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Submitted Via: www.regulations.gov docket number HHS–OPHS–2015–0008

Subject: Comments regarding the NPRM changes to Section §__.114 (b) Cooperative research

Dear Dr. Menikoff:

On behalf of the Dana-Farber/Harvard Cancer Center (DF/HCC), I am writing to comment on the proposal to require mandated single IRB review for all cooperative research. I am a pediatric oncologist by training and I have been employed by the Dana-Farber Cancer Institute (DFCI), Office for Human Research Studies (OHRS) as a Medical Reviewer working closely with study teams on their IRB submissions for the past six years. I am also an IRB member of all of our IRBs and serve as the IRB Chair as necessary.

In my experience working with various research sponsors with varying review processes, including my experience with our reliance on the National Cancer Institute (NCI) Central IRB, I do not believe that a mandated Single IRB review for all cooperative research is a realistic option at this time. Mandated Single IRB review would create challenges both for investigators and institutions without uniform review and submission processes; and raises concerns regarding expertise in local issues and local populations. In addition, this rule presents significant problems for NCI-Designated Cancer Centers which have a mandated scientific review process prior to IRB review. This will be discussed in more detail later in this comment. If this rule is implemented, I would respectfully request that OHRP create an exception for NCI-Designated Cancer Centers due to the NCI's unique institutional scientific review requirements.

As a matter of background, the DFCI IRB functions as the Single IRB of record for the institutions that comprise the DF/HCC. All cancer-related research conducted by the following five Harvard clinical institutions falls under the jurisdiction of the DFCI IRB acting on behalf of the DF/HCC: Boston Children's Hospital; Beth Israel Deaconess Medical Center; Brigham and Women's Hospital; Dana-Farber Cancer Institute; and the

Massachusetts General Hospital. The DFCI OHRS is the office that oversees the DFCI IRB.

The NCI Cancer Center Support Grant (CCSG) guidelines require that each designated cancer center have a Protocol Review and Monitoring System (PRMS) which is responsible for the scientific review, monitoring, and oversight of cancer clinical trials. The OHRS also manages this scientific review process required by the CCSG. The CCSG guidelines require that the scientific review (done by committees) be complementary to IRB review and it must occur prior to IRB review. Significant scientific questions raised during the IRB review must go back for review by a scientific review committee, if that review has not already been conducted. Lastly, OHRS coordinates the implementation of cancer research studies at each of our relying sites (termed 'protocol activation').

Comments Regarding the Proposed Rule

Burden of Navigating Multiple IRBs

It is my belief that mandated Single IRB review would not decrease the burden for investigators but would in fact increase the burden in both the long and short term. Currently, an average oncology investigator will work with his local IRB and may be involved with multiple protocols, involving numerous sponsors and lead institutions. Under the proposed rule, she might have to deal with multiple unique Single IRBs, each with a wide variety of policies, procedures, forms, systems, and personnel. This would pose an unreasonable additional burden on the average oncology investigator to manage.

Specifically, IRBs have divergent policies regarding who can consent to research; what types of events need to be submitted for IRB review; how IND safety report review is managed, among other issues. In addition, many studies require data and safety monitoring which is institution specific and typically is done by a committee with a close relationship to the local IRB.

The lack of uniformity among reviewing IRBs would require investigators and institutions to navigate the submission and reporting requirements on a protocol-by-protocol basis. This will result in increased time and expense by the investigators and institutions conducting the research. Errors due to confusion about the requirements are to be expected. Such errors may result in delays in the review and implementation of research locally. They may also result in more serious issues if, for instance, procedures are not followed for reporting safety concerns.

An analysis of our consortium's protocol portfolio makes the magnitude of the unintended burden clear. DF/HCC is a large consortium with a significant number of research studies led by multiple research sponsors. In 2014 we had 260 unique sponsors of "cooperative research" defined in the proposed rule as projects that involve more than one institution. The average number of clinical studies led by each of our 271 investigators in 2014 was six. The tables below detail the protocols of a randomly-selected principal investigator. As depicted in these tables, the investigator has 50 protocols. There are currently two IRBs of record. Under the proposed regulations,

there would be a minimum of ten different IRBs of record. This is a conservative estimate, and assumes that industry sponsors would use the same central IRB for every study they sponsor and that NIH group sponsors use a central IRB such as the NCI CIRB. As a result, the investigator would need to work with at least an additional eight IRBs (ten in total), each with unique and complex requirements.

Mandated Single IRB review would not eliminate the challenges associated with multi-center trials. Rather, it would shift the burden from sponsors to investigators, who are less equipped to deal with these particular issues. On an institutional level, centralized systems will need to be developed and sustained in order to manage Single IRB reviews. Resources and personnel will need to be allocated in order to assist investigators and ensure that arrangements are appropriately made with external IRBs, taking into account the requirements and issues unique to each one. Again, administrative costs will not be eliminated but instead will simply be shifted. These increased costs and bureaucratic obstacles risk dramatically slowing down important research.

Table 1: Academic Oncology Principal Investigator: IRBs of Record

Using data from calendar year 2014, the following table represents the number of IRBs of record a moderately active academic Oncology PI utilized for the review of research under the current regulations: **Fifty trials, thirteen unique sponsors, and two IRBs of Record.**

Sponsor	# of Trials	IRB of Record
Industry 1	13	Institutional IRB
Industry 2	4	Institutional IRB
Industry 3	1	Institutional IRB
Industry 4	4	Institutional IRB
Industry 5	3	Institutional IRB
Industry 6	1	Institutional IRB
NIH / NCI Coop Group 1	2	Institutional IRB
NIH / NCI Coop Group 2	2	Institutional IRB
NIH / NCI Coop Group 3	2	Institutional IRB
NIH / NCI – CTEP 1	2	Institutional IRB
NIH / NCI – CTEP 2	1	NCI CIRB
Investigator Initiated	14	Institutional IRB
Foundation	1	Institutional IRB

Table 2: Academic Oncology Principal Investigator: Single IRB Requirement for Cooperative Research – IRBs of Record

Using the same 2014 data as used in Table 1, the following table represents the number of possible IRBs the same PI would potentially have to interact with if the requirement for Single IRB review is implemented as proposed in the NPRM: **Fifty trials, thirteen unique sponsors, and twenty-nine different IRBs of Record.**

Note: This table assumes each sponsor has the possibility of using a different Single IRB for each study they sponsor and that the NIH / NCI Sponsored trials all utilize the established NCI CIRB.

Sponsor	# of Trials	IRB of Record
Industry 1	13	Single IRBs 1 – 13
Industry 2	4	Single IRBs 14 – 17
Industry 3	1	Single IRB 18
Industry 4	4	Single IRBs 19 – 22
Industry 5	3	Single IRBs 23 – 25
Industry 6	1	Single IRB 26
NIH / NCI Coop Group 1	2	NCI CIRB
NIH / NCI Coop Group 2	2	NCI CIRB
NIH / NCI Coop Group 3	2	NCI CIRB
NIH / NCI CTEP 1	2	NCI CIRB
NIH / NCI CTEP 2	1	NCI CIRB
Investigator Initiated	14	Institutional IRB
Foundation	1	Single IRB 27

Duplication of Effort

In addition to the burden of navigating multiple IRB processes, mandated Single IRB review would not improve efficiency during the course of the overall protocol review and institutional implementation of the study. Rather, it would serve to duplicate reviews and could create new questions and issues without a local forum to readily address concerns. The relying institution would remain responsible for conducting institutional reviews including: HIPAA, conflict of interest, radiation safety, and bio-safety reviews, among others. Therefore, investigators would still be burdened with submitting protocols to their own local institutions, and local institutions would still need to perform extensive reviews. The IRB review itself is only one component of a much larger review process that includes many other interdependent components. Isolating only the IRB review itself would result in duplication of effort. Furthermore, it would result in questions regarding the role and responsibility of the institution versus the reviewing Single IRB.

Local Context

Importantly, safety evaluations are more effective, efficient, and meaningful when done in the local institution and in local context. Such issues as privacy, electronic record keeping, pharmacy and nursing procedures are all evaluated best in a setting that is

aware of institutional policies, practices, and institutional history. This also demands a strong local knowledge of a protocol. A mandated Single IRB model would not enable our institution to maintain the high and layered level of oversight currently employed.

Operational Issues: Experience Serving as a Central IRB and Working with a Central IRB

The DFCI IRB has experience both serving as a central IRB and working with an external central IRB. These experiences have afforded us with a unique perspective and understanding of the Single IRB review process and challenges.

DF/HCC Single IRB Review

The DFCI IRB functions as the Single IRB of record for the five clinical institutions that comprise the DF/HCC. The consortium institutions have worked through a variety of issues relating to divergent policies and systems. Several mechanisms and practices have enabled us to efficiently conduct and review research—but we are all geographically close to one another. First, institutions have all signed on to a uniform set of policies. Representatives of the institutions serve on a joint committee which meets in-person regularly to address any issues. Second, investigators from all institutions serve on the DFCI IRB, ensuring that the Board has the benefit of all perspectives and that there are members who can speak to questions or issues specific to an institution. Third, and perhaps most importantly, relationships among IRB members, departments, and investigators have been cultivated over many years across the institutions. Without these relationships and emphasis on the involvement of all institutions, the Single IRB review system would be unworkable even within our consortium.

NCI CIRB

Our institution utilizes the central IRB review process for NCI-funded studies. This has entailed implementing a separate and parallel structure as well as revisions to all of our IRB reliance agreements. Many questions have been raised regarding which submissions need to be sent to which IRB, as the NCI CIRB's review guidelines do not match up with our local SOPs. The DFCI IRB is still responsible for the review of adverse events, violations, and deviations that do not meet the NCI CIRBs reporting criteria. Additionally, when incorrect information has been found in study documents by IRB staff or other departments there have been significant delays in the implementation of a centrally reviewed study while our local IRB awaits the review of the revision by the central IRB.

Based on our institution's experience both serving as a central IRB and as working with the NCI CIRB, I anticipate a large number of operational issues that would require complex and costly infrastructure changes in order to safely and efficiently conduct and review research within a Single IRB framework.

Issues Unique to NCI-Designated Cancer Centers

For CTEP studies, the CCSG guidelines require only an administrative review for prioritization which is why Designated Cancer Centers can rely on the NCI CIRB for NCI CTEP studies. For investigator-initiated studies, or industry-sponsored studies that are multi-center studies, each individual Cancer Center must conduct its own scientific

review through a scientific review committee. The CCSG guidelines do not permit reliance on another Cancer Center's scientific review committee. Therefore, for both investigator-initiated and industry-sponsored cooperative studies where a Designated Cancer Center is a site, any protocol changes that are more than minor would have to undergo scientific review at that Cancer Center. In the case of a multi-site trial, the protocol would have to be returned for review by multiple scientific review committees at each relying institution. Additionally, there is a need for local continuing review and safety reporting and evaluation.

Because of the CCSG requirements, a mandated Single IRB model for collaborative research would result in duplicative work both for investigators and institutions. It may also create issues if the Single IRB review and the institution's scientific review are inconsistent with one another. Furthermore, it raises questions as to how a Single IRB would handle a situation where the scientific reviews from individual institutions are inconsistent with one another or where any one of the many scientific reviews is conditioned upon changes to the research requiring re-review and approval by the Single IRB.

Requested Revisions to the Proposed Rule

Based on the concerns outlined above, I propose the following measures be implemented if a Single IRB review system is required:

- *Limit Single IRB review to multi-site trials involving more than four sites*. The work involved in relying on another IRB and the benefits of such reliance decrease when there are fewer institutions involved. Institutions are free to voluntarily enter into such relationships where there are fewer than four sites.
- *Create exception for NCI-Designated Cancer Centers*. Because of the CCSG guidelines, requiring NCI-Designated Cancer Centers to rely on Single IRBs would result in duplicative work and would create complications with respect to scientific reviews. The specific requirements for NCI-Designated Cancer Centers create unique questions and concerns which would make a Single IRB review mandate unworkable.
- *Create an exception where the Institutional Official certifies that the participant population is a vulnerable population such that IRB review needs to remain with the local institution*.
- *Suspend implementation until HHS has identified a single technology that will be cost effective for all institutions; a submission system that will be uniform; and policies and procedures that will be standardized*. While the NPRM focuses on template reliance agreements specifically, our institution's concerns are not limited to contractual arrangements. Rather, our primary concerns are with the actual submission forms, processes, and policies. Provision of uniform documents and software would alleviate many of our concerns regarding the burden of Investigators navigating multiple IRB processes.

I appreciate the underlying rationale for moving towards a Single IRB mandate. However, I do not anticipate that it would improve efficiency, but rather expect that it would increase the burden for investigators and institutions. This burden would risk stifling research, and the added bureaucratic complexities would increase the probability for errors. If a Single IRB review model is required, I respectfully request that the concerns and suggestions articulated above be considered.

Sincerely,

Daniel Kronish MD

Daniel Kronish, MD