Points to Consider in Assessing When an Investigational Device Exemption Might be Needed

This document has been developed by NHGRI and does not replace or substitute for the official US Food and Drug Administration (FDA) guidance documents. It is intended to provide a plain language resource for researchers to consider how FDA's Investigational Device Exemption regulations might apply to their proposed clinical genomics research projects.

To ensure that research use of new medical devices (those that have not yet been cleared or approved by FDA) have appropriate oversight and do not put human research participants at undue risk, FDA requires that certain clinical research projects (or "investigations") be granted an **Investigational Device Exemption** (IDE) before the study is initiated (21 CFR 812).

FDA defines molecular diagnostics, like all in vitro diagnostics, as medical devices (21 USC 321). In the case of genome sequencing applications, FDA currently considers the entire test pipeline to be the device**.** Therefore, the sequencing platform, its analysis and informatics pipeline, and interpretation of the results for return to a clinician or participant represent a single device (as opposed to many individual devices). IDEs are required for research where FDA believes there is the potential for significant risk to the participants as a result of acting on false positive diagnosis (or as a result of inaction due to a false negative diagnosis).

Do I need to apply for an IDE?

Not all clinical studies involving genome sequencing (or other new devices) require IDEs. If you do not intend to return the medically relevant results of a genomic assay to a participant, their physician, or will enter those results into their medical record, and the results are not being used to direct or inform the clinical care of that participant, an IDE is not required (i.e., the study is IDE exempt).

A study may also be IDE exempt if results from the assay are confirmed using a second, "medically established" procedure. Currently, FDA considers Sanger sequencing to be a 'medically established' diagnostic device; the Illumina MiSeqDX platform has been cleared by FDA for targeted sequencing applications, and the Thermo Fisher Ion PGM DX

platform has been registered with FDA as an equivalent device to the MiSeqDX. Therefore, an investigator confirming DNA sequence-based research findings with these methods **is unlikely to need to apply to the FDA for an IDE**.[i]

If, in contrast, you intend to use a genomic assay to diagnose a medical condition or inform a participant's clinical care, or to return potentially actionable health information to a participant or their physician, you ***may*** need to apply for an IDE. The level of risk posed to the research participant through the clinical study is the key factor in this determination.

What constitutes risk for the purposes of an IDE?

FDA's regulations distinguish between two classifications of risk (to an individual participant) in clinical studies that require an IDE:

- Nonsignificant risk
- Significant risk

If you are the study's sponsor or sponsor-investigator (see glossary), you should make the determination of whether a study poses significant or nonsignificant risk to the participants, and present this to your IRB IRB when seeking approval to initiate the study.

For molecular diagnostic devices, there are a number of factors to consider when determining risk:

Risks from incorrect results: With regard to molecular diagnostic devices, the key question when assessing risk is to **consider the consequences of either a false positive or false negative result**:

- Could a false negative result in a participant not receiving a medically necessary treatment?
- Could a false positive result in a participant being exposed to a medically unwarranted intervention and serious or life-threatening adverse events (beyond the standard of care for that participant)?

If the answer to either of those questions is yes, FDA might view the risk as significant.

Participant health: **The health of the research participants, as well as the availability of any treatment options,** is important when determining risk for the purposes of IDE submissions. For instance, if a participant has a serious or life-threatening condition with no available treatment options outside the use of the device, that study would be considered to pose less risk than a study that potentially exposes healthy participants to

an unnecessary medical intervention due to a false positive result. Thus, each study must be evaluated based on the intended use of the genomic test (device) in the study and in the context of the study population.

Sampling procedure: Does the sampling procedure constitute a risk? Typically the answer is no for genomics studies. For example, in the case of studies where the sampling is a venous blood sample, the risk is not significant because it is not considered an invasive procedure.[ii]

Who determines risk?

If you are the study sponsor or sponsor-investigator (see glossary), you have the primary responsibility for determining whether an IDE is needed. If an IDE is needed, the next question is to consider whether the use of DNA sequencing technology in the study is of significant or nonsignificant risk. You should present their assessment to the IRB along with the study protocol before beginning the study.

Your IRB must then review the risk assessment and agree or disagree. FDA's guidance for IRBs on this responsibility recommends that established written procedures explain how the IRB distinguishes significant from nonsignificant risk. The IRB should provide a written justification or description explaining why the proposed study poses either significant or nonsignificant risk for the study records. This can be helpful in providing clarity to FDA (and to you) regarding the basis of IRB decision-making.

Nonsignificant risk: If you determine that the use of genomics technology poses nonsignificant risk to your participants, and your IRB concurs, you *does not* need to submit an IDE application to FDA before enrolling participants. **FDA considers the study in these cases to have an approved IDE for a nonsignificant risk device** even though FDA has not been consulted**.** Your study must comply with the abbreviated IDE requirements, which include labeling, monitoring participants, and keeping certain records. It is important to note, however, that **FDA retains the authority to overrule the IRB's determination** and require you to submit an IDE application to the agency.

Significant risk: If you or your IRB determines that the use of genomics technology in the study poses a significant risk to participants, **you must acquire an IDE from FDA before conducting the study**. Studies determined to pose significant risk may still be undertaken; however, the IDE application must be approved before you can begin enrolling participants (see below for more on this). In the event of that an IRB disagrees with your determination that the proposed study is significant risk, the IRB's determination (i.e., nonsignificant risk) would apply.

What if I need to apply to the FDA for an IDE?

Pre-Submission: You may pursue pre-submission with FDA concurrent with seeking IRB protocol approval, because the application review by FDA and the IRBs are independent of one another (pre-submission is the process of communicating with FDA regarding a study and the possible need for an IDE). It *might* benefit you to wait for your IRB's approval before entering into discussion with FDA, since IRB action might clarify or modify some of the information FDA will need to review. However, this could increase the total time elapsed before the research can commence.

When the use of genome sequencing technology poses significant risk to participants, **you are encouraged to contact FDA for guidance and discussion prior to submitting an IDE application**. Early interaction between sponsors/sponsor-investigators and FDA is helpful both for you (increased understanding of FDA's rules and requirements as they apply to their specific study) and FDA (better understanding of the particular novel technologies involved with the submission).

While it is not required by FDA to do this, and may be seen as an "extra" step, ultimately the discussions may serve to speed up the process overall. In the course of a pre-submission, you can ask FDA to make a formal risk determination for the proposed study. It is possible to have more than one pre-submission discussion with FDA, which has been found to be helpful in previous cases.

When talking to FDA, **you should be prepared to describe your clinical protocols in specific detail**, which is why having an IRB approved protocol might be useful. In particular, details about the test (what it is, where and how will it be used, what sort of sample is required, etc.), the population that will be studied, and the types of treatment decisions that might be made based on test results should be clear. Presenting FDA with an assay validation plan and asking the agency if it is adequate can be very helpful.

In defining the diseases or conditions that will be seen in the study, you should describe the expected prognosis for patients, and, if it exists, what standard of care is for those condition. FDA must judge each study on its specifics details, so a lack of clarity on your part with regard to the proposed research makes it difficult for FDA to assess the need for an IDE, the level of risk posed to research participants, or to discuss options available to the investigator to mediate risk in any detail. Note that, for the purposes of risk determination during pre-submission discussions, detailed information about a test's analytical performance is not required. This information would be evaluated in an IDE submission, should one be required.

Formal Submission: **If an IRB or FDA determines that a study poses significant risk to the research participants, or if pre-submission discussions with the FDA indicate so, you must submit a formal IDE application to FDA prior to commencing the study.** FDA has 30 days to review your application and respond after its receipt. If an application is missing required elements, such that it cannot be reviewed completely, the application will be returned with a 'Refuse to Accept' decision. This will stop the review clock until

the you resubmit a complete application. **If the IRB has approved the investigation, and FDA does not respond in 30 days after receiving the IDE application**, the IDE is considered approved and your study may commence.

What information is required in an IDE application?

- Unfortunately, there is no standardized form or format for an IDE application (unlike, say, an NIH grant application).
- A complete report of prior investigations of the device and an accurate summary of the proposed investigation, including the intended use of the device (this may be the clinical protocol submitted to the IRB).
    - The report of prior investigations is specific to the intended use in the study. Therefore, a study proposing to (for example) use exome sequencing to guide treatment strategies for abdominal aortic aneurysms would need to report on prior investigations of exome sequencing specifically with regards to abdominal aortic aneurysms, but nothing beyond that.
- A description of the methods, facilities, and controls used for manufacture, processing, packing, storage, and installation of the device.
- A list of all the investigators involved in the study, plus a copy of the agreements they have entered into with you, the sponsor/sponsor-investigator.
- Details about the IRB of record for the clinical study/investigation, e.g., the Federal-Wide Assurance number, information on membership, etc.
- Copies of the device's labeling. Labeling is a broad term, and can include not only information on a device's packaging (where appropriate) but also any written, printed, or graphic material "accompanying" the device[iii].
- Copies of all the forms and information that you will give to participants (including informed consent forms that make clear to the participant that the study involves an investigational device).
- Any other relevant information that FDA requests. If any is required, FDA will notify you and specify the type of information to provide. The potential need for such additional material is an example of how a pre-submission process can facilitate the ultimate IDE application review.

What are the monitoring requirements for IDEs post-approval?

Once the FDA has approved your IDE application, you can begin your study. However, **you have additional responsibilities during the course of the study.**

- Report any **adverse events** to FDA.
- Designate **monitors** for the study. Monitors are responsible for securing compliance with the IDE regulations, including:

- Ensuring that investigators comply with the investigational plan as approved by the IRB and FDA;
- Evaluating any unanticipated adverse event due to the device to determine if your participants are being subjected to an unreasonable risk;
- Terminating the study or portion of the study In the case of an unreasonable risk to your participants being identified; and
- Submitting annual progress reports, and a final report (once the study is complete) to the FDA and the IRB, including details on:
  - Study progress in relation to the approved investigational plan;
  - Number of subjects enrolled;
  - Brief summary of results and (in the final report) any conclusions;
  - Summary of anticipated and unanticipated adverse device events;
  - Description of any deviations from the approved investigational plan; and,
  - Reprints of any articles published by you in relation to the study.

Glossary:

- **Approved Device:** a medical device that has obtained a successful Premarket Approval (PMA) from FDA. PMA is only required for the highest risk devices, and the PMA process is the most rigorous device review conducted by FDA.
- **Cleared Device:** a medical device that has obtained premarket clearance, also known as 510(k) clearance, from FDA. Devices that are determined to be substantially equivalent to other legally marketed devices need only go through this process, which is less rigorous than PMA.
- **Diagnostic Medical Device:** defined by section 201(h) of the Federal Food Drug and Cosmetic Act as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
  - Recognized in the official national formulary, or the US Pharmacopeia, or any supplement to them,
  - Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or,
  - Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended

purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

- **IDE exemption:** This is admittedly a confusing phrase because of its redundancy. This is a process whereby the IRB determines that an application to the FDA for an IDE is not needed (so, exemption from FDA submission). This determination can be based on the IRBs assessment that the risk of the protocol is nonsignificant, or can also be made by FDA following a presubmission. In effect, it is an IDE granted by the IRB for investigations determined to pose nonsignificant risk to participants.
- **IDE submission**: the formal submission to FDA of an Investigational Device Exemption for approval.
- **Investigation**: a research study involving one or more identifiable human participants, or identifiable human samples, to determine the safety or efficacy of a medical device (a sample is considered deidentified in this context if the investigators do not have access to the identifiers and make a good faith effort not to reidentify participants).
- **Investigational Device Exemption (IDE)**: an exemption that allows the use of an unapproved device in a clinical investigation.
- **Investigator**: an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. A Principal Investigator may be the same as the study's sponsor (see below), although this may not always be the case. Investigators other than a study's lead investigator would almost never be the study's sponsor, who is the individual that takes responsibility for the study with FDA.
- **Nonsignificant Risk Device**: an investigational medical device that does not meet the definition of a Significant Risk Device
- **Significant Risk Device**: an investigational medical device that:
    - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject (not relevant for sequencing).
    - Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject
    - 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
    - Otherwise present a potential for serous risk to the health, safety, or welfare of the subject
- **Sponsor**: a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.
- **Sponsor-investigator:** An individual who both initiates and actually conducts, alone or with others, an investigation under whose immediate direction the investigational device is administered, dispensed or used. This may be the Principal Investigator.

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[i] The problem has been that if Sanger (or MiSeqDX or Ion PGM DX) is being used to confirm a variant for which the clinical/diagnostic interpretation is uncertain, then FDA would not consider that to be "medically established" and hence not confirmation for the purposes of determining IDE exemption.

[ii]If the research participants are young children or infants, FDA has required that the blood draw amounts be consistent with WHO guidelines. Alternatively, a tissue biopsy that carries > 2% risk of severe and/or life threatening complications (including overnight hospitalization) may be considered "significant risk". So investigators should explain what the risk of the biopsy is expected to be (and document this estimate) when presenting to IRB.

[iii] the term "accompanying" interpreted liberally to mean more than physical association with the product, and can include posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. Note that journal articles, talks at conferences, and other activities that may include discussion of the test are fine as long as the investigator does not make unsupported claims about the performance or clinical relevance of the test. However, discussion of previously obtained results and presentations of hypotheses and models are permissible with appropriate disclaimers.

- For an investigation, the label must include the following statement: "CAUTION Investigational device. Limited by Federal (or United States) law to investigational use." The labeling must also include: all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Because genomics tests are not typically discrete devices and not distributed, but are instead run as laboratory developed

tests, the information relevant to the test, including the required statement, may be provided on the test report.

- The labeling may not contain any false or misleading statements or imply that the test is safe and effective. Given the potentially broad nature of labeling, which could extend to published research reports or reviews, depending on the situation, you should be careful about making unsupported claims about the device.