OPERATION TRIALBLAZER

HHS Roadmap to Maintaining U.S. Leadership in Early Clinical Research and Development

2026

Executive Summary

The United States has long set the global standard for pharmaceutical innovation and regulatory rigor. But the global pharmaceutical landscape is more competitive than ever, with other countries designing their regulatory systems and clinical research infrastructure to lure early-stage clinical investment away from the U.S. It is critical to protect clinical research in the U.S. because it ensures that American patients will continue to have earlier access to new therapies and are protected by the world's most advanced regulatory oversight.

The Department of Health and Human Services operating divisions, including the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Advanced Research Projects Agency for Health (ARPA-H), the Office of the Inspector General (OIG), and other relevant HHS components, are committed to maintaining U.S. global leadership in biomedical research and pharmaceutical innovation. This requires coordinated action across all of HHS to eliminate the unnecessary delays, redundant requirements, and regulatory ambiguity that currently slow and disincentivize U.S.-based development, while encouraging the broader biomedical research ecosystem to do the same. This coordinated approach is intended to foster a clinical research economy that delivers timely, safe, and effective medical products to support a healthy America.

This roadmap describes a strategic set of initiatives and reforms designed to modernize and accelerate all stages of medical product development, from target and treatment identification, initial planning, through the transition into Phase 2 clinical studies, and beyond. This HHS-wide effort aims to identify and remove unnecessary burden from the path between a promising scientific discovery and the patients who need it, without compromising the privacy, safety or ethical standards that Americans expect and deserve.

Many of the initiatives detailed here will initially focus on early-phase research, given the importance of supporting American leadership from the earliest stages of innovation and rapidly emerging evidence of its offshoring. Because HHS both regulates and funds early-stage clinical research and development, the Department plans to use its influence to align expectations, incentives, and standards across the biomedical ecosystem.

HHS will advance this mission across several fronts:

1. modernizing regulatory requirements and processes
2. improving transparency for regulated entities
3. encouraging the adoption of more efficient practices

4. ensuring federal dollars are spent on adequately powered and designed trials
5. better utilizing existing data sources and technologies for regulatory and data-generation purposes
6. improving patient and participant access and engagement in clinical trials and removing disincentives preventing healthcare workers from being involved in the conduct of research

Background

The United States has long been the world's engine of biomedical innovation, but that role is not guaranteed. Where the U.S. once dominated the earliest stages of drug discovery and human testing, it now faces competitors that are moving faster, scaling quickly, and winning the race for the investment and intellectual capital that follow.

This is not just an economic concern. For decades, Americans in the United States have had access to cutting-edge and advanced treatments and new drugs. Over half of all new drugs launch first in the U.S., giving American patients access to innovative drugs before they become available in other countries.[1] Clinical trials are essential to the discovery and development of innovative medicines and in enhancing the scientific understanding of human diseases and conditions. Clinical trials allow health care professionals to provide patients with the most effective treatment options available, and help patients to live longer, healthier lives. In some cases, such as cancer, clinical trials may also offer a critical opportunity to access cutting-edge treatments when all other treatment options have been exhausted. Additionally, biotechnology underpins national security through pandemic preparedness to pharmaceutical supply chains for acute and chronic diseases. The National Security Commission on Emerging Biotechnology has warned that the United States has a critical window, measured in years, not decades, to act decisively or risk ceding military, geopolitical, and economic advantages to China.[2]

China has made biotechnology a strategic national priority, systematically expanding its clinical research infrastructure with government backing, streamlined regulatory pathways, and sustained investment. In 2021, China's global share of Phase 1 trials surpassed the United States' share for the first time, a milestone that would have seemed unlikely just a decade earlier. And in 2024, China surpassed the United States in the total number of clinical trials registered, with over 7,100 registered, representing 39% of global trials.[3] Australia has also found success in early stage trials, being widely regarded as a top-tier country for Phase 1 clinical trials, and has one of the highest trials-per-capita rates in the world.[4]

Globally, speed and efficiency are a critical factors for overall success. Australia's Clinical Trial Notification System allows trials to begin in fewer than 70 days after a final protocol is submitted, with regulatory approval granted in as little as 21 to 28 days and sites activated within 6 to 12 weeks.[5] China has matched that pace: following nationwide reforms in 2015 and September 2025 that reduced approval backlogs and increased public investments in biomedicine, respectively, their early discovery-to-IND

cycles are now 50% to 70% faster than the rest of the world.[6,7] For certain cutting-edge modalities, including cell and gene therapy, radioligand therapy, and stem cell therapy, China uses investigator-initiated trials to provide additional flexibility, though with some tradeoffs around oversight and quality control.[8] This means that drugs can move into human testing if a researcher has an interest and funding. In the U.S., comparable trials might wait years to start.

In the United States, sponsors may request consultation with FDA prior to submission of an IND in the form of a Pre-IND meeting. The time between this meeting request and IND submission is an average of 380 days, with a range of almost 700 days, reflecting the diversity of molecular entities and the complexity of collaborating with sponsors varying widely in their regulatory science experience and phase 1 IND studies. In the U.S., IND applications go into effect after 30 days from receipt by the FDA, comparable to China and Australia, but other requirements, including Institutional Review Board (IRB) approval and contract negotiation, can add up to 13 months of additional delay before a single patient is enrolled.[9] By contrast, China requires IND applicants to commit to initiating their trial within 12 weeks of the application being submitted.[10] Too often, the U.S. pathway can be measured in years, while other countries' pathways are measured in months.

In the U.S., much of the delay occurs at the pre-IND stage. Sponsor misunderstanding of upfront Chemistry, Manufacturing, and Controls (CMC) requirements and Pharmacology/Toxicology testing often delay the IND submission and trial initiation due to sponsors generating unnecessary data at a stage where there is still considerable uncertainty about a therapy's effectiveness. Additionally, sponsors often must wait up to 60 days just to have a pre-IND meeting with the FDA. While sponsors in the U.S. work through these requirements and wait for FDA feedback, sponsors abroad may already be generating human data that can attract investment.

And, once the IND is granted, there are further delays and challenges associated with complexity of clinical trials, study start-up and patient recruitment and retention that increase costs and delay access to novel treatments and drugs.[11] For many sites, the gold standard of study activation is the National Cancer Institute's recommended 90-day "time to activation"[12], some data indicate prolonged trial activation times that well exceed 160 days.[13,14] Key barriers to trial activation are associated with budget and contract negotiation that involve among other, frequent protocol amendments during clinical trial agreements, misaligned timelines and prioritization, poor communication, lack of start-up process

roadmap, and challenges with technology and systems.[15] For example, the process of securing an agreement on the budget can range from a couple of weeks to several months. The use of master trial agreements and improved communication and education can shorten contract negotiation and speed up trial activation. Recruitment and retention are a major challenge for clinical trial sites. Physicians play a crucial role in patient engagement in clinical trials.[16] The level of physician engagement affects not only patient recruitment and retention, but also the quality of data collected, which can in turn affect the overall success of a trial and get new treatments to patients faster. However, physicians face severe time constraints from clinical practice and may struggle with awareness of patient eligibility and complex clinical trial logistics and protocols, as well as administrative infrastructure and institutional barriers.[17,18] Removing barriers for physician engagement presents a great opportunity for unlocking efficiencies in trial recruitment and retention, data collection, and start-up time, and reducing costs. Restrictive enrollment criteria may also affect clinical trial recruitment and represents a key cause for delays in clinical trials.[19] In addition to using more expansive eligibility criteria, alternative clinical trial designs – for example, use of master protocols or adaptive enrollment mechanisms – may help with clinical trial enrollment.[20] Clarifying regulatory guidance on adaptive designs and streamlining the IRB approval process are promising pathways for improving recruitment through the use of alternative trial designs.

The financial burden of participating in a clinical trial may also impact a patient's decision-making about participating or staying in a trial, particularly for those who are lower-income, underinsured or uninsured, or live far from a trial site. Although compensation for participating in clinical trials has been increasingly touted as an important approach to improve access to and participation in clinical trials,[21] some studies report that compensation is rare or inadequate in some if not most clinical trials.[22,23] Providing and allowing clinical trial compensation requires balancing regulatory protections and ethical considerations as well as logistical and structural barriers. Addressing financial toxicity associated with participating in a clinical trial can have meaningful impacts on patient's financial well-being, which also impact a patient's overall health and well-being, and affect patient retention in the trial as well as the decision to participate at all.

America's competitive shortcomings have massive financial consequences. American innovation dollars are increasingly purchasing Chinese research or financing American research in Chinese patient populations. In 2025, global companies spent over $137 billion on licensing China-based assets.[24] This means

that American investment is helping Chinese companies build intellectual property, generate first-in-human data, and create clinical track records that attract long-term investment, all outside the United States. If current trends continue, drugs developed by Chinese biotech companies are projected to account for 35% of FDA approvals by 2040.[25] The way to reverse this trend is to ensure that innovation is rooted in the U.S. from the earliest stages.

FDA

The FDA's mission is to protect and promote public health. This requires rigorous oversight to ensure safety and effectiveness as well as regulatory flexibility to respond to innovation and promote timely access to new treatments. Moreover, the agency's ability to fulfill its public health mission depends, in part, on the continued vitality of the U.S. biomedical ecosystem it regulates.

FDA is committed to reversing the current trajectory of research leaving the U.S. by focusing on two strategic priorities: (1) accelerating the time to first-in-human clinical trials by addressing the regulatory requirements for IND applications, and reimagining the pre-IND phase, and (2) accelerating later-stage clinical development and reducing administrative burden by pursuing significant IRB reform and increasing trial access and participation.

Accelerating the Time to First-In-Human Clinical Trials

1. **Clarifying the Regulatory Requirements for Investigational New Drug (IND) Applications**

Historically, the FDA has not clearly communicated its requirements for starting first-in-human trials. The absence of explicit, phase-specific requirements has left sponsors to guess what data is necessary. Thus, sponsors may err on the side of submitting too much data, conduct months of unnecessary studies before submitting a first-in-human IND application. Competitor nations are capitalizing on U.S. regulatory ambiguity by offering clearer, faster pathways to first-in-human milestones, and are capturing the investment and intellectual capital that follow.

The FDA's primary focus at the Phase 1 stage is the safety of the investigational product, and every component of the proposed investigational plan should be

calibrated to that objective. Generating data beyond what is necessary to ensure safety of study participants in early phase studies delays the moment when a therapy can first be evaluated in the people it is designed to help. By focusing only on risk-based and phase-appropriate requirements, FDA believes sponsors can save up to 6 to 12 months of development versus current IND submissions.

a) Streamlined Chemistry, Manufacturing, and Controls (CMC) IND Requirements

In order to help accelerate trial initiation while maintaining patient safety, FDA is clarifying what CMC data sponsors should submit before a Phase 1 clinical trial. To this end, FDA has released a webpage clarifying common Phase 1 CMC data misconceptions to streamline CMC data requirements. For example, some companies submit INDs containing more than 6 months of stability data, whereas FDA guidance[26] indicates FDA's recommendation that stability data to support the proposed duration of the Phase 1 clinical study is sufficient, rather than a full long-term stability package. Or in other cases, sponsors submit details around their commercial manufacturing process or complete exhaustive impurity profiling before starting phase 1 trials. However, early clinical batches of the drug are often made in a highly controlled environment, ensuring safety for typically small, short-duration studies meaning the fully developed and validated commercial process is unnecessary at this stage.

The FDA also recognizes the importance and complexity of advanced therapies, including therapies for rare diseases, where manufacturing is challenging and incredibly expensive. Some sponsors often approach new products independently, running a complete set of manufacturing, testing, and safety studies. Using common sense to ease this burden, the FDA plans to expand the use of prior knowledge from standardized and well-understood methods of manufacturing and drug delivery so that sponsors can reuse data from one product to support the next, dramatically reducing time and cost and incentivizing the use of platform knowledge to support future submissions. The FDA has also released a draft guidance[27] outlining specific types of prior knowledge and how to leverage them for Cell and Gene Therapies, creating new pathways for sponsors to eliminate redundant testing, and will work to incorporate feedback in an iterative process. Beyond these examples, the FDA will examine all IND requirements stated in regulation and clearly communicate the data that is required or deferred for a Phase 1 IND submission to save sponsors time, money, and ultimately accelerate Phase 1 trial initiation.

b) Streamlined Pharmacology & Toxicology IND Requirements and Eliminate Unnecessary Animal Testing Where Appropriate

FDA is taking a science-driven risk-based approach to nonclinical development of pharmaceuticals to eliminate unnecessary animal toxicology studies that may add substantially to drug development timelines without being necessary for ensuring safety of subjects in Phase 1 trials. The burden of unnecessary studies is significant, both in time and resources. For example, the development of a monoclonal antibody may use hundreds of animals as part of its pharmacology and toxicology stage. In certain cases, sufficient human data may exist to inform product safety, or the animal studies may be known to not produce useful information for a given product class, or a drug may belong to a well-understood class where toxicology outcomes are highly predictable. In all these cases, conducting additional animal studies delays development without meaningfully protecting patients.

Historically, toxicology data from two animal species have been used to support INDs for small molecules and some conjugated products. However in certain cases, safety concerns could be addressed in a single species, or novel alternatives could reduce or replace animal testing altogether. The FDA is fundamentally modernizing its approach to nonclinical safety studies using a risk-based approach. The approach will take into consideration 1) population risk (e.g. healthy volunteers vs unmet severely debilitating or life-threatening [SDLT] diseases) and 2) pharmaceutical risk (e.g., novel molecular target/modality vs well-understood target/modality),and will consider other relevant information (e.g. knowledge of animal-to-human translation) to encourage a fit-for-purpose nonclinical safety package. The FDA is also exploring uses for a "Weight of Evidence (WoE)" approach, leveraging all available nonclinical and clinical data to make a knowledge-based safety evaluation. A risk-based approach to nonclinical safety studies, use of WoE risk assessments, and incorporation of new approach methodologies (NAMs) are anticipated to result in greater efficiencies in drug development and reduce animal testing The goal is faster patient access to safe drugs, particularly for the areas of greatest unmet medical need, while maintaining necessary standards for nonclinical characterization of safety.

The agency has already made significant progress, including the release of the Monoclonal Antibodies: Streamlined Nonclinical Safety Studies draft guidance in December 2025 [28], the General Considerations for the Use of New Approach Methodologies in Drug Development draft guidance in March 2026 [29], and the

Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products draft guidance in May 2026 [30], and has a public resource inventory [31] of drug development contexts for which CDER is open to a streamlined nonclinical program. These actions reflect the FDA's commitment to modernizing toxicity assessment and providing clarity to sponsors. The FDA is planning to address public comments to finalize these guidances to provide additional clarity to sponsors, to issue more guidance documents, and to revise existing guidances.

c) Streamlined Clinical Protocol Development and Amendment Process

The FDA also plans to address two common challenges that sponsors face when creating the trial's clinical protocol for the IND. They are: building flexibility into the initial protocol submission to minimize the need for protocol amendments and, when needed, ensuring protocol amendments do not delay the continuation of a clinical trial. An HHS study found that 45% of protocol amendments were somewhat or completely avoidable[32], and since protocol amendments can be expensive[33], this can impose significant (self-inflicted) burden on sponsors. A related HHS study estimated that simplifying clinical trial protocols and reducing amendments could result in efficiencies that translate into an overall reduction in the estimated cost of bringing a drug to market by up to 22%.[34]

The FDA plans to refine best practices for dose selection and escalation strategies, and to offer advice on how sponsors can structure their initial clinical protocols in ways that reduce the likelihood of needing amendments in the first place. However, protocol amendments (changes to the clinical plan that are made after a Phase 1 IND has been submitted) are sometimes necessary, and can be a common source of delay and uncertainty for sponsors, even when sponsors are not required to wait for agency feedback before proceeding with the amendment. To provide sponsors with more transparency, FDA plans to implement a real-time status tracker that allows sponsors to see when their amendment has been reviewed, and FDA has determined that no action is indicated. This simple transparency measure will eliminate an important source of uncertainty for sponsors, allowing them to proceed with confidence without an expectation for a formal communication from the FDA.

2. Reimagining the Pre-IND Phase to Deliver on Both Speed and Oversight: The Expedited-IND Acceleration Pilot

Reaching a first-in-human milestone as quickly as possible is one of the most strategically important goals in early drug development. It is also a shared challenge. Sponsors face competitive pressure to move fast, while FDA reviewers manage substantial and growing portfolios of INDs, marketing applications, and adverse event reports. The Expedited-IND Acceleration Pilot is designed to address both sides of this equation.

The pilot will establish a network of Qualified Research Institutions ("QRIs"), including academic medical centers, healthcare networks, contract research organizations, and regulatory advisors, who will partner with sponsors to develop and review IND submissions for first-in-human clinical trials. Sponsors will retain full ownership of their IND, and the QRI network will serve as a review and advisory resource, specifically assessing their pharmacology/toxicology, clinical, and CMC components of the submission. Concurrently, the FDA will establish a new real-time rolling submission platform that would allow the FDA to review QRI recommendations and components of the IND submission on a rolling basis and communicate securely with the sponsor to provide timely guidance. Similar to the rolling review of an NDA or BLA under FDA's expedited review programs, this approach would allow individual IND components to be reviewed prior to formal IND submission. This model allows for a collaborative, iterative approach to the Pre-IND process, and allows FDA reviews to focus their attention where it is most needed while accelerating the sponsor's path to IND readiness. FDA will retain full regulatory authority and decision-making on the INDs.

The pilot will also be used to explore creative ways to address the delays that occur after an IND is granted, from IRB approval to site contracting and patient enrollment, which has become a rate-limiting step in the efficiency of U.S. clinical trial initiation.

Accelerating Later-Stage Clinical Development and Reducing Administrative Burden

3. **IRB Reform**

Institutional Review Boards (IRB) are federally mandated committees operating either within academic institutions or healthcare systems, or as independent nonprofits or for-profit third-party organizations that review and monitor human subjects research funded by the federal government or regulated by the FDA.[35,36], In accordance with FDA regulations, IRBs are empowered to approve, require

modifications to, or disapprove research protocols, making their review a safeguard for the rights and safety of clinical trial participants in any study conducted under an IND. That oversight protects patient safety, but the current IRB review process can unnecessarily delay initiation of clinical trials, adding significant time to study start-up before a single patient is enrolled.

The cause of that delay is largely structural. Under the current model, some IRBs wait for an IND to go into effect before reviewing the clinical protocol, which delays the initiation for single-site trials. In multi-site trials that do not receive federal funding, each site may conduct its own independent review of the same protocol. When dozens of sites separately evaluate an identical document, this duplicative process can result in inconsistent timelines and an administrative burden that accumulates without any corresponding benefit to research participants.

FDA is considering rulemaking to require the use of a single Institutional Review Board (sIRB) model for multi-site cooperative studies[37]. Under this approach, one IRB would serve as the "IRB of record" for all participating sites, streamlining the process while maintaining rigorous oversight. This reform would align FDA regulations with the existing federal policy for the protection of human subjects (the "Common Rule") and NIH policy, which already require sIRB review of most US-based and federally funded nonexempt human subjects research, and would represent a meaningful step toward a more efficient and consistent clinical research infrastructure. Lastly, FDA will explore how IRB review can be streamlined during the Expedited IND pilot, working with institutions to incentivize earlier reviews and coordination to accelerate clinical trial initiation.

4. **Increased Trial Access and Participation by Patients and Clinicians**

Clinical trials can only deliver results as quickly as they enroll patients, but enrollment is consistently one of the most significant bottlenecks in clinical development, and the consequences often fall on patients. A 2024 study found that fewer than 5% of cancer patients receive treatment within the context of a clinical trial, despite more than 70% of patients being willing to participate.[38] Barriers to participation operate on two distinct fronts: the clinicians who must identify and refer eligible patients, and the patients who must weigh the practical and financial consequences of enrolling, along with a study's risks and potential benefits. FDA is committed to addressing both and recognizes that doing so will require sustained collaboration with partner agencies and stakeholders beyond FDA's own regulatory authority.

For clinicians, the challenges are largely structural. Clinicians are often disincentivized to refer patients to clinical trials due to the time spent on identification, explanation, and coordination of the trial. Clinicians must also understand stringent and complex trial eligibility requirements which may exclude many potential participants.[39] Participating in a clinical trial also creates administrative burden, workflow disruption and lacks a reimbursement structure that reflects that investment. Additionally, many clinicians, especially in community care centers, have limited familiarity with the clinical trial landscape and lack the tools to systematically identify eligible patients at the point of care.[40] Without meaningful incentives, education, and robust patient identification systems for those clinicians, trial enrollment depends heavily on individual clinician awareness and initiative. FDA will work with relevant stakeholders to explore how regulatory frameworks, guidances, and incentive structures can drive clinical engagement.

For patients, the barriers are often financial. In some cases, the act of participating in a clinical trial can create significant economic hardship for patients and their families and may impact patient retention in the trial as well as their decision to participate.[41,42,43,44] Patients may face co-payment obligations for standard-of-care services delivered during a trial, unexpected tax liability for trial-related compensation and most critically for certain populations, trial participation can potentially jeopardize their eligibility for federal programs such as Medicaid. Practically, geography also disincentivizes trial participation, with many primary patient treatment sites not offering trials.[45] These are not minor inconveniences; they are structural disincentives that disproportionately affect the patients most in need of access to innovative therapies, and that directly undermine efforts to ensure diverse and representative trial enrollment. Thus, increasing patient access and engagement in clinical trials offers opportunities to improve enrollment and retention in clinical trials, helping ensure interventions can be evaluated effectively and that clinical research dollars are used efficiently.[46]

Expanding trial access cannot be accomplished by FDA alone. FDA will actively pursue collaboration with the Centers for Medicare & Medicaid Services (CMS), the Office of the Inspector General (OIG), the Office of Human Research Protections (OHRP), National Institutes of Health (NIH), the rest of the federal government, private insurers, and other relevant stakeholders to identify and dismantle the financial and logistical barriers that disincentivize patients and clinicians from participating in clinical trials. FDA will also continue to advance guidance on integrating randomized controlled trials into routine clinical care, reducing the logistical burden on both patients and clinicians by embedding trial

participation into existing care pathways rather than requiring patients to seek out specialized trial sites.

5. **Enhanced Regulatory Guidance to Drive Efficiency**

The FDA is also enhancing its guidance for industry that may facilitate greater efficiency further along the drug development continuum. For example, in a newly released revised draft guidance, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, the FDA clarifies how many drugs can rely on one rigorous, adequate and well-controlled clinical investigation, plus confirmatory evidence, to demonstrate substantial evidence of effectiveness for drug approval. The guidance recognizes that advances in our understanding of biological processes and the increasing availability of high-quality data have transformed the evidentiary landscape for drug development. Another revised draft guidance, Master Protocols for Drug and Biological Product Development, provides insight into building single overarching clinical trials that govern multiple sub-studies, which may evaluate different medicines, different patient populations, or both simultaneously. By coordinating multiple investigations under one framework, master protocols can reduce duplicative infrastructure, streamline data collection, and accelerate the generation of evidence needed to support regulatory decision-making.

These guidances represent the FDA's ongoing commitment to create efficiency across drug development. As the world evolves, new technologies emerge, and understanding of disease and data deepens, so too must our regulatory frameworks. This work is an ongoing, iterative process: one that will require collaboration, stakeholder engagement, and innovation to ensure our guidance remains relevant, science-based, and responsive to the realities of modern drug development.

Expanding Practical Resources Available to Sponsors to Remove Ambiguity

Navigating the regulatory requirements for early clinical development is genuinely complex, and the complexity is felt disproportionately by smaller companies. The following initiatives are designed to make FDA's expectations and resources more visible, more accessible, and more actionable for all sponsors.

7. **Phase 1 Clinical Trial Resource Site**

In many cases, ambiguity around IND requirements leads to sponsors submitting additional data to the FDA to minimize risk. Sponsor uncertainty regarding IND requirements leads to uncertainty in the types of studies necessary to support the proposed first-in-human study. In all cases, the speed of a drug development program should be dictated by the strength of science, not inhibited by regulatory uncertainty. To ensure maximum clarity, the FDA will launch a dedicated Phase 1 First-In-Human IND landing page, a centralized digital hub that explicitly outlines phase-appropriate regulatory requirements, links to relevant guidance documents, highlights practical data examples, and answers the most common questions sponsors bring to the FDA. This consolidated resource will prevent sponsors from having to piece together regulatory expectations from multiple sources or default to overly conservative interpretations.

8. **Phase 1 Clinical Trial Contact Center**

The FDA has long recognized the importance of timely feedback for sponsors, as even quick clarification can spare sponsors months of guesswork and significant expense.[47] Sponsors without dedicated regulatory teams may spend millions on external advisors simply to navigate FDA requirements that are documented but difficult to locate and interpret. To ensure maximum transparency and minimize delays caused by uncertainty leading up to and during a first-in-human trial, the FDA has launched a live contact center staffed by experts who can answer general questions about regulatory requirements and other early phase trial considerations in real time, or connect sponsors with a point of contact in the relevant review division to address disease- or product-specific questions. This resource reflects the broader philosophy that a more accessible FDA is a more effective FDA. This is not intended to replace product-specific Pre-IND meeting interactions but by giving sponsors a direct line to knowledgeable staff, the contact center may help resolve some issues quickly, reduce uncertainty, and build sponsor confidence in FDA's expectations before and during trials.

To use the Phase 1 support line, please call 240-276-9358, or email Phase1Questions@fda.hhs.gov.

9. **Public Roundtable Series**

HHS will host a series of roundtables to gather stakeholder input on methods to streamline the IND process and clinical trial initiation, improve hospital contracting and IRB reform, accelerate Phase 1 clinical trials, and reduce regulatory uncertainty around participant and sponsor payment. FDA will also advance the dialogue by opening a public feedback docket to ensure that voices from across the research,

industry, and patient advocacy communities can contribute to the ongoing development of these reforms and be a part of refining the path forward for the good of American patients.

NIH

Over the course of the last decade, NIH has focused on the need to modernize its clinical research enterprise to meet the needs of today and tomorrow. As NIH's mission is to improve the health of the Nation, efficient, robust clinical research is paramount. NIH intends to move the following efforts forward to improve trial speed and operational efficiency and reduce costs:

1. **Ascertain and promulgate key metrics for overseeing clinical research studies.** Key metrics of success for a clinical trial can range from completion of target enrollment in the trial to generation of reproducible study results or data necessary for regulatory approvals to implementation of clinical practice guidelines or transformative medical products into healthcare practice. Given the wide variability among clinical trials and the health-related biomedical outcomes they are assessing, there is a strong need to determine which metrics are indicators of clinical trial progress and ultimately what is indicative of trial success. NIH will issue an RFI to gather additional data that can inform ways to increase clinical trial start-up efficiency and on-going performance, allow for early intervention to enable trials to successfully complete, or make go/no-go decisions to maximize investments in research that will produce the most impactful gains for the health of Americans.

2. **Leverage efficiencies of NIH-supported clinical trial networks.** Increasingly, clinical research is conducted in collaborative, interdisciplinary teams that function across multiple institutions and geographical sites. NIH has several networks in place , such as the NCI Designated Cancer Centers and the Clinical and Translational Science Awards (CTSAs). These and other NIH-supported programs are not only places to conduct trials; they are platforms to test better ways of doing trials. Together, these networks provide opportunities to improve overall trial efficiency in areas such as trial design, activation, participant recruitment and retention, contracting, regulatory readiness, and oversight. These efforts include developing and disseminating reusable clinical and regulatory playbooks that captures the key scientific, clinical, manufacturing, regulatory, and operational steps so each new program does not have to start from scratch,

1.improving and expanding the use of SMART IRB — a national platform and reliance agreement designed to streamline IRB review for multi-site studies — along with developing approaches for designing studies that can toggle efficiently from n-of-1 or highly individualized trials to larger Phase 1/2 studies. NIH-supported networks also provide an opportunity to advance the use of New Approach Methodologies (NAMs), including human cell-based and computational models, to generate stronger preclinical evidence and support better decisions about which therapeutics are most promising to advance into clinical testing.

3. **Bolster inclusion of real world data in product development.** NIH, in conjunction with the MAHA initiative, is further exploring how to augment the use of real-world data and causal inference methods to improve protocol feasibility, recruitment planning, and evidence generation in ways that make trials both faster and more informative. As this landscape of data sharing evolves, NIH is poised to work with other federal and non-federal partners to strive toward interoperability and maximum utility of data from a variety of sources, including electronic health records and claims data, to expedite regulatory decisions.

4. **Advance policies to bolster rigor in clinical research.** Because the clinical trial enterprise has been criticized for conducting small, underpowered studies and given NIH's role as steward of taxpayer investments in clinical research, NIH has a responsibility to ensure that it supports scientifically sound and rigorously designed clinical trials. NIH is undertaking several key efforts to enhance the rigor of the studies it supports, including:

   a. Enhancing the merit review of its applications through the development of a semi-structured application form for clinical trials that will make it easier for reviewers and staff to assess potential significance.
   b. Updating its 1998 Data and Safety Monitoring Policy to ensure high quality data generation and participant safety, while reducing administrative burdens.
   c. Developing a new return of research results policy to further engage participants in clinical research, incentivize their participation in clinical research studies, and promote trust.

5. **Expand delivery of clinical research to underserved and rural populations.**

NIH will advance decentralized and hybrid clinical trial models that bring research closer to where people live and receive care, including in rural, Tribal, and other underserved communities. Building on programs such as NIH CARE for Health[48], NIH will explore approaches that embed research in community-based care

settings and leverage telehealth, AI-enabled tools, remote monitoring, and real-world data to support recruitment, consent, follow-up, and evidence generation while maintaining rigor, privacy, and participant protections. NIH will also investigate opportunities to expand this work by partnering with other agencies to align rural health investments with research infrastructure, support pragmatic trials in rural care settings, and evaluate approaches that improve access, retention, outcomes, and cost-effectiveness.

ARPA-H

ARPA-H is advancing several programs intended to reduce major scientific and operational bottlenecks in early-stage drug development. Through programs such as CATALYST, ARPA-H is supporting the development of predictive human and computational models designed to improve the ability to evaluate drug safety and efficacy before human testing begins. These efforts aim to reduce reliance on animal testing where scientifically appropriate, improve the prediction of toxicities that may not be captured in traditional models, and generate evidence that may support more efficient early clinical development pathways. ARPA-H is coordinating closely with FDA on these efforts, including supporting development of regulatory science capabilities relevant to these approaches.

ARPA-H is also supporting new approaches to clinical trial and development models for advanced therapies and genetic medicines. Programs such as THRIVE are exploring platform-based and umbrella trial approaches intended to allow multiple related therapies or disease targets to be evaluated within more flexible development structures. These efforts align with broader FDA activities related to innovative trial designs, flexible chemistry, manufacturing, and controls (CMC) approaches, and the use of prior knowledge to support development programs. These initiatives are intended to reduce repeated development work across similar products and therapeutic platforms.

ARPA-H programs ENGINE and UNICORN are focused on improving the consistency, scalability, and predictability of advanced therapy manufacturing and clinical evaluation. These efforts include development of computational and AI-enabled tools to support manufacturing optimization, reduce batch variability and failure rates, improve product quality, and better predict long-term clinical outcomes for cell and gene therapies. ARPA-H is also exploring how these approaches may support the development of more standardized methods and

decision-support tools for complex therapies, particularly in areas where existing development pathways remain highly individualized and operationally challenging.

ONC

Office of National Coordinator for Health Information Technology (ONC) is the principal federal entity charged with coordination of nationwide efforts to implement and use the most advanced health information technology and the electronic exchange of health information and will support HHS efforts to modernize clinical research through several initiatives:

1. **Integrate Clinical Trial Systems with EHRs**
The ONC Health IT Certification Program ensures that Certified Health Information Technology meets the technological capability, functionality, and security requirements adopted by HHS. ONC Certified EHRs are now a cornerstone in our health system, with about 99% adoption by hospitals and 90% by providers.

ClinicalTrials.gov is a US government website and online database of clinical research studies and information about their results. ClinicalTrials.gov website contains information that can support trial identification and preliminary eligibility screening, including disease focus, recruitment status, enrollment timelines, and study locations.

ONC could propose the capability for certified EHRs to integrate with the publicly available ClinicalTrials.gov API in the upcoming Health IT Certification regulation. Once finalized, it would provide clinicians with capability within their EHRs to discover clinical trials information for preliminary eligibility screening during care delivery.

2. **Make Computable Clinical Trial Protocol Computable**
Clinical Trial protocols are currently written as unstructured documents, making it difficult to automatically perform patient screening for eligibility. Additionally, regulators cannot automatically validate submissions and sponsors cannot reuse protocol logic across systems. There are several international standards organizations that are actively building the interoperable foundation required for scalable, computable eligibility screening. The International Council for Harmonization (ICH M11/ceSHarP), the Clinical Data Interchange Standards

Conclusion

Consortium Unified Study Definitions Model (CDISC USDM), and HL7 FHIR-based Clinical Study Protocol (HL7 UDP) initiatives are working to develop standardize digital protocols.

There is opportunity for HHS to accelerate the development and adoption of the standards for clinical trial protocols by providing substantial investments to the standards development activities. This would enable faster and more accurate patient matching to clinical trials, reduce burden on sponsors, and, in theory, allow for the development of tools to automate patient matching trials they are eligible for, thereby reducing burden on clinicians.

Conclusion

This HHS roadmap is a coordinated response to a genuine and growing competitive challenge with real consequences for American patients, industry, and national security. This roadmap addresses that challenge across six interconnected areas:

1. modernizing regulatory requirements
2. improving transparency for regulated entities
3. encouraging the adoption of more efficient practices
4. ensuring federal funding dollars are spent on adequately powered and designed trials
5. better utilizing existing data sources and technologies for regulatory and data-generation purposes
6. improving patient access to clinical trials and removing disincentives preventing healthcare workers from being involved in the conduct of research

The United States already possesses the world's deepest research institutions, the most dynamic biotech ecosystem, and the most trusted regulatory standard in the world. These reforms are how HHS ensures that the next generation of breakthrough therapies is developed faster, more efficiently, and in the United States, while maintaining the highest ethical and safety standards.

References

[1] https://www.rand.org/pubs/research_reports/RRA788-4.html
[2] https://www.biotech.senate.gov/final-report/
[3] https://www.biotech.senate.gov/final-report/chapters/
[4] https://pmc.ncbi.nlm.nih.gov/articles/PMC10952960/
[5] https://novotech-cro.com/sites/default/files/Novotech_WP_20160701_v2.1.pdf
[6] https://www.mckinsey.com/industries/life-sciences/our-insights/the-emerging-epicenter-asias-role-in-biopharmas-future
[7] https://www.nber.org/papers/w34977
[8] https://doi.org/10.1007/s44178-024-00123-7
[9] https://link.springer.com/article/10.1177/21684790177514O3
[10] https://english.nmpa.gov.cn/2025-10/14/c_1138493.htm
[11] https://www.wcgclinical.com/wp-content/uploads/2025/10/siteChallengesReport25_final.pdf
[12] https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.6542
[13] https://www.aaci-cancer.org/Files/Admin/2023-April-AACI-Commentary.pdf
[14] https://www.appliedclinicaltrialsonline.com/view/accelerating-clinical-trial-activation
[15] https://www.aaci-cancer.org/Files/Admin/2023-April-Trial-Activation-White-Paper.pdf
[16] https://pmc.ncbi.nlm.nih.gov/articles/PMC10922044/
[17] https://aspe.hhs.gov/sites/default/files/documents/88c76ada610b54b5a0ab8447463ed990/ASPE-Environmental-Scan.pdf
[18] https://pmc.ncbi.nlm.nih.gov/articles/PMC5927782/
[19] https://www.globaldata.com/media/pharma/increased-use-virtual-trials-contributed-improved-patient-accrual-rates-says-globaldata/
[20] https://www.fda.gov/media/134754/download
[21] Hurt S. Making the case for fair compensation in clinical trials. STAT News. 2024. https://www.statnews.com/2024/05/23/clinical-trials-participation-fair-compensation/
[22] Olivier T, Haslam A, Prasad V. Is financial toxicity captured in quality of life assessments in oncology randomized clinical trials? J Cancer Policy. Jun 2023;36:100423. doi:10.1016/j.jcpo.2023.100423
[23] https://aspe.hhs.gov/sites/default/files/documents/f2d094c11fcef7a4cc4398479e0211e9/Financial-stress-IB-final-clean.pdf
[24] https://pharmasource.global/content/china-biopharma-out-licensing-surges-to-record-137-7b-in-2025-2026-on-pace-to-break-it-again/
[25] https://www.morganstanley.com/insights/articles/china-biotech-boom-generics-to-innovators
[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-phase-1-investigational-drugs
[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-prior-knowledge-development-human-gene-therapy-products-incorporating-genome-editing

[28]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/monoclonal-antibodies-streamlined-nonclinical-safety-studies
[29]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-use-new-approach-methodologies-drug-development
[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oncology-pharmaceuticals-streamlined-nonclinical-safety-studies-biologics-and-conjugated-products
[31] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cderoffice-new-drugs-streamlined-nonclinical-studies-and-acceptable-new-approach-methodologies-nams
[32]https://aspe.hhs.gov/sites/default/files/documents/509e0cabf9dac33db3a1bb90c79927d3/enviro-scan-expert-elicit-findings.pdf
[33]https://preludeedc.com/resource/cost-of-protocol-amendments-phase-1/
https://www.precisionformedicine.com/blog/the-amendment-trap-why-76-of-clinical-trials-face-six-figure-protocol-changes
[34]https://aspe.hhs.gov/sites/default/files/documents/ce102c41a7626cd885f7c88a9f2c4807/drug-development.pdf
[35]https://www.hhs.gov/ohrp/regulations-and-policy/regulations/index.html
[36]https://www.fda.gov/about-fda/cder-offices-and-divisions/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials
[37] https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=202504&RIN=0910-AI08
[38] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2817926
[39] https://www.ncbi.nlm.nih.gov/books/NBK215076/
[40] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2817926
[41] https://aspe.hhs.gov/reports/compensation-clinical-research
[42] https://globalforum.diaglobal.org/issue/december-2024/breaking-financial-barriers-making-the-shift-to-reasonable-compensation-for-clinical-trial-participants/
[43] https://aspe.hhs.gov/reports/clinical-trial-costs-patients
[44]https://aspe.hhs.gov/sites/default/files/documents/f2d094c11fcef7a4cc4398479e0211e9/Financial-stress-IB-final-clean.pdf
[45] https://ncoda.org/news/the-challenge-of-patient-enrollment-in-clinical-trials/
[46]https://aspe.hhs.gov/sites/default/files/documents/32f96e701a972323b4a21f99d36730ab/Empowering-Patients-%20through-Clinical-Trials-%203.13.25_clean.pdf
[47]https://www.fda.gov/news-events/press-announcements/fda-pilots-faster-clarifications-meeting-minutes
[48]https://commonfund.nih.gov/clinical-research-primary-care