REAGAN-UDALL FOUNDATION FOR THE FDA

Enhancing Early-Stage Drug Development

IN THE UNITED STATES

ABOUT THE REAGAN-UDALL FOUNDATION FOR THE FDA

The Reagan-Udall Foundation for the FDA (Foundation) is an independent nonprofit created by Congress to advance regulatory science to help the U.S. Food and Drug Administration accomplish its mission. The Foundation manages a suite of programs that assist the FDA in engaging with external stakeholders and that facilitate evidence generation, improve public understanding of the FDA, and deliver more accessible health information to the public.

FUNDER

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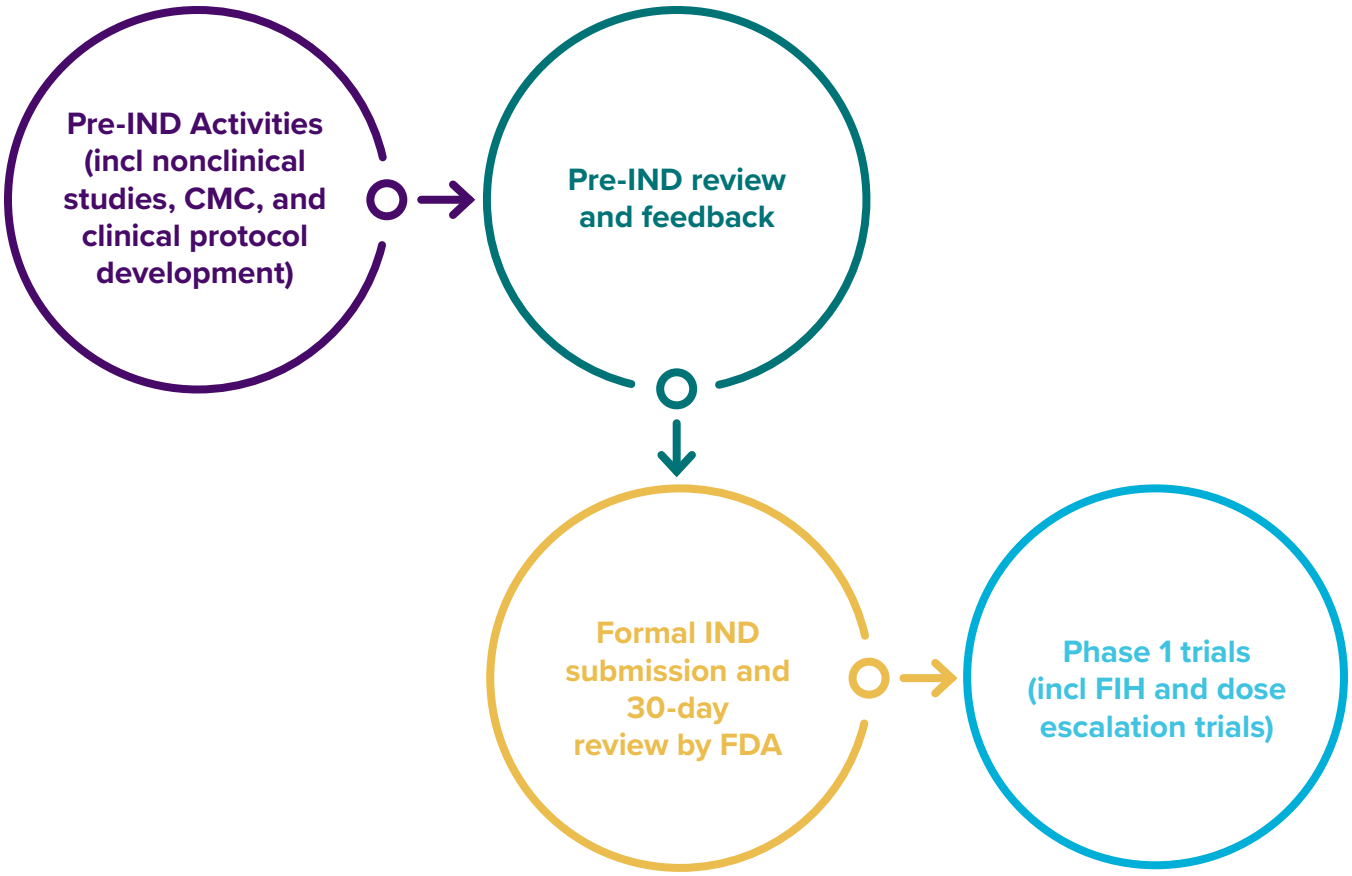
Contents

Meeting Purpose

Early-stage drug development—encompassing preclinical research, Investigational New Drug (IND) activities, Phase 1 clinical trials (including First in Human (FIH)), and dose escalation—is the gateway through which laboratory discoveries become next generation medicines (Figure 1). The United States has long been the global leader in early-stage drug discovery and development. However, that leadership is increasingly threatened as other countries and regions have made deliberate, strategic investments designed to increase their competitive edge. Further, continued erosion of Phase 1 trials in the U.S. could lead to reduction in the number of later-stage U.S. clinical trial activities, as sponsors often build those later-stage activities around the investigator and site relationships established during FIH studies.[1]

In late March 2026, the Reagan-Udall Foundation for the FDA (the Foundation), convened a roundtable to build upon previous conversations about experiences in the U.S. and other regions and explore what incentives are needed to maintain leadership in First in Human and Phase 1 clinical trials.[1] Specifically, the meeting focused on opportunities for the U.S. to: 1) improve and modernize IND requirements and review processes and 2) streamline and expedite initiation of Phase 1 trials in the U.S.

FIG. 1: MEETING FOCUS



Executive Summary

On March 26, 2026, the Reagan-Udall Foundation for the FDA, in collaboration with the Biotechnology Innovation Organization (BIO), convened an invitation-only Roundtable with representatives from academic medical centers, biopharmaceutical companies, clinical research organizations (CROs), patient organizations, and regulatory agencies.

The discussions explored practical solutions to modernize Investigational New Drug (IND) requirements and IND review processes and to streamline and expedite initiation of Phase 1 clinical trials in the United States. Participants emphasized that modernization cannot be achieved through guidance and statutory revision alone; it will also require cultural change within FDA and among clinical trial sponsors, clinical trial sites, and Institutional Review Boards. The discussion emphasized the importance of developing actionable recommendations and the need for prompt action. Specifically, the roundtable developed 17 recommendations and a wide range of supporting solutions addressing:

Modernizing IND Requirements and Processes

1. Adopt risk-proportionate IND submission requirements and triage review processes
2. Advance rolling IND submissions
3. Modernize nonclinical requirements and practices
4. Update and streamline chemistry, manufacturing, and controls (CMC) requirements
5. Clarify required and presumed-required IND data
6. Improve safe-to-proceed and clinical hold communications
7. Enable a Phase 1 Clinical Trial Notification pathway

Modernizing Phase 1 Clinical Trials and Tools

8. Support greater use of innovative clinical trial designs
9. Increase inclusion of patient perspectives in early-stage drug development
10. Develop artificial intelligence (AI)-enabled sponsor-facing decision support tools

Optimizing FDA–Sponsor Early-Stage Engagements and Processes

11. Enhance pre-IND meeting and IND review best practices
12. Capture IND regulatory decision-making trends
13. Incentivize fit-for-purpose IND submissions and engagements

Building a Streamlined and Dedicated U.S. Phase 1 Infrastructure as part of a National Clinical Trial Infrastructure and Coordinating Strategy

14. Build and fund a dedicated network of Phase 1-capable clinical trial sites
15. Create a national Phase 1 coordinating strategy
16. Streamline Institutional Review Board (IRB) and site activation processes

Mitigating Litigation Risk for Phase 1 Clinical Trial Sites

17. Explore safe harbors and insurance reforms for FIH and Phase 1 trials

See Appendix I for complete table of recommendations and solutions.

Global Landscape of Clinical Trial Starts

Developing novel drugs and biologics is a high-risk, time-intensive, and costly endeavor. It takes an average of 9 years to progress from FIH studies to New Drug Application/Biologics Licensing Application and can cost over $2 billion to bring a treatment to market (estimates include both failed and successful research).[2,3] Furthermore, the return on research and development (R&D) investment has declined over the past two decades (3–5% in the 2020s versus 12–15% in the 2000s). Trials have become more complex (e.g., data volume has increased from 1.8 million in 2015 to about 4.9 million in 2025)[a] but clinical trial success rates have remained steady over the past two decades (Figure 2). Spending for more complicated clinical trials and technology vendor services has more than doubled since 2010 ($43.1 to $95.6 billion).[4] Additionally, the average enrollment timeline for all clinical trials across all therapeutic areas is increasing with the largest increase seen in Phase 1 trials (5 month duration increase from 2019 to 2023).[5] These points illustrate a key concern: more R&D money is being spent ($94.2 billion in the 2000s; $188.1 billion in the 2020s) but the ecosystem is less efficient.[4] Participants highlighted that not only has clinical development become more complex and expensive, but the financing environment is demanding more capital efficiency and regulatory/manufacturing/evidence frameworks have not fully adapted to the needs of new modalities.

FIGURE 2. CLINICAL PHASE TRANSITION PROBABILITIES (SUCCESS RATE OF MOVING TO THE NEXT PHASE)

	1999 to 2004	2014 to 2021
Phase 1 to 2	64%	63%
Phase 2 to 3	39%	31%
Phase 3 to Submission	66%	58%

Modified from CTTI State of Clinical Trials Presentation by Ken Getz. May 2025 (Reference 4)

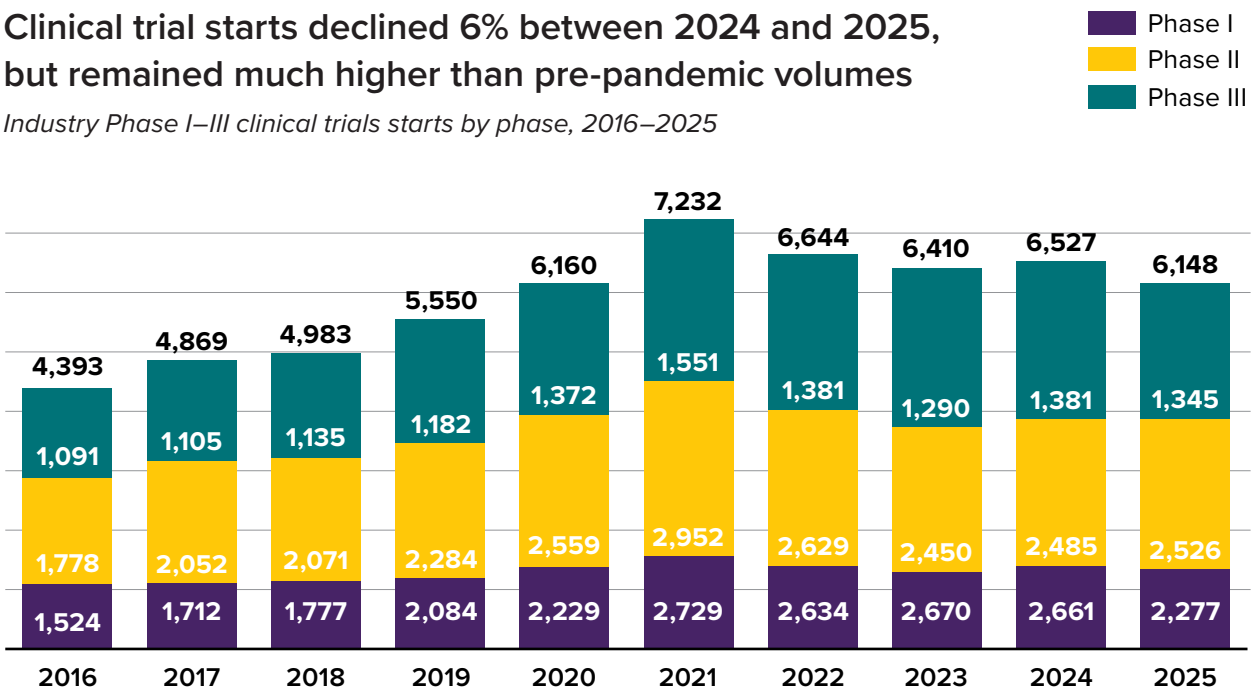
The clinical development landscape is reacting and evolving to these realities. In 2025, there was a 6% decrease in the number of clinical trial starts compared to 2024, though the total number of clinical trials was still significantly higher than prepandemic levels (Figure 3). The main reduction was in the number of Phase 1 trial starts (-14%) from sponsors headquartered outside of the U.S. In 2025, U.S.-headquartered sponsors accounted for 35% of all global clinical trial starts, China-headquartered sponsors accounted for 32%, and European-headquartered sponsors' share held steady at 20%. U.S. companies accounted for over half of the trial starts in the U.S. (60% in 2025), European companies accounted for 26%, and Chinese and Japanese companies each accounted for 5%. Similar to the U.S., European companies accounted for over half of trial starts in Europe. China-headquartered sponsors accounted for 77% of China's trial starts in 2025 with U.S.-, Europe-, and Japan-headquartered companies accounting for 11%, 8%, and 2%, respectively. Notably, Chinese-headquartered sponsors ran 88% of their trials exclusively in China.[6]

a Total data volume calculated as the sum of total endpoints, eligibility criteria, procedures, countries, investigative sites, patients randomized

FIGURE 3.

Clinical trial starts declined 6% between 2024 and 2025, but remained much higher than pre-pandemic volumes

Industry Phase I–III clinical trials starts by phase, 2016–2025



Source: Citeline Trialtrove, Jan 2026; IQVIA Institute, Feb 2026.
Report: Global R&D Trends 2026. IQVIA Institute for Human Data Science.

The U.S. medical innovation ecosystem provides patients with first access to investigative and innovative medicines and is a significant driver in the U.S. economy.[7,8] For many U.S. patients, access to later-stage clinical trials and experimental medicine provides the only opportunity to obtain the best treatment for their disease; in oncology, access to clinical trials has become part of the evolving standard of care. For early-stage clinical development, competition is particularly intense with China and Australia, two countries that have been developing initiatives to foster a more competitive early-stage clinical development ecosystem.[9] While the U.S. is still the global leader in overall medical innovation, the migration of preclinical research, Phase 1, and Phase 2 trials away from the U.S. to international jurisdictions, particularly China, Australia, and select European countries, as well as a surge in China-initiated activity, threatens that leadership. There have also been concerns about the reduction in FDA workforce (about 20%) and funding (about 2.9% from FY 2024) and its potential effect on managing workloads. FDA leadership has stated that the use of AI and centralizing certain functions at the FDA will enable the Agency to do more with less.

In 2009, the Chinese company share of trial starts was only 1%.[10] Last year, China-headquartered companies accounted for 39% of global oncology clinical trial starts, 36% of vaccine, 33% of immunology, 32% of metabolic/endocrinology, and 30% of cardiovascular starts. The overall number of international deals for China-based companies increased significantly in 2025, with 94 mergers and acquisitions or licensing deals versus 71 in 2024, with almost half involving a U.S. partner.[6]

The number of innovative treatments developed by Chinese companies doubled from 2021 to 2024 (2,251 to 4,391) and the number of innovative drug approvals in China increased from 627 in 2019 to 1,918 in 2023.[11,12] The number of clinical trials for China-originated new drugs in the U.S. increased 82% between 2019 and 2023; Chinese biopharmaceutical companies account for roughly one-third of new compounds entering the U.S. pipeline and are projected to account for 35% of FDA approvals by 2040.[13,14] A 2026 McKinsey report stated

that early discovery-to-IND cycles in China are 50-70% faster than the rest of the world due to streamlined workflows, a dense CRO ecosystem, talent pool, and government support, including expanding the number of the country's drug and biologics regulator's (the National Medical Products Administration) reviewers from 200 in 2017 to 1,300 in 2024.[15]

The number of companies initiating Phase 1 clinical trials in Australia has been significantly increasing. More than 18,000 active trials were conducted in Australia between 2006 and 2020, with the proportion of early-stage trials increasing during that time period from 9% to 40%.[16] The number of Phase 1 oncology trials initiated in a given year increased from 18 in 2012 to 75 in 2022, with most of those trials sponsored by emerging biopharmaceutical companies from North America.[17] Factors driving these increases include the ability to initiate trials much faster than in the U.S., in part due to more centralized IRB and enrollment capabilities and a clinical trial notification pathway with documentation requirements that are more streamlined than the U.S. IND process. Each of these contributes to lower Phase 1 costs.

In summary, it has become increasingly attractive to initiate FIH and Phase 1 trials ex-U.S., especially in China and Australia. This reality could equate to delayed access for U.S. patients. Further, China's biopharmaceutical industry has emerged as a massive engine of innovation that could attract investment away from the U.S. medical research and clinical trial ecosystem. To improve U.S. positioning in early-stage product development, roundtable participants crafted the following solutions for consideration.

I.

Modernizing Investigational New Drug (IND) Requirements and Processes

Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes

Roundtable participants discussed the value of adopting a tiered, risk-proportionate approach to IND application requirements and review process that distinguishes routine lower-risk INDs—well-characterized modalities, known mechanisms, and platforms with established safety records—from high-risk novel-modality INDs for which more traditional FDA engagement is appropriate. For the low-risk tier, guidance would specify which nonclinical studies can be omitted and which CMC elements can be deferred, enabling a streamlined IND package and filing and a faster, lighter-touch review. Sponsors could rely on platform data to support a streamlined initial IND data package; higher-risk INDs would require a more iterative, collaborative review process.

Participants discussed assessing risk across five dimensions—molecular target, modality, mechanism of action, trial design, and patient population—with the patient-perspective dimension receiving particular emphasis. This architecture could have manifold benefits. First, it allocates finite FDA reviewer capacity toward the programs where agency judgment adds the greatest value. Time spared on routine INDs could be redirected to support iterative engagements that genuinely novel modalities require. Second, a risk-based framework would formalize Phase 1 review requirements for each modality and therapeutic area, unwinding the drift by which optional qualifications have morphed into de facto requirements. Third, this could streamline IND package preparation, which is a significant investment of sponsor resources and time. The approach is consistent with the International Council on Harmonisation E6(R3) guidance, formally adopted in September 2025, which explicitly embeds risk-based and risk-proportionate approaches across the lifecycle of a clinical trial, instructing investigators to determine which data and clinical trial processes are most important to participant safety and data integrity and to focus efforts accordingly.[18,19]

However, participants cautioned against over-engineering the framework into a complex risk-stratification algorithm that may yield more rigidity than flexibility. It was noted that Australia's success with their Clinical Trial Notification (CTN) pathway is the product of iterative collaboration rather than complex tiering. Moreover, Australia's Therapeutic Goods Administration (TGA) can reliably defer to the commercialized Human Research Ethics Committees (HREC), which are well staffed to review both the ethical and scientific merits of clinical trial protocols based on nonclinical data.

The roundtable participants also proposed a simpler, two-dimensional "triage" framework as a starting point, which would facilitate implementation without a complex algorithm. Under this approach, the depth of required nonclinical diligence would be set by the intersection of 1) subject risk—from normal healthy volunteers or patients with mild disease, through moderate-risk, to severely debilitating or life-threatening (SDLT; 21 CFR 312.81) or progressive unmet disease—and 2) therapeutic intervention risk—from pharmacokinetics (PK)-modified or

well-characterized pharmacology through novel pathways or molecular targets with adequate nonclinical translation to molecules with known class flags for severe adverse events or poorly translating models.[20] For well-characterized pathways and modalities, a fit-for-purpose package using a weight of evidence risk assessment, including prior human drug-class data, leveraging new approach methodologies, structural hazard data, and generally accepted scientific knowledge (GASK) would be appropriate. When disease risk outstrips drug risk, a flexible approach is also warranted. This concept draws explicitly on the compassionate use ethical framework, applies the International Council for Harmonisation (ICH) S9 logic currently reserved for oncology to others regardless of modality, and does not distinguish between small molecules, biologics, cell therapies, or gene therapies. An illustrative matrix is shown below (Figure 4).

FIGURE 4. ILLUSTRATIVE TRIAGE MATRIX FOR CALIBRATING NONCLINICAL SAFETY DILIGENCE TO THE INTERSECTION OF SUBJECT RISK AND DRUG RISK

This figure is meant to illustrate a matrix only.

Drug risk	PK precedented / well-characterized pharmacology	Improved pharmacology & highly related SAR	Novel pathway / structure; good* nonclinical translation	Known severe adverse event flags or poorly* translating models
Subject Risk				
NHV / mild disease	Streamlined**	Moderate***	Moderate	Case-by-case****
Moderate-risk patient population	Streamlined	Moderate	Moderate	Case-by-case****
Severe debilitating disease	Streamlined	Streamlined	Moderate	Streamlined
Life-threatening unmet disease	Streamlined	Streamlined	Streamlined	Streamlined

* *Although not conclusive, animal toxicology of small molecule drugs has reasonably good clinical translation, and clinical translation is poor for certain biological products.*

** *Streamlined in this context is to be interpreted as less rigorous diligence required for safety assessment rather than needed for a moderate review (e.g., severely debilitating disease may require a less rigorous nonclinical safety package compared to what is expected for normal healthy volunteer studies).*

*** *Moderate in this context means more safety diligence than streamlined.*

**** *Case-by-case in this context means a review that may require specialty expertise and considerations*

Participants also discussed the potential value in FDA establishing a dedicated FIH specialist review unit with accumulated experience in novel technologies. Such a review unit could yield more consistent feedback, provide internal FDA training and consultation across divisions and centers, and serve as an identifiable point of contact for sponsors who want to partner on process improvement. This review unit would coordinate with therapeutic area specialists and other FDA experts as appropriate (e.g., CMC and pharmacology/toxicology staff). A specialist review unit would also help advance risk-based approaches that rely on platform data that require triaging FDA reviewer time.

RECOMMENDATION #1

Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes

SOLUTIONS:

a. Develop specific recommendations for risk-proportionate IND submission requirements and triaged review processes. Efforts could include:
   - Developing and implementing risk-proportionate IND review timeline (e.g., 14-day IND review for well-characterized platforms, simple formulations, microdosing, exploratory INDs).
   - Developing and implementing a triaged IND classification based on drug risk vs. subject risk that determines the level of submission requirements and reviewer time.
   - Establishing principles and developing modality-specific guidance that describes what data are required for low-, medium-, and higher-risk INDs.
   - Developing FDA internal training and standard operating procedures about how to triage FDA reviewer time based on need.

b. Establish a dedicated FIH specialist review unit at FDA for novel-modality or high-risk INDs, consolidating expertise currently distributed across multiple divisions.

c. Invest in a specialized FIH-review workforce at FDA that delivers clear, consistent, and modality-aware early-phase regulatory expectations, reducing variable cross-division feedback.

Advance Rolling IND Submissions

FDA leadership has publicly identified reform of the IND process as a priority for the Agency. This reform is alongside broader modernization initiatives such as AI-assisted scientific review intended, in part, to accelerate review of complex pharmacology/toxicology packages, phased reduction of animal-testing default requirements, and rethinking Phase 1 IRB requirements to shorten the time to FIH studies.[21,22]

Roundtable participants recommended allowing alternative approaches to requiring complete IND packages, such as a rolling or staged submission model. In such an approach, sponsors submit and receive FDA feedback on discrete package components—protocol design, safety monitoring plans, stopping rules, inclusion and exclusion criteria—before all toxicology data are finalized, with starting dose set after the toxicology package is complete. A more aggressive version of this recommendation would permit FIH dosing at low doses to proceed based on non-good laboratory practices (GLP) studies (i.e., preliminary nonclinical studies used to evaluate drug safety, efficacy, absorption, distribution, metabolism, and excretion) and good monitoring practices (GMP)-like materials, while GLP and GMP finalization work continues in parallel while subject to defined guardrails (e.g., well-characterized modality class, sponsor commitment to complete the full IND package within a set time period). Another potential approach, modeled on the Australian CTN and HREC processes, is to create an "Investigator Brochure (IB) and Standard for Exchange of Nonclinical Data (SEND) dataset" model that would allow the IB, as well as draft study reports, with the protocol and informed consent form for submission upfront and provide SEND datasets after IND submission. This process would preserve FDA's capacity for independently analyzing raw data while reducing documentation burden at initial filing. FDA's existing Phase 1 guidance provides a foundation for this direction: its guidance acknowledges that 1) the agency does not expect full stability data and complete CMC documentation at Phase 1 and 2) the nonclinical and CMC content of an early-phase IND can be limited to an integrated summary of toxicology, a full tabulation

of data of each toxicology study to support the safety of the proposed investigation (21 CFR 312.23(a)(8(ii)), and minimal CMC details.[18,23] This approach also better aligns with clinical trial application requirements outside the U.S.

The operational logic underpinning these recommendations is that protocol synopsis and many aspects of clinical trial design and monitoring could be generated early in development and that the protocol can be adjusted as toxicology data become available. The final clinical protocol would be submitted when the toxicology program ends. Resolving these issues in parallel with remaining toxicology work compresses the overall timeline without compromising the safe-to-proceed determination. FDA's rolling mechanisms for later-phase submissions can serve as a template. For example, FDA's Fast Track and Breakthrough Therapy designations (Sections 506(a) and 506(b) Federal Food, Drug, and Cosmetics Act, 21 U.S.C. 356) allow clinical development programs with these designations to submit complete modules of a marketing application on a rolling basis with the expectation that all portions would be submitted within approximately one year of the initial portion.[24] The Real-Time Oncology Review program further permits early FDA access to components of clinical and safety data before formal submission to identify review issues and enable early feedback to the applicant.[25] Such an approach is consistent with recent FDA announcements. On April 28, 2026, the Agency announced it is taking steps to implement real-time clinical trials, initiating two proof-of-concept clinical trials that will report endpoints and data signals at specified intervals to the FDA in real-time. A pilot may also be used to rethink how and when data is submitted to the FDA.[26]

RECOMMENDATION #2

Advance Rolling IND Submissions

SOLUTIONS:

a. Adopt a modular, rolling IND review pathway: a sequential nonclinical package and Phase-appropriate CMC data package enabling first-cohort dosing. Elements of the pilot could explore:
   - Cases where FIH dosing could proceed based on non-GLP studies and GMP-like materials.
   - An Investigator Brochure (and draft study reports) to enable start of FIH plus SEND datasets submitted at a later date.

Modernize Nonclinical Requirements and Practices

Overall, the purpose of FIH clinical trials is to evaluate the tolerability, safety, PK, and pharmacodynamics (PD) of a new drug/biologic in humans and to examine how effects seen in nonclinical studies translate into humans. Nonclinical safety data is used to characterize the safety profile and inform proposed dosing ranges. Within the FIH trial, dosing ranges are important: a higher allowed dose likely allows researchers and investors to determine more quickly and definitively the potential of a drug candidate. A more risk-averse, lower maximum dose may result in indeterminate findings in the FIH trial, requiring additional research time, cost, and human exposure. Initiation of the FIH trial at very low doses may delay reaching therapeutic levels and increase the overall timeline for drug development.

FDA has explored improving FIH dosing. In 2021, FDA's Oncology Center of Excellence launched Project Optimus and later published guidance to reform dose selection protocols in oncology from a maximum tolerance dose approach protocol to protocols intended to identify the optimal dose for patients.[27,28] Under these new requirements, Phase 1 oncology protocols are expected to include PK sampling and analysis plans

covering first dose through steady state at each dosage level, with population PK analysis initiated early to identify populations with clinically meaningful exposure differences. This approach often means that Phase 1 oncology trials have larger enrollment and longer timelines than under the prior maximum tolerated dose paradigm.[29] Further, there are challenges in demonstrating efficacy differences between doses with small sample sizes.[30] Participants discussed how the implementation of Project Optimus might be meaningfully improved, expanded, and simplified through greater use of model-informed drug development (MIDD) and population PK modeling to fill dose-optimization data gaps, in collaboration with the FDA's Office of Clinical Pharmacology. This approach could streamline development activity, rather than duplicating Phase 1 cohorts across every tumor type, indication, and combination partner. Such an expansion would require partnering with industry on acceptable modeling parameters and equipping the Office of Clinical Pharmacology's pharmacometrics group to review modeling-based, dose-optimization submissions consistently across FDA divisions. The Agency has successfully partnered with industry via the MIDD pilot program, and it could be scaled and integrated into routine drug development and review.

In oncology, where FIH are in patients versus healthy volunteers, results of nonclinical studies are used to set a FIH dose instead of a dose range. Optimal approaches for FIH dose selection were not specifically discussed at this meeting; however, FDA flexibility in nonclinical studies for anticancer products was noted as necessary by roundtable participants. Medical researchers, clinical researchers, and regulators continue to examine and refine how best to approach early-stage dosing goals and requirements, and a variety of approaches for FIH dose selection for anticancer agents are presented in FDA guidance and publications and by IQ DruSafe.[31,32,33,34,35,36,37,38] A 2024 analysis by the Health and Environmental Sciences Institute Immuno-Safety Technical Committee found that FIH dose selection for immunomodulators—traditionally anchored to the minimum anticipated biological effect level (MABEL)—often yields subtherapeutic starting doses and prolonged, costly escalation phases, confirming conclusions observed in FDA oncology publications. An accompanying industry survey reflected growing preference for more dynamic PK/PD-based approaches, and the authors observed that FDA has become increasingly receptive to non-MABEL strategies.[39] A 2024 FDA oncology publication also concluded that for closely related antibodies, clinical data can inform FIH dose selection.[38]

Roundtable participants recommended applying any early-stage dosing framework across any severe, progressive, life-threatening, or disabling disease—not only cancer. Additionally, it was recommended that such a framework be applied across modalities beyond small molecules, antibodies, and traditional biologics and include genetic and nucleic acid-based platforms as well. They further cautioned that starting-dose conventions developed for healthy volunteers—which rely on conservative safety margins below the no-observed-adverse-effect level (NOAEL)—are not appropriate for patient populations in which untreated disease poses a greater risk than the investigational drug. Finally, participants noted the importance of building learnings across disease areas to ensure regulatory decisions about dose selection and escalation based on consistent scientific principles that consider the drug or biologic being tested and the needs of the patient population. For example, a roundtable participant presented a situation where FDA required a pediatric starting dose higher than the sponsor proposed, on the posture that every patient should be able to benefit from treatment. Following that directive, the second and third cohorts developed reversible toxicity. The clinical development program was then placed on a clinical hold for nearly one year. In a separate example, a single observation in a single animal led to an operational cap on dose escalation at tenfold *below* the NOAEL—a cap that the relevant guidance document did not require. Both examples illustrate how the absence of clear, published criteria for dose-setting decisions introduces unpredictability that extends timelines and may not be in the best interest of the patient or healthy volunteer. Cross-center and review-division knowledge management initiatives and rotation of pharmacology and toxicology (Pharm-tox) staff would broaden exposure to different diseases and patient populations and likely improve sponsor and regulator understandings about

regulatory expectations. Documentation, shared with sponsors, of the scientific rationale applied to support dose selection and escalation requirements would support both regulators and the regulated industry in continuing to learn and deploy best practices.

Roundtable participants examined the pattern of some sponsors conducting animal studies based on what was utilized in earlier FDA-reviewed packages, beyond scientifically necessary studies to address the key FIH questions of safety. For example, participants noted unnecessary, chronic, repeat-dose toxicology studies in two species were often conducted by sponsors because they were included in a previous New Drug Application for a different compound in the same class. This is an example where FDA guidance is *not* mandating such behavior; rather, the culture of default among sponsors (and FDA reviewers) is driving these potential redundancies.[b] It was also noted that despite sponsors' proposals to conduct a single species toxicology study with the most relevant and predictive species and supporting extensive nonclinical platform experience, FDA has rejected such proposals and defaulted to requiring two species toxicology studies. Participants underscored the value of the FDA sharing information about when more streamlined approaches could be applied (e.g., one species versus two species toxicology studies) would help cross-pollinate best practices across the FDA and among sponsors.

Roundtable participants welcomed FDA's March 2026 draft guidance on New Approach Methodologies (NAMs) as a meaningful signal. However, practical uptake by sponsors and regulators will require both cultural changes and increased scientific understandings about NAMs and their ability to answer key safety questions. Pharm-tox and CMC reviewers have been trained to default to animal studies, and at times, regardless of whether the animal model is appropriately predictive. The task of justifying deviation from animal testing will require thought leadership from both the biopharmaceutical industry and FDA. Reviewer training and education on accepting nontraditional methods can be as important as new and updated guidance. A structured Pharm-tox reviewer rotation program was again raised as a potential solution, as certain FDA divisions were viewed as more flexible than others in accepting streamlined approaches for comparable cases. In this context, such a rotation would expose Pharm-tox reviewers to different risk models across therapeutic areas and modalities—and accelerate the necessary cultural shift that guidance publication alone cannot achieve.

b The dynamic of overloading IND packages based on a presumption of required information is further discussed in Recommendation #5 in this report

RECOMMENDATION #3

Modernize Nonclinical Requirements and Practices

SOLUTIONS:

a. Develop dose selection scientific principles that consider disease severity and distinguishes first-in-healthy-humans needs from first-in-patient needs.

b. Refine Project Optimus implementation through greater use of model-informed drug development (MIDD) and population PK modeling to optimize dose selection and escalation and address data gaps.

c. Convene meetings among regulators, biopharmaceutical companies, CROs, and medical researchers to discuss how to advance the utilization of New Approach Methodologies (NAMs) and create a pathway for sponsors to secure endorsement to use a single species toxicology study, including reliance on nonclinical platform data that can be carried forward to future IND submissions. This effort should include development and implementation of FDA internal training programs exploring a review posture in which applications are presumed adequate with in vitro/comparative biology data unless reviewers provide scientific rationale for an animal study and provide insight on which species might be most predictive. The substance of these trainings may be strengthened with input from external experts.

d. Formalize a structured Pharm-tox reviewer rotation program across FDA divisions and centers to cross-pollinate risk-tolerance frameworks.

Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements

Recent stakeholder meetings examining the shift of early clinical development away from the U.S. have identified FDA's pre-IND submission requirements for CMC as an important determinant.[1] For example, stability requirements for study material often far exceed study duration. A 2026 presentation from Canal Row Advisors posited that CMC is an area where sponsors are likely providing more than is required. Earlier this year, FDA's Center for Biologics Evaluation and Research (CBER) announced its goal of having a more flexible approach to CMC requirements for cell and gene therapies. CBER clarified that manufacturers are not required to meet Current Good Manufacturing Practices (cGMP) requirements under 21 CFR Part 211 before Phase 2 or 3 clinical trials. Participants recommended the FDA formalize this announcement with official guidance and apply it to other modalities.

Roundtable participants pointed to Belgium's Phase 1 Clinical Trial Application framework as an illustrative model for potential FIH/Phase 1 trial CMC reforms. The Belgian authorities accept short-term or accelerated CMC stability data with a scientifically justified shelf-life covering only the clinical dosing period, paired with a sponsor commitment to continue stability testing during the trial. By contrast, FDA currently expects substantially more detail in the Drug Substance and Drug Product application sections, including: more granular manufacturing-process description and in-process controls rather than a high-level flow description; broader specifications rather than safety-critical-only specifications; and longer-term stability strategy with shelf-life extrapolation rather than data covering only the dosing period. The current approach requires significant upfront investment to manage the bioreactor size needed and to pay for facilities with the necessary

cGMP release testing capabilities. This investment is particularly challenging for pre-commercial startups. Participants noted that the relevance of long-term stability for Phase 1 trials is minimal as the drug substance and product are manufactured for near-term use. Importing elements of the Belgian approach—while preserving FDA's full safety authority—would streamline U.S. Phase 1 CMC without compromising subject safety or robustness of clinical-trial data.

Roundtable participants also highlighted CMC burdens for comparator drugs in combined Phase 1/2 trials. FDA considers any drug not approved for U.S. marketing as investigational, triggering the full IND CMC requirements of 21 CFR 312.23(a)(7).[40] This posture means a drug rigorously characterized and approved by the European Medicines Agency (EMA) or Japan's Pharmaceuticals and Medical Devices Agency (PMDA) still requires independent, full CMC characterization to serve as a comparator in a U.S. IND.[41] EMA, by contrast, requires substantially less CMC documentation for comparators authorized in the EU or any ICH region, including the U.S., Japan, Canada, Switzerland, and the United Kingdom.[42] Full CMC characterization is a multimillion-dollar undertaking—benchmarked at an average of $3.1 million per program and up to $20 million for complex products—thus, these additive costs can render a U.S. IND economically nonviable, especially for small companies.[43] An FDA approach accepting CMC characterization performed by EMA, PMDA, Health Canada, Swissmedic, or other ICH Regulatory Members for proof-of-concept studies, and eliminating the need to submit separate U.S.-specific CMC documentation, would align U.S. practice with peer regulators and improve U.S. competitiveness. A precedent already exists: in March 2026, the FDA issued revised draft guidance permitting biosimilar sponsors to use non-U.S.-licensed comparator products approved by ICH-aligned regulators (e.g., EMA) in clinical studies supporting U.S. biosimilar marketing applications, eliminating the long-standing default requirement for a three-way PK bridging study between the proposed biosimilar, the U.S.-licensed reference product, and the foreign comparator. One of the goals of this change was to reduce duplicative development work.[44]

In addition to the previously discussed risk-proportionate approach to IND submission requirements, participants debated the potential benefits of a more systematic, risk-based pathway to waive or streamline routine CMC submission and review for defined categories of Phase 1 studies. FDA regulations and guidance already recognize that the extent of CMC information required in an IND should be commensurate with the scope of the study and phase of development (21 CFR 312.23(a)(7)) and the Agency's Phase 1 and Phase 2/3 CMC guidance documents. However, in practice this flexibility is not consistently applied by reviewers or sponsors as expectations for Phase 1 CMC data and documentation are often indistinguishable across submissions that fall at opposite ends of the risk-benefit spectrum. Complying with cGMP requirements comes with significant investment and prolonged development timeline and is particularly challenging for bespoke/rare disease therapies. A formal framework that defines when Phase 1 CMC packages can be waived or streamlined—while preserving patient safety and focusing FDA resources on higher-risk cases—could meaningfully incentivize U.S. early trial initiation.

Participants identified several categories where a CMC waiver or streamlined package may be appropriate: 1) products manufactured using well-established platforms or with extensive prior sponsor experience with analogous FDA submissions, where prior knowledge mitigates the need for duplicative upfront data generation, consistent with FDA's Platform Technology guidance and ICH Q14; 2) products for serious and life-threatening, ultra-rare, or N-of-1 conditions, where urgency supports a higher tolerance for residual CMC uncertainty; 3) very low-risk study designs such as microdosing studies (where systemic exposure is extremely low and safety risk is negligible) and exploratory INDs for which FDA's existing exploratory IND guidance already provides for reduced CMC and nonclinical requirements; and 4) simple formulations using known excipients and standard manufacturing processes (e.g., immediate-release oral tablets, aqueous solutions) where short-term Phase 1 exposure poses low risk of novel toxicities.

In these low-risk scenarios, required CMC information should be narrowly targeted to safety-critical attributes, with non-critical elements deferred to later development stages. Examples of more limited information include batch analysis data demonstrating identity, potency, and a safety-relevant impurity profile; sterility assurance for parenteral products; short-term or accelerated stability data covering the clinical dosing period (paired with a commitment to continued stability monitoring and progressive refinement of specifications and process understanding as development advances); and early-stage specifications limited to safety-critical tests. For biologics in particular, where FDA has historically expected stability data to be generated on the clinical (cGMP) lot, the Agency could, at Phase 1, accept accelerated stability data (together with any available short-term, real-time data) from a representative lab-scale batch as preliminary support that the product remains within acceptable limits over the period of clinical use, rather than as a basis for establishing shelf life. To show the lab-scale material represents the clinical lot, the sponsor would rely on platform data or a comparability assessment of potency and impurity profile and would commit to placing the actual cGMP clinical lot into a formal stability study (including sterility and container-closure integrity testing for parenterals) once manufactured, reporting results and any quality- or safety-relevant signal through the IND. This approach would allow Phase 1 initiation without delays tied to long-term stability generation, while preserving the data generation activity needed to support later phases.

To uphold public confidence and FDA's ability to protect public health, roundtable participants articulated several safeguards for any such pathway. First, sponsors should retain the option to request a full Phase 1 CMC review, recognizing its value for new companies, investigator-initiated trials, or programs pursuing accelerated development where additional considerations may be involved. Second, FDA must retain explicit authority to require broader CMC review when it deems necessary; however, the criteria and process for triggering such a requirement should be rapid, transparent, and communicated well in advance of IND submission (e.g., at a pre-IND meeting or under a written request with a prespecified response timeline), so sponsors can seek preliminary waivers or streamlined-assessment pathways before investing in submission preparation. Broader platform-based or product-class-based waivers could be discussed between FDA and sponsors based on demonstrated prior knowledge and experience, with sponsors attesting that no substantive changes have been made to processes or controls relative to prior FDA-reviewed submissions. Even under a waiver, core safety-critical data (e.g., sterility and viral clearance information where applicable, mutagenic impurity information, certification that clinical batches have been directly qualified in nonclinical studies) could be required for defined product classes to mitigate well-characterized risks while avoiding time-intensive studies with limited additional benefit. Clear guidance and training across FDA would help ensure consistent application of any such pathway across centers and divisions.

Lastly, participants recommended that FDA regularly publish an anonymized list (a sort of "Top 10" collection) of common CMC deficiencies and remediation pathways to help align understandings between sponsors, CROs, and regulators and facilitate shared learning.

RECOMMENDATION #4

Update and Streamline Chemistry, Manufacturing, and Controls (CMC) Requirements

SOLUTIONS:

a. Expand the January 2026 CBER CMC flexibility announcement into formal guidance covering cell and gene therapies, explicitly clarifying that cGMP under 21 CFR Part 211 is not required before Phase 2 or Phase 3, and extend analogous flexibility to other modalities when supported by risk-benefit determination.

b. Streamline CMC content required for certain Phase 1 trials to allow short-term or accelerated CMC stability data with a scientifically justified shelf-life covering only the clinical dosing period, paired with a sponsor commitment to continue stability testing during the trial. This could be modeled after Belgium's Phase 1 CMC submission model.

c. Issue a formal policy statement on cross-regional comparator characterization, enabling sponsors to rely on drug characterization accepted by EMA or other ICH regulators.

d. Establish a risk-based pathway to waive or streamline routine Phase 1 CMC submission and review for defined categories, including: 1) products manufactured using well-established platforms or with extensive prior sponsor experience with analogous FDA submissions; 2) products for serious, life-threatening, ultra-rare, or N-of-1 conditions; 3) very low-risk study designs such as microdosing studies and exploratory INDs; and 4) simple formulations using known excipients and standard manufacturing processes (e.g., immediate-release oral tablets, aqueous solutions).

e. Routinely publish an anonymized list of common CMC deficiencies and remediation pathways.

Clarify "Required" IND Data

While the formal IND review period is 30 days, that review period follows many months of investment by sponsors to compile and assemble the IND package. Package information includes nonclinical studies, including animal testing and CMC data and additional information regarding plans for clinical trials. The overall IND-enabling nonclinical safety studies typically take 12–18 months, with parallel CMC activities—including detailed stability data generation and analytical method validation—also requiring significant time and investment.[45]

Roundtable participants discussed the importance of a well-constructed IND package to protect volunteers and patients and advance product development, and the importance of FDA's review of that package. Studies examining IND clinical holds have found that common deficiencies for small molecules include lack of stability assurance for clinical lots, missing batch analysis data, and insufficient specifications for quality attributes. For biologics, inadequate potency and purity specifications, lack of clinical batch analysis data, and inadequate viral clearance processes were common reasons.[46] A study of cell and gene therapy INDs between 2020 and 2022 found that CMC deficiencies accounted for 21% of the clinical holds and took an average of six months to resolve.[47] Further communication and alignment on regulatory expectations for INDs could significantly help sponsors avoid unnecessary clinical holds based on submission deficiencies. These communications and efforts to align on regulatory expectations will also be critical to developing reliable AI-enabled tools.

The scale and scope of the IND package is more flexible than many industry sponsors perceive. Over-submission of data is a practice that is adding unnecessary time and costs to both regulators and regulated industry. All-inclusive interpretations of guidance documents and reliance on precedent that has been socialized over time often leads to a kitchen-sink, more-must-be-better approach to data submission and regulator requests. A critical factor driving these behaviors is the need to derisk delays in starting Phase 1 trials. This factor is especially important for smaller companies, as early proof-of-concept data is foundational to obtaining investment for clinical development programs. Likewise, if there is a perceived lack of clarity about current regulations and what reviewers seek, trial sponsors are likely to submit more information than is needed. Conversely, regulators may routinely request more than is strictly required, resulting in significant delays in preparing and reviewing the IND package. These two realities yield a presumption of data package requirements that far exceeds what is actually required.

Further, roundtable participants observed that while a reviewer may receive more material and data than is strictly necessary, it is rare that a sponsor will be directed to provide less data. The perceived alternative to submitting what information *might* be required is to risk a clinical hold on the drug development program. Excessive data submission or regulator requests for additional data strains regulators and sponsors and increases clinical trial time and costs. An opportunity to right-size the approach includes having sponsors provide scientific justification supporting determinations that certain data or studies are not needed. Similarly, regulator requests for additional data should include the scientific rationale. The communication of these rationales should be used to improve alignment of regulatory requirements across FDA and among sponsors.

Roundtable participants discussed factors to determine what is needed scientifically to review an IND and initiate Phase 1 clinical trials, such as whether current requirements are appropriately risk-based and allow for disease- or product-specific issues (e.g., whether use of a placebo is ethical or complex CMC processes are necessary). There was robust discussion about how current expectations for, and approaches to, INDs and Phase 1 trials in the U.S. are cautious and are perceived by many as exceeding what is necessary to protect early-phase trial participants. As mentioned in discussion of Recommendation #3 in this report, participants also articulated the need for risk-based approaches to distinguish between requirements needed for FIH *volunteers* (healthy volunteers) and *patients* (who have treatment needs).

Participants strongly recommended that FDA work with stakeholders to publish updated, modality-specific guidance and case studies clarifying minimum nonclinical and CMC expectations for Phase 1 INDs by scenario (i.e., small molecule, large molecule, biologic, cell or gene therapy, trial population), clearly articulating what studies and data are required for submission versus what may have been presumed to be required. Such publications should include information on the scientific rationale for required data and discuss how to properly analyze precedents to avoid continued defaulting to over-submission of data. Participants further proposed that FDA supplement this with narrative guidance documents such as Q&A-style tools or decision trees that translate regulatory expectations into structured, scenario-specific outputs. A decision-tree format would allow sponsors to answer a discrete set of questions about modality, therapeutic area, prior human data, and study design to yield a transparent articulation of the minimum CMC and nonclinical package required for their specific Phase 1 study—reducing reliance on individual sponsor-FDA conversations to surface known expectations. This approach could reduce the guesswork and precedent-borrowing that drives over-submission and help shift from implied knowledge to documented, understandable scientific rationale and principles about how to determine what is actually required.

Relatedly, roundtable participants briefly discussed the impact of disincentivizing sponsors from running any early-stage trials outside the U.S. However, raising the evidentiary bar for acceptance of foreign data as IND-supporting may compound, rather than relieve, competitive pressures. U.S. sponsors could become less

cost- and time-competitive with other countries and U.S. patients would lose the benefit of early foreign data that can refine trial design, reveal PK/PD behavior, and surface safety signals before domestic dosing. Many opined that a productive posture continues case-by-case scientific review of foreign data, with acceptance as the default where reliability and relevance are established, and targeted non-acceptance for defined scientific or data-integrity concerns.

RECOMMENDATION #5

Clarify Required IND Data

SOLUTIONS:

a. Publish updated, modality-specific guidance and case studies clarifying minimum IND data expectations for Phase 1 INDs by scenario (e.g., small molecule, oligonucleotide, oncology, viral vector, cell therapy).

b. Develop Q&A-style or decision-tree guidance tools that supplement narrative guidance documents, allowing sponsors to arrive at a transparent articulation of minimum CMC and nonclinical package requirements for their specific Phase 1 study based on modality, therapeutic area, prior human data, and study design.

Improve "Safe-to-Proceed" and "Clinical Hold" Communications

A critical stage in the drug development process is the submission of the IND package to FDA. An IND Safe to Proceed notification by FDA (or expiration of the waiting period without objection) is required before FIH trials can be undertaken in the U.S. The IND process is governed by 21 CFR Part 312. Once a sponsor submits an IND, they must observe a 30-day waiting period before initiating clinical trials. FDA may communicate safety concerns or request additional information and stop the initiation of the FIH trial. Absent such a communication, the IND is deemed to be approved by a "Safe-to-Proceed" default.[48] This default, however, is received skeptically by some in industry and by many investors, particularly when some applications receive a written response confirming safe to proceed status and others do not. Product developers report having to document, and defend, the absence of a positive FDA statement to investors and investigative sites with some trial sites refusing to start studies without FDA notification. Roundtable participants observed the value of communication confirming the safe to proceed status to ensure that there are no potential last-minute comments or holds as, on occasion, post-30-day-waiting period communications have occurred.

Participants further recommended that, when the IND is not deemed safe to proceed—or a clinical hold is issued later in the process—that the communication provide sufficient information and rationale identifying the deficiency, the regulatory basis, and clear, actionable recommended path(s) for resolution. Roundtable participants noted that the financial impact of such actions are not just costs associated with delays but also impact future investment decisions if clinical hold rationale is not well understood or there is a significant delay in providing regulatory input.

One language adaptation may be helpful. Participants recommended that situations where more information is requested by the regulator *before* any human has been dosed be labeled "notice of additional information requested" rather than "clinical hold." Reframing this terminology would not change FDA's substantive authority

or the regulatory consequence, but it would reduce the disproportionate reputational (and financial) penalty currently associated with clinical holds, which sponsors report is a meaningful factor in the decision of whether to initiate clinical trials outside the U.S. Furthermore, participants suggested that FDA provide sponsors with an opportunity to address the aAgency's concerns before placing an IND on partial or full clinical hold.

RECOMMENDATION #6

Improve "Safe-to-Proceed" and "Clinical Hold" Communications

SOLUTIONS:

a. Establish "Safe-to-Proceed" coordinated processes within FDA including:
   - Consistent, timely notifications across all review divisions within the 30-day statutory period.
   - Written rationale on all clinical holds that identifies the deficiency, the regulatory basis, and the recommended resolution path.

b. Reframe 30-day IND notification terminology for pre-dosing actions where no patient has been dosed and the action is informational from "clinical hold" to "notice of additional information required."

Enable Greater Use of a Phase 1 Clinical Trial Notification (CTN) Pathway

The discussions on reforming the IND process outlined earlier often included dialogue about why biopharmaceutical companies, particularly emerging biotechnology companies, often choose to initiate their Phase 1 clinical trials in Australia. Their Clinical Trial Notification pathway, along with a more centralized IRB process, has been posited to be a key driver of that country's increased share of Phase 1 clinical trials. Under Australia's CTN scheme, the sponsor notifies the TGA of its intention to run a trial involving an unapproved therapeutic; the TGA does not assess any data relating to the proposed trial at the time of notification. Scientific and ethical review is instead delegated to the HREC.

Relatedly, participants noted that China's parallel regulatory architecture surrounding investigator-initiated trials (IITs) has been touted as compressing innovation cycles and accelerating development and review timelines.[49,50] In China, the National Health Commission (NHC) oversees IITs, which hospitals can launch after local ethics committee approval and a simple filing. Their National Medical Products Administration (NMPA) operates the traditional IND pathway, with full preclinical and manufacturing review, and is the only route to a marketed product. Under the NHC's April 2026 interim guidance, sponsors choose which track they want to utilize: an NHC filing for a new biomedical technology or a full NMPA review. The benefit of the IIT track (in addition to speed to start-up and execution) is that data collected under that pathway can later be used in an NMPA IND application, allowing developers to gather human evidence before committing to the slower, costlier registration path.

FDA has proposed creating an optional, risk-based CTN pathway for certain Phase 1 clinical trials where there is existing nonclinical and/or relevant clinical data that can potentially satisfy the regulatory standard, and which could be supplemented with NAMs, as needed.[51] This proposed new pathway could reduce duplicative and time-consuming requirements while maintaining safety and ethical standards.

Roundtable participants further discussed the value of developing a hybrid FDA-IRB parallel-review model that would allow the FDA to focus on scientific sufficiency and safety while the IRB leads protocol, informed consent, and ethical considerations—shifting the current sequential handoff from regulator to IRB to an agreed-upon parallel timeline—thus shortening the lag between IND clearance and site activation. Such a change may require amending the Food, Drug, and Cosmetic Act, but is worth exploration. The recommendations discussed later in this report focused on building a national clinical trial infrastructure and strategy could serve to better enable this model.

RECOMMENDATION #7

Enable Greater Use of a Phase 1 Clinical Trial Notification (CTN) Pathway

SOLUTIONS:

a. Develop and implement FDA's proposed CTN pathway for certain Phase 1 trials.

II.

Modernizing Phase 1 Clinical Trials and Tools

Enable Use of Innovative Phase 1 Clinical Trial Designs

Roundtable participants recommended a coordinated set of actions to modernize the methodological, patient-facing, workforce, and technology infrastructure necessary to support a strengthened Phase 1 clinical research system. As a first step, review and update innovative clinical trial design guidance and develop accompanying FAQs that provide early-phase-specific examples for Bayesian adaptive dose-escalation, seamless Phase 1/2 designs, and biomarker-stratified expansion cohorts. Second, permit adaptive Phase 1 designs that allow modifications to dose range, escalation increment, indication focus, and therapy line based on emerging clinical data, without protocol amendment but operating under prespecified guardrails (e.g., defined maximum dose ceilings, stopping rules, biomarker-selected populations). Such an approach should allow sponsors to reach therapeutically active doses sooner. FDA's Real-Time Clinical Trials initiative could help inform these first two recommendations. Third, modernize Form FDA 1572 and associated delegation-of-authority guidance to reflect decentralized-element trial models, as well as facilitate state-level alignment on telehealth-delivered research activities for Phase 1 trial sites so that rural and medically underserved populations can participate in Phase 1 research from their home communities.

RECOMMENDATION #8

Enable Use of Innovative Clinical Trial Designs

SOLUTIONS:

a. Review and update innovative clinical trial design guidance and develop accompanying FAQs that:
   - Provide early-phase-specific examples for Bayesian adaptive dose-escalation, seamless Phase 1/2 designs, and biomarker-stratified expansion cohorts.
   - Permit adaptive Phase 1 designs to allow modifications to dose range, escalation increment, indication focus, and therapy line based on emerging clinical data—without protocol amendment but operating under pre-specified guardrails.

b. Modernize Form FDA 1572 to reflect decentralized-element trial models and facilitate state-level alignment on telehealth-delivered research activities.

Increase Inclusion of Patient Perspectives in Early-Stage Drug Development

The benefit-risk calculation of early-stage trials varies with the disease target of interest. Participants discussed the potential benefits of increasing the role of the patient voice in nonclinical risk-benefit determinations in

Phase I research to address serious and life-threatening conditions. For example, patients and clinicians are willing to accept a higher level of nonclinical uncertainty to gain earlier access to a potentially transformative therapy in areas like rare pediatric disease, where the alternative is progression to disability or death. Patient perspectives could be documented in pre-IND interactions and utilized to inform toxicology requirements. Existing FDA patient-focused drug development frameworks provide a precedent for incorporating patient perspective into benefit-risk assessment at the efficacy and endpoint level; the same logic could be extended to the toxicology-expectation side of the FIH trials. Guardrails would ensure that patient-preference input cannot be used to waive findings of clear mechanistic toxicity.

RECOMMENDATION #9

Increase Inclusion of Patient Perspectives in Early-Stage Drug Development

SOLUTION:

a. Develop a review matrix that documents when patient perspectives were used to inform toxicology requirements.

Develop Artificial Intelligence (AI)-Enabled Sponsor-Facing Decision Support Tools

The FDA is working to improve knowledge management and utilization of its data repository, such as the ingestion of historical INDs into AI systems. In addition to enhancing internal knowledge management, these efforts may also enable the development of sponsor-facing decision-support tools. For example, sponsors might eventually have access to a virtual FDA reviewer to provide feedback and help design and test protocols and data submissions, further supporting a 'truly required' approach (a minimal-but-sufficient approach) to IND submissions. However, AI training should be calibrated across an array of submissions, along with updated guidance parameters, because calibrating to the most conservative historical packages risks hard-coding into automated tools that could lead the very over-submission culture the reform seeks to address. Roundtable participants recommended creating a meeting series focused on how these knowledge management initiatives could help serve as a basis for the development of AI-enabled sponsor-facing decision tools. These meetings should also address issues such as establishing mechanisms to assess the reliability of AI-enabled reviews and when sponsors or reviewers would, and should, override AI-based decisions.

RECOMMENDATION #10

Develop Artificial Intelligence (AI) Enabled Sponsor-Facing Decision Support Tools

SOLUTION:

a. Develop a meeting series for FDA and stakeholders to collaborate on developing and implementing knowledge management initiatives that can serve as the basis for the development of AI-enabled sponsor-facing decision support tools.

III.

Optimizing FDA-Sponsor Early-Stage Engagements and Processes

Enhance Pre-IND Meeting and IND Review Best Practices

Roundtable participants discussed the current benefits and limitations of pre-IND meetings. The pre-IND meeting was formalized under PDUFA VII and allows sponsors to discuss development plans with the FDA prior to submitting an IND. These meetings are designed to enable early issue identification and resolution,[52] and operate under a philosophy of advisory rather than directive. This philosophy and its resulting feedback may not be sufficient. Sponsors who present a lean package perceive no signal that the information package is adequate and will allow them to proceed with the study; sponsors who present an overbuilt package perceive tacit confirmation. The result is another self-reinforcing cycle in which the sponsor's perceived risk of under-inclusion outweighs the actual cost of over-inclusion.

A distinct but related issue raised at the roundtable was inconsistency between pre-IND submission comments and IND review comments. Sponsors reported agreeing with a division on inclusion/exclusion criteria at the pre-IND meeting, only to receive materially different comments during the IND review.[c] Participants recommended that pre-IND meeting outputs be standardized to produce three explicit documented conclusions: 1) what is required for the proposed initial study; 2) what is optional but potentially helpful for safety and toxicology assessment; and 3) what appears unnecessary. Pre-IND alignment on specific elements —particularly inclusion/exclusion criteria, starting dose methodology, and proposed CMC scope—should be treated as commitments that the subsequent IND review does not revisit without written justification describing the emerging knowledge that prompted a changed position.

There was an active dialogue among roundtable participants about the preferred approach to IND review and comments. For example, reviewers often include comments in IND reviews intended to enable early identification and potential resolution of issues that may arise later in the clinical development program, such as observations about endpoints or pivotal trial designs. In some cases, sponsors feel obligated to make amendments and resubmit their application to address these observations, which restarts the IND review clock. The reaction to these forward-looking comments is variable: some participants found the additional insight valuable, while others viewed the input differently and proposed that a minimum comment/minimum viable product approach to IND-stage feedback is preferable. A minimum comment approach would limit regulatory comments to what is strictly necessary for Phase 1 safety clearance. It was noted that any changes to how IND reviews are conducted should consider impact on reviewer workload management. The minimum viable product recommendation envisions a voluntary option on the IND cover form through which a sponsor could affirmatively request that FDA limit its Phase 1 feedback to the statutory safety determination and defer forward-looking comments to later meetings and subsequent IND amendments. This may be a particularly useful option for well-characterized modalities and could be implemented through guidance and/or tested through a voluntary pilot.

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c As with other components of this report, these inconsistencies should be examined carefully when building reliable AI-enabled tools.

Participants reflected on the more iterative engagement approach utilized by FDA during the COVID-19 pandemic and currently used by Australia's HREC to streamline initiation of Phase 1 clinical trials. The Australian CTN model enables weekly touchpoints with HREC alternately dedicated to CMC, clinical, and nonclinical issues, with the sponsor and the HREC working collaboratively to resolve issues. The group recommended that the FDA examine both the Australian model and apply lessons learned from the pandemic to enable more iterative early-stage development engagements. It was further recommended that the FDA consider updating and reviving the (now-withdrawn) Target Product Profile framework as a sponsor-facing tool (it was withdrawn as guidance in 2017) rather than a guidance document. This framework could be used to support a more iterative engagement model by surfacing assumptions earlier and provoking structured dialogue before formal IND submission.

RECOMMENDATION #11

Enhance Pre-IND Meeting and IND Review Best Practices

SOLUTIONS:

a. Standardize pre-IND meeting outputs to produce three documented conclusions: 1) required; 2) optional but potentially helpful; and 3) unnecessary for the proposed initial study. Treat pre-IND alignment on specific elements (e.g., inclusion/exclusion criteria) as commitments the IND review will not revisit without written justification.

b. Pilot an IND-stage sponsor "Safe-to-Proceed" checkbox enabling sponsors to elect minimum-comment Phase 1 safety review, deferring forward-looking protocol, endpoint, and development-strategy feedback to later meetings; FDA's clinical hold, safety reporting, and inspection authorities are fully preserved.

c. Pilot an iterative, weekly Australian-style engagement model for pre-IND and IND-stage interactions. This effort could be supported by updating and reviving the Target Product Profile (TPP) as a sponsor-facing tool rather than a binding guidance designed to support a more iterative engagement model that surfaces assumptions earlier and provokes structured dialogue before formal IND submission.

Capture IND Regulatory Decision-Making Trends

The challenge of perceived, and actual, inconsistent feedback across FDA divisions and centers is a long-standing discussion. Roundtable participants asserted the value of capturing evidence and identifying trends of consistent or differing feedback on distinct topics. The Biotechnology Innovation Organization (BIO) is developing a new platform, entitled BRIDGE, to capture regulatory trend data based on sponsors describing their interactions with the FDA. In addition, participants called for the establishment of disease-area or modality-specific shared learning forums (e.g., rare disease, chronic disease, gene therapy). These could be public or semi-public meetings convened periodically at which sponsors, contract manufacturing organizations, CROs, sites, investigators, and FDA reviewers could share above-product information about pre-IND meetings, IND submission packages, and IND reviews and discuss what has worked, what has not, and where expectations have shifted. The premise is that much of the cultural friction discussed at this convening—reviewer variability, over-submission patterns, inconsistent dose-setting—persists, at least in part, because sponsors do not have a structured venue for discussing such challenges openly with one another. These shared learning forums would complement, not replace, individual sponsor-FDA meetings, and facilitate

cross-sponsor pattern recognition that could help advance reforms in a timelier manner. It was also recommended that the FDA develop internal mechanisms to capture trends of consistent or differing feedback on specific IND-related topics, examining deviations from routine data requests and identifying emerging consensus on INDs for new modalities.

RECOMMENDATION #12

Capture IND Regulatory Decision-Making Trends

SOLUTIONS:

a. Support stakeholder efforts to capture evidence and identify trends of consistent or differing feedback on distinct IND topics, such as BIO's BRIDGE platform, designed to capture regulatory trend data from sponsors describing their interactions with the FDA.

b. Convene disease-area or modality-specific shared learning forums (e.g., rare disease, chronic disease, gene therapy) to share information about pre-IND meetings, IND submission packages, and IND reviews and discuss what has worked, what has not, and where expectations have shifted.

c. Encourage FDA to develop internal mechanisms to capture trends of consistent or differing feedback on specific IND-related topics and cross-pollinate learnings.

Incentivize Fit-for-Purpose IND Submissions and Engagements

Roundtable participants emphasized that reform of FDA communication and feedback must be paired with reciprocal accountability from sponsors. Oversight and accountability are bidirectional: sponsors that submit over-built, precedent-borrowed packages with limited scientific justification contribute to the feedback-loop pathology as much as reviewers who default to conservative approaches requesting increasing amounts of data. Changing the culture of the more-must-be-better approach to de-risking IND review will likely require incentives. Participants proposed rewarding sponsors that submit appropriately scoped, high-quality packages. For example, the FDA could develop best practice templates and pre-IND checklists that, when followed, provide the sponsor reasonable assurance that regulatory expectations have been met, and IND-stage changes would be limited to instances of emerging safety or scientific knowledge. Additionally, these programs could be granted some form of accelerated Phase 1/pre-IND interactions (e.g., expedited Type B meeting). The logic is that the cost of expedited Phase 1 service for a well-run program is beneficial both for FDA and sponsors; providing it as a structured benefit aligns incentives toward higher-quality early-stage submissions without adding to net reviewer workload. Implementation would require FDA to define and publish Phase 1 quality thresholds, so that the incentive operates as a predictable motivation rather than a discretionary reward.

Lastly, roundtable participants discussed the potential benefit of establishing an expedited pre-IND pathway for U.S. biotech sponsors developing truly novel modalities or molecule types, modeled on EMA's PRIME (PRIority MEdicines) early-entry program. Key features could include multiple documented interactions with FDA prior to IND filing, routed through a single FDA project lead; fit-for-purpose background materials; and post-meeting clarification questions returned through the project lead to the sponsor to enable meaningful bilateral engagement. It was noted that such a pathway should have clear eligibility criteria targeting the most cutting-edge science to limit over-burdening FDA staff.

RECOMMENDATION #13

Incentivize Fit-for-Purpose IND Submissions and Engagements

SOLUTIONS:

a. Develop incentives for high-quality, appropriately scoped IND submissions. For example, FDA should develop best-practice templates and pre-IND checklists that, when followed, provide the sponsor reasonable assurance that regulatory expectations have been met, and IND-stage changes would be limited to instances of emerging safety or scientific knowledge.

b. Establish an expedited pre-IND pathway for U.S. biotech sponsors developing truly novel modalities or molecule types, modeled on EMA's PRIME early-entry program.

IV.

Building a Streamlined and Dedicated U.S. Clinical Trial Infrastructure as Part of a National Clinical Trial Infrastructure and Coordinating Strategy

The roundtable focused on early-stage clinical development and review, thus the discussions and recommendations discussed in this section focus on Phase 1 clinical trial site needs and reforms. However, these recommendations should be undertaken as part of a cohesive National Clinical Trial Infrastructure and Strategy. Investments in Phase 1 clinical trial sites should enable expansion of capabilities for later stage clinical trials, where appropriate.

Landscape of Phase 1 Clinical Trial Site Capacity in the U.S.

Initiating Phase 1 trials in the U.S. is a complex endeavor requiring navigating a siloed clinical trial ecosystem plagued with inefficiencies. Decisions about where to initiate and expand early-stage clinical development programs (i.e., IND and Phase 1 trials) are driven by several factors including: time and cost considerations; talent and technology capabilities; regulatory environment; and post-approval market potential.[12]

A 2023 survey of clinical trial staff (93% were U.S. respondents) reported that 35% of sites had activation timelines of 91 days or more, with only 19% activating sites ≤ 30 days. Interestingly, sites with small portfolios were more likely to enable activations under 30 days while those with large portfolios (>300 trials/year) reported timelines of ≥ 121 days. Less than 19% of respondents completed budget negotiations under 30 days and 25% reported IRB turnaround times >30 days.[53] Other countries are taking steps to streamline and expedite these timelines to make them a more attractive choice for Phase 1 clinical trial starts (See Appendix II).

Capacity and infrastructure needs are not uniform. For example, compared to availability of clinical pharmacology trial sites conducting traditional healthy-volunteer Phase 1 studies, there are larger capacity gaps for sites able to conduct hybrid FIH designs—where dose-escalation cohorts in healthy volunteers move seamlessly into patient cohorts—and for sites able to manage specialized Phase 1 oncology units capable of integrating dose escalation cohorts with the larger, randomized dose-optimization cohorts.[27,28,29,54,55] These units require different staffing, regulatory integration, and financial models than a traditional healthy-volunteer clinical pharmacology units.[56] For example, such units require molecular profiling, biomarker, and dose escalation expertise and capabilities required to manage cell and gene therapies.

Roundtable participants reported that site-level staffing has become a rate-limiting factor for trial execution,[57] which is a trend that the COVID-19 pandemic exacerbated and remains today.[58,59] They flagged that while

general national credentials exist for these roles, none are Phase 1-specific and no credentialing pathway formally recognizes early-phase competencies, such as FIH dose escalation or management of dose-limiting toxicities.[60] Several participants noted that the regulators, sponsors, and sites who most effectively navigate the current system are those whose staff have fulfilled roles across sectors—from FDA to industry, from large pharma to biotech, from academic center to sponsor—suggesting the value of a deliberate cross-sector talent-mobility program. They also noted the importance of early-stage drug development workforce programs.

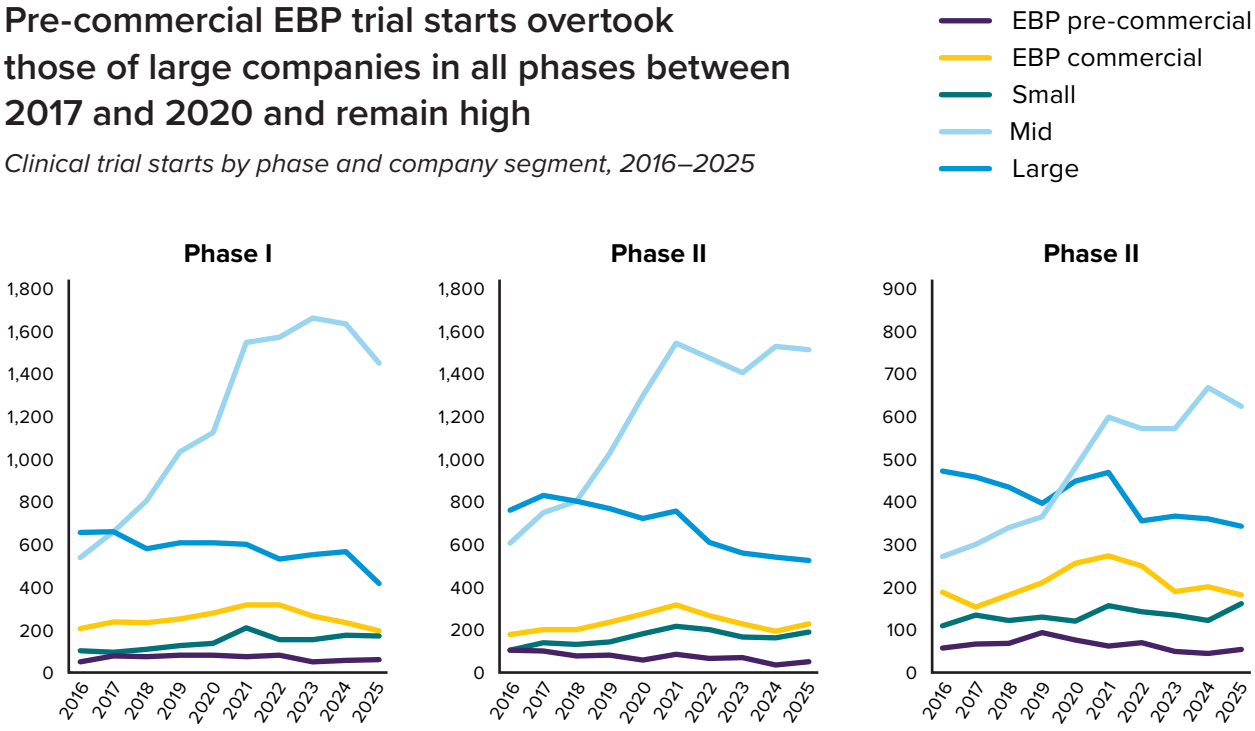
A 2025 Milken Institute study examined the supply of clinical trial sites (not limited to Phase 1) in the U.S. and found that 45% to 60% of trial sites created in a given year do not host any new clinical trials the following year.[61] This indicates that there is not only a siloed system, but also an inefficient system requiring continuous and significant infrastructure work setting up new clinical trial sites.

These clinical trial infrastructure realities affect sponsors, and the landscape of companies' engagement in clinical trials is also evolving. Pre-revenue biopharmaceutical companies accounted for 68% of clinical trial starts in 2025 and their share of Phase 1 trials has increased 174% since 2016.6 (Figure 5).[8] The ability of these companies to effectively manage time, costs, and the regulatory environment can make the difference between advancing or shuttering clinical development programs. Emerging biopharmaceutical companies typically work in fewer countries and, because of cost considerations, are more likely than larger biopharmaceutical companies to run single-country trials. Specifically, 87% of Phase 1 trials sponsored by emerging biopharmaceutical companies were single-country trials.[7] Thus, decisions by these companies about where to initiate Phase 1 trials are highly influential.

FIGURE 5. EMERGING BIOPHARMA (EBP)

Pre-commercial EBP trial starts overtook those of large companies in all phases between 2017 and 2020 and remain high

Clinical trial starts by phase and company segment, 2016–2025



Source: Citeline Trialtrove, Jan 2026; IQVIA Institute, Feb 2026.
Report: Global R&D Trends 2026. IQVIA Institute for Human Data Science.

EBP: research & development spend = less than $200 million/year; global revenue/sales = less than $500 million/year.

Build and Fund a Dedicated Network of Phase 1-Capable Clinical Trial Sites

In general, roundtable participants concluded that stakeholders (including FDA, National Institutes of Health (NIH), Centers for Medicare & Medicaid Services (CMS), Congress, academia, CROs, site organizations, IRBs, and biopharmaceutical companies) should collaborate to reinforce, expand, and coordinate a durable national infrastructure for clinical trials that includes a focus on early phase trials. Specifically, Phase 1 centers of excellence committed to utilizing a single-IRB process (see Recommendation #16) and pre-agreed, streamlined study start-up processes (e.g., budget negotiations, contracts, training) should be designated across the country. These efforts should expand rural and underserved Phase 1 access by encouraging connectivity with other sites, developing and expanding hub and spoke models, with defined FIH/FIP (First in Patient) capabilities, that could reach large treatment-naive populations in healthcare deserts or away from major academic centers. These sites should include end-to-end early development capabilities to ensure a durable translational infrastructure that can support next-generation clinical programs (e.g., excellence in translation science, advanced diagnostics, biomarker integration, cGMP capabilities, recruitment and enrollment, timely site activation capabilities). Developing and maintaining this early-stage clinical trial infrastructure and expertise would also be beneficial to implementing approaches such as a CTN pathway and more centralized IRB processes.

RECOMMENDATION #14

Build and Fund a Dedicated Network of Phase 1-Capable Clinical Trial Sites

SOLUTIONS:

a) Direct NIH and FDA to develop and/or designate FIH/Phase 1 centers of excellence, including using a single IRB process and other streamlined site activation processes.

b) Provide federal funds to support a national Phase 1 clinical trial infrastructure.

Create a National Phase 1 Coordinating Strategy as Part of an Overall National Clinical Trial Strategy

Participants discussed the importance of developing an overarching national strategy for early-stage development. In addition to Recommendation #14 (developing a dedicated Phase 1 infrastructure), a national strategy should include the advancement and integration of translational sciences, GMP capabilities, precision medicine, biomarker development and utilization, and AI-enabled data systems. No single federal entity is responsible for U.S. clinical trial capacity, heightening the need for coordination. Without deliberate investment and direction, the U.S. will continue to lose Phase 1 programs to countries that have made precisely that investment. Participants also emphasized that NIH basic research funding plays a foundational role in a successful early-stage drug development ecosystem. Proposals to significantly decrease NIH funding would damage the pipeline of assets that lead to U.S.-based trial starts at precisely the moment when China has expanded its own biomedical investment in a coordinated, state-directed manner. Sustained investment in merit-based, peer-reviewed science has historically been a cornerstone of biomedical progress, and under-valuing the impact of these commitments in U.S. innovation risks may slow advancements for years to come.

Roundtable participants emphasized that prior federal efforts have already produced numerous, but heretofore dormant, recommendations to strengthen the U.S. early-stage drug development ecosystem. For example, National Academies of Sciences, Engineering, and Medicine reviews have twice in the past 20 years produced nearly identical sets of recommendations on U.S. clinical trial infrastructure reform. The Clinical Trials Transformation Initiative, the COVID-19 lessons-learned process, and prior Foundation analyses each have identified overlapping priority actions. The problem is not knowledge, it is execution. No federal entity has been charged with accountability for implementing these recommendations. The National Biotechnology Initiative Act of 2025 (S.1387 / H.R.2756), which would establish a National Biotechnology Coordination Office, is one potential mechanism that could help address this accountability gap.

Participants specifically recommended that the U.S. Government formally designate the life sciences industry and clinical trial infrastructure as national assets vital to our economy, health, and national security. Such a designation would place early-stage biomedical research on comparable policy footing with semiconductor manufacturing, domestic energy production, and other sectors where the federal government has adopted coordinated investment-directed strategies in response to foreign competition. Designation alone does not produce outcomes, but it is the predicate for the kind of cross-agency resource allocation, Defense Production Act-adjacent authorities, and sustained capital investment that other sectors have received.

A prerequisite to coordinated action is basic visibility into the U.S. clinical trial site landscape. No federal entity currently maintains a comprehensive inventory of U.S. Phase 1 sites (e.g., how many there are, where they are located, what modalities they have worked with, which have conducted more than one trial, which have retained investigator and coordinator staff across consecutive studies). ClinicalTrials.gov includes completed and ongoing studies, but does not track site capacity, longevity, or repeat-trial capability. As a result, policy discussions about site network design, single-IRB scope, workforce credentialing, and site-of-excellence designation proceed with limited empirical grounding. Roundtable participants recommended that NIH and FDA jointly commission—and maintain—a national Phase 1 site inventory that captures site type (i.e., academic, community, dedicated healthy-volunteer unit), modality capability, activation and enrollment metrics, workforce composition, and continuity of trial activity. The inventory could also be used to capture modality-specific capabilities such as molecular profiling, biomarker and companion diagnostic infrastructure, radiopharmaceutical readiness, AI-enabled trial matching, cell and gene therapy handling expertise, and GMP manufacturing access. The inventory should be machine-readable and accessible to sponsors, investigators, and policymakers, and should be updated at least annually. This inventory is the data layer that could support centers of excellence designations, and rural-access expansion decisions. Federal funds could support these efforts.

Finally, the national coordinating strategy should include a nationwide communication campaign on the value of clinical trial participation. This campaign should be paired with expanded community-practitioner education that better enables patients to hear about relevant trials through their primary care and specialty clinicians.

RECOMMENDATION #15

Create a National Phase 1 Coordinating Strategy as Part of an Overall National Clinical Trial Strategy

SOLUTIONS:

a. Create a National Phase 1 Coordinating Strategy. The strategy could include:
   - Establishing a National Biotechnology Coordination Office.
   - A jointly published U.S. Life Sciences Competitiveness Roadmap with explicit benchmarks from NIH and the FDA.
   - Formally designating the U.S. life sciences industry as a national treasure that defines clinical trial infrastructure as a critical national infrastructure, enabling cross-agency resource allocation and sustained capital investment consistent with other strategically significant sectors.
   - Commissioned and annually maintain national Phase 1 clinical trial site inventory capturing site type, modality capability, activation and enrollment metrics, workforce composition, and continuity of trial activity.
   - Creating a nation-wide communication campaign on the value of early-phase trial participation paired with expanding community-practitioner education about clinical trial opportunities.
   - Continuing investment in NIH basic research funding.
   - Developing a competency/certification framework for research nurses, coordinators, and pharmacists (with loan-repayment incentives).
   - Developing a centralized investigator database consolidating investigator credentials, training records, and site qualifications to eliminate duplicative sponsor-specific training.

NOTE: These solutions should be part of an overall national clinical trial infrastructure and coordinating strategy.

Streamline IRB and Site Activation Processes

The IRB process is particularly complex in the U.S. More centralized approaches, such as those in Australia and China, are often cited as reasons for initiating Phase 1 trials in those countries first. In the U.S., each participating clinical trial site institution has historically conducted its own IRB review, a system that produces duplicative, often conflicting, stipulations on consent language, protocol design, and safety reporting. The NIH mandated a single IRB (sIRB) for its multisite studies starting in 2018 and the revised Common Rule extended that requirement to all federally-funded cooperative research as of January 2020.[62] The FDA proposed a parallel sIRB rule for all FDA-regulated trials in September 2022.[63] The final rule was expected in 2025 but, as of June 2026, the rule has not yet been published. While a more centralized approach to IRBs would streamline duplicative processes, it may not sufficiently shorten review times.

The development of Phase 1 centers of excellence (Recommendation #14) includes steps to ensure a more streamlined Phase 1 IRB process. Most Phase 1 trials are single-sponsor, single-site and would not directly fall under a cooperative-research single-IRB rule. Therefore, the practical reform opportunities are different. First, many large academic medical centers currently insist on an additional parallel local IRB review, even when deferring to a central IRB. A structural expectation—potentially through rulemaking or through NIH-funding

conditions—that single-site Phase 1 trials should accept, where appropriate, an outside IRB review for efficiency would eliminate this duplication. Second, the expertise that a well-functioning IRB needs for Phase 1 work—pharm-tox, CMC, clinical scientific review—is not consistently present at academic IRBs. If the U.S. moves toward a notification-based pathway for certain Phase 1 trials or defer to a central IRB, accredited enhanced IRBs with this expertise are essential.

Participants also discussed the value of developing a hybrid FDA-IRB parallel-review model that would allow the FDA to focus on scientific sufficiency and safety while the IRB leads protocol, informed consent, and ethical considerations—shifting the current sequential handoff to an agreed-upon parallel timeline and shortening the lag between IND clearance and site activation. This approach is focused on streamlining IRB processes and is not meant to replace the important insights gained from early-stage engagements between sponsors and regulators about protocols and clinical trial designs.

The FDA 2025 guidance, Sponsor Responsibilities–Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies, was identified by multiple roundtable participants as operationally problematic.[64] Under the current framework, individual sites can reach divergent judgments about whether a Suspected Unexpected Serious Adverse Reactions (SUSARs) warrant changes to the informed consent form (ICF) or the IB, producing inter-site inconsistency that creates risks for both participants and sponsors. Some participants posited that it would be more operationally sound to assign the ICF/IB-change determination to the sponsor as the owner of the program-wide safety picture, with IRB oversight of resulting language.

Roundtable participants flagged a specific IRB behavior pattern contributing to FDA resource strain: IRBs are increasingly referring questions that may not require agency insight. For example, FIH studies are unlikely to meet the regulatory definition of exempt research, but IRBs frequently ask FDA to assess whether a FIH study is exempt. A cultural shift in which IRBs operate at the maximum level of their authority—rather than deferring uncertainty upward—would free FDA reviewer capacity without requiring any regulation change.

Additional operational frictions and reforms that would reinforce a national strategy were acknowledged by roundtable participants, but discussions were largely deferred to prior work and existing recommendations. These included mentions of how standardized informed consent templates for Phase 1 studies—developed jointly by FDA, NIH, IRBs, and academic medical centers—would reduce site-by-site consent negotiation delays that sponsors routinely identify as a rate-limiting step. The importance of extending financial and career incentives, including CMS reimbursement for time spent on trial identification, consenting, and referral, to clinician-investigators to broaden the pool of practicing clinicians who participate in research was acknowledged. Additionally, the misalignment between CMS and FDA on what distinguishes permissible incentives from impermissible inducement for clinical trial participants was noted as problematic. Roundtable participants identified a harmonized policy statement clarifying permissible patient-support practices for clinical trial participants with explicit carve-outs for reimbursement of documented travel, lodging, and opportunity-cost expenses as an opportunity to meaningfully reduce patient and volunteer burdens. Roundtable participants noted that site contracting and budget negotiation timelines in the U.S. are driven by the absence of standard master agreements. Several of these concepts were discussed during a 2025 Foundation roundtable on the challenges associated with activating and conducting multiregional clinical trials (MRCTs) for oncology treatments. (See Box 1)

RECOMMENDATION #16

Streamline IRB and Site Activation Processes

SOLUTIONS:

a. Finalize single-IRB rule.

b. Develop a national strategy to support single and centralized IRB capacity needs, including:
   - Requiring an sIRB process.
   - Developing enhanced Phase 1 IRBs that could be used as an outside sIRB authority.
   - Creating a pool of FDA certified regulatory auditors who could augment centralized IRB processes at clinical trial sites by providing technical CMC/safety seals of approval.
   - Embedding FDA subject matter experts within major academic medical centers to support centralized IRB processes at clinical trial sites.

c. Pilot a hybrid FDA-IRB parallel-review model with FDA focus on scientific sufficiency and safety and IRB focus on trial protocol, informed consent, and ethical considerations, both of which are completed on an agreed-upon parallel timeline rather than the current sequential approach.

d. Develop standardized informed consent templates for Phase 1 studies to reduce site-by-site consent negotiation delays.

e. Extend financial and career incentives to clinician-investigators (e.g., reimbursement for time spent and execution of specific tasks). (See Box 1.)

f. Expand rural and underserved Phase 1 access via academic satellite locations and hub-and-spoke models with limited but defined FIH/FIP capabilities (e.g., lower-risk/less-complex studies).

V.

Mitigating Litigation Risks for Phase 1 Clinical Trial Sites

Explore Safe Harbors and Insurance Reforms for First in Human (FIH) and Phase 1 Trials

A key consideration of Phase 1 clinical trial sites is managing litigation risks. Roundtable participants raised this topic as a potential limiting factor in the ability of the U.S. to deploy widespread sIRB processes. Australia has addressed this issue: under their CTN approach, insurance coverage for Phase 1 FIH studies is a mandatory condition of the centralized HREC approval process. Sponsors, sites, and investigators all carry insurance as a condition of proceeding to FIH and Phase 1 trials. This insurance structure removes the need for individual, redundant indemnification negotiations at each site; creates a defined, shared liability framework; and gives the TGA confidence that risk has been addressed outside the regulatory review process, enabling a lighter-touch notification approach.

Roundtable participants discussed the potential value of exploring safe harbors for clinical trial sites conducting Phase 1 clinical research. Additionally, participants noted that it would be worthwhile to examine insurance coverage practices for potential reforms that better protect Phase 1 clinical trial sites from litigation risks while continuing to protect volunteers and patients.

RECOMMENDATION #17

Explore Safe Harbors and Insurance Reforms for FIH and Phase 1 Trials

SOLUTION:

a. Explore federal safe harbors for Phase 1 clinical research sites and examine insurance coverage practices for potential reforms that would help mitigate litigation risks.

Conclusion

The U.S. has long been the global engine of early-stage drug development, but that leadership is at risk. Other countries have implemented competitive financial and regulatory incentives to attract early-stage drug development activities (Appendix II). The scientific, regulatory, and operational frictions discussed at this roundtable are addressable, but require a dynamic and collaborative ecosystem in which regulators, sponsors, clinical trial sites, patient communities, and policymakers work together. This report's recommendations, if implemented, would help modernize how INDs are prepared and reviewed, improve how learnings are captured and shared across the system, and strengthen the U.S. position as a global leader in early-stage drug development. To fully optimize and realize the benefits of a world-class early-stage drug development ecosystem in the U.S., the federal government must recognize early-stage biomedical research as a national asset worthy of coordinated and sustained investment.

BOX 1

Reagan-Udall Foundation for the FDA Report Recommendations on Improving U.S. Clinical Trial Ecosystem (including Phase 1 Trials)[65]

On September 4, 2025, the Reagan-Udall Foundation for the FDA convened an invitation-only roundtable focused on the challenges of activating and MRCTs for oncology treatments. The following are recommendations relevant to identifying best practices and policies to improve the U.S. early-stage clinical development ecosystem.

Unlock the Potential of Network Approaches

- Collectively define specifics of operational and regulatory compliance processes for site networks (e.g., hub-and-spoke models), ideally harmonized with international standards.

Improve Referral and Screening Processes

- Develop precompetitive platform approaches to enable screening of patients for a broad array of trials and referring to the trial(s) that best fit their needs.

Explore Common Budget and Contract Processes for U.S. Trial Sites.

- Develop baseline budget and contracting processes for U.S. clinical trials and establish an iterative process for publishing case studies and capturing data about how best to manage site budget and contract variabilities.
- Develop data-driven processes for clinical trial costs and how to structure budgets.
- Develop and implement streamlined payment processes.
- Develop a framework that promotes best practices and enables widespread adoption of AI and platform approaches to streamline clinical trial budget and contract processes.
- Develop common compensation for physician referrals and physician participation in clinical trials (e.g., reimbursement for time spent and execution of specific tasks)
- Develop multisponsor and site budget and contract templates.
- Develop actionable recommendations for building collective resources and funding for site budget and contract needs, including outsourcing certain functions.

Reduce Patient and Family Financial Burdens

- Promote policies that reduce financial burdens on patients and advocate for the removal of statutes that prohibit or limit trial sponsors' ability to reduce patient burdens.

Ensure Utilization and Deployment of Technology Yield Benefits

- Develop a framework describing best practices for determining when sites should be able to select or use their own vendors/technology resources or when they need to deploy a specifically requested technology that works to promote a more integrated and consistent approach to site technology demands.

Align on Training Needs and Minimize Duplicative Activities

- Construct collective, or at least aligned, training requirements to minimize duplicative clinical trial site activities.

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Appendix I

Enhancing Early-Stage Drug Development in the United States

Consolidated Recommendations and Solutions

SOLUTIONS	STAKEHOLDER LEADS
Modernizing IND Requirements and Processes	
Recommendation #1: Adopt Risk-Proportionate IND Submission Requirements and Triage Review Processes	
a) Develop specific recommendations for risk-proportionate IND submission requirements and triaged review processes. Efforts could include: i. Developing and implementing risk-proportionate IND review timeline (e.g., 14-day IND review for well-characterized platforms, simple formulations, microdosing, exploratory INDs). ii. Developing and implementing a triaged IND classification based on drug risk vs. subject risk that determines the level of submission requirements and reviewer time. iii. Establishing principles and developing modality specific guidance that describes what data are required for low-, medium-, higher-risk INDs. iv. Developing FDA internal training and standard operating procedures (SOP) about how to triage FDA reviewer time based on need. b) Establish a dedicated first-in-human (FIH) specialist review unit at FDA for novel-modality or high-risk INDs, consolidating expertise currently distributed across multiple divisions. c) Invest in a specialized FIH-review workforce at FDA that delivers clear, consistent, and modality-aware early-phase regulatory expectations, reducing variable cross-division feedback.	**FDA:** Generate guidance documents; implementation of review, training, and organization reforms **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations
Recommendation #2: Advance Rolling IND Submissions	
a) Adopt a modular, rolling IND review pathway: a sequential nonclinical package and Phase-appropriate CMC data package enabling first-cohort dosing. Elements of the pilot could explore: i. Cases where FIH dosing could proceed based on non-GLP studies and GMP-like materials. ii. An Investigator Brochure (and draft study reports) to enable start of FIH plus SEND datasets submitted at a later date.	**FDA:** Develop and implement new pathway(s) implementation **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations

SOLUTIONS	STAKEHOLDER LEADS
Recommendation #3: Modernize Nonclinical Requirements and Practices	
a) Develop dose selection scientific principles that take into consideration disease severity and distinguishes first-in-healthy-humans needs from first-in-patient needs. b) Refine Project Optimus implementation through greater use of model-informed drug development (MIDD) and population PK modeling to optimize dose selection and escalation and address data gaps. c) Convene meetings among regulators, biopharmaceutical companies, CROs, and medical researchers to discuss how to advance the utilization of New Approach Methodologies (NAMs) and create a pathway for sponsors to secure endorsement to use a single species toxicology study including reliance on nonclinical platform data that can be carried forward to future IND submissions. This effort should include development and implementation of FDA internal training programs exploring a review posture in which applications are presumed adequate with in vitro/comparative biology data unless reviewers provide scientific rationale for an animal study and provide insight on which species is most predictive. The substance of these trainings may be strengthened with input from external experts. d) Formalize a structured pharm-tox reviewer rotation program across FDA divisions and centers to cross-pollinate risk-tolerance frameworks.	**FDA:** Develop and implement principles, rotation program **Collaborators:** Biopharmaceutical companies, Reagan-Udall Foundation for the FDA, medical researchers, patient organizations
Recommendation #4: Update and Streamline Chemistry, Manufacturing and Controls (CMC) Requirements	
a) Expand the January 2026 CBER CMC flexibility announcement into formal guidance covering cell and gene therapies, explicitly clarifying that cGMP under 21 CFR Part 211 is not required before Phase 2 or Phase 3, and extend analogous flexibility to other modalities when supported by risk-benefit determination. b) Streamline CMC content required for certain Phase 1 trials to allow short-term or accelerated CMC stability data with a scientifically justified shelf-life covering only the clinical dosing period, paired with a sponsor commitment to continue stability testing during the trial. This could be modeled after Belgium's Phase 1 CMC submission model. c) Issue a formal policy statement on cross-regional comparator characterization, enabling sponsors to rely on drug characterization accepted by EMA or other ICH regulators. d) Establish a risk-based pathway to waive or streamline routine Phase 1 CMC submission and review for defined categories, including: (i) products manufactured using well-established platforms or with extensive prior sponsor experience with analogous FDA submissions; (ii) products for serious, life-threatening, ultra-rare, or N-of-1 conditions; (iii) very low-risk study designs such as microdosing studies and exploratory INDs; and (iv) simple formulations using known excipients and standard manufacturing processes (e.g., immediate-release oral tablets, aqueous solutions). e) Routinely publish an anonymized list of common CMC deficiencies and remediation pathways.	**FDA:** Publish policy, guidance and top 10 list; implement new pathway **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations

SOLUTIONS	STAKEHOLDER LEADS
Recommendation #5: Clarify Required IND Data	
a) Publish updated, modality-specific guidance and case studies clarifying minimum IND data expectations for Phase 1 INDs by scenario (e.g., small molecule, oligonucleotide, oncology, viral vector, cell therapy). b) Develop Q&A-style or decision-tree guidance tools that supplement narrative guidance documents, allowing sponsors to arrive at a transparent articulation of minimum CMC and nonclinical package requirements for their specific Phase 1 study based on modality, therapeutic area, prior human data, and study design.	**FDA:** Develop and publish guidance, case study and decision-tree publications **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations
Recommendation #6: Improve "Safe-to-Proceed" and "Clinical Hold" Communications	
a) Establish "Safe-to-Proceed" coordinated processes within FDA including: i. Consistent, timely notifications across all review divisions within the 30-day statutory period. ii. Written rationale on all clinical holds that identify the deficiency, the regulatory basis, and the recommended resolution path. b) Reframe 30-day IND notification terminology for pre-dosing actions where no patient has been dosed and the action is informational from "clinical hold" to "notice of additional information required."	**FDA:** Develop and implement new processes and communications, organizational reform **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations
Recommendation #7: Enable Greater Use of a Phase 1 Clinical Trial Notification (CTN) Pathway	
a) Develop and implement FDA's proposed Clinical Trial Notification pathway for certain Phase 1 trials.	**FDA:** Develop and implement pathway **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations
Modernizing Phase 1 Clinical Trials and Tools	
Recommendation #8: Enable Use of Innovative Clinical Trial Designs	
a) Review and update innovative clinical trial design guidance and develop accompanying FAQs that: i. Provide early-phase-specific examples for Bayesian adaptive dose-escalation, seamless Phase 1/2 designs, and biomarker-stratified expansion cohorts. ii. Permit adaptive Phase 1 designs to allow modifications to dose range, escalation increment, indication focus, and therapy line based on emerging clinical data—without protocol amendment but operating under pre-specified guardrails. b) Modernize Form FDA 1572 to reflect decentralized-element trial models and facilitate state-level alignment on telehealth-delivered research activities.	**FDA:** Develop and issue new documents **Collaborators on Substance:** Biopharmaceutical companies, Reagan-Udall Foundation for the FDA; medical researchers, patient organizations

SOLUTIONS	STAKEHOLDER LEADS
Recommendation #9: Increase Inclusion of Patient Perspectives in Early-Stage Drug Development	
a) Develop a review matrix that documents when patient perspectives were used to inform toxicology requirements.	**FDA:** Develop and publish review matrix **Collaborators** Biopharmaceutical companies
Recommendation #10: Develop Artificial Intelligence (AI) Enabled Sponsor-Facing Decision Support Tools	
a) Develop a meeting series for FDA and stakeholders to collaborate on developing and implementing knowledge management initiatives that can serve as the basis for the development of AI-enabled sponsor-facing decision support tools.	**Reagan-Udall Foundation for the FDA:** Develop and implement meeting series **Collaborators:** Biopharmaceutical companies, FDA; medical researchers, patient organizations
Optimizing FDA–Sponsor Early-Stage Engagements and Processes	
Recommendation #11: Enhance Pre-IND Meeting and IND Review Best Practices	
a) Standardize pre-IND meeting outputs to produce three documented conclusions: (i) required; (ii) optional but potentially helpful; and (iii) unnecessary for the proposed initial study. Treat pre-IND alignment on specific elements (e.g., inclusion/exclusion criteria) as commitments the IND review will not revisit without written justification. b) Pilot an IND-stage sponsor "safe-to-proceed checkbox" enabling sponsors to elect minimum-comment Phase 1 safety review, deferring forward-looking protocol, endpoint, and development-strategy feedback to later meetings; FDA's clinical hold, safety reporting, and inspection authorities fully preserved. c) Pilot an iterative, weekly Australian-style engagement model for pre-IND and IND-stage interactions. This effort could be supported by updating and reviving the Target Product Profile (TPP) as a sponsor-facing tool rather than a binding guidance designed to support a more iterative engagement model that surfaces assumptions earlier and provokes structured dialogue before formal IND submission.	**FDA:** Develop and implement approach **Collaborators on Substance:** Biopharmaceutical companies, medical researchers, patient organizations

SOLUTIONS	STAKEHOLDER LEADS
Recommendation #12: Capture IND Regulatory Decision-Making Trends	
a) Support stakeholder efforts to capture evidence and identify trends of consistent or differing feedback on distinct IND topics, such as BIO's BRIDGE platform, designed to capture regulatory trend data from sponsors describing their interactions with the FDA. b) Convene disease-area or modality-specific shared learning forums (e.g., rare disease, chronic disease, gene therapy) to share information about pre-IND meetings, IND submission packages, and IND reviews and discuss what has worked, what has not, and where expectations have shifted. c) Encourage FDA to develop internal mechanisms to capture trends of consistent or differing feedback on specific IND related topics and cross-pollinate learnings.	**Reagan-Udall Foundation for the FDA:** Institute meeting series **FDA:** Implement internal trend/ knowledge management **Collaborators:** Collect trend data and platform development
Recommendation #13: Incentivize Fit-for-Purpose IND Submissions and Engagements	
a) Develop incentives for high-quality, appropriately scoped IND submissions. For example, FDA should develop best-practice templates and Pre-IND checklists that, when followed, provide the sponsor reasonable assurance that regulatory expectations have been met, and IND-stage changes would be limited to instances of emerging safety or scientific knowledge. b) Establish an expedited pre-IND pathway for U.S. biotech sponsors developing truly novel modalities or molecule types, modeled on EMA's PRIME early-entry program.	**FDA:** Implement meeting reform and new pathway implementation **Collaborators:** Biopharmaceutical companies, medical researchers, patient organizations
Building a Streamlined and Dedicated U.S. Phase 1 Infrastructure as Part of a National Clinical Trial Infrastructure and Coordinating Strategy	
Recommendation #14: Build and Fund a Dedicated Network of Phase 1 Capable Clinical Trial Sites	
a) Direct NIH and FDA to develop and/or designate FIH/Phase 1 centers of excellence, including using a single IRB process and other streamlined site activation processes. b) Provide federal funds to support a national Phase 1 clinical trial infrastructure.	**FDA and NIH** **Collaborators:** Biopharmaceutical companies, Reagan-Udall Foundation for the FDA, medical researchers, patient organizations

SOLUTIONS	STAKEHOLDER LEADS
Recommendation #15: Create a National Phase 1 Coordinating Strategy (as part of an overall National Clinical Trial Strategy)	
a) Create a National Phase 1 Coordinating Strategy. The strategy should include: i. Establishing a National Biotechnology Coordination Office. ii. Jointly publishing a U.S. Life Sciences Competitiveness Roadmap with explicit benchmarks by NIH and the FDA. iii. Formally designating the U.S. life sciences industry as a national treasure that defines clinical trial infrastructure as a critical national infrastructure, enabling cross-agency resource allocation and sustained capital investment consistent with other strategically significant sectors. iv. Commissioning and annually maintaining a national Phase 1 clinical trial site inventory capturing site type, modality capability, activation and enrollment metrics, workforce composition, and continuity of trial activity. v. Creating a nation-wide communication campaign on the value of early-phase trial participation paired with expanding community-practitioner education about clinical trial opportunities. vi. Continuing investment in NIH basic research funding. vii. Developing of a competency/certification framework for research nurses, coordinators, and pharmacists (with loan-repayment incentives). viii. Developing a centralized investigator database consolidating investigator credentials, training records, and site qualifications to eliminate duplicative sponsor-specific training. *NOTE: These solutions should be part of an overall national clinical trial infrastructure and coordinating strategy.*	**FDA and NIH** **Collaborators:** Biopharmaceutical companies, Reagan-Udall Foundation for the FDA, medical researchers, patient organizations

SOLUTIONS	STAKEHOLDER LEADS
Recommendation #16: Streamline IRB and Site Activation Processes	
a) Finalize single-IRB rule. b) Develop a national strategy to support single and centralized IRB capacity needs including: i. Requiring an sIRB process. ii. Developing enhanced Phase 1 IRBs that could be used as an outside sIRB authority. iii. Creating a pool of FDA certified regulatory auditors who could augment centralized IRB processes at clinical trial sites by providing technical CMC/safety seals of approval. iv. Embedding FDA subject-matter experts within major academic medical centers to support centralized IRB processes at clinical trial sites. c) Pilot a hybrid FDA-IRB parallel-review model with FDA to focus on scientific sufficiency and safety and IRB focus on trial protocol, informed consent, and ethical considerations, both of which are completed on an agreed-upon parallel timeline rather than the current sequential approach. d) Develop standardized informed consent templates for Phase 1 studies to reduce site-by-site consent negotiation delays. e) Extend financial and career incentives to clinician-investigators (e.g., reimbursement for time spent and execution of specific tasks). (See Box 1.) f) Expand rural and underserved Phase 1 access via academic satellite locations and hub-and-spoke models with limited but defined FIH/FIP capabilities (e.g., lower-risk/less-complex studies).	**FDA:** Finalize sIRB rule, implement parallel-review model **FDA and NIH:** Implement national sIRB capacity and strategies **Collaborators:** Biopharmaceutical companies, Reagan-Udall Foundation for the FDA; medical researchers, patient organizations **Biopharmaceutical Companies and Clinical Trial Sites:** Develop standardized templates and hub-and-spoke models **Stakeholders:** Advocate for financial incentives and clinical trial reimbursement reforms **Trial Sites:** Develop standardized templates and hub-and-spoke models **Biopharmaceutical Companies and Clinical:** Advocate for financial incentives and clinical trial reimbursement reforms
Mitigating Litigation Risk for Phase 1 Clinical Trial Sites	
Recommendation #17: Explore Safe Harbors and Insurance Reforms for FIH and Phase 1 Trials	
a) Explore federal safe harbors for Phase 1 clinical research sites and examine insurance coverage practices for potential reforms that would help mitigate litigation risks.	**Congress:** Enact safe harbor and master insurance laws **Collaborators:** FDA, NIH, Biopharmaceutical companies, Reagan-Udall Foundation for the FDA; medical researchers, patient organizations

Appendix II

Country Comparison — Phase 1 Clinical Trial Landscape

Country	Regulatory Pathway & Initiatives	Ethics Review Process	Time to First Patient	Phase I Cost Estimate	Tax/R&D Incentive	Key Strengths & Limitations
Australia	Path 1: Clinical Trial Notification (CTN) — no Investigational New Drug (IND) equivalent required;[1] TGA acknowledges notification within 5–10 business days. Trial may proceed upon ethics committee approval and institutional governance authorization[2] Path 2: Clinical Trial Approval (CTA) — For Class 4 biologicals and other products where HREC lacks scientific/technical expertise to assess product safety	Path 1: National Mutual Acceptance (NMA) supports the single review of multi-center human research proposals; The Human Research Ethics Committee (HREC) is the primary scientific/ethical reviewer;[2] Public HREC process: 8–12 weeks public hospitals; 6–8 weeks private sites[3] Path 2: HREC reviews scientific and ethical issues of proposed clinical trial protocol	Path 1: Clinical trial start time 6–12 weeks from time of CTN application[4] Path 2: TGA evaluates product data and must approve the trial before it proceeds	Path 1: Phase 1 trials typically range from $1.2–2.5M USD (28% lower than the U.S. before tax incentives)[5]	Either Path: 43.5% refundable cash rebate[5] on eligible research and development (R&D) spend; available to pre-revenue companies with no tax liability[6,7]	**Strengths:** • Expedited ethics review and time to start timelines • Refundable R&D incentives • Phase I clinical trial infrastructure **Limitations:** • Limited population for later stage clinical trials

Country	Regulatory Pathway & Initiatives	Ethics Review Process	Time to First Patient	Phase I Cost Estimate	Tax/R&D Incentive	Key Strengths & Limitations
China	Path 1: Investigator-Initiated Trials (IITs) require only health-system level reviews. Existing regulations on clinical trials do not prohibit IITs involving unapproved drugs Path 2: Standard IND: 60 working-day pathway; Expedited: 30 working-day pathway (finalized 2025; NMPA Announcement No. 86) for eligible innovative drugs;[9] Ethics review runs in parallel with IND submission[10]	Path 1: Health-system review Path 2: Implied approval for IND after 60 or 30 days if no notice of rejection or query;[11,12] multi-center ethics review process[13]	Path 1: No NMPA/CDE IND review; trial begins after local ethics-committee approval; real-world estimates ~6 months from concept to first patient dosed, faster for well-supported programs; pathway used most for cell/gene therapies[14] Path 2: Average start-up time from lead-site ethics approval to first subject enrolled is 67.4 days for new drugs[15] (GlobalData showed Phase 1 and 2 trials can be 60–70% faster than U.S.[16])	China Clinical trials estimated to be 50–60% cheaper than US[14]	R&D 200% pre-tax deduction for activities that do not form intangible assets; if intangible assets are created, R&D expenses can be amortized before tax at 200% of cost with no time limit;[17] high-tech enterprises are eligible for reduced corporate tax rate (15%);[18] rising share of innovative drugs reaching the National Reimbursement Drug List within one year of approval (53% in 2022, up from 24% in 2020)[19]	**Strengths:** • Improved first-to trial timelines • Lower costs • Tax incentives and process for expedited coverage of breakthrough treatments **Limitations:** • Path 1: limited regulator visibility into activity • Path 2: Complex ethics review processes
Japan	30 days after CTN submission;[20] implied approval to proceed after 30 days if no rejection or query; in 2023, Japan relaxed its requirement for additional Phase 1 studies in Japan before joining multi-regional trials (waivable case-by-case with PMDA agreement).[20]	IRB approval is required prior to CTN application; Ethics Committees and IRBs not centralized. IRB approval 4–8 weeks.[22]	~70 days for approx. 50% of Phase 1 trials[23]	Median Phase 1 cost is $7.9M USD[22]	R&D tax credit 1–14% determined by company's increase or decrease in R&D spend relative to 3 year average (not refundable);[25] Sakigake Premium allows 10–20% price increase for certain innovative drugs developed and submitted for approval in Japan first[26]	**Strengths:** • Efforts to expedited Phase 1 timelines **Limitations:** • Non-centralized IRB process

Country	Regulatory Pathway & Initiatives	Ethics Review Process	Time to First Patient	Phase I Cost Estimate	Tax/R&D Incentive	Key Strengths & Limitations
Denmark	Danish Medicines Agency (DKMA) and Medical Research Ethics Committee (MREC) review runs concurrently — 14 day expedited pathway launched in 2025 for mono-national applications (EU standard pathway is 45 days)[27]	Danish National Center for Ethics coordinates all MREC reviews — decisions within 45 days (standard CTR) or 14 days under the expedited mono-national Phase I pathway[28]	Specific timelines N/A; historically EU trials have taken several months; Steps are being taken to streamline trials in Europe (e.g., Accelerating Clinical Trials in the EU; Clinical Trials Regulation (CTR) single authorization portal)[29]	EU Clinical trials estimated to be 50–60% cheaper than US[14] European trial costs generally lower than the U.S., though Denmark sits at the higher-cost end of Europe (strong infrastructure and data systems; higher labor costs)[30]	22% cash payment on R&D tax losses for loss-making companies with R&D expenditures with deductibles at an enhanced increasing rate (114% in 2026 increasing to 120% in 2028)[31]	**Strengths:** • Centralized ethics review • Expedited Phase 1 pathway for mono-national trials only • Lower costs • Cash payment for R&D tax losses **Limitations:** • Limited population for later stage trials
Spain	Spanish Agency of Medicines and Medical Devices (AEMPS) has a 26-day fast track for biologic oncology and rare disease Phase 1 trials[32]	AEMPS reviews Part I (scientific, medicinal and regulatory assessment) first then the Ethics Committee for Research with Medical Products (CEIm); review of Part II (ethical, local, subject-related issues) cannot be finalized until Part I is complete; both must agree on Part I and II. (45–96 days)[33]	Spain was among the first to operationalize the Clinical Trials Regulation (CTR)[34]	30–40% cheaper than in the U.S.; (estimated per patient cost in Spain is $15,000–$25,000, depending trial phase and complexity)[35]	25% R&D tax credit, increasing to 42% exceeding 2-year trailing average and an additional 17% credit for R&D personnel costs; credits that cannot be applied against tax liability can be monetized (up to 80%); 60% reduction in net income derived from licensing qualified Investigational Product (IP) assets[36,37]	**Strengths:** • Lower costs due to centralized health care system • Monetizable tax credits • IP patent box **Limitations:** • Sequential ethics review can increase timelines

Country	Regulatory Pathway & Initiatives	Ethics Review Process	Time to First Patient	Phase I Cost Estimate	Tax/R&D Incentive	Key Strengths & Limitations
United States **Benchmark**	FDA has pre-IND meeting process (target of responding to the meeting request within 21 days); 30-day IND review period, implied approval if no rejection or query[38]	Trial may not begin without both IND approval and compliance with 21 CFR Parts 50 and 56 (IRB reviews); IRB approvals can be obtained prior to 30 day window;[39] sIRB has been shown to reduce initial IRB reviews from 66.7 days to 24 days but total time increased (111.2 to 123.3 days) due to individual institutions maintaining oversight[41]	Median time for trial activation 8.12 months (academic centers) and 4.37 months independent sites[37]	$1.4M–$6.6M[42]	R&D tax credit is 20%;[43] Orphan Drug tax credit 25%[44]	**Strengths:** • High expertise and talent pool • Attractive post approval market • Access to large number of patients **Limitations:** • Complex clinical trial ecosystem and IRB review process • High per patient costs

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Country Comparison — Phase I Clinical Trial Landscape

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Appendix III

Enhancing Early-Stage Drug Development in the United States

An invitation-only roundtable hosted by the Reagan-Udall Foundation for the FDA in collaboration with Biotechnology Innovation Organization

MARCH 26, 2026
1333 New Hampshire Ave NW, Washington, DC 20036

10:00 am	**Opening Remarks** Susan C. Winckler, RPh, Esq., *CEO, Reagan-Udall Foundation for the FDA*
10:05 am	**Welcome and Introductions** (~60 seconds per participant) **Name, title, organization** • What is one thing you would change about early-stage drug development in the U.S.?
10:40 am	**The Phase I Clinical Trials Environment: A Brief Background** • Cynthia Verst, President, Design and Delivery Innovation, R&D Solutions, IQVIA
10:55 am	**Solution Area #1: FDA Requirements for Investigational New Drug (IND) Package** • How might we consider streamlining, staging, or crafting a fit-for-purpose IND package? What does better look like? • What specific components (clinical; nonclinical; chemistry, manufacturing, and controls) of the IND package could be streamlined?
12:15 pm	**Lunch**
12:45 pm	**Solution Area #2: FDA IND/First-in-Human (FIH) Review Posture and Communication** • What is the perception of FDA's assessment/review of IND packages? • Should the US risk tolerance for FIH be modified and, if so, under what conditions? • Are there lessons to be learned from different risk tolerance for oncology and rare disease that might be applied to newer technologies, such as cell and gene therapy? • Would a rubric support assessment of FIH trials and risk tolerance?
2:00 pm	**Solution Area #3: U.S. Phase 1 Trial Infrastructure** • How do we build/strengthen/increase Phase 1 trial capacity? • How can barriers and delays to site activation and patient enrollment at a hospital-, clinician-, and patient-level be addressed? • What is needed for increasing Phase 1 units (e.g., funding, vision, etc.)?
3:20 pm	**Final Thoughts**
4:00 pm	**Adjourn**

Biotechnology Innovation Organization (BIO) provided funding for this meeting.

Appendix IV

Roundtable Contributors

We appreciate the contributions of the following individuals to the roundtable. While all had the opportunity to review the draft report, their inclusion does not represent their endorsement of or an agreement with the content of this report, either individually or on behalf of their organization. The Reagan-Udall Foundation for the FDA retains sole responsibility for this report.

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