National Human Genome Research Institute (NHGRI) Investigational Device Exemptions (IDEs) and Genomics Workshop

June 10, 2016
8:00 a.m. – 4:00 p.m.
5635 Fishers Ln, Rockville, MD 20852

Meeting Report: Summary, Standing Questions, and Next Steps

Executive Summary

On Friday, June 10th, 2016, the National Human Genome Research Institute (NHGRI) held an all-day workshop on "Investigational Device Exemptions (IDEs) and Genomics". The goal of the workshop was to discuss the Food and Drug Administration's (FDA) IDE regulations as they apply to clinical research that uses genomics technologies such as next-generation sequencing (NGS). The FDA considers NGS-based tests to be *in vitro* diagnostic devices (IVDs) that in many cases, when used in research, are also "investigational". Certain studies that are considered "significant risk" must receive an IDE from the FDA before they may begin. Since the shift of genomic technology toward clinical application has been rather recent, many genomics researchers are unfamiliar with FDA regulations such as the IDE. Academic researchers are often unused to navigating FDA regulations because they have no prior interaction with FDA, lack sufficient regulatory affairs support, and have limited time and resources to conduct their studies. Additionally, the FDA's 30-day turnaround time for IDE review requires submitters to be quick and responsive to FDA communications, which can be difficult given resource constrains and limited experience.

Speakers representing the investigator, institutional review board (IRB), FDA, and NHGRI perspectives were charged with identifying knowledge and understanding gaps surrounding the IDE regulations through a series of panel discussions. They shared experiences with investigators and IRB members who may encounter the need for an IDE. NHGRI collaborated with FDA's Center for Devices and Radiological Health (CDRH) to develop the content of this event. CDRH reviews IDE submissions and is responsible for FDA's medical device regulations.

Each workshop session addressed a different component of the IDE process. Obtaining an IDE from the FDA requires several steps, including determining if the regulation is applicable to a given protocol, determining the risk posed by use of the investigational IVD in the study, and, if necessary, preparing and submitting an IDE application to the FDA for review. For some studies, the IDE does not apply and the studies are therefore exempt from the IDE regulations. For those studies that are deemed "nonsignificant risk", the investigator need only comply with abbreviated IDE requirements that involve labeling, monitoring participants, and keeping certain records. For those studies that are deemed significant risk, investigators must apply for an IDE before they can begin their study.

In “Session I: What is an Investigational Device in the Context of Genomics Research?” speakers defined terms relevant to the IDE and spoke to the obstacles that investigators face when attempting to fulfill IDE requirements. Many genomics researchers do not know what the FDA considers a device, and also do not know what parts of the NGS pipeline count as part of the device. The FDA considers the device as any component of the genomic test pipeline that that leads to the production of information that might be returned to patients or participants, including any instrumentation, reagents, software, and databases, to be part of the device.

The purpose of “Session II: Analytical Validation and IDEs” was to discuss the analytical validation data that the FDA requests in an IDE submission. The FDA assesses analytical validity data to determine if the device is plausibly effective. Reviewers are particularly interested in the false positive and false negative rate of the device. Though Sanger confirmation can minimize false positives and the FDA recognizes Sanger as a comparator method for NGS, Sanger confirmation does not address all concerns about analytical validity, and reporting variants confirmed by Sanger does not necessarily make a study exempt from the IDE regulations.

The third and fourth workshop sessions dealt with risk assessment. The risk of an investigational device study determines whether an IDE application is necessary. The risk of a study often does not depend on the type of IVD being used, but rather on how IVD results will be used in the study. FDA views risk on a case-by-case basis. The investigator bears the primary responsibility for determining the risk of a study, and their determination to their IRB for evaluation. If the IRB determines that a study is significant risk, the investigator should be directed to approach the FDA. If the study is nonsignificant risk, then it is considered to already have an IDE and the investigator does not have to apply to FDA before beginning the study. Nevertheless, to maintain the IDE for an NSR study, the investigator must comply with abbreviated IDE requirements that include proper labeling, IRB approval, informed consent, monitoring, keeping certain records and reports, and a prohibition against promotion. FDA maintains the authority to overrule the risk determinations made by an IRB, but does not review every investigational device study protocol for the purpose of determining risk.

There were some differences in the way researchers, IRB, and FDA think about the risk of genomic studies. FDA does not take into account benefit or potential benefit when it makes its risk assessment. FDA staff considers the worst-case-scenario that could occur in a given study, and determines risk based on this. If the genomic test used in the study bears the risk of inappropriately directing participants away from the standard of care, FDA will consider the possible harms of such a situation when making a risk determination. From the perspective of an IRB member participating in the workshop, although there are some risks to genomic research including breach of confidentiality, disclosure of findings, and conflicts with participants’ values, there have been no reported cases of significant harm from genomics research, and studies indicate a low frequency of adverse psychological outcomes. The IRB panelist also added that the research community may believe that measures to offset potential harms such as adequate informed consent, genetic counseling services, and following professional guidelines such as those created by the American College of Medical Genetics and Genomics (ACMG) could help mitigate the risk of a study. FDA said that these factors would not necessarily affect risk determination, although all risk determinations are study specific.

Finally, "Session V: Steps after Determining Risk" covered the investigator's responsibilities after determining the risk of a study. For nonsignificant risk studies, the investigator may begin their study after receiving IRB approval and meeting the abbreviated IDE requirements for labeling, monitoring, reporting, and keeping certain records apply. For significant risk studies, FDA must approve the IDE submission before the study may commence, and investigators must include a specific list of content in these submissions. FDA has a 30-day review period for IDE submissions. Significant risk studies are also subject to follow-up reporting necessary for maintaining an approved IDE. The appendix contains checklists and other resources (FDA and non-FDA) for more guidance.

Outstanding Questions

1. Although the FDA suggests that investigators apply for a pre-submission meeting to address any questions about the IDE submission process, members of the research community have indicated that applying for pre-submission can be burdensome and lengthy, especially given the limited time and resources that academic researchers face. Is it possible for researchers to receive substantive guidance without having to apply for a pre-submission meeting?

2. Professional guidelines (i.e. ACMG) and community opinion is increasingly leaning toward the return of secondary findings. At what point does the FDA consider these guidelines to be standard of care, and if these guidelines are deemed standard of care, how does FDA factor them into risk determination?

3. If a study does not intend to return results to patients or providers, do the IDE regulations apply?

Next Steps

- **NHGRI and CDRH will continue to engage in open dialogue with the research community to address standing questions and offer resources and information about the IDE regulations.**

- **NHGRI and CDRH will continue efforts to bridge knowledge gaps between the regulatory and genomics research communities with the goal of streamlining the IDE process.**

- **NHGRI will release a white paper to provide investigators with points to consider when conducting genomics research that could require an IDE.**

Workshop Session Summaries

NHGRI Director Dr. Eric Green opened the workshop. Genomic technology is rapidly entering the clinic and holds great promise in improving patient care. NHGRI will continue to work with CDRH to meet the twin needs of promoting innovation and patient safety.

Policy Context of IDEs: Why IDEs and Why Now?

Speaker

David Litwack, **Ph.D.** – Food and Drug Administration

Genomic research and IDEs have not traditionally intersected due to the former's focus on basic research, but today, as new genomic technologies move rapidly into the clinic, more studies are potentially subject to the IDE regulation. Academic researchers are often unused to navigating FDA regulations because they have no prior interaction with FDA, lack sufficient regulatory affairs support, and have limited time and resources to conduct their studies.

Understanding the IDE regulation will help academic researchers be better prepared to plan ahead and enter the process. FDA is open to conversing with sponsors and investigators regarding the IDE process, and investigators are encouraged to apply for a "pre-submission" meeting, a one-time meeting with FDA staff to discuss the possible need for an IDE or particular elements that must be included in an IDE submission.

In conclusion, **Litwack** stated that IDE approval aims to ensure that risks are outweighed by anticipated benefits to participants, informed consent is adequate, and the investigational device is plausibly effective. The primary intent is to protect participants in research by evaluating the safety and ethics of a study.

Session I: What is an Investigational Device in the Context of Genomics Research?

Speakers

Stephen Kingsmore, M.D., D.Sc. - Rady Children's Institute for Genomic Medicine
Paula Caposino, Ph.D. - Food and Drug Administration

In this session, speakers gave a broad overview of the IDE process and defined terminology important to understanding the IDE regulations. **Stephen Kingsmore**, an investigator participating in the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) consortium, spoke about his experience with the IDE process. NSIGHT is co-funded by NHGRI and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). **Kingsmore** explained that academic researchers already face a large burden to comply regulations from NIH, IRBs, and the Clinical Laboratory Improvement Amendments (CLIA), the College of American Pathologists, and the State of California. After the FDA notified NSIGHT of the IDE requirement, it took 10 months for **Kingsmore**'s group to go through pre-submission, submission, and protocol revision before they could begin enrolling patients. The study was ultimately determined nonsignificant risk, so **Kingsmore** only had to fulfill abbreviated IDE requirements rather than submit a full IDE application.

Paula Caposino gave a legal definition of a "device" and an *in vitro* diagnostic (IVD), which FDA regulates as a device. NGS tests are considered IVDs. She clarified the definition of an investigation as it pertains

to the need for an IDE. If an investigator is conducting clinical research involving one or more subjects and expects to learn about the safety and effectiveness of an investigational device, then the IDE regulations apply. An investigational device is one that is not legally marketed for the intended use or indication for use being tested in the study, whether or not it has been previously cleared or approved for a separate intended use.

One important gap in understanding is that academic researchers do not know what FDA's definition of a device is, and what parts of the genomic test pipeline count as part of the device. Understanding this definition is critical because FDA requires that submitters describe their device in the IDE submission. The FDA's defines the device as any component of the genomic test pipeline which can span from sample to test report. This can include instrumentation, reagents, software, and databases. The sponsor of a study – the person who initiates but does not actually conduct a study – or the sponsor-investigator – the person who initiates and conducts an investigation – is responsible for the investigational device in their study. Throughout the course of research, it is common for investigators to modify their pipelines as new techniques and technologies become available. If the study is a significant risk study, then, investigators need to contact the FDA to update them on modifications. FDA is most interested in modifications that alter the risk or performance of the genomic test. If the study is nonsignificant risk and the modification would change it to significant risk, the investigator would have to apply for an IDE.

An audience member asked if the IDE regulations apply if an investigator does not plan to return results to patients or providers. FDA staff present suggested that there are different factors that could affect whether or not the IDE regulations would apply to this type of study.

Session II: Analytical Validation and IDEs

Speakers

Jonathan Berg, M.D., Ph.D. - University of North Carolina
Sharon Liang, M.D., Ph.D. - Food and Drug Administration
Haja El Mubarak, Ph.D. - Food and Drug Administration

The purpose of this session was to discuss the analytical validation data that the FDA requests in an IDE submission. **Jonathan Berg**, also an NSIGHT investigator, leads a study that was determined significant risk by the FDA. He described his experience submitting analytical validity data for a whole exome sequencing test used in his study. The components of a single test can be obtained from multiple sources that may have been individually validated, or perhaps validated in previous literature. It would be difficult to independently validate the test components in the way one would do to commercially market a product. **Berg**'s group cited publications and mentioned previous experience in sequencing as analytical validity data for their IDE submission.

FDA is interested in analytic data regarding false positive and false negative results. False positives can be minimized through orthogonal confirmation by Sanger, but this is expensive. FDA recognizes Sanger as a comparator method for NGS, although it also recognizes that Sanger is lacking in some aspects. In

particular, it is not possible to verify all "negative" results by Sanger sequencing and therefore the true rate of "false positives" from an NGS experiment is difficult to ascertain. Additionally, if Sanger sequencing is considered the "gold standard" but is itself not perfect, it is possible that some "true positive" NGS results might fail to be confirmed by Sanger sequencing and thus be lost. An important question to ask is if the researcher is responsible for quantifying the analytical validity of a device before engaging in research. The community is already working on initiatives such as Genome in a Bottle and precisionFDA to create better reference materials and develop genomic data analysis tools, respectively.

Validation of a genome test also relies upon clinical validity in addition to analytical validity.[1] This is another area where the community is working to develop standards, but more time is needed. Nothing is perfect, and although there is room for improvement, knowledge is improving and everyone wants to apply the best, most novel methods.

Sharon Liang and **Haja Sittana El Mubarak** said the basic components of an IDE submission include the intended use of the device, the device description and controls, summary of prior investigations, the clinical protocol, analytical validity, description of how results will be interpreted, and some administrative items detailed in the FDA's IDE checklist resource. The IDE only requires a few, critical pieces of analytical validity data such as analytical accuracy as compared to validated comparator methods, analytical sensitivity (LoD), precision and reproducibility, analytical specificity if applicable, and pre-analytical information on sampling methods and handling. This is less information than is required in a pre-market review application, because for IDE submissions FDA only wants to assess that the device is *plausibly* effective.

Session III: Risk Assessment

Speakers
Jeffrey Seidman, M.D. – Food and Drug Administration
Sara Chandros Hull, Ph.D. – NHGRI

Session III panelists talked about the risk determination step of the IDE process. **Jeffrey Seidman** spoke about how the FDA determines whether an *in vitro* diagnostic device study is significant risk and therefore requires an IDE. He explained that the risk of a trial typically depends not on the IVD, but rather on how the information generated by the IVD will be used in a specific trial. Therefore, different studies that use the same device can have different risk determinations. **Seidman** further explained that aspects not considered in a risk determination include benefit or potential benefit and number of patients in a trial. In order to determine risk, the FDA requires a device description and a complete clinical protocol of the trial, including proposed interventions and how the device will be used to make decisions about treatment. Lastly, **Seidman** explained that FDA often makes risk determinations by referring to guidelines about standard of care for conditions. For example, the National Comprehensive

[1] Although clinical and analytical validity are both important to show the validity of a genomic test, in the context IDEs, FDA I only interested in assessing the analytical validity of the test. The FDA does not consider clinical validity when reviewing IDE submissions.

Cancer Network considers clinical trials as a first-line therapy for some cancers. In this case, FDA makes its determination with the understanding that a clinical trial does not mean that a patient is forgoing better care.

Sara Chandros Hull described an IRB's role and considerations for making risk determinations for genomic research IDEs. She noted that the landscape has shifted from a time when most genetic results would not be disclosed to now when the general agreement in the field is that there is some affirmative obligation to disclose primary and secondary findings. Some risks of genomic research stem from breaches of confidentiality, some from disclosure of findings, and some from uses that conflict with donors' values; however, thus far, there are no reported cases of significant harm from genetic research and studies indicate a low frequency of adverse psychological outcomes.

Hull described that IRBs are well-positioned to make determinations about the return of secondary findings as well as the availability of resources that would enable this return of information. IRBs can also help investigators find ways to manage disclosure risks, such as clinical validation of results, genetic counseling, best practices for informed consent, and evaluating thresholds for clinical relevance using professional society lists and expert review committees. IRBs may consider these factors sufficient to lead to nonsignificant risk determinations in genomic research.

During the Q&A, **David Litwack** reinforced that while IRBs and investigators should feel empowered to make risk determinations, FDA can ultimately make the decision to change a risk determination. If IRBs and investigators have done their due diligence, there will be no consequences to these parties for a nonsignificant risk determination that is later deemed to be significant risk. **Kellie Kelm** (FDA) also expressed discomfort with allowing patients to decide whether they would like their findings to be confirmed in a research study for cases where suspected germline variants are found while sequencing tumors. She was concerned about the analytical validity of these germline variants. **Litwack** added that the risk determination for tumor sequencing would depend on the type of cancer and the available treatment options for that cancer. If the cancer is not curable, then returning a variant that might have an effect 10-30 years in the future would not bear as much risk. **Jonathan Berg** noted that he believes a risk determination is difficult when FDA is not taking benefit into account.

Session IV: Risk Assessment Case Studies

Panel Moderator
Laura Lyman Rodriguez, Ph.D. – NHGRI

Panelists
Anastasia Wise, Ph.D. – NHGRI
Kellie Kelm, Ph.D. -- Food and Drug Administration
Jeffrey Seidman, M.D. – Food and Drug Administration

To offer the audience practice in determining the risk of genomic research protocols, **Laura Lyman Rodriguez** moderated a case studies panel to assess the risk – significant or nonsignificant – of three hypothetical research protocols that involve the use of NGS technology.

Protocol X was the following:

- 100 healthy newborns are enrolled in an NGS (WGS) screening study
- All pathogenic results are confirmed by Sanger sequencing in a CLIA-certified lab
- Results predicting non-medically actionable, childhood-onset conditions will be reported to parents
- Results predicting medically-actionable, adult-onset conditions also will be reported to parents
- Trio NGS conducted to ascertain if pathogenic variants are *de novo* or inherited
- Parents can consent to receive ACMG incidental findings for themselves
- A genetic counselor provides services before and after testing and also facilitates the return of results.

Based on the information given in the protocol and what was currently understood about FDA's view on risk, **Rodriguez** proposed that this study might be determined to be significant risk. Returning results that predict disease in a healthy study population is risky, as is the trio-based whole genome sequencing. She asked the panel to comment.

Kelm concurred that a major aspect of this case study is that the investigator proposes to return results to a healthy study population. Genetic counseling could address some risks, but would not necessarily alter the overall risk determination. Though the investigators propose to return incidental findings according to ACMG guidelines, FDA does not believe that this mitigates risk. **Kelm** agreed that this protocol would likely be deemed significant risk.

An audience member asked if this protocol would actually be exempt from the IDE regulations since it proposes the use of Sanger sequencing to return pathogenic results to patients. **Kelm** replied that although Sanger is analytically valid, it is not clinically valid. According to the Code of Federal Regulations, a device is exempt from the IDE regulations if it "is not used as a diagnostic procedure without confirmation of the diagnosis by another, *medically established* diagnostic product or procedure," (21 CFR812.2 (2015)). Medically established procedures are clinically valid. Testing a healthy population is not the standard of care, and therefore this newborn testing would not be medically established or clinically valid. The audience and panel discussed that there is still no clear definition of "medically established" and "standard of care" in the context of genetic testing.

Another audience member asked why FDA is focused on the danger of NGS producing false results given that NGS has a high level of accuracy. The response to this question was that FDA staff considers the worst-case-scenario when they make a risk determination. In the case that a false result is returned, FDA will consider what the implications of this event would be.

Protocol Y was the following:

- Phase III clinical trial: 500 patients with relapsed colorectal adenocarcinoma are randomized to standard treatment vs. targeted therapy by NGS tumor sequencing
- Oncopanel analyses of both tumor & germline (blood) in a CLIA-certified laboratory
- Primary analysis: Tumors are analyzed for somatic variants that are targetable, based on literature search
- Secondary analysis: Germline variants known to predispose to inherited susceptibility to colon cancer
- Primary outcome: Participants with druggable somatic variants treated with therapeutic and survival time and/or recurrence will be compared to standard treatment
- Secondary outcome: Participants will receive molecular diagnostic reports of both the somatic and germline variants. Those with germline variants will be offered genetic counseling.

Again, based on the given information and what was understood about FDA's view on risk, **Rodriguez** proposed a theoretical risk determination, this time of nonsignificant risk. The aspects of this protocol that were thought to decrease the risk were the fact that the patients had relapsed cancer and that genetic counseling would be provided.

The limited information provided in this case study led the FDA panelists to disagree on the nonsignificant risk determination. The researchers would have to provide more information on what targeted treatments the investigators would offer. One would have to compare the benefits and potential negative side effects of the drugs used in the study. Another factor to take into consideration is the difference between the standard of care for the study population and the investigational treatment proposed in the trial. Diverting participants from the standard of care could potentially lead to harm.

Returning germline results also heightens the risk of this study because it exposes an individual's family to risk. In this case, FDA would be interested to know how individuals consent to receive germline results.

Protocol Z was the following:

- Large 800,000 person nationwide cohort for a longitudinal study
- Cohort includes individuals recruited directly from healthcare provider networks
- Pharmacogenomics array and NGS exome sequencing in CLIA-certified lab
- Participants may download un-interpreted sequence data
- Incidental findings are reported according to ACMG guidelines
- Sequence data are deposited in EHRs and can be shared with providers upon participant's request
- De-identified, individual-level data are accessible to secondary investigators through a controlled-access process

- Investigators performing secondary analyses on the pharmacogenomics and exome data may return individual-level results of their analyses to participants

The panel discussed the possible risk-heightening and risk-decreasing aspects of this study. An audience member asked if secondary analysis would qualify as an additional device and how this would affect risk determination. **Kelm** responded that it is almost impossible to assess the risk in this case because there are so many unknowns. Secondary analysis could introduce "unlimited" risk, making this protocol a significant risk study. Investigators proposing to conduct secondary analysis would likely have to determine the risk of their studies individually and submit individual IDE applications to FDA if their studies bear significant risk. However, if they receive permission to do so, secondary investigators could submit a master file of the NGS exome sequencing and pharmacogenomics panel as part of their IDE submission.

An audience member asked if returning un-interpreted sequence data, assuming that this data is perfectly analytically valid, to patients would automatically qualify this protocol as significant risk. **David Litwack** said that patients could take un-interpreted sequence data to another party and have the data interpreted outside of the study. FDA needs to explore the implications of this scenario further in order to come to a decision.

Session V: Steps after Determining Risk

Speakers

Jelena Petrovic Berglund, Ph.D., R.A.C. – Duke Clinical & Translational Science Institute
David Litwack, Ph.D. – Food and Drug Administration

The purpose of this session was to discuss what happens after a risk determination is made. **Jelena Petrovic Berglund** shared Duke Clinical & Translational Science Institute (Duke CTSI) templates for IDE submissions and discussed the content, order of content, and format of an IDE submission.[2] Duke CTSI offers a free, remote-participation training program on medical device regulations for those who wish to learn more about IDEs and other medical device regulations.

David Litwack offered additional tips. A well-organized submission with a detailed and hyperlinked table of contents and logical sections is easier to review. Investigators should be ready to respond to emails and calls from IDE reviewers during the 30-day review cycle. Within 30 days, the IDE reviewers may take the following actions: approve the IDE, meaning that the study may commence once IRB approval is obtained; approve with conditions, meaning that the study may commence once IRB approval is obtained and on the condition that within 45 days of notification, the investigator must submit information to the FDA to address identified issues; disapprove, meaning that the study cannot begin until identified deficiencies are resolved.

[2] For a more detailed list Duke CTSI's recommendations for IDE submissions, please see Petrovic Jelena Berglund's slides here: https://www.genome.gov/multimedia/slides/ideworkshop/11_berglund.pdf

If investigators and their IRBs have determined that a study is significant risk, they should apply for an IDE. The study may only commence once the investigators have received approval from the FDA. After receiving an IDE for their significant risk studies, investigators must file annual reports to the FDA to maintain the IDE. If the study is determined to be nonsignificant risk, then investigators only need to comply with abbreviated IDE requirements, which include labeling[3], IRB approval, informed consent, monitoring participants, record keeping and adverse event reporting, and a prohibition against promotion and other practices. Nonsignificant risk studies do not require a full IDE submission. Though there is no standard format for IDE submissions, the FDA does require certain information to be included in the submission.

Once investigators obtain an IDE, they must take certain actions to maintain the exemption. The FDA requires annual reports and a final report. If investigators wish to make significant modifications to the study protocol and/or device, investigators should submit an IDE supplement to the FDA for approval before implementing these changes. Significant modifications are those that could affect the safety of the trial and affect the performance of the device. Certain smaller modifications do not require an IDE supplement and can be reported to the FDA within five working days ("5 Day Notice") or in the annual report.[4]

The FDA has several online resources to help investigators learn more about IDE and other medical device regulations.[5] **Litwack** encouraged investigators to ask questions about IDE requirements in a pre-submission. He also encouraged investigators to call or email reviewers if they do not understand any aspect of FDA's letters.

Appendix

Additional Resources on IDEs

- **Device Advice: Investigational Device Exemption** (FDA): This online resource provides information on the IDE regulations and how to comply with them.
- **eCopy Program for Medical Device Submissions** (FDA): This guidance describes how to prepare and submit electronic copies of medical device submissions. FDA requires investigators to send two electronic copies of their IDE submissions.
- **FDA Decisions for Investigational Device Exemption Clinical Investigations** (FDA): This guidance explains how FDA makes decisions on IDE submissions and the different outcomes that may result from the review of an IDE application.

---

[3] The "label" of a genetic test could include the test report and other materials intended to communicate information to study participants and providers. Relevant labeling components may vary depending on the test.
[4] The criteria for modifications that meet the FDA's 5 Day Notice are here: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm
[5] Please see appendix for a list of links and resources.

- **IDE Template Documents** (Duke CTSI): Duke Clinical & Translational Science Institute has created templates for pre-submission requests, IDE submissions, and other paperwork related to the IDE.
- **IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed**: This guidance for IRBs provides information on how to determine if an IDE is necessary.
- **Medical Device Regulatory Training Program** (Duke CTSI): Duke CTSI offers a free, online training course of those who would like to learn more about medical device regulations including the IDE.
- **Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff** (FDA): This guidance describes the pre-submission mechanism and how applicants can request a pre-submission meeting with FDA staff.
- **Significant Risk and Nonsignificant Risk Medical Device Studies** (FDA): This guidance provides advice to investigators and IRBs on how to determine the risk of an investigational device study.

Glossary

The following are terms that appear in this meeting report or that are commonly used to discuss medical devices and IDEs.

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.

***In vitro* Diagnostic 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.

Investigational Device Exemption (IDE): an exemption that allows the use of an investigational device in a clinical investigation.

IDE submission: an application to FDA for an Investigational Device Exemption.

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.

Investigator: an individual who 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 that does not meet the definition of a Significant Risk Study (see definition of "Significant Risk Study").

Significant Risk Study: a study that proposes the use of 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 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 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.