Charting a Conditional Approval Pathway for Rare Disease Drugs – A Top Priority for a Revamped FDA?

On April 18, U.S. Food and Drug Administration (FDA) Commissioner Marty Makary **announced plans** to roll-out a new approval pathway for rare disease drugs. Commissioner Makary's comments build on sentiments expressed across both the patient community and industry that rare disease drug development needs greater regulatory flexibility in order to speed access to treatments for patients with no or limited options. This is an initiative that has also been **trumpeted by Janet Woodcock**, former Principal Deputy Commissioner and Acting Commissioner of the FDA, in her work since retiring from the FDA. Prior legislative proposals (including the "Promising Pathway Act" **proposed** in 2024) have attempted to create a time-limited conditional approval pathway in the rare disease space, and Commissioner Makary's remarks may signal a renewed push for action.

In last week's interview, Commissioner Makary emphasized the following potential eligibility factors in how he is thinking about a new "conditional" approval pathway: rare conditions affecting only a small number of people, where a randomized clinical trial has not been conducted and is not feasible, but where a "plausible mechanism" physiologically exists. Commissioner Makary also noted that post-approval monitoring of adverse events and other data may be an important tool to support more flexible regulatory decision making about drug approvals.

Whether *and when* the FDA or Congress will take further steps in outlining a conditional approval pathway, and what form that outline may take (e.g., Agency guidance, expansion of the current accelerated approval authorities, or new legislation), remains unclear at this time. This is an area rare disease researchers and developers should monitor for developments, including any opportunities to provide comments to the FDA on its potential plans.

Form FDA 483 Response Best Practices Announced by the FDA

 In Draft Guidance published this week by the U.S. Food and Drug Administration (FDA), **Guidance for Industry – Processes and Practices Applicable to Bioresearch Monitoring Inspections**, the Agency provides some wisdom on best practices for responding to Form FDA 483s, albeit in the context of its Bioresearch Monitoring (BIMO) program inspections, but very much translatable to *any* Form FDA 483 response. FDA notes the following best practices:

> A response should demonstrate the establishment's acknowledgment and understanding of FDA's observations. It should also demonstrate the establishment's commitment to address the observations, including a commitment from senior leadership.
>
> Responses should be well-organized and structured to:
>
> - Address each observation separately
> - Note whether the establishment agree(s) or disagree(s), and why
> - Provide both corrective and preventive actions and timelines for completion
> - Provide both completed and planned actions and related timelines
> - Provide a method of verifying or monitoring the effectiveness of the actions
> - Submit documentation (e.g., training, Standard Operating Procedures (SOPs), corrective action plans, records, etc.)

Importantly, FDA also states that timely Form FDA 483 responses that include "appropriate corrective and preventive actions could impact FDA's determination of the need for subsequent Agency action." FDA encourages responses within 15 business days after the end of an inspection and, helpfully, notes that any responses received within that window "will be considered before further Agency action or decision." Interested stakeholders may submit comments **here** on FDA's Draft Guidance until August 5, 2024.

*Please contact **Julie Tibbets** or any member of our **Life Sciences Regulatory & Compliance practice** with questions on FDA's Draft Guidance or on responding to Form FDA 483s.*

Master(ing) Protocols for Randomized Umbrella and Platform Trials

 The U.S. Food and Drug Administration (FDA) recently issued a draft guidance, "**Master Protocols for Drug and Biological Product Development**", that echoes and builds on principles that the Agency previously set forth in guidance for **COVID-19 master protocols (2019)**, **master protocols in oncology (2022)** and **clinical trials for multiple versions of cellular or gene therapy products (2022)**. The draft guidance offers numerous (and at times *very* detailed) recommendations to facilitate the design, efficient analysis of data, and regulatory review of clinical trials conducted under such master protocols.

As a starting point, this draft guidance defines several key terms, including the types of trials that can be conducted under a master protocol:

Master Protocol	a protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more medical products in one or more diseases or conditions within the overall study structure.
Umbrella Trial	evaluates multiple medical products concurrently for a single disease or condition
Platform Trial	evaluates multiple medical products for a disease or condition in an ongoing manner, with medical products entering or leaving the platform
Basket Trial	evaluates a medical product for multiple diseases, conditions, or disease subtypes

Master protocols offer sponsors the ability to streamline drug development through shared control groups, study infrastructure and oversight. However, these protocols also involve increased complexities and design challenges that generally require a higher degree of coordination. Here, we highlight some key design and analysis considerations addressed in the draft guidance:

Randomization

Sponsors should consider allocating more subjects to control arms than for each individual drug arm to increase power and reduce the risk of a poorly or highly performing control arm. For a platform trial, a sponsor should create a plan for changes to the randomization ratios that can occur as products enter and exit a platform trial. In umbrella or platform trials comparing different drugs, the sponsor should ensure that the randomization process prevents subjects from being randomized to drugs they are not eligible to receive given each drug's exclusion criteria.

Informed Consent

Sponsors should cover all treatment arms in their informed consent and obtain consent prior to randomization. In a platform trial where drugs are entering and exiting the study, consent forms should be modified accordingly to reflect the drugs currently under evaluation. FDA also

recommends the use of a central IRB to review informed consent forms, the protocol, and other relevant documents for monitoring of a trial conducted under a master protocol.

Blinding

Given the potential for different administration methods for various drugs included in umbrella or platform trials, unique blinding challenges may arise and sponsors should discuss their proposed approach to blinding with FDA early in the planning stage.

Safety Data

Safety data from a master protocol can be considered part of overall safety database but data from other sources may be needed to support approval. The type of master protocol and the drugs being evaluated will impact the approach to safety data collection. FDA also recommends that a data monitoring committee (DMC) or other independent, external entity review accumulating safety and efficacy data to minimize inadvertent dissemination of information that could pose risks to trial integrity.

Regulatory Review Considerations

Each master protocol should be submitted as a new IND, and FDA recommends that the sponsor request a pre-IND meeting to discuss the protocol and other IND submission details. Given the potentially rapid pace of changes in a master protocol, the draft guidance recommends specific procedures for protocol amendments, including cover letters for each protocol amendment that update on the status of each drug and notifying the RPM at least 48 hours before submitting any protocol amendment that could substantively affect the master protocol. The IND should also include a well-designed communication plan to facilitate timely and effective communication between multiple stakeholders, including rapid communication of serious safety information and protocol amendments to investigators and FDA.

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Comments on this draft guidance are due February 22, 2024. Please contact the authors or your Goodwin attorney with any questions or if you would like to submit a comment.

Common FDA Bioresearch Monitoring Violations: Updates from FY 2022 to Now

 The Bioresearch Monitoring (BIMO) Program, operated by the U.S. Food and Drug Administration (FDA), conducts on-site inspections and data audits in order to effectively monitor the compliance of all FDA-regulated research.

As a follow up to our **June 2022 post**, we highlight the most common violations identified in Fiscal Year (FY) 2022, in addition to those observed thus far in FY 2023. BIMO conducted 766 inspections in FY 2022. The majority of these inspections (approximately 79%) were of drug, biologic, or medical device study clinical investigators, institutional review boards (IRBs), sponsors, clinical research organizations (CROs), and sponsor-investigators. Some of the most common inspection outcomes are highlighted below. Our methodology included a search of FDA's Warning Letter database for FY 2022 and 2023, to date, for letters issued by BIMO and the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health to IRBs, CROs, clinical investigators, sponsors, and sponsor-investigators.

FY 2022:

BIMO conducted 504 inspections of clinical investigators (468 of which were assigned to FDA's drug, biologic, and device Centers), making up over half of BIMO's inspections conducted in FY 2022. Inspections of IRBs, sponsors, CROs, and sponsor-investigators assigned to FDA's drug, biologic, and device Centers comprised another 138 inspections in FY 2022. Of the 504 clinical investigator inspections, only 9 resulted in a classification of "Official Action Indicated" (OAI) and 87 resulted in a classification of "Voluntary Action Indicated" (VAI). The most common inspection observations included: (1) failure to comply with Form FDA 1572 requirements and protocol compliance; (2) failure to follow the investigational plan and protocol deviations; (3) inadequate and/or inaccurate case history records and inadequate study records; (4) inadequate accountability and/or control of the investigational product; (5) safety reporting and failure to report and/or record adverse events; and (6) inadequate subject protection and informed consent issues.

Of the Warning Letters that were issued in FY 2022 to clinical investigators, the most common observations were:

- **Failure to ensure that a clinical investigation was conducted according to its investigational plan.** This finding in various Warning Letters included failure to properly consent participants, failure to properly randomize participants, and/or failure to properly screen potential participants to ensure they met a protocol's inclusion and exclusion criteria prior to enrollment in an investigational plan. For example, in one **Warning Letter**, an investigator did not ensure that subjects randomized to a specific intervention group received the assigned investigational drug for that intervention group and did not adhere to the blinding protocol.
- **Failure to submit an IND application for the conduct of a clinical investigation with an investigational new drug.** For example (and similar to trends observed in FY 2021), the

> FDA noted that one **clinical investigator** failed to submit an IND for the use of a product that was determined by the FDA to be a drug. The study design demonstrated that the investigational product was intended to cure, mitigate, and/or treat a disease or condition and therefore, an IND application should have been submitted to the FDA prior to commencing any research activities. Another **Warning Letter** included a finding that a protocol comprised of a combination product (a drug and device component) required an IND application.

BIMO conducted 81 inspections of sponsors and CROs in FY 2022 (all but one were assigned to FDA's drug, biologic, and device Centers). Of these, 0 resulted in a finding of OAI, though 15 were classified as VAI. The most common inspection observations included: (1) failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan; (2) failure to meet the abbreviated requirements for investigational device exemptions (IDEs); (3) failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; (4) accountability for the investigational product; (5) failure to comply with Form FDA 1572 requirements; (6) financial disclosures; (7) failure to submit an Investigational New Drug (IND) application and IND safety reports; and (8) failure to submit current list of all participating investigators to FDA at the six-month interval after FDA approval of the study.

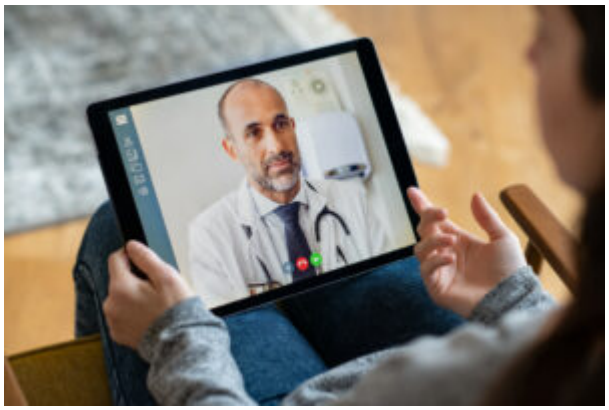
FY 2023 Trends (to date):

In 2023, we have already observed six Form FDA 483 Warning Letters issued to clinical investigators and IRBs, three involving the failure to submit an IND for the conduct of a clinical investigation with an investigational new drug, two involving failure to follow the clinical investigation according to its investigational plan, and one involving overall lack of IRB oversight and IRB compliance. For example, in a 2023 **Warning Letter** issued to an IRB, the FDA noted that the IRB: (a) failed to review proposed research at convened meetings at which a majority of IRB members were present; (b) failed to maintain adequate documentation of IRB activities, including keeping an active list of active IRB members; and (c) failed to ensure that information provided to study subjects as part of the informed consent process was done in accordance with applicable FDA regulations. Although sponsors may often make the decision to utilize a central IRB to oversee the conduct of a clinical investigation, some participating sites may be required to utilize their own local IRB, and it is important to remember that any IRB which does not adhere to FDA's requirements can introduce a compliance risk for studies it is engaged to oversee.

Sponsors, clinical investigators, CROs, and IRBs should review the FDA's **BIMO Compliance Program Guidance Manuals** regularly to ensure that they understand their responsibilities when carrying out clinical research involving human subjects. Sponsors, clinical investigators, CROs, and IRBs should ensure inspection readiness at all times while bioresearch is ongoing and following completion of bioresearch that may support marketing applications submitted to the FDA. Ensuring diligence in the research site selection process, careful monitoring during clinical trials, and corrective actions when deviations occur can help manage the risk of inspection findings of noncompliance or Warning Letters issued by the FDA. The Goodwin Life Sciences Regulatory & Compliance team provides regulatory counseling on FDA's Good Clinical Practice requirements and the resolution of BIMO inspection findings and Warning Letters when they occur.

Contact our team to learn more.

The ABCs of DCTs: New FDA Guidance Provides Recommendations for the Conduct of Decentralized Clinical Trials



On May 2, 2023, the U.S. Food and Drug Administration ("FDA") published draft guidance titled "***Decentralized Clinical Trials for Drugs, Biological Products, and Devices***" (the "Draft Guidance"). The Draft Guidance expands on the FDA's **2020 recommendations** issued in response to the COVID-19 pandemic and its **2021 draft guidance** on the use of digital health technologies ("DHTs") in clinical trials, and fulfills the directive under **Section 3606 of the Food and Drug Omnibus Reform Act** to "issue or revise draft guidance [ ] to clarify and advance the use of decentralized clinical studies to support the development of drugs and devices" no later than December 29, 2023.

The Draft Guidance defines a decentralized clinical trial ("DCT") as a clinical trial where some or all of the trial-related activities occur at locations other than traditional trial sites. The FDA clarifies that its regulatory requirements for clinical investigations are the same for DCTs as for traditional clinical trials; however, the Draft Guidance outlines how clinical trial sponsors, investigators, and other stakeholders may meet these requirements in the context of DCTs given the FDA's recognition of the significant potential benefits of DCTs, such as expanding access to clinical trials, increasing trial efficiency, and improving trial participant engagement, recruitment, enrollment, retention, and diversity.

Some of FDA's key recommendations include:

- An important initial determination is whether it is appropriate for a particular trial to be conducted as a fully decentralized or hybrid DCT. Whereas a fully decentralized trial may be appropriate for an investigational product ("IP") that is simple to administer, has a well-characterized safety profile, and does not require complex medical assessments, a hybrid approach may be more appropriate where the trial involves more complex medical assessments or supervision and monitoring of IP administration. The FDA recommends that questions related to the feasibility, design, implementation, or analysis of a DCT should be discussed early with the relevant FDA review division.
- Given that trial-related activities for a DCT may involve a network of locations where clinical trial personnel, local health care providers ("HCPs"), and trial-related services (e.g., labs) may be provided, for inspectional purposes the investigator should select a physical location, to be listed on Form FDA 1572 – Statement of Investigator or in the investigational device

exemption ("IDE") application, where trial participant records will be stored and where trial personnel may be interviewed.

- Both sponsor and investigator should evaluate whether certain trial-related activities may be delegated to DCT personnel located near participants' homes. Such activities should not require detailed knowledge of the protocol or IP. Trial-related activities that are unique to the trial or require detailed knowledge of the trial protocol or the IP should be performed by qualified trial personnel who have been appropriately trained.
- Obtaining informed consent remotely may be appropriate for a DCT as long as the process is adequate and appropriate. Oversight by institutional review boards ("IRBs") should ensure that electronic informed consent at remote locations meets applicable requirements, and the FDA recommends the use of a central IRB in DCTs to provide for more streamlined review of the informed consent documents as well the protocol and other trial-related documents.
- As with any trial, sponsors must ensure proper monitoring of DCTs based on the sponsor's risk assessment. Sponsors should also implement a safety monitoring plan that accounts for the decentralized nature of the clinical trial, including by prespecifying whether safety data will be collected via telehealth or in-person visits and whether DHTs will be used to collect certain safety information. The Draft Guidance underscores the importance of providing sufficient instruction and contact information to the trial participant should an adverse event occur and allowing the participant to arrange an unscheduled visit (either remotely or in-person), as appropriate. The FDA also recently finalized its **Q&A guidance on risk-based monitoring of clinical investigations**, which we blogged about **here**.
- FDA notes that the "variability and precision" of data obtained from a DCT may differ from data obtained in a traditional site-based clinical trial. For example, remote assessments may vary from on-site assessments, particularly if trial participants are performing their own assessments at home. Similarly, assessments performed by local HCPs may be less precise and consistent than assessments conducted by on-site trial personnel. FDA states that while such variability may not affect the validity of a finding of superiority, it could compromise a finding of non-inferiority relative to an active control drug that has been evaluated in a traditional site-based trial. FDA therefore recommends that sponsors consult with the relevant review division if planning a DCT with a non-inferiority design.
- For telehealth visits during a DCT, investigators should confirm a participant's identity during each visit and complete the relevant case report forms and other documentation for each visit. Additionally, the sponsor and investigator are responsible for ensuring that remote clinical trial visits comply with relevant state telehealth laws and as applicable, the telehealth laws of countries outside the U.S.
- Given multiple sources of data collection in a DCT, the sponsor should develop a data management plan that includes the data origin and data flow from all sources to the sponsor; methods for acquiring remote data from trial participants and personnel; and a list of vendors for data collection, handling, and management.

The Draft Guidance demonstrates the FDA's support of more widespread use of DCTs. At the same time, the Agency acknowledges that DCTs can be challenging to implement successfully, including because DCTs require coordination of trial activities with numerous parties in multiple locations that are not traditional trial sites. The Draft Guidance also notes that if significant safety risks emerge due to remote administration or use of an IP, or if other circumstances arise that warrant in-person visits, the sponsor should discontinue remote administration or use of the IP, inform the FDA, IRB, and investigators, and determine whether the trial should be amended or continue.

Interested stakeholders may submit comments on the Draft Guidance by August 1, 2023 to Docket **FDA-2022-D-2870**.

Contact the authors or another Goodwin FDA team member with any questions or if you would like to submit comments to the FDA on the Draft Guidance.

FDA's Final Q&A Guidance on Risk-Based Monitoring of Clinical Trials Provides Additional Recommendations for Sponsors

The U.S. Food and Drug Administration (FDA) recently finalized its guidance, "***A Risk-Based Approach to Monitoring of Clinical Investigations***" (the "2023 RBM Guidance") which follows up on the Agency's March 2019 draft guidance (the "Draft Guidance") of the same name and expands on (but does not supersede) the FDA's August 2013 guidance, "***Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring***" (the "2013 RBM Guidance"), with new recommendations summarized below to aid sponsors in implementing an effective and efficient risk-based approach to monitoring both risks to participants and to data integrity throughout all stages of clinical investigations of human drug and biological products, medical devices, and combination products.

(1) Approach: Identify, assess and re-assess risks. Create a plan to manage, mitigate, and/or eliminate those risks, including those risks that are newly identified or may not have been anticipated.

- Risk assessments should inform clinical trial protocol design, investigational plans, and monitoring plans and should be reevaluated and revised throughout the investigation. The monitoring plan should be comprehensive in highlighting identified risks, even those less likely to occur but that could have a significant impact on trial quality or subject safety, and should note how risks will be managed, mitigated, or eliminated.
- Consider how easily detectable the identified risks are, and the severity and consequences of those risks to human subject welfare and data quality if not detected and addressed.
- Assess systemic risks, as well as site-specific risks, and consider whether site-specific risks have the potential to become systemic risks.
- Determine an approach to on-site monitoring visits by taking into account the risks identified and the complexity and intensity of a clinical investigation. Monitoring activities should evolve based on risks identified during trials and should be proportionate to the risks to participants' rights or safety or to data integrity.
- Implement a centralized monitoring approach to help minimize missing data and protocol deviations in real-time, such as through the use of electronic data capture systems.

- The risk assessment should guide how and to what extent source data verification (SDV) will be utilized during on-site monitoring visits.
- Establish processes to ensure appropriate blinding is maintained. Identify and monitor deviations which could result in unintentional unblinding.
- Be prepared during an FDA inspection to furnish documentation of the sponsor's initial risk assessment, if requested.

(2) Content: Components of the monitoring plan should help explain how the sponsor intends to address the risks that could affect the investigation.

- Include the following components (in addition to those recommended in the 2013 RBM Guidance) in the monitoring plan:
    - Overall investigation design, including blinding and randomization procedures and processes for confirming randomization is performed according to the protocol and investigational plan
    - Sample plan(s), including rationale for, and approach to, identifying the records and data that will be monitored
    - Description of particular issues that would trigger immediate escalation
    - Approach for assessing and addressing a site issue that could escalate into a systemic issue that may warrant protocol or investigation plan changes
- Reference other clinical investigation management plans in the monitoring plan rather than repeating the information in the current monitoring plan to avoid inconsistencies.

(3) Communicate: Promptly address and communicate monitoring results to the appropriate parties to mitigate and eliminate risk.

- Perform monitoring in accordance with the pre-established monitoring plan and address issues as the monitor identifies them, including escalation, if needed.
- Perform a root-cause analysis of issues and promptly implement corrective and preventive actions (CAPAs).
- Consider amendments or revisions to the protocol or the investigational plan.
- Communicate and document significant issues to the relevant parties involved at the sponsor and site level, which may also include institutional review boards, data monitoring committees, and/or regulatory agencies, such as the FDA.
- Provide reports of monitoring activities in a timely manner to the site and discuss the findings with the clinical investigator and site staff. Reports should follow the 2013 RBM Guidance.

While the FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations, there are no specifics on *how* sponsors are to conduct such monitoring. FDA's guidance provides helpful direction on clinical trial monitoring while recognizing that a monitoring approach should evolve over the course of a trial as risk assessments evolve. Sponsors with upcoming or ongoing clinical trials should consider FDA's recommendations in monitoring plan development and execution of monitoring activities throughout a trial.

Leveraging Investigator-Initiated Trials in Rare Disease Drug Development

Investigators interested in rare disease treatment development have the opportunity to approach drug and biologic developers to obtain investigational drug supply for trials in which the investigators, typically at academic institutions, act as sponsor-investigators. Similarly, companies open to extending their product development pipelines can look to investigator-initiated trials as a mechanism to better understand the overall safety profile for their product candidates while exploring the potential therapeutic utility of their product candidates in diseases where unmet medical needs remain. So often, those needs exist in rare diseases where populations are small and investment returns are difficult to project. Drug developers deciding whether to supply investigational products to sponsor-investigators looking to explore therapeutic potential in areas of their research interests should evaluate what level of involvement to exercise over the investigator-initiated trial. We highlight some of these considerations below.

Ultimately, drug developers hold the decision-making power over whether to allow investigator-initiated research for their product candidates. Thereafter, the contracting process around the setup of an investigator-initiated trial and clinical supply agreement provides drug developers the opportunity to negotiate their level of involvement in the research of their candidates. In negotiating the setup of investigator-initiated research supply, drug developers often balance their support of research into what are often unmet needs with limited company resources, limited supply that may be available and any potential risks that may flow from trial learnings in the proposed disease space. As an upside, investigator-initiated trials afford developers the opportunity to extend their research reach and product development pipelines, so any interest by investigators to conduct research with industry candidates warrants consideration.