



**REVIEW OF AN INVESTIGATOR'S REQUEST FOR A
WAIVER OF SELECTED INCLUSION/EXCLUSION CRITERIA
FOR A SINGLE PERSON**

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Investigators are responsible for conducting research with humans according to the signed investigator statement, the investigational plan and applicable federal regulations (as stated in 21CFR312.60) and institutional policies. Sponsors and investigators occasionally use waivers of specific inclusion / exclusion (I/E) criteria for clinical investigations without a sound regulatory basis or prior IRB approval. There is no FDA policy or guidance permitting or precluding this practice, although a common finding reported by FDA compliance auditors is the inappropriate use of such waivers. The DUHS IRB does not support the routine use of waivers of objective I/E criteria for clinical investigations involving an FDA regulated product (drug, device or biologic).

An investigator may encounter a potential research participant who does not satisfy all of the I/E criteria of a research protocol. Examples include a patient being considered for inclusion into a study involving an investigational drug or device, and whose qualifying radiologic images were obtained days to a few weeks earlier than permitted by the protocol, or whose blood chemistry values fall slightly outside of the protocol's required ranges, or who is slightly older or younger than permitted by the protocol. If the investigator concludes that such a person is so close to meeting I/E criteria that the person's inclusion would not place him/her at an increased risk of harm from study participation, and participation in the study would be in the person's best interest because alternatives are limited to less favorable options, often the investigator will consult with the study sponsor and the IRB about obtaining a waiver to permit inclusion of the person. The IRB is asked to approve this waiver, usually after the sponsor has approved it. But often neither the investigator nor the sponsor intends to submit an amendment to incorporate such broadened I/E criteria so as to include both the current person and similar people in the future. Or if such an amendment were to be submitted, the timing of its submission would not permit inclusion of the current person.

Federal regulations and DUHS IRB policy permit use of the expedited review procedure to approve a change in previously approved research only when the proposed change is minor and occurs during the period (one year or less) for which approval was authorized. The IRB defines a change as "minor" if:

- (a) the change does not adversely alter the overall risk/benefit ratio;
- (b) the change will not potentially adversely affect the willingness of current participants to remain in the study or the willingness of potential participants to enroll in the study;
- (c) the change will not diminish the scientific validity of the study,
- (d) any added revision or procedure involves no more than minimal risk to subjects, and
- (e) any added procedure falls into one of the categories (1)-(7) of research that can be reviewed using the expedited procedure.

The IRB's amendment policy gives examples of changes that may be approved using the expedited procedure, and those that may not. Examples of amendments that may be reviewed using the expedited procedure include:

- The addition of research activities that would be considered exempt or eligible for expedited review if considered independent from the main research protocol;
- An increase or decrease in the proposed enrollment of research subjects without prolonging any subject's period of exposure to study risks that are more than minimal, or without adversely affecting the study design;
- Narrowing the range of the inclusion criteria;
- Broadening the range of the exclusion criteria;
- Alterations in the dosage form (e.g., tablet to capsule or oral liquid) of an administered drug, provided the dose and route of administration remain constant;
- Decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations;
- An increase in the length of confinement or number of study visits for the purpose of increased safety monitoring;
- A decrease in the length of confinement or number of study visits, provided that such a decrease does not affect the collection of information related to safety evaluations;
- Alterations in human research participant payment or liberalization of the payment schedule with proper justification;
- Changes to improve the clarity of statements or to correct typographical errors, provided that such a change does not alter the content or intent of the statement;
- The addition or deletion of key personnel;
- The addition of study sites (which may require a Federal Wide Assurance (FWA) and appropriate IRB approval) or the deletion of study sites.

Examples of amendments that are not minor and may not be approved using the expedited procedure include:

- The addition to the informed consent document of a description of serious unexpected adverse events or other risks;
- Broadening the range of inclusion criteria;
- Narrowing the range of exclusion criteria;
- Increase in the dosage or alteration in the route of administration of a drug;
- Extending the duration of exposure to the test material or intervention;
- The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations; or
- Changes, which, in the opinion of the IRB Chair/designee, do not meet the criteria or intent of a minor modification.

Based on the examples above, a change to expand the inclusion criteria or reduce the exclusion criteria would **not** be a minor change and thus would require review by a convened IRB (and would be submitted by the investigator as a protocol amendment).

If an investigator encounters a potential research participant who does not satisfy all of the inclusion/exclusion (I/E) criteria of a research protocol, and the investigator concludes that such a person is so close to meeting I/E criteria that the person's inclusion would not place him/her at an increased risk of harm from study participation, and participation in the study would be in the person's best interest because alternatives are limited to less favorable options, and the research is not DHHS regulated, the investigator has several choices:

- 1) Not recruit the person;
- 2) Obtain IRB approval of an amendment to alter the I/E criteria to permit inclusion of the person and other such people;
- 3) If time does not permit the investigator to submit such an amendment, or if the sponsor chooses not to amend the overall study, but does approve the change in I/E criteria for this single person, the investigator must notify the IRB of his/her plans to:
 - a) ensure that the proposed research is not subject to DHHS regulations;
 - b) obtain from the study's principal investigator and sponsor documentation that the potential research participant may be included and will not be inevaluable based on not meeting I/E criteria;
 - c) declare to the IRB that participation in the study would be in the person's best interest because alternatives are limited to less favorable options;
 - d),seek from a colleague uninvolved in the care of the person an endorsement of the inclusion of the ineligible person because alternatives are limited to less favorable options;
 - e) request and receive a statement from the IRB that it finds the person's inclusion to represent appropriate medical practice.

Only then may the investigator seek the person's consent for research participation.

If the IRB reviewer chooses to provide this statement, the reviewer must make clear to the investigator that this does not represent IRB approval for the inclusion of an ineligible person into the study. The reviewer must inform the investigator to notify in writing the ineligible potential research participant that participation may involve unforeseen risks beyond those experienced by eligible participants, and the person's research data may not be evaluable or useable. Also the investigator must be reminded that if the study involves the use of an FDA-regulated product, all FDA reporting requirements must be met, including reporting to the IRB, sponsor and FDA of any unanticipated problems involving risks to the ineligible person or to others.

The investigator must submit all of his/her related correspondence with the sponsor, uninvolved colleague and/or the IRB by uploading all (electronic) documents into the e-IRB. This correspondence becomes part of the IRB-approved protocol file.