Points to Consider Regarding the Food and Drug Administration's

Investigational Device Exemption Regulations in the Context of Genomics Research

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Disclaimer: The content of this resource is not intended to provide official guidance from the National Human Genome Research Institute (NHGRI) or from the Food and Drug Administration (FDA). This resource reflects information presented at NHGRI's "Investigational Device Exemptions (IDE) and Genomics Workshop," held in June 2016, and is also informed by the experience of NHGRI grantees complying with the Investigational Device Exemption regulation.

Overview

The FDA **Investigational Device Exemption (IDE)** regulation has been in place since 1976, and is applicable to some clinical genomics research. The purpose of the IDE regulation is to oversee clinical research involving "investigational" medical devices - those that have not yet been cleared or approved by FDA - and to protect human research participants from undue risk. FDA defines genomic tests, like all other *in vitro* diagnostics (IVDs), as medical devices (21 USC 321 (h)). The agency considers software, reagents, instruments, and other components across the testing pipeline, from sample to test report, to be part of a single device. In some cases, investigators leading clinical genomics investigations must obtain an IDE before they can initiate their studies (21 CFR 812).

In the context of genomics research, the purpose of the IDE process is to demonstrate that a test has plausible analytical validity and to protect the interests of study participants who might receive test results that could affect their clinical care. If a study proposes to use a genomic test that is not FDA-cleared or -approved, the investigator of the study - must consider FDA's IDE regulation before proceeding with enrollment. There are also some situations when clinical genomics research is exempt from the IDE regulation, or "IDE exempt". Factors that make a study IDE exempt are outlined in the section, "Does the IDE Regulation Apply to Your Study?"

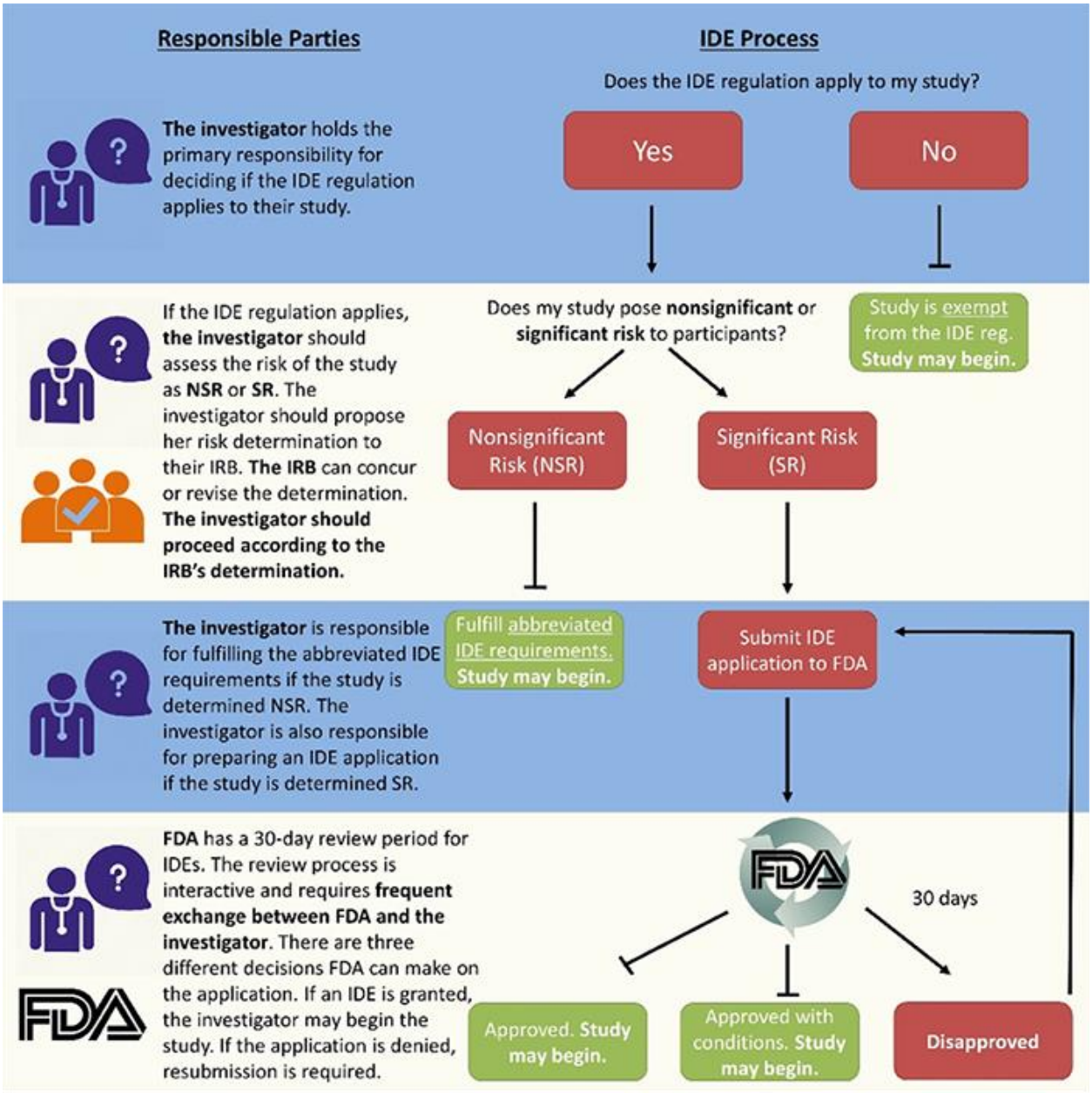
If the IDE regulation does apply, then a critical part of compliance starts with determining the risk of the study. When a study involving a research test is determined to pose "significant risk" for participants, investigators must apply to FDA for an IDE before they begin their research. A significant risk (SR) study, for example, might involve genome sequencing of healthy participants with an intent to return variants of unknown significance (VUS). In this instance, the risk might stem from concern that test results with unknown clinical significance would lead healthy individuals to pursue unnecessary treatments that could expose them to harm. If this study design does not also include appropriate risk-mitigating measures, it could be considered SR. A study determined to pose "nonsignificant risk" (NSR) study, can begin without

FDA review but still requires compliance with a set of "abbreviated IDE requirements" that will be discussed later in this resource.

Together with their Institutional Review Board (IRB), investigators play a role in determining whether a study poses SR or NSR, thereby influencing which pathway must be followed in order to comply with the IDE regulation. If a study is deemed to be SR, investigators should be aware of the time and resources that are necessary to prepare an IDE submission and see it through FDA review, as investigators bear much of the responsibility in the IDE process.

This resource provides points for genomics researchers to consider when deciding whether and how the IDE regulations apply to their research. It also describes the IDE submission process and other related steps that investigators may need to take in order to fulfill regulatory requirements. The points to consider resource attempts to answer questions investigators may have and serves as a complementary resource to FDA's existing "Device Advice" webpages that can be found here.

The following graphic depicts the IDE process and identifies the parties responsible at each step. The steps in the graphic are described in closer detail in the following sections of this resource.



Does the IDE regulation apply to my study?

FDA regulates genomic tests and other IVDs under its authority to regulate medical devices. The primary division of the FDA that implements device regulations is the Center for Devices and Radiological Health (CDRH). When reviewing genomic tests, FDA considers the entire pipeline, from sample to test report generation, to be a single device.

The first step of the process is to decide if the IDE regulations are applicable to a particular study or if the study is exempt from these regulations. **The study sponsor or sponsor-investigator has the primary responsibility for determining whether an IDE is needed**. IDE regulations apply to studies that expect to

learn about the safety and effectiveness of an investigational device, even if this is not the primary purpose of the research. Therefore, if an investigator proposes to sequence participants' genomes with a platform that is not FDA-cleared or -approved, then the IDE regulation applies. If the investigator wants to use a sequencing platform that has received FDA approval or clearance but would like to use this platform outside of its specified intended use, the IDE regulations would apply. IDE regulations would not apply if the investigator wants to use the FDA-cleared or -approved device for its specific intended use. For example, FDA cleared Illumina's MiSeqDx System for cystic fibrosis testing. If an investigator wants to use this platform to test for cystic fibrosis, then this is within the cleared intended use and the IDE regulations would not apply. Here, the genetic test would not be considered "investigational". However, if the investigator wants to use the MiSeqDx system to interrogate other regions of the genome, the IDE regulations would apply and the test would be considered investigational.

If the investigator does not propose to return results to participants or their physicians, and the results will not otherwise be used to direct or inform the clinical care of that participant, then the investigational device study is exempt from the IDE regulation.

A study may also be IDE exempt if results from the assay are confirmed using a second, "medically established" procedure. FDA does not have a formal definition of "medically established", but generally, a medically established procedure is one that is part of the standard of care for the study population. For instance, in some cases, FDA considers Sanger validation of next-generation sequencing (NGS) test results to be a medically established procedure[1]. If an investigator proposes to return Sanger validated variants with known clinical relevance, then the study could be IDE exempt. If, however, the research entails discovery and return of new variants with unknown clinical relevance, the study might not be exempt despite the use of Sanger confirmation of variant information.

Does my study pose nonsignificant risk (NSR) or significant risk (SR) to participants?

If a study is not exempt from the IDE regulation, then the next task is to determine the risk of the study. Risk determination establishes whether or not the investigator has to engage with the FDA before proceeding with the research. As stated above, FDA has two classifications of risk for studies that require an IDE: significant risk (SR) and nonsignificant risk (NSR). These classifications are based solely on the risks posed to the study participants.

The sponsor/sponsor-investigator of a study is the first to assess whether a study poses SR or NSR. It is important for investigators to be familiar with the IDE regulation and understand FDA considerations about risk determination so that their classifications are aligned with how FDA reviewers might assess the study. **Investigators should present their risk determination to the IRB when submitting their IRB protocol for review. The IRB will concur with the investigator's determination or reclassify the proposed study's risk.** The IRB's role in the IDE process is discussed later in this document.

Aspects of the Study That May Affect Risk

FDA considers risk with a different lens than that commonly used by investigators and IRBs. To promote dialogue and bridge gaps in understanding between all parties, NHGRI held a workshop on June 10th, 2016, entitled, "Investigational Device Exemptions and Genomics" that featured a diverse set of panelists, including FDA reviewers, to comment on aspects of clinical genomics research that they consider when conducting IDE risk determinations. It is important to note that FDA evaluates risk on a case by case basis,

and considers the risk of the *worst-case-scenario.* Some common themes about risk concerns for FDA reviewers that emerged from the workshop include, but are not limited to:

1. **Risks from incorrect results**: With regard to molecular diagnostic devices, a key question when assessing risk is to consider the consequences of either a false positive or false negative result. Could a false negative test report result in a participant not receiving a medically necessary treatment? Could a false positive test report result in a participant being exposed to a medically unwarranted intervention and serious or life-threatening adverse events? Even if the test has a low false positive/negative rate, the FDA considers the worst-case scenario.

   If false negative or false positive results could prevent participants from seeking necessary treatment or cause them to pursue dangerous, unnecessary treatment, then this may increase the risk of a study.

2. **Standard of care**: This point is connected to the previous issue of risks from incorrect results. How might the results of a test affect the clinical care a participant receives, and could the resultant treatment fall outside the standard of care? For example, if an investigator plans to sequence the tumor DNA of colorectal cancer patients and prescribe targeted therapies based on the specific mutations found in the tumor, what drugs does the investigator intend to prescribe? How do these drugs compare to standard treatment for colorectal cancer patients?

   If receiving test results could cause participant care to deviate from standard of care, then this may increase the risk of a study.

3. **Health status of study population**: The health status of research participants is important in 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 (e.g., genome sequencing), that study could be considered to pose less risk than a study that potentially exposes healthy participants to the risks of an unnecessary medical intervention due to a false positive result.

   If a study proposes to generate genome sequences for healthy individuals and return the research results, then this may increase the risk of a study.

4. **Return of incidental findings**: It is now becoming more common for investigators to return incidental findings to study participants. Depending on the nature of these incidental findings and other risk increasing or mitigating factors in the study, such as the health status of the participants, FDA could view the return of incidental findings as significant risk.

   If a study proposes to return incidental findings to participants, then this may increase the risk of a study.

5. **Availability of genetic counseling services**: Facilitating the return of results via a genetic counselor could mitigate the risk of a study, although it would not automatically make a study nonsignificant risk. If a protocol makes genetic counseling mandatory, rather than offering it as an optional service

that participants can choose to access, it can be viewed as a more compelling risk management approach.

If a study provides participants with genetic counseling services to accompany the return of research results, the risk of the study may be mitigated, but it is *not* automatically sufficient to diminish risk to the point of making the study NSR.

6. **Sample collection procedure**: Does the sample collection procedure constitute a risk to participant safety? Typically, the answer is no for genomics studies since the sampling is often via a venous blood draw, which is not considered an invasive procedure. An instance when obtaining a sample for genomics research could be high risk would be if the study involved sequencing tumor DNA, and the tumor biopsy could only be obtained through surgery.

If the proposed sample collection procedure is invasive, then this may increase the risk of a study.

Aspects of the Study that Do Not Affect Risk Determination

There are aspects of study design that are not considered by FDA in their assessment of risks pertinent to IDE submissions. These include:

1. **Size of the cohort**: A small cohort would not be lower risk than a large cohort. Regardless of the number of participants in the study, FDA will take the worst-case scenario for a single individual into consideration.

2. **Adherence to community expert recommendations (as opposed to practice guidelines)**: When weighing the risks of a study, FDA may view adherence to practice *guidelines* as a risk mitigating factor. However, the agency does not consider following expert *recommendations* as something that could reduce the risk of a study. This means that the FDA would not consider adherence to the American College of Medical Genetics and Genomics (ACMG) return of incidental findings recommendations as a factor in the IDE risk determination. The distinction between guidelines and recommendations is that the former are thought to be standard of care, whereas the latter are not.

3. **Incorrect exclusion from the trial**: If genetic sequencing is used to determine inclusion in or exclusion from a trial, the possibility of incorrect exclusion would not affect the risk determination. This is because individuals excluded would be expected to revert to the standard of care.

4. **Potential benefits to the study participants**: FDA does not view potential benefits that participants might derive from a study as something that would balance the study's risks. This is in contrast with the typical IRB approach, which would be to weigh benefits and risks to determine the risk of a study.

Approaching the Investigational Review Board (IRB) for a Risk Determination

Once an investigator has determined the risk of a study, they should present their assessment to the IRB in the course of submitting the study protocol for review. **The IRB must review the risk assessment provided by the investigator and ultimately decide if the study is SR, NSR, or even IDE exempt**. FDA's guidance for IRBs on this responsibility recommends that IRBs establish written procedures on how they distinguish between SR and NSR studies. 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 should questions arise later regarding the basis of IRB's decision-making. Next steps for investigators to comply with the IDE regulation depend on the IRB's risk determination, since there are different requirements for significant versus nonsignificant risk studies.

Note that FDA retains the legal authority to overrule an IRB's risk determination, but the agency encourages IRBs to make independent risk determinations. FDA's support for the IRB role in IDE risk determinations is evidenced by FDA's IDE guidance for IRBs, as well as ongoing dialogue between FDA and the research community regarding this issue.

Approaching the FDA for Clarification on Risk Determinations: FDA Pre-Submission Process

Since the relevance of the IDE regulation in the genomics field is relatively new, IRBs may be unfamiliar with making risk determinations that could affect regulatory compliance in this space. If investigators or their IRBs seeks more clarity on the IDE regulation's applicability to a given study, investigators can apply for a "Pre-Submission meeting" with FDA staff. The purpose of the pre-submission meeting is to communicate with FDA regarding a study's possible need for an IDE, including discussions of any risk factors. FDA provides guidance on requesting pre-submission meetings. Note that preparing a pre-submission meeting application could require some time, since the application packet must include components such as a detailed description of the genomic test in question, an intended use statement for the proposed study, and an overview of previous clinical data that has already been collected with the same test. **FDA is required to respond within 75-90 days from receipt of a pre-submission meeting request.** While reviewing a pre-submission meeting request, FDA may contact investigators frequently to ask for additional information. They may also set tight turnaround times for requested information. It is advised that investigators designate a point of contact who can be alert and highly responsive to FDA's communications.

When talking to FDA**,** investigators should be prepared to describe their clinical protocols in specific detail, so having an IRB-approved protocol before this step is 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. In addition, presenting FDA with an assay validation plan and asking the agency if it is adequate can be very helpful. Having an adequate assay validation plan is important because if an IDE submission is deemed necessary, FDA reviewers will ask investigators to include detailed validation data in their submission in order to verify that a test is plausibly analytically valid. **Note that for pre-submission discussions, detailed information about a test's analytical performance is not required. This information would only be evaluated in an IDE submission, should one be required.**

In defining the diseases or conditions that will be seen in the study, investigators should describe the expected prognosis for patients, and, if it exists, what the standard of care is for those conditions. FDA must judge each study on its specific details, so any lack of clarity with regard to the proposed research makes it difficult for FDA to assess the need for an IDE or the level of risk posed to research participants. It also confounds the determination of options available to the investigator to mediate any risks.

What do I do if my study is a nonsignificant risk (NSR)?

If an investigator has determined that their study is **NSR** and the IRB concurs, the investigator ***does not*** need to submit an IDE application to the FDA before enrolling research participants. **FDA considers**

NSR studies to have an IDE once the IRB concurs with the NSR determination, even though FDA has not been consulted for risk determination.

There are "abbreviated IDE requirements" that NSR studies must comply with in order to maintain the IDE. These requirements include:

- Appropriate labeling in accordance with 21 CFR 812.5
- Obtaining and maintaining IRB approval as an NSR study throughout the course of the investigation
- Obtaining documented, informed consent from study participants, unless documentation is waived by the IRB
- Monitoring to protect study participants, and assuring compliance with approved protocols
- Maintaining records of participants' case history and exposure to the device[2]
- Submitting appropriate reports in the case of an adverse event caused by the genomic test, withdrawal of IRB approval, or failure to obtain informed consent

If the investigator believes a study is NSR, but the IRB determines it is SR, then the IRB's ruling prevails and the investigator must submit an IDE application to the FDA before beginning research. It is possible for the investigator to consult the FDA and obtain a second opinion through FDA's pre-submission meeting mechanism. As noted previously, the FDA's risk determination would be final and would take precedence over the IRB's determination.

What do I do if my study is a significant risk (SR)?

If the investigator has determined that their study is **SR** and the IRB concurs, the investigator **must submit an IDE application to the FDA before beginning research.** Studies determined to be SR may still be undertaken; however, the IDE application must be approved before you can begin enrolling participants.

IDE Submission

To apply for an IDE, the investigator must gather information relevant to the genomic test and the study design and submit it in a paper and electronic format. While FDA does not have a template or specific format for IDE applications, the agency does require certain pieces of information to be included in the submission. Appendix II lists required components of an IDE application. General formatting tips are to be organized, descriptive, and to include a detailed table of contents in the application.

Upon receipt of an IDE application, FDA is required to make a decision within 30 days. The review process is dynamic and will require substantial communication between the investigators and FDA reviewers. Reviewers may reach out to ask for clarification on portions of the application or request supplementary information. If investigators are unable to fulfill FDA reviewers' information requests before the 30-day deadline, FDA may restart the clock and extend the total review time beyond 30 days. If FDA requests certain information between a 1 to 2-day turnaround period and investigators are unable to meet the deadline, the FDA may also decide to restart the clock. Therefore, investigators are advised to be alert and highly responsive to FDA communications. If the IRB has approved the investigation's protocol and FDA does not respond within 30 days of receiving the IDE application, the IDE is considered approved and the study may commence.

There are three different decisions that FDA can make on an IDE application. FDA has a guidance document describing these IDE decision outcomes.

1. **The IDE is granted.** In this case, investigators may begin research upon receipt of IRB approval.

2. **The IDE is granted with conditions.** This decision means that FDA has determined that it is safe to begin enrolling patients, but that there are minor information gaps in the application or minor issues (not related to study design) that the agency suggests investigators to address. In this scenario, the investigator may initiate their study immediately upon receipt of FDA's approval with conditions letter and IRB approval. The only caveat is that approval with conditions requires investigators to submit an amendment to the IDE application within 45 days of receipt of the FDA's approval with conditions letter. In the amendment, investigators should respond to the issues referenced in FDA's letter. If investigators do not send responses within the 45-day deadline, the FDA will place the study on hold until all concerns are addressed.

3. **The IDE application is disapproved.** In such cases, the study cannot proceed as submitted. The disapproval letter will describe problematic areas within the study or application materials. Investigators may submit an amendment to the IDE to make modifications. If FDA is satisfied with the response, then investigators may receive an IDE to begin their research.

Post-Approval Requirements for Significant Risk Studies

Significant risk studies may begin once the investigator has obtained an IDE from FDA in addition to IRB approval. The investigator should designate monitors for the study who are responsible for securing compliance with the IDE regulation. These monitors will:

- Ensure that investigators comply with the investigational plan as approved by the IRB and FDA
- Evaluate any unanticipated adverse events due to the test to determine if participants are being subjected to an unreasonable risk
- Terminate the study or a portion of the study if an unreasonable risk to participants is identified
- Submit annual progress reports and a final report to the FDA and the IRB once the study is complete

Investigators should plan accordingly to fulfill the reporting requirements necessary to maintain the study's IDE. Annual and final reports should include the following information:

1. IDE number
2. Name of the test
3. Study progress in relation to the approved investigational plan
4. Number of subjects enrolled
5. Brief summary of results and (in the final report) any conclusions
6. Summary of anticipated and unanticipated adverse device events
7. Description of any deviations from the approved investigational plan
8. Reprints of any articles published by investigators in relation to the study.

There are other instances when investigators may have to file additional reports with FDA. In the case of an unanticipated adverse event or withdrawal of IRB approval, investigators must immediately report to FDA. If an investigator wants to significantly modify their investigational plan or test pipeline in a way that could greatly affect the validity of the data or the safety of participants, they must submit an IDE supplement to FDA and receive approval before the modifications can take place. Less significant modifications that do not constitute a substantial change in the design of the study, affect the validity of

data, or affect the safety of participants can be implemented immediately as long as the investigator provides notice to FDA within five working days of making those modifications.

Since genome sequencing technology is constantly evolving, it is commonplace for investigators to modify parts of their testing pipeline throughout the course of a study. Depending on the study, FDA may require submission of an IDE supplement when investigators make changes to the testing pipeline. In some cases, a five-day notice could be sufficient. It is best to discuss what type of modifications constitute an IDE supplement versus a five-day notice with FDA early on in the IDE process, whether in a pre-submission meeting or during the IDE review.

The FDA Device Advice online resource provides more information on IDE reports and suggested formats.

A complementary NHGRI resource on the suggested IDE Submission Format can be found here.

Glossary

- **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:

    1. Recognized in the official national formulary, or the US Pharmacopeia, or any supplement to them,
    2. 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,
    3. 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.

- **FDA-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.
- **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.
- **Investigational Device Exemption (IDE)**: an exemption that allows the use of an unapproved device in a clinical investigation.
- **IDE exempt:** refers to situations when an IRB or the FDA has determined that the IDE regulation is not applicable to a study. It is admittedly a confusing phrase because of its redundancy.
- **IDE submission**: the formal submission to FDA of an Investigational Device Exemption for approval.
- **Incidental finding:** a finding that is not related to the study protocol but is discovered through the course of research and is potentially of medical relevance to a research participant
- **Investigational device study**: a research study involving an investigational medical device that includes one or more identifiable human research participants, or identifiable human samples, to determine the safety or efficacy of the medical device
- **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 Study:** a study involving an investigational medical device that does not meet the definition of a Significant Risk study (see below).
- **Pre-submission process:** a process through which study sponsors/sponsor-investigators may apply to the FDA for a Pre-submission meeting. During this meeting, sponsors/sponsor-investigators or their IRBs can ask FDA for more clarity on the IDE regulation's applicability to their studies.

- **Significant Risk Study**: an investigation that
  - Intends to implant a device in participants that presents a potential for serious risk to the health, safety, or welfare of those participants (not relevant for sequencing)
  - Uses a device that 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
  - Uses a device that holds 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 serious 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 directly 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.

Footnotes

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[1] Though it is true that Sanger has been referred to by some as the gold standard for sequencing, it has never gone through the FDA's premarket review process. Nevertheless, due to its long-standing history, Sanger sequencing has been grandfathered in as a medically-established technology and is frequently looked to for orthogonal validation of NGS.

[2] A case history could include case report forms and supporting data, signed and dated consent forms and medical records, physician notes, hospital charts, and nurse's notes.

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