Trinity Health

December 12, 2022

Robert Califf, Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Re: FDA-2019-N-2175; Institutional Review Boards; Cooperative Research

Submitted electronically via http://www.regulations.gov

Dear Dr. Califf,

Trinity Health appreciates the opportunity to comment on the proposed rule and questions included in FDA-2019-N-2175. Trinity Health agrees with the FDA's goal of reducing barriers and eliminating redundancies, as discussed in the preamble of this proposed rule. However, we have concerns regarding the proposal to move to a single Institutional Review Board (IRB) review for FDA regulated clinical trials. Our comments and recommendations reflect our position that local IRB reviews are critical to the conduct of research and protection of research participants, and to move to a single IRB review will be detrimental to research participants and the overall conduct of research.

Trinity Health is one of the largest not-for-profit, Catholic health care systems in the nation. It is a family of 123,000 colleagues and more than 26,000 physicians and clinicians caring for diverse communities across 26 states. Nationally recognized for care and experience, the Trinity Health system includes 88 hospitals, 135 continuing care locations, the second largest PACE program in the country, 136 urgent care locations and many other health and well-being services. Trinity Health has 15 medical groups with 1,324 primary care providers and 4,193 specialty care providers. Based in Livonia, Michigan, its annual operating revenue is $21.5 billion with $1.4 billion returned to its communities in the form of charity care and other community benefit programs.

Trinity Health has 17 Clinically Integrated Networks (CINs) that are accountable for approximately 2 million lives across the country through alternative payment models. Our health care system participates in 14 markets with Medicare Shared Savings Program (MSSP) Accountable Care Organizations (ACOs), which includes eleven markets partnering in one national MSSP Enhanced Track ACO, Trinity Health Integrated Care. All of these markets participated in the "enhanced track", which qualifies as an advanced alternative payment model (AAPM). Two of the 14 markets also participate in CPC+. In addition, we have had 33 hospitals participating in the Bundled Payments for Care Improvement Advanced (BPCIA) initiative, and three hospitals in the Comprehensive Care for Joint Replacement (CJR) program. Our work—and experience in value-based contracting—also extends beyond Medicare as illustrated by our participation in 123 non-CMS APM contracts.

FDA regulated clinical trials are typically conducted to determine safety and efficacy. These trials are not typically considered minimal risk research. These types of trials are interventional in nature and typically have many significant risks associated with the effort. It is the position of Trinity Health that the proposed rule is taking the local oversight of significant risk research and placing it in the hands of a single IRB that will not have any local association whatsoever.

Conflict of interest in research

The proposed rule does not provide guidelines for how a single IRB will be selected. The FDA stated in the proposed rule that to stand up a single central IRB like what the National Institutes of Health/National Cancer Institute has done for oncology trials would be detrimental and out of the scope for the FDA to manage and oversee. Instead, the proposed rule infers that the sponsor (in this case, the drug company) will be able to select an IRB for its drug/device trial based on its own internal business criteria. One can expect these IRB selections will be commercial IRBs for hire, what the industry calls "for profit commercial IRBs".

The very essence of the sponsor selecting and contracting with an IRB is a conflict of interest. That is, the sponsor will select an IRB and that will have the appearance of bias and supports its business interests.

Trinity Health believes that having a single IRB that is not 'local' puts the sponsor ahead of the participant. Research participants will not understand that this shift to a single IRB removes any local jurisdiction oversight, placing that oversight squarely on a for profit company contracted by the sponsor for services rendered, with no connections to the local community. If participants have a question and contact the IRB noted within the consent document, they will be calling an IRB that has no local connections of any kind, no understanding of the local community, and no understanding of the local culture of the research participant.

Human subject protections

The preamble states, "…. site specific, local IRB reviews of such a protocol would not be likely to provide additional human subject protections beyond those provided by a single IRB with appropriate expertise to evaluate the risks and benefits of the study, the adequacy of the informed consent process and document, and local issues." (section II.E, page 58756).

Trinity Health strongly believes local IRB reviews *do* play a critical role in ensuring human subject protections. Over the years, our local IRBs have experienced numerous times how a central/single IRB has missed or overlooked critical aspects of protocol review; had the local IRB not reviewed the protocol and simply allowed the central/single IRB's approval to stand, research participants would not have been protected in accordance with FDA regulations.

One very recent example: A *Phase II* randomized placebo-controlled test article trial recently reviewed at a local IRB meeting revealed that it **did not contain any data monitoring or adequate provision of any kind to ensure the safety of research participants.** In addition, neither the protocol nor the Investigator's Brochure contained any previous outcomes or findings from Phase I trials, so the IRB could not make any rendering regarding the risk benefit ratio to potential research participants. It is critical to note this protocol was reviewed and approved by a central/commercial IRB (for profit) prior to coming to the local IRB. **Had the**

local IRB not reviewed this trial, these errors would have been overlooked and the local research participants placed at undue risk for participating in the trial.

In addition, local IRB reviews have noted that consent documents issued by central/single IRBs typically contain all the required elements; however, in many cases there is a lack of specificity in using lay language within the consent to satisfactorily address the purpose of the trial, explaining the nature/mechanism of the test article, and why a participant was being asked to consider joining the trial. **Again, without local IRB review, these gaps, overlooked by the central / single IRB, would have occurred.**

Administrative burden

The preamble states, “a single IRB would provide FDA with a single focal point for an IRB inspection for a given investigation.” **If one of the underlying goals of the regulation is to reduce travel and inspection burden as it relates to FDA inspectional activity, we urge the FDA to consider other inspectional options or activities for IRBs that are less burdensome in lieu of finalizing the proposed rule**. For example, Sponsor Monitors now use remote tools developed just for this work.

It is Trinity Health’s position that the proposed rule will shift administrative burden to local principal investigators, research coordinators and research nurses. Those responsible for investigations will have to be familiar with multiple IRB submission formats, policies, and procedures for reporting to the single IRB for adverse event reporting, protocol deviations, and instances of non-compliance, as required. Further, local institutions/sites will have to address how to manage a process to adhere to “56.112 Review by institution”, as it states that an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. Therefore, while an external IRB has reviewed and approved the study, each local hospital/site will need to determine the most efficient way to approve or disapprove from an institutional perspective as local IRB reviews will no longer occur.

Unclear processes

The proposed rule does not address how Institutional Officials (IOs) will be notified per 56.109(e). Local IRBs communicate and inform the IOs through distribution of detailed IRB meeting minutes to make them aware of all ongoing research activity. In addition, IRB leadership meets routinely with IOs to better ensure that practice adheres to policy.

It is not clear how local sites will monitor their human subject protection program as FDA clinical trial review will be outside local purview. Local sites conduct research and sites that are conducting research have an FWA on file with a high-ranking local official signing as responsible for oversight of the conduct of research that is being performed. **We urge the FDA to clarify the following questions prior to finalizing the rule:**

- What will be the guidance on the interface that may be needed between an external IRB and a local IO?
- How will local institutions collect and assimilate all in the information from varied sources?
- How will external IRBs effectively monitor research at the various institutions and sites?

Also, local context assessment is performed only once, prior to IRB approval. **We urge the FDA to clarify the following questions prior to finalizing the rule:**

- How will a local research site monitor the Human Subject Protection Program effectively to ensure that local sites are provided necessary education, and training?
- How will a single IRB know if the physicians acting as a principal investigator or sub-investigators need to be credentialed for a particular procedure, especially if it is novel?
- Local context review occurs only at the initiation of the trial. What happens if the protocol methods change, or if the study consent has to be modified, and subsequently these changes affect local context?
- How will changes to the trial to be announced/shared with the Institutional Official, and what will be the process by which Institutional Officials that have ethical concerns on a trial can communicate this concern to the single IRB? Once this concern is raised, what process must the single IRB follow?

<u>Exceptions</u>

The proposed rule addresses two (2) exceptions; however, it does not address planned emergency research and single emergent use of a test article categories. While these are two very small categories in research, there is a significant local workload that occurs locally.

A recent example: the last planned emergency research study that we experienced was a trial on ‘out of hospital’ cardiac arrest, with more than 20 sites across several counties for the conduct of the community consultation. The IRB Chair, Compliance Director, and IRB Administrator spent many hours conducting and attending local community consultations within the various counties to meet the regulatory requirements.

We urge the FDA to clarify the following questions prior to finalizing the proposed rule:

- How will single IRB review occur, and how will IRB members of a single IRB assist in conducting local community consultations within the community or communities in which the research is being conducted (21 CFR 50.24)?
- How will a single IRB be a part of community consultation work effort, which can range from 5 to 25 sites?
- How does single IRB review effectively determine that the results of the community consultation have satisfactorily been addressed and vote to approve?

<u>Faster initiations of clinical investigations</u>

The preamble outlines increased efficiencies for the oversight of clinical trials may facilitate faster initiation of clinical trials for the development of new medical products to benefit the public health due to the reviews from multiple IRBs.

Trinity Health supports the rigor of examining the length of time it takes for an IRB to review and approve a trial, and notes there may be more activities contributing to delays in the conduct of clinical trials that can be addressed at an operational level (such as FDA guidance documents) other than IRB reviews.

Trinity Health’s IRB review metrics demonstrate that the local full board review turnaround times in 2021 were on average 19 days from submission to determination notification sent to PI. Our metrics are published annually to be transparent regarding our service level. Our expedited review times are published as well, and in 2021 we reviewed an average of 108 revisions for ongoing research, with an average of a five (5) day turnaround. In our experience, it is not unusual for the IRB to approve a trial, yet the trial will not start to recruit participants for months because of contract negotiations between institutions and the sponsors. Site notification processes as well as site training also takes time to conduct and must be completed prior to the initiation of a trial.

It is our extensive experience that the IRB will promptly review and approve a trial, however, the delay to initiate a trial occurs due to drawn out contract negotiations, protocol design changes, and structure of patient recruitment tactics.

We urge the FDA to provide guidance on other opportunities to streamline the drug development process in the U.S. that would bear more return on investment. Examples of recently issued FDA guidance addressed trial design opportunities entitled: *Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry* and *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry.*

<u>Impact on diversity and inclusion in research</u>

There is a justified, refreshed focus on diversity, inclusion and equity in this country. These issues are local and *require* a local lens in the conduct of research. Local governance bodies must reflect on local demographics, values, and needs of the local communities that are served. Trinity Health is concerned this cannot be accomplished through single IRB review. Our local IRB members live and work in our surrounding "communities" and cultural competency is paramount to who we are and how we approach health equity. Single IRB review will not have the ability to be locally connected to all possible clinical trial site locations. It is imperative now more than ever to have a pulse on local "norms" throughout trial conduct. **A single IRB review will dilute the meaningful efforts that have been established to bring down barriers in the name of health equity, diversity, and inclusion.**

<u>Conclusion</u>

Trinity Health appreciates the opportunity to comment on the proposed rule. If you have any questions on our comments, please feel free to contact me at jennifer.nading@trinity-health.org.

Sincerely,

/s/

Jennifer Nading
Director, Medicare and Medicaid Policy and Regulatory Affairs
Trinity Health