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OFFICE OF THE VICE PRESIDENT – RESEARCH AND INNOVATION

OFFICE OF THE PRESIDENT
1111 Franklin Street, 11th Floor
Oakland, California 94607-5200

Sent via https://www.regulations.gov/commenton/FDA-2021-N-0286-0001

December 20, 2022

Robert M. Califf, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
North Bethesda, MD 20852

RE: Docket No. FDA-2021-N-0286 for "Protection of Human Subjects and Institutional Review Boards" (September 28, 2022)

Dear Dr. Califf:

I write on behalf of the University of California (UC) system in regards to the Notice of Proposed Rulemaking (NPRM) titled "Protection of Human Subjects and Institutional Review Boards" published in the Federal Register on September 28, 2022.

The UC system is comprised of ten research-intensive campuses, six medical schools, and three affiliated U.S. Department of Energy national laboratories. As a system, UC receives approximately $7 billion annually of extramural awards to support research conducted throughout all UC locations, with nearly half of the funds supported through federal funding.[1]

We appreciate the work the Food and Drug Administration (FDA) undertook to harmonize its human subject protection regulations with the Federal Policy for the Protection of Human Subjects (Common Rule). UC asks that FDA take further steps to fully align with the Common Rule. Our specific comments are provided below.

I. New and Revised Definitions

The terms "identifiable private information" and "identifiable biospecimen" state that it pertains to information/biospecimens that may be readily ascertained by the *sponsor* or investigator. The inclusion of "sponsor" is a departure from the Common Rule definitions of these terms, and a direction that UC does not support. Given that sponsors obtain information from multiple studies across their organizations, it is possible that a sponsor would be more readily able to identify a

[1] University of California Accountability Report 2022: https://accountability.universityofcalifornia.edu/2022/chapters/chapter-9.html

subject from private information provided by an investigator than an investigator would. However, the Institutional Review Board (IRB) may not be aware of all of the information a sponsor has, and therefore the IRB would have to assume that all information could be readily identifiable. This in turn could make it difficult, if not impossible, to conduct certain types of studies where a waiver of the documentation of consent is needed in order to conduct the research.

In addition, the inclusion of "sponsor" in the terms "identifiable private information" and "identifiable biospecimen" may have an impact on future research. If a sponsor potentially has the ability to re-identify data in its possession, then most IRBs would likely determine that study participants would need to be informed through the informed consent process that their identifiable information could be used for future research without additional consent, which could have a chilling effect on participation. This is the opposite intent of both HHS and FDA in revising their rules as well as the purpose of the CURES Act. **UC strongly recommends that the FDA not include "sponsor" in the terms "identifiable private information" and "identifiable biospecimen," and instead fully align with the Common Rule on these terms.**

Lastly, in agreement with SACHRP and in order to harmonize this area of regulation among all parts of HHS, UC suggests that FDA clarify in regulation how in-vitro diagnostic research using leftover de-identified samples ought to be handled. FDA's investigational device exemption ("IDE") regulations define a "subject" to include individuals "on whom or on whose specimen an investigational device is used or as a control." FDA has interpreted this to include studies involving prospective collection of specimens and the use of leftover de-identified specimens. This is in contrast to the Common Rule, which would not consider research using leftover de-identified specimens to constitute research involving a human subject, given that such research does not involve intervention with a living human being or the use of identifiable private information or identifiable biospecimens.

II. Updated Informed Consent Requirements

The proposed new required element of informed consent at 21 CFR 50.25(a)(9) would require IRBs and investigators to inform prospective subjects through the consent process about future uses of their data. UC appreciates that FDA intends to align with spirit of the Common Rule requirement through a less prescriptive approach. In practice though, it is very likely that in order to reduce administrative burdens and simplify the process for investigators IRBs will encourage investigators to use one of the two Common Rule statements on future research. In addition, as mentioned above, if the terms "identifiable private information" and "identifiable biospecimen" maintain the inclusion of "sponsor" in the definitions, then it is unclear whether data collected can ever be considered to be truly "de-identified," or may discourage research subject participation in future research activities. While FDA has attempted to improve the language by making it more open ended, this does not outweigh the value of harmonization across the HHS and FDA consent regulations, in particular when possible future uses may be unknown at the time the present research is being developed. **As such, UC prefers that FDA fully harmonize with the Common Rule at 46.116(b)(9) and not introduce the new proposed regulatory language at 21 CFR 50.25(a)(9).**

III. Activities Preparatory to Research

FDA asked for public comment on the following: "We request comment on whether FDA's current policy adequately addresses screening, recruiting, or determining eligibility for an FDA-regulated clinical investigation, or if including the revised Common Rule provision at 45 CFR 46.116(g) would be useful for FDA-regulated clinical investigations."

UC recommends that FDA adopt the Common Rule language at 46.116(g) and harmonize with HHS. While FDA may see the definition of "clinical investigation" as distinct from the Common Rule definition of "research," the processes involved in both activities (whether clinical investigation or research) overlap, especially in the beginning when an investigator is identifying potential subjects, contacting subjects and recruiting subjects. Adopting the Common Rule provision at 46.116(g) verbatim into the FDA regulations would not only help clarify FDA's position on the matter but would harmonize with HHS and HIPAA regarding activities preparatory to research.

IV. Waiver of Informed Consent Documentation

The FDA asked for comment on whether the waiver for documentation of informed consent criterion at §__.117(c)(1)(i) should be considered for inclusion in the FDA regulations at 21 CFR 56.109(c) and, if so, for examples of when this would be useful.

UC believes that FDA should adopt the waiver of documentation criterion at §__.117(c)(1)(i). Given FDA's interest in collecting more types of data as real-world evidence (RWE) about the products they regulate, such studies would employ one of two methodologies (survey or chart review) or possibly both. If an investigator would conduct a chart review, this study would likely receive a waiver of informed consent. However, if an investigator conducts a survey, the investigator would currently need to seek documented informed consent, unless the FDA adopts new exemption criterion. Requiring documented consent in our current digital age could be challenging given FDA's Part 11 signature requirements, especially for studies that likely present no more than minimal risk of harm to subjects and do not involve procedures for which written consent is normally required outside the research context.

V. IRB Continuing Review

The FDA stated that they are not considering adopting the Common Rule provision at §__.109(f)(i) to allow in certain circumstances to not maintain continuing review. We believe that continued IRB oversight of such studies would offer added human subject protection only to those studies in which there are ongoing interactions or interventions with the subjects of the study. **Therefore, UC recommends that FDA adopt the Common Rule provision at §__.109(f)(i) when there is no interaction or intervention with subjects.**

VI. Effective Date

The FDA has requested comment on the 180-day effective date proposal. UC believes that the changes FDA is proposing are significant and will take time for the regulated community to socialize changes, update policies and practices, and fully conform to the changes. **As such, UC recommends that the FDA provide a 365-day effective date from the date of publication of the Final Rule.**

The FDA has also requested comment on their approach to not enforce certain provisions of the proposed final rule on studies that were initially approved by an IRB prior to the proposed effective date. **UC agrees with this approach.**

If you have any questions concerning these comments, please contact me at agnes.balla@ucop.edu.

Sincerely,

Agnes Balla

Agnes Balla
Sr. Research Policy Manager
Research Policy Analysis and Coordination
University of California, Office of the President