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American Heart Association | American Stroke Association

October 26, 2011

Jerry Menikoff, MD, JD
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: HHS-OPHS-2011-0005

Dear Dr. Menikoff:

On behalf of the American Heart Association (AHA), its American Stroke Association (ASA) division and over 22 million AHA and ASA volunteers and supporters, we appreciate the opportunity to submit our comments in response to the advance notice of proposed rule-making (ANPRM) regarding the Common Rule.

The AHA is dedicated to building healthier lives, reducing death and disability from cardiovascular diseases and stroke, and addressing issues of access, quality, and cost from the patient's perspective. Although the United States has been successful in reducing death rates for coronary heart disease and stroke – the #1 and #3 leading causes of death in the United States – much work remains to be done.

Progress in addressing cardiovascular disease depends upon a broad, nationwide set of research efforts, and the participants who generously volunteer for that research. We are therefore extremely interested in the nation's system of protections for human research subjects, including the Common Rule and its implementation across federal agencies.

Overall, we would like to commend the Department for establishing a comprehensive process to review and update the Common Rule based on evolutions in the research landscape. We agree that it is critical to streamline the institutional review board (IRB) process where appropriate to stimulate research progress and use research dollars efficiently. At the same time, the rights of patients and of study participants must be vigilantly protected, not only by targeting review to higher-risk protocols, but also by ensuring that consent is truly informed, and by adequately protecting personal information.

Our primary concerns are detailed below. (Our specific responses to a select number of questions are included in Appendix A of this letter).

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AHA Supports the Use of One IRB of Record for Multi-Center Trials

AHA is supportive of mandating one IRB of record for domestic multi-site research studies. We believe this will save time and money, and potentially provide more robust enrollment. Furthermore, official recognition of one IRB of record would relieve local institutions of concerns about liability that currently lead many to conduct duplicative reviews.

We believe there are significant inefficiencies created by local IRB review of multi-site studies. The current system leads in some cases to 50 or even 100 separate reviews of the same protocol and consent form, with each IRB generating its own list of suggestions and issues for revision. This is followed by negotiation with each IRB, primarily by the site's Principal Investigator (PI) and overall study PI. When the protocol is already FDA approved, in most situations, any changes for a site generate an amendment to the FDA, after which the cycle begins again.

Designating one IRB of record for a multi-center study would address these problems. If the processes within the central IRB are robust, and its views and interpretations do not differ significantly from those of local institutions, we do not believe that the proposed changes create concern. We would suggest that HHS describe the central IRB process in a way that makes its processes and decisions transparent and consistent.

Experienced researchers on AHA scientific councils have commented that they do not typically see local site IRBs generate significant revisions to the consent or protocol. Rather, most often they request use of a local convention for expressing risk, or a similarly specific change. To allow for the inclusion of such viewpoints while streamlining the overall process, we would recommend giving local IRBs the opportunity to participate in the central IRB review and decision process when appropriate, such as when a specific protocol may intersect with local norms in a unique way.

We agree that it will be important to identify a consistent way of selecting the one IRB of record to avoid "IRB-shopping" or confusion. For NIH-funded studies, we believe the IRB could be the study PI's institution. For FDA studies, a possibility is for the FDA itself to establish a central IRB.

AHA Believes the Informed Consent Process Should be Streamlined While Keeping Participant Understanding Paramount

The AHA believes that, for the sake of participant comprehension, it is extremely important to streamline the informed consent process. In current research studies, the consent process can at times take as much as 3-4 hours, with many pages of documents that participants have to read through.

We recommend that the Department develop consistent language and tools that could be accessed online by researchers looking for "safe harbor" informed consent documents. These forms could offer clear, simple language on common items that appear in consent forms, such as explanations of HIPAA applicability, or descriptions of common side effects such as nausea. These forms should be adaptable to specific types of research and to appropriate reading levels for study populations. The National Institutes of Health, as well as the Association for the Accreditation of Human Research Protection Programs, would be appropriate entities to help develop language for these consent form templates.

An appropriately adapted consent form could then be distributed to study participants in innovative ways, for example with a mobile device, so that patients clearly understand the risks and nature of the study. HHS should also, as appropriate, explore and disseminate methods for determining if prospective participants have truly understood the information they have been given, instead of relying solely on a signature or initialed pages as reflecting informed consent. The Department should make clear when this level of assessment is appropriate or required.

AHA believes that streamlining and optimizing the informed consent process is important primarily because research participants who are overwhelmed by information are less likely to fully understand the nature of research to which they are agreeing. As an additional effect, streamlining is likely to reduce the amount of paperwork, time and money that researchers currently need to invest in the informed consent process. We believe that this will be an important positive effect for research. However, we urge HHS to keep the needs of participants paramount in developing protocols that streamline the consent process. We also note that attention should be paid not only to informed consent documents, but to the entire recruitment and consent process.

AHA Supports Enhanced and Standardized Protection of Participant Data

AHA strongly supports the enhanced and standardized protection of participant data across the range of research categories described in the proposal, including categories that will be exempt or "excused" from full IRB review. We believe that data should be de-identified according to clear protocols to minimize the risks of violations of participant privacy.

We are also aware of the burden that data privacy protection can place on researchers. Researchers are not all experts in information technology, and while they are familiar with the details of their type of data, they may not be familiar with all of the ways in which the data could potentially be compromised. We urge HHS to develop clear guidelines that put appropriate responsibility on researchers while recognizing that researchers are not technology specialists.

AHA Supports the Proposed Consent Process for Future Use of Biospecimens and Data

AHA supports the proposed development of a standardized, general consent form to permit future research on biospecimens and data. In the era of personalized medicine and genomics, more and more specimens and information are being collected for non-specified future research use. A standardized consent process that contemplates broad future uses would appropriately balance research flexibility with patient awareness and understanding.

We also urge HHS to establish requirements that maximize deidentification of data and biospecimens to the extent feasible. However, as the ANPRM notes, with DNA analysis, full "de-identification" is essentially impossible for biospecimens. This should be made clear to participants in the consent process. In addition, strict standards should be established to ensure that biospecimens are not in any way used for DNA analysis in the criminal justice system or in any other uses outside the scientific research arena.

We believe that any new consent rules should be applied prospectively, both to data and to biospecimens. For data and biospecimens provided prior to establishment of any new requirements,

we believe that if the patient gave informed consent for an initial study, then the data or specimens can be used again for another study in the future, *if and only if* the material is de-identified to the extent possible.

Conclusion

Thank you for the opportunity to comment on this important ANPRM on the Common Rule and human research subject protections. The topic's importance is matched by its complexity, and we look forward to reviewing more concrete proposals as the process moves forward.

If you have any questions or require any additional information, please contact Gayle R. Whitman, Senior Vice President of Science Operations, at 214-706-1168 or Gayle.R.Whitman@heart.org.

Sincerely,

Gordon F. Tomaselli, MD, FAHA
President
American Heart Association

SPECIFIC FEEDBACK ON PROPOSED CHANGES TO THE COMMON RULE

There are a number of significant changes being considered:

1. Establishing mandatory data security and info protection standards for identifiable info & rules protecting against the inappropriate re-identification of deidentified information that is collected or generated as part of a study to minimize informational risks and thereby eliminate the need for IRBs to review informational risks of the research. For purposes of the Common Rule, we are considering adopting the HIPAA standards regarding what constitutes individually identifiable information, a limited data set, and deidentified information, in order to harmonize these definitions and concepts. Since this provision would cover studies currently considered ''exempt'' from the current regulations, a change in terminology would need to be considered (see Section B(3), below).

   AHA RESPONSE: **AHA is supportive of the suggestion to develop mandatory standardized data protections rather than IRB review to protect against informational risks. We believe this would streamline the process both for the IRB and the investigators without sacrificing patient protection. The development of generalized biobanks will also streamline the process and provide significant benefit. Brevity and ease of completion should always be kept in mind.**

2. Revising the rules for continuing review. Continuing review would be eliminated for all minimal risk studies that undergo expedited review, unless the reviewer explicitly justifies why continuing review would enhance protection of research subjects. For studies initially reviewed by a convened IRB, continuing review would not be required, unless specifically mandated by the IRB, after the study reaches the stage where procedures are limited to either (i) analyzing data (even if it is identifiable), or (ii) accessing follow-up clinical data from procedures that subjects would undergo as part of standard care for their medical condition or disease (such as periodic CT scans to monitor whether the subjects' cancers have recurred or progressed).

   AHA RESPONSE: **AHA is supportive of the recommendation that continuing review would be eliminated for all minimal risk studies that undergo expedited review unless there is a justification to do otherwise. We also support that following a full convened IRB review, a continuing review is not required if the remaining activities are either data analysis or accessing follow up clinical data. We believe that this will further streamline the work of the IRB while still protecting patients.**

3. Revising the regulations regarding expedited review to provide for mandatory regular updating of the list of categories of research that may be reviewed under this mechanism, creating a presumption that studies utilizing only research activities that appear on that list are indeed minimal risk, and providing for streamlined document submission requirements for review.

   AHA RESPONSE: **We are also supportive of the three changes suggested in this area. (a) Your plan to update the 1998 list of the current research activities that are eligible for expedited review plus putting in a mandatory update from a federal panel at a minimum**

of every two years is very reasonable. This will prevent the variability that currently occurs between individual IRBs. Feedback on the list should be provided by the research community.

Additionally, we are in agreement that a study which includes only activities on this list is a minimal risk study and can qualify for expedited review. We are also in agreement with streamlining submission requirements to the IRB.

(b) We agree with the recommendation to eliminate and require no continuing reviews for studies that qualify for expedited reviews.

(c) We also agree that efforts should be made to streamline the documentation requirements for expedited reviews. The development of standard templates and consent forms would be most helpful.

4. Revising the regulations regarding studies currently considered exempt to, among other things: 1) Require that researchers file with the IRB a brief form (approx 1page) to register their exempt studies, but generally allow the research to commence after the filing; 2) Clarify that routine review by an IRB staff member or some other person of such minimal risk exempt studies is neither required nor even recommended; 3). Expand the current category 2 exemption (45 CFR 46.101(b)(2)) to include all studies involving educational tests, surveys, interviews, and similar procedures so long as the subjects are competent adults, without any further qualifications (but subject to the data security and information protection standards discussed above); 4) Add a new category for certain types of behavioral and social science research that goes beyond using only survey methodology, but nonetheless involves only specified minimal risk procedures, so long as the subjects are competent adults (but subject to the data security and information protection standards discussed above); 5) Expand the current category 4 exemption (regarding the collection or study of existing data, documents, records and biospecimens) (45 CFR 46.101(b)(4)) to include all secondary research use of identifiable data and biospecimens that have been collected for purposes other than the currently proposed research, provided that specified new consent requirements are satisfied. This expanded category 4 exemption would apply to the secondary use of identifiable data and biospecimens even if such data or biospecimens have not yet been collected at the time of the research proposal, and even if identifiers are retained by the researcher (instead of requiring at least expedited review, as is currently the case); and 6) Require random retrospective audits of a sample of exempt studies to assess whether the exemptions were being appropriately applied.

AHA RESPONSE:

(a) We are in agreement with revising the category of exempt research to an "excused" category.

(b) AHA is also supportive of the other specific aspects that will be changed in this excused category. These include:

- **The retention of the existing six exempt categories**
- **The review and revision of the current criteria**

- **The expansion of current categories. This includes the expansion of the exempt category. Specifically this revision states that research conducted with competent adults, that involve educational tests, surveys, focus groups , interviews and similar procedures would qualify for the new excused category, regardless of the nature of the information being collected, and regardless whether data is recorded in such a manner that subjects can be identified.**

(c) We are also supportive of including certain types of benign interventions on the excused study list which are relevant to social and behavioral research conducted on competent adults.

(d) Additionally, we are supportive of eliminating the limitations specified in the current exempt category 4 (research involving the use of existing information or bio-specimens).

(e) We support the development of a mechanism to track excused research and a small audit of a portion of that research.

5. Generally requiring written consent for research use of any biospecimens collected for clinical purposes after the effective date of the new rules (such as research with excess pathological specimens). Such consent could be obtained by use of a brief standard consent form agreeing to generally permit future research. This brief consent could be broad enough to cover all biospecimens to be collected related to a particular set of encounters with an institution (*e.g.* hospitalization) or even to any biospecimens to be collected at any time by that institution. These studies using biospecimens collected for clinical purposes would also fall under the expanded and revised exempt categories described in (4), above, and thus would not require IRB review or any routine administrative review but would be subject to the data security and information protection standards discussed above. This change would conform the rules for research use of clinically-collected biospecimens with the rules for biospecimens collected for research purposes. The general rule would be that a person needs to give consent, in writing, for research use of their biospecimens, though that consent need not be study-specific, and could cover open-ended future research.

***AHA RESPONSE*: Technology has already begun, and will continue, to make it easy to identify subjects from a wide range of materials and data including any number of "biologic" specimens such as cellular and molecular material, but also many other classes of data beyond typical "biospecimens" including facial or iris images, voice recordings, daily patterns of behavior, etc.**

Currently, many complicated systems have been developed to de-identify data. AHA is supportive of the development of Federal regulations to provide guidance to IRBs about what constitutes reasonable and safe use of all potentially identifiable materials and data based on balancing individual benefits of privacy and self-determination with the societal (and individual) benefits of advances in human health that could result from appropriate research using these types of materials and data. This could include the permitted uses of the data, as well as what constitutes appropriate safeguards to prevent the data from falling into the hands of someone who would use it for nefarious

purposes. Also, some legislative action similar to GINA to provide some consequences for anyone using these material and data for unapproved purposes would be helpful.

A human bio-specimen should be considered identifiable in and of itself. We also suggest that in addition to determining if specimens are identifiable, more guidance on how to make best use of these materials would be equally beneficial to the field.

We believe that both genome wide SNP analyses and whole genome sequences are identifiable.

Answers to some of the specific additional questions:

QUESTION 1: We feel that the current definition of "minimal risk" is appropriate. Making it more liberal would open it up to less subject protection, and making it less open would make research more problematic.

QUESTION 2: AHA supports that therapeutic interventional trials that qualify for an initial expedited review should however still undergo continuing review; anything that involves talking to a patient should undergo continuing review.

QUESTION 3: For research posing minimal risk, AHA does not believe that annual continuing review needs to be required if the remaining study activities only include those that could have been approved under expedited review. However, there is a caution to be made in this situation. It is critical to assure that no changes in the protocols or materials have occurred and that participants (especially those who are 'patients' and perhaps more vulnerable) be pressured or harassed for continuing participation.

QUESTION 4: AHA does <u>not</u> support changes in regulations that would indicate that IRB should only consider "reasonably foreseeable risks or discomfort". We feel that adverse events are sometimes hard to predict and often in the eye of the beholder.

QUESTION 5: AHA defers to psychological experts but offers these insights. It seems that even with the above rule passage, the guidance as to what needs to be submitted or reviewed by the committee will be vague. The risks incurred cannot be determined unless there is a full description of the population to be studied, the methods and instruments or procedures to be used with that specific population. Review by these by non-scientists sometimes provide jarring insight since the scientists' view is often hampered by the commonality of the questions that are used in their therapeutic practice daily. Lay review helps to provide reminders to them that these questions and procedures are not part of the therapeutic environment but are within a research context.

QUESTION 6: While there are parts of the proposed rule change that we believe will increase subject safety and decrease PI and commercial-sponsor burden, there are several

proposed changes that decrease the level of protection currently enjoyed by subjects in human research. Pre-review by persons with expertise in ethics as well as regulatory requirements seems imperative in order to ensure that busy, well-meaning experts do not miss or underestimate the effect that instruments or procedures they use routinely in treatment, or that they developed through the lens of an expert, may have on others naive to such approaches. There is no doubt that attention needs to be paid to questionnaires dealing with abuse, illegal behavior, emotionally traumatizing events (suicide of a loved one, etc). These would be classified by most IRBs as having a higher risk of triggering psychological pain than one would typically experience in daily life outside the study.

We are not aware of a list of questionnaires that may have this impact. In some cases the same questionnaire may be appropriate as a minimal risk instrument for one group and not for another. The age of subjects and study inclusion criteria, along with other factors helps the IRB determine this risk.

Additionally, because many surveys and interview instruments are developed by investigators as a result of their identification of areas where little knowledge on a topic already exists, it is very important to have some pre- review of these instruments before making a final risk determination. The rule changes do not address how a pre-review could be woven into the system and seem to indicate instead that if the investigator believes the study to meet minimal risk criteria and the research involves only survey or interview data, they may simply inform the IRB of the study and begin working with subjects. This rule change does not take into account the concerns on how investigators will know whether their instrument is really minimal risk, or that a certificate of confidentiality is needed to protect subjects from legal action, even if the data are stored in a sufficiently protective environment to adequately reduce breach of confidentiality.

Experienced investigators usually have a good understanding of these issues, but often IRBs point out potential risk to seasoned researchers that they had not considered. New investigators are almost always helped by IRB review of minimal risk research.

QUESTION 7: None of the items listed in AHA's view are minimal risk. Minimal risk items would be: routine lab work, chart review, talking to a patient, 6-minute walk.

QUESTION 8: AHA would support the identification of a specific level of background radiological exposure which could be identified as "minimal risk."

QUESTION 9: AHA suggests that the list of research activities that qualify for expedited review should be updated every 1-2 years.

QUESTION 11: AHA supports the concept that an appropriately trained manager from the individual IRB office (not a member of the IRB) would be an appropriate person to conduct an expedited review.

QUESTION 12: AHA believes that there are a number of changes that could be made to reduce the burden imposed on research staff in terms of the requirements to submit documents to the IRB without decreasing protection of subjects.

These include:
a. Consent forms are very long and tedious to read (especially for the potential research participant). IRBs require that several elements be included in the consent document. While all elements are useful, addressing them in a document can result in a 20+ page document. One could argue that the potential participant will not be able to comprehend nor retain the information in a document that is long and laborious to read.

b. Consent forms often contain redundant information. Sections within the consent form could be combined and redundant information removed. This might shorten the ICF while also making the ICF more clear to read for the participant.

c. This is especially true in minimal risk research – such as an epidemiology study or social science research. It should seem logical that less than minimal risk or minimal risk consent forms should be written more briefly than other ICFs. But this is not currently true.

d. One could argue that the true consent process is much more than the consent document and as such the consent process should be appropriately documented.

e. Another area where the burden of consent might be made easier would be to not require IRBs to obtain a witness signature and make this consistent across all IRBs. It is arguable if this adds to human subject protection. Some IRBs require this and some do not, depending on the institution's policy for requiring a witness signature. It seems that this should be a standardized requirement. If HHS made a clear statement that the witness signature was not required, IRBs should not require it and remove it from internal policies.

f. IRBs are required to show that they are adhering to federal regulations and thus have created an abundance of forms and paperwork to be submitted to get research approved at institutions (especially universities). Many IRBs are requiring this paperwork to also be in compliance with Association for the Accreditation of Human Subjects Protections Programs (AAHRPP) requirements for accreditation. There should be a detailed look at the paperwork required to make sure that what is required if really needed, and not duplicative, thus making the research process more burdensome.

g. More creative strategies to convey information should be developed by DHHS which can then be used by all investigators. Specifically, creating templates for on-line applications which can be shared on mobile devices with research subjects; use of self assessment questions (again on-line) which could really assess if a subject understood the purpose of the research and their risks (as opposed to having them sign 20 sheets with their initials) etc. These need to be developed by DHHS so that a research team could easily insert their relevant information in less than one hour and that a potential subject could read and respond to within 15 minutes. The tool would provide options for subjects to havethe option for one on one conversation with the research team if they desire.

While privacy and confidentiality is important, IRBs often require a section on how PHI will be used. This information can add several pages to consent forms using templates commonly provided by IRBs. Often these disclosures are at the end of the consent form. If so, potential subjects may be weary from reading the consent at this point and may not absorb the contents of this section. The HIPAA privacy language is often written in legalese language, potentially making the subject anxious about the entire study as written in the consent. DHHS should develop common user friendly language that all studies can use. Eliminate the subject initial on every page. This adds to the complexity and not sure there is evidence that this adds to protection.

IRBs are inconsistent in required documents as a general rule. University IRBs may have a more rigorous review process and require more documents while other community hospitals may not require the volume of documents that University IRBs do. It would seem that the required questions asked of some IRBs could be condensed with questions consolidated and still get the same result. The burden of filling out IRB paperwork falls on the study staff working for the investigator. For some IRB paperwork, this can take many hours or even days (including paperwork prep, and writing consent forms).

An information sheet could be provided to the subject along with the consent as a way of streamlining the information presented in the consent document. It could highlight the purpose of the study and the risks and benefits only. It could prompt the subject to read other sections for more detail if they wish or prompt them to ask for a discussion. Again electronic versions for the subject and the research team would facilitate communication.

We would suggest that DHHS invest in subject information tools. For example, thousands of subjects no doubt are told potential complications are nausea or numbness or tingling. If the tools were electronic, DHHS could develop a symptom / complication icon similar to WEB MDs graphic where one enters their symptoms and then are routed to a site describing what it is discussed. The research team could pre- selected the potential problems resulting from the research and their subject would see those highlighted. This would provide a common definition of some basic complications which are now explained

thousands of times by thousands of staff. It also assures that the explanations are clear in language and graphics. Only DHHS has the fiscal resources to produce this patient/ subject interface with understanding research.

Many universities have on-line programs researchers take to understand the research process. DHHS should investigate developing consumer friendly on-line programs which could be used to "certify" a subject took, understood and agreed to be involved in the research.

An organization such an AHHRP or perhaps the NIH might be appropriate for developing standardized language and templates.

QUESTION 13: We agree that periodic reports should be provided to the OHRP related to times that an IRB can override the defaults.

QUESTION 14: AHA supports doing away with concept of exempt; however there should still be caution with the excused category and the use of patients.

QUESTION 15: AHA suggests that the excused category could include: a) all studies with data access but no patient contact and b) use of stored specimens for additional studies.

QUESTION 16: AHA suggests caution in determining what 'emotionally charged' topics or questions are. "Emotionally charged" is in the eye of the beholder but perhaps suggesting small pilots with five subjects could help provide somewhat of an assessment of the impact and thus a minimum protect of future potential responders.

QUESTION 18: We do not believe this should be the responsibility of the IRB. Sharing clinical results with patients is and should remain the responsibility of the investigator.

QUESTION 19: AHA believes that research, even in the excused category, should not start until administrative approval from the IRB has been provided to the investigator.

QUESTION 20: We feel the term 'exempt' is better than 'excused.'

QUESTION 21: If excused studies can be executed without approval per se then this step of auditing should be mandatory.

QUESTION 22: The process should not be retrospective but rather prospective and easy to conduct.

QUESTION 23: Using information (data or specimens) already collected irrespective of reason should be allowed to be used again without contacting the patient and no further written consent is required. And exception might be research that a

significant segment of the population may object to, such as creating cell lines or reproductive research.

As pointed out earlier, it is reasonable to assume that with advances in technology there truly will be no data that can be de-identified. Thus, legislation such as GINA with heavy penalties for violation may be more appropriate.

QUESTION 24: We support the adoption of the HIPAA Privacy Rule language as it describes quite nicely QI activities.

We also support providing clarity that certain study designs are allowed e.g. cluster randomization. This is appropriate when a new intervention might be implemented in different ways at the same time in order to find the one that most cost-effectively improves outcomes for those patients. For example, there might be two ways to reduce the risk of central line infection, and it might make sense to try one method in the surgical ICU and the other in the Medical ICU. So long as you are not randomizing at the patient level, and you believe that each intervention will improve the outcomes for the patients based on existing evidence, then these should not require the informed consent of the patient. By contrast, any studies which randomly assign patients to different treatments, or which use blinding in treatment delivery, should not fall under the scope of exempt studies.

A further clarification would be whether or not the IRB needs to review the commonly used quality improvement activities to rule them as exempt/excused, or whether or not hospitals can simply do them and report them as such since this seems to take up a fair amount of IRB time as well.

We also support the use of an institutional or centralized IRB to review research proposals that are seeking to advance the general knowledge based on analyzing data that was collected under exemption but is now aggregated under one roof. This also has implications for more widespread use of large aggregates of quality data to support patient oriented outcomes research and effectiveness research.

It is unrealistic to differentiate between costs, systems assessment, etc. and QI and quality research. Any data used for QI or research purposes – if already present, should be waived for consent, even if used for publication (pending patient confidentiality of course) but if new data are collected for research specifically consent should be obtained.

QUESTION 28: AHA is supportive of this recommendation since at times proposals are reviewed by people who do not have the content expertise. It is impossible for an IRB to have expertise in every area. Thus the appeal process is a good idea. Each location has unique issues, so it would be best for the appeal to go through

another IRB within the same institution. If an institution has only one standing IRB, then there should be a special appeal IRB.

QUESTION 30 We are supportive of mandating one IRB of record for domestic multi-site research studies. We believe this will save time, costs and potentially provide more robust enrollment. We do not see any untoward effects unless specific institutional policies and perspectives are at odds with the universal IRB views.

QUESTION 31: All of these questions are theoretical possibilities but in real life applicable in a distinct minority of situations, especially if the processes within the central IRB are robust. Our suggestions is a) make the central IRB process detailed and b) given an option for the local institution to opt out but after participating in central IRB review and decision, on a one by one basis, as opposed to blanket non-participation

QUESTION 33: We believe there are significant inefficiencies created by local IRB review of multi-site studies. This provides in some cases 50 to 100 separate reviews of the same protocol and consent. Each generating their one list of suggestions and critical issues for revision. Then each must be negotiated with, primarily by the site PI and study PI. As the protocol is already FDA approved, in most situations, any changes for a site generate an amendment to the FDA. Then the cycle begins again. Experienced researchers comment that they have not seen any local site IRB generate a truly meaningful and important revision to the consent or protocol. Rather, most often they are almost always for a local convention for expressing risk or something else that is idiosyncratic. It would be important to assure that across state legal and regulatory concerns are aligned if DHHS movers in this direction.

QUESTION 34: For NIH-funded studies, we believe the one IRB of record could be the study PI's institution where the grant was awarded. For FDA studies, perhaps the FDA itself.

QUESTION 35: There are several factors that contribute to the excessive length and complexity of informed consent forms and following are the AHA's thoughts on how these factors might be addressed:

a) IRBs often require a lengthy explanation of what the study is about, asking for more detail than subjects can reasonably absorb, especially if the consent document is lengthy. Even if the language is written at an 8th grade level, potential subjects become weary when reading the consent form. The consent document may actually have a deterrent effect as the subject may feel overwhelmed with the document and either stop reading it, and then not participate because the consent sounds too ominous, or will sign prematurely without having a basic understanding of the consent.

b) The consent documents are often written in legal sounding language, rather than in plain everyday language that all persons can understand. Legal language often scares potential participants.
c) The HIPAA language within the consent document is often long and can take up several pages in the consent document. This should be shortened.

DHHS should provide common language that can be used in the legal and HIPAA sections. Using other mediums, such as audio, videos, self assessment questions might provide a more understandable explanation of the study and the issues that participants need clarity on.

QUESTION 36: The current standards are cumbersome but important and hence not much change is really necessary.

QUESTION 37: Modifications to the length of the consent form should aid in making the document more readable and understandable to the potential subject. In this way, this should enhance the quality of the consent document and process overall.

QUESTION 38: It would be helpful to be able to determine if the subject really understood what the study and consequences of a study are. It would be fine for the study team to be the ones to assess this as long as the assessment is objective e.g. quick self assessment test, assuring this is not onerous and that it is documented.

QUESTION 40: Many IRBs do require that a statement of disclosure of financial relationships be included in the consent document. This does seem appropriate so that subjects are informed about the researcher's interests.

The consent process should include a written narrative of the how the consenting process began and what the end result was. This would document the process ending with either signed written consent or the subject denying participation in the study.

QUESTIONS 41- 43: AHA would not favor oral consents. The current process of obtaining a waiver is important – even if it slows the process.

QUESTION 44: We believe any activity done for research purposes should go thru the IRB, even if exempt and reviewed by administrative staff and not committee. This helps investigators get their thoughts collected and also adhere to the rules.

QUESTION 45: It seems reasonable that patients/ subjects should have some control about their data; especially if it can be linked back to them. But if de-indentified data are used, then consent should be waived. It also seems reasonable that upon the original collection of data that the subject/ patient can be asked to allow his/her data to be used in the future.

For public education surveys there can simply be an opt out action provided.

QUESTION 46: If the material is de-identified and the patient gave original consent for data use for an initial study then the specimens can be used again for another study in the future. Societal good should over rule individual consent for future research with de-identified data or specimens.

QUESTION 47: If there are specimens that are de-identified from other types of surgery they can and should be used for other research.

QUESTION 48: Additional analysis of biospecimens should be allowed as long as they have been protected by standard privacy and HIPAA rules.

QUESTION 50: AHA feels it would be very difficult to provide a list of potential areas of research for subjects to choose from and indicate they would be interested in for future research. One suggestion would be to have a common portal where subjects could indicate their interest in future research. A portal more broadly marketed to the public so that the mystic of research is limited. Providing options for global opt in and opt out selections would seem the best.

QUESTION 52: AHA believes the new consent rules should be applied prospectively.

QUESTION 53: If the research data are deidentified then rules can be waived regardless of the number of subjects involved. If however, the data are identifiable then subjects should be contacted regardless of number and practicality.

QUESTION 54: The intent of the HIPAA standards would be applicable. However, they need to be streamlined and improved.

QUESTION 55: If new security risks are identified then indeed mechanisms need to be re-evaluated.

QUESTIONS 56 & 57: New rules should not inhibit research. Publication and reporting should be of deidentified data only. Identification based on genetic data should not be allowed outside of the scope of the research.

QUESTION 58: The new data security and information protection standards should only be applied prospectively. It would be an excessive administrative burden to apply these retrospectively.

QUESTION 59: We feel study subjects would be sufficiently protected from informational risks if investigators are required to adhere to a strict set of data security and information protection Standards.

QUESTION 60: There is no need for additional standardized data security and information protection requirements that would apply to the phase of research that involves data gathering through an interaction or intervention with an individual (*e.g.* during the administration of a survey).

QUESTION 62: We believe that with a shorter and revised data use agreement, it would be acceptable for HIPAA covered entities to disclose limited data sets to investigators for research purposes.

QUESTION 64: Prohibition for reidentification is a problem and should be discussed carefully; this will impede research.

QUESTION 68: Data on the number of research participants is already reported. Full trial data should also be reported and be in a public domain after a certain time period of preference for the original researchers.

QUESTION 70: We do not feel that the current method of reporting adverse events is adequate to inform the public as the data fields are too limited.

QUESTION 71: AHA believes that the Common Rule should be extended to all research that is not federally funded that is being conducted at a domestic institution that receives some federal funding from research with human subjects from a Common Rule agency. This will be difficult but in principle we favor this.

QUESTION 72: We believe that the differences in guidance from agencies do weaken protections for patients. For example, the exempt components in HIPAA regarding quality improvement efforts blurs the line between protected PHI research and identified PHI quality efforts. Moreover, the standards that underpin de-identification are not solid and re-identification of personal health information can occur. To further compound the issue, there are no uniform standards applied to IRBs and the interpretation of both HIPAA and the Common Rule and thus interpretation occurs at local levels where there is great disparity.

QUESTION 73: We believe the differences between domestic and international guidance also weaken subject protection. Aligning and harmonizing them would make research conduct easier.

QUESTION 74: We are supportive of this as comprehensive guidelines that are responsive to regional and institutional differences can be created and would facilitate research conduct.