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IRB Essentials:

Nuances of Re-consent/Participant Notification in Human Subjects Research

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Training Agenda

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Let's Talk about "Re-consent"…

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"Re-consent" in the Federal Regulations

Pop Quiz!

Q1: How many times is the word "Re-consent" found in the Department of Health and Human Services (HHS) regulations?

A. 2
B. 16
C. 9
D. 0

Answer: 0

The term "Re-consent" is not mentioned anywhere in the HHS regulations.

"Re-consent" in the Federal Regulations

Pop Quiz!

Q2: How many times is the word "Re-consent" found in the Food and Drug Administration (FDA) regulations?

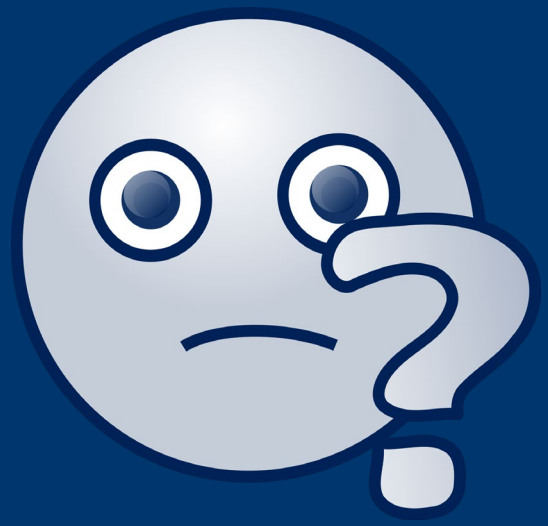
A. 1
B. 0
C. 13
D. 4

Answer: 0

The term "Re-consent" is not mentioned anywhere in the FDA regulations.

"Re-consent" Defined

- **Re-consent is not a concept that is described or defined in the regulations.**
- The regulations require that researchers provide subjects with significant new findings developed during the course of the research when those findings may impact a subject's willingness to continue participation in the research.
- So, while the regulations are clear that new information must be provided to subjects, they do not define a threshold for the significance of the information nor prescribe a specific mechanism for implementing the requirement.



So Where Did "Re-consent" Come From…

- Guidance from Secretary's Advisory Committee on Human Research Protections (SACHRP) [March 11, 2020]: New Information Provided to Previously Enrolled Research Subjects (Attachment A)

  - Although the term "re-consent" is not defined as a regulatory term or concept, §46.116(c)(5) is clear that researchers have an obligation to provide subjects with new findings, and that the information may lead to a subject's reconsideration of their initial consent. **In the research community this process is colloquially referred to as "re-consent."**

  - In general, the idea of re-consent is understood at a high level by the research and IRB communities. However, specific internal IRB definitions of re-consent and requirements for obtaining re-consent are variable.

  - This should not be regarded as a regulatory problem, as the circumstances that create the need to provide new information will be variable, and IRBs should have the flexibility to adjust the mechanism for re-consent or participant notification to the facts of the situation in which the need arises.

U.S. Regulatory Requirements

- The federal regulations include the following sections, relevant to the discussion of "re-consent"*:
  - "Informed consent will be sought from each prospective subject or the subject's legally representative, in accordance with, and to the extent required by, §46.116." (§46.111(a)(4))
  - "An investigator shall seek informed consent only under circumstances that provide the subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence." (§46.115(a)(2))
  - "An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following: … Statements of significant new findings provided to subjects, as required by §46.116(c)(5)." (§46.115(a)(7))
  - "The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information." (§46.116(a)(4))
  - "the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative: … A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject." (§46.116(c)(5))

*Cited from 2020 SACHRP Guidance: New Information Provided to Previously Enrolled Research Subjects (Attachment A)

Now Let's Reframe…

- While neither the HHS nor the FDA regulations use the term "re-consent" or describe a process for approving the mechanism for providing new information to subjects who are already enrolled in a research study, there are regulatory provisions related to this topic that MUST be followed.
  - §46.116(c)(5): When appropriate, significant new findings developed during the course of the research "that may relate to the subject's willingness to continue participation will be provided to the subject."
    - **IMPORTANT NOTE:** providing new findings is not the same as asking an individual to explicitly review their consent to participate in research and confirm their willingness to continue participation.
    - **IRBs can be flexible with this requirement!** Throughout this session, we will discuss mechanisms for providing new information to subjects in a manner that is both consistent with the principle of respect for persons and compliant with the federal regulations.

Re-Consent vs. Providing Information

- **Re-consent**
  - SACHRP "defines" re-consent to mean that subjects will go through a complete consent process that supersedes the original consent using a document that contains all required elements of consent and is documented in accordance with the federal regulations.

VS.

Providing New Information

- When new information is provided through other mechanisms, such as a consent addendum or an information sheet, there is no expectation that this information is presented in a manner that would be considered legal informed consent. Rather, it signifies that there is information that should be provided to subjects who then have an opportunity to consider the information and reaffirm their willingness to continue participating in the research.

Re-Consent vs. Providing Information

- The provision of significant new information in the context of a given study will depend upon many factors, including the nature of the study, the nature and urgency of the new information, and the status of subjects *(i.e., the phase of the research the subjects are in)*.

- Providing the new information creates an explicit opportunity for subjects to exercise their ongoing right to continue their participation or withdraw from the research.

- Researchers and IRBs must work together to ensure that respect for persons is maintained throughout the duration of an individual's participation in research by implementing a robust consent process that allows for the ongoing provision of information relevant to participation.

- When there is a need to present subjects with new information, **IRBs should encourage use of the least burdensome approach for the subject.**
  - For example, the provision of new information should not automatically result in a process whereby subjects are expected to review and sign a new full consent document every time there is a minor change.

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Current IRB Practices & Investigator Responsibilities

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Current IRB Practices

- There is known variability in IRB approaches to requiring explicit renewal of consent over the course of a research study, however, there are a few options that are used most frequently in regular practice.

- The choice of pathway may be influenced by factors including the nature of the new information, its perceived impact on currently enrolled subjects, and/or the status of the research (e.g., enrolling, long term follow-up only, near completion). **Possible approaches to providing new information include:**

    - Require researchers to repeat the informed consent process with the revised informed consent document(s) and document consent following the requirements for documenting consent at 45 CFR 46.117.
    - Require that researchers present the new information through the use of an addendum to the original informed consent document and either obtain documentation (signature) directly or describe the communication process in the subject's research records.
    - Allow researchers to orally communicate the new information and document the communication process in each subject's research records.
    - Provide subjects an information sheet describing the new information.
    - **Documentation is key!**

Current IRB Practices

- With each option, the timing may vary depending on the perceived urgency of the new information.
- Depending on the specific circumstances (including whether any subjects are at immediate risk), the IRB may instruct the researchers to bring subjects back immediately, provide information by telephone, or wait until the next scheduled subject visit.
- The requirements for use of any revised consent materials (e.g., consent document, addendum or notification) may be adapted to the population of subjects the changes affect.
  - For example, an addendum or notification may be appropriate for current subjects or a subset of current subjects, while a revised consent document would usually be the appropriate document for use with new subjects.

SACHRP Guidance: Reconsent Appendix I

- APPENDIX I (New Information Provided to Previously Enrolled Subjects)

- Examples of instances where changes to the study may affect a research participant's willingness to continue and therefore should be disclosed to participants include, but are not limited to, the following:
  - Identification of new research-related risks;
  - Increase in the frequency or magnitude of previously described risks (e.g., serious cardiac event, severe allergic reaction);
  - Unanticipated problem that exposes subjects to new risks, such as a data breach;
  - Decrease in expected benefits to participation (e.g., limited efficacy of experimental therapy);
  - Change to the research that results in increased burden/discomfort;
  - Availability of new alternative therapies (e.g., FDA approval of a new drug or device for the condition under study);
  - Impact of participation on alternative therapies (e.g., investigational agent reduces effectiveness of alternatives or precludes future treatment with standard of care therapy).

Investigator Manual (Section 6.7 – Reconsent Process)

- "Subjects need to be informed of any significant new information that emerges during the course of the study that may affect subjects' willingness to continue to participate. Subjects should be informed in a timely manner about issues that affect their health and well-being."
- The following questions and considerations will aid you in the determination of notification vs. re-obtaining consent from subjects:

Questions	Considerations
Who must be notified or have consent re-obtained?[5] • All subjects ever enrolled in the study regardless of their current status; • Only subjects active on study intervention or another subset of subjects.	Does the change affect different groups of subjects differently? If so, which groups of subjects are affected? Does it depend on the subject's status (active, previously enrolled), arm of the study, or gender or age groups? Will the impact of the change affect subjects after the study is complete?
What exactly is the change that requires communication? • New risks • New inconveniences • New procedures • New treatment alternatives • New costs • Other significant findings	Could the information affect a subject's willingness to continue participation? Will the change require a different level of commitment from the subject; e.g., additional procedures?

[5] Note – FDA does not require re-consenting of subjects that have completed their active participation in the study, or of subjects who are still actively participating when the change will not affect their participation; for example, when the change will be implemented only for subsequently enrolled subjects. (See Institutional Review Boards Frequently Asked Questions)

Investigator Manual (Section 6.7 – Reconsent Process)

- Below are examples of changes that could affect study participants based on their study status. The following considerations will aid you in the determination of notification vs. re-obtaining consent from subjects:

Active Study Participants	
New Information Likely to Affect Participants	**Information Not Likely to Affect Participants**
• New or increased risks of the study intervention/study procedures; • Additional study procedures required by the study; e.g., additional Lumbar Puncture or MRI; • Changes in doses or frequency of the study drug; • Modifications to the study design; e.g., timeline of their study visits; • Changes to payments or cost for participation; e.g., previously provided drug now being charged to participant's insurance, changes to payment; • New FDA approval of drugs involved in the study or those that create new alternative treatment.	• Administrative changes such as the date or version number of the consent form; • Modifications to the arm of the study that does not apply to all participants; e.g., changes for non-smokers while the subject is enrolled in the arm for smokers; • Addition of procedures that the subject will not be asked to undergo; e.g., baseline MRI • Minor editorial changes in the consent/protocol for clarity

Previously Enrolled Study Participants Who Concluded Their Participation	
Information Likely to Affect Participants	**Information Not Likely to Affect Participants**
• Newly discovered long term side effects of the study drug; • New adverse events associated with the implanted study device.	• New short term side effects of the study drug/procedure; • Changes to the study design; • Any information that would not affect currently enrolled subjects.

Investigator Manual (Section 6.7 – Reconsent Process)

- The choice of the appropriate method of subject notification depends on many factors including the urgency of the information, a requirement set by the sponsor or the IRB, and a necessity for the action on part of the participant (e.g., agreement to the new study procedure or continuation in the study given the new information). Investigators are encouraged to rely on their professional judgment to determine how quickly the new information must be communicated to the participants.
- The following questions and considerations will aid in the determinations regarding methods and timeline for re-consenting and notification:

Questions	Considerations
When must notification or re-consent occur to protect subject safety and rights (regardless of logistics)? • Immediately (as soon as possible); • Before next study visit; • Before specific study procedures; • Within specified time period; • Dependent on affected participant subset.	Are subjects coming in for study visits or are remaining study procedures done at home or over the phone? Are subjects impacted now or in the future? Are subjects who have completed study procedures/visits impacted?
Where and **How** should notification be implemented? • In-person visit; • Letter with phone follow-up; • Revised consent form/addendum.	**Consider:** • Complexity and need for interactive explanation and discussion; • Need for physical demonstration or other presentation of information best done in person; • Timeline for next subject visit; • If the participant is decisionally impaired or a minor, need for legal guardian or parent to be involved and re-consented.

Investigator Manual (Section 6.7 – Reconsent Process)

- Examples of methods for subject notification/re-consenting:

	Affected Participants
Research participant's decision needed regarding their continued participation	• **Consent addendum** – allows for emphasis on the new information with the understanding that information presented in the main consent may still apply (e.g., new risks are discussed in the consent addendum, but protections of confidentiality do not change). • **Full Revised Consent Form** – should be used when changes to the consent form are extensive. Can be used with a memo/cover letter that highlights the changes, which would also be addressed during the re-consenting discussions.
Notification needed only **OR** **Only verbal consent required**	• **Documented phone call** – participants may be informed via phone call when their participation has concluded and they do not need to provide continued consent. The IRB can also determine that research participant's verbal agreement to continue to participate in the study is sufficient (e.g., addition of a questionnaire that would be conducted over the phone). • **Informational Letter** – participants are informed via written communication. Receipt should be acknowledged and documented in the study file, can be followed by a phone call.
Immediate notification needed	• **Phone Call** – when the study participants are at immediate risk and an action is needed (e.g., stopping the study medication), a phone call should be placed as soon as the new information emerges, prior to the approval of the notification documents by the IRB. The phone call should be documented and followed by written notification/re-consenting.

➢ There is also information that may not need to be communicated to research subjects. Examples include changes to the inclusion criteria that have no impact on previously enrolled subjects *(e.g., increase to upper age limit from 60 to 70, or an increase in the overall number of subjects).*

Decision Process – Investigator Responsibilities & Yale IRB Determinations

- **Investigators should follow this process:**
  - Make an initial determination whether new information should be communicated to current and/or previously enrolled study participants and decide on the most appropriate form of communication.
  - Submit a modification to the consent form and the protocol in IRES IRB.
  - Include their proposed plan for notification of the participants or rationale for why the new information does not need to be communicated to participants.
  - Once IRB approval is obtained, review the finding in the letter to communicate to your research team members. Investigators must comply with the IRB's decision.
  - If re-consent is required, ensure that participants provide their consent prior to their involvement in the procedural change.

- **IRB Determinations**
  - The IRB will review the investigator's plan for subject notification and determine whether any additional actions are needed.
  - The IRB can be flexible and creative with their requirements!
  - ★ **The IRB determination will be included in the approval letter of the Modification.**

What if I Initially Used a Short Form for Consent?

- **Background:** A "short form" may be used for obtaining consent from individuals who do not speak English in situations where there is not sufficient time to translate the consent document into his/her language. There are specific requirements regarding using a short form for obtaining consent *(full requirements outlined in Section 6.3. of the HRPP Investigator Manual and Section 14.8 of the HRPP SOP Manual).*

- The possible inclusion of non-English speaking participants or participants who are not fluent in English in research and the use of a short form must be described in the protocol application and approved by the IRB.

- If new information becomes available during the course of the research, and the IRB requires re-consent OR participant notification of enrolled subjects, if individuals were enrolled using a short form, **you should NOT re-consent them using the short form.**

- The IRB will be clear in the Modification approval letter if full re-consent is required OR if participants only need to be notified of the changes/new risks.
  - For non-English speaking participants originally enrolled using a short form, the IRB might determine a translated copy of the full consent form must be used for re-consent, or, if only notification is required, a translated written summary of the changes may be provided to the participant if deemed appropriate by the IRB.
  - **Follow the IRB's determinations/guidance and ask for clarity if needed!**

External IRB Determinations

- External IRBs that serve as the IRB of record for Yale/YNHHS research have the same authority as the Yale IRB and all determinations and requirements of the external IRBs are equally binding.

- Investigators must be familiar with and comply with the external IRB's policies and procedures, and any additional requirements or procedures outlined in the IRB reliance agreement.
  - **This include re-consent/notification requirements!**

- While most changes to external IRB studies must be submitted directly to the external IRB of record, there are some changes that also must be submitted to the Yale HRPP for review, including change of PI, addition of a new consent form, changes in funding, changes in local recruitment plans, etc. *(full list found in Section 13.2 of the Yale HRPP Investigator Manual)*.

- **NOTE:** For National Cancer Institute (NCI) Central Institutional Review Board (CIRB) studies, changes in PI require **notification to participants** (but not formal re-consent)
  - Other external IRBs will have their own policies and requirements for re-consent or notification when there is a change in PI (or other types of modifications). The PI must adhere to the external IRB's requirements.

IRB Decision Process

- SACHRP's Attachment A2 - Reconsent Appendix 2 provides IRBs with a framework for evaluating new information considering the nature of the information, the status of the research and the perceived urgency of disseminating the information, and what mechanisms may be used to disseminate the information and documenting that the information was provided.

IRB Decision Process

- When information is NOT time-sensitive…

Information is:	Study status is:	Information represents a minor change (likely would not change the individual risk/benefit calculus or an individual's willingness to participate):	Information represents a significant change (some possibility that the individual risk /benefit calculus will be changed or an individual's willingness to participate):	Information represents a major change (changes the overall risk/benefit and is likely to affect an individual's willingness to participate):
Not time-sensitive	**Not yet recruiting**	Full consent form	Full consent form	Full consent form
	Recruitment started and still open	Verbal communication with documentation in the study record	[1]Information sheet/addendum with signature for existing participants*, full consent for new participants	Full consent form
	Recruitment complete: intervention ongoing	Verbal communication with documentation in the study record	Information sheet/addendum with signature.	Information sheet/addendum with signature.
	Recruitment complete: intervention complete**	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record

** There may be interventions that cannot be considered "complete" (e.g. implantable devices). In such circumstances, the judgement of the study team and IRB should dictate whether participants are asked to reaffirm their participation by signing a new information sheet or addendum.

➢ SACHRP's Attachment A2 - Reconsent Appendix 2

IRB Decision Process

- When information IS time-sensitive…

Information is:	Study status is:	Information represents a minor change (likely would not change the individual risk/benefit calculus or an individual's willingness to participate):	Information represents a significant change (some possibility that the individual risk /benefit calculus will be changed or an individual's willingness to participate):	Information represents a major change (changes the overall risk/benefit and is likely to affect an individual's willingness to participate):
Time-sensitive	**Not yet recruiting**	Full consent form	Full consent form	Full consent form
	Recruitment started and still open	Verbal communication with documentation in the study record (no change in full informed consent form for any group)	[1]Information sheet/addendum with signature for existing participants*, full consent for new participants	Full consent form
	Recruitment complete: intervention ongoing	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record, followed by information sheet/addendum with signature.	Verbal communication with documentation in the study record, followed by information sheet/addendum with signature.
	Recruitment complete: intervention complete**	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record

** There may be interventions that cannot be considered "complete" (e.g. implantable devices). In such circumstances, the judgement of the study team and IRB should dictate whether participants are asked to reaffirm their participation by signing a new information sheet or addendum.

➢ SACHRP's Attachment A2 - Reconsent Appendix 2

IRB Decision Process

- When information is URGENT…

Information is:	Study status is:	Information represents a minor change (likely would not change the individual risk/benefit calculus or an individual's willingness to participate):	Information represents a significant change (some possibility that the individual risk /benefit calculus will be changed or an individual's willingness to participate):	Information represents a major change (changes the overall risk/benefit and is likely to affect an individual's willingness to participate):
Urgent	**Not yet recruiting**	Full consent form	Full consent form	Full consent form
	Recruitment started and still open	Verbal communication with documentation in the study record (no change in full informed consent form for any group)	[1]Verbal communication with documentation in the study record, followed by Information sheet/addendum with signature for existing participants*, full consent for new participants	Verbal communication with documentation in the study record, followed by full consent for all participants
	Recruitment complete: intervention ongoing	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record, followed by information sheet/addendum with signature.	Verbal communication with documentation in the study record, followed by information sheet/addendum with signature.
	Recruitment complete: intervention complete**	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record	Verbal communication with documentation in the study record

** There may be interventions that cannot be considered "complete" (e.g. implantable devices). In such circumstances, the judgement of the study team and IRB should dictate whether participants are asked to reaffirm their participation by signing a new information sheet or addendum.

SACHRP's Attachment A2 - Reconsent Appendix 2

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Scenarios for Discussion

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Scenario #1

Scenario #1*: A Data Safety Monitoring Board (DSMB) has identified a trend in elevated blood pressure among study subjects (this risk was not previously identified in the consent form).

- **Question for Discussion:** Should currently enrolled participants be re-consented with a full version of the newly revised consent form? Sign a consent addendum? Provided with notification only? Any other options?

*Scenario cited from University of Rochester's Office for Human Subject Protection resource on Re-Consent

Scenario #1- Points to Consider

- This new information presents a potential safety issue that subjects should be informed about in a timely manner.

- One appropriate method for providing the new information would be to contact subjects via telephone to discuss the newly identified risk with them (documenting this conversation in the study record) and then follow-up with a mailed consent addendum describing the new potential risk for subjects to review. Further review of the addendum and documentation (signature) would then be obtained at the next study visit.

- **INTERESTING NOTE:** The benefit of using a consent addendum in this scenario is that the formatting will help pinpoint the new information that needs to be disclosed to the subject.

    - When a small number of revisions are made to a consent form and a full version of the consent form is utilized to re-consent the subject, the new information can get "lost" among other details.

    - When/if a full version of the consent form is utilized to re-consent subjects when only a few revisions have been made to the research, effort should be made to emphasize the revised portions of the document when discussing the changes with the subject (e.g., highlighting or specifically pointing out revisions).

Scenario #2

Scenario #2*: Additional funding for the study has been obtained, and subjects will now be paid for their participation.

- **Question for Discussion:** Should currently enrolled participants be re-consented with a full version of the newly revised consent form? Sign a consent addendum? Provided with notification only? Any other options?

*Scenario cited from University of Rochester's Office for Human Subject Protection resource on Re-Consent

Scenario #2- Points to Consider

- Although providing payment to existing subjects (when it previously was not offered) is unlikely to change subjects' willingness to continue participating, payment is still an element of consent that requires disclosure to the subject.

- Mailing an information letter or providing the information verbally (with documentation in the study record) may be sufficient, over requiring re-consent via full consent or signing a consent addendum.

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Summary & Resources

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Summary

- Re-consent is not a concept that is described or defined in the regulations. However, federal regulations require that researchers provide subjects with significant new findings developed during the course of the research when those findings may impact a subject's willingness to continue participation in the research.

- The provision of significant new information in the context of a given study will depend upon many factors, including the nature of the study, the nature and urgency of the new information, and the status of subjects (i.e., the phase of the research are the subjects are in).

- Researchers and IRBs must work together to ensure that respect for persons is maintained throughout the duration of an individual's participation in research by implementing a robust consent process that allows for the ongoing provision of information relevant to participation.

Resources

- Guidance from Secretary's Advisory Committee on Human Research Protections (SACHRP) [March 11, 2020]:
  - New Information Provided to Previously Enrolled Research Subjects (Attachment A)
  - Reconsent (Appendix 1)
  - Reconsent (Appendix 2)

- Yale HRPP Investigator Manual (Section 6.7 – Reconsent Process)

- 45 CFR 46 (HHS Regulations – Protection of Human Subjects)

- FDA FAQ Document - Institutional Review Boards Frequently Asked Questions)

- University of Rochester's Office for Human Subject Protection (Re-Consent)

Questions?

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