Division of Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852


Dear Sir or Madam:

On behalf of AdvaMed, the Advanced Medical Technology Association, we are pleased to submit these comments in response to the Food and Drug Administration’s (FDA) proposed rule on Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations.

The Advanced Medical Technology Association (AdvaMed) is the world’s largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed has general and specific comments below.

GENERAL COMMENTS

HIPAA Related Issues

The proposed rule appropriately implements the requirements set forth in Section 3224 of the 21st Century Cures Act. Specifically,

SEC. 3024. INFORMED CONSEN T WAIVER OR ALTERATION FOR CLINICAL IN VESTIGATIONS.  
(a) DEVICES.—Section 520(g)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j(g)(3)) is amended—(1) in subparagraph (D), by striking “except where subject to such conditions as the Secretary may prescribe, the investigator” and inserting the following: “except where, subject to such conditions as the Secretary may prescribe—“(i) the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject; or ”(ii) the investigator”; and (2) in the matter following subparagraph (D), by striking “subparagraph (D)” and inserting “subparagraph (D)(ii)”.

February 13, 2019
As such, the informed consent document is utilized to inform potential subjects of the purpose of the research, its potential risks, benefits and obligations as well as the specific rights the subject has with respect to their participation. By signing the informed consent document, a subject attests to the fact that they have read and understand the document, have been allowed to ask any questions they may have and to provide their consent in the affirmative to participate in the research.

Most human subject research, however, is also subject to the Privacy Rule and its requirement to obtain the subject’s authorization for the use and disclosure of protected health information (PHI). Consequently, many investigators choose to combine the requirements of the Common Rule, 21 CFR part 50 and the Privacy Rule into a single document. This may be readily accomplished due to the fact that the Privacy Rule’s requirements are largely compatible with the Common Rule’s (and 21 CFR 50) informed consent elements.

Permitting an Institutional Review Board (IRB) to waive the requirement for Informed Consent for research within the scope of this proposed rule does not necessarily remove the requirement for obtaining subject authorization as specified in the Privacy Rule. We suggest the FDA provide clarification or advisory text for Sponsors, Investigators and IRBs to carefully consider the specific data elements to be collected as part of the research in order to determine the applicability of HIPAA Privacy Rule requirements. While retrospective collection of anonymized data or research on anonymized biospecimens obtained in a previous research study, would not typically require consent under the Privacy Rule, many low-risk, retrospective, post-market clinical follow-up studies may require collection of PHI and, therefore, may still require subject authorization under the Privacy Rule.

Finally, FDA should consider working with U.S. Department of Health and Human Services (HHS) to determine the potential impact of the multiple consent requirements in the Common Rule, 21 CFR 50 and the Privacy Rule on the collection and use of real-world evidence (RWE). Consideration might also be given to development of guidance for IRBs on when privacy requirements apply. We recommend that FDA and HHS work to harmonize these requirements in the future.

Need for Clarification on the Term Impracticable

Although this proposed rule suggests an easing of the regulatory requirements for minimal risk clinical trials, in practicality, it will be of very limited applicability because of the requirement in §50.22(c) which states that a prerequisite for the waiver of informed consent is that “the clinical investigation could not practicably be carried out without the waiver….”. FDA endorses the interpretation of italicized language that HHS gives in its interpretation of the identical language in the Common Rule from which it is drawn, namely, that “the emphasis … is that it is impracticable to perform the research, and not just impracticable to obtain consent”. This effectively means that obtaining the subjects’ consent would only be impracticable if the scientific validity of the study would be compromised by asking the subjects to consent.
We recommend that FDA revise or clarify in the preamble or other accompanying text to the final rule that one of the objectives of the proposed regulatory change is to provide IRB’s with the latitude to allow a sponsor to obtain access to and utilize data and/or biospecimens that have already been collected without having to obtain informed consent. Inclusion of examples would help IRB’s understand that they have the flexibility to make real-world assessments of whether the research would be rendered impractical because of the unavailability of subjects to give new individual consents.

**Examples of Minimal Risk Research**

The ability to use existing data for future research has been generally encouraged by FDA in its real-world evidence (RWE) initiative. Examples include: allowing a sponsor to pursue minimum risk studies that involve previously collected subject biospecimens and/or data from prior studies, with the safeguard that subjects’ personal data must remain protected from public disclosure; retrospective or prospective use of de-identified subject data collected in registries (e.g., nested studies supplementing registry data); use of de-identified electronic health record (EHR), claims or provider data in real-world evidence (RWE) analyses such as those being piloted by the Medical Device Innovation Consortium (MDIC) National Evaluation System for Health Technology Coordinating Committee (NESTcc); and studies using residual de-identified biospecimens collected during routine clinical practice. The NESTcc pilot projects are demonstrating that combining data from registries, insurers, etc. provides more complete data and information on patient outcomes. For example, patients that drop out of a registry can be followed through payer data providing important information on device survivorship.

HHS itself appeared to acknowledge such latitude in recommendations made by the Secretary’s Advisory Committee on Human Research Protections (SACHRP) where it was noted that scientific validity might be compromised if consent were required where:

“The subjects for whom records would be reviewed are no longer followed and may be lost to follow-up. For example, the proportion of individuals likely to have relocated or died may be a significant percentage of the subject population and the research results may not be meaningful and lose statistical power.”

The SACHRP recommendation appears to address the situation where a sometimes long-closed study contains records of patients who may no longer be able to be contacted to provide their consent to the new research.

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1 From Subpart A Subcommittee, SACHRP (HHS Secretary’s Advisory Committee on Human Research Protections) “Recommendations Regarding the Provisions for Waiver or Alteration of the Informed Consent Requirements Under Department of Health and Human Services (HHS) Regulations at 45 CFR 46.116(d)”
Last, in the preamble to the final rule, we recommend that FDA make a clear statement that consent can be waived, or elements be modified, for post approval studies (including registries) where all that is being done is the collection of anonymized standard of care data from the patient’s medical records.

**Use of Left Over De-Identified Biospecimens**

The ability of sponsors to use leftover human biospecimens that are not individually identifiable without informed consent has been long-recognized by the FDA, most notably in their 2006 guidance, entitled “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.” This long-standing policy also includes specimens obtained from specimen repositories and specimens previously collected for other unrelated research, if those specimens are not individually identifiable. While the proposed rule does include clear intent for IRBs to decide whether or not to waive informed consent in certain minimal risk clinical investigations, the current proposed changes to parts 50 and 812 do not adequately and clearly address waivers of informed consent on the grounds that the specimens used in the study are not identifiable and/or that they are remnants of human specimens collected for routine analysis.

Therefore we suggest that the proposed changes to the new Section 50.22 of the proposed rule reference FDA’s long-standing de-identified biospecimen policy, especially the key elements of Section 4 of the 2006 guidance and clarify that IRBs may waive the requirement to obtain informed consent if they determine the study is exempt from IDE regulation per 21 CFR 812.2 (c) (3), reviewed by an IRB per 21 CFR 56, and any specimens or remnants of specimens used for the study are leftover from routine clinical care or unrelated research or are obtained from specimen repositories and are not individually identifiable, or the study meets the requirements described in the proposed 50.22 (a) through (d). This clarification language could be incorporated as new subsections to Sec. 50.22 (a). The language we suggest is consistent with FDA’s long-standing policy and thus should be non-controversial. We suggest language as follows:

(a) The clinical investigation involves no more than minimal risk to the subjects. Such investigations include, but are not limited to:

- investigations that are exempt from IDE regulation and have been reviewed by an IRB,
- the investigational testing uses only remnants of biospecimens collected for routine clinical care or analysis that would have been discarded, leftover specimens that were previously collected for other research purposes, or specimens obtained from specimen repositories; and
- the identity of the subject of the biospecimen is not known to, and may not readily be ascertained by, the investigator or the sponsor
Specific Comments

Response to Invitation for Comment

Should the FDA adopt the fifth criteria from the Common Rule?

Response:

No, because it is not necessary. The fifth criteria, “if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format” could be considered a special subset of criteria 50.22 (c) and is therefore redundant.

In closing, thank you for this opportunity to provide our comments on the proposed rule on IRB waiver of informed consent for minimal risk clinical investigations. Please do not hesitate to contact me if you have any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs