FRIENDS of CANCER RESEARCH

Reducing Avoidable Delays in U.S. Oncology First-in-Human Studies

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Executive Summary

The initiation of first-in-human (FIH) oncology studies requires sponsors to navigate complex scientific, regulatory, and operational considerations. As FIH studies increasingly incorporate multiple clinical objectives and become more globally distributed, sponsors may face uncertainty regarding evidence expectations and how U.S. Food and Drug Administration (FDA) guidance applies to their individual development programs. Such uncertainties can contribute to major protocol amendments, operational disruptions, and delays in study initiation.

The FDA has issued guidance and established initiatives that support flexible, scientifically justified, product-specific, risk-based approaches for drug development. However, sponsors may still face uncertainty about how these flexibilities apply to individual products and when different types of evidence can be most effectively used. Sponsors may also encounter challenges obtaining actionable feedback through pre-Investigational New Drug (IND) interactions. New regulatory paths as well as more effective use of existing regulatory approaches could help sponsors make better-informed and more rapid development decisions while maintaining appropriate patient protections and scientific rigor.

To explore opportunities to improve the efficiency and predictability of oncology FIH study initiation, Friends of Cancer Research convened a multi-stakeholder working group including experts from the FDA, pharmaceutical companies, academia, and patient advocates. The group identified four areas where targeted approaches could help:

- Aligning evidence expectations with initial protocol objectives: Tailoring evidence expectations to the objectives of initial study components, product characteristics, and potential risks could support more streamlined FIH study initiation while maintaining patient safety.
- Improving the actionability of pre-IND interactions: Selecting FDA interaction mechanisms that best match specific development contexts and questions could help sponsors obtain more actionable feedback to inform more efficient development decisions.
- Strengthening product-specific, risk-based approaches: Considering the available evidence, remaining uncertainties, and appropriate safeguards for managing uncertainty could support flexible, risk-based approaches tailored to individual products and development contexts.
- Minimizing downstream operational disruptions: Better aligning the timing and scope of study start up activities with regulatory interactions could help reduce avoidable delays in FIH study initiation.

Together, these approaches emphasize better alignment of evidence generation, regulatory input, and operational activities with the objectives and risks at each stage of FIH development. The goal is not to lower evidence expectations or create new regulatory mechanisms, but to make existing flexibilities and interactions more predictable and useful in supporting safe and efficient development of promising treatments for patients in need.

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We thank the working group members for their expertise and contributions that helped shape the development of this white paper. The views expressed here represent the collective insights from working group discussions and do not necessarily reflect the official positions of any individual organization.

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Table of Contents

Executive Summary 1

Authors 2

Table of Contents 3

Introduction *4*

Focus Area 1: Aligning Evidence Expectations with the Scope of the Proposed Initial Study 5

The Evolving Scope of Oncology First-in-Human Studies *6*

Potential Approach: Aligning Evidence Timing with Protocol Components *6*

Focus Area 2: Improving the Actionability of Early Pre-IND Interactions 7

Proposed Approach 1: Earlier Alignment on Recurring Protocol Issues *8*

Proposed Approach 2: Best Practices and Considerations for Tailoring Pre-IND Interactions to Sponsors' Specific Questions *9*

Focus Area 3: Strengthening Product-Specific Justifications for Risk-Based Approaches 13

Current Regulatory Landscape *13*

Characterizing Product-Specific Uncertainty *13*

Potential Approach: A Framework to Guide Sponsor Justifications *15*

Focus Area 4: Minimizing Downstream Operational Disruption from Regulatory Interactions and Protocol Amendments 16

Discussion 19

References 21

Introduction

Maintaining and advancing the U.S. as an efficient, predictable, and scientifically rigorous environment for first-in-human (FIH) oncology studies is a critical policy priority. A robust early-development ecosystem supports timely patient access to promising therapies, enables generation of early safety data in U.S. patients, and sustains U.S. leadership in biomedical research. As oncology drug development becomes increasingly global,[1] sponsors have multiple options when deciding where to initiate clinical studies, making it increasingly important for the U.S. regulatory environment to support efficient and predictable study initiation while maintaining appropriate patient protections and scientific integrity.

Sponsors consider a range of regulatory, operational, and scientific factors when determining where and how to initiate FIH studies, such as the efficiency and predictability of study start up, availability of early-development expertise, trial design and population requirements, enrollment feasibility, and the ability to generate high-quality data. These considerations may be particularly important when studies involve biomarker-based patient selection, biopsies, intensive pharmacokinetic (PK)/pharmacodynamic (PD) sampling, or other features that can affect site and patient participation. Operational challenges including site contracting and activation, budget negotiations, legal review, and variability in institutional review board (IRB) processes can further delay study initiation and conduct. Lack of product-specific evidence expectations, coupled with FDA questions raised during Investigational New Drug (IND) review, often triggers protocol amendments, operational disruptions, and additional delays. Although some protocol changes are necessarily driven by emerging data, others may be anticipated and addressed through earlier and more targeted sponsor-FDA engagement.

Oncology FIH development operates within a regulatory framework that recognizes the unique characteristics of advanced cancer populations and the need for flexibility in early development. The International Council for Harmonisation (ICH) S9 guideline and the accompanying Questions & Answers document provide a foundation for tailored nonclinical approaches to the characteristics of a product and its development context.[2,3] The FDA has also supported scientifically justified, product-specific approaches that may differ from conventional development strategies when adequately supported by available evidence.[4] Recent initiatives—including Operation TrialBlazer,[5] the FDA Expedited IND Pilot Program,[6] and broader agency efforts to modernize early development expectations[7]—further reflect continued momentum in this direction. The opportunity is therefore not simply to create additional flexibility, but to make existing flexibilities more predictable and actionable by better aligning evidence expectations with the scope and risks of the proposed study, strengthening product-specific scientific justification, and resolving high-impact questions earlier in development.

Building on these modernization efforts, Friends of Cancer Research convened a working group including experts from the FDA, pharmaceutical companies, academia, and patient advocates to examine opportunities to support a more predictable, efficient, and transparent pathway for oncology FIH development in the U.S. This white paper focuses on four key areas:

1. Aligning evidence expectations with the scope of the proposed initial study. Sponsors could align evidence generation with the objectives and risks of specific study activities and use targeted FDA interactions at key decision points to resolve uncertainty, assess emerging evidence, and guide progression to subsequent protocol components;

2. Improving the actionability of early pre-IND interactions. Earlier alignment on recurring protocol issues and tailoring the timing, content, and type of FDA interaction to the sponsor's development context and questions could provide more actionable feedback and help reduce avoidable delays;
3. Strengthening product-specific justifications for risk-based approaches. A structured approach to considering available evidence, remaining uncertainty, safeguards, and planned evidence generation could help sponsors communicate scientifically justified, product-specific approaches to support their FIH studies; and
4. Minimizing downstream operational disruptions from regulatory interactions and protocol amendments. Better coordinating the timing and extent of study start up activities, including site engagement, contracting, budgeting, and IRB review, with regulatory interactions could help reduce rework when protocol changes occur.

This white paper is part of a set of complementary Friends of Cancer Research white papers focused on modernizing early phase oncology development to support safe, efficient, and evidence-based development of new therapies for patients.[8,9]

Focus Area 1: Aligning Evidence Expectations with the Scope of the Proposed Initial Study

This white paper focuses on oncology FIH studies, where the objectives, risks, and clinical context can differ from those in other therapeutic areas. Unlike many non-oncology FIH studies, which may enroll healthy volunteers or patients with available standard of care (SOC) treatment options, oncology FIH studies are typically conducted in patients with advanced cancer who have exhausted available treatment options and face significant unmet medical need. Accordingly, decisions regarding uncertainty, risk mitigation, and evidence requirements are informed by the clinical context.

Oncology FIH studies do not follow a single development path, as relevant considerations may vary based on factors such as:

- Patient population and clinical context. Patients may range from those with advanced or refractory disease to those who are newly diagnosed but have few, if any, available treatment options. These populations may differ in disease biology, prognosis, underlying health conditions, available SOC, and potential for meaningful clinical benefit.
- Therapeutic modality, target, and product characteristics. Evidence expectations may differ based on the modality, the extent of prior knowledge about the target, manufacturing complexity, pharmacologic and biological properties, mechanism-based toxicities, prior experience with related products, and characteristics of the intended patient population. For example, a first-in-class product directed at a novel target may raise different questions than a product directed at a well-characterized target with substantial prior clinical experience.
- Study design and evolving treatment context. Combination therapies may introduce additional considerations related to drug-drug interactions and overlapping toxicities, while evolving SOC may affect trial design and interpretation, including through changes in comparator selection or available therapeutic options.
- Sponsor and regulatory context. Sponsors range from large pharmaceutical companies to smaller biotechnology companies, academic institutions, and other research organizations, and differences in

resources, development experience, organizational structures, and expertise can influence how sponsors prepare for regulatory interactions and develop briefing packages. Products reviewed by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) may also raise distinct considerations related to chemistry, manufacturing, and controls (CMC), pharmacology, toxicology, and clinical development, particularly for complex modalities where manufacturing processes, product characteristics, and their implications for patient safety may be difficult to fully characterize.

- Global development considerations. Because FIH studies often enroll patients across multiple regions, sponsors may need to account for differences in SOC, clinical practice, patient populations, regulatory expectations, and other region-specific factors.

Together, these considerations underscore the importance of avoiding a one-size-fits-all approach to oncology FIH studies. Instead, evidence expectations should be calibrated to the characteristics of the investigational product, therapeutic modality, mechanism of action, patient population, clinical context, and objectives of the proposed initial study.

The Evolving Scope of Oncology First-in-Human Studies

In oncology, FIH studies have evolved from traditional Phase 1 dose-escalation trials focused primarily on establishing initial safety and tolerability. Early clinical studies are increasingly designed to achieve multiple objectives within a single protocol, progressing from initial safety and dose finding to the generation of preliminary evidence of antitumor activity or other information intended to support later development decisions. Oncology FIH protocols may incorporate dose expansion cohorts, biomarker-selected populations, combination cohorts, or integrated Phase 1/2 designs. A single protocol may therefore serve multiple objectives ranging from characterizing PK and assessing safety and tolerability to identifying a recommended Phase 2/3 dose, evaluating PD activity, and generating preliminary evidence to support subsequent development phases.

This evolution has important implications for regulatory expectations: the evidence needed to safely initiate the first component of a FIH study may not be the same as the evidence needed to support later protocol components. For example, the data needed to support first patient dosing and dose escalation may differ from those needed to support expansion cohorts, longer treatment exposure, combination cohorts, biomarker-selected populations, or efficacy-focused assessments. Although the initial IND submission must provide sufficient evidence to support the study activities included in the proposed protocol, not all components of a FIH study present the same type or level of risk. The depth and scope of supporting information, including CMC data, may evolve as clinical development progresses past dose escalation and additional study components are introduced. Expectations should remain phase-appropriate, with information generated and refined at a pace aligned with the study's objectives, the product's characteristics, and the risks associated with each study component, while maintaining appropriate safeguards for patient safety.

Potential Approach: Aligning Evidence Timing with Protocol Components

The key question is not whether evidence requirements should be reduced, but whether all potentially relevant evidence is necessary upfront to support a specific study activity. As oncology FIH studies increasingly incorporate multiple protocol components with distinct objectives and risk profiles, there may be opportunities to better align evidence expectations with the timing, objectives, and risks of each component.

Under a more iterative approach, the initial IND submission would provide sufficient evidence to safely support the initial study activities proposed, such as dose escalation, while evidence needed to support later components could, where scientifically appropriate, be generated or assessed as the study progresses and clinical data mature. As data are generated, sponsors could evaluate emerging clinical safety, PK/PD, and preliminary activity data, and available nonclinical or CMC evidence to determine what additional information, if any, is needed to support later protocol components. Progression to a subsequent component would be informed by whether the available evidence is sufficient to address the risks and objectives of that component; where additional evidence is needed, sponsors would generate or submit that evidence before initiating the subsequent component. Evidence requirements could therefore evolve with the actual risks and objectives of the study rather than being established entirely based on the anticipated scope of the program at the time of the initial IND submission. Because evidence may evolve as the study progresses, informed consent should communicate upfront that some aspects of the study may be refined as new data emerge; material changes in risks or uncertainties should be explained in clear, patient-centered language, and patients should be kept informed of significant emerging data that might affect their willingness to remain on the study.

Existing regulatory mechanisms provide multiple opportunities for sponsor-FDA interactions as development progresses, including through formal meetings, protocol amendments, and other established interactions. However, these mechanisms may not always provide the timing or frequency of interaction needed to address time-sensitive questions that arise between established regulatory touchpoints, potentially leaving sponsors to choose between waiting for more comprehensive FDA input or proceeding with greater regulatory uncertainty. Targeted FDA interactions at a limited number of high-impact decision points could help address this gap by focusing discussions on the specific questions most consequential at a given stage of development. To be effective, these interactions should build on existing mechanisms rather than create new review pathways and should be structured around clear, focused questions supported by sufficient information to enable meaningful feedback while accounting for FDA capacity.

The transition from dose escalation to expansion may represent a particularly important opportunity for targeted interactions. While dose-escalation strategies are typically based on the evidence available at IND submission, emerging safety, PK/PD, and preliminary activity data may inform subsequent dose selection and the design of expansion cohorts. A focused interaction following dose escalation could provide an opportunity to discuss these emerging data and the proposed path forward, such as proceeding to refining dose selection, expansion, or pursuing further randomized dose optimization. This may be particularly valuable for integrated Phase 1/2 studies, where study objectives, patient populations, and evidence needs often evolve as clinical data accumulate.

Importantly, the objective would not be to reduce evidence expectations, require FDA interaction at every milestone, or delay development while awaiting regulatory agreement. Rather, the goal would be to ensure that evidence is generated and assessed when it is needed, while identifying a limited number of high-value decision points where timely FDA-sponsor alignment could help resolve uncertainty, reduce avoidable delays, and support an appropriate transition to the next stage of development.

Focus Area 2: Improving the Actionability of Early Pre-IND Interactions

The pre-IND period provides an important opportunity for sponsors to engage with the FDA and align expectations before initiating a clinical study. Sponsors commonly use this period to seek feedback through formal interactions, including pre-IND meetings, on key aspects of their development program. While preparing for these interactions

can be resource-intensive, well-prepared sponsors can use these meetings to ask focused, targeted questions and obtain actionable feedback for their development plans. The value of these interactions is therefore closely tied to the quality and completeness of the information sponsors provide and the extent to which it enables the FDA to address their specific questions.

For FIH studies, sponsors generally anticipate that protocols will evolve as clinical development progresses. Protocol amendments are therefore not indicative of a problem but rather may be expected as part of an iterative development process. Among the protocol elements most commonly subject to change are eligibility criteria, as sponsors may refine patient populations based on emerging clinical or safety information, or modify criteria when enrollment is slower or more difficult than anticipated.[10] However, the scope and timing of requested amendments can have significant implications for development timelines. Targeted requests addressing a limited number of discrete issues may be implemented relatively quickly, whereas broader requests requiring substantial additional information can create considerably more downstream work and delay study initiation.

Sponsors have also raised concerns when feedback provided during pre-IND meetings appears to differ from recommendations received during subsequent IND review. While consistency across interactions is important, maintaining identical recommendations or ensuring that the same reviewers participate at every stage may be difficult to operationalize. Differences between pre-IND feedback and formal IND review may instead reflect differences in the amount and type of information available at each stage of development. During a pre-IND meeting, the FDA may be reviewing a draft protocol, synopsis, or preliminary data package and therefore provide recommendations based on an incomplete set of information. At the time of IND submission, the FDA has access to a more comprehensive package and must evaluate the totality of available evidence, which may raise new questions or affect the assessment of previously discussed issues. This dynamic may be particularly relevant for CMC and nonclinical information, where additional data generated between the pre-IND and IND stages can materially influence the overall assessment. This underscores the importance of tailoring the timing and content of pre-IND interactions to the specific questions sponsors are seeking to address.

These considerations highlight an opportunity to make pre-IND interactions more targeted and fit-for-purpose. More deliberate preparation and appropriately scoped questions may help sponsors better anticipate FDA expectations and reduce the likelihood of avoidable downstream requests that could delay study initiation or progression.

Proposed Approach 1: Earlier Alignment on Recurring Protocol Issues

Dose-escalation strategies, dose-limiting toxicity (DLT) criteria, and inclusion and exclusion criteria are among protocol elements that may generate questions or changes as FIH studies progress. However, pre-IND interactions often focus on other aspects of the development program, such as toxicology assessments. Sponsors could use the pre-IND period more strategically to seek earlier alignment with the FDA on key protocol elements that may affect subsequent study start timelines. Because these elements are highly product- and data-dependent, however, earlier alignment should focus on the rationale underlying sponsors' proposed approaches and the factors that may influence the FDA's assessment rather than using a prescriptive or one-size-fits-all recommendation.

Where recurring questions arise across development programs, product-agnostic guidance could also help establish a general framework for sponsor-FDA interactions. For example, guidance on DLT criteria could provide greater clarity on general considerations for defining and assessing DLTs while allowing sponsors to address product-specific considerations through appropriate regulatory interactions.

Importantly, earlier alignment should not come at the expense of flexibility or discourage sponsors from pursuing scientifically justified, innovative approaches. There is a potential tradeoff between designing protocols conservatively to minimize the likelihood of future protocol amendments or feedback and allowing sufficient flexibility to pursue approaches that may accelerate development. Sponsors may intentionally adopt more innovative approaches to dose escalation or other aspects of study design if the potential benefits, including avoiding unnecessary patient exposure to subtherapeutic doses or supporting more efficient development, outweigh the possibility that the FDA may subsequently request modifications. Conversely, a conservative approach may reduce the likelihood of an early amendment but could also constrain study execution or introduce delays later in development. Targeted sponsor-FDA interactions during the pre-IND period could provide a mechanism for sponsors to test key assumptions, identify potential areas of regulatory concern, and better anticipate issues that could otherwise result in avoidable delays, while preserving sponsor flexibility to pursue scientifically justified approaches.

Proposed Approach 2: Best Practices and Considerations for Tailoring Pre-IND Interactions to Sponsors' Specific Questions

Sponsors have multiple opportunities to engage with the FDA during early development, and formal pre-IND meetings should be viewed as one component of a broader set of regulatory interaction mechanisms. Rather than approaching pre-IND preparation as a single, comprehensive exercise, sponsors should consider which questions they need to address, what information is needed to support those questions, when feedback is most useful, and which interaction mechanism and format are best suited to obtain meaningful FDA feedback. Strategically sequencing interactions in this way could help sponsors obtain feedback when it is most useful while avoiding unnecessary preparation and review burden.

An important consideration is determining how much information is needed to enable meaningful FDA feedback. The amount and type of information needed will vary depending on the development program and the questions being addressed. Nonclinical and toxicology information may be important to support most discussions, while a well-articulated protocol draft or synopsis can provide important context for evaluating the proposed clinical approach. However, a complete nonclinical package or extensive *in vivo* data may not be necessary to facilitate a useful exchange. Greater clarity around the information most useful for different types of pre-IND questions could help sponsors focus their preparation on the data most likely to inform FDA feedback, rather than providing increasingly comprehensive packages by default.

Sponsors could then consider whether a formal pre-IND meeting is the most appropriate mechanism for their particular questions. Existing FDA mechanisms, including INTERACT, Type D, and pre-IND (Type B) meetings, provide different opportunities for sponsors to obtain feedback as development programs evolve. Although FDA guidance outlines these options,[11] sponsors may be uncertain about which mechanisms are appropriate during FIH development or may not be fully taking advantage of the available options. Sponsors should consider the stage of development, nature of the questions, information available, and timing needed for feedback when determining the most fit-for-purpose mechanism for engagement.

For example, early questions about alternative evidence-generation strategies may be appropriate for an INTERACT or Type D meeting rather than waiting until a pre-IND meeting.[11] If a sponsor is considering whether additional studies or data are necessary to address uncertainty, an early, targeted interaction could allow discussion of the scientific rationale before undertaking a potentially resource-intensive study. Similarly, if a

sponsor believes that generating Good Laboratory Practice (GLP) data in a particular animal species would not provide meaningful additional information based on the product's mechanism of action or other scientific considerations, preliminary toxicology data could be used to support an early discussion with the FDA about whether the proposed approach adequately addresses the relevant uncertainty.[8]

The appropriate interaction mechanism also depends on when feedback is needed. Meeting types differ in timelines and flexibility; for example, Type D meetings may provide a relatively efficient mechanism for focused questions and can accommodate multiple related topics, whereas Type C meetings may be less suitable when feedback is needed to inform an imminent development decision. Sponsors should consider the nature, urgency, and timing of their questions when sequencing interactions. The FDA's pre-IND guidance provides information on meeting types and their associated timelines.[11]

As development programs mature and additional data become available, sponsors could use pre-IND interactions to address more specific or mature clinical development questions. For example, questions about starting dose, dose-escalation strategies, or other aspects of clinical development may more appropriately be addressed through a formal pre-IND meeting once sufficient data are available to support a meaningful discussion. Where toxicology data provide confidence that potential adverse effects are reversible and can be appropriately monitored, a sponsor could discuss whether a more flexible starting dose or dose-escalation strategy may be appropriate, potentially reducing the number of patients exposed to subtherapeutic doses while maintaining appropriate safety considerations.

The format of a pre-IND interaction may also affect its utility and efficiency. Sponsors should consider whether their questions require the discussion afforded by a teleconference, hybrid, or in-person meeting, or whether written feedback may be sufficient. Focused questions with clearly defined response options may be adequately addressed through written responses, whereas complex or interdisciplinary issues may benefit from real-time discussion between sponsors and the FDA. Meeting availability and format may also vary depending on the interaction mechanism and FDA resources, including the increasing use of written response only formats.[12] Sponsors should therefore consider both the substantive needs of the questions and the available format when determining how to engage with the FDA. FDA performance data reports may provide additional context on which meeting formats are used most frequently and the response timelines sponsors can expect in practice.[13]

Sponsors may also have opportunities for continued interaction after a pre-IND meeting. Follow-up questions by email, as well as additional Type C or Type D meetings when appropriate, can allow sponsors to address discrete questions as the development program evolves rather than carrying unresolved questions into IND submission. However, sponsors have reported that the flexibility available within existing regulatory frameworks may not always translate into flexibility in practice, including instances where FDA reviewers directed sponsors to proceed to IND submission rather than continue pre-IND discussions. Greater clarity around when and how these mechanisms can be appropriately leveraged could help sponsors take fuller advantage of available opportunities for engagement.

Table 1 maps illustrative FDA interaction mechanisms during the pre-IND period to the types of questions sponsors may be seeking to address, the level of information generally needed to support each interaction, and when each mechanism may be most appropriately leveraged. The table is intended to provide a framework to help sponsors identify which mechanism may be most appropriate for their specific questions rather than to prescribe a particular pathway.

Table 1. Illustrative FDA Interaction Mechanisms During Early Development

Type of FDA Interaction	Questions, Feedback, or Goals	Expected Level of Supporting Information	When Each Interaction May Be Most Appropriately Leveraged
INTERACT meeting	Early feedback on novel development approaches, including certain nonclinical, toxicology, or CMC considerations; sponsors could potentially use a focused INTERACT meeting to discuss whether a proposed approach could support a waiver of a toxicology study requirement (e.g., non-human primate or chronic toxicology study)	Preliminary data and information sufficient to explain the proposed approach and specific questions; the appropriate level of briefing materials may depend on the complexity of the issue and the comfort of both the sponsors and FDA reviewers with discussing the question	When sponsors are considering novel approaches early in development and would benefit from FDA input before substantial additional work; not appropriate after a formal pre-IND meeting
Type D meeting	Focused discussion of a specific question, protocol element, or narrow issue; limited to a maximum of three disciplines	Targeted supporting materials and data relevant to the specific questions; typically less comprehensive than a formal pre-IND meeting package	When sponsors have discrete questions that do not warrant a broader formal meeting; after a formal pre-IND meeting if outstanding questions remain
Type B: Formal pre-IND meeting	Broad feedback on the development program, including key nonclinical, CMC, clinical elements (e.g., trial design, starting dose selection, dose-escalation strategy, safety monitoring), or regulatory questions	More comprehensive briefing package; draft protocol/synopsis and data to support relevant questions	When sponsors have multiple substantive questions or need broader alignment before IND submission; depending on the FDA office and circumstance, sponsors may be able to request another formal pre-IND meeting as a follow-up
Type C meeting	Discussion of important aspects of a development program that do not fit within another meeting type; flexible in terms of topics that can be addressed	Data-supported briefing package with clearly defined questions or discussion topics	After a formal pre-IND meeting if outstanding questions remain

Type of FDA Interaction	Questions, Feedback, or Goals	Expected Level of Supporting Information	When Each Interaction May Be Most Appropriately Leveraged
Follow-up interaction	Clarification or additional discussion following prior FDA feedback; intended to address outstanding questions rather than introduce new data or substantive topics	Updated or supplemental information directly relevant to the outstanding questions	When questions remain after a formal meeting and can be resolved through a focused clarification; the relatively short response timeline may be useful for resolving outstanding targeted questions quickly
Ad hoc interaction	Administrative, logistical, or other relatively straightforward questions that can be addressed over email; not intended to obtain substantive scientific or regulatory advice	Email with focused questions and information necessary to address the issue	When the question is administrative in nature or straightforward and does not require substantive scientific or regulatory feedback; sponsors should not rely on these interactions as a substitute for documented FDA advice

Abbreviations: CMC, Chemistry, Manufacturing, and Controls; FDA, U.S. Food and Drug Administration; IND, Investigational New Drug

Taken together, strategically sequencing FDA interactions based on the questions being addressed, stage of development, information available, timing considerations, and most appropriate format could help shift pre-IND engagement from a single, comprehensive interaction toward a more iterative and fit-for-purpose approach. This could help sponsors obtain more actionable feedback, identify and address uncertainty earlier, reduce unnecessary data generation, and make more efficient use of both sponsor and FDA resources.

Focus Area 3: Strengthening Product-Specific Justifications for Risk-Based Approaches

Because oncology FIH programs vary by modality, mechanism, target biology, manufacturing complexity, prior knowledge, and patient population, sponsors should not expect a uniform evidence package to apply across programs. At the same time, flexibility depends on a clear scientific rationale. Sponsors should explain how the available evidence supports the proposed study, what uncertainty remains, and how that uncertainty will be managed.

Current Regulatory Landscape

The FDA has issued guidance documents, launched pilot programs, and established other initiatives that support flexibility and fit-for-purpose evidence generation in FIH development.[2-6] The agency has also indicated that scientifically justified, risk-based approaches—including deferral of certain evidence when appropriate—may be acceptable when sponsors propose alternate approaches, provide appropriate supporting data, and demonstrate that patient safety will not be compromised. These efforts reflect the FDA's recognition that evidence expectations should be tailored to the characteristics and risks of individual development programs.

Despite these flexibilities, sponsors may face uncertainty about how existing guidance and flexibilities apply to a specific product, evidence package, and clinical context. The product-specific nature of oncology FIH development means that general guidance, by design, cannot anticipate every scenario; this makes early, focused engagement between sponsors and the FDA particularly valuable. This uncertainty may contribute to more conservative development strategies or additional evidence generation even when a more tailored, risk-based approach may be scientifically appropriate.

Characterizing Product-Specific Uncertainty

To better determine what evidence is necessary for a specific FIH program, sponsors should consider the characteristics of the product and development context that inform both known and potential risks. The goal is not to establish a lower or uniform evidence threshold, but to support scientifically justified, risk-based approaches that align evidence generation with the characteristics, uncertainties, and objectives of each development program. No single factor will determine the appropriate evidence package. Evidence needs should instead be informed by the totality of product-specific characteristics, how they collectively shape potential risks to patients, and the uncertainties that must be addressed before clinical testing. Sponsors should also consider applicable FDA guidance and recommendations for IND submissions,[14-16] as well as other guidance relevant to their specific product, modality, and clinical context. Friends of Cancer Research also wrote a white paper on risk-based nonclinical strategies that provides a more detailed discussion of how product-specific characteristics can inform nonclinical and toxicology considerations.[8] Key product and development considerations related to CMC, dosing, and other aspects of clinical development include:

- Mechanism of action and drug target. The extent of knowledge surrounding a drug target and mechanism of action is an important consideration in assessing risk and determining evidence needs. For well-characterized targets, particularly those with multiple approved or investigational therapies, existing knowledge of target biology, pharmacology, and associated toxicities may provide a foundation for evaluating potential risks. By contrast, novel targets or mechanisms of action may present greater uncertainty regarding on- and off-target effects and may warrant additional characterization before clinical exposure. The relevant question is therefore not simply whether a target is novel, but the extent to which existing knowledge can inform the specific risks of the proposed product and where meaningful evidence gaps remain.

- Therapeutic Modality. The therapeutic modality influences both the nature of potential risks and the evidence needed to support a FIH study. Even when products share a target or mechanism of action, their risk profiles may differ based on whether the target is pursued through a small molecule drug, antibody, cell and gene therapy (CGT), or other modalities. Modality-specific characteristics and regulatory expectations should therefore inform the assessment of what evidence is needed to adequately characterize potential risks. This may be particularly important for modalities in which characteristics of the product or its administration introduce risks that are not readily informed by experience with other therapeutic approaches.

- Prior Experience and Platform Knowledge. Prior experience with similar products, mechanisms, or platforms can provide important context for assessing risk, identifying evidence gaps, and determining what additional evidence may be necessary for a specific FIH program. The extent to which such knowledge can inform the proposed program will depend on the relevance and comparability of the available data, including similarities in mechanism of action, cancer type, patient population, dose or exposure, product characteristics, manufacturing processes, and delivery approaches. Where prior experience is sufficiently relevant, existing data may help reduce uncertainty and support a more targeted evidence package focused on questions that remain specific to the individual product. Conversely, substantial differences between the prior and proposed contexts may limit the extent to which existing data can be extrapolated and may warrant additional evidence to address product-specific risks.

- Manufacturing Complexity. Manufacturing considerations can introduce additional sources of uncertainty, particularly for complex or individualized products. Sponsors should demonstrate sufficient understanding of the product and manufacturing process to identify and address characteristics that could affect product quality, patient safety, or the comparability of clinical material across lots and studies. The complexity and scalability of the manufacturing process, the ability to consistently produce clinical material, and the extent to which manufacturing characteristics may affect product quality or clinical risk should be considered when determining the appropriate CMC data needed for FIH trial initiation. For some products, manufacturing complexity may represent an important component of the overall risk assessment and require additional characterization before clinical testing.

Case studies or illustrative examples provided by sponsors could help further demonstrate how these principles can be applied in practice. Examples of situations in which available evidence supported a more streamlined approach could help clarify how sponsors can justify evidence deferral or alternative approaches. Conversely, examples in which a proposed approach was not considered sufficient and additional evidence was requested

could help sponsors better understand what evidence may be necessary to address specific risks and uncertainties. Collectively, such examples could provide greater clarity on how scientifically justified, risk-based approaches can be applied while maintaining appropriate safeguards for patient safety.

Potential Approach: A Framework to Guide Sponsor Justifications

A product-specific, fit-for-purpose approach to evidence generation could be supported by a structured framework for sponsors to justify why the available evidence is sufficient to support the proposed FIH study. Under this approach, sponsors proposing to defer or modify certain evidence expectations would provide a clear rationale that links the available evidence to the specific objectives of the proposed study, the uncertainties that remain and associated risks, why those uncertainties are acceptable, and how they will be managed through study design, monitoring, and continued evidence generation. This approach could help avoid unnecessary frontloading of evidence that may be more efficiently or informatively generated during clinical development, while maintaining appropriate safeguards for patient safety. As part of this justification, sponsors should clearly articulate:

- Evidence supporting starting dose and regimen. Describe the available nonclinical, CMC, and other relevant evidence supporting the safety of the proposed starting dose and dosing regimen, as appropriate to the product and development context.
- Remaining uncertainty. Identify the key uncertainties that remains regarding the product, including uncertainty related to safety and potential adverse effects, pharmacology, manufacturing, or other aspects of the development program.
- Rationale for why this uncertainty is acceptable for the proposed study. Explain why the remaining uncertainty is acceptable for the proposed FIH study, considering the potential risks, available evidence, clinical context, study design, and objectives of the study.
- Safeguards and monitoring. Outline the measures in place to identify and mitigate potential risks, including dose-escalation strategies, stopping rules, safety monitoring, or other safeguards.
- Evidence generation planned during drug development. Identify evidence that will be generated during the FIH study to address remaining uncertainty, including the development milestones or decision points by which that evidence is expected to be available to inform subsequent development decisions.

Taken together, these elements would provide a structured, risk-based framework for sponsors to assess and justify whether an evidence package is sufficient to support a specific FIH study while transparently identifying what uncertainties remain and how those uncertainties will be managed. This approach could help sponsors and the FDA distinguish between uncertainties that can be appropriately managed through study design, monitoring, and iterative evidence generation and uncertainties that must be resolved before FIH study initiation.

This approach could be applied across all stages of evidence generation and study design but may be particularly useful in areas where sponsors have identified challenges or delays that can increase development timelines, resource requirements, and patient burden. For example, starting dose selection and dose-escalation strategies may warrant consideration, as highly conservative starting doses can result in multiple subtherapeutic cohorts before reaching potentially active dose levels; this can be particularly consequential for patients with advanced disease who may have limited treatment options and are participating in early-phase studies with the expectation that the investigational therapy may provide clinical benefit. Other potential areas include DLT assessment, other safety monitoring approaches, and requirements for biomarker-selection assays in Phase 1 studies, where fit-for-

purpose approaches may be possible when supported by appropriate evidence and safeguards. These considerations may also be especially relevant for complex modalities like CGTs, where conventional evidence expectations can require substantial time, resources, and data, creating a significant development burden. Applying a risk-based framework across these areas could help identify opportunities to modernize FIH development when strong scientific justification and appropriate safeguards support an alternative approach.

Focus Area 4: Minimizing Downstream Operational Disruption from Regulatory Interactions and Protocol Amendments

As sponsors engage with the FDA to resolve regulatory questions, they are simultaneously initiating site-level activities such as IRB submission, budget negotiations, contracting, and other trial start up activities. When regulatory feedback or subsequent protocol changes occur after these activities have begun, they can create downstream operational rework.

Regulatory efficiencies may shorten the time required to obtain FDA feedback but do not necessarily translate into shorter overall trial start up timelines, particularly when downstream activities have already begun and require rework following regulatory feedback or when operational inefficiencies contribute to delays. Sites may therefore take different approaches to the timing of start up activities; some sites may wait for FDA feedback before initiating activities with a finalized protocol, while others may begin certain activities at-risk in parallel with IND submission, recognizing that FDA feedback may subsequently require protocol amendments or other changes. Although at-risk activities may create additional work if substantive changes are needed, initiating activities such as budget and contracting negotiations in parallel with IND review may help expedite site activation.

These considerations highlight the importance of calibrating the timing of downstream activities to the level of regulatory uncertainty. Sponsors and sites therefore have opportunities to identify and address operational considerations earlier in study development. Potential approaches and their associated limitations and tradeoffs are summarized in Table 2.

Many of these approaches have been identified previously or are already used in some settings, including central IRBs, parallel processing, master service agreements, earlier site engagement, and at-risk review. A key opportunity is to better understand what limits their broader or more consistent use, including institutional requirements, site-specific processes, resource constraints, and the risk of rework when study requirements change. The potential benefit of these approaches must also be weighed against additional costs and the risks of rework if study requirements change. Better coordination of regulatory and operational activities may help accelerate trial initiation while minimizing downstream disruption from protocol amendments.

Table 2. Potential Approaches to Address Operational Challenges with Study Start Up

Key Considerations	Potential Approach	Potential Limitations and Tradeoffs
Timing of site engagement and start up	Early site input during protocol development to identify operational considerations and site-specific requirements before finalizing the protocol	Earlier engagement may require sites to review evolving study concepts and may result in rework if the protocol changes substantially; site capabilities or input may change during IND review
	At-risk review of draft protocols or other study materials before final FDA feedback	Can expedite start up, but conducting activities at-risk may place additional burden on sponsors and sites if protocol amendments require previously completed work to be revisited; some sites may not offer at-risk review or charge additional fees; may be less effective when substantial FDA feedback is anticipated due to remaining uncertainty
	Alliances, master research agreements, and longer-term collaborations with preferred sites	May streamline communication, contracting, and start up by leveraging established relationships, but may limit flexibility in site selection or be less feasible for smaller biotechnology sponsors without these relationships; repetitive requests from sponsors and contract research organizations for basic site capabilities may also create burden for sites and divert attention from site-specific feasibility questions
	Rapid start up processes offered by institutions to expedite site activation	May require additional fees and institutional resources; availability and eligibility vary across sites and may be challenging for smaller biotechnology companies with limited budgets
Protocol and site feasibility	More flexibility during protocol development, including consideration of eligibility criteria, treatment schedules, visit requirements, and other site-level feasibility considerations	Changes made late in development may create additional rework, and operational feasibility should be balanced against scientific, regulatory, and study objectives
	Engage scientific experts, advisory boards, steering committees, and sites to inform study design	Early input may improve study design and feasibility, but recommendations may evolve as additional scientific or regulatory information becomes available; incorporating input from multiple stakeholders may add time and coordination requirements
Site preparation and product administration	Earlier conversations to assess site capabilities and product- and auxillary-specific needs, including whether stability data support	Requires sufficiently detailed information early in development; product-specific requirements may evolve as development progresses

Key Considerations	Potential Approach	Potential Limitations and Tradeoffs
	anticipated transportation, preparation, and administration processes	
	Early input from sites on capabilities, workforce capacity, personnel, laboratory resources, and other study-specific requirements	Site capacity can change over time, and early assessments may not fully predict conditions at study initiation
Contracting and budget negotiations	Conduct contract and budget negotiations in parallel with other site activities rather than sequentially	Parallel processes may shorten timelines but can increase the risk of rework if protocol or site requirements change
	Master services agreements to establish contractual and financial terms in advance for recurring sponsor-site collaborations[17]	Can reduce repeated negotiations and streamline start up for subsequent studies, but require upfront effort and may not address study-specific details; may be less feasible for sponsors without established site relationships and smaller biotechnology companies
	Incorporate potential patient costs and logistical requirements early, including unexpected visits or overnight stays, patient and caregiver travel, and reimbursement	Actual patient needs may be difficult to anticipate before enrollment; additional requirements may affect budgets and site feasibility
IRB and institutional review of protocol changes	Central IRBs to reduce duplicative review across participating sites[18]	May not eliminate other institutional, Cancer Center Support Grant, or site-specific review requirements; use of central IRBs may be more limited among industry sponsors, whereas academic sponsors with NIH-funded grants may have greater opportunities to use them
	Decision rules for which protocol changes require additional IRB or institutional sign-off, allowing routine or low-impact changes to proceed without restarting the full review process	Requires clear agreement and discussion on which changes can proceed without additional review; requirements may vary by institution and protocol and may be easier to implement with local IRBs than central IRBs; regulatory and institutional requirements may still require review for certain changes

Abbreviations: IND, Investigational New Drug; FDA, U.S. Food and Drug Administration; IRB, Institutional Review Board; NIH, National Institutes of Health

Discussion

As the complexity of oncology FIH studies continues to evolve, ensuring that regulatory and operational considerations support efficient study initiation will be important to maintaining the U.S. as a location for early development. Figure 1 provides an overview of the key regulatory and operational considerations that arise throughout the FIH study initiation process.

This white paper highlights opportunities to improve the predictability and efficiency of FIH study initiation in oncology drug development within existing regulatory frameworks. The FDA already provides flexibility through guidance and initiatives that allow sponsors to address uncertainty in ways appropriate to their specific products and development programs and to pursue risk-based approaches when they are scientifically justified and maintain patient safety. The opportunity is not simply to create additional flexibility, but to enable sponsors to apply existing flexibility more predictably and effectively. This includes helping sponsors better understand how existing guidance and flexibility may apply to their specific development context, distinguish uncertainties that are critical to address before FIH study initiation from those that can be addressed as development progresses, and engage with the FDA when regulatory input can meaningfully inform development decisions.

Importantly, regulatory interactions represent only one component of FIH study initiation. Operational considerations, including site engagement, contracting and budgeting, and IRB review, also affect how quickly studies can begin and sponsors' decisions about where to conduct them. Protocol design can also influence the burden placed on patients, including the frequency and duration of study visits, required procedures, and other logistical requirements. Considering these factors earlier in study development may help identify opportunities to reduce avoidable burden for both sites and patients and support more efficient study initiation and enrollment. Further work in these areas could help develop and implement approaches to reduce avoidable delays and support sponsors in initiating and retaining FIH studies in the U.S.

Many of the opportunities described in this white paper can be advanced through greater alignment and collaboration within existing regulatory and operational frameworks. Continued discussion among sponsors, the FDA, patient advocates, and other stakeholders will be important to identify additional opportunities to improve FIH study initiation and address challenges beyond those covered in this white paper. Ultimately, a more predictable U.S. FIH development environment will not depend on requiring more evidence or more regulatory interactions upfront, but on ensuring that evidence, regulatory input, and operational activities are aligned with the decisions and risks at each stage of development.

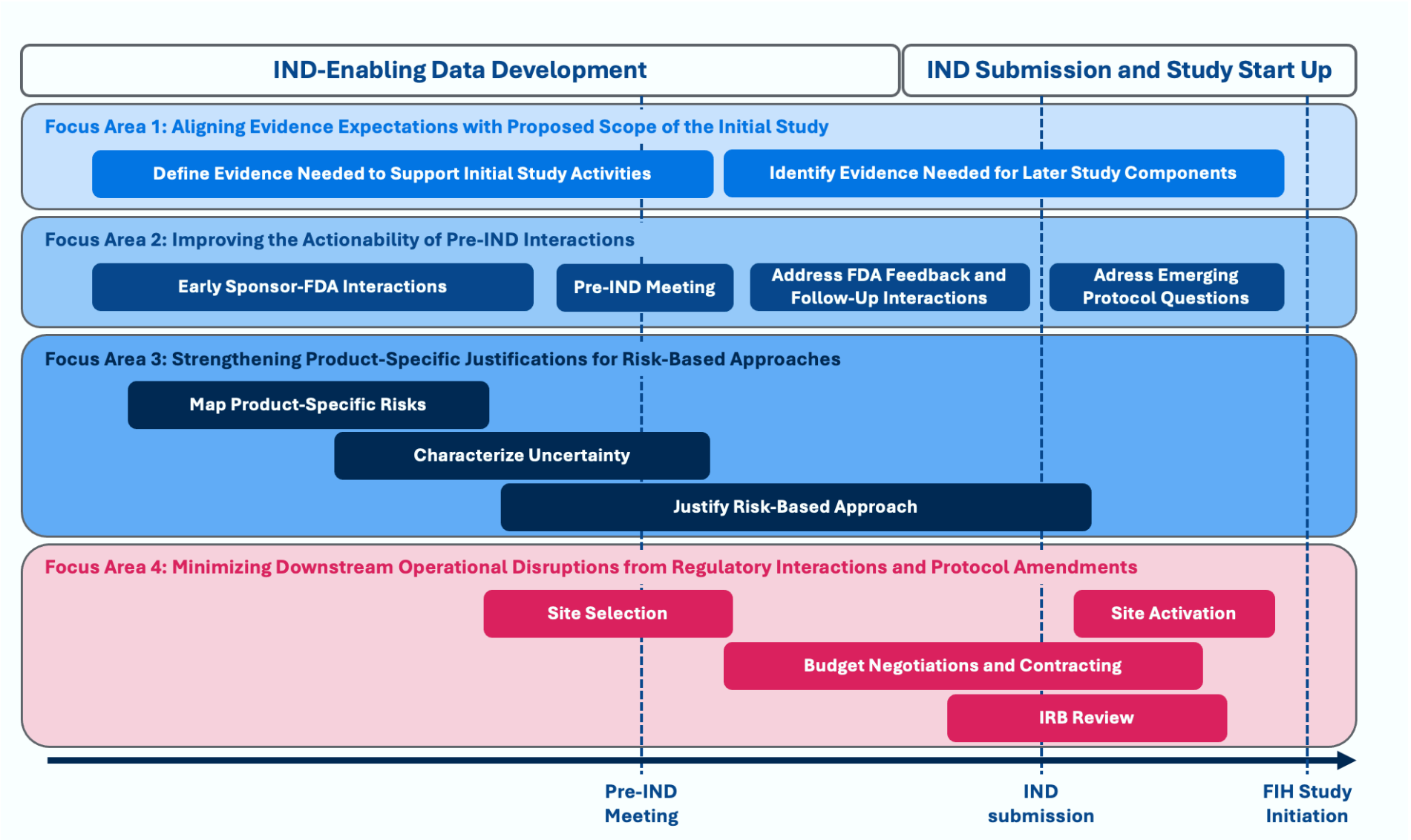

Figure 1. Timeline of Key Regulatory and Operational Considerations for FIH Study Initiation

Abbreviations: IND, Investigational New Drug; FDA, U.S. Food and Drug Administration; FIH, First-in-Human; IRB, Institutional Review Board

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