

DRAFT: Comments on Proposed Modification of the Common Rule by the Clinical Research Program of the Massachusetts General Hospital and its Clinical Investigative Community

Background and Source of This Response

The Massachusetts General Hospital Clinical Research Program is submitting comments concerning HHS's important proposed changes in the Common Rule designed to:

- a) improve its functionality;
- b) update the safety standards for participants in clinical research studies; and consequently
- c) preserve the public trust in the clinical research enterprise.

Our comments summarize the collective opinions of MGH clinical investigators voiced at several open meetings to which they were invited as well as serial surveys of our institution's clinical investigative community. This document provides general comments on key issues and a table of responses to issues presented at

<http://www.hhs.gov/ohrp/humansubjects/anprmchangetable.html>

The Clinical Research Program (CRP) of the Massachusetts General Hospital (MGH) was established 16 years ago to provide institutional infrastructure to MGH clinical investigators. Thus, our responses to these proposed changes to the Common Rule are independent from those provided by the Humans Research Committee (our IRB) which oversees human research and is responsible for compliance with the federal regulations. Rather, our comments reflect the unique perspective and broad interests of MGH's clinical investigators who are executing clinical research studies on a day-to-day basis. While our comments are in substantial agreement with the responses of the Partners Health Care System Human Research Committee, we believe that the perspectives of clinical researchers merit a separate consideration.

General Institutional Perspective of These Responses

Prior to specific comments that are attached below, we believe it important to understand four overarching contexts that have shaped these comments from the MGH's Clinical Research program.

The first is that our investigative community universally agrees that that the safety of all participants in human research is of paramount importance and hence our first overarching concern flows directly from this guiding principle. This principle is that the increasing regulatory burden of clinical research is diluting if not actually impeding the pursuit of this central goal of patient safety. **We strongly believe that efficiency is not the enemy of safety; rather it must be its constant partner.** We therefore endorse the proposed changes to provide clinical investigators relief from routine administrative demands that are not risk-based. Our clinical investigators heartily endorse the efforts to address regulatory inconsistencies, provide clear definitions, and attempt resolution of the various ambiguities of terminology which bedevil current regulatory and governmental interactions. We thus applaud the broad's reevaluation of the types of studies which can be Exempted/Excused from IRB review. We agree the local IRBs should be given discretion to assess the risks of a specific

study when assessing if it meets the minimal risk criteria and can then receive an expedited review. We also agree with carefully reexamining the need for subsequent annual reviews that are generally time-consuming and often wasteful of administrative effort.

A second broad concern is the unintended consequences of the increasing administrative burdens that are the collective consequence of layering on regulations not central to the safety of research studies. A poster child for this issue is the consent form that now routinely ranges to 20-25 pages. In addition, these consent forms are now being required for studies where the potential research risk may be minimal (e.g. research involving blood draws for within the parameters of clinical care) or somewhat more than minimal but not involving substantial risks. Their spiraling length is a direct result of legal and regulatory language that attempt to limit institutional/sponsor liability for injury and HIPAA information and now routinely appear without regard to whether their language is appropriate to a specific study. Consequently, few of our research subjects now take the time to read these lengthy documents. Thus, this is a well-intended regulatory process gone awry such that we are now in perfect compliance with all legal mandates but have thwarted the intended dialogue between investigator and patient addressing the specific risks of the research study. Relief is clearly needed. Proscribing a format and context would be welcomed by nearly all participants in the research process including the patients.

Third, mentors are daily witness to the chilling effect these rising regulatory burdens have upon young investigators beginning their research careers. All investigators, both young and old, report that the current regulatory burdens make the conduct of clinical research invariably more costly and often less efficient. As Dr. Elias Zerhouni observed when he was Director of the NIH: “When the cost of regulating an activity exceeds the cost of actually executing that activity, one has to wonder whether or not we are in an over-regulated environment.” Nearly all clinical researchers report having to add new personnel whose major role is to manage the process of regulatory compliance and not really participate in the study’s science. Continued recruitment of our nations’ best and brightest is essential if clinical research is to thrive nationally. Streamlining and harmonizing these regulations throughout government agencies as well as across academic/industrial partnerships will be key to making research more efficient and thus are essential to our nation’s future.

The final general point we believe to be a key contextual issue is the crucial need to rebalance the issue of individual subject safety as an absolute risk with the overall needs and benefits to our society of important research being conducted and facilitated. This issue is especially poignant in the consideration of requiring consents from all patients in biorepositories prior to the use of their sample. Here the issues of costs, protections, and practicalities of obtaining individual consents from either previously or prospectively collected but deidentified samples with the minimal individual risks to patients needs to be balanced with the fact that if such consents are required for all specimens, this regulation would almost certainly make certain type of biomarker research quite difficult.

As our population ages, healthcare costs associated with chronic and devastating diseases is impacting upon society’s ability to support other functions. As such, biorepositories will grow and electronic medical records will more widely adopted. Hence, useful biomarker research as well as clinical effectiveness and population research studies will present remarkable new opportunities to improve clinical care and reduce risk of ineffective treatments

with minimal risk to individual patients but substantial benefits to our populations. Such studies are dependent on the coordinated access to biological specimens and clinical data. Investigators thus strongly support HHS's support of common standards to protect health information but also to enable a freer use of such samples once collected as these represent substantial national investments in biomedical research that must be leveraged if we are to alleviate human suffering effectively. Thus, we believe HHS should update guidance to review committees which will encourage taking a closer look at the risk / benefit ratio direct benefit to the patients to a more global benefit to society in which case the efficiency and effectiveness of research become important considerations in the regulatory process.

Our specific comments on the individual HHS proposed changes are attached.

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Draft Responses: Submitted by the Massachusetts General Hospital’s Clinical Research Program (MGH CRP)

The MGH’s Clinical Research Program is not commenting on each of the nineteen issues presented by HHS at <http://www.hhs.gov/ohrp/humansubjects/anprmchangetable.html>. Rather, we are commenting on issues about which we have received comments from our clinical investigator community in a series of open meetings to which all clinical investigators within our institution were invited as well as email comments from those who were unable to attend.

The proposed changes to the Common Rule afford a unique opportunity to modernize and enhance protection of human subject research in a way that will maintain and potentially enhance public confidence and support for this vital enterprise as well as to reduce administrative burden on investigators and on IRBs. We endorse this enhanced focus on subject protection based on a realistic and balanced assessment of potential risks weighed in relation to the benefits to individuals and to society; national standards for data protections; allowing IRB discretion in establishing requirements for annual review of studies; and updating now and regularly assessing activities which may be deemed minimal risk and eligible for expedited review. Addressing inconsistent definitions and differing regulatory requirements that have arisen over the years will greatly benefit investigators and reduce inconsistencies among IRBs. We hope that HHS, as it has suggested, will assume leadership in this direction by providing templates for shortened consent forms and for providing updated guidances for investigators and IRB members to review and comment upon. These proposals collectively will serve to increase efficiencies.

While the advance notice is necessarily vague about some crucial details in several areas, we anticipate HHS will address them in the next notice of proposed rule making. These areas include:

- a) clarifying accountability when a single IRB of record is responsible for multicenter studies;
- b) local investigator versus institutional responsibility for investigator misjudgments in determining the excused status of a study; and
- c) sponsor vs. local investigator responsibility for assessing AEs/SAEs reported to a central database, etc.

The following are the issues we believe merit specific comments:

Issue 1:

Current: There are no specific data security protections for IRB-reviewed research: regulations require IRBs to determine, for each study, “when appropriate [that] there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.”

Proposed Change: Specified data security protections would apply to such research, calibrated to the level of identifiability of the information being collected.

Response: MGH CRP supports HHS's efforts at developing national data security and information protection standards and urges HHS to develop standards that resolve existing inconsistencies in definitions which appear in HIPAA and HHS regulations. IRBs whose institutions have already met these standards should have the discretion to determine when studies that rely on patient data can be granted Expedited Review and not require individual patient consent to use de-identified data/health information.

Issue 2:

Current: Research using existing biospecimens (clinical or from prior research) can be done without consent by stripping the specimens of identifiers.

Proposed Change: Reforms would require written consent for research use of biospecimens, even those that have been stripped of identifiers. Consent could be obtained using a standard, short form by which a person could provide open-ended consent for most research uses of a variety of biospecimens (such as all clinical specimens that might be collected at a particular hospital). This change would only apply to biospecimens collected after the effective date of the new rules.

Response: Our clinical investigative community is quite divided on this proposed change. Many do not support this change and urge HHS to carefully consider this proposed change in light of four different considerations:

- a) the known risk to persons from the use of unidentified specimens and data;
- b) the logistical complexities arising from accessing "grandfathered" databases;
- c) the difficulty in developing and managing institutional databases of persons who have consented and those who have declined the use of their tissue and data; and
- d) the significant technical challenges involved in obtaining patient consents in institutions where patients intersect with the healthcare system in a wide variety of hospital settings, community centers and practices.

With those practical considerations in mind, we agree that obtaining patient consent is crucial to maintaining public support of research.

On the other hand, those clinical researchers who favor this position point to the fact that most other international research communities in Europe and Asia have already migrated to this position. These communities have apparently solved these more global consent issues and have developed the abilities to track the patients who declined to participate and those who withdraw their tissue and data from the biobanks. Perhaps most persuasively, this global migration to the 'fully consented model' has now established a virtual international standard from which the US and Canada now deviate. These investigators point out that such adherence to these older standards will create substantial barriers for our country in fully engaging in the types of international collaborations which all consider essential for the future of clinical research.

Issue 3:

Current: Federal protections only apply to studies that are funded by certain federal agencies (Common Rule agencies), or to clinical investigations that involve products regulated by the FDA.

Proposed Change: Regulations would apply to all studies, regardless of funding source, that are conducted by a U.S. institution that receives some federal funding for human subjects research from a Common Rule agency.

Response: The MGH CRP agrees with the proposed change which will assist in making protections more uniform across the nation. Extending the Common Rule should only take place after proposed data protection standards to enhance subject protections, reducing the regulatory burden, and harmonizing definitions and reporting requirements have been adopted by HHS and the other Common Rule agencies.

Issue 4:

Current: Adverse events and unanticipated problems occurring in research are reported to multiple agencies and with various time-lines, with no central database as a repository for such data.

Proposed Change: A single web site would be created for the electronic reporting of all such events: this would meet all federal reporting requirements and the collected data would be stored in a single database. Reporting requirements would be harmonized across agencies.

Response: The MGH CRP agrees with the rationale that this reform would enhance the capacity to harness information quickly and efficiently and to identify and respond to risks from experimental interventions. In addition, it would decrease administrative burdens imposed by existing framework. The MGH CRP endorses the proposal to extend the existing NIH and FDA AE reporting system for gene-transfer studies to other studies. However, for this new AE reporting system to strengthen subject protection, the revised Common Rule should ultimately clarify that:

- 1.) the study sponsor is accountable for assessing the risks, amending protocols as necessary, and reporting risks to the IRB; and
- 2.) neither the IRB nor individual investigators participating in multicenter trials will be accountable or liable for making ongoing risk assessments.

Issue 5:

Current: The provisions of the Common Rule provide only basic information about the elements of informed consent and how consent documents should be written. Many consent

forms are too long and hard to understand, and fail to include some of the most important information.

Proposed change: The regulations would be revised to provide greater specificity about how consent forms should be written and what information they should contain. The goal would be consent forms that are shorter, more readily understood, less confusing, that contain all of the key information, and that can serve as an excellent aid to help someone make a good decision about whether to participate in a study.

Response: MGH CRP endorses this change and strongly urges HHS/OHRP to develop templates for shortened consent forms that are specific to a variety of studies (e.g. minimal risk studies which require subject consent; studies involving healthy persons undergoing interview or questionnaire studies, one-time blood collection for de-identified, cross-sectional studies; clinical effectiveness research studies randomizing persons to currently approved therapies for the purpose of assessing health outcomes; studies requiring full board IRB review involving non FDA approved drugs and/or devices). Enacting this change in the absence of HHS templates will place an additional new administrative burden on hundreds of IRBs across the country that will engage in a duplicative effort to develop shortened templates which will meet HHS/OHRP requirements. This effort would thus contradict the Executive Order 13563 of January 18, 2011: Improving Regulation and Regulatory Review.

Additionally, HHS/ OHRP should update its guidelines on information which can be presented to subjects in format other the research study consent form (i.e. research subject rights and responsibilities, HIPAA regulations; institutional and/or state responsibility for covering costs of injury arising out of participation in research.)

Issue 6:

Current: Each site in a study requires IRB review. Although the regulations allow one IRB to carry out the review for multiple sites, it is common for a single study conducted at multiple sites to have many IRBs separately reviewing the study.

Proposed: For all of the U.S. sites in a multi-site study, the changes propose a single IRB of record.

Response: The MGH CRP supports this proposed change. A single IRB of record will significantly lessen the regulatory burden on IRBs and on investigators not only for the initial review but over years of ongoing oversight and regulatory submissions. However before implementing this change the MGH CRP makes the following recommendations.

First , to deal a concern about “IRB shopping” (FR Question 34) and protect the integrity of the IRB review process, sponsors and PI-sponsors whose studies are governed by FDA regulations should supplement the IND/IDE application with a list of IRBs which have previously reviewed the protocol and supply all study documents and report the outcomes of each review. For studies which are not governed by FDA regulations, a report on the outcomes of each prior

review should be provided to the IRB selected to review the protocol and supporting documents. We believe this stipulation would address this issue.

Second, a mandate for a single IRB for multicenter studies should not be put in place until OHRP makes it clear that the central IRB of record will be accountable for noncompliance, not each site's local IRB. In addition, a mandate is not optimal. Sponsors should have the option of selecting investigators at study sites whose local IRB retains the right to review studies.

Third, since FDA regulations applicable to device studies link the local IRB to the parent institution, these FDA regulations would need to be revised prior to mandating or encouraging the use of a single IRB of record for multicenter studies.

Fourth, once the final regulations regarding a single IRB are put into effect, multicenter studies sponsored by NIH, DOD, AHRQ and other federal agencies should implement the single IRB of record by soliciting bids from AAHRPP-accredited IRBs to act as the IRB of record. The central IRB should be supported in same way as multicenter Cores support data analysis, Core laboratories, etc. IRBs at local sites whose investigators intend to accept a federal subcontract could then decide if it could accept the IRB of record's initial and continuing oversight of the study, and, if not, the reasons supporting the use of the local IRB. These reasons might include access to special and/or vulnerable patient populations, largely non English speaking populations, etc. If PI-sponsor for the multicenter study feels that these reasons are justified, the funding agency should have the option to allow local IRB review.

Fifth, we recognize that in addition to local IRB review of the protocol and study documents, institutions continue to require that investigators obtain administrative approvals from department chairs and administrative departments which support studies and offer valuable professional advice (e.g. IND pharmacy; radiation, biosafety, nursing review, etc.) before studies can be initiated. We do not think that these responsibilities will delay study start up for sites that can use a central IRB.

Issue 9:

Current: Research that requires review by a convened IRB requires continuing review at least annually.

Proposed change: Continuing review would generally not be required after all subjects in the study have completed all study interventions, and the only remaining procedures are standard-of-care procedures that are used to obtain follow-up clinical information (e.g., standard annual CT scans to detect any spread of the patient's cancer), and the analysis of the research data.

Response: MGH CRP supports this change to provide the local IRB discretion to apply continuing review to studies presenting risks to patients regardless of funding source. This will decrease the regulatory burden on IRBs and investigators without placing subjects at risk.

Issue 10:

Current: Research that poses minimal risk and includes only research activities in a list approved by the HHS Secretary is eligible to be reviewed in an “expedited” manner (e.g., with one reviewer, instead of a convened IRB).

Proposed change: This list would be updated now, and at regular intervals, using appropriate data about risks to the extent possible.

Response: MGH CRP supports this change and recommends that the list be updated every 2 years based on evidence of risk to subjects. We agree with examples of studies presenting minimal risk in FR Question 7 (allergy skin testing; skin punch biopsy (limited to 2 per protocol); additional biopsy during a clinical test; glucose testing among adults.) In addition, HHS should 1.) clarify current language “ordinarily encountered in daily life” and consider language which ties the risks to treatments patients routinely undergo for treatment of their medical condition, and 2.) clarify radiological dose levels in adults which would meet the minimal risk bar. Studies where the sole risk is potential “information risk/breach of confidentiality” should be treated at minimal risk where the institution has met the national standard for data protection and HIPAA policy is in place for its employees.

Issue 11:

Current: Research that is eligible for expedited review requires continuing review at least annually.

Proposed: Continuing review would not be required of studies that are eligible for expedited review unless the reviewer, at the time of initial review, determines that continuing review is required, and documents why.

Response: MGH CRP agrees with this change. This revision would give IRB’s discretion to assess level of risk so specific studies, reduce regulatory burden on IRB’s and investigators, and meets the intent of the Executive Order of January 18, 2011: Improving Regulation and Regulatory Review.

Issue 14:

Current: Six categories of studies qualify as “exempt” from the regulations, meaning that they do not have to comply with any of the requirements of the regulations. (CRP faculty see below)

Proposed change: These studies would no longer be fully exempt from the regulations. In particular, they would be subject to the new data security protections described above; and for some studies (e.g., those using biospecimens) new consent requirements would apply.

Response: the MGH CRP agrees that these 6 categories of studies should adhere to reasonable data security protections. The following should remain Exempt (under new terminology “Excused”) from the IRB regulations: survey procedures where no identifiers are collected, and specimens and data which are stripped of identifiers. These studies would be conducted under the new national data security standards. Since there are no linked subject identifiers, subjects will not be placed at risk. Therefore, these studies should still be considered “Exempt” from IRB review. These studies would be subject to “Registration.” by the investigator (see Issue 16, below.)

Issue 15:

Current: The categories of studies that qualify as “exempt” are not very clearly defined. As a result, it is sometimes difficult to determine whether a study qualifies as exempt.

Proposed change: The criteria for determining whether a study is exempt would be more clear-cut and less open to interpretation.

Response: The MGH CRP supports clarification of which studies are exempt. We suggest adding the following studies to the Exempt classification: local quality improvement and practice improvement projects that may include controlled allocation of an intervention versus usual care; clinical effectiveness and outcomes studies using de-identified clinical data sets; analysis of identified data using a minimum data set as specified by HIPAA, and tissue for analysis by investigators who have no interaction with the patients, or where tissue has been collected at another institution and institutional data use agreements apply. Since data will be de-identified and recorded according to HIPAA and other national standards for data security and patient protections, and institutions will have a clear HIPAA policy, there is no foreseeable increase in risk to subjects from the change in policy.

Issue 16:

Current: Although the regulations do not require administrative review before a study is determined to be exempt, most institutions follow current federal recommendations and carry out such an administrative review.

Proposed change: The recommendation that all such studies undergo administrative review would be eliminated. Researchers would file a brief “registration” form with their institution or IRB, and would be permitted to commence their research studies immediately after filing the form. Audits of a small percentage of studies would take place to ensure appropriate application of and compliance with the revised regulation.

Response: MGH CRP generally accepts this proposed change in concept and pending further clarification from HHS. HHS should:

- 1.) offer guidance on whether this Registration Form would be filed with the IRB or other institutional office,

- 2.) develop a template for the Registration Form which should contain a brief description of the study, and
- 3.) clarify the IRB will not be held liable for investigators who file Registration Forms and initiate non qualifying studies if they failed to seek the IRB's opinion about study's qualification.

Several investigators whose studies were deemed “not human subjects” following peer review have indicated their willingness to use a Registration form for future studies. Other investigators report that the IRB staff is a valuable resource since they are consistently up-to-date on the regulations. IRBs should continue to offer investigators the option to obtain administrative review as a service to our community. We agree that the institution's audit of a percent of these studies should suffice, but clarification is needed about who will do the audit and who will receive the results of such audits.

Issue 19:

Current: One of the six exempt categories applies to research involving the use of existing data, documents, records, and pathological or diagnostic specimens, but only if the sources are publicly available or if the information is recorded by researchers in such a manner that subjects cannot be identified, directly or through identifiers linked to them.

Change: HHS proposes eliminating the requirements that (1) all data or specimens must exist as of the time that the study commences, and (2) the researcher cannot record and retain information that identifies the subjects. If a researcher chooses to obtain and record identifiable information, subject consent would be needed, but would often have been obtained at the time that materials were collected by using a general, open-ended consent for future research. Rationale for the change is that the new data security protections will apply to these studies so there should be no need for these limitations (1) and (2) to apply.

Response: The detailed ANPRM makes it clear that going forward, with regard to pre-existing data (i.e., data previously collected other than for the proposed research study), if the data was originally collected for research purposes, then consent would be required regardless of whether the researcher obtains identifiers. Per the ANPRM “... the allowable current practice of telling the subjects, during the initial research consent, that the data they are providing will be used for one purpose, and then after stripping identifiers, allowing it to be used for a new purpose to which the subjects never consented, would not be allowed.” In particular, this means that if a study has been completed and consent to use the data for other later research purposes has not been obtained, it would not be permissible to analyze that data set for other research purposes. Unmodified, this proposal could have two major unintended and serious negative consequences:

First, it is a potentially disastrous blow for statistical methods development and dissemination. Real data sets offer both the most useful test-bed for developing and testing new methods, and are essential in illustrating relative strengths and limitations of newly proposed methods. If the proposed change is implemented, statisticians would only be able to develop, test, and disseminate new methods using data from studies in which prospective consent for this use was

obtained, even if the data are de-identified and there is no prospect of recovering information from the data set that would compromise the privacy of the subjects.

Second, "participation in a research study (such as a clinical trial) could not be conditioned on agreeing to allow future open-ended research using a biospecimen." No mention is made of other research data. Study sponsors (both commercial and investigator sponsors) could avoid the possibility of having their analyses subject to scrutiny by purposely omitting consent for later data use from their informed consent process. By not documenting open-ended consent to use de-identified data, investigators could invoke the Common Rule to prohibit any further of their data by others.

10-23-11

The Clinical Research Program has not commented on the following because we did not receive comments from our faculty.

Issue 7:

Current: Each Common Rule agency is authorized to issue its own guidance on how it interprets and implements human subject regulations. Standardize common rule regulations across federal agencies

Change: HHS would assess the differences and the agency's justification with intent of making guidances more uniform.

Issue 8: Current: Research involving more-than-minimal risk requires review by a convened IRB.

Issue 12: Current For a research study to be eligible for expedited review, an IRB member must determine that it is minimal risk.

Issue 13:

Current: For a research study to be approved, even if it qualifies for expedited review, the same approval criteria must be met as for studies that are approved by a convened IRB.

The ANPRM does not propose a specific change, but through questions seeks to determine whether some approval criteria do not meaningfully increase protections for subjects (i.e., in the case of studies that otherwise would qualify for expedited review).

Issue 17:

Current: One of the six exempt categories applies to research using educational tests, survey procedures, or observation of public behavior, but not if both (i) information is recorded in a way that allows subjects to be identified, and (ii) disclosure of the subjects' responses outside of the research could reasonably place subjects at risk of criminal or civil liability or cause damage to financial standing, reputation, or employability.

This exempt category would be broadened by eliminating criteria (i) and (ii) for studies that involve competent adults, i.e., such research would be exempt even if the information was recorded in an identifiable way and the disclosure could pose such risks to the subject.

Issue 18:

Currently, research studies in the social and behavioral sciences that do not qualify for exemption category 2, but that involve certain types of well-understood interactions with subjects (e.g., asking someone to watch a video and then conducting word association tests), require IRB review.

10-23-11

