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Owen Faris, Ph.D.
Principal Deputy Director
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue, Room 1670
Silver Spring, MD 20993

Dear Owen:

On behalf of AdvaMed's members, thank you for proactively issuing the immediately in effect ***FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic.*** It provides important clarification on a number of challenges our companies are encountering as they conduct trials during the pandemic.

During a recent emergency call of AdvaMed's Clinical Trial Working Group and AdvaMed Accel division members, a number of additional challenges, as well as possible solutions, were discussed which the guidance did not completely address. We would like to engage in an immediate dialogue with FDA to determine whether FDA would consider additional flexibility along the lines of the proposals below. Under normal circumstances, our members would not be asking the FDA to consider many of the concepts below. However, many of our companies are facing extraordinary challenges related to COVID-19 and some of these proposals may enable sponsors to successfully maintain and support ongoing trials, protect the significant resources invested in these studies thus far, and ensure that the contributions already made by human subjects in affected trials are not lost. We are concerned that without additional flexibility, ongoing trials may have to be terminated. This will prevent important and innovative new medical devices from reaching patients and may mean many small companies will not survive. Data from subjects who are already enrolled and contributing to our knowledge might be lost or no longer valid.

We respectfully request your consideration of the following proposals[1]:

[1] The proposals included in this communication are intended as a catalyst for an immediate dialogue with FDA regarding the possibility of additional flexibility beyond what we believe is described in the COVID-19 guidance. On a longer-term basis, AdvaMed would like to engage in dialogue with FDA about the possibility of considering other options such as Conditional Approval with a follow-up or RWE study where appropriate, or automatic simple trials with broader populations and relaxed inclusion / exclusion criteria to capture key long-term follow-up issues.

General

- Will FDA allow companies to submit one comprehensive protocol deviation (PD) that encompasses all COVID-19 related protocol deviations in the study rather than submitting a separate protocol deviation for each element of the study?

- According to FDA's COVID-19 guidance, sponsors and investigators are encouraged to work with their institutional review boards (IRBs) to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants. It is unclear what FDA has delegated to IRBs in the guidance. Can IRBs go beyond what FDA expects of sponsors during this time? For example, a sponsor protocol states that an "Investigator must not make any changes or deviate from the protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred, or per prevailing local requirements, if sooner than five working days". This reflects the reporting requirement in 21 CFR 812.150 (4) Deviations from the investigational plan. In this example, can an IRB extend the reporting timeframe?

- Can FDA provide more detail regarding the threshold sponsors should use to determine when approval from FDA or an IRB should be sought prior to implementing a change or deviation (e.g., in study protocol, study monitoring plans, or internal Good Clinical Practice standard operating procedures (SOPs) related to good clinical practices)? There are a number of examples listed in the questions below that go toward this issue.

- Can sponsors enter PD for sites and have sites acknowledge the PD? This will allow for tracking the impact of COVID-19 in detailed analyses without undue burden on the site.

IVD Studies

- Can reproducibility testing be conducted at testing laboratories that are not focused on COVID-19 testing or internal testing sites in lieu of testing sites impacted by COVID-19?

Protocol Changes/Statistical Analysis Plans

The draft guidance indicates the sponsor should consider consulting with the applicable review division. Many members interpret "should consider" as a requirement to consult but review divisions may be overwhelmed with such requests. Responses to the following proposals would be helpful to provide companies with greater flexibility to move forward expeditiously to make changes.

- Can options such as retrospective review of electronic health records (EHRs), subject self-monitoring tools, and/or claims data be used to help fill COVID-19-caused data gaps in patient clinical trial records?[2]

- For studies that are in long-term follow-up that would normally require an in-person visit, will FDA consider allowing that to be done via telephone by clinic staff from sites and/or third parties and relaxing the narrow window for that visit? Long-term follow-up of serious adverse events would require careful evaluation.

- Can qualified third-parties partner with sites to remotely contact patients even though remote follow-up is not in the protocol? This will allow follow-up data to be gathered remotely without placing patients at undue risk or burdening the site.

- Since many subjects will miss visits during this time, will FDA consider relaxing the percentage requirements and windows for follow-up visits so long as enough critical long-term evaluations are made to assure safety? Labeling can clearly identify any residual unknowns.

- Can enrollment caps be increased to allow for the possibility of additional subject replacement? Subjects diagnosed with COVID-19, subjects who feel unsafe returning to the site due to COVID-19 concerns, elderly subject population with underlying health condition(s), subjects in self-quarantine or self-isolation, subjects in cities or states with local travel restrictions (e.g., shelter in place), subjects participating in hospital-based trials where the hospital has restricted unnecessary visits including clinical research or clinical researchers or coordinators who are at sites that have implemented restrictions on employee's ability to work at the site will all be prevented from or fail to attend follow-up visits and these would otherwise be deemed a study failure. This proposal would address this and similar scenarios.

- We understand that maintaining population safety is the key priority at this point. "Shelter in place" is being encouraged or mandated in more and more state and local jurisdictions. In order to provide additional time (specifically for any primary endpoint visit that may occur during the peak of COVID-19 outbreak estimated now to be between March 2020 and Summer 2020), can out-of-window visits be an option to extend follow-up timeframes? Similarly, could the duration for primary endpoint data collection be extended or could a new primary endpoint be included to extend the timeframe for data collection?

- Would FDA consider allowing retrospective use of fully de-identified RWE (real-world evidence) without IRB review (due to IRB focus on pandemic or life-supporting, life-

[2] These options could have the added benefit of helping to demonstrate the value and utility of Real World Evidence.

sustaining trial issues)? Using already collected de-identified data does not pose risks to human subjects and should be allowed to be used without IRB approval. Such data could be used to substitute for or supplement trials that are failing to enroll.

- Can sponsors develop web-based or phone-based data collection (e.g., for collection of PROs) in lieu of on-site visits if these are non-validated? Sponsors have considered delivery of written surveys however, in many instances there are no investigation personnel on site (due to requirements to work remotely) to Fedex/mail the survey to the patients. Some investigation site personnel have expressed support for these approaches.

- Can sites coordinate with subjects to visit local physicians and/or specialists where ECG, physical exams or other relevant tests can be performed and then transmit data to the investigation site via EHR or other modalities?

- Can adjudications be postponed since source documents are not readily available from Sites due to COVID-19? How should that be represented in Annual Reports?

- What is the guidance and timing for updating clintrials.gov? Given the fluidity of the situation and the many unknowns, it is not clear what the requirements are related to maintaining the website?

Monitoring

- Can EHRs and source documents (both paper and electronic) be monitored using screen-sharing technologies?

- Can unredacted source documents, electronic charts and/or medical record systems be reviewed using screen sharing technologies? In this scenario, the sponsor monitor sees the same documents as they would during an on-site monitoring visit, and the records are not copied, nor do they leave the site.

- Can sponsors who were performing on-site monitoring convert to remote monitoring or risk-based monitoring with the potential to have more flexibility on redaction?

- Will FDA consider working with the Health and Human Services Office of Civil Rights to allow for scanning of source documents or sharing of source documents via a portal? Some investigational sites have opposed this due to HIPAA concerns and the need for additional subject consent.

- Is it acceptable to use video sharing technologies like Zoom, Facetime, Skype, Teams or other to Source Document Verification (SDV) for redacted or unredacted data (e.g. Informed consent document, Informed consent process, Regulatory binder documents, etc.)?

- Is it acceptable to receive redacted source document via e-mail/fax etc. with the intent of remote SDV?

Control of Product

- May sponsors ship certain clinical trial materials directly to patients (e.g., approved meters and strips, and perhaps even investigational supplies) to reduce the impact of subjects not being able to come to the investigational site. Companies could work with the site to obtain patient consent for such activities.

- May sponsors offer at-home visits (arranged through investigational staff) for subjects with medical devices that must be adjusted per protocol? Subjects would have to approve entry into the home and sponsor staff would use appropriate PPE (personal protective equipment) while interacting with the subject.

In closing, we sincerely appreciate FDA's consideration of these proposals. Please don't hesitate to contact me if you have additional questions.

Sincerely,

/s/

Tara Federici
Vice President, Technology and Regulatory Affairs
AdvaMed