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The U.S. Food and Drug Administration (FDA) recently issued a draft guidance, "**Master Protocols for Drug and Biological Product Development**", that echoes and builds on principles that the Agency previously set forth in guidance for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 The draft guidance offers numerous (and at times *very* detailed) recommendations to facilitate the design, efficient analysis of data, and regulatory review of clinical trials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As a starting point, this draft guidance defines several key terms, including the types of trials that can be conducted under a master protocol: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 Here, we highlight some key design and analysis considerations addressed in the draft guidance: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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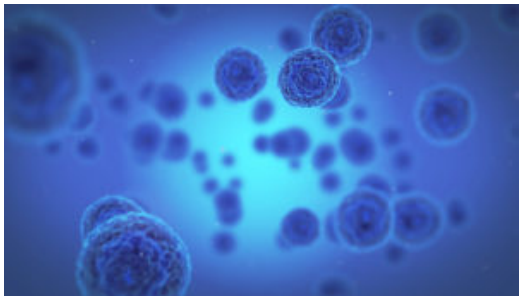
Comments on this draft guidance are due February 22, 2024. Please contact the authors or your Goodwin attorney with any questions or if you would like to submit a comment.

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



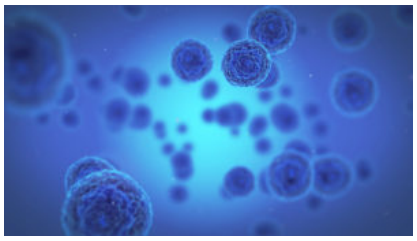
On March 24, 2023, the FDA's Center for Devices and Radiological Health announced the issuance of two much anticipated final guidances that describe the Agency's transition plans for medical devices that fall within certain COVID-19 enforcement policies or that were issued emergency use authorizations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

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**.

Potential AI/ML Learnings to Come from FDA Public Advisory Committee Meeting on Skin Lesion Analyzer Technology in Late July

 On July 28, 2022, the U.S. Food and Drug Administration (FDA) will hold a public advisory committee meeting to discuss skin lesion analyzer (SLA) technology and its application to detecting skin cancers in various patient care settings. This meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee will focus on algorithm-based SLA devices for adjunctive detection of skin lesions, including skin cancers, and stands to provide industry another layer of thinking on FDA's perspective on artificial intelligence and machine learning (AI/ML) device technologies.

In announcing this meeting, FDA explained that in recent years it has observed an increased interest in SLA devices employing AI/ML. The agency is seeking expert input from the panel on approaches to evaluate the performance of SLA devices, which have a range of technologies and indications.

The committee will discuss and provide recommendations to FDA on: (1) the diagnosing standard, or ground truth, that should be used as a comparison for the performance of diagnostic devices, e.g., histology, consensus opinion of a panel of dermatologists, opinion of a single dermatologist, or other means; (2) acceptable sensitivity and specificity thresholds based on the target diagnosis (melanoma, basal cell carcinoma, squamous cell carcinoma) or intended user (dermatologist, primary care physician, lay user); (3) patient characteristics, including lower or higher incidence populations, that should be tested before marketing; and (4) the balance of increased access with risk mitigation measures that are appropriate when the devices are used by lay people, by populations with very high or very low incidence of melanoma, by populations with low incidence, but high mortality associated with melanoma, or by the target diagnosis/lesion type.

Additionally, on July 29, 2022, the committee will discuss the possible reclassification of two class III, PMA approved computer-aided melanoma detection devices, MelaFind (P090012) and Nevisense (P150046), both of which are intended for use on cutaneous lesions suspicious for melanoma when a dermatologist chooses to obtain additional information when considering biopsy. According to the FDA announcement, "The committee will discuss if there is sufficient information to reclassify computer-aided devices for adjunctive diagnostic information of lesions suspicious for melanoma from class III to class II, and what special controls may be appropriate to provide reasonable

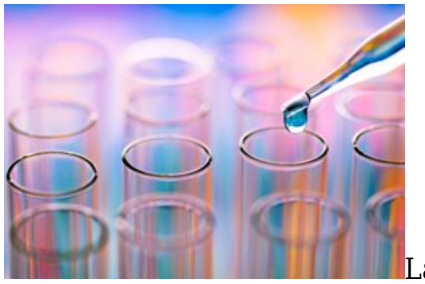
assurance of safety and effectiveness" if they are reclassified.

This meeting, and any actions the FDA takes as a result, could offer industry further insight into the FDA's approach to regulating AI/ML diagnostic and screening products more broadly.

The meeting will be held virtually on July 28, 2022, from 9 am to 5:45 pm ET and July 29, 2022, 9 am to 4 pm ET. Comments received on or before July 11, 2022 will be provided to the committee and the public docket will remain open for comment for FDA's consideration until August 29, 2022.

For more information see the **Meeting Notice on the Federal Register**.

Things for Pharma and Biotech Companies to Watch in the Cures 2.0 Proposed Legislation



Last week, Diana DeGette (D-CO) and Fred Upton (R-MI) introduced in the House highly anticipated bill language for "Cures 2.0", a follow-up to the transformational 21st Century Cures Act enacted in 2016. For full text of the bill, click **here**. The 21st Century Cures Act included a variety of measures seeking to accelerate medical product development and bring advancements and innovations to patients more efficiently. Cures 2.0 seeks to improve and expand on those strides, as well as address pressing public health priorities that became apparent through the COVID-19 pandemic.

The Cures 2.0 bill is structured around five main topics:

- Title I—Public Health
- Title II—Patients and Caregivers
- Title III—Food and Drug Administration
- Title IV—Centers for Medicare & Medicaid Services
- Title V—Research

While all of these sections are ripe for further analysis, we selected a few provisions to highlight here that may be of particular interest for the pharmaceutical and biotechnology companies out there. We'll keep tracking these as the bill moves through the legislative process:

Section 204: Patient Experience Data

- Would require sponsors developing a drug under an IND to collect standardized patient experience data during clinical trials and include that patient experience data "and such related data" in an NDA or BLA; and
- Would direct FDA to consider this patient experience data and "related information" in its approval decision for the NDA or BLA.

- These proposals to standardize and require patient experience data collection could be significant, and they underscore lawmakers' continued interest in elevating the relevance of clinical outcomes that are meaningful to patients living with a disease or condition.

Section 302: Grants for Novel Trial Designs and Other Innovations in Drug Development & **Section 310:** Recommendations to Decentralize Clinical Trials

- Section 302 would appropriate $25 million annually, for 3 years, for the FDA to award grants to clinical trials conducted under an IND with protocols incorporating complex adaptive or other novel trial designs and that collect patient experience data. The section further specifies that grant awards should prioritize the incorporation of digital health technologies and real world evidence.
- Section 310 proposes a multi-stakeholder meeting, including industry representatives and patient advocacy groups, to discuss incentives to adopt decentralized clinical trials. The section also would adopt a definition of decentralized trials: "a clinical trial method that includes the use of telemedicine or digital technologies to allow for the remote collection of clinical trial data from subjects, including in the home or office setting."
- These provisions reflect a sustained emphasis on fostering clinical trial innovation, including building on the experience with remote clinical trials during the COVID-19 pandemic.

Section 304: Increasing Use of Real World Evidence (RWE) & **Section 309:** Post-Approval Study Requirements for Accelerated Approval

- Section 304 would call for new guidance on the use of RWE in post-market review of drugs that were designated as a breakthrough therapy or fast track product, or considered for accelerated approval. Section 309 would further specify that the post-approval study requirements to verify and describe the clinical benefit for products granted accelerated approval could be satisfied through RWE, including analyses of data in clinical care repositories or patient registries.
- Section 304 also would establish a permanent Real World Evidence Task Force to coordinate programs and activities within the Department of Health and Human Services related to the collection and use of RWE.
- These and other sections of Cures 2.0 share a common theme of enhancing the use of RWE in regulatory decision-making. Although the inherent variability in RWE likely will continue to present challenges to doing so, the signal is clear that legislators would like to see FDA and HHS continue to move forward in this area.

Last week's introduction of Cures 2.0 and President Biden's announcement that he will nominate Robert Califf for FDA Commissioner contributed to a newsworthy week for those of us who follow the FDA. We look forward to seeing how Cures 2.0 develops and how the Agency's policy priorities unfold in the coming months.

FDA Issues Guiding Principles for Good Machine Learning Practice for Medical Device Development

On October 27, 2021, the U.S. Food and Drug Administration (FDA), Health Canada and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) **issued** a set of ten guiding principles meant to aid the development of Good Machine Learning Practice (GMLP).

Artificial intelligence and machine learning (AI/ML) offers the potential to analyze the vast amount of real-world data generated from health care every day to provide transformative insights. These insights can not only help improve individual product design and performance, but also hold the promise of transforming health care.

However, AI/ML technology has unique complexities and considerations. The goal of these guiding principles is to help promote safe, effective, and high-quality medical devices that use AI/ML to best cultivate the future of this rapidly progressing field.

Although not formal or binding, as companies continue to leverage AI/ML in their medical devices, they should remain mindful of each of the ten guiding principles:

1. **Leveraging Multi-Disciplinary Expertise Throughout the Total Product Life Cycle**

   Companies should leverage internal and external multi-disciplinary expertise to ensure they have a thorough understanding of the model's integration into the clinical workflow, and the desired benefits and associated patient risks, to ensure the safety and effectiveness of the device while serving clinically meaningful needs throughout the product lifecycle.

2. **Implementing Good Software Engineering and Security Practices**

   Companies should implement as part of model design data quality assurance, data management, good software engineering practices, and robust cybersecurity practices.

3. **Utilizing Clinical Study Participants and Data Sets that Are Representative of the Intended Patient Population**

   Companies should ensure that their data collection protocols have sufficient representation of relevant characteristics of the intended patient population, use, and measurement inputs in an adequate sample size in their clinical study and training and test datasets so that results can reasonably be generalized to the population of interest. Data collection protocols appropriate for the intended patient population may help to identify where the model may underperform and may mitigate bias.

4. **Keeping Training Sets and Test Sets Independent**

   Companies should consider and address all sources of dependence between the training and test datasets, including patient, data acquisition, and site factors to guarantee independence.

5. **Selecting Reference Datasets Based Upon Best Available Methods**

   Companies should use accepted, best available methods for developing a reference dataset, *i.e.*, a reference standard, to ensure clinically relevant and well characterized data are collected (and that the reference's limitations are understood). Where available, companies should use accepted reference datasets in model development and testing that promote and demonstrate model robustness and generalizability across the target population.

6. **Tailoring Model Design to the Available Data and Reflecting the Intended Use of the Device**

   Companies should have a solid understanding of the clinical benefits and risks related to the product and utilize this understanding to create clinically meaningful performance goals. Additionally, companies should ensure the model design is suited to the available data and supports active mitigation of the known risks.

7. **Focusing on the Performance of the Human-AI Team**

   Where the model has a human element, companies should consider human factors and human interpretability of the model outputs.

8. **Testing Demonstrates Device Performance during Clinically Relevant Conditions**

   Companies should develop statistically sound tests and execute them to assess device performance data independent of the training data set. Such assessment should be conducted in clinically relevant conditions with consideration given to the intended use population, important subgroups, clinical environment and use by the Human AI-Team, measurement inputs, and potential confounding factors.

9. **Providing Users Clear, Essential Information**

   Companies should provide users ready access to clear, contextually relevant information that is appropriate for the target audience. Such information includes not only information pertaining to the product's intended use and indications for use, performance of the model for appropriate subgroups, characteristics of the data used to train and test the model, acceptable inputs, known limitations, user interface interpretation, and clinical workflow integration of the model, but also users should be made aware of device modifications, updates from real-world performance monitoring, the basis for decision-making (when available), and a way to communicate product concerns to the company.

10. **Monitoring Deployed Models for Performance and Managing Re-Training Risks**

    Companies should deploy models that are capable of being monitored in real-world usage with a focus on maintaining or improving safety and performance. Further, when models are trained after deployment, companies should ensure there are appropriate controls in place to manage risks that may impact the safety and performance of the model.

FDA's expectations with respect to GMLP will continue to advance and become more granular as additional stakeholder input is considered. The docket for FDA's GMLP Guiding Principles, **FDA-2019-N-1185**, is open for public comment.

Visit the **Goodwin on Medtech hub** to stay informed on important developments affecting medtech innovators and investors.

Real-World Evidence: Challenges and Opportunities During COVID-19

The urgent needs of the COVID-19 pandemic have more squarely brought into focus the role real-world evidence (RWE) can play in analyzing and informing product development and clinical and public health decisions. Specifically, the U.S. Food and Drug Administration (FDA) is participating in the COVID-19 **Evidence Accelerator**, in partnership with Friends of Cancer Research and the Reagan-Udall Foundation, to bring leading experts together to share insights and use RWE to help answer the most pressing research questions raised by the pandemic.

The FDA believes that RWE can play an informative role in analyzing potential therapies, vaccines, and diagnostics for COVID-19. At the recent "Establishing a High-Quality Real-World Data Ecosystem" **workshop** hosted by the Duke Margolis Center for Health Policy, Amy Abernethy, the Principal Deputy Commissioner of Food and Drugs and Acting Chief Information Officer at the FDA, highlighted the work of the Evidence Accelerator initiative, noting that RWE allows the FDA to constantly update its understanding of COVID-19 and recurrently analyze data to address changing needs. Amongst the other presenters, the general discussion focused on the many hurdles industry needs to address to establish a robust and more accurate RWE data ecosystem, including efficient capture of reliable data at the source. While internet access, smartphones, and wearable technology enable consumers and patients to keep meticulous records of their biometric data, the vast amount of collected data does not necessarily lead to efficient or fruitful analysis currently. FDA noted during the workshop that, to be more insightful, RWE stakeholders must narrowly tailor their collection to what is actually useful and relevant to clinical endpoints, fit for purpose, rather than merely what is easily accessible. Eric Perakslis, a Rubenstein Fellow at Duke University, noted that stakeholders must balance the usefulness of RWE collection against the risk of over-surveillance for each data point collected. While not discussed during the workshop, collecting massive data sets must also be weighed against the ever-present risk of data breach. Finally, speakers also discussed patient-generated health data (PGHD) and the need for aligned stakeholders who are motivated to collect this data and understand the process for doing so, including a plan for handling outlier data which is unavoidable with PGHD.

In the context of the COVID-19 pandemic, RWE presents an opportunity for real-time learnings toward quicker identification and development of treatments and vaccines. As a result, the pandemic has only strengthened the importance of RWE in product development and, if deployed well, could

help support more efficient and expedited product development plans.

*Emily Tribulski, a 2020 summer associate in Goodwin's Washington, D.C. office, contributed to this post.