Effectiveness-Implementation Study Actors	Example Hybrid Effectiveness-Implementation Study Activities	Example Hybrid Effectiveness-Implementation Study Action Targets	Example Hybrid Effectiveness-Implementation Study Temporality & Dose	Example Hybrid Effectiveness-Implementation Study Proximal Outcomes
Digital Interventions	Healthcare Consumer	1. Health information consumption 2. Symptom/activity reporting 3. Cognitive behavioral therapy	1. Educate patients 2. Increase patient awareness of illness or behavior 3. Manage problems by changing thought and behavior patterns of patients	Digital intervention is available to patients after randomization for X number of weeks (temporality) in which they can engage with up to Y number of digital intervention modules (dose)	**Clinical outcomes:** change in behavior or symptoms
Clinical Support Services	Individuals within the healthcare delivery organization Representatives of the vendor providing the digital intervention	1. Assistance with digital access, app set-up 2. Technical support 3. Supporting digital intervention content 4. Encouragement of skills practice 5. Monitoring treatment engagement and completion	1–2. Address barriers to digital intervention use by patients Offload responsibilities of clinicians 3-5. Support patients' behavior change	Onboarding and technical support provided immediately after app provision (temporality), lasting approximately Y minutes, or as needed (dose) Ongoing clinical support service provided Y number of minutes every Z weeks (dose), spaced evenly across X number of weeks after randomization (temporality)	**Workflow-related outcomes:** Engagement with program content, successful movement through a process
Implementation Strategy	Individuals within the healthcare delivery organization Representatives of the vendor providing the digital intervention Researchers or other external partners who facilitate implementation	1. Education and marketing 2. Audit & feedback 3. Plan-do-study-act cycles 4. Constituent engagement	1. Create clinic-wide demand 2. Clarify measurable goals to improve performance of clinicians who prescribe the app 3. Reinforce patient mastery of treatment concepts 4. Expand support for local clinic implementation	A Y-hours training (dose) with constituents before implementation (timing) Y number of meetings with constituents (dose), spaced out over the course of X number of weeks of active implementation (timing)	**Implementation outcomes:** reach, fidelity, adoption or penetration among providers

[1] Adapted from Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci. 2013;8:139 [23].
[2] Justification is also a dimension articulated by Proctor et al., 2013. Justification may be related to rationale in Phase 1 and will be study specific (see Table 4 for study-specific examples).

settings. The same individual may perform different activities in different domains, depending on the trial. For instance, in some trials, digital intervention coaches might train consumers on a digital intervention as a clinical support service. In others, they may educate providers about the coaching activities, which is an implementation activity. Depending on the study's focus, the clinician-facing features of digital interventions such as dashboards and their use by clinicians to monitor performance and influence practice behavior may be considered clinical support services or implementation activities. The delineation process is flexible, allowing for inevitable variation resulting from introducing novel digital interventions.

Phase 3: specify core features of trial design

After articulating the research question in Phase 1 and clarifying trial domains in Phase 2, Phase 3 specifies core features of trial design.

PICOTS

We use a method that reframes research questions in a precise and testable manner (PICO, for population, intervention, comparison, and outcomes) [41], adding two features—timing and setting—that enhance its applicability to trials of digital interventions (PICOTS; Table 3) [42].

Population. Clearly articulate the primary population targeted by the trial domain—likely one or more actors specified in Phase 2. For instance, in a trial evaluating clinical outcomes of a digital intervention, the primary population is likely healthcare system patients. Trials with more than one level of randomization may target multiple populations, such as patients and providers. Trials with a single randomization level may target one population but influence behaviors of other actors. The goal of defining the population is clearly identifying people targeted by the experimental component of the trial whose outcomes will be measured as a consequence of the randomized intervention or strategy (e.g., providers whose intervention adoption is measured), rather than others who are secondarily impacted.

If the primary population is patients, consider sociodemographic characteristics, condition severity, social or cultural factors, attitudes or beliefs about the intervention, digital literacy, access to digital devices and the internet, preferred language and if the intervention is offered in that language. These considerations may lead to research questions or intervention activities that could be investigated through subgroup analyses of intervention effects.

Intervention and comparator. Experimental designs seek to isolate the impact of an intervention. This can be achieved by comparing the intervention to a comparator group(s). In the intervention group, the researcher adds, removes, or otherwise modifies a domain. Consider whether and how each domain (digital intervention, clinical support service, implementation strategy) will be empirically tested using experimental methods.

The appropriate comparator depends on the research question and domain under study. Resources to help select a comparator group

Table 3
Specifying core features of trial design using PICOTS framework.

	Description	Digital Intervention Considerations	Examples
Population of interest	Who is the trial targeting? What are the important characteristics of this population?	Who are the patient consumers of digital interventions? What healthcare providers or clinical staff will be involved?	• Primary care adult patients who report symptoms of depression • Integrated mental health providers
Intervention	What is being tested by the experiment?	Are researchers testing the effectiveness of a digital intervention, and/or evaluating clinical support services or implementation strategies?	• Digital therapeutic for anxiety disorders that delivers cognitive-behavioral techniques • Workflows optimized to support primary care providers in introducing patients to the digital intervention, assisting with setup, monitoring progress, and providing follow-up • Audit and feedback to increase provider awareness of the extent to which they prescribe the digital intervention when indicated
Comparator	What is the control or comparator?	How will you isolate the digital component (digital intervention, clinical support service, or implementation strategy) under study?	• No treatment or waitlist control • Alternative digital intervention • Usual care • Different dosage or level of support offered
Outcome	What does the researcher hope to accomplish or improve?	Is this an effectiveness, process of care, or implementation outcome?	• Patient behaviors, symptom reduction • Structure and process of care for use of digital intervention, time it takes to link patients to digital intervention and activate it, change in organizational readiness for a digital intervention • Acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainment
Timing	Over what period will the trial occur? What is the period for follow-up and outcome monitoring? How long will it take to reach important implementation benchmarks?	Will the digital intervention change (versioning) over that period? How might clinical support services change? Will there be ongoing adaptation of implementation strategies, and if so, how will adaptations be tracked?	• Trial will begin enrolling patients January 1, 2022 and outcomes will be measured for each participant over a 3-month period • Expectation of 'app' updates • Iterative formative evaluation and quality improvement cycles will lead to adaptations • Dates important implementation benchmarks are reached
Setting	Where does the intervention occur?	Where and under what circumstances will patients be offered a digital intervention?	• Outpatient or primary care clinics • Inpatient or specialty clinics • Direct-to-consumer

Abbreviation: PICOTS, population, intervention, comparison, outcomes, timing, setting

include the Pragmatic Model for Comparator Selection in Health-Related Behavioral Trials. This model outlines comparators for evaluating if a digital intervention works, how well it works relative to a clinically relevant alternative, and how or why it works [40,64].

Trials evaluating effectiveness of digital interventions may compare groups that use and do not use the intervention (e.g., no treatment or waitlist group). These trials answer the question: *Should a healthcare system use this digital intervention?* Trials may compare groups that use different digital interventions, answering the question: *Which digital intervention should be used?* Alternatively, trials may compare groups that use different components of a digital intervention (e.g., digital placebo) [34,65], answering the question: *Which components of the digital intervention provide therapeutic benefit?*

Trials evaluating clinical support services may compare two or more approaches for facilitating the use of a digital intervention. These trials answer questions such as: *Does proactive patient outreach improve patient use of a digital intervention more than provider referral*? These trials manipulate the type or level of clinical care supporting an efficacious treatment [35].

Trials evaluating implementation strategies may compare two or more techniques for enhancing adoption, implementation, and sustainment of a digital intervention in a clinical setting. These trials answer questions such as: *Does audit-and-feedback* [66] *increase provider referral of a digital intervention beyond provider training only?* Delineating domains (Phase 2) will help researchers isolate implementation strategies being tested from clinical support services and digital interventions that are part of the trial but not the experiment.

The Pragmatic Model for Comparator Selection helps researchers select experimental and comparator arms that align with the research question while anticipating challenges and limitations of comparator choices [40,64]. An example is the feasibility and appropriateness of isolating a domain to a specific person or group. Trials evaluating the level of clinical support services needed to sustain a digital intervention might target patients or providers. However, trials evaluating implementation strategies are often cluster-randomized since most implementation strategies often target clinics or providers. Other challenges that might impact selection of experiments and comparators include technology development [21,30], proprietary algorithms in commercial products [56], digital intervention costs and reimbursement, evidence for effectiveness, staffing needs and clinic resources, financial or material support from the researcher, and the technology environment [67].

Outcome selection

Evaluating digital intervention effectiveness. Outcome selection for effectiveness is defined by the field of study. For instance, studies on the clinical impact of digital interventions for substance use disorder may focus on abstinence, use, and treatment retention. Studies of depression may focus on psychological symptoms and mood. Studies seeking clearance from the FDA or other regulatory bodies to establish claims for a digital therapeutic follow disease-specific guidelines for outcome selection.

Evaluating clinical support services. Outcome selection for clinical support services may seek to evaluate cost, efficiency/speed, clinical effectiveness, safety, or implementation outcomes versus a comparator support model. However, we recommend considering proximal outcomes for clinical support services that may be closely linked to care process measures. According to the Structure, Process, Outcomes model for assessing healthcare quality, process measures answer the question: Was good medical care applied [68]? Sociotechnical models [69,70] provide a similar perspective on workflow: Outcomes can be directly linked to actions or processes in a work system.

An example is the activity of obtaining symptom information about a

patient from a digital intervention's clinician dashboard, which can target monitoring patients' behavior change. It could produce the outcome of engagement by contributing patient self-reported information to decision-making while showing patients that clinicians value data that patients input into the digital intervention (Table 2) [69]. Stress, medical errors, and satisfaction may be proximal outcomes for clinical support services that are important to patients, professionals, and/or organizations in settings that experience high burnout, turnover, and ongoing innovation [70]. For trials of digital interventions, pertinent proximal outcomes may include patient or clinician time for patients to install and activate an app, or ease with which providers monitor patient progress (e.g., via follow-up calls, clinician dashboard).

Evaluating implementation strategies. For outcomes appropriate to implementation in general [71], Proctor et al. describe eight distinct implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainment. Hermes et al. recharacterized these outcomes to consider actors, activities, and action targets specific to digital intervention implementation [21]. For example, implementation outcomes are traditionally measured at the provider and clinic level. But digital intervention trials may study patients as direct consumers of digital interventions [72]. Adoption is often considered a provider-level outcome. For digital interventions, adoption can be a patient-level outcome that reflects engagement with the digital intervention [19] or other actors (e.g., coaches, peers) who support digital intervention use. Digital interventions have unique, varying technological infrastructure needs (e.g., technical support, electronic health record integration) that may be targeted by implementation strategies.

Considering mechanisms of change. The most relevant outcomes may be identified by linking digital intervention activities, clinical support services, or implementation strategies to their mechanisms of action, meaning the processes or events through which an implementation strategy or other domain affects effectiveness or implementation outcomes [48]. Mechanisms of action may be one or more action target from Phase 2. For example, a digital intervention to increase physical activity may increase patients' self-efficacy leading to behavior change. A clinical support service that provides a peer-supported digital intervention may increase patient feelings of connectedness leading to higher patient engagement, while a clinical support service that includes optimized workflows for delivering a digital intervention may increase provider efficiency leading to intervention adoption. An implementation strategy of audit-and-feedback may enhance provider awareness and psychological capability to think through the steps necessary to sustain the digital intervention [73]. Causal pathway models can help researchers understand how an implementation strategy impacts proximal and distal outcomes of interest as well as identify determinants that modify the effect [48].

Timing. Research questions should reflect the timing of trial outcome assessment and the extent of possible intervention change during the trial. While dimensions of time are in Phase 2, temporality relates to articulating the time and duration of specific activities. In Phase 3, researchers should consider aspects of timing that relate to the experimental design, which may include the number of weeks or months the intervention is expected to impact clinical outcomes, the number of months or years of active implementation activities, and adaptations over time. Longer trials may be more affected by change over time and experience contextual complexities during implementation [47]. For example, software updates of a digital intervention present challenges for its implementation and evaluation [21,30]. Researchers should be explicit about when they will collect data to track and monitor adaptations to digital interventions, clinical support services (e.g., changes to address staff turnover) and implementation strategies (e.g., changes to address determinants) using established frameworks [74] or how they will use continuous evaluation methodology [75] to routinely and iteratively collect data to compare outcomes over time.

Recent calls have emphasized the need to better understand and measure implementation speed using appropriate metrics [76]. Digital interventions are well-suited for this focus because their scalability is often seen as a key advantage over other approaches. One way to assess implementation speed is by measuring how quickly different phases of implementation are completed. The Stages of Implementation Change (SIC), an implementation process framework [77,78], could be used to track the speed of implementing digital interventions over implementation phases [79] and important benchmarks (e.g., span of time needed for clinicians to consistently demonstrate behaviors needed to competently support patient engagement with the digital intervention, or for health systems to reach sufficient adoption benchmarks) [77,78]. Other digital intervention-specific outcomes could include the time from intervention development to accounts created on a platform and could also consider this with regards to other implementation considerations like reach, in terms of how the demographics of the users creating accounts match desired target populations.

Setting. Setting affects the repurposability of a digital intervention's effectiveness and implementation evidence. For instance, abstinence-based or recovery-oriented digital interventions for substance use disorder may be appropriate at specialty addiction treatment settings whereas substance use reduction apps may be more acceptable to patients in primary care. Types of clinical support services are also setting-dependent. A virtual clinic or department dedicated to providing apps [80] may work in settings with appropriate infrastructure while peer support may be optimal for community-based organizations or health systems like the U.S. Department of Veterans Affairs that provide services to patients that share lived experiences. Implementation strategies may depend on whether the digital intervention requires a prescription or can be downloaded directly. Characterizing setting may help researchers determine what aspects of a trial might apply when 'scaling out' to other settings or populations [27].

Design: hybrid studies

Hybrid studies simultaneously address research questions about intervention effectiveness and implementation. Hybrid studies have a primary focus, often studied with experimental methods, and a secondary focus, sometimes studied observationally. Curran and colleagues classified hybrid studies (I-III) based on their relative focus on effectiveness and implementation [26].

For digital interventions, hybrid studies offer several advantages. First, they are faster than traditional methods of first producing effectiveness data in one study before evaluating implementation in subsequent studies [26]. Digital interventions require a more agile approach to keep up with technology advancement and consumer appetite [75]. Second, effectiveness of a digital intervention may depend on its implementation. For example, if a digital intervention is not implemented with adequate support for patients, it may only improve care for patients with high digital literacy, widening health inequities. Third, effectiveness measured under real-world conditions necessitate some level of implementation activity, making it practical to study both aspects together. Finally, implementation strategies can be tested while questions about clinical effectiveness still exist. This often occurs when health systems begin implementing a digital intervention before clinical effectiveness data is available or when some data is available but questions remain. While our opinion is that researchers should consider NICE standards when selecting a digital intervention (e.g., as above, NICE standards 1–9 provide guidance for generating digital intervention effectiveness) [29], digital interventions that do not meet evidence standards regarding effectiveness data should be tested in a Hybrid Type I trial [26,81].

For studies that investigate the impact of clinical support services, two factors help identify the hybrid design's type: the primary outcome

Table 4
Example application of this framework for designing trials of digital interventions.

	Example #1 (Tula) [32]	**Example #2 (DIGITS)** [31]
Summary of the trial	Tula was a patient-level randomized clinical trial testing the effectiveness of a digital intervention to address the broad spectrum of alcohol use disorder using three different clinical support services for intervention delivery in community-based and healthcare settings [21]. Primary outcomes included costs and likely effects of three approaches to implementing digital interventions that scaled the degree of human touch associated with delivering them. Tula was a Hybrid Type I trial because its primary outcomes evaluated clinical effectiveness (i.e., reductions in risky drinking days and improved quality of life). The study also collected data to evaluate implementation strategies [43,46] directed at health system leaders and clinic staff. These strategies raised visibility of the digital intervention within the health system to drive patient recruitment into the research study.	DIGITS (Digital Therapeutics for Opioids and Other SUD) was a clinic-level randomized clinical trial that implemented a smartphone app for substance use disorder in 22 primary care clinics of a healthcare system [31]. Primary outcomes included reach and fidelity, evaluated using a 2×2 randomized factorial design to simultaneously compare up to one clinical support service (health coaching) and one experimental implementation strategy (practice facilitation) compared to standard implementation. Secondarily, the trial compared population-level effectiveness across clinics that implemented with different models. DIGITS was a Hybrid Type III trial because primary outcomes evaluated implementation, and the trial leveraged clinical staff to conduct clinical support services. The trial had no direct comparator for the digital intervention because of strong inferential evidence for its effectiveness.
Phase 1: Framing the Research Question		
Framing the research question in terms of the components to be tested	What level of person/clinical support (i.e., "human touch") is needed to improve effectiveness of a digital intervention for unhealthy alcohol use?	What implementation strategies and clinical support services can maximize reach and fidelity of a digital intervention for substance use disorder?
Rationale (or Justification)	While it is widely acknowledged that digital interventions hold potential for chronic disease management, little is known about how to optimally integrate them within healthcare systems and the level of human or clinical support needed to optimize treatment effectiveness.	Health systems must solve barriers clinicians face when offering digital interventions to patients, such as tailoring the implementation to their local environment.Patients need support to help them engage in digital interventions, but the best approach for supporting patients within busy primary care settings, without overburdening primary care teams, is unknown.
Specify trial components	**Digital Intervention:** Tula[1] **Clinical Support Services**: Self-monitoring (app only; low touch), peer support from a community organization (medium touch), health coaching within primary care health system (high touch) **Implementation Strategies:** Clinical study champions	**Digital Intervention:** reSET® and reSET-O®[2] **Clinical Support Services:** Primary care staff-delivered support, health coach-delivered support **Implementation Strategies:** Standard implementation, practice facilitation
Phase 2: Delineate components under study by domain		
Digital intervention	**Actors:** Patients with risky alcohol use **Activities:** Spend time using app to engage in: 1) self-assessments; 2) multi-media journaling and communication tools; 3) content and resource library **Action Target:** 1) patients set and review goals; 2) enhance patient motivation; 3) patients gain knowledge and skills **Temporality & Dose:** 90-day access to smartphone app (temporality); patient use of the app is self-guided **Proximal Outcome:** risky drinking reductions, quality of life	**Actors:** Patients with substance use disorder **Activities:** Spend time using app to engage in: 1) community reinforcement approach; 2) contingency management; and 3) fluency training **Action Target:** 1) Increase patient knowledge about healthier ways to meet needs, and desires; 2) Stimulate the brain's reward system when the patient completes learning modules; and 3) Confirm patient understanding of treatment concepts and reinforce mastery **Temporality & Dose:** 12-week smartphone-based prescription (temporality) with recommendation that patients complete 4 modules per week (dose) **Proximal Outcome:** Positive behavior change
Clinical support services	**Actors:** Staff members from community partner outside of healthcare system; health coaches who are employees of the healthcare system **Peer Support Activities:** 1) Provide interpersonal communication via app, 2) Monitor discussion forum **Health Coaching Activities:** 1) Provide up to three 1:1 coaching sessions via phone, 2) Monitor discussion forum, 3) Monitor patient health via a dashboard **Action target (for both activities):** 1) Provide social support and motivation enhancement for patients, 2) engage patients in use of app, 3) Support patients in meeting their goals for alcohol use **Temporality & Dose:** 1 welcome message with ongoing support provided as needed through private messaging and discussion forums (peer support dose) or 3 1:1 coaching sessions (health coaching dose) during the 90-day access period (temporality for both) **Proximal Outcome:** Clinician/implementer engagement, patient engagement, healthcare use and implementation costs, relatedness (measure of social support)	**Actors:** "Centralized" medical assistant who is an employee of the healthcare system **Activities:** 1) conduct phone outreach to patients who might benefit, 2) monitor and encourage engagement, 3) Encourage practice of skills, 4) Facilitate follow-up with care team **Action target:** 1 & 2) Activate patients and reduce burden on clinicians, 3) Support patients' skill development, 4) Promote collaboration between patients and providers **Temporality & Dose:** 4 30-minute health coaching sessions followed by 5 electronic messages (dose) spaced out approximately weekly during the 12-week prescription (temporality) **Proximal Outcome:** Fidelity, increased feasibility of offering support
Implementation strategies	**Actors:** Clinical study champions **Activities:** 1) Engage with local leaders, 2) Build or fortify relationships with underrepresented and minoritized communities, 3) Use targeted digital and print media **Action Target:** 1) Partner with and recruit clinicians and staff from community-based organizations; 2) Invite participation and inclusion of diverse voices, perspective and experiences; 3) Promote the study broadly **Temporality & Dose:** ongoing support for the intervention (dose) before and active implementation **Proximal Outcome:** Clinician perspectives on implementation	**Actors:** Practice facilitator **Activities:** In the context of a supportive relationship, deliver: 1) Education, 2) Audit & Feedback, 3) PDSA cycles; 4) Engagement **Action Target**: 1) Create clinic-wide demand, 2) Clarify measurable goals to improve performance of clinicians who prescribe the app, 3) Reinforce patient mastery of treatment concepts, 4) Support local clinic implementation efforts **Temporality & Dose:** 1 meeting with clinic leadership followed by 12 facilitation visits (dose), scheduled monthly during active implementation (temporality) with ad hoc support (dose) provided via email, phone, or videoconferencing during implementation (temporality) **Proximal Outcomes**: Prescription of the digital therapeutic to eligible patients (reach)
Phase 3: Specify core features of trial design		

(*continued on next page*)

Table 4 (*continued*)

	Example #1 (Tula) [32]	**Example #2 (DIGITS)** [31]
Population	Patients with risky alcohol use	Primary care providers; patients with a drug use disorder
Intervention	Two randomized interventions: 1) Clinical support strategy #1: Peer support (moderate touch) 2) Clinical support strategy #2: Health coaching (high touch)	Two randomized interventions: 1) Clinical support strategy: health coaching 2) Implementation strategy: practice facilitation
Comparator	Self-monitored app-use (low touch)	Standard implementation
Outcome (primary)	Effectiveness (reduction in risky-drinking, quality of life), cost-effectiveness	Fidelity and reach
Timing	3-month active intervention 9-month follow-up Context: COVID−19 required adjustments to the timing of recruitment and implementation.	12-week active intervention (fidelity) 1-year active implementation (reach) Context: Adaptations were made and documented due to COVID−19 disruptions, staffing shortages
Setting	Integrated healthcare setting with partnership from community organizations	Integrated healthcare setting
PICOTS specified research questions	In the context of an integrated healthcare setting with partnership from community organizations (S), do patients with risky alcohol use (P) randomized to use Tula with greater levels of human interaction in the form of either peer-support from community-based partners (moderate support) or health-coaching from the healthcare system (high support) compared to self-monitored use of Tula (low support) have greater reductions in risky drinking (O) over the 3 month intervention and 9-month follow-up period (T)?	1) Clinical support service research question: In the context of an integrated healthcare setting (S), do primary care clinics randomized to health coaching (I) compared to standard implementation (C) have a higher mean number of weeks in which patients with documented drug use disorder (P) use reSET and reSET-O as recommended [fidelity] (O) over the 12-week intervention (T)? 2) Implementation strategy research question: In the context of an integrated healthcare setting (S), do primary care clinicians who care for patients with a drug use disorder (P) in clinics randomized to practice facilitation (I) compared to standard implementation (C) prescribe reSET and reSET-O to a higher proportion of eligible patients with documented drug use disorder [reach] (O) during a 1-year active implementation period (T)?
Hybrid design classification	**Hybrid Type 1:** primary research question(s) related to effectiveness while gathering information on implementation	**Hybrid Type 3:** primary research question(s) related to implementation with a secondary focus on effectiveness

[1] Tula (Sanskrit for "balance"), a digital intervention that operates on smart phones for addressing the broad spectrum of issues related to alcohol use disorder using principles of the Whole Health model [32].

[2] reSET® and reSET-O®, prescription digital therapeutics that operate on smart phones to address SUD and opioid use disorder, respectively using a community reinforcement, contingency management, and fluency training to reinforce concept mastery [93].

(s) and the intervention exposure that will be randomized. For example, a study with clinic-level randomization may test support from a centralized care manager versus from a clinician at the clinic. A Hybrid Type I trial would focus on which approach produced better clinical outcomes (e.g., comparing proportions of patients with improved depression scores). A Hybrid Type III trial would test which approach produced better implementation outcomes (e.g., comparing proportions of patients reached).

Also helpful is considering whether researchers or clinical staff will support the digital intervention. Studies often employ researchers for clinical support services such as identifying patients who could benefit from the intervention, assessing them for appropriateness, providing enrollment and/or technical support, and offering motivational support to engage in the intervention. These studies are likely Hybrid Type I, focusing on effectiveness, and not Hybrid Type III, focusing on implementation, because researchers would not provide clinical support services in real-world care.

The hybrid effectiveness-implementation framework is flexible and subject to revisions [82] given the multitude of implementation study designs and fields that use implementation science. Outcomes most proximal to clinical support services may include process, workflow, or service system outcomes such as timeliness, which are conceptually distinct from clinical and implementation outcomes [69,71]. This may challenge classification of hybrid studies, but these outcomes are unlikely to be primary in randomized controlled trials.

Examples of framework utility

Table 4 illustrates the utility of the framework with two example protocol papers [31,32]. Neither of these trials were designed using the proposed framework; however, this post facto demonstration illustrates how future trials could be specified according to the trial design framework. The lead authors of both protocol papers reviewed and confirmed the application of the framework to their respective trials.

Discussion

The demand for data on the effectiveness and implementation of digital interventions increases the need for trial designs that meet these demands. Healthcare leaders considering deploying digital interventions would benefit from randomized controlled trials designed with considerations to inform their decisions. Our framework supports designing hybrid studies for digital interventions by distinguishing between 3 domains of digital intervention trials: digital intervention effectiveness, clinical services that support digital intervention use in healthcare, and implementation strategies that influence their adoption, implementation, and sustainment (Phase 1). This a working framework that will evolve as the field develops.

Using digital interventions in healthcare raises many questions, so trials may focus on more than one domain. Further, digital interventions, clinical support services, and implementation strategies are often interdependent. For example, a randomized controlled trial may compare several approaches for supporting a digital intervention, with each clinical support service requiring a different implementation strategy (e.g., electronic health record tools to help providers prescribe the digital intervention, plan-do-study-act cycles to refine workflows to support patient use of an intervention). Alternatively, a trial may have a randomization arm for some clinics to use an implementation strategy that tailors and adapts the intervention or support model. This interdependence increases the importance of articulating domain dimensions (Phase 2) and trial features (Phase 3), and the hybrid design classification is well-suited to studying both effectiveness and implementation.

While this framework is scoped to behavioral health interventions, it may scale to other health conditions because digital interventions across all conditions tend to have similar features. For example, digital medical interventions (e.g., for diabetes, hypertension) often have behavior change components (information provision, reminders and tracking, rewards or motivation enhancement) [83]. Similarly, digital behavioral interventions may have objective health measurements and collect biological samples (e.g., breathalyzers, skin blood alcohol readings,

opioid mouth swab tests). However, the implementation needs may differ between medical and behavioral interventions, and aspects of this framework may need to be adapted to the healthcare condition and clinical setting.

Overcoming challenges in specifying trial designs

A challenge in designing hybrid effectiveness-implementation trials of digital interventions is that, with notable exceptions [21,84], early guidance about implementation science methodology was conceived in consideration of human-delivered care. Digital interventions are novel services integrating into traditional care. Challenges to trials to test their effectiveness and implementation include lack of broad reimbursement for digital interventions [85], issues with technological infrastructure, staffing resources, site-specific workflows [69], and barriers to digital literacy [86]. Phase 1 of this framework emphasizes the importance of engaging constituents early to design trials that address these issues. Key constituents include vendors, delivery system leaders, clinicians, consumers as well as people who indirectly interface with the digital intervention such as insurance commissioners, information technology and security officers, and regulatory agencies.

Another challenge is that in addressing site-specific issues, digital intervention trials may generate information that cannot be used in other settings. However, if adaptations to address site-specific implementation determinants are appropriately documented, then findings could more easily be repurposed in other studies [74]. Compared to psychosocial interventions, the need for ongoing adaptations to maximize fit between the intervention and context is likely amplified in the case of digital interventions because they require frequent updates to be contemporary and aligned with technology advancement. Digital technologies, clinical support services, and implementation strategies benefit from contextualized adaptation [30], and delineating trial domains in Phase 2 can increase the specificity and documentation of adaptations. In Phase 2, researchers should consider proximal outcomes for each domain whether or not they are primary trial outcomes. Trials that rigorously document context and/or that explore mechanisms of action underlying implementation are more likely to produce transferable knowledge. Trial findings might guide subsequent implementations or products such as concept maps, implementation toolkits, or service strategy blueprints that can promote knowledge transfer.

A third challenge is that digital interventions that are effective and implemented in one healthcare system may not be feasible in another. Again, this concern is not unique to digital interventions, but the diversity of digital interventions, the lack of healthcare personnel designated and trained to support their delivery, and the technological skills required to implement digital interventions present new challenges to generalizability. While individuals can download apps directly to their digital device, digital interventions are rarely "plug-and-play" when integrated into a service setting. Specifying the core features of the trial design in Phase 3 may determine how a setting is similar or different to other digital intervention settings across PICOTS dimensions. Future research will help determine which features are most important to understanding setting similarity or to define ways to organize contextual variables to support decision-making [87].

Limitations

This framework focuses on the design of hybrid effectiveness-implementation trials of digital interventions for behavioral health in healthcare settings. Questions pertaining to the efficacy or development of new digital interventions were considered out-of-scope although we noted relevant resources [29,56,57]. Similarly, our definition of digital interventions was focused on patient-facing software (with or without clinician facing components) to improve health; the relevance of this framework to other products (e.g., diagnostic, telecommunication, and health information technology) or use of digital interventions outside of healthcare settings is not covered in the framework. Development of this framework was based on an iterative synthesis of coauthor experience with existing literature from various sources ranging from clinical trials to implementation and integrating aspects from those fields that might apply to research conducted in healthcare settings, but our literature review may not have been exhaustive of all potentially relevant resources. Application of this framework also reflected coauthor expertise in mental health and substance use, specifically. While we believe this framework is broadly applicable to other digital interventions for behavioral health, adaptations may be needed for health conditions that have no behavioral component. Finally, this is a new framework and will need to be prospectively tested, particularly the novel concept of clinical support services.

Conclusions

We hope that this framework helps researchers design, review, and execute trials on the effectiveness and implementation of digital interventions to treat behavioral health conditions and helps decision-makers understand how to apply trial findings. While not an implementation framework, our trial design framework helps address evidence standards [29] while advancing translation of evidence to practice so digital interventions are more widely adopted by healthcare settings and patients. Future efforts could build out this framework (e.g., with design templates, CONSORT [88] or StaRI [89] extension) to support its application. Additionally, researchers should update this framework as digital capacity expands and research questions evolve.

CRediT authorship contribution statement

Glass Joseph E.: Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Hermes Eric D. A.:** Writing – review & editing, Methodology. **Matson Theresa E:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Wilson Sarah M.:** Writing – review & editing, Methodology. **Schueller Stephen M.:** Writing – review & editing, Methodology. **Quanbeck Andrew:** Writing – review & editing, Methodology. **Lyon Aaron R.:** Writing – review & editing, Methodology.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.annepidem.2025.02.007.

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