Investigational In Vitro Diagnostics (IVDs) utilized in Clinical Investigations of Therapeutic Products
IRBMED Guidance

I. INTRODUCTION

Human subjects research applications received by IRBMED include clinical investigations of therapeutic products (drugs, biologics, medical devices, etc.) that propose to utilize in vitro diagnostic (IVD) tests or assays. An IVD is most frequently used in clinical investigations for one or more of the following reasons: (1) to determine or classify a subject's condition in order to enroll them in the research or assign them to a specific research arm; (2) to identify a specific dose of the investigational drug; and/or (3) to evaluate the response to investigational treatment. Multi-site research projects (i.e., the same research protocol conducted at multiple sites) may permit each participating site to use a site-specific test/assay. Based on the type of IVD use, U-M researchers will need to comply with additional regulatory responsibilities, as applicable. These circumstances are complex and increasingly common with the rise of personalized medicine in research.

The FDA issued "draft" guidance in December 2017 titled, "Investigational IVDs Used in Clinical Investigations of Therapeutic Products". This guidance was intended to help sponsors and institutional review boards (IRBs) make determinations about the risks of investigational IVDs used in therapeutic product studies. To date, the guidance has not been finalized. FDA guidance documents do not establish legally enforceable responsibilities, but describe the agency's current thinking on a topic and are only recommendations unless specific regulatory or statutory requirements are cited. In the absence of final guidance from the FDA, IRBMED is issuing this guidance to guide decision-making for clinical investigations utilizing IVDs.

II. DEFINITIONS (per FDA)

- *In vitro diagnostic (IVD) products* are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVDs are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.
- According to the 2017 FDA IVD draft guidance: "an *Investigational* IVD is an IVD "that is the object of an investigation" (21 CFR 812.3(g)). An investigation is defined as a "clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device" (21 CFR 812.3(h)). When an investigational IVD is used to determine the therapeutic management of subjects in a therapeutic product trial, **and** trial results provide information on the safety and effectiveness of the investigational IVD in addition to the safety and effectiveness of the investigational therapeutic product, FDA believes that the trial falls within the definition in 21 CFR 812.3(h)."
- A laboratory developed test (LDT) is a type of in vitro diagnostic test (IVD) that is designed, manufactured, and used within a single laboratory.

  NOTE: LDTs are generally regulated under the Clinical Laboratory Improvement Amendments (CLIA) by the Centers for Medicare and Medicaid Services (CMS). If the intended use of LDT testing meets the FDA definition of investigational IVD, it will also be regulated as a medical device. Conducting a test in a CLIA certified laboratory is not the same as the FDA approval/clearance for its intended use.
- A significant risk (SR) device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health.
- Non-significant risk (NSR) device – a device that does not meet the definition of significant risk (SR) device.

III. WORKFLOW PROCESS

A. Research studies initiated by U-M Investigators

1. Investigational IVD and Object of the Investigation

For the purpose of the IRBMED review, IVDs will be reviewed as *investigational* IVDs (eResearch 7-2.1 must be checked "yes") in the following circumstances:

- The IVD is the **object of the investigation.** This is interpreted by IRBMED to include IVDs used in studies whose results provide information on the safety and effectiveness of the investigational IVD in addition to the safety and effectiveness of the investigational therapeutic product. This interpretation is independent of - whether or not the IVD is approved or cleared by the FDA for its intended use,. Examples of investigational IVD's may include, but are not limited to:
    - A biomarker (molecular, imaging, or other) that serves as an eligibility criterion in a study
    - A biomarker (molecular, imaging, or other) that guides subject management during a study
- In some circumstances, the investigational IVD may have been used prior to the research (such as MiOncoSeq). In general, all studies utilizing MiOncoSeq should check "yes" to 7-2.1, since this is an investigational assay.

For the purpose of the IRBMED review, the following assays/tests, if performed in a CLIA-certified clinical laboratory prior to the research, will generally **not** be considered *investigational* IVDs (eResearch 7-2.1 will be checked "no") because IRBMED interprets that they are **not the object of the investigation**:

- IVDs that are routinely used to diagnose and otherwise classify the particular disease or condition (e.g., generally billed as a clinical service).
- IVDs that are supported by published clinical guidelines to evaluate a patient for standard of care therapies.
- IVDs used before or during the research to establish organ function to preserve safety, such as complete blood counts, serum chemistries, and assays to exclude pregnancy or viral infection
- IVDs that are FDA cleared for the use described in the study, which are used in the study to narrow the population to be studied, but are not being evaluated as "companion diagnostics". This category may apply to many NGS tests such as FoundationOne and Tempus, when used in an oncology setting.
- IVDs utilized on samples that are collected as part of the clinical investigation for post-hoc (correlative) testing, as long as there is no intent to submit the data to the FDA as part of a marketing application.

2. eResearch Application

For *investigational* IVDs, the eResearch application should be completed as outlined below:

a. Question 7-2.1 should be checked "yes"
b. The IVD should be listed in Section 16 per its intended use in the proposed research study and if it is FDA approved/cleared for this purpose.
    - An assessment should be made on whether the IVD is exempt from IDE requirements. Section 16 of the IRB application includes a question (*question 16.2.6 for FDA-not approved* and *16.2.22 for FDA-approved used off-label*) for this purpose.
    - If the IVD is exempt from the IDE regulations, a risk determination (Significant Risk (SR) or Non-Significant Risk (NSR)) is not necessary.

- If the IVD is not exempt from the IDE regulations, a risk determination (Significant Risk (SR) or Non-Significant Risk (NSR)) should be made. According to the FDA, "*Sponsors are responsible for making the initial risk determination and presenting it to the IRB.*" If the U-M PI is the sponsor-investigator, they should submit the risk assessment (SR or NSR) to IRBMED utilizing the MIAP IVD worksheet. The Sponsor-Investigator also has the option of submitting a risk determination request to the FDA by working with IRBMED and MIAP (MICHR IND/IDE Investigator Assistance Program (MIAP)). If the U-M PI will be submitting a risk determination to the FDA, IRBMED should be informed of this as part of the IRB application.

c. The informed consent document should clearly capture the investigational nature of the IVD testing, as well as alternatives to study participation. Also, the informed consent should clearly describe the risks associated with the use of the IVD (i.e., the risks of inaccurate test results, the risks of sample collection and use, etc.).

NOTE 1: If the IVD testing is used as approved/cleared by the FDA, and the IVD is the object of the investigation, eResearch 7-2.1 should be answered "Yes" and Section 16 should be completed.

- The eResearch application requires documentation (generally, FDA 510(k) notification letter or the PMA approval letter or a confirmation from the FDA medical device database) so the IRB can confirm that the proposed use of the IVD is in accordance with the approved labeling. MIAP can assist with obtaining the necessary documentation if requested by the U-M sponsor-investigator.

NOTE 2: If the IVD testing was already completed for clinical care purposes and the IVD is the object of the investigation, eResearch 7-2.1 should be answered "Yes" and Section 16 should be completed. Additional details on the specific test used at U-M are needed to determine whether the IVD testing is investigational. For these situations, the study team should reach out to appropriate departments (pathology, etc.) within U-M to obtain additional information regarding the IVD test used.

- If there are no known FDA-approved/cleared tests for the intended IVD testing, the IVD can be listed under "16.2.1 Not Approved by the FDA" with the completed IVD worksheet which captures the required information for the SR/NSR assessment.
- If the test is FDA-approved/cleared and used at U-M per its FDA approval/clearance, the IVD should be listed under "16.2.28 being used On-label". For this situation, appropriate documentation (such as PMA letter and/or other similar as identified in NOTE 1 above) should be provided.

3. Ensuring Compliance with FDA medical device regulations

Once a determination is made that an IVD is subject to FDA regulations, and does **not** meet the IDE exemption criteria, the Sponsor-Investigator (U-M PI in these situations) must comply with the applicable FDA regulations (21 CFR 50, 56, 812, etc.).

In the absence of the final guidance from the FDA, IRBMED advises the Sponsor-Investigators to maintain appropriate documentation that demonstrates how they are complying with applicable requirements (especially, the design controls and good manufacturing practice regulations (21 CFR 812.140 (b) (4)(v)) and labeling requirements). The documentation may identify the challenges (when the testing is conducted at a different lab or as part of the clinical care) and the steps they have taken to ensure compliance. MIAP can assist with this documentation, as they would for IND/IDEs held by the UM sponsor-investigator.

B. **Special considerations for studies where the University of Michigan PI is NOT the Regulatory Sponsor (e.g., there is an external industry sponsor)**

Although the December 2017 IVD guidance is a "draft" (the document indicates "Not for implementation. Contains non-binding recommendations."), U-M is aware that FDA is utilizing this draft guidance in their decision-making process. However, not all external sponsors may be following the draft guidance. For consistency with IRBMED review, the following processes are to be followed:

1. **If the External Sponsor has identified an investigational IVD**, the eResearch application will be completed as described above for U-M Investigator-Initiated studies (III.A.2.).

2. **If the External Sponsor has not identified an investigational IVD**, and there appears to be an investigational IVD that is the object of the investigation (as identified either by the U-M study team or IRBMED), the U-M study team should contact the Sponsor to clarify the IVD status and request a risk determination as appropriate.

3. **If the External Sponsor declines to acknowledge an IVD as being investigational**, the IRBMED convened board will discuss the circumstances and assess the appropriateness of IVD status based on the general risk/benefit profile of the use of the IVD in the study.
    - In the absence of the Sponsor's determination, IRBMED will ask the U-M PI to provide an opinion of the risk of the investigational IVD that will be used at U-M. The MIAP IVD worksheet can be utilized in this process.
    - IRBMED may approve the study if the Board determines that the IVD testing doesn't present a significant risk to subjects and all other criteria for IRB approval are met. The Board may utilize the MIAP IVD worksheet in this process, however, this does not constitute a formal device risk determination. Information will be documented in the IRBMED meeting minutes.
        - The IRB application (Section 16, etc.) will need to be completed as identified above (III.A.2.). The study Sponsor should be informed of this outcome.

For questions, contact IRBMED (734.763.4768 or irbmed@umich.edu) or MIAP (MICHRMIAP@med.umich.edu).

IV. RESOURCES

1. FDA's 2017 draft guidance: "Investigational IVDs Used in Clinical Investigations of Therapeutic Products"
2. FDA's 2019 final guidance: "Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry"
3. FDA's medical device classification database: "Product Classification"
4. FDA's web-page guidance on "Laboratory Developed Tests"
5. In Vitro Diagnostic (IVD) Device Studies -Frequently Asked Questions: https://www.fda.gov/media/71075/download
6. MICHR MIAP web-page: https://michr.umich.edu/rdc/category/Regulatory+Support+%28MIAP%29
7. For a list of FDA cleared or approved nucleic acid based tests, visit https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests
8. For a full list of FDA cleared or approved companion diagnostic devices, visit https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools