Devices
21 CFR 812

Significant Risk (SR)

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk (NSR) Abbreviated IDE (Checklist 418 Required)

IDE exempt (no Checklist required)

Determinations

Approval
Approval with Minor Modifications
Deferred
Disapproval

RNI Determinations

Non-Compliance: Failure to comply with the requirements of an applicable law, regulation, or institutional policy of the protection of human subjects, and/or with the requirements or determinations of an IRB that poses a risk of harm to subject's rights, safety or welfare, or the integrity of the research data.

Continuing Non-Compliance: A **pattern** of noncompliance that indicates an **inability** or **unwillingness** to comply with the requirements of an applicable law, regulation, or institutional policy of the protection of human subjects and/or with the requirements or determinations of an IRB.

Serious Non-Compliance: Noncompliance that adversely affects the rights or welfare of participants. *Note special standard for DoD funded research.

Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO): An incident, experience, or outcome that is Unexpected, Related/Possibly Related, **and** suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized, even if no harm has occurred.

None of the Above (Acknowledge)

Is an IND Required?

- Is drug FDA approved? If "No"– IND required
- If "yes" Is the drug used off label? If no – No IND
- If "yes" Does the investigation involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product? If yes – IND required

Studies with/of Supplements

- Supplement breakdown
- Where is the supplement coming from: Company or OTC
- Statement of Ingredients
- Check inclusion/exclusion criteria & ICF for Food Allergies or considerations
- Composition and microbial analysis report
- Is an IND required?
- Following Current Good Manufacturing Practices (cGMP) for dietary supplements being followed

Skin Biopsy Guidance

Minimal Risk

- 2mm in diameter or less
- No sutures are required

Greater than Minimal Risk

Skin biopsies not meeting the criteria above (i.e. biopsies >2mm, biopsies requiring sutures, biopsies done without EMLA, or biopsies done when a less invasive procedure could be done instead) will be considered greater than minimal risk. If the study targets a condition which makes the acquisition of even small biopsies without a suture problematic, this should be taken into account.

Criteria for Approval

45 CFR 46.111 and 21 CFR 56.111

1. Risks to subjects are minimized by (1) using procedures, consistent with sound research design; using procedures already being done on the subjects for other purposes; and (2) without exposing subjects to unnecessary risk. Ask: Is there any way to minimize risk?
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
3. Selection of subjects is equitable.
4. Additional safeguards have been included in the study to protect the rights and welfare of subjects who are vulnerable to coercion or undue influence.
5. The research plan has adequate provision for monitoring the data collected to ensure subject safety.
6. There are adequate provisions to protect the privacy of subjects.
7. There are adequate provisions to maintain the confidentiality of data.
8. The informed consent process is adequate.
9. The documentation of informed consent is adequate.

Definition of Minimal Risk

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Conflicts of Interest as a Reviewer

The following would fall under financial conflicts of interest as a Reviewer (including subsidiaries and parent companies):

- Consultant/Speaker bureau
- Advisory board membership
- Honorarium recipient
- Stockholder
- Editorial board involvement
- 1571/1572 investigator/collaborator

Investigator Conflict of Interest Management Plans

- Standard Disclosure
- Conflicted party cannot obtain consent
- Conflicted party cannot recruit
- Conflicted party cannot analyze data
- Conflicted party cannot be associated with the research

CAPA

What was the error?

Who was responsible, and how does PI responsibility relate?

How did the error occur?

Why did the error occur?
(ask how and why five times!)

What are the corrective actions?
- Disclosure
- Reconsent
- Redoing procedures
- Excluding data

What are the preventive actions?
- Checklists
- Independent Monitoring
- Subject specific documentation

Is new training needed?

Is re-evaluation needed within a timeframe (6-9 months)

Document Everything

Criteria for Minors

Subpart D
45 CFR 46

404 – Level 1
- Minimal Risk
- Benefit or no direct benefit
- 1 Parent Signature

405 – Level 2
- Greater than minimal risk
- Risk is justified by anticipated benefit
- Risk/benefit at least as favorable as alternative approaches
- 1 or 2 Parent Signatures

406 – Level 3
- Minor increase over minimal risk
- Commensurate
- Likely to yield generalizable knowledge of vital importance
- 2 Parent Signatures
- Any skin biopsy that requires suturing in a study that does not have the prospect of direct benefit to the child participants will be considered a minor increase over minimal risk.

407 – Level 4

DHHS Review and approval required

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General Required Elements of Consent

- The consent language is understandable.
- The consent does not include exculpatory language.
- The consent does NOT provide merely isolated facts, but rather facilitates understanding of why one might or might not want to participate.
- The subject is provided with the information a reasonable person would want to have in order to make an informed decision about whether to participate.
- A statement that the study involves research.
- An explanation of the purpose of the research.
- A description of the procedures to be followed.
- Identification of any procedures which are experimental.
- The expected duration of the subject's participation.
- A description of any reasonably foreseeable risks and discomforts.
- A description of any reasonably expected benefits.
- A disclosure of any appropriate alternative procedures or treatments.
- The extent to which confidentiality of records identifying the subject will be maintained.
- How to contact the research team for questions, concerns, or complaints related to the research.
- How to contact someone independent of the research team for questions, concerns, or complaints about the research; questions about the subjects' rights; to obtain information; or to offer input.
- A statement that participation is voluntary.
- A statement that refusal to participate or that discontinuing participation will involve no penalty or loss of benefits to which the subject is otherwise entitled.

Consent Requirements for FDA-Regulated Research

- A description of the probability for random treatment assignment.
- A statement that the FDA may inspect the records.
- A statement that the data collected on a subject up to the point of withdrawal remains a part of the study database and may not be removed.
- A statement that the investigator will ask a subject who is withdrawing whether the subject wishes to provide further data collection from routine medical care.

Additional ICH E6 R2 Consent Requirements for FDA-Regulated Research

- A statement that the study has been approved by the IRB.
- A description of the subject's responsibilities.
- The important potential risks and benefits of alternative procedures or treatments.
- When there is no intended clinical benefit to the subject, a statement to this effect.
- A statement that the various regulatory authorities and monitors will be granted direct access to the subject's original medical records.
- That records identifying the subject will be kept confidential and not be made publicly available to the extent of the law.

Waiver or Alteration of the Consent Process

- Does **NOT** involve non-viable neonates
- Does **NOT** meet the state of CA definition of a medical experiment

General Waiver

You must be able to say "YES" to all of the following

✓ Minimal Risk

✓ The waiver or alteration will **NOT** adversely affect the rights and welfare of the subjects.

✓ The research could **NOT** practicably be carried out without the waiver or alteration

✓ Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

✓ The research is reviewed under the Pre-2018 Common Rule **OR** the research uses only de-identified or anonymous private information or biospecimens **OR** the research cannot practicably be carried out without using identifiable private information or biospecimens.

For research involving public benefit and service programs

- **Not** FDA-regulated or
- FDA Regulated and Minimal Risk

✓ The research or demonstration project is to be conducted by or subject to the approval of state or local government officials.

✓ The research or demonstration project is designed to study, evaluate, or otherwise examine one or more of the following:

  - Public benefit or service programs.
  - Procedures for obtaining benefits or services under those programs.
  - Possible changes in or alternatives to those programs or procedures.
  - Possible changes in methods or levels of payment for benefits or services under those programs.

✓ The research could NOT practicably be carried out without the waiver or alteration.

Waiver of Documentation of Consent

- Minimal risk
- No procedures that usually require consent

Or

- Not FDA regulated
- Principal risk is breach of confidentiality.
- Only record linking subject to research would be the consent document

Additional Elements of Informed Consent (Include when applicable)

- A statement that the particular treatment or procedure may involve risks to the subject that are currently unforeseeable.
- The foreseeable circumstances and/or reasons that a subject's participation in the research may be terminated.
- Whom to contact in the event of research-related injury.
- The anticipated expenses for participating in the research.
- A description of the prorated subject compensation plan.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination.
- A statement that significant new findings discovered during the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- The approximate number of subjects in the study.
- For greater than minimal risk research, an explanation of whether compensation and/or medical treatments are available if injury occurs and, if so, what it consists of or where further information may be obtained.
- For studies which are a clinical trial or if otherwise applicable, ClinicalTrials.gov statement.
- For research funded by the NIH or if otherwise applicable, Certificate of Confidentiality statement.
- When using electronic consent, a clear statement of subject's rights with respect to the electronic document.
- For research that meets California's definition of a medical experiment, the "Experimental Subject's Bill of Rights".

Consent Requirements for 2018 Common Rule

- The informed consent begins with a focused summary of key information to help a subject understand whether they want to participate.
- The informed consent is organized and presented to facilitate comprehension.

Additional 2018 Common Rule Requirements

- A statement that the subject's biospecimens may be used for commercial profit and whether or not they will share in this profit.
- A statement about whether clinically relevant research results (aggregate or individual) will be disclosed to subjects and when.
- For research involving biospecimens, a statement as to whether the research will involve whole genome sequencing.
- If private identifiable information or identifiable biospecimens are being collected, a statement that they might be used for future research or distributed to another investigator for future research after removing the identifiers without additional informed consent.

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