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August 20, 2026

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2026-N-4699; Expedited Investigational New Drug Pilot Program

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the Agency's Request for Information, *Expedited Investigational New Drug Pilot Program; Request for Information*.

BIO is the premier biotechnology advocacy organization representing biotech companies, industry leaders, and state biotech associations in the United States and more than 35 countries around the globe. BIO members range from biotech start-ups to some of the world's largest biopharmaceutical companies – all united by the same goal: to develop medical and scientific breakthroughs that prevent and fight disease, restore health, and improve patients' lives. BIO also organizes the BIO International Convention and a series of annual conferences that drive partnerships, investment, and progress within the sector. Learn more at bio.org.

BIO agrees with FDA that it is critical to shorten the time it takes from drug identification to first-in-human (FIH) study. The proposed pilot presents a timely opportunity to test approaches that could meaningfully reduce delays and improve predictability in early-stage clinical development while preserving safety, scientific rigor, and regulatory oversight. We welcome further dialogue on these issues and appreciate FDA's consideration of our feedback. Please do not hesitate to contact the undersigned with any questions regarding these comments.

Sincerely,

/s/
Allison Kolbe
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

/s/
Snehal Naik
Vice President, Science and Regulatory Affairs
Biotechnology Innovation Organization

General Comments

BIO appreciates the opportunity to provide feedback on FDA's Expedited Investigational New Drug (IND) Pilot Program. BIO welcomes FDA's efforts to modernize the regulatory framework for review of IND applications and shares the goal of accelerating first-in-human (FIH) clinical development in the United States. The pilot represents a timely opportunity to explore approaches that could improve early-stage clinical development. At the same time, it is not yet clear that adding a third-party layer through Qualified Research Institutions (QRIs) will meaningfully improve timelines beyond what could be achieved through more direct, FDA-led reforms.

In practice, delays in FIH initiation arise from a combination of factors, including front-end uncertainty, iterative rework, and downstream bottlenecks such as IRB review, contracting, site activation, and FDA protocol review. Broader considerations such as cost, access to specialized sites, and challenges in participant enrollment also influence sponsors' decisions to conduct early-phase trials outside of the United States. Incremental improvements in IND review efficiency alone are therefore unlikely to materially shift the timelines for FIH initiation or onshore early-phase development. Meaningful impact will require a comprehensive approach that addresses the full ecosystem, from study start-up through enrollment and site activation, so that earlier regulatory readiness translates into tangible advantages for conducting trials in the United States. The pilot should therefore be structured in a way to identify and target the true bottlenecks of early-phase drug development, and evaluated based on whether it produces net, end-to-end improvements.

Because of these challenges, BIO strongly recommends that FDA consider whether alternative approaches, particularly expanded use of rolling review decoupled from QRI review and earlier, structured FDA-sponsor engagement could achieve similar or greater efficiency gains with less complexity. Rolling review offers a more direct mechanism to enable earlier issue resolution and parallel preparation of nonclinical, CMC, and clinical components, and warrants continued exploration independent of the QRI framework.

BIO also notes that it is difficult to fully assess or provide detailed feedback on specific elements in isolation without a clearer understanding of the intended workflow. In particular, the interaction among QRI review, FDA rolling review, and downstream processes such as IRB review and site activation will be critical to determining whether the pilot delivers true net efficiencies or simply redistributes timing across steps. A more complete picture is necessary to allow stakeholders to evaluate how the proposed model would operate holistically and where targeted refinements could most effectively reduce delays. Accordingly, we encourage FDA to consider convening a public workshop on the pilot program to discuss implementation considerations, including how the various components of the proposed model interact and how best to evaluate its impact on end-to-end timelines, quality, and feasibility. **Given the number**

of variables FDA appears to be testing – including the QRI model, rolling submissions, IRB review, and site activation – BIO urges FDA to design the pilot with clear success metrics that can distinguish the impact of each component. Without such a design, the pilot may yield inconclusive results about which changes meaningfully reduce time to trial initiation. Having clear metrics to identify and measure the impact of each component will be critical in understanding how the program can be sustainably scaled across the clinical trial ecosystem.

If FDA proceeds with the pilot as currently envisioned, BIO recommends that the Agency consider the following core principles to guide design and evaluation:

- Pursue a phased approach to establish processes, evaluate outcomes, and identify implementation challenges before expanding to more complex modalities and patient populations. The initial phase should be intentionally focused on use cases where bottlenecks are most likely to be addressable through the proposed model, enabling rapid evaluation of whether the approach produces measurable net efficiencies.

- Preserve FDA authority and clarify the QRI role. FDA should avoid ambiguity in how QRI assessments are used and ensure the model does not introduce duplication or blur responsibilities across FDA, sponsors, and QRIs.

- Streamline pre-IND engagement and predictability. More consistent, predictable, and iterative early engagement, along with clearer communication of FDA expectations, may achieve many of the same goals without added structural complexity or additional layers of bureaucracy.

- Avoid creating new bottlenecks outside FDA review. The pilot should be evaluated holistically to ensure it does not shift delays to QRI qualification, sponsor-QRI contracting, rolling review logistics, or downstream steps such as IRB and site activation. In particular, FDA should consider whether parallel improvements such as greater use of centralized IRBs and more efficient site activation models are needed to ensure that earlier IND readiness translates into actual FIH initiation.

- Define success using balanced, end-to-end metrics. The pilot should be evaluated based on time, quality, safety, feasibility, and access measured across the full pathway from candidate selection to FIH initiation. Critically, success should reflect net improvement, not just faster IND clearance, and should account for whether gains are offset by delays or burdens elsewhere.

- Ensure meaningful net efficiency and FDA capacity. The pilot should not simply shift workload from sponsors to FDA. It is unclear how the addition of QRI review and rolling submission will reduce FDA burden unless paired with clear process simplification and adequate FDA resourcing. The model should demonstrate reductions in clinical holds, improved submission quality, and genuine time savings across the full pathway. Typically, the 30-day IND statutory review window is not responsible for any major delays in initiating a FIH study.

- Consider scalability and broader applicability. Any successful elements of the pilot such as rolling review, standardized templates, clearer safe-to-proceed communication, and phase-appropriate expectations should be designed for broader application to the IND process, not limited to participants. FDA should also consider how lessons from international early-phase models and existing FDA programs can inform potential IND process improvements.

- Consider how fees, capacity, and eligibility criteria may affect equitable access and ensure that the standard IND pathway remains viable and appropriately supported. While QRI engagement may provide value, the fee-for-service model described in the RFI would introduce additional cost and complexity that could limit participation, particularly for smaller sponsors. The expedited IND review pathway should not become a de facto premium pathway accessible only to well-resourced sponsors.

We appreciate FDA's willingness to explore novel approaches to accelerating FIH development and share the goal of improving the efficiency and predictability of early-phase clinical research. With clear role definitions, risk-proportionate design, appropriate safeguards, and attention to both upstream and downstream bottlenecks, the proposed pilot could generate valuable insights while preserving FDA's standards and strengthening the broader FIH ecosystem. We look forward to continued engagement as FDA refines the pilot design.

Responses to FDA Questions

A. Pilot Program Design and Implementation

1. QRI Qualification and Capabilities

i. What specific changes, if any, would you recommend regarding FDA's thinking on the capabilities, infrastructure, and/or leadership expertise research institutions must demonstrate to qualify for the pilot program?

The proposal to establish Qualified Research Institutions (QRIs) as expert partners in the expedited IND pilot raises important questions regarding how FDA will define, evaluate, and certify these entities, and how it will ensure they possess the appropriate expertise for the specific product type, therapeutic area, aspect of drug development (e.g., CMC, clinical, nonclinical, biostatistics, trial design), and patient population under development. The success of the model will depend on FDA's ability to implement clear, transparent, and risk-appropriate qualification criteria that reflect both the intended role of QRIs and the diversity of development programs expected to participate.

First, FDA should consider whether QRIs will be formally accredited by FDA or designated through another defined mechanism, and who within FDA will be responsible for making qualification determinations. FDA should clearly specify how QRI candidates will demonstrate a "track record of success in regulatory affairs," with measurable indicators of success (e.g., outcomes of prior submissions). FDA might also consider requiring prospective QRIs to complete a parallel review or mock review exercise as part of a standardized, objective qualification process. Setting clear, measurable, and transparent criteria will help ensure consistency and credibility across QRIs.

Second, while minimum qualification criteria are necessary, BIO cautions against a one-size-fits-all approach. FDA might consider allowing specialization by therapeutic area, modality, or function rather than requiring each QRI to have comprehensive expertise across all domains. Broad qualifying criteria may be impractical and could significantly narrow the pool of eligible institutions; a specialized approach would better reflect the realities of early-stage drug development and the diversity of IND programs. Few entities are likely to combine deep regulatory-submission experience with the full range of capabilities detailed in the RFI, such as clinical trial site infrastructure, translational science, and CMC expertise. Academic medical centers may appear to be natural candidates, but for product types where specific expertise is needed, such as cell and gene therapies or certain rare diseases, academic medical centers also sponsor their own INDs. Thus, some of the institutions with the most critically needed expertise may also have conflicts of interest limiting their ability to serve as QRIs. Conversely, other entities such as patient advocacy organizations may lack the technical expertise needed to conduct meaningful IND reviews. These issues underscore the importance of a flexible model that allows QRIs to leverage external expertise while maintaining accountability, independence, and quality standards.

Accordingly, FDA should consider whether:

- The ability for a QRI to qualify will be dependent on its ability to perform a full package review or if review of a specific portion of an IND in concordance with their expertise would suffice;

- QRIs may operate through formal partnerships or networks with clinical sites, IRBs, or specialized experts; and
- QRIs may coordinate multidisciplinary assessments across multiple entities where expertise is distributed.

This flexibility would help ensure that the program is scalable and does not exclude otherwise qualified institutions due to structural or resource limitations.

Finally, FDA should consider related program design questions, including:

- The scope of eligible programs (e.g., whether including research INDs, INDs for new indications, etc.);
- How participation will be initiated (sponsor vs. QRI) and the entity responsible for ensuring an appropriate match between product type and QRI expertise;
- Whether FDA will establish standardized review timelines for QRIs or allow them to be negotiated individually.

In the August 6 Expedited IND Pilot Program Educational Webinar, FDA provided additional details about the application process, including its expectation that sponsors identify and partner with a QRI at the point of application. Although some sponsors may have pre-existing relationships with institutions that could potentially serve as QRIs or provide similar support, BIO is concerned that making such relationships a practical prerequisite for participation could significantly limit the pilot's usefulness. Sponsors with established institutional relationships may already have benefited from that expertise, meaning QRI involvement may provide limited incremental improvement in submission quality. As a result, the pilot may disproportionately enroll sponsors that are already relatively well positioned to prepare high-quality IND submissions, while failing to reach those most likely to benefit from structured QRI support. It is also unclear how sponsors would independently determine whether a potential partner satisfies FDA's qualification criteria. BIO therefore encourages FDA to consider mechanisms to support sponsor-QRI matching or otherwise ensure that first-time IND applicants and smaller sponsors are not excluded by application-stage partnership expectations.

Clear, consistent, and transparent governance will be critical to ensure that QRIs are credible, that qualification is not overly burdensome or exclusionary, and that the pilot achieves its intended goal of accelerating high-quality first-in-human development without undermining safety, scientific rigor, or regulatory accountability.

ii. Are there additional required capabilities FDA should assess across clinical and translational science expertise, CMC capabilities, or therapy/domain area knowledge?

QRIs should be capable of determining whether development packages are fit-for-purpose based on product risk, patient population, disease severity, modality, and prior knowledge. For CMC, this means that QRIs should have phase-appropriate expertise – identifying what is

safety-critical for FIH initiation, what can be deferred, and how platform knowledge or prior experience may support streamlined, risk-proportionate approaches without imposing late-stage expectations. FDA should also assess specific scientific and technical competencies, particularly those that directly inform FIH starting dose decisions and monitoring strategies. Reliance on general nonclinical expertise alone risks allowing QRIs to qualify without the specialized skills needed to appropriately evaluate human safety for all product types.

Beyond the core capability requirements outlined in the RFI, FDA should consider additional capabilities to ensure that QRIs have the depth and specificity of expertise needed for FIH IND development. These should include demonstrated operational readiness, secure data-sharing infrastructure, record retention and inspection readiness, and sufficient review capacity. QRIs should also be required to demonstrate direct, recent experience with FDA interactions and IND submissions, such as FDA review experience or equivalent industry regulatory experience.

Given the sensitive nature of the information involved, clear infrastructure and data security requirements are needed, including standards for intellectual property protection, confidentiality agreements, and information firewalls. These safeguards are essential to maintain sponsor trust, particularly where QRIs may interact with competitively sensitive data or with multiple sponsors in similar therapeutic areas.

More broadly, depending on the application, QRIs may need cross-functional expertise in translational science, clinical pharmacology, model-informed drug development (including QSP), dose selection, biomarker strategy, New Approach Methodologies (NAMs), and modality-specific development issues. These capabilities support translation of nonclinical data into human risk assessment, inform starting dose and escalation strategies, and help identify key uncertainties prior to IND submission. QRIs should also be able to evaluate the robustness of QSP models and other mechanistic approaches, including assumptions and data inputs, and identify where such methods can reduce unnecessary conservatism and iterative rework.

Finally, these requirements should be defined with sufficient specificity to ensure meaningful capability, while allowing flexibility for specialization by therapeutic area, modality, or function, including the use of partnerships or networks where expertise is distributed. The framework should avoid requiring every QRI to possess all capabilities across all domains, so long as coordination, accountability, and quality standards are clearly established.

iii. Are any of the listed QRI qualification considerations unfeasible or unattainable by potential QRIs?

As noted above, some expectations may be difficult for a single institution to satisfy comprehensively. Requiring each QRI to have broad expertise across all modalities, therapeutic

areas, CMC issues, IRB ownership, and site ownership could limit participation to a small number of very large institutions.

FDA could allow QRIs to qualify through defined partnerships, consortia, or networks, provided there are clear agreements, accountability mechanisms, quality systems, conflict-of-interest procedures, confidentiality protections, and documentation expectations. This would allow the pilot to leverage existing expertise across academic medical centers, healthcare networks, CROs, regulatory advisors, IRBs, and Phase 1-capable sites without unnecessarily narrowing participation.

iv. Should different specializations exist based on QRI therapeutic area focus or therapeutic modality expertise?

As discussed above, FDA should support specialization among QRIs by therapeutic area, modality, or function where appropriate. Different therapeutic areas and patient populations have materially different evidentiary standards, translational constraints, and development pathways, which makes a one-size-fits-all model impractical and potentially limiting.

Accordingly, FDA should consider the range of product types and development contexts eligible for the pilot. If the pilot is intended to be broadly applicable, QRIs should demonstrate expertise appropriate to the relevant product category, modality, and regulatory framework. A specialized QRI model would improve review quality and consistency, reduce the risk of generic or inapplicable recommendations, and support more reliable application of phase-appropriate expectations.

v. To ensure faster FIH initiation, should QRIs be required to have a self-owned and operated IRB and/or clinical trial site? If not, would a partnership with an IRB and/or trial site network be sufficient?

FDA should not require QRIs to own or operate IRBs or clinical sites. The QRI's primary value is its regulatory review expertise, not site infrastructure. Accordingly, QRIs should be able to rely on formal partnerships with IRBs, site networks, academic centers, healthcare systems, or CROs, provided roles, timelines, accountability, confidentiality, and independence safeguards are clearly defined. Requiring self-owned infrastructure would unnecessarily narrow the pool of qualified institutions without advancing the pilot's goal of faster FIH initiation.

FDA should clarify the end-to-end workflow, including the sequencing of QRI review, FDA review, and IRB approval, and whether QRI involvement occurs before, during, or after IRB review. FDA could consider mechanisms for parallel or coordinated FDA and IRB reviews to reduce duplicative review cycles and accelerate study activation timelines. Harmonized IRB

standards or centralized IRBs could also encourage consistency, predictability, and efficiency in protocol and amendment reviews.

vi. If the QRI serves in a dual capacity as both an IRB and regulatory advisor, are there additional considerations or reporting that would be helpful to prevent potential conflicts of interest and ensure QRIs are objective and reliable?

QRI objectivity is a central concern, particularly if an entity serves multiple roles (e.g., regulatory advisor and IRB). Even though FDA would retain final regulatory authority, the pilot introduces potential structural conflicts that differ from those faced by FDA employees, which are governed by strict ethics and financial conflict-of-interest standards.

If FDA chooses to allow QRIs to serve in multiple capacities, robust safeguards are essential. These should include structurally separate IRB and advisory functions (with distinct leadership, reporting lines, and no shared personnel on a given program), documented independence, defined recusal procedures, and clear reporting to FDA on how conflicts are identified and managed. QRIs should be required to disclose any financial relationships with sponsors (e.g., grants, sponsored research agreements, equity) at the time of IND submission to support transparency and assessment of conflicts of interest.

2. Pre-IND and IND Review Process

i. What changes, if any, would you recommend regarding QRI responsibilities and expected tasks during the pilot? Are any tasks unfeasible or should be undertaken by the sponsor rather than the QRI?

BIO recommends that FDA narrow the scope of QRI responsibilities to ensure the pilot is focused on its intended goal of accelerating FIH initiation. The QRI's responsibilities should center around regulatory submission review and decoupled from clinical trial site qualification and IRB functions, which are distinct capabilities.

FDA should also consider whether the envisioned QRIs will be sufficiently capable of providing the same level of expertise as FDA reviewers. Without comparable expertise, QRI-led review may add unnecessary complexity and potential inconsistency.

We recognize that FDA retains authority over studies proceeding. To make the QRI program successful, however, we believe the recommendations from QRIs must carry meaningful weight in FDA's review process. Within that role, appropriate QRI functions could include structured review of sponsor materials, identification of potential deficiencies, recommendations on FIH readiness, and planning support for rolling submissions and parallel IRB/site activation, along

with documentation of unresolved issues and identification of likely FDA questions and clinical hold risks. QRIs should also provide the sponsor with a formal recommendation letter summarizing their assessment and key issues, which the sponsor could then submit to FDA as part of the IND package. Sponsors should retain the ability to submit their own scientific and regulatory rationale, including alternative positions or justifications where they disagree with, modify, or provide additional context for QRI recommendations.

FDA should also provide an illustrative end-to-end workflow showing how QRI engagement, IND submission, FDA review, and IRB and site activation are coordinated, including the role of the 30-day clock.

ii. What should be the output of QRI advice and review? What information from this review should be submitted to FDA?

FDA might consider providing a standardized QRI assessment report template to ensure consistency across QRIs. The QRI's advisory dialogue with the sponsor should not be submitted to FDA, as it would not ordinarily be part of FDA's review and would add burden without improving decision-making.

BIO recommends that FDA does not include QRI outputs in the IND record unless submitted by the sponsor as part of the review package. Additionally, FDA should clarify which elements must be submitted (e.g., all recommendations versus those relevant to rolling review) and how sponsors may respond to or contextualize QRI findings. While we envision that an integrated, decision-ready recommendation package provided by the QRI that includes a cross-component safety assessment integrating nonclinical, clinical, and CMC considerations would be ideal to enable FDA to evaluate one consolidated rationale, the agency should clarify how module-specific QRI output would enable rolling review and support the goal of shortening review timelines and gaining efficiencies. FDA should also define record-retention and inspection expectations for QRI-related materials, including sponsor-QRI interactions. Clear guidance on the interaction between QRI advice and FDA review is essential to ensure transparency, consistency, and efficient implementation of the pilot.

iii. How can the pilot ensure QRIs provide independent, objective review while partnering with sponsors?

Conflict-of-interest screening alone does not address the structural conflict inherent in a sponsor-funded QRI reviewing that sponsor's own IND. Screening identifies relationships but does not eliminate financial incentives. FDA should therefore establish clear conflict controls, analogous to its third-party programs, including restrictions on financial interests, payment structures (e.g., not contingent on outcomes), and clear guidelines on sponsor-directed funding.

Strong safeguards should include written conflict-of-interest policies, mandatory disclosures of financial and operational relationships (including grants, equity, active/planned IND applications, and sponsored research), documentation of reviewer roles, and independent oversight. QRI compensation should not be tied to favorable recommendations, IND clearance, or expedited outcomes. FDA should also consider whether additional protections such as confidentiality firewalls, personnel separation, and restrictions on advising competing sponsors are needed to protect sensitive commercial information.

To reinforce accountability, FDA should implement performance monitoring and enforcement, including periodic evaluation of QRI outputs for recurring deficiencies and a clear penalty framework for noncompliance or compromised objectivity. Robust independence safeguards, combined with proactive disclosure and meaningful enforcement, are essential to maintaining trust in the model.

Finally, FDA should consider whether structural separation mechanisms (e.g., blinded reviewers or strict internal firewalls between commercial and review functions) are necessary where QRIs operate across multiple sponsors, to further reduce bias and preserve objectivity.

iv. How should expedited INDs during the pilot differ in requirement from standard IND submission, if at all?

Expedited INDs should differ in process only, not in any evidentiary standards. The pilot should be carefully designed so as not to create uncertainty about the information needed to support FIH initiation.

FDA should consider whether a shortened post-submission review timeline is appropriate where key IND components have already undergone QRI review and FDA rolling review. In such cases, FDA may have sufficient familiarity to issue a “safe to proceed” determination more quickly than under the standard 30-day clock, provided that all safety-relevant issues are resolved. However, the pilot should define clear, measurable expectations for what constitutes meaningful acceleration (e.g., earlier safe-to-proceed decisions, fewer holds or review cycles, and reduced information requests), if the 30-day review clock remains in effect. FDA could also use the pilot to evaluate whether IND content can be staged or tailored based on risk and context, with components reviewed earlier or submitted on a rolling basis while preserving FDA’s authority to require additional information before allowing a study to proceed.

FDA should also clarify how feedback provided during rolling review will be documented and shared with sponsors, whether and how sponsors may rely on that feedback, and under what circumstances FDA may revisit prior feedback as additional IND components are submitted. FDA should also define expected timelines for feedback on rolling IND components, because predictable feedback will be important for planning nonclinical, CMC, protocol finalization, IRB

review, contracting, and site activation activities. Feedback timelines and reliance expectations should be described clearly to support planning across nonclinical, CMC, and site activation activities.

3. Drug Eligibility and Participation

i. Should all drug products be considered in the pilot or are there specific types of drug products and/or specific disease or conditions that are better suited for the pilot (e.g., small molecules, large molecules, cellular & gene therapies, nucleic acid-based therapies, combination products, etc.)?

Product selection should be driven by the purpose of the pilot and aligned with FDA's intended evaluation strategy. FDA should consider what range of product types and therapeutic areas is necessary to generate meaningful evidence regarding the feasibility, effectiveness, and scalability of the proposed approach. Whether the pilot begins with a narrower or broader scope, it should be designed so that the resulting data can inform potential application across indications, review centers, and patient populations, including programs reviewed by both CDER and CBER.

FDA could consider a risk-stratified, phased approach to eligibility, focusing on areas where earlier coordination could reduce avoidable delays. At the same time, the pilot should include enough diversity to generate useful learnings across sponsor types, product types, and development contexts. More complex modalities, such as cell and gene therapies, nucleic acid-based therapies, novel biologics, and certain combination products may benefit from the pilot but may require specialized QRI expertise and additional safeguards. FDA could include these programs through specialized QRI tracks or later pilot phases.

FDA should also ensure that product eligibility aligns with the actual availability and specialization of certified QRIs, recognizing that QRI establishment and qualification may be a rate-limiting step. The pilot should avoid predetermined scope assumptions and instead reflect real-world QRI capacity and expertise.

To support implementation, FDA should clarify timing and entry requirements, including when sponsors must commit to pilot participation relative to pre-IND interactions and FIH initiation, so that QRI engagement is properly integrated into development plans.

ii. How should drug products be prioritized for participation in the pilot and why?

BIO recommends prioritizing products where the pilot is most likely to generate meaningful learnings without creating undue risk. FDA should also prioritize programs where the pilot can

demonstrate clear operational value, including those with unmet medical need, strong scientific rationale, sponsor readiness, and the potential to reduce avoidable IND delays through earlier coordination, including product types with a higher rate of clinical holds. Additional considerations include areas where phase-appropriate expectations would be informative and ensuring diversity across sponsor size, product type, and therapeutic area to avoid biasing participation toward only large or well-resourced sponsors.

Additionally, sponsor eligibility and readiness should be considered explicitly, including whether sponsors have the resources and organizational capacity to engage meaningfully. FDA should ensure that participation criteria do not inadvertently restrict access or create a de facto premium pathway.

4. Pilot Scope and Scale

i. How many QRIs and therapeutic areas/modalities be included in the pilot to represent industry research and different public health needs?

FDA should design the pilot to include a manageable number of QRIs and programs while ensuring sufficient diversity to evaluate different QRI models, sponsor types, product categories, and operational settings. The pilot should remain limited enough to allow consistent assessment, but broad enough to reflect the proposed QRI pool and avoid over-indexing on a single model or use case.

FDA should also ensure that the number, distribution, and specialization of QRIs do not create a new bottleneck. Capacity, scheduling availability, therapeutic-area coverage, geographic reach, and modality-specific expertise should be explicitly evaluated as part of the pilot.

The August 6 Expedited IND Pilot Program Educational Webinar indicated that the pilot may test multiple distinct elements, including the QRI model, rolling submissions, parallel IRB review, and streamlined site activation processes. Because each element is complex and could be implemented in different ways, FDA should ensure that the pilot is designed with sufficient sponsor-QRI pairs and a clear evaluation framework to assess the impact of each variable. Otherwise, the pilot may yield inconclusive results regarding which changes actually reduced time to trial initiation.

ii. What duration or volume of participation is appropriate for the pilot phase before evaluation?

The pilot should be time-bound and include sufficient programs to meaningfully evaluate whether the model improves IND quality, timelines, and FIH initiation. After determining the

appropriate scale for the pilot, FDA should establish predefined evaluation milestones, including a minimum number of IND submissions, FDA review outcomes, and FIH study initiations, to ensure the pilot is assessed on a sufficient data set.

5. Implementation and Feasibility

i. What resources would QRIs need to develop and maintain IND review and recommendation capabilities (staff, quality systems, technology infrastructure, estimated costs)?

QRIs will require dedicated staff, cross-functional expertise, quality systems, secure data-sharing infrastructure, documentation tools, conflict-of-interest processes, training, and governance structures to operate effectively. The pilot would benefit from fit-for-purpose digital infrastructure, including structured submission workflows, real-time status tracking, and standardized data exchange tools. Depending on the roles and responsibilities of QRIs versus sponsors in the rolling submission process, QRIs may require interoperable systems to support electronic submission and coordinated review, ensuring seamless information exchange while maintaining confidentiality and data integrity.

ii. Are there existing models, research networks, pilot programs, or international examples that could inform implementation? Please describe relevant examples and lessons learned.

Relevant lessons can be drawn from a range of existing regulatory and operational models, including structured scientific advice mechanisms, early engagement pathways, rolling review programs, and centralized or networked clinical trial infrastructure. These approaches collectively offer useful precedents for staged submission, early feedback, coordinated IRB/site activation, and risk-proportionate review, all of which are central to the proposed QRI concept.

Internationally, several frameworks are especially informative:

- EMA's Innovation Task Force (ITF) demonstrates the value of structured early dialogue for novel technologies, particularly in defining expectations and aligning stakeholders before formal submission.
- MHRA's Innovative Licensing and Access Pathway (ILAP) illustrates a coordinated, multi-stakeholder model with defined milestones, providing a useful template for QRI–FDA–sponsor interaction and timeline management.
- FDA's Oncology Center of Excellence (OCE) Project Orbis shows that parallel, multi-party review can be implemented effectively, provided there is strong coordination infrastructure and clear governance.
- The EU Notified Body opinion process highlights potential pitfalls, including added time and sponsor burden from introducing an additional review layer, underscoring the importance of keeping the QRI model efficient and non-duplicative.

Rolling review and early-phase trial pathways both within and outside of the U.S. offer relevant insights into how iterative submission and feedback can accelerate development when paired with clear expectations and defined roles. Similarly, centralized or networked trial infrastructure models provide practical examples of how to enable faster site activation and more consistent execution across geographies. However, not all elements are directly transferable to the U.S. IND context. FDA should carefully assess which aspects align with its statutory authority and FIH safety requirements, and which may require adaptation to preserve regulatory rigor.

FDA should conduct a formal comparative analysis of these models to identify best practices and avoid known pitfalls, particularly around coordination complexity, added burden, and inefficiencies, before finalizing the QRI pilot design.

B. Risks, Oversight, and Evaluation

1. Risks and Safeguards

i. Are there any risks worth noting associated with the proposed pilot program?

The principal risk is that the pilot could add an additional layer of review rather than reduce time to safe-to-proceed, particularly if FDA must review both the QRI's output and the underlying components. Unless QRI review is clearly decoupled from FDA's own review, the model risks increasing workload rather than delivering efficiency gains. FDA should consider whether alternative approaches, as described elsewhere in this letter, may better address the underlying causes of delay.

A broader set of risks should be explicitly addressed in program design. These include blurred accountability among FDA, sponsors, QRIs, IRBs, CROs, and sites; unclear regulatory status of QRI advice; inconsistent or unpredictable FDA feedback during rolling review; variability in QRI quality; over-reliance on QRI recommendations; conflicts of interest and fee structures that could create bias or barriers to access; and the potential for a de facto premium pathway favoring well-resourced sponsors. Additional concerns include limited QRI capacity creating new bottlenecks, competitive sensitivity where QRIs advise multiple sponsors in similar spaces, uneven application across FDA divisions, unclear record-retention expectations, and shifting bottlenecks to QRI qualification, contracting, or downstream operational steps. There are also fundamental structural questions around the specific roles and responsibilities of FDA, QRIs, and sponsors that need to be addressed to fully consider risks of the program.

Finally, FDA should clarify whether and how QRI review will be structured to avoid bias, including whether reviewers could be blinded to sponsor identity and whether robust internal

separation between commercial and review functions is required. These safeguards, combined with clear governance and enforcement, are essential to ensure independence, maintain public trust, and preserve the integrity of the pilot.

ii. Could the pilot inadvertently compromise clinical trial participants' safety, scientific rigor, or ethical standards, and if so, what suggestions does the commenter have for mitigating such an outcome?

The pilot should preserve the existing safety standard for FIH studies, which is already strong, and focus on improving process efficiency. The goal should be faster identification of issues and better-prepared submissions. As long as FDA maintains full oversight of IND submissions and full authority to make regulatory decisions, safety, scientific rigor, and ethical standards will not be compromised.

iii. Could this pilot create inequitable access favoring well-resourced sponsors over smaller companies?

FDA notes in the RFI an expectation that sponsors will pay fees directly to QRIs following the pilot phase of this program. If access to rolling review is dependent on fee-driven QRI engagement, this will inherently disadvantage smaller companies, academic institutions, and resource-constrained sponsors.

To ensure equity in the pilot program itself, FDA should prioritize transparent selection criteria and mechanisms to support participation by a range of sponsor types. FDA should also make clear that non-participation in the pilot will not disadvantage sponsors or imply lower-quality submissions. As noted above, BIO also encourages FDA to consider that requiring sponsors to co-apply with a QRI may inherently discourage participation from less-experienced sponsors or small companies that do not have pre-existing relationships with potential QRI entities.

iv. Please include how identified risks can be mitigated.

BIO encourages FDA to carefully consider the risks and potential strategies to address them outlined in sections above, including transparency in selection criteria and processes, appropriate, pre-defined evaluation strategies, conflict-of-interest management, and program scope.

2. Oversight and Accountability

i. In the case of disagreement between FDA and QRIs/sponsors on recommendations, what processes, timeline, discussion forums, or mitigation should be used to quickly reach a resolution?

It is our understanding that QRI input is clearly advisory and FDA completes its own reviews. Because FDA retains full decision-making authority, it is unclear why a separate dispute resolution framework would be needed. Dispute resolution procedures described in statute and FDA regulations should remain available for sponsors participating in the pilot.

ii. What oversight and compliance mechanisms should apply if QRIs fail to meet performance standards? What performance thresholds or other events should trigger FDA intervention or removal of QRIs?

FDA should establish clear QRI performance standards upfront, with defined metrics such as timeliness of review, alignment with FDA findings, rate of significant deficiencies or clinical holds in QRI-supported programs, and the consistency and usability of QRI advice. Additional indicators should include conflict-of-interest compliance, documentation quality, record-retention and inspection readiness, and maintenance of required expertise and quality systems.

Performance standards and enforcement should be defined by FDA and FDA should be able to require corrective action, suspend participation, or remove a QRI based on clear triggers such as recurring poor-quality recommendations, missed timelines, inadequate documentation, failure to manage conflicts or protect confidential information, or capacity limitations that undermine program goals. For longer term implementation beyond the pilot, FDA should consider annual performance reviews and audits of QRIs to ensure continued compliance.

At the same time, there is some ambiguity in how performance should be anchored, including whether benchmarks like FDA's own review timelines (e.g., PDUFA dates) are appropriate, and how QRI performance should be measured relative to FDA outcomes. This underscores the need for FDA-defined, standardized criteria rather than leaving evaluation to QRI-driven or self-reported measures.

iii. How can the pilot ensure transparency while safeguarding the sponsor's confidential commercial, trade secrets, and other sensitive information?

FDA should establish clear, defined confidentiality and conflict-of-interest safeguards for QRIs before any sensitive sponsor information is shared. Screening alone will be insufficient; FDA should specify binding confidentiality obligations, disclosure requirements, and oversight mechanisms to protect proprietary development information and prevent competitive or data-use risks.

Transparency in pilot performance should be achieved through aggregated and anonymized metrics, not disclosure of sponsor-specific data. Pilot findings should be shared in a way that supports broader learning without exposing confidential commercial information.

3. Success Metrics and Evaluation

i. What data should be collected throughout the pilot to enable evaluation? Who should collect this data (FDA, QRIs, sponsors, third party evaluators)?

BIO supports a standardized, FDA-owned evaluation framework for the pilot, with input from sponsors and QRIs to ensure consistent data collection and comparability. Metrics should capture the full end-to-end pathway from QRI engagement through IND submission, FDA review, and timeline to FIH initiation, and distinguish whether the pilot delivers true net time savings or simply shifts delays to other steps (e.g., contracting, IRB review, or site activation). FDA should ensure that there are sufficient data points to enable evaluation of each strategy being tested (i.e., QRI type, rolling submission approach, therapeutic area, IRB review, site activation, etc.).

Core data should include timeline elements (QRI engagement, rolling submissions, FDA feedback, IND decision, safe-to-proceed timing, and FIH initiation), review quality indicators (information requests, clinical holds, and whether FDA revisits prior feedback), and operational measures (resource burden, QRI capacity and performance, and FDA workload). Evaluation should also assess downstream execution, including whether earlier IND readiness translates into earlier study start or whether bottlenecks are displaced.

FDA should collect comparative and aggregate measures, such as proportions of INDs proceeding without hold, agreement or divergence between FDA and QRI assessments, and overall cost-benefit analysis from the perspective of both FDA and the sponsor. Importantly, the pilot should be evaluated based on whether it produces meaningful end-to-end improvements.

ii. What metrics should define pilot success? Please address time, quality, safety, and specify any others.

Pilot success should be assessed on a balanced set of time, quality, and safety outcomes. The current FIH system already demonstrates strong safety performance, so the pilot should focus on whether it improves process efficiency and review quality without compromising participant protection or regulatory rigor.

For time, success would reflect measurable acceleration across the pathway – earlier safe-to-proceed decisions, fewer clinical holds, reduced information requests, and shorter time

to FIH initiation – while also demonstrating that any gains are not simply shifted to other steps (e.g., contracting, IRB review, or site activation). On quality and safety, FDA should track indicators of review quality such as post-authorization safety amendments and concordance between QRI and FDA assessments including the identification of deficiencies missed by the QRI.

Additional measures should confirm end-to-end impact and scalability, including reduced iterative rework, improved IND completeness, predictable FDA feedback timelines, reasonable resource burden, and equitable access across sponsor size and product categories. Critically, the pilot should demonstrate net time savings from candidate selection to FIH initiation, not just improvements in a single segment, and should show that any added QRI layer does not introduce offsetting delays or costs that negate efficiency gains.

FDA should also evaluate the individual components of the pilot (QRIs vs rolling review) and their individual impact. FDA could do this by making participation in the QRI and rolling submission processes distinct elements of the Pilot Program where a sponsor can elect, on a voluntary basis, to participate in one or both processes.

iii. At what point is the pilot deemed successful (i.e., after the first successful IND submission, after the entire pilot cohort is finished with IND submission, etc.)?

The pilot should not be deemed successful based on a single IND submission or early safe-to-proceed decision. A meaningful determination requires a sufficient cohort of programs to progress through the full sequence of QRI engagement, IND submission, FDA review, and FIH initiation, so that outcomes can be evaluated on a representative and comparable basis in aggregate.

Success should be assessed only after enough programs have completed these milestones to allow robust evaluation of time, quality, and safety impacts, including whether the model consistently improves outcomes across different product types and development contexts.

iv. If successful, how should the pilot expand? How can innovation from the pilot be scaled to maximize impact for the FIH clinical trial ecosystem?

If successful, FDA should expand the pilot gradually and based on evidence, using predefined outcomes such as improvements in quality, safety, feasibility, access, FDA and QRI capacity, and timelines. Expansion should be phased and controlled, with the initial pilot informing selection of additional product modalities, therapeutic areas, sponsor types, and QRI specializations. FDA should ensure that equitable access is maintained as the pilot expands.

FDA should also ensure that any lessons learned from the pilot are translated into broader IND modernization, such as standardized FIH templates, improved safe-to-proceed communications, clearer clinical hold rationale, risk-proportionate CMC and nonclinical expectations, predictable rolling review processes, and better coordination of IRB and site activation.

C. Additional Considerations

1. What additional/alternative approaches could achieve similar goals of accelerating Phase 1 FIH IND study initiation in the U.S.?

FDA could achieve similar goals through IND process modernization and risk-based review improvements, without introducing a third-party layer.[1] Key approaches include risk-proportionate IND requirements, clearer expectations of FDA requirements, improving consistency of IND reviews, updating guidance to reflect phase-appropriate expectations (particularly for CMC and nonclinical packages), and strengthening mechanisms to reduce and resolve clinical holds more efficiently.

While this pilot couples QRI review and rolling reviews, BIO encourages FDA to consider how rolling review could be implemented on its own. Rolling reviews would likely result in significant time savings by enabling earlier FDA engagement and parallel preparation and earlier resolution of nonclinical, CMC, and clinical issues. QRI review is less likely to benefit sponsors with significant regulatory experience, but rolling review would benefit all sponsor types. Together with improved communication and triaged review approaches, this could reduce clinical holds and shorten time to safe-to-proceed decisions.

Additional process improvements could further advance the same objective, including standardized FIH templates, clearer clinical hold rationale, more predictable communication of FDA expectations, iterative FDA-sponsor discussions (mid-cycle meeting at day 15 and shorten timeline for FDA-Sponsor Pre-IND Meetings), and formal review timelines for protocol amendments. FDA could further improve efficiency by allowing refusal of grossly deficient submissions, enabling cross-referencing of prior data, and leveraging platform knowledge, model-informed approaches, and New Approach Methodologies (NAMs) to reduce iterative rework. FDA could also consider how other processes, such as the 60-day protocol review period, may contribute to delayed initiation of FIH trials even after sponsors receive a safe-to-proceed notification.

[1] See recommendations: Reagan-Udall Foundation for the FDA, “Enhancing Early-Stage Drug Development in the United States” (2026). https://reaganudall.org/publications/enhancing-early-stage-drug-development-united-states

To support faster initiation, FDA could consider a clinical trial notification pathway that adapts elements of international early-phase models alongside more consistent IND review and streamlined pre-IND engagement. Finally, parallelization of IRB review, contracting, and site activation, supported by dedicated Phase 1 infrastructure and improved site readiness, and greater utilization of centralized IRBs would address downstream bottlenecks that often limit FIH speed.

2. What are the advantages and disadvantages of the proposed pilot compared to these alternatives?

BIO agrees with FDA that QRIs could improve submission quality, enable earlier identification of issues, and support better coordination across nonclinical, clinical, and operational elements of FIH initiation. However, compared to alternatives such as risk-proportionate review, clearer guidance, standardized templates, and enhanced FDA engagement, the pilot introduces additional complexity, cost, and operational layers. Our concerns are outlined throughout this letter.

The pilot's value depends on whether it can demonstrate clear advantages that are not achievable through simpler, more scalable alternatives. When evaluating success of the pilot, FDA should consider how alternatives such as rolling review decoupled from QRI review compare on a net benefit basis across the full IND lifecycle, including cost, feasibility, and access, in addition to time.

3. How should FDA take into account the information submitted, and should that be different depending on the risk of the product under investigation?

FDA should apply a risk-based approach. The level of QRI input, FDA rolling review, supporting documentation, and operational readiness expectations may need to vary based on product complexity, novelty, modality, disease severity, patient population, and potential participant risk. Higher-risk or more complex products may require more specialized expertise, earlier FDA engagement, and more extensive documentation. Lower-risk or well-characterized programs may be appropriate for more streamlined review.

4. Are there important considerations or concerns not addressed in the questions above?

<u>FDA-Sponsor Interaction and Existing Pathways</u>

FDA should consider how the pilot interfaces with and improves upon existing engagement mechanisms, such as the INTERACT program in CBER, which already provides structured early dialogue. FDA should evaluate whether the QRI model meaningfully improves upon these interactions or simply duplicates them with additional time and resource consuming workloads.

Clear alignment with existing pathways is essential to avoid layering additional process without added value.

FDA could establish harmonized templates and clear expectations for protocols, investigator brochures, statistical analysis plans, and IND submission modules to improve the quality, consistency, and efficiency of sponsor submissions and regulatory review. Furthermore, FDA could create a common contractual and budgetary framework for QRIs participating in the pilot program to reduce negotiation timelines, streamline site activation, and promote operational efficiency across sponsors and institutions.

Leveraging Technology

Consistent with other FDA initiatives, FDA should explore digital tools and shared data platforms that could support more efficient IND preparation and review while enabling appropriate protections against improper use and disclosure of confidential information. For example, a common submission environment with continuous data uploads could facilitate rolling review by allowing FDA to evaluate information as it becomes available rather than waiting for a complete IND package. FDA also could explore AI-enabled tools that provide sponsors with early feedback on protocol design and submission content based on existing FDA guidance, helping identify potential issues earlier and reducing the likelihood of delays during formal review.

Long-Term Vision

The pilot describes the role of QRIs as restricted to advice and preliminary review, not regulatory decision-making. However, FDA also notes that the pilot could inform a future QRI certification process and broader changes to FDA's IND review. Should FDA envision a transfer of regulatory decision-making to QRIs, as in the third-party 510(k) review system, FDA should consider implications for safeguards, oversight, and program design. BIO recommends that FDA consider the long-term vision for this program and design the pilot accordingly.

Knowledge Transfer and Scalability

FDA should consider how pilot learnings will be shared broadly and translated into durable IND process modernization. The pilot should not become a limited pathway available only to participants who can access QRIs. FDA should identify which elements could be scaled to the broader FIH ecosystem or even subsequent phases of development.