

# Envisioning clinical trials as complex interventions

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Clinical trials are critical components of modern health care and infrastructure. Trials benefit society through scientific advancement and individual patients through trial participation. In fact, billions of dollars are spent annually in support of these benefits. Despite the massive investments, clinical trials often fail to accomplish their primary aims and trial enrollment rates remain low. Prior efforts to improve trial conduct and enrollment have had limited success, perhaps due to oversimplification of the complex, multilevel nature of trials. For these reasons, the authors propose applying implementation science to the clinical trials context. In this commentary, the authors posit clinical trials as complex, multilevel evidence-based interventions with significant societal and individual benefits yet with persistent gaps in implementation. An application of implementation science concepts to the clinical trials context as means to build common vocabulary and establish a platform for applying implementation science and practice to improve clinical trial conduct is introduced. Applying implementation science to the clinical trials context can augment improvement efforts and build capacity for better and more efficient evidence-based care for all patients and trial stakeholders throughout the clinical trials enterprise. **Cancer** 2022;128:3145-3151. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](#) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

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## INTRODUCTION

Clinical trials are critical components of modern health care and infrastructure. Trials benefit both society and individuals through knowledge generation and improved care, with some considering enrollment in a clinical trial as the best management for a patient with cancer.<sup>1</sup> Accordingly, billions of dollars are invested annually in clinical trials, with nearly \$10 billion invested each year in oncology trials alone.<sup>2</sup> Despite these significant advantages and investments, one in five cancer clinical trials fails in its primary aims (e.g., not reaching its primary end point), and enrollment rates remain low even for eligible patients.<sup>3,4</sup> Clinical trial improvement attempts to date have neither produced significant improvements to completion and enrollment rates of existing trials nor advanced our understanding of how best to implement a new trial.<sup>5-7</sup> In other words, clinical trials have significant evidence-based societal and individual benefits, yet persistent gaps in implementation. For other interventions, we could look to dissemination and implementation research to help bridge such a research-to-practice gap. For example, we know that smoking cessation improves health; implementation science looks to optimize real-world health outcomes by improving the implementation of evidence-based smoking cessation programs. We propose a new approach: adapting implementation research into the clinical trials context. We envision studying clinical trials as complex evidence-based interventions, often with poor implementation, to help address gaps in the successful implementation of trials.

This framing serves to fill a gap in the science of clinical trials. Prior work on trials has focused on statistical design and outcome analysis, primarily for the design of trial protocols, but has underemphasized methods to study and improve how trials are implemented. By approaching trials as complex interventions with poor implementation, we can apply the growing knowledge base of implementation science in considering the varied contexts of clinical trial conduct, opportunities to tailor trial improvement interventions, and data-driven design at the outset to improve clinical trial conduct. In this commentary, we will first consider the evidence base supporting clinical trial benefits and challenges facing trial implementation, then review prior attempts to improve trial conduct. Next, we will describe implementation science approaches and outline their application to the trials context, including a worked example considering a hypothetical cancer clinical trial. Finally, we will propose next steps for approaching cancer clinical trials in the implementation

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science context. Through these efforts, we hope to build a platform of clinical trials science to enhance trial improvement efforts out of the implementation science field, establish a shared vocabulary to facilitate theory-based development and comparison of trial improvement strategies, and support improved return on investment for patients, investigators, and sponsors.

## EVIDENCE FOR CLINICAL TRIAL BENEFITS AND PRACTICE GAP

First, we must ask: why it is necessary to improve clinical trial implementation (i.e., the implementation of a clinical trial itself)? The benefits of well-conducted clinical trials are widespread and robust. These benefits apply both to society and to participants in trials. Participation in cancer clinical trials saves lives and is indispensable to research infrastructure. For example, an estimated 3 million life-years were gained through 2015 from just 23 Southwest Oncology Group cooperative group trials.<sup>8</sup> Individuals benefit from enrollment in clinical trials, including participants in standard of care arms, perhaps due to a “trial effect” or improved local infrastructure.<sup>9–11</sup> Some benefits may be ascribed to a “protocol effect,” because the care provided on a clinical trial is essentially perfectly delivered in alignment with the trial protocol, most often by specifically trained research staff who are dedicated to the trial. This results in near-perfect implementation of treatments on trials within a highly controlled context. In contrast, real-world implementations often result in lower effectiveness, representing the “implementation gap,” experiencing a “voltage drop” in benefits between trials and the real world.<sup>12</sup> In simple terms, participants in a well-designed clinical trial can expect better care. These findings demonstrate clinical trial benefits for society and patients regardless of treatment arm, when trials are implemented well.

However, significant gaps remain in clinical trial implementation. For instance, approximately one in five cancer clinical trials will fail to reach its anticipated end point, mostly due to poor accrual.<sup>4,7,13</sup> Even for trials considered “completed,” an additional one in three does not attain at least 85% of its target enrollment.<sup>14</sup> At the patient level, only an estimated 2% to 8% of patients with cancer are enrolled into clinical trials.<sup>3,15</sup> These poor enrollment and completion rates result in significant waste, delays, and challenges in interpreting clinical trial results.<sup>13,16</sup> Furthermore, the population enrolled into trials is generally not representative of the population as a whole, as most trial participants identify as White and

are more likely to have higher socioeconomic status than the general population.<sup>3,17</sup> If cancer clinical trials provide treatment at least equivalent to and likely better than standard of care, poor enrollment suggests cancer patients are missing treatment opportunities and the benefits of trials are inequitably distributed due to poor trial implementation. The reasons for these gaps and how best to address them remain unclear.

## INTERVENTIONS TO SUPPORT TRIAL IMPLEMENTATION: PRIOR APPROACHES TO TRIAL IMPROVEMENT

Recognizing the gap in trial enrollment and completion issues, past improvement interventions have primarily focused on improving enrollment to existing trials. However, a lack of prospective, experimental designs, limited contextual assessments and overarching frameworks to guide these efforts unfortunately leads to low-quality evidence and difficulty replicating interventions.<sup>5</sup> Some programs are currently working to improve trials. Trial Forge in the United Kingdom and the US-based Clinical Trials Transformation Initiative, for example, are working to improve trial processes, including developing methods to test trial improvement interventions.<sup>18–21</sup> However, the lack of a consolidating theory and approach to trial improvement makes comparison between strategies, and theory-based design for new strategies, difficult. This results in an ironic lack of evidence for how best to implement evidence-generating trials.

## IMPLEMENTATION SCIENCE APPROACHES

Taken together, clinical trials have evidence-based benefits that are often diminished by poor implementation, and prior attempts at trial improvement have not made significant impacts. Implementation science approaches may aid in addressing these gaps. Implementation science is a growing field integrating contextual assessment and behavior change to improve the sustainable uptake of evidence-based interventions.<sup>22</sup> The field focuses on taking interventions with proven benefits and addressing the “evidence to practice gap” between the theoretical benefit of interventions, such as the results from clinical trials, and their real-world benefits. The difficulty in translating benefits is at the core of implementation science: for example, it is well-known that smoking cessation and appropriate diabetes care save lives, but achieving these goals in the real world requires varied and context-dependent strategies for effective implementation.<sup>23</sup> Even if a smoking cessation program is proven beneficial in a clinical trial,

this program may not work in every setting, and strategies to implement it must be studied, tested, adapted, and deployed to optimize the chances of sustainably reducing the smoking rate.<sup>24</sup>

The difficulty of implementing such programs is partially due to the multiple levels, components, processes, and stakeholders involved in a smoking cessation program, referred to as a complex intervention.<sup>25, 26</sup> These difficulties often result in an evidence-to-practice gap between how complex interventions perform in experiments versus in the real world, in this example a lower rate of smoking cessation due to a cessation program. The state of science for smoking cessation currently is in developing the best ways to bridge this gap and implement smoking cessation programs, for example, efforts within NCI-designated cancer centers.<sup>24</sup>

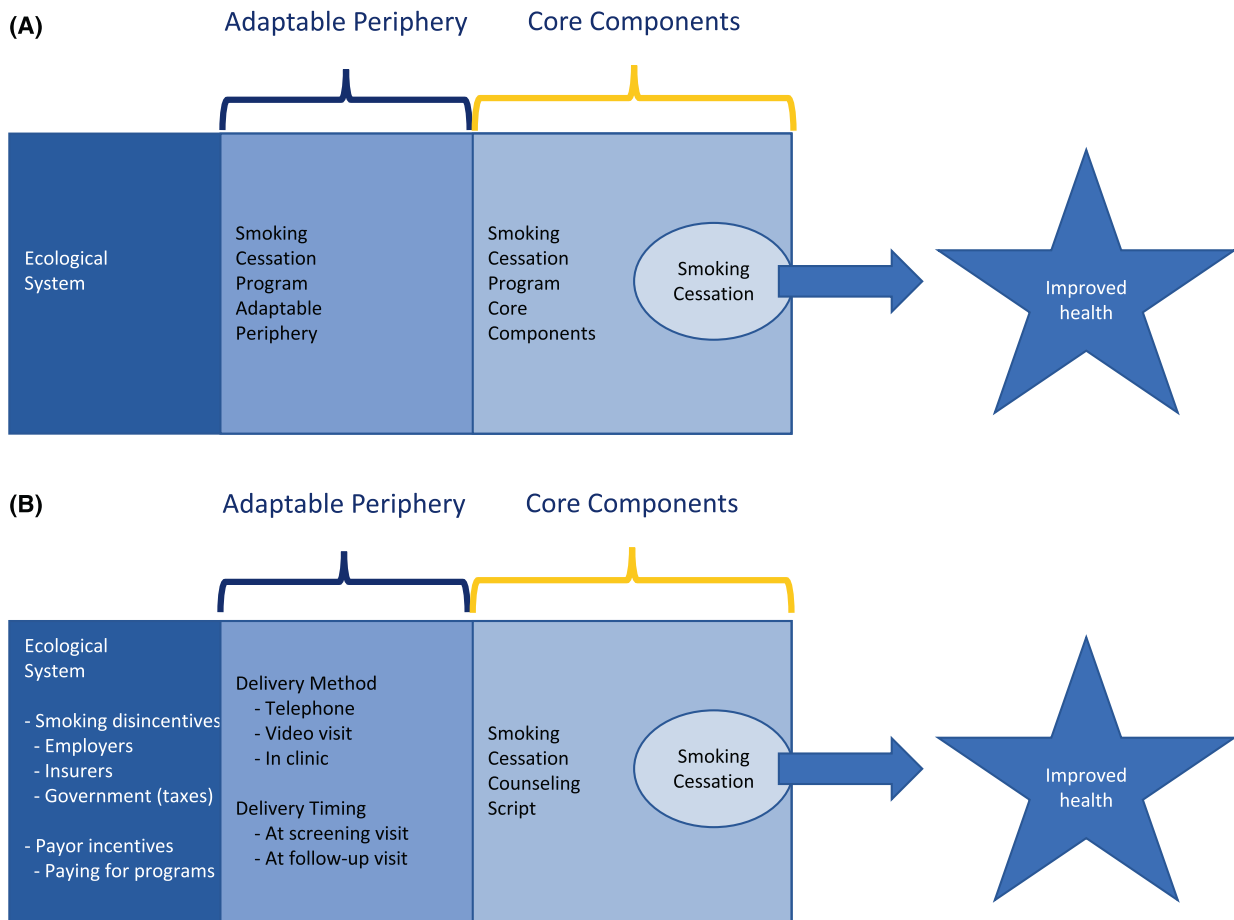
## CONSIDERING CLINICAL TRIALS AS COMPLEX INTERVENTIONS

Similarly, clinical trials involve numerous stakeholders, processes, and components at multiple levels, and thus can be considered complex interventions.<sup>25</sup> A clinical trial aims to improve health by enrolling participants in a protocolized delivery of specific interventions, as a smoking cessation program aims to improve health by enrolling participants into a protocolized delivery of a smoking cessation intervention. These complex interventions have certain core components that must be applied uniformly and other portions that can be tailored to specific contexts called the adaptable periphery (Fig. 1A).<sup>27</sup> For example, a smoking cessation program may have a counseling script as an immutable core component, with adaptable components including how the script is delivered (e.g., telephone vs. in-person) and when it is delivered (e.g., at a screening clinic visit vs. at a follow-up time), among other adaptable components (Fig. 1B).<sup>24</sup> Combined, the core components and adaptable periphery encourage improved health outcomes through tailored interventions targeting sustainable smoking cessation. These components all fit within a wider ecological system, including external incentives, government regulations, and other factors influencing intervention success.

Clinical trials similarly have clear demarcations of core components and adaptable periphery fitted within a grander ecological system. The core components of an approved clinical trial are contained in the trial protocol (Fig. 2A). These fixed components, including trial design features (e.g., number of arms, comparator arms, and eligibility criteria), are the same across sites

for the sake of consistent comparisons and maintenance of trial internal validity. How this protocol is implemented, however, can have substantial variability from site to site. Even how sites are selected for participation in a trial, and thus become eligible for implementing the trial protocol, can be adapted based on different trials. Other aspects, such as how trials are advertised to providers or patients, how patients are identified for potential participation, or how frequently enrollment goals are assessed, are generally not specified in trial protocols. Prior research into trial conduct has primarily focused on the core components of trials through protocol changes such as expanding eligibility criteria to facilitate trial success.<sup>28</sup> Although these design changes can be helpful, they do not guarantee uptake of trials at all sites or reaching all potential participants. Approaching trial improvement through implementation science can add emphasis on the adaptable periphery, identifying and targeting strategies for how best to implement trial protocols in different contexts.

Conceptualizing the trial and trial protocol as a complex intervention also facilitates addressing struggling trials. If a trial is not enrolling well, understanding reasons for poor enrollment, and how best to address those issues, is important, but methods for doing so are limited. One problem is that many trial improvement efforts begin with a specific proposed improvement intervention (e.g., increase trial staffing and enrollment feedback) rather than a rigorous, theory-based assessment of the underlying causes of trial problems. Although there are existing interventions aiming to improve trial enrollment, poor enrollment has a variety of upstream etiologies and the extent to which these are individually considered in prior studies remains unclear.<sup>5</sup> For example, in a cancer drug trial, low enrollment may be due to low regional cancer incidence, strong provider preferences for standard of care (or the experimental drug), overly restrictive eligibility criteria, or providers may be too busy with other duties to participate in clinical trials. Each of these “causes” may benefit most from a different type of improvement intervention, and may face different barriers to implementation. Designing an intervention to address one of these problems may not work in settings where the root cause of poor enrollment is different. For example, hiring research staff to recruit patients in clinic may improve enrollment if the root cause is that eligible patients are not identified, but would likely not improve enrollment if there are simply not many eligible patients in the region. In other words, although hiring additional trial enrollment staff



**Figure 1.** Conceptual model of a smoking cessation intervention. (A) Description of core components and adaptable periphery. (B) Examples of applied core components and adaptable periphery in a hypothetical smoking cessation intervention.

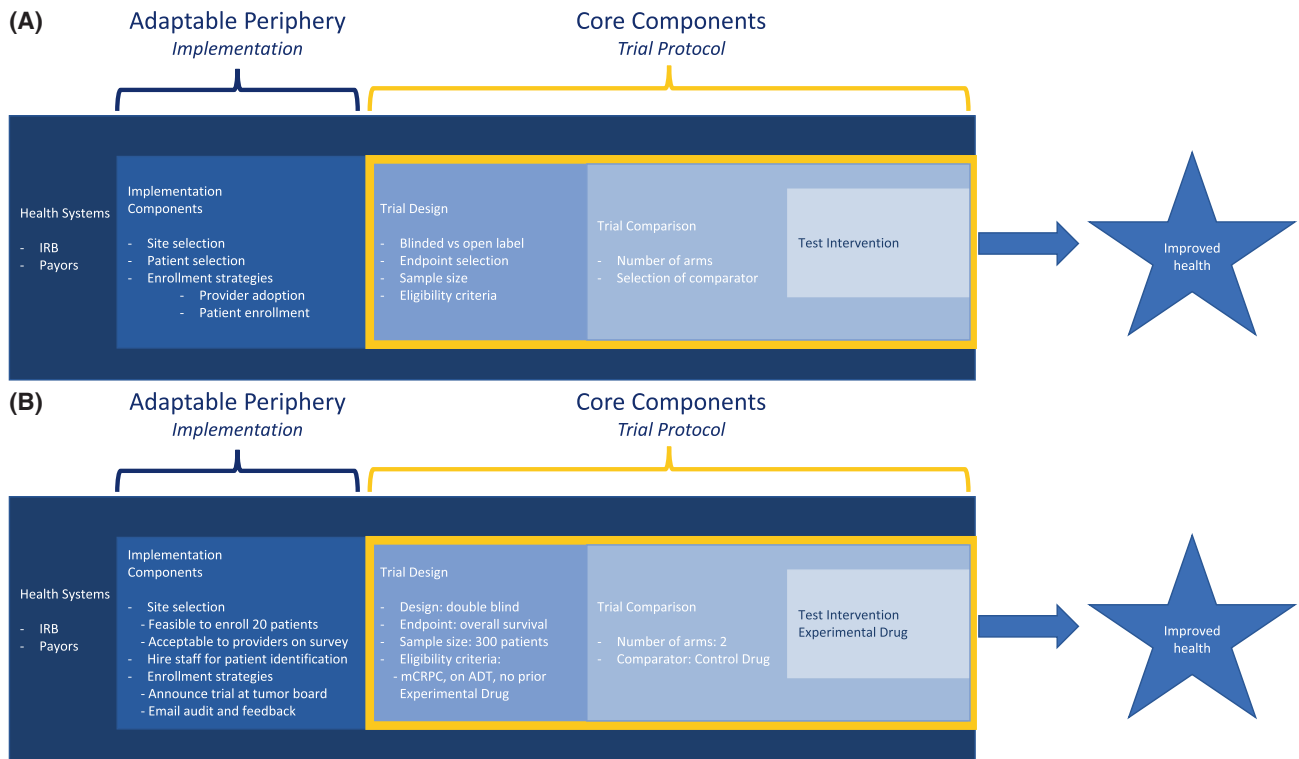
may be helpful in some contexts, if only 50 people with prostate cancer present to your clinic every year, you can never hire enough staff to recruit more than those 50 patients a year into a trial. Without assessing local context, barriers and facilitators, and other factors, attempts to improve clinical trials may be ineffective, or their effectiveness may be entirely unknown despite substantial expense.

#### ADAPTING EXISTING IMPLEMENTATION FRAMEWORKS TO THE TRIALS CONTEXT

The steps leading to trial improvement interventions can be structured around existing implementation science frameworks. A major benefit of adapting existing frameworks is to foster shared vocabulary and link existing frameworks together in an interoperable way. Specifically, identifying barriers and facilitators to

enrollment could be facilitated with the Consolidated Framework for Implementation Research (CFIR), a commonly used determinants framework used to assess context including provider, clinic, and organizational factors.<sup>27</sup> The specific identified barriers could be linked to targeted, evidence-based implementation strategies through the Expert Recommendations for Implementing Change (ERIC) project, a compilation of 73 improvement strategies.<sup>29</sup> The success of the selected strategy could be evaluated using Proctor's Implementation Outcomes Framework.<sup>30</sup>

Put together, we can design trial improvement interventions tailored to specific contexts. For example, we may use the ERIC strategy audit and feedback (such as emails to providers reporting clinical trial enrollment relative to their peers) to target the CFIR construct reflecting and evaluating and increase the number of providers offering a trial to patients (adoption from Proctor's



**Figure 2.** Conceptual model of a clinical trial as a complex intervention. (A) Description of core components and adaptable periphery. (B) Examples of applied core components and adaptable periphery in a hypothetical clinical trial.

Outcomes).<sup>27,29,30</sup> Furthermore, we could study how well audit and feedback works compared to another strategy, like a pop-up advisory in the electronic medical record, within the trial.<sup>31</sup>

### AN EXAMPLE OF APPLYING IMPLEMENTATION SCIENCE TO A CANCER DRUG TRIAL

To ground these concepts in real-world trial practice, we will consider a worked example of a trial for a new drug for metastatic prostate cancer, Experimental Drug. The core components of this trial protocol include a randomized, double-blinded design comparing to a hypothetical standard of care, Control Drug; a primary end point of overall survival; an estimated sample size of 300 patients; and relatively pragmatic eligibility criteria (Fig. 2B). When this trial is opened at any site, none of these protocol elements (i.e., core components) can be adapted.

However, trial site selection is part of the adaptable periphery of our trial, and we can apply an implementation approach to improve our site selection

process. For example, we may first consider the feasibility of completing enrollment at a given site, with the knowledge that cancer trials are more successful in areas with higher cancer incidence.<sup>32</sup> We may only select sites where prior enrollment rates and number of metastatic prostate cancer patients presenting to clinic exceed per-site goals (e.g., 20% historical enrollment numbers \* 100 eligible patients per year = 20 anticipated participants per year). Additionally, we may specifically evaluate acceptability of a trial protocol at potential trial sites, for example through a survey. Selected sites may have a minimum number of providers rating a trial as “very interesting” or “very likely to enroll patients,” suggesting adoption by providers at that site may be high. This would help guide our Experimental Drug versus Control Drug trial away from sites where providers would not offer the trial.

Once sites are selected, each site must consider how best to identify eligible patients and offer the trial. There may be trial materials available, for example patient handouts, but our trial protocol would not likely otherwise specify how these components should be handled. It is unclear how a trial should be launched, for example.

In some settings, announcing a new trial at a multidisciplinary tumor board meeting may be best, whereas in other settings having a trial site lead directly contact providers to discuss the trial may be more effective. Similarly, some settings may benefit from a dedicated trial coordinator to screen potentially eligible patients and aid with consent logistics, whereas in other settings this hire may be too expensive to justify.

After trial enrollment has begun, we would continue to be challenged with finding evidence-based strategies to improve trial enrollment. Consider two trial sites each only enrolling 10 patients in a year. Without considering local context, we may start email audit and feedback at both sites. Perhaps this slightly improves enrollment at Site A. However, if Site B has 2 providers who each see only five eligible patients per year, an audit and feedback intervention cannot improve adoption or penetration, as all providers and eligible patients are already perfectly engaged in trials. This would result in wasted resources spent instituting this strategy at Site B. Furthermore, sending emails to these providers may annoy providers (low acceptability), and may lead to disengagement from trials in the future. The resources wasted on this audit and feedback at Site B might be better spent incentivizing the providers to continue enrolling to this trial or engaging with future trials (targeting sustainability), or in identifying new trial sites.

To address these implementation issues, we could apply our proposed frameworks as described above to identify what may work well for both launching our trial and for improving enrollment. This could potentially lead to improved enrollment, decreased cost, and more rapid completion of our trial.

### THE PATH AHEAD FOR TRIALS IMPLEMENTATION SCIENCE

As we have outlined, there appears to be a clear role for implementation science in improving clinical trials. Additional work is needed to more specifically adapt and refine implementation science frameworks to the trials context. How to apply each of Proctor's Outcomes and the CFIR constructs to the trials context could be helpful both in establishing a shared vocabulary and in working through barriers to clinical trial success. These concepts must also align with the interests of trial stakeholders, including trialists, sponsors, and patients. These frameworks could then be applied to existing trials to help identify targets for trial improvement.

As a further step, these trial improvement interventions could be rigorously tested, for example, in hybrid effectiveness-implementation studies within a trial as suggested by Trial Forge.<sup>19,33</sup> This could generate more generalizable knowledge about what works best for trials, advancing both trial conduct and science. Furthermore, this could also encourage broader dissemination of the hybrid trial design, leading to better understanding of both the efficacy and implementation effectiveness of new interventions.

Further work is needed on a "basic science of implementation" to adapt existing frameworks to the clinical trials context, and to generate buy-in on the concepts underlying trial improvement strategies. We believe that implementation science holds promise for applications to trials, but generating buy-in from trial stakeholders including trialists, sponsors, and patients will take substantial effort.

To improve the rigorous development of clinical trial improvement interventions, we propose the consideration of clinical trials as complex interventions to be analyzed within the context of implementation science. In this manner cancer clinical trial failures can be considered problems of poor implementation. Importantly, our proposal does not invalidate prior work or obviate the need for further trial research; indeed, our work has grown out of the arduous work of multiple investigators and groups. Adapting and applying implementation science to the clinical trials context can establish common vocabulary, build a sustainable foundation for trial knowledge generation and improvement, augment efforts to improve clinical trials, and build capacity to bring better and more efficient care in an evidence-based manner to all patients through the clinical trials enterprise.

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