Exclusion criteria explained

Part 4 of MESM's series on proposed federal research regulation amendments and the impacts on commericial sponsors and research organisations

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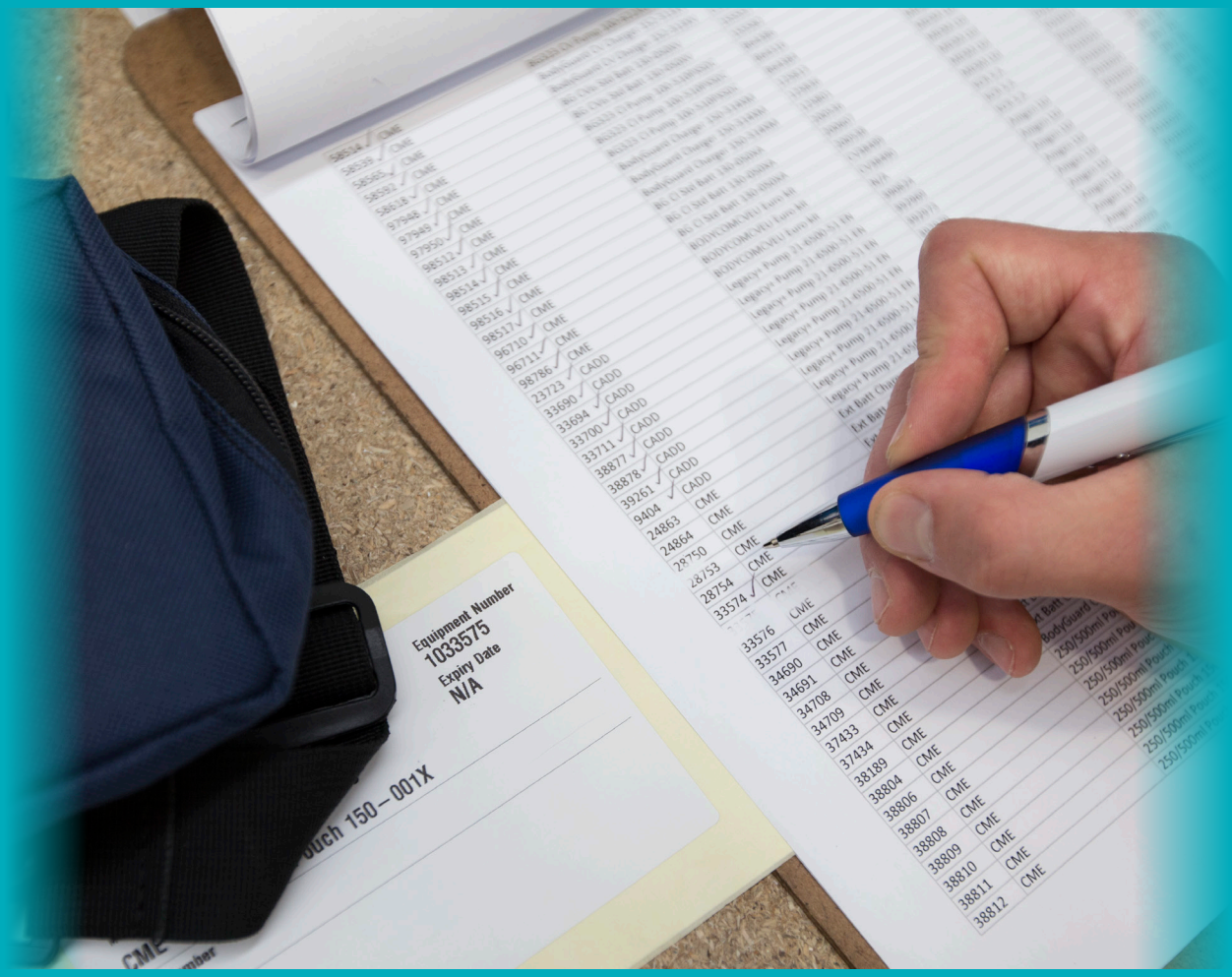

Introduction

In part one of this series, we introduced a broad overview of the proposals and proposed timelines for changes to the Common Rule of HHS Regulation (45 CFR 46, Subpart A) and the Notice of Proposed Rule Making (NPRM).

In part two, we discussed the reclassification of biospecimens as human subjects under the NPRM and the potential impacts of these proposed changes on clinical researchers.

In part three, we reviewed the proposed changes to informed consent and the potential impacts for life science companies and academic research institutions.

In this article we review what research may be excluded or exempted from the Common Rule, and consider the impacts of changes to independent review board (IRB) requirements, and amendments to requirements for continual review of clinical trials.

A number of research activities may be excluded or exempted from the changes.

Research excluded from the NPRM

Under the NPRM proposals, a new section has been created for regulation of research that would be excluded from the Common Rule.

Unlike exempt research, 'excluded' activities would not be required to undergo any institutional, administrative or IRB review to determine whether the activity is excluded; instead investigators would self-determine whether their research is excluded.

The following categories of activities, among others, would be considered 'excluded' under the NPRM:

Excluded category 1: Activities not considered as research

1. Certain internal program improvement activities

2. Certain oral history, journalism, biography, and historical scholarship activities

3. Criminal investigations

4. Certain quality assurance or improvement activities

5. Public health surveillance

6. Intelligence surveillance

Excluded category 2: Activities that are considered low-risk or where appropriate safeguards are already in place

1. Research involving educational, survey procedures, interview procedures or observation of public behaviour where there are no interventions

2. Research involving the collection or study of existing data, documents, records, pathological specimens

3. Certain federal government-conducted research using government generated / collected information obtained for non-research purposes

4. Certain research involving the use of protected health information regulated elsewhere under HIPAA

Excluded category 3: Activities that are low-risk and "do not meaningfully diminish subject autonomy"

1. Secondary research use of a non-identified biospecimen that is designed only to generate information about the person that is already known

2. The development of tests and some assays e.g. research to develop a diagnostic test using specimens from patients known to have or not have a specific condition, as well as quality assurance and control activities

Research excluded from the Common Rule

Exemption categories of research in the current Common Rule will continue under the NPRM as either exclusions or exemptions. However, the NPRM proposes that a voluntary 'exemption determination tool' will be made available that institutions can use to indicate whether a study qualifies for exemption or not.

In addition, other exemptions are proposed as follows:

1. Low-risk interventions subject only to documentation requirements

The NPRM introduces a new class of exempt research involving what are termed 'benign interventions'. These are those interventions classified as brief, harmless, not physically invasive, painless, and unlikely to have a lasting impact on research subjects.

This might include research where a subject is asked to read or review materials or perform cognitive tasks. The subject would have to prospectively agree to the research and data collection, and information would have to be recorded in such a way that the subjects could not be identified directly. Additionally, any disclosure of the subject's responses outside the research should not reasonably place the subject at risk of civil or criminal liability, or be potentially damaging to their financial standing, employment prospects, educational advancement or reputation.

2. Exemptions for research that may involve sensitive information that requires application of standards for information and biospecimen protection

This includes secondary research use of identifiable private information originally collected for non-research purposes if prior notice has been given to the subjects that such information may be used in research.

3. Exemptions for secondary research involving biospecimens and identifiable private information that requires application of privacy safeguards, broad consent, and limited IRB review

This exemption covers storing or maintaining biospecimens and identifiable private information for future unspecified secondary research studies, when a broad consent template (to be developed by the HHS) is used, information and biospecimen privacy safeguards are followed, and limited IRB approval of the consent process used is obtained.

Changes to IRB requirements for co-operative research

One of the most significant proposals of the NPRM is the mandate that only one IRB can act as the reviewing IRB for US sites taking part in a multi-centre study. The IRB of record will be selected by either the federal department or agency supporting the research, and for studies that have no funding agency, the lead institution conducting the research would be wholly responsible.

US sites taking part in multi-centre trials may soon need just one independent review board.

This requirement would not apply to:

a) cooperative research for which more than a single IRB review is required by law (e.g. FDA-regulated devices); or

b) research for which the federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for a particular study.

However, the NPRM clarifies that this proposal will not relieve any research site of its other regulatory obligations to protect human subjects. Although a local IRB may conduct its own internal review, such a review would not be binding on the local site if it was not subsequently adopted by the single IRB.

The NPRM also recognises that many institutions will have to implement policy and procedure changes to outsource ethics review to a single IRB of record. For this reason, the NPRM proposes that the requirement for a single IRB of record will not take effect until three years from publication of the final rule.

Potential impacts for clinical trials

It is likely that the use of single IRB review will develop into a general policy for all research carried out at an individual research institution and will become the required standard even for industry sponsored research.

Additionally, if the FDA does update its legislation to bring it in line with the NPRM Common Rule, it can be anticipated that the use of a single IRB for multi-site industry sponsored clinical trials will become standard. This could be a major benefit to life science companies, who have long advocated the use of a single lead IRB in industry sponsored trials. This would ease the administrative burden arising from dealing with multiple local IRBs at each study location.

Changes to requirements for continuing review of studies

The NPRM reports that continuing review of study protocols currently comprises 52% of all reviews carried out each year. The proposed rule aims to create additional regulatory flexibility by reducing the need for continuing reviews that do not meaningfully enhance protection of subjects.

Unless the reviewer documents why continuing review should continue to occur, the NPRM proposes to eliminate the requirement for continuing review both for minimal risk studies that undergo expedited review, and for studies that have completed their study interventions.

Continuing review will be waived when the study has reached:

a) a stage where researchers are either analysing data; or

b) researchers are only accessing data from observational follow-up in conjunction with standard clinical care for their medical condition or disease; or

c) both of the above.

The NRPM estimates that 90% of continuing reviews would no longer be needed, with estimated cost savings to research greater than $100 million.

The IRB of record will still require an annual confirmation that the research is ongoing, and that no changes have been made that would require the introduction of continuing review. However, this change does not alter reporting obligations of investigators with respect to changes of protocol and unanticipated problems.

Summary

The most important points to take away from this article are:

- While the proposed regulation changes will require greater levels of informed consent for research subjects, there are several types of research that will be exempt or excluded from these requirements.

- The wording of the Final Rule will clarify exactly which activities can be exempt or excluded, and resources to help identify how different research activities are affected will be provided by the regulatory authorities.

- One of the major expected benefits will be the requirement for a single independent review board in multi-centre studies – this will dramatically reduce administrative burdens (and associated costs) for research organisations.

- It is also likely that the requirements for continuing review of study protocols will be relaxed in cases where these reviews do not meaningfully enhance protection of subjects. This will also remove a significant administrative burden for researchers.

In part five of this series we summarise the key impacts of the proposed changes contained within the NPRM, and consider what life science companies should do next to prepare for changes once the Final Rule has been published.

Sources

U.S. Department of Health and Human Services. Notice of Proposed Rulemaking for Revisions to the Common Rule. Federal Register. 2015;80:53 933-4061. http://goo.gl/GOmByB

Impact of Proposed Federal Research Regulation Amendments (the Common Rule NPRM) on Life Sciences Companies – Bloomberg Law http://goo.gl/kLoLty

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