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to Monitoring of Clinical Investigations***" (the "2023 RBM Guidance") which follows up on the Agency's March 2019 draft guidance (the "Draft Guidance") of the same name and expands on (but does not supersede) the FDA's August 2013 guidance, "***Oversight of Clinical Investigations – A Risk-Based Approach to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.

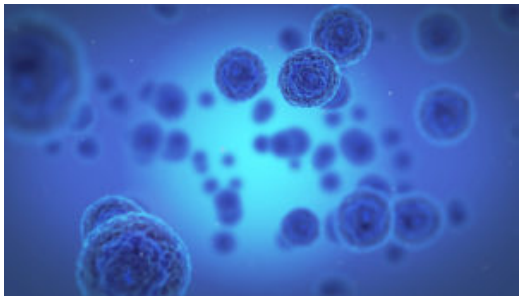
- Include the following components (in addition to those recommended in the 2013 RBM Guidance) in the monitoring plan:
    - Overall investigation design, including blinding and randomization procedures and processes for confirming randomization is performed according to the protocol and investigational 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.

The Long (Un)Winding Road Part 2: FDA's Final Transition Guidances for COVID-19 Devices



On March 24, 2023, the FDA's Center for Devices and Radiological Health announced the issuance of two much anticipated final guidances that describe the Agency's transition plans for medical devices that fall within certain COVID-19 enforcement policies or that were issued emergency use authorizations ("EUA"s):

- **Transition Plan for Medical Devices That Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency** (the "Enforcement Policies Final Guidance")
- **Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19)** (the "EUA Transition Final Guidance")

The guidances follow the announcement in early 2023 that the Biden Administration plans to wind-down a number of pandemic-related programs and to allow the COVID-19 public health emergency ("PHE") declaration, which has been in effect since January 2020, to expire on May 11, 2023.

We summarize some of the key takeaways from FDA's finalized transition plans. Read the client alert **here**.

US Artificial Intelligence Regulations: Watch List for 2023

Companies are developing, deploying, and interacting with artificial intelligence (AI) technologies more than ever. At Goodwin, we are keeping a close eye on any regulations that may affect companies operating in this cutting-edge space.

For companies operating in Europe, the landscape is governed by a number of in force and pending EU legislative acts, most notably the EU AI Act, which is expected to be passed later this year; it was covered in our prior client alert here: **EU Technology Regulation: Watch List for 2023 and**

Beyond. The United Kingdom has recently indicated that it may take a different approach, as discussed in our client alert on the proposed framework for AI regulation in the United Kingdom here: **Overview of the UK Government's AI White Paper**.

For companies operating in the United States, the landscape of AI regulation remains less clear. To date, there has been no serious consideration of a US analog to the EU AI Act or any sweeping federal legislation to govern the use of AI, nor is there any substantial state legislation in force (although there are state privacy laws that may extend to AI systems that process certain types of personal data).

Read the client alert **here**.

FDA Issues Guidance Document on Animal Studies for the Evaluation of Medical Devices

The U.S. Food and Drug Administration (FDA) recently issued **General Considerations for Animal Studies Intended to Evaluate Medical Devices – Guidance for Industry and Food and Drug Administration Staff (fda.gov)**. Following a 2015 draft guidance and replacing a 2010 guidance focused on animal studies for cardiovascular devices, this guidance document identifies general considerations for animal studies intended to provide evidence of safety, including performance and handling, in device premarket submissions "when a suitable alternative to an animal study is not available." Among other topics, the guidance provides recommendations related to personnel credentials, selecting an appropriate animal model, testing facility selection, and how to prepare an animal study report for premarket submissions to FDA. The Agency encourages sponsors with specific questions on an animal study, including the animal model selected, or compliance with FDA's Good Laboratory Practice (GLP) regulations, or who seek to use a non-animal testing method, to request feedback from FDA through the Q-Submission process.

Clinical Trial Diversity Plans and Rare Diseases

 Clinical trial diversity is not a new concept–the U.S. Food and Drug Administration (FDA) issued a **draft guidance** providing specific recommendations to industry on how to improve diversity in clinical trials in April 2022 which we blogged about **here**–but the passage of the Food and Drug Omnibus Reform Act, or FDORA, highlighted that the FDA will continue pushing sponsors to make progress on this front. Sponsors of rare disease trials, in particular, know that the act of *increasing* clinical trial diversity is not an easy undertaking, especially when working with already limited rare disease populations. However, the FDA's focus on ensuring diversity among trial participants may present new opportunities for designing and executing clinical trials in rare disease indications.

Under **FDORA**, sponsors of new investigational drugs will be required, unless waived by the FDA, to submit a "diversity action plan" for all Phase 3 clinical trials or, as appropriate, another pivotal study in support of a future marketing application (there is also a similar requirement for sponsors of medical devices where a trial is conducted under an investigational device exemption). Under FDORA, this plan is required to include the sponsor's goals for enrollment in the study, the rationale for those goals, and an explanation of how the sponsor intends to meet those goals. While FDORA requires these elements to be included and that FDA issue guidance on the form and format of diversity plans, FDORA does not expressly restrict a sponsor from providing additional information with its description of goals. For rare diseases, some education and background on the disease population may be warranted in submission of sponsor diversity plan goals.

Under FDORA, sponsors must submit their plan no later than when they submit their Phase 3 or other pivotal trial protocol, and the FDA has the authority to modify the plan or to waive the requirement for a plan altogether in certain circumstances, such as if conducting a clinical trial in accordance with a diversity action plan would otherwise be impracticable.

During FDA's Rare Disease Day 2023, agency officials noted that the FDA has long encouraged diversity, including through guidances issued prior to the April 2022 draft guidance, but the passage of FDORA marks the first time that addressing diversity with a prospective plan is a *requirement* in the development process. With that in mind, speakers pointed out that developing a candidate in a rare indication is all the more reason to develop a strategy to enroll as many eligible patients as possible.

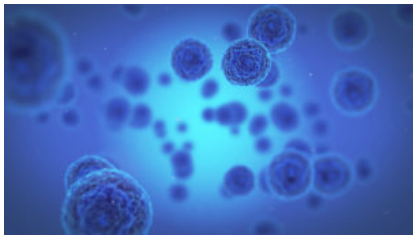
Sponsors in the rare disease space should consider the following strategies to increase diversity in their trials, where feasible:

- Engage advocacy groups and community health groups (early and often), as these groups

deeply understand their populations' specific barriers to research participation and the types of accommodations that should be considered when designing trials to minimize burdens and maximize participation;
- Create more inclusivity at the study design stage, such as by widening eligibility criteria, re-enrolling early phase participants in later phase studies, where possible, or conducting cross-over extension trials, which could make a significant difference in a patient's willingness to participate;
- Simplify the complexity of trials and minimize burdens to patients to participate, where possible, such as through the use of local laboratories for testing, or consolidating assessments to be done at a smaller number of in-person visits during the trial;
- Adopt as part of the trial design access to telemedicine and technology-driven solutions, which can help promote more inclusiveness with respect to socioeconomic, travel/location, and language barriers; and
- If using a contract research organization, or CRO, partner with a CRO, or other third-party vendor, that can demonstrate experience supporting and achieving diverse population enrollment and a community-first approach.

We anticipate that the FDA's specific recommendations for sponsors will continue to evolve, as FDORA requires the FDA to issue new draft guidance or update existing draft guidance within 12 months of the enactment of FDORA. At this stage, however, sponsors have an opportunity to propose creative and innovative approaches to designing, recruiting patients for, and conducting their Phase 3 and pivotal clinical trials, even in the rare disease space.

The Long (Un)Winding Road: FDA Maps Out How the End of the Public Health Emergency Will Impact its COVID-19 Policies



Since the beginning of the COVID-19 pandemic, the United States Food and Drug Administration ("FDA") has issued more than eighty (80) guidance documents describing flexibilities that would be available to manufacturers of medical devices, drugs and biological products, and foods during the public health emergency. Several of these guidance documents have been modified, updated, or withdrawn as circumstances have changed, and on March 13, 2023, the FDA issued a **notice** in the Federal Register that outlines how it intends to unwind a large swath of COVID-19-related guidance documents that are still in effect. FDA sorted seventy-two (72) COVID-19-related guidances into several categories, based on how long and in what form they will continue to be in effect after the expiration of the public health emergency declaration, which is expected on May 11, 2023.

Read the client alert **here**.

HHS to Create New Potential Medicare Pricing Models for Cell and Gene Therapy, Drugs Subject to Accelerated FDA Approval, and "High-Value" Generics

On February 14, 2023, the U.S. Department of Health and Human Services (HHS) published a **report** identifying three models that the Center for Medicare & Medicaid Services' (CMS) Center for Medicare & Medicaid Innovation (CMMI) will test to try to improve the affordability and accessibility of prescription drugs. The report responds to the state of prescription drug costs and access in America, as well as the widespread changes introduced by the Inflation Reduction Act of 2022 and President Biden's **Executive Order 14087** (October 2022), both intended to help lower prescription drug costs for Americans. The three selected models will test the feasibility of methods to: (i) offer generic prescription drugs at $2 or less for Medicare patients; (ii) reduce Medicaid costs for novel cell and gene therapies through outcomes-based agreements with manufacturers on a multistate level; and (iii) improve the safety and efficacy of drugs approved through the FDA's Accelerated Approval Program by aligning payment methods with stakeholders' incentives. More detail on these three models is expected, and Goodwin attorneys will continue to monitor for additional guidance and any opportunities for public comment.

Read the client alert **here**.

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.

340B Drug Pricing Program Reform Considerations

The 340B Drug Pricing Program is a government program, administered by the Health Resources and Services Administration (HRSA), that allows qualifying hospitals and clinics that treat low-income and uninsured patients to buy certain prescription drugs at a steep discount from drug manufacturers. Drug manufacturers participate in the 340B Program

as a condition of obtaining Medicaid coverage of their drugs. For the many drug manufacturers who want their products to reach the broadest patient population, participation in the 340B Program is essentially mandatory.

The program is intended to help safety-net health care providers' financial resources reach more financially vulnerable patients and deliver comprehensive services.[1] At the same time, drug manufacturers have concerns about the program:

- Manufacturers are concerned that deeply discounted prescription drugs should only go to covered entity patients and not diverted to individuals who are not covered entity patients, i.e., a practice commonly known as drug diversion.
- Manufacturers are concerned that the covered entities do not get both a deep Section 340B discount and any additional discounts and rebates under Medicaid, i.e., duplicate discounts.

Balancing the interests of covered entities and drug manufacturers has been a challenge, and one that has come under scrutiny in recent years. Drug manufacturers have no way of tracking how covered entities use the discounts paid under the Section 340B program, and there is no legal requirement for covered entities to pass the savings they received from manufacturers to patients.

There are four emerging areas of tension between the interests of covered entities and drug manufacturers related to the 340B program :

- Section 340B telemedicine standards and patient eligibility;
- Contract pharmacy utilization;
- Section 340B covered entity child sites; and
- Drug manufacturer audit limitations.

Until these four key areas are addressed, the Section 340B program will not serve its true goals; and drug manufacturers and covered entities will face increasing conflict over ambiguous and outdated regulations.

For more information regarding these controversies in the 340B Program, please see our recent Health Law360 and Life Sciences Law360 article, "**4 Key Issues Driving Drug Discount Abuse Must Be Addressed**" (Jan. 9, 2023) as well as our recent Goodwin Procter LLP client alert, **Federal Court of Appeals Rejects HHS Stance on Section 340B Contract Pharmacies** (Feb. 1, 2023).

[1] Health Resources & Servs. Admin., 340B Drug Pricing Program (Dec. 30, 2022).

Understanding Data Monitoring Committee Conflict of Interest Limitations

 For sponsors utilizing a data monitoring committee in their trial designs to monitor for emerging safety signals, lack of effect, and/or futility of treatment, understanding data monitoring committee conflict of interest limitations is important to ensuring an objective view of the data from a trial. Where we see these conflict of interest considerations put to the test most often is in rare disease trials where the available pool of informed experts can be just as small as the patient populations under study. As explained in FDA's final **guidance** for industry on this topic, core considerations for avoiding potential conflicts of interest in data monitoring committee member selection include:

- **Financial interests.** Here, careful consideration must be given to whether any prospective committee member holds ownership interests in the sponsor entity or stands in a position to benefit financially from the outcome of the trial. This can include equity or stock interests, employee or temporary employee status, paid consulting or advisory board relationships with the sponsor, prior research funding from an institution involved in the study, whose product is being evaluated in the study or competes with a product being evaluated in the study, among other things. FDA generally recommends against appointing any committee members with *ongoing* financial relationships to the trial's sponsor.

- **Other roles in the trial.** Those individuals entering subjects into and conducting a trial stand in a considerable conflict position given their knowledge of interim data emerging from subjects at their trial site which could influence the recruitment or monitoring trends of those individuals for the trial. As such, FDA generally recommends against appointing any committee member who is serving as an investigator in the trial the data monitoring committee would oversee. Additionally, FDA disfavors appointment of any members that have had input into the design of the trial or are involved in the conduct of the trial in any other role for similar reasons.

- **Intellectual conflicts.** Perhaps most challenging to evaluate and navigate in rare disease trials is the risk to objectivity that strongly held views of prospective data monitoring committee members could play in their ability to review the data in a fully objective manner. This could include prospective committee members with strong views on the relative merits of the intervention under study vs. others under development. Additionally, FDA recommends against appointing committee members with strong relationships to or personal differences with trial investigators or to sponsor employees which are likely to cloud their objectivity.

FDA recognizes the tension that sponsors must navigate between placing a high value on independence and avoidance of conflicts of interest in the composition of its data monitoring committees, on the one hand, and understanding the importance of a well-informed data monitoring committee to the effective oversight of emerging data from a trial, on the other. While there is no one-size-fits all approach, data monitoring committee charters and sponsor conflict of interest policies can be helpful in this regard to establish and document the sponsor's limitations on engagement and interaction with the committee and vice versa. The more interconnected the

sponsor-developer and investigator communities become, the more challenging it may become for sponsors, particularly those in the rare disease space, to ensure the objectivity of its data monitoring committees.