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HHS and Congress Push to Streamline and Onshore Clinical Trials

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Conducting first-in-human clinical trials in the United States is often associated with significant cost, complexity and delay. There is a growing consensus among policymakers that the current US requirements are unnecessarily rigid and burdensome for early-stage clinical development. Companies often view foreign jurisdictions, such as Australia and China, as offering faster, more flexible pathways for initiating clinical trials. On June 22, 2026, the US Department of Health and Human Services (HHS) announced a coordinated, departmentwide effort – Operation TrialBlazer – to reverse that trend and restore American leadership in clinical research. As part of this initiative, the Food and Drug Administration (FDA) and other HHS agencies, including the HHS Office of Inspector General (OIG), are advancing reforms aimed at streamlining the clinical trial process, eliminating inefficiencies, increasing participation and improving transparency for biopharmaceutical companies and other stakeholders. Momentum for streamlining and improving the clinical trial process extends beyond the executive branch, with Congress also actively considering proposals to accelerate early-phase development, reduce administrative burdens and encourage sponsors to keep early-stage clinical research in the US. Companies, particularly small and mid-size biopharma companies, should closely monitor these initiatives and leverage this momentum to engage with FDA, OIG and other HHS agencies to help shape reform efforts.

Efforts to address a long-standing shift of early clinical research overseas

The migration of clinical research from the US to foreign countries is not a recent phenomenon. For example, in 2010, HHS reported that more than half of all clinical trial sites were located outside the US, and that 80% of marketing applications submitted to FDA contained data from foreign studies. In April 2026, then-FDA Commissioner Martin Makary noted that China had four times more Phase 1 trial initiations than the US since at least 2024, and that the average time between a pre-investigational new drug (IND) request and IND go-ahead is approximately 380 days in the US versus 220 days in China, with China having announced plans to reduce that timeline even further.

China is not the only country that has attracted early-stage research; Australia has also become a popular jurisdiction for initiating clinical trials. Australia's appeal stems in part from its regulatory framework, which allows certain clinical trials to proceed using a streamlined notification process. These competitive pressures have not gone unnoticed. HHS agencies, including FDA and OIG, and Congress have begun taking concrete steps to reclaim the US's position as the preeminent destination for early-phase clinical research.

FDA's request for an expedited IND pathway

Before creation of Operation TrialBlazer, in an effort to reshore clinical trials, FDA had already asked Congress to create a risk-based expedited IND pathway for certain Phase 1 clinical trials. This pathway would serve as an alternative to the traditional IND process intended to reduce duplicative and time-consuming requirements that are not necessary to maintain safety and ethical standards. FDA recognizes that such a pathway is particularly important for smaller companies, which face proportionally greater barriers under the current framework. Those barriers that have contributed to the migration of preclinical and early Phase 1 research to jurisdictions like China and Australia. According to FDA's request, the proposed pathway would be optional and risk-based and rely more heavily on existing preclinical evidence and validated alternative testing methods to accelerate initiation of US-based Phase 1 programs.

FDA RFI on expedited IND pilot program

Without waiting for Congress to act, FDA has also moved administratively to pilot a version of this approach. As part of Operation TrialBlazer, on June 24, FDA published a request for information (RFI) soliciting public comments on a proposed Expedited Investigational New Drug Pilot Program designed to shorten the time from drug identification to first-in-human Phase 1 clinical trials. The pilot would enlist a network of Qualified Research Institutions (QRIs), such as academic medical centers and contract research organizations (CROs), to partner with sponsors in developing and reviewing Phase 1 IND protocols. QRIs would provide advisory recommendations on the pharmacology/toxicology, clinical, and chemistry, manufacturing and controls (CMC) components of an IND submission, with the aim of improving submission quality and reducing the incidence of clinical holds. QRIs would also support parallel activities, such as Institutional Review Board (IRB) review and clinical trial site activation, while FDA retains full oversight and regulatory authority, including the ability to issue clinical holds, disqualify investigators and conduct inspections. The pilot also proposes a rolling IND submission process, which would allow sponsors to receive earlier and more frequent feedback from FDA. According to FDA, the pilot's core objectives are to improve IND submission quality, reduce FDA review time, and accelerate the interval from nonclinical research to first-in-human study initiation. FDA is seeking input from sponsors, CROs, academic institutions, health networks/systems, IRBs, patient advocacy organizations, investors and other stakeholders on the pilot's structure, scope and implementation.

Comments are due by July 22, 2026.

FDA AI initiatives

FDA has also been pursuing a related initiative that predated the June 22 HHS announcement. Nearly two months earlier, in late April 2026, FDA published an RFI on a proposed pilot program focusing on improving efficiency and decision-making quality within the existing Phase 1 trial framework. FDA sought input on how AI could support dose selection, safety monitoring, patient recruitment and go/no-go decisions while maintaining FDA's existing scientific and regulatory standards. The fact that FDA subsequently launched a separate, more sweeping set of initiatives as part of the June 22 HHS announcement suggests the agency concluded that AI-enabled optimization of the current process, while valuable, is not sufficient on its own to close the competitiveness gap with countries like Australia and China. This gap is rooted in the regulatory process itself, which no amount of AI-driven efficiency within FDA's existing framework can eliminate. The June 22 initiatives, by contrast, take aim at that structural gap directly. FDA received nearly 200 comments in response to the AI RFI, and the comment period closed on June 29, 2026.

OIG RFI on potential fraud and abuse barriers to clinical trial participation

As part of Operation TrialBlazer, OIG issued an RFI seeking public input "on whether any additions or modifications are needed to the safe harbor regulations under the Federal Anti-Kickback Statute [(AKS)] or the exceptions to the civil monetary penalty [(CMP)] provision prohibiting inducements to beneficiaries … for remuneration provided to individuals in connection with their participation in clinical trials."[1]

The inclusion of this RFI within HHS's broader clinical trial reform framework reflects a recognition that fraud and abuse compliance uncertainty may itself be a barrier to advancing clinical research. To the extent such uncertainty exists and remains, it may undermine the administration's broader goals of accelerating drug development, increasing participation in clinical research and expanding patient access to innovative therapies.

Clinical trial participation imposes real costs on patients, including transportation to and from trial sites, childcare, time away from work and other out-of-pocket burdens. Financial constraints may result in enrollment failure and participant dropout. These challenges are particularly acute in rare disease research, where enrollment difficulty is compounded by small patient populations. Further, as participants and/or trial sites may be, and often are, geographically dispersed, participants may need to travel substantial distances to reach a qualifying trial site. In such contexts, the ability to offer meaningful logistical and financial support to participants could be determinative of whether certain individuals are able to participate.

However, sponsors seeking to offer such support have faced uncertainty and persistent compliance questions. In the RFI, OIG notes that it has published 10 favorable advisory opinions over the past two decades permitting certain cost-sharing waivers or subsidization of certain federal healthcare program cost-sharing obligations for clinical trial participants in specific situations and circumstances, but that it has "not issued any advisory opinions

or guidance relating to other remuneration provided to clinical trial participants, such as transportation costs, childcare costs, or stipends."[2] In the absence of clear guidance, sponsors considering whether to offer such support face questions and uncertainty in seeking to assess whether a given arrangement may or may not be viewed as compliant. That uncertainty can have a chilling effect. As a result, sponsors potentially may either forego compensation programs entirely or limit them in ways that could contribute to or perpetuate enrollment challenges.

OIG's new RFI is a step toward addressing these questions and the uncertainty that sponsors and other organizations currently face. OIG is seeking public input on a number of areas, including, among others:

- Whether, and if so, how, clinical trial participation is meaningfully enhanced by providing appropriate remuneration to federal healthcare program enrollees.
- Whether clinical trial sponsors, clinical trial sites or other organizations view the AKS and Beneficiary Inducements CMP as barriers to providing appropriate remuneration to clinical trial participants, and, if so, why.
- The types and amounts, if applicable, of remuneration stakeholders may seek to provide to clinical trial participants to facilitate participation.
- The fraud and abuse risks that may be associated with the offer and provision of such remuneration.
- The types of arrangements necessary to provide such remuneration.
- Safeguards that may be necessary or prudent to prevent fraud and abuse when clinical trial participants receive remuneration.

OIG states that it is seeking to identify ways in which it might modify or add new AKS regulatory safe harbors or new exceptions to the Beneficiary Inducements CMP's regulatory definition of "remuneration" to address these considerations. Additionally, OIG seeks to identify other guidance it could publish or amend "to foster arrangements that facilitate clinical trial participation, while also protecting against harms caused by fraud and abuse."[3] The RFI also lists several specific questions for stakeholder input.[4]

Comments are due no later than 5:00 pm ET on August 24, 2026.

FDA draft guidance on substantial evidence of effectiveness

The June 22 HHS announcement also referenced a new FDA draft guidance titled, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. While this draft guidance addresses the evidentiary standard for drug approval broadly and not the IND process specifically, it is directly relevant to sponsors conducting early-phase trials in the US, as it signals FDA's latest interpretation of the statutory standard for the data that will ultimately be required to support approval. This 2026 draft guidance revises a 2019 draft guidance and contains significant substantive updates reflecting FDA's evolving views on topics such as externally controlled trials and Bayesian statistical analysis. More broadly, the 2026 draft guidance moves away from the rigid examples provided in the 2019 draft guidance toward a more comprehensive view of the overall development program, the broader context of the disease state, and the role of external and real-world evidence when assessing whether a sponsor has met the substantial evidence standard.

Perhaps the most notable example of this shift is the reorganization and reframing of the discussion around the number of clinical trials required to demonstrate effectiveness. While the 2019 draft guidance positioned two adequate and well-controlled clinical trials as the standard approach for demonstrating substantial evidence of effectiveness, the 2026 draft guidance reframes multiple clinical trials as one possible way that sponsors may meet this requirement depending on the needs of the drug development program. Likewise, the 2026 draft guidance expands the potential scenarios in which one adequate and well-controlled trial may be sufficient to meet the substantial evidence standard. Whereas the 2019 draft guidance organized regulatory flexibilities around three scenarios – life-threatening or severely debilitating diseases, rare diseases and situations where human efficacy trials are infeasible – the 2026 draft guidance does away with these distinct categories and instead states that the clinical context is critical to informing the approach to establishing substantial evidence of effectiveness. While regulatory flexibilities may still be warranted for a rare disease, those flexibilities may differ for a life-threatening rare disease with no current treatment options versus one that is less debilitating and/or has available treatment options.

Trial design is another area that received a significant update in the revised draft guidance. The 2026 draft guidance devotes considerable discussion to study designs, such as noninferiority studies and external controls, but expands upon the situations in which these designs can offer meaningful evidence of efficacy, consistent with FDA's more flexible approach across the updated guidance. The guidance also notes that trial design elements, such as eligibility criteria, a control arm and supportive therapies that reflect standard of care, and a meaningful primary endpoint, should be selected to provide results that are relevant to patients and prescribers. FDA states that trial design is an area where the agency may exercise regulatory flexibility, including by relying on trial designs that generate less certainty regarding efficacy if warranted based upon a holistic view of clinical considerations.

One area where the 2019 and 2026 draft guidance overlap is in the categories of confirmatory evidence that may be considered to demonstrate substantial evidence of effectiveness. Specifically, FDA confirms that mechanistic evidence, natural history data and data from trials in a related disease or condition are examples of types of confirmatory evidence. With the 2026 draft guidance, FDA provides some additional confirmatory evidence considerations. For example, FDA cautions that natural history data used as confirmatory evidence should be separate from any data used as a control for a single and adequately controlled clinical trial. FDA also specifically addresses real-world data as a subset of natural history data that may be appropriate as confirmatory evidence in rare diseases or conditions, depending on considerations such as reliability and relevance of the data source and appropriateness of the study design and statistical methods for studies that leverage this data.

FDA is also accepting comments on the newly released Substantial Evidence of Effectiveness draft guidance. This comment period is an important opportunity for any company seeking drug or biologic approval and is especially relevant for sponsors developing treatments for rare, serious or life-threatening conditions, or those who may be planning to rely on single trial or novel trial designs to support approval.

Comments are due by September 22, 2026.

Bipartisan proposals on Capitol Hill

Along with these FDA and other HHS initiatives, Congress is developing its own proposals seeking to align with and compliment FDA's recent actions. In May 2026, Rep. Jake Auchincloss (D-MA), a member of the House Energy and Commerce Committee, released a legislative discussion draft of the Cures in Care Initiative, which outlines a broad plan to modernize the US clinical trial system. The draft proposes to revamp FDA oversight of first-in-human and Phase 1 studies, including modernizing IRBs and streamlining Phase 1 processes. It also points to Australia's notification process as a model and calls on FDA to pilot a third-party oversight framework, termed an "IND alternative pathway," and issue guidance for pre-certifying third-party organizations.

Similarly, in a February 2026 roadmap of various FDA reforms, Sen. Bill Cassidy (R-LA), chair of the Senate Committee on Health, Education, Labor, and Pensions, proposed that the agency launch a pilot program testing expedited clearance of low-risk Phase 1 studies, similar to the regulatory framework used in Australia.

The House Appropriations Committee made a similar recommendation in a report accompanying its markup of the FDA Fiscal Year 2027 appropriations bill. The committee directed FDA to revise its IND processes and data requirements for initial human trials to streamline administrative requirements, reduce filing burdens and tailor the process and requirements to make them risk and trial phase appropriate. The committee also encouraged FDA to develop and implement a pilot program to test an Australian-style clinical trial notification system in the US.

While committee report directives and draft legislative language do not carry the force of law, they are powerful policy signals from Congress to FDA. These bipartisan, bicameral signals bear watching for future congressional action as the appropriations bills and Prescription Drug User Fee Act (PDUFA) reauthorization work their way through the legislative process.

Opportunities to shape reform efforts

These developments signal a rapidly growing momentum within the government to modernize and accelerate the clinical trial framework in the US. The FDA and OIG RFIs and FDA draft guidance, in particular, represent concrete and time-sensitive opportunities for sponsors and other stakeholders to provide input that can help

shape the contours of future US clinical trial reform. For sponsors, especially small and mid-size biopharma companies, these comment periods present important vehicles for communicating ideas and perspectives that could meaningfully accelerate development timelines.

Cooley's life sciences and healthcare regulatory team will continue to closely monitor these developments and their implications for companies across the clinical and commercial landscape. For any questions on how these proposals might affect your development timelines, how to engage with FDA, or how to submit comments in response to the RFIs or FDA's guidance documents, please contact one of the lawyers listed below.

Cooley senior regulatory analyst Kelly Marco also contributed to this alert.

Notes

1. Medicare and State Health Care Programs: Fraud and Abuse; Request for Information Regarding the Federal Anti-Kickback Statute and Beneficiary Inducements CMP, 91 Fed. Reg. 37902 (June 24, 2026).
2. Id. at 37903.
3. Id.
4. Id. at 37904 – 37905.

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