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Embedding clinical trial elements into clinical practice: Experiences from trial designers and implementers

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Abstract

Introduction: Researchers and policymakers recognize that leveraging data routinely collected in clinical practice can support improved research and patient care. Embedding elements of clinical trials, such as patient identification and trial data acquisition, into clinical practice can enable research access and increase efficiencies by reducing duplication of trial and care activities. Yet, cultural, administrative, and data barriers exist. The Clinical Trials Transformation Initiative (CTTI) developed evidenced-based, multi-partner recommendations to facilitate embedding interventional, randomized trials into clinical practice. *Methods:* We conducted in-depth interviews (IDIs) with trial designers and implementers to describe their motivations for embedding interventional, randomized trials into clinical practice. Additionally, we aimed to identify barriers and potential solutions to implementing such trials. Interviews were audio-recorded and analyzed using applied thematic analysis. *Results:* We conducted 16 IDIs with 18 trial designers and implementers. Motivations for embedding trials into clinical practice included the desire to implement a learning health system and evaluate trials in real-world settings. Barriers to trial implementation focused on limited staff time and availability, the lack of buy-in, and difficulties using electronic health record data. Solutions included minimizing healthcare settings and patient burden, having a sufficient data and research infrastructure in place, and creating a culture change. *Conclusion:* The results informed CTTI recommendations to facilitate the design and operation of embedded trials. These recommendations emphasize areas where sponsors and investigators can rethink the design and conduct of clinical trials to ultimately realize an aligned system of research and care.

Introduction

Over two decades ago, the National Academy of Medicines (formerly the Institute of Medicine) set a goal that by the year 2020, "90 percent of clinical decisions will be supported by accurate, timely, and up-to-date clinical information [1]." Traditionally, researchers have considered randomized clinical trials as the gold standard for determining the safety and efficacy of medications or other interventions. However, randomized trials are frequently criticized for their lack of generalizability to patient care in routine clinical practice settings [2,3].

To enable evidence generation to inform patient care, researchers and policymakers have begun to appreciate the potential of studies in which elements of clinical trials, such as patient eligibility and identification, randomization, and data acquisition, are embedded into clinical practice settings when patients are seeking routine care from their healthcare providers [4,5]. These studies align with clinical workflows and leverage clinical care data sources for research purposes. They can increase clinical trial access to representative populations and have the potential to increase trial efficiencies by reducing duplication of trial and care activities, such as data collection.

The concept of embedding clinical trials into clinical practice is not new [6,7]. The National Institutes of Health's Health Care Systems Research Collaboratory initiative was created in 2012 with a mission to "strengthen the national capacity to implement cost-effective large-scale research studies that engage healthcare delivery organizations as research partners [8,9]." However, implementation remains an issue. In addition, the terminology around embedding trials into clinical practice has not reached a state of consensus [10,11]. The literature often associates embedding trials with being pragmatic as viewed through the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)-2 scale, yet the threshold of what is considered pragmatic is not consistent [10–13].

The Clinical Trials Transformation Initiative (CTTI), a public–private partnership, conducted a multi-partner project to appreciate: (1) the rationale for integrating trials into clinical practice, (2) the optimal methodological and operational approaches for embedding trials, and (3) the infrastructure needed to facilitate system-wide integration of trials at the point of care.

The intention of this project was not to define how pragmatic a trial is or whether it is considered a point-of-care trial. Rather, recognizing that cultural, administrative, financial, and data barriers exist and that operational direction is needed to assist with embedding trials, we aimed to develop evidence-based recommendations on how to design and conduct embedded trials, especially those intended for regulatory review of a medical product. Here, we present the qualitative research findings from CTTI's evidence-gathering phase and offer recommendations informed by the findings to facilitate the integration of clinical trials into clinical practice [14,15].

Materials and methods

CTTI projects follow an evidence-based methodology that includes stating an efficiency and quality impediment to clinical trials, convening a multi-partner project team, gathering evidence to understand barriers, and translating the findings into actionable recommendations and tools [16]. The CTTI Trials in Clinical Practice Project Team consisted of partners representing academia, industry, government agencies, institutional review boards, professional societies, patient representatives, and patient advocacy organizations [14].

Study design and participants

As part of our evidence gathering, we conducted a qualitative descriptive study [17,18] using in-depth interviews (IDIs). Study participants were trial designers (those responsible for designing and making decisions about the trial) and implementers (those carrying out day-to-day operations for the trial) of embedded interventional clinical trials with at least one site in the USA. We did not seek to interview representatives from all possible embedded US-based trials but rather we purposively selected [19] designers and implementers who were engaged in US-based trials to ensure that they could comment specifically on challenges and solutions to embedding trials in the context of the US regulatory environment. We also selected designers and implementers who were engaged in registrational trials, or in non-registrational trials intended to be submitted for regulatory review, and whose trials we considered to be embedded into clinical practice because they were integrated into healthcare delivery, closely aligned with clinical workflows, and leveraged existing infrastructure and clinical care data for research purposes, such as using electronic health records (EHRs) to collect research data. Additionally, designers could participate if they took part in the trial decision-making and design process; implementers could participate if they were engaged in the day-to-day operations of an embedded interventional trial.

We drew upon CTTI's multi-partner project team and other expert contacts to identify potentially eligible trials and then representatives of those trials (i.e., designers and implementers). We also conducted informal searches on ClinicalTrials.gov [20] for interventional studies from January 2011 to April 2021 using the search terms "embed," "integrate," "pragmatic," "practical," "large simple trial," "real world," "learning health care," and "point of care," and filtering for interventional trials with a location within the USA. We identified approximately 20 trials that met our selection criteria, and introductory emails were sent to contacts either listed in ClinicalTrials.gov, identified by CTTI's multi-partner project team, or recognized as authors of publications about the study. Upon further screening, six of those individuals did not meet the criteria, as their studies were not leveraging existing data infrastructure, such as the EHR, or were not US based, which was outside of the scope of this research. Additionally, three individuals did not respond; one was unable to meet our timeframe to conduct an interview, and one was not interested in participating. The final interview sample provided sufficient information power [21], which occurs when a qualitative dataset provides rich, descriptive evidence that is useful for understanding the concept under investigation – and in our case, information that is helpful for developing recommendations that are grounded in the experiences of developers and implementers.

Data collection

We first identified conceptual categories to investigate in the interviews based on the study objectives and CTTI project team members' knowledge of the type of experiential information needed to design and operationalize clinical trials in healthcare settings. Next, we developed interview questions for each category and tailored them based on the participants' role and trial type: (1) trial designers, registrational; (2) trial designers, non-registrational; (3) implementers, registrational; and (4) implementers, non-registrational. Interview questions for trial designers focused on the rationale for conducting an embedded trial versus a conventional trial; how healthcare settings were chosen; details about how elements of clinical trials were integrated into the healthcare settings, including any modifications that were necessary and how data were captured and harmonized; perceived benefits, barriers, and risks to using an embedded trials approach; and lessons learned. Trial designers of registrational trials were also asked to describe any conversations they had with regulators during the trial design process. All implementers were asked the same questions. Their interview questions primarily focused on identifying the details of integrating clinical trial elements into healthcare settings, including hiring, recruitment, consent, randomization, scheduling, and data capture and entry; implementer interviews also covered how trial processes were woven into standard of care and any modifications that were necessary for either the trial team or the healthcare setting, as well as benefits, barriers, and drawbacks of the embedded trials approach and lessons learned.

Two trained qualitative interviewers conducted telephone interviews from April 23 to December 17, 2021. Either individual or group interviews (i.e., two people from the same trial) were conducted, depending on participant preference. Demographic information was collected from each participant.

Data analysis

Interviews were audio-recorded with participants' permission, and verbatim transcripts were created using a transcription protocol [22]. Participant demographic characteristics were summarized using descriptive statistics, and applied thematic analysis [23] was used to analyze participant narratives. NVivo version 12 (QSR International) [24] qualitative data analysis software was used to organize the data and apply codes [25] to the transcripts. Two trained analysts first independently applied structural (a priori)

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codes to segment participant narratives into conceptual categories related to the study objectives (e.g., motivations for conducting an embedded interventional trial). Next, the analysts identified and applied content-driven (emergent) codes to participant narratives in each conceptual category, reflecting specific details of designer and implementer experiences with the design and conduct of embedded trials. Inter-coder reliability [26] was assessed on approximately 15% of transcripts during each phase of analysis, and where necessary, discrepancies in code application were resolved through discussion, and agreed-upon revisions to the codebook and coding were made.

Following the completion of coding, analysts reviewed the content coding frequencies to identify common perceptions and experiences. Perceptions and experiences varied greatly. The analysts therefore primarily focused on identifying perceptions and experiences that were shared by three or more trials or participants. However, acknowledging the valuable expertise of all IDI participants, we did occasionally report on experiences or suggestions that were only noted once or twice, where these appeared particularly salient for informing actionable recommendations for successfully embedding interventional trials. Of note, when participants described the same procedures for their specific trial, we combined their narratives and described findings at the trial level. When participants described their own perspectives or opinions, or when they provided information on a topic specific to their role, we described the findings at the individual level. Findings were described in analytical summaries, including illustrative quotes, to convey participant experiences with integrating interventional trials into clinical practice.

Ethics

The Duke University Health System Institutional Review Board (IRB) determined that this research was exempt from further IRB review and waived documentation of informed consent. During the recruitment process, participants were provided with an informational sheet that described the purpose of the interviews and related information (e.g., potential risks). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on research with human participants.

Results

Study participants

We conducted 16 interviews with 18 participants (14 individual interviews and two group interviews), representing 9 embedded trials (4 registrational trials and 5 non-registrational trials). Of the 16 interviews, 9 were with trial designers (representing 4 registrational trials and 5 non-registrational trials), and 7 interviews were with implementers (representing 3 registrational trials and 4 non-registrational trials). For seven of the trials, we interviewed both a designer and an implementer; for two of the trials (one registrational and one non-registrational), we interviewed a designer only.

Participants represented a diversity of trial designs and disease areas. Study designs were adaptive platform, Phase 2 open-label, Phase 3 placebo-controlled double-blind, virtual decentralized, and label extension. Disease areas were COVID-19, cardiovascular disease, multiple sclerosis, fibromyalgia, and Crohn's disease. A majority of participants represented and conducted trials in academic settings. Tables 1 and 2 provide descriptive characteristics of the participants interviewed and their organizations.

Motivations for conducting an embedded interventional trial

Rationale for embedding interventional trials

Trial designers listed three primary reasons for choosing to integrate interventional trials into clinical care, versus conducting conventional clinical trials primarily within clinical research facilities or in healthcare facilities but outside of the clinical care process. First, designers explained that they implemented a learning health system perspective, where they aimed to narrow the gap between clinical care and clinical research to improve knowledge generation and its translation back into clinical care. Second, designers explained that they designed trials to evaluate treatment approaches in real-world clinical practice settings under the premise that conducting pragmatic or naturalistic studies would enable them to determine whether the intervention would prove effective under routine practice conditions. Third, designers said they considered the potential cost savings associated with leveraging existing health networks, informatics infrastructure, and previously curated EHR data. Some designers noted that the high costs of conducting conventional clinical trials can serve as a deterrent to research.

Prospective patient benefits

Participants shared several anticipated benefits to patients that served as motivation to embed trials, including that the results of such trials are likely to be more generalizable than those of conventional trials. Participants also described that these types of trials are powered to detect small differences that matter to patients and may be clinically relevant, and they may facilitate clinician engagement in evidence-based practice.

Prospective healthcare system benefits

Participants postulated that embedding trials holds potential benefits for healthcare systems as well. Participants described that health centers at all levels could increase their visibility by participating in trials, stating that becoming known as a place where cutting-edge clinical research is performed may serve to draw more patients to the healthcare setting. They expressed that this could also improve the retention of existing patients within the healthcare setting.

Prospective sponsor benefits

Participants also pointed out potential benefits to sponsors, suggesting that the possibility of increased efficiency and cost savings across clinical care, research, and discovery could motivate sponsors to become involved with embedding interventional trials.

Perceived and actual benefits after conducting embedded trials

Reflecting on their experiences with integrating interventional clinical trials into clinical care, participants described perceived and actual benefits in two main categories: operational benefits and patient benefits. Operationally, both designers and implementers expressed that the embedded trials methodology enabled a larger scale of operation and larger trials, which in turn allowed for

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Table 1. Participant characteristics

Characteristic	N (%) ($n = 18$)
Type of organization/institution/company	
Academia	12 (67%)
Integrated healthcare system	2 (11%)
Nonacademic medical center	1 (6%)
Integrated healthcare delivery system with embedded regional research division	1 (6%)
Pharmaceutical or medical device industry	1 (6%)
Not-for-profit foundation	1 (6%)
Role at organization/institution/company	
Faculty/clinician	10 (56%)
Program manager/project leader	3 (17%)
Clinical development lead	1 (6%)
Project scientist	1 (6%)
Associate director, research section	1 (6%)
Deputy director, coordinating center	1 (6%)
Chief executive officer	1 (6%)
Number of years in role	
1–2 years	5 (28%)
3–4 years	1 (6%)
5–10 years	6 (33%)
More than 10 years	6 (33%)
Number of years in clinical research	
5–10 years	2 (11%)
More than 10 years	16 (89%)
Number of years of personal engagement integrating interventional trials into healthcare settings[1]	
Less than one year	1 (6%)
1–2 years	2 (12%)
3–4 years	1 (6%)
5–10 years	6 (35%)
More than 10 years	6 (35%)
Not sure	1 (6%)
Number of trials embedded into healthcare settings[a]	
1–2	4 (24%)
3–5	10 (59%)
6–10	2 (12%)
>10	1 (6%)
Role on current study that is embedded into healthcare settings[a]	
Principal investigator/co-principal investigator	10 (59%)
Lead physician	1 (6%)
Program manager/project leader/manager/coordinator	6 (35%)

[a]Data are missing from one participant.

Table 2. Characteristics of participant organizations, institutions, and companies

Characteristic	N (%) ($n = 16$)
Academic[a]	***n* = 11**
Type of university[b]	
Public	6 (55%)
Private	6 (55%)
Approximate amount of NIH funding the university was awarded in fiscal year 2019	
$100 million to up to $299,999 million	2 (18%)
$300 million to up to $499,999 million	1 (9%)
$500 million or more	3 (27%)
Not sure	5 (46%)
Number of years university has been engaged in integrating interventional trials into healthcare settings	
1–2 years	1 (9%)
5–10 years	2 (18%)
More than 10 years	5 (46%)
Not sure	3 (27%)
Pharmaceutical or medical device industry	***n* = 1**
Size of company: A large-size company (market cap over $10 billion)	
Type of product company develops: • Drugs, either therapeutic or preventive • Devices • Biologics • Consumer products	
Nonacademic medical center	***n* = 1**
Medical center size: A large medical center with 500 or more beds	
Number of years medical center has been engaged in integrating interventional trials into healthcare settings: 5–10 years	
Other organization[c]	***n* = 3**
Number of years organization/institution/company has been engaged in integrating interventional trials into healthcare settings: More than 10 years	

[a]Two participants were from the same academic institution.
[b]One participant had joint appointments at both a public and a private institution.
[c]Two participants were from the same "other" organization. NIH, National Institutes of Health.

cheaper and more efficient trial conduct. One participant described that their trial had been able to enroll 15,000 patients using only 40 sites. Patient-related benefits of embedded trials included the ability for patients to take advantage of evidence-based care. Participants described that embedded trials can provide a scientific basis for improvement in health care and can serve as a fair test of whether new interventions are effective.

Utilizing existing healthcare infrastructure was also perceived to potentially increase diversity and representation by making it easier for patients from traditionally underrepresented populations to participate in trials. Table 3, Section 1 includes illustrative participant quotes related to motivation for conducting an embedded interventional trial.

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Table 3. Select participant quotes

Topic		Participant quote
Section 1: Motivations for conducting an embedded interventional trial		
Rationale for embedding interventional trials	Using a learning health system approach	*But my whole philosophy is that care has to look more like trials, and trials has to look more like care. And that you don't need a separate system for research and a separate system for care. In fact, you need one good system because neither of them are very good, and they both need to feed and learn. And that there should be this real-world evidence or observational arm as part of it. Because then, at any point, you always have another way of saying well, what's happening in that routine care group?* —Designer, registrational trial, academia
		I think the reason we decided . . . we want to become – in the IOM's version of learning healthcare system – where we're leveraging the informatics infrastructure, as well as the clinical experience and the research expertise, really to learn how to care for our patients. —Designer, non-registrational trial, integrated healthcare system
	Conducting a pragmatic study to evaluate treatment in a real-world setting	*And the idea is that it's a naturalistic study in the sense that what we're observing is not only the treatment philosophy, but also how the treatment philosophy is used in clinical practice. So, we didn't want to constrain that by anything artificial. And so, we really wanted to evaluate a treatment approach as used in clinical practice, but with the rigor of a randomized clinical trial.* —Designer, non-registrational trial, academia
		Our study team thought it was important to do this as a pragmatic trial capturing as close to real-world patients as possible so that we would have very generalizable results. —Designer, non-registrational trial, academia
	Taking advantage of cost savings conferred by existing infrastructure	*The main consideration was costs here . . . was that if we were able to do this, integrate with healthcare systems, then we can take advantage of already curated data for any of these hundreds of thousands of patients.* —Designer, non-registrational trial, academia
Prospective benefits to conducting embedded trials	Benefits to patients	*I think that an embedded research infrastructure allows for the healthcare system to make better decisions and to help us learn, in order for us to make better decisions, what may be most beneficial to a patient. So, there's a couple of areas of benefit. Number 1 is for patients, whether it is this patient right now that we're enrolling, or future patients. The idea is that we find something that works, or we find something that doesn't work and it gets removed as an option, which hopefully saves time from a patient trying one drug and having to switch to another, or we find that drugs are equivalent, and perhaps we can save money or reduce symptoms in some way.* —Implementer, registrational trial, academia
		I think the biggest benefit is that you study the actual type of patients who are going to be receiving the intervention in the future so that the results should be very generalizable to clinical practice and you use the measures of success often that are used to measure success in everyday clinical practice and so you're not extrapolating from "Well, gee, 30% of patients met the trial endpoint, but that's not really an endpoint that we use every day, and so maybe it will be 40% of patients who would benefit using a different measure that fits with the clinical measure." So, I think that's a major benefit . . . if one can enroll greater numbers of participants, you'll have greater statistical power to identify smaller differences between, say, Treatment A and Treatment B. At least in rare diseases, a lot of times studies are powered to find a blockbuster difference, and finding a smaller difference that may still be clinically relevant is underpowered because of sample size issues. And it would be nice to be able to detect smaller differences that matter to patients, rather than the blockbuster differences that can be detected with smaller numbers of participants. —Designer, non-registrational trial, academia
	Added value to the healthcare system	*I think there's a belief, in some places, that clinical trials are optional, and I think that we need a different perspective . . . access to clinical trials is providing the best clinical care. As opposed to just being optional. I think people are recognizing that they get to choose where they get their care, and if you're at a place where you can get access to newer therapies beyond top clinical care based on existing data, that's a positive thing. And so, I think that healthcare systems will increasingly recognize that's a real value to their membership if they can offer them – effectively offer them, of course.* —Implementer, registrational trial, integrated healthcare delivery system with embedded regional research division
	Increased efficiency in both clinical care and research	*I think the more that they're done, the more that they will become more efficient. And it goes back, I think, to this notion that we face so much uncertainty in the decisions that we make every day in medicine. That seems very much a natural*

(*Continued*)

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Table 3. (*Continued*)

Topic		Participant quote
		direction to aim US health care in order to make both more efficient discoveries, but then to provide just more efficient care in general. But I think that there's not just efficiencies from a clinical trial perspective, but efficiencies from a care delivery perspective that are benefits of this approach. —Designer, registrational trial, academia
Perceived and actual benefits to conducting embedded trials	Operational benefits	*I think being able to hopefully enroll larger numbers of participants because maybe the cost per participant is a little bit lower or the efficiency of recruitment is a little bit greater.* —Designer, non-registrational trial, academia
	Benefits to patients	*Right now a lot of our [trial] work is focused on determining ways that we can have more effective, efficacious, and cleaner care to a patient. We want to get to a point where if you watch one TV show, there's five different psoriasis pills that you can take. Well, what is actually the best one? Is there a best one? Those are the types of things that we try to investigate. We want to be able to help our patients and our providers make smarter decisions financially or symptom-wise for a patient, or anything that you can put in there, if they still maintain that level of function and efficacy for the patient. If you're going to have the same outcome no matter what drug you take, how can we make it work faster, work smarter, and be less expensive for you? That's our goal, whatever disease state that we're in.* —Implementer, registrational trial, academia
		And, I think, the other part was, is that we were impressed that we could reach a much larger population, particularly under-represented groups because it was a lot less burden for them. We could do all of the work centrally and just reach out to them through phone, video, and get people who didn't have to leave work, for example, to come into a dedicated study visit. —Implementer, registrational trial, integrated healthcare delivery system with embedded regional research division
Section 2: Barriers to conducting embedded trials		
Training and study start-up in research-naïve sites		*Just the identification of, screening of patients is very difficult for them; getting them through the first stage because it's not part of their routine day-to-day efforts. And I think that's really been the biggest barrier is getting them to identify and start a screen on a subject. The other big thing is we've had to work with them on kind of what's their elevator pitch for the study so that when the patient comes in and they might be a participant excited to participate, you can give them a two-minute elevator speech and get them excited enough to take the screen. And that is not part of what they do. They don't really understand that. We've had to work really hard to get them to get to that point. None of these clinics, turns out, had much experience at all and they were pretty much research naïve. So, there was just learning what they can and cannot do in terms of doing the research project, what human subjects mean and training. We had to go through a lot of that process and then just kind of the protocols.* —Designer, non-registrational trial, academia
Lack of buy-in at the healthcare system level		*Most IT leaders in hospitals are "pull up the moat, throw the crocodiles in, fill it with boiling water, and never come near IT" people. But in order for data to be transferred, you have to be able to bridge that gap. And that's not how hospital IT people work. They work by thinking if there's a data breach, it's the end of the world. So, the way they achieve that is just by putting up the most colossal barriers to collaboration of anything I've ever seen in medicine. And so, we have to partner with the medical leadership to open the eyes and minds of the IT individuals. And once they see it, they're like "Oh, there's a huge improvement, we should definitely do this sometime." But they had to hear it first before you knew the chance was for the better, and not just super scary and a risk, something bad.*—Designer, registrational trial, academia
Difficulty accessing and using EHR data		*Maybe interoperability of the EHRs or at least in terms of the backend data, maybe having a common nomenclature and maybe an interoperable data model would be helpful. Another "nice to have" would be an EHR system that was adaptable for research. Some are very difficult to adapt.* —Designer, non-registrational trial, integrated healthcare system
		Basically, we created a mapping matrix for each site. We had a spreadsheet with information that we asked the site to provide for us. That enabled REDCap Cloud to know what the data was that they were getting and what format. And then, REDCap Cloud on their side would take the data and make sure that it was in a homogeneous enough fashion for us to be able to look uniformly at data across all sites. —Designer, registrational trial, pharmaceutical or medical device industry

(*Continued*)

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Table 3. (*Continued*)

Topic		Participant quote
Section 3: Overcoming barriers to conducting embedded trials		
Create culture change/ paradigm shift	Institutional level	*It really takes culture change. Embedding these trials, even though it's not a lot, takes a little bit of extra effort from everyone who's in that process of delivering care, without any recognition, without any reward. And until the culture is changed so that it's expected that research is embedded in clinical care and good clinical care is defined by learning from every patient in a learning health system fashion, it's going to be really hard to do these as a one-off.* —Designer, non-registrational trial, academia
		Safety reporting was fundamentally redesigned because we do not have a traditional safety reporting mechanism, because people aren't filling out forms or surveilling for adverse events and serious adverse events. These are docs in the field that are practicing medicine. —Designer, non-registrational trial, integrated healthcare system
		The other thing is that we don't really consider these medications investigational drugs, which means that we're not paying for them and we're not tracking them. There's a lot of red tape and paperwork that goes along with study medications. Pharmacies have to track consent and all this stuff. We don't have any of that in this case. —Implementer, non-registrational trial, integrated healthcare system
	Funding agencies/ sponsors	*And changing the culture of some of these other sponsors as to what it is they're looking for. The NIDDK, which is the NIH branch that studies digestive diseases, for example, is really interested in mechanistic studies and less interested in real-world evidence, comparative effectiveness studies for the moment. And so, part of that is culture change.* —Designer, non-registrational trial, academia
		And this is new. I think the FDA, for example, should, hopefully, have an open mind to more studies being designed this way because I think it challenges prior traditional ways in which we enroll and also monitor patients. —Implementer, registrational trial, integrated healthcare delivery system with embedded regional research division
		Just as much as industry needs a pipeline of things that we need to do, when we start thinking about demonstration projects or other kinds of issues in this area, we actually need to think about things beyond demonstration projects. And think more along the lines of pipelines to say, okay, at varying stages of involvement, that this is what's on the conveyer belt, to give us a little bit more certain future of how these structures will work and how these structures will grow. Even across teams, institutions, and stakeholders and domains. —Designer, registrational trial, academia
Obtain buy-in and engagement	All levels	*There's so much education required . . . educating people to get the buy-in that you need. Buy-in is so important. Buy-in of the patients, buy-in of the providers, buy-in of leadership, buy-in of the pharmacy. Everybody's got to be on board in order for this to run seamlessly because they're all part of the usual care process. If they don't understand, or they don't agree, then it's going to break.* —Implementer, non-registrational trial, integrated healthcare system
	Health system leadership	*The thing that I would highlight, probably most importantly, would be system-level leadership engagement, because I think that we've been able to do this in an incredibly efficient way. But there is still a requirement, especially, to get going for a substantial amount of resources and focus and dedication across innumerable areas of a health system. As this becomes more and more part of care delivery, the activation energy will ideally become lower. But there's no way that we would have been as successful as we have been if we didn't have top-level leadership support.* —Designer, registrational trial, academia
	Patients	*Finding different ways to engage the patient was very important for us. So, not just at getting the gathering of the data, but also at the design level, patient recruitment materials or retention materials. Just so many things along the way where a patient's input [has] shifted the course, the direction of however that was going. So, it was very important.* —Implementer, non-registrational trial, academia
	Sponsors	*There are not opportunities for truly embedded trials, at least that I know of or that are widely advertised. So, we are very restricted in the types of funding that we receive, what we can spend that money on, rules that the FDA has that we must follow that do inhibit an embedded trial or make it quite difficult to accomplish something that is truly embedded.* —Implementer, registrational trial, academia

(*Continued*)

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Table 3. (*Continued*)

Topic	Participant quote
Reduce burden/minimize impact on the healthcare system	*If you go to a small hospital who's never done research before and you say that you want to run a double-blind, placebo-controlled trial on [condition]-positive patients, it can be quite overwhelming. Just those words are a mouthful. So, telling them that because we've designed the system in a way that you don't have to worry about anything extra, all I need you to do is fill out that intake form and I'll do everything else for you, it allows us to expand our population that we're studying, but it was quite a challenge to get that invested and agreeable. We succeeded, and our community hospitals are actually our best enrollers now.* —Implementer, registrational trial, academia
	If you can reduce the burden of redundant data entry, I think that would really help a lot of hospitals work in a research setting more efficiently. Instead of entering the same data in the electronic medical record, and then a lot of the same data into a registry that they may be participating in, like the [Name] registry, and then entering it a third time into a study-specific case book. If you could somehow use one of those other entry points to collect the majority of the data, I think that would help the coordinator focus more on other aspects of the trial, such as patient recruitment and retention. —Implementer, registrational trial, academia
Invest in research infrastructure	*What we were asking the clinical people to do is do what you normally do. And so, we purposefully tried to change their flow and how they take care of patients as little as possible. And what we tried to do is ask them to document things the way they normally would. And then, it would be our job to have a research person that would extract the data in a way that made it comparable and made its fidelity high. I mean, the truth is that we've got a pretty large clinical trials unit here. I think we've got something like 10 coordinators or something. So, we pulled our most senior coordinator at the time to be the one who ran the study.* —Designer, non-registrational trial, academia
	We nested this in routine care. And I'll start with clinicians. Most sites would have one or two clinicians that were involved and trained on the study protocol and part of the IRB. But we worked very hard with a central IRB to define the role of each patient's physician that is different from being a research position if you will. And so, at our practice, I'm part of the research team and was there overseeing recruitment, data entry, dispensing of study medication, assessing eligibility, all of that study stuff. But my [clinical] partner was not because he's a busy clinician. —Designer, non-registrational trial, academia
	What's unique in our setting is that we were able to have a centralized team that was only research staff. And so, because of the way that [company's name] is structured, we are a regional division of research that's embedded within our healthcare delivery system. —Implementer, registrational trial, integrated healthcare delivery system with embedded regional research division
Manage interoperability of EHR systems	*EHR data could be pulled from Epic and Cerner, and most of our sites were Epic and Cerner sites. And then otherwise there were electronic case report forms that could be accessed by any site that had access to the internet.* —Designer, registrational trial, academia
	I think that this is an area that, whether it's clinical research or quality improvement or federal oversight of outcomes across health systems, there's definitely a recognition of the need to be able to leverage EHR data in a more consistent way; make these types of approaches more widespread. —Designer, registrational trial, academia
	The first thing, I think, is having electronic health record systems be able to have consistent information across them. That if I want to grab, say, for example, a pain rating on a 0 to 10 scale, that that would be similar in terms of, no matter which electronic health record system, they would have that as a data point that I could potentially collect. Sometimes just that whole coding piece is a bit of a challenge, and consistency across that. —Implementer, non-registrational trial, academia
Section 4: Lessons learned	
Embedded trials benefit patients	*And we can reach so many more patients conducting studies this way; patients that don't normally get to participate in things. There's a few small clinical communities like in cancer. Clinical trials are a standard of care in cancer at this point. Patients get referred to studies all the time kind of regardless of where they live. But at least, especially in the [national healthcare system], it's the same medical centers that we recruit from time and time again because they're the biggest centers. We want the most bang for our buck when we're recruiting*

(*Continued*)

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Table 3. (*Continued*)

Topic	Participant quote
	patients. So like, world centers don't get included. It's hard to recruit women in the [national healthcare system, but you could in theory target women a lot more easily. —Implementer, non-registrational trial, integrated healthcare system
Embedded trials have the potential to transform health care	*The lesson is we just have to keep doing it more to impress upon more people that it is the right way to do it, so that more people will buy into it, and that this will become a transformation for all health care.* —Designer, registrational trial, academia

EHR, electronic health record; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health.



Figure 1. Improvements for overcoming barriers to conducting embedded trials.

Barriers to conducting embedded trials

Site staff time, availability, and perceived burden of taking part in the trial

Participants explained that clinicians have limited time and fewer incentives to participate in research if it takes time away from their numerous clinical tasks. Finding time to familiarize clinicians with the study concept and conduct training sessions could also be challenging. Training and study start-up were particularly time-consuming with research-naïve sites, where the research team needed to educate site personnel about all aspects of conducting a trial, and where conducting screening and recruitment activities was not always top-of-mind for clinical practice staff.

Lack of buy-in at the health system level

Participants noted that it would be much more difficult to conduct embedded trials without supportive and engaged healthcare system personnel. While buy-in at all levels was deemed important, support from top-level leadership, particularly IT leadership, was seen as critical; participants explained that a lack of IT collaboration could impede trial conduct.

Difficulties encountered accessing and using EHR data

Participants noted that in addition to challenges with obtaining approval to export and use EHR data outside of the healthcare system, interoperability of systems was sometimes an issue. While many healthcare systems use the same EHR programs, some participants noted that they still needed to develop separate templates or platforms to extract and harmonize EHR data across systems. Table 3, Section 2 includes illustrative participant quotes on the barriers to conducting embedded trials.

Solutions: overcoming barriers to conducting embedded trials

Participants offered several recommendations for overcoming barriers to embedding trials into clinical practice. The most commonly mentioned improvements are discussed below and listed in Figure 1.

Create culture change/paradigm shift

Both trial designers and implementers spoke about the importance of changing culture at the institutional and/or designer level in order for embedded interventional trials to gain acceptance as a viable research model. Participants described the need for a change in perspective regarding the relationship between clinical research and clinical care, noting that ideally, research would come to be viewed as a normal part of clinical care, with the clinical team also serving as the research team. Closer alignment between clinical care and clinical research requires changing the way that clinical care and research are conceptualized, integrated, and supported; therefore, participants noted the importance of having engaged leaders who support changes to the traditional research approach. Some participants also called for funding agencies and sponsors to take a greater interest in alternate study designs, such as embedded trials. In particular, participants voiced that it would be helpful for the US Food and Drug Administration (FDA) to be open to the embedded trial model and that the National Institutes of Health, FDA, and other agencies should learn from adjustments made during the COVID-19 pandemic to encourage more adaptation and innovation in the way trials are run.

Participants described concrete ways in which embedded trials represent a paradigm shift from conventional clinical trials and require new ways of thinking about research processes. For example, safety reporting may be different in embedded trials. A participant explained that rather than aiming for drug approval, their non-registrational trial looked at the bigger picture of whether overall treatment paradigms affect patient disability outcomes; this meant that unless an event caused the patient to change therapies, there was no need to report it. Another described that their study medication processes involved much less administrative burden than those of conventional trials, as their study medications were already FDA-approved, and the trial was only tracking outcomes after patients were randomized to receive one of the medications. Participants additionally noted that a change in research culture could encompass an increased acceptance of more parsimonious data collection or changes to institutional cold call policies.

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Obtain buy-in/engagement

Participants expressed that successfully conducting embedded trials often requires staff in the healthcare setting to change elements of their usual procedures. For example, clinicians could be asked to screen and introduce the trial to potentially eligible patients, or they may need to adapt the way they present treatment options to their patients to accommodate randomization. IT or informatics personnel may need to add study-specific programming to the EHR to enable accessing, sorting, and extracting EHR data while pharmacy personnel may be asked to deviate from their normal processes for handling study medications. Thus, obtaining buy-in from healthcare setting staff at all levels was viewed as important for engaging site staff with the study and setting up an effective and collaborative partnership.

Some participants also noted the importance of both provider and patient engagement for successful trial conduct, commenting that providers who are interested and invested in the study are more likely to sign on to the trial themselves and encourage others to participate. Patient buy-in was described as useful for both recruitment and retention and could also be helpful during earlier stages, when engaged patients may inform aspects of study design. Additionally, participants expressed a need for buy-in at the sponsor level, noting that funding for embedded interventional trials needs to be expanded.

Reduce burden/minimize impact on the healthcare system

Participants described that sites and healthcare system staff may be more likely to participate if embedded trials did not impose much additional burden. For example, regulatory reforms around embedded interventional trials could help to alleviate the administrative burden on healthcare sites. Eliminating perceptions of clinician and staff burden, and making the trial seem more approachable, could be accomplished by demonstrating that the trial does not need to impede clinical workflow and will only require minimal effort from clinicians. Participants also noted that providing research support to clinical staff would reduce the burden and make it more likely that they would participate by minimizing the number of tasks staff have to perform in addition to their normal clinical duties. A participant specifically advocated for reducing the burden of redundant data entry, explaining that it would take less time and increase efficiency if data could be entered only once and then transferred into other systems that need it.

Invest in research infrastructure

Designers and implementers expressed that investments in research infrastructure could also serve to minimize burden on site personnel, for example, by having research staff available to assist with regulatory issues. Many participants described that research coordinators played a key role in embedded trials, with duties that included enrolling patients and obtaining informed consent, tracking and scheduling the collection of various data elements, performing data entry, and assisting with data extraction. A few participants explained that their research team included individuals versed in data management, analytics, and statistics who dealt with searching, abstracting, and analyzing the EHR data while other teams included research clinicians, such as physicians or nurses whose responsibilities could include overseeing the study personnel, ensuring proper study conduct, conducting chart reviews, confirming patient eligibility, and conducting study assessments that were outside of routine care. In some settings, these research clinicians were members of a larger research unit that was embedded in the healthcare system and that routinely assisted with the conduct of clinical trials across the enterprise.

Manage interoperability of EHR systems

Participants most commonly reported managing data collection across EHR systems using conventional electronic data capture platforms. To address the challenge of interoperability issues across healthcare EHR systems, participants developed a variety of solutions, many of which involved creating templates to extract data from EHRs or abstracting data manually. A trial designer mentioned specifically partnering with health networks that used the PCORNet Common Data Model, which includes curated EHR data, to address the issue of interoperability [27]. To facilitate embedded trials, participants suggested that changes are needed to EHR systems to make it easier to obtain enrolled patient data from any healthcare system and leverage EHR data in a more consistent way across healthcare systems. Table 3, Section 3 includes illustrative participant quotes on overcoming barriers to implementing embedded trials.

Discussion

Embedding randomized clinical trials into routine clinical practice is a noteworthy goal, yet experience remains limited. Indeed, for such trials to be utilized more, it is important to leverage the learnings from those who have previously conducted embedded trials.

This research describes experiences from trial designers and trial implementers and highlights a number of key suggestions, specifically, minimize the impact on healthcare settings and patients; obtain buy-in from healthcare settings and staff; have sufficient data and research infrastructure in place; and create a culture change facilitated by tailored messages to partner groups and education of partners who are part of "the usual care process" (e.g., patients, providers, leadership, and pharmacists). Understanding these barriers and proposed solutions is necessary to develop evidence-based, actionable recommendations to implement embedded trials.

The results of these qualitative interviews along with input from two CTTI-hosted Expert Meetings, informed a set of actionable recommendations developed by the multi-partner project team to facilitate the integration of randomized, interventional trial elements into clinical care [14]. These recommendations provide study design considerations, operational approaches, and suggestions on the cultural shifts needed to enable widespread integration (Figure 2). The recommendations emphasize that embedding elements of a trial into clinical practice is not "all or none." Benefits can be gained regardless of the number of elements embedded. The recommendations also note that (1) the use of healthcare data sources for research purposes should be fit for purpose; (2) the trial design should aim to align with clinical workflows; (3) healthcare settings and sponsors should ensure site readiness to embed trial elements; and (4) leaders at the regulatory, funding, and health system level need to recognize and advance the message that embedding trials can improve evidence generation. In order to appreciate site readiness, CTTI developed the Embedding Trials Feasibility Survey for sponsors and researchers to assess the capacity and feasibility of sites to embed elements of a clinical trial into clinical practice [14,28]. Five case examples accompany the recommendations, illustrating individual trials that have embedded trial elements into care [14]. The case examples feature experiences within and outside the USA, review challenges

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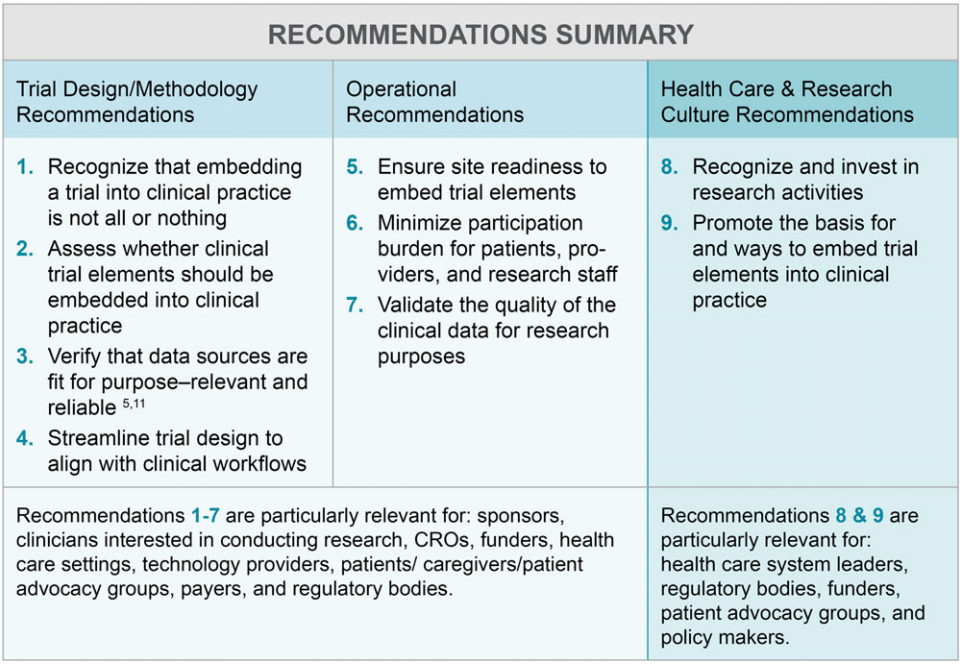


Figure 2. Summary of CTTI's embedding clinical trials into clinical practice recommendations. CTTI = Clinical Trials Transformation Initiative.

encountered, and provide words of wisdom to those who may consider integrating a trial into clinical practice. The RECOVERY study is one such example in which patients in intensive care units in the United Kingdom were randomized to different investigational and approved medical products to assess appropriate interventions for COVID-19, and data collection was facilitated with linkage to national healthcare datasets [29]. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) is yet another example, with hundreds of sites throughout the United States and globally, which used the EHR to identify patients and capture outcomes and endpoints that aligned with routine care [30]. Both examples aimed to make relevant results available in close to real time.

In addition to CTTI's work, other initiatives are focused on advancing the ability of healthcare systems to integrate trials [31]. The Duke-Margolis Center Health Policy Center conducted meetings on the subject of point-of-care trials, released a white paper on the topic, and created the Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC) to understand and implement well-designed, large-scale point of care trials [32,33]. FDA leadership continues to emphasize the importance of exploring the potential for embedding trials, acknowledging the need to integrate clinical trials directly into clinical care to avoid a separate infrastructure for clinical research [4]. The Advanced Research Projects Agency for Health recently launched the Advancing Clinical Trial Readiness (ACTR) initiative to establish a robust clinical trial infrastructure to enable 90% of eligible Americans to take part in a clinical trial within a half hour of their home [34]. ACTR aims to demonstrate the trial design and infrastructure needed to operate trials at the point of care [34].

This work acknowledges the benefits of embedding trials into clinical practice, while also appreciating the barriers, and provides operational recommendations to facilitate integration. Ultimately, this work aims to draw attention to areas where researchers and policymakers can rethink the design and conduct of clinical trials to ensure appropriate protection and respect of participants, allow for the collection of quality data to answer meaningful research questions, and encourage the development of a learning health system through improved clinical evidence generation. Additional work is needed to fully appreciate the implementation of these trials in various contexts and how the recommendations provided here support successful implementation.

Limitations

A limited number of trials met our inclusion criteria for an embedded clinical trial. Although we were able to group narratives and identify commonalities within some of the topics investigated, some of the information we provided was mentioned by only one trial or one participant. Additionally, a different group of participants may have described different or additional experiences to those documented here. However, particularly given the challenge of identifying the specific design and methodology that reflect this type of trial, recognizing that we viewed the term "pragmatic" in the definitional, practical sense rather than based on a PRECIS-2 score [32], we believe our findings are broadly reflective of the motivations, barriers, and facilitators to conducting these types of trials. It is also important to acknowledge that barriers and facilitators to integrating research into practice may vary according to the trial's context, including the setting (e.g., academic medical center vs. community setting), approach (pragmatic vs. traditional), question of interest (e.g., efficacy vs. effectiveness), and intervention (medication vs. behavior vs. healthcare delivery). Lastly, we note the focused scope of the study and the accompanying CTTI recommendations. The recommendations focus on operational and design considerations of embedding elements of clinical trials into clinical practice. Topics, such as financial and ethical implications, were outside the scope of this work.

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Conclusions

Embedding elements of clinical trials into clinical practice can enhance knowledge generation and promote the translation of that knowledge into improved patient care. It also has the potential to increase trial quality and efficiency by reducing duplication of trial and care activities and lessening patient burden by allowing patients to participate in research in their usual routine care setting. The research and recommendations outlined in this article recognize the barriers to embedding trials into clinical practice, provide operational recommendations to facilitate integration, and draw attention to areas where we can rethink the design and conduct of clinical trials to ultimately improve access to research and care.

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