FDA Oversight and IRB Review of Studies that Include In-Vitro Diagnostics

May 14, 2015
1:00-2:30 PM ET

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Webinar Objectives

- Be able to identify when a clinical study includes an investigational in vitro diagnostic device (IVD).
- Understand the responsibilities of the IRB with regard to IVDs.
- Be able to determine if an investigational IVD is exempt from the requirements for an IDE
- Understand the considerations in determining if an investigational IVD is non-significant risk (NSR) or significant risk (SR)

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Issues

- FDA is seeing more researchers apply discoveries in the clinic
- Increasing use of IVDs in drug trials and other types of investigations
- Many researchers do not understand their obligations under the IDE regulation
- Many academic institutions do not provide adequate regulatory support

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IVD Regulation

- In Vitro Diagnostic tests (IVDs) are a critical component of current clinical care, influencing 80% of all clinical decision-making
- Through the 1976 medical device amendments to the FFDCA, FDA has the authority to regulate all laboratory tests, regardless of whether they are commercially distributed or developed by a laboratory
- FDA is charged with ensuring that IVDs are safe and effective (do what they say they will do) for their intended use so that patients are not unnecessarily harmed

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FDA's Risk-Based Approach to Regulation

Premarket submission	Clinical trial using investigational device
3 classification levels: • Class I: common, low-risk devices – 510k (usually exempt) • Class II: more complex, moderate risk – 510k • Class III: most complex, high risk - PMA	3 categories: • IDE exempt • Nonsignificant risk • Significant risk
Risk is based on consequences of a false result in the context of clinical care	Risk is based on the consequences of a false result in the context of a clinical protocol
Decision is based on risk-benefit analysis (safety and effectiveness)	Decision is based on risk (safety only)

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IDE Regulation (21 CFR 812)

- "…purpose…is to encourage, **to the extent consistent with the protection of public health and safety and with ethical standards,** the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose."
- An IDE is a **regulatory submission** that permits clinical investigation of devices/IVDs.
- An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device **without complying with other requirements** of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution.
- Focused on risk
- Delegated responsibilities

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IDE Regulation (21 CFR 812)

Several parts of the Code of Federal Regulations (21 CFR) pertain to IDEs:

- Part 812 - Investigational Device Exemptions
- Part 50 - Protection of Human Subjects and Informed Consent
- Part 54 - Financial Disclosure of Investigators
- Part 56 - Institutional Review Boards
- Part 820 Section 30 – Design Controls (Quality Systems Regulation)

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Some common misconceptions

- It is not a test, it is a process
- It is not an IVD if it is in the research and development stage
- It is not an IVD if I don't plan to market the test
- The IDE regulation does not apply if I don't plan to market the test
- I have CLIA certification, so I don't need to worry about the IDE regulation
- I can never generate enough data to submit an IDE
- If it is a commercially-offered LDT, I don't need an IDE
- If the test has been cleared or approved by the FDA, I don't need an IDE for any intended use in a clinical study

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Does the IDE Regulation Apply?

To answer this question, investigators and IRBs must:

- Identify the "test"
- Determine investigational status
- Determine risk

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In Vitro Diagnostics (IVDs)

- In vitro diagnostic devices include "…those reagents, instruments, and systems intended for use in the 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. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act " (21 CFR § 809.3)
- Intended use: How will the device will be used in the clinical study? Encompasses:
  - Analyte to be detected
  - Type of result (quantitative, semi-quantitative, qualitative)
  - Specimen type(s)
  - Disease to be screened, monitored, treated, or diagnosed
  - Target subject population
  - Etc.

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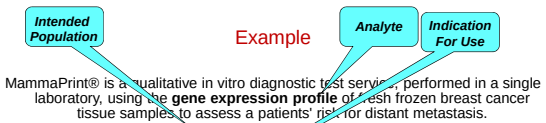
Intended Use

What assay measures, how to use results



MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the **gene expression profile** of fresh frozen breast cancer tissue samples to assess a patients' risk for distant metastasis.
The test is performed for **breast cancer patients** who are less than 61 years old, with Stage I or Stage II disease, with tumor size <= 5.0 cm and who are lymph node negative. The MammaPrint® result is indicated for use **by physicians** as a **prognostic marker** only, along **with other clinicopathological factors**.

Types of **studies** depend on IU claims;
Less dependent on the technology or assay format

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Things that are or can be **medical devices include**

- Instrumentation
- In vitro diagnostic kits
- Reagents used for laboratory testing
- Some apps
- Software
- Algorithms

Medical devices are subject to regulatory requirements.

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Is the test investigational?

- *Investigational device* means a device… that is the object of an investigation
- An investigational IVD is not legally marketed for the intended use or indication for use identified in that study, whether or not it has been previously cleared or approved for a separate intended use
- Important to distinguish from off-label use or practice of medicine
- Investigational use requires an exemption from premarket approval requirements for new drugs and devices

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IDE: A Risk-Based Approach to IVD Regulation

- IDE requirements depend on the risk of the test use to study subjects in the investigation.
- For IVD tests, it is important to think about the risks associated with erroneous test results. What would happen if the test results are wrong?
  - False positive or false negative results mean that a patient may be diverted from therapeutic options which may be more beneficial to them
  - Patients may be subject to adverse events from the investigational trial when they are not intended to be the subject of the investigation

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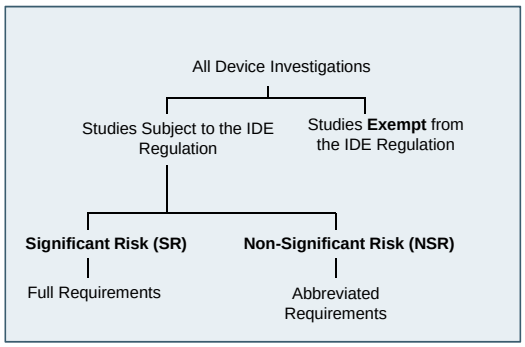
Does the study need an IDE?



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IDE Exempt

- 812.2(c)(3): A diagnostic device [is exempt], if the sponsor complies with applicable requirements in 809.10(c) [labeling] and if the testing:
  - (i) Is noninvasive,
  - (ii) Does not require an invasive sampling procedure that presents significant risk,
  - (iii) Does not by design or intention introduce energy into a subject, and
  - (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- Example: Use of an in vitro diagnostic in a retrospective study of accrued specimens (without return of results).
- Depends on interpretation of "medically established".

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Nonsignificant Risk (NSR)

- Does not meet the definition of significant risk (SR) in 812.3(m)
- Abbreviated requirements:
  - Labeling (812.5)
  - IRB approval
  - Informed consent (part 50)
  - Monitoring (812.46)
  - Records (812.140) and reporting (812.150) (sponsor and investigator)
  - Prohibition against promotion and other practices (812.7.)
- No IDE application to the FDA required. Meeting the abbreviated requirements (including IRB approval!) means that you have an approved application for an IDE.
- Example: Use of an investigational IVD test to stratify patients for treatment in a clinical trial.

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Significant Risk (SR)

- *Significant risk device* (812.3(m)) means an investigational device that:
  - 1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
  - (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- Example: Use of an in vitro diagnostic test to select patients for a clinical trial.

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Two Areas Where Risk Assessment is Challenging

- Drug trials that use investigational IVDs (e.g., companion diagnostics)
- Genetics/genomics

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Risk assessment in drug trials

- Many oncology trials use an investigational IVD
- Increasing inclusion of exploratory research in clinical trials
- Principles of risk assessment can be applied to other types of IVD investigations

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Balanced Approach to IVD Risk

Context and effect of an incorrect test result

Cancer is a serious disease. Any effect on a treatment decision arising from IVD use poses significant risk.

Cancer is a serious disease. Large and unmet medical need makes any IVD risk minor.

- Accrual by test result
- Rx assignment
- Safety signal for Rx
- Targeted biomarker
- Invasive sampling

- All-comers accrual
- Stratification
- No "known effective" Rx
- Convenience biomarker
- Non-invasive sampling

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Clinical Trial Features with Lesser Relevance for IVD Risk Determination

- Size of trial
- Access to "other trials"
- Clinical trial phase

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Assessing Risk

1. Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?
2. Will use of the investigational test results expose trial subjects to safety risks (e.g., adverse events from the experimental therapy) that (in some "net" sense) exceed the risks encountered with control therapies or non-trial standard of care?
3. Is it likely, based on a priori information about the investigational therapy, that incorrect test results would degrade the safety or efficacy of subjects' treatment?
4. Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?

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Risk in Ongoing Trials

- Risk can change during the course of a trial
  - Adaptive trials
  - Protocol changes
  - New information (DSMB review)
- If IVD use becomes SR in the middle of a trial, an IDE is required
- Ongoing surveillance is recommended

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Genetics/Genomics Investigations

- Increasing use of panels, whole exome sequencing, and whole genome sequencing in investigations
- Problem of incidental findings

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Risk in Investigations Using Genetic Testing

- What are the clinical indications for testing?
- Are the results confirmed by an acceptable technique? What is an acceptable technique?
- Are results returned?
- Will results be placed in the medical record?
- How are results communicated to the treating physician?
- What are the risks of an incorrect test result?
  - What clinical actions might be taken based on test results?
  - How urgent are the results?
- For genetic testing, risk may depend on the disease; the risks of treatment/procedure(s) after a screen positive result; the consequences of the genetic result in the medical record; other factors

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Delegated Responsibilities and Risk Determination

- Sponsor makes initial determination and presents to IRB

- IRB reviews determination; agrees or modifies

- FDA can help; FDA determination is final

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FDA Policy for CDx Trials

- **SR IVD:** An IDE is required for an investigation *even if* there is an IND for use of the drug, or if the drug is IND exempt
- **NSR IVD:** An IDE is not required, and cannot be accepted for review
  - The trial still has to comply with the abbreviated requirements
  - Some information on the test may be requested in the IND
  - A presub with CDRH is recommended
- A trial may not proceed until it has received IND and/or IDE approval AND IRB approval

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IDE Decisions

- Sponsor submits IDE application to FDA for SR studies
- FDA **approves, approves with conditions,** or **disapproves** IDE within 30 calendar days
- Sponsor obtains IRB approval
- After **both** FDA and IRB approve the investigation, study may begin
- Changes in an existing study → amendments
- New studies with the same device → supplements
- **"Approved with Conditions"** signifies that the study may begin, but that certain conditions have been stipulated and must be met by the sponsor within 45 calendar days
- **Minor and Major Study Design Considerations** are recommendations (but not requirements) regarding study design to help study achieve its goals

30

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Resources

- **Medical Device Databases** (Different databases for 510k, PMA, and de novo)
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm
- **Guidance**
  - IRB Responsibilities
    www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf
  - FDA Decisions for IDEs
    www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf
  - Significant Risk and Nonsignificant Risk Medical Device Studies
    www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf
  - Others at www.fda.gov
- **Device Advice**
  - www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
- **CDRH Learn**
  - www.fda.gov/Training/CDRHLearn/default.htm

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Pre-submission Meetings

- Sponsors can meet with the FDA for nonbinding discussions and advice:
  - **before** conducting studies, including clinical trials
  - **before** submitting a marketing application
- This is an opportunity to address new scientific and regulatory issues
- **Can obtain a formal risk determination**
- Guidance on the pre-submission process
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

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Challenges for IRBs

IRBs shoulder a great deal of responsibility for assuring that FDA regulations are properly followed for human subjects research

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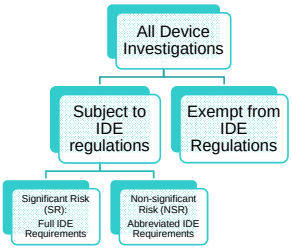
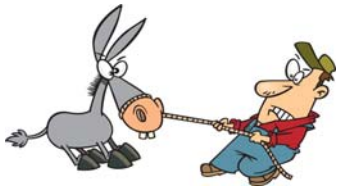
IRB responsibilities for IVDs

Apply the FDA device regulations



What's needed

- Education
- Process
- Patience
- Persistence



Stakeholders

- IRB staff
- IRB chairs
- IRB committee members
- Investigator
- Regulatory support staff
- Institution
- Sponsor

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Education

- Formal presentations
  - IRB chairs
  - IRB committees
  - Clinical Research Departments
  - Laboratories
- One on one discussions
  - PI's
  - Sponsors
  - FDA

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Process

- Identification
- Discussion
- Determination

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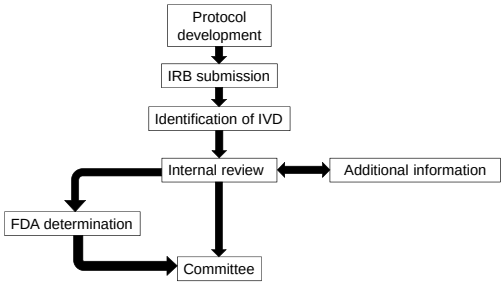
Process



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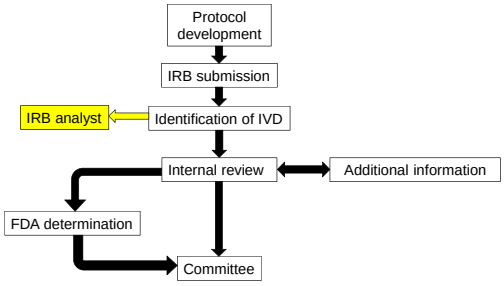

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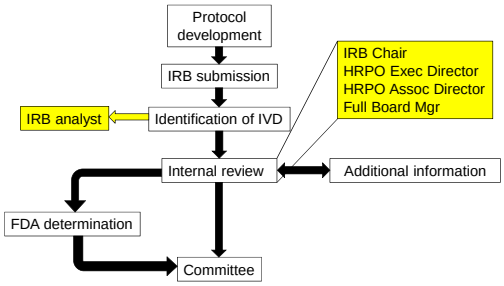

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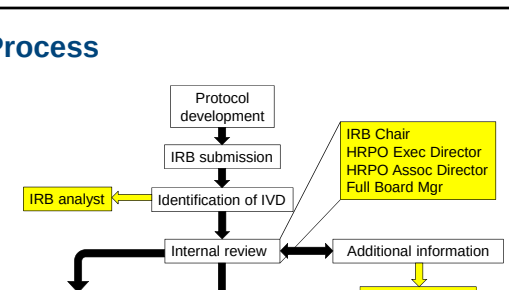

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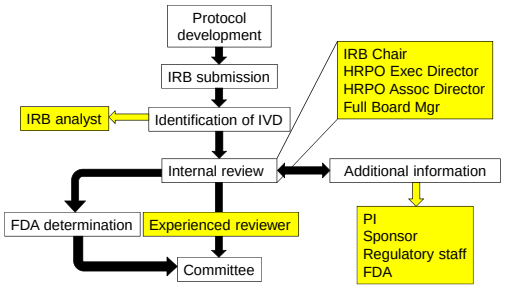

What do you need in your IRB submission/application

- Full protocol
- Information about the test itself
- Information about specimen collection
- Information about how the test result will be used

Identification of an IVD

- Protocol document

Now answer 4 questions

- Is the test an IVD?
- If so, is it investigational?
- If so, is it exempt?
- If not, is it NSR or SR?

Identification of Investigational IVD

- Is the test an IVD?
  - Is the test a laboratory assay performed on a sample of blood or tissue obtained from a participant and the result used for trial specific purposes (eligibility, stratification, treatment assignment)?
    - Y=IVD
    - N=No IVD?

Is it investigational?

- If an IVD, is the IVD investigational in this study?
  - If the test is being performed for clinical purposes, and the testing is not dictated solely for purposes of the trial, it may not be investigational.
  - If the test is not being performed for clinical purposes, it may be investigational.

If investigational…is it exempt?

- Exempt
  - Legally marketed device used according to its label
    - FDA databases
    - Sponsor
  - OR is
    - Noninvasive
    - Doesn't require invasive sampling
    - Does not introduce energy into subject AND
    - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

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If not exempt…SR or NSR?

- Sponsor is responsible for initial determination
- IRB must agree or disagree
- When in doubt, go to the FDA

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SR or NSR

- What is the additional risk to participants if test result is incorrect?
  - Consequences of a false positive or false negative?
  - What is the normal course of disease/treatment?
  - If drugs have serious side effects, is test SR?
  - What about unknown risks (FIH/Phase 1)?
  - How is this different than overall risk:benefit as assessed by criteria for approval?
  - What is the risk of specimen collection?

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Case 1

Dr G wishes to open a phase 2 industry sponsored trial examining the safety and effectiveness of new drug XYZ in combination with erlotinib (Tarceva™) for patients with metastatic non-small cell lung cancer.

Eligible participants will be randomized to either erlotinib in combination with XYZ or placebo.

End points are overall survival, progression-free survival, as well rates of complete/partial responses.

Additional endpoints include safety/toxicity data.

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Case 1

- The inclusion/exclusion criteria are as follows
  - > 18 yo
  - Confirmed dx of NSCCA lung (path sent for central review)
  - Expected survival > 6 months
  - Adequate organ function
  - Presence of an exon 19 deletion or exon 21 L858R substitution in the EGFR gene as determined by the Cobas EGFR mutation test

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Case 1

- Is there an IVD being used in this study protocol?
  - Yes
  - No

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Case 1

- Mutation testing will be performed on formalin fixed, paraffin embedded tissue previously collected for clinical reasons at the time of initial diagnosis of the tumor. Test results from any CLIA approved laboratory may be used for eligibility determination.

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Case 1

- Is the IVD considered investigational?
  - Yes
  - No

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Case 2

Investigator-initiated pilot study to evaluate the ponatinib in the treatment of FGFR mutation positive recurrent or persistent ovarian carcinoma.

All eligible patients will take oral ponatinib daily.

Primary objective is to assess the activity of the drug by evaluating CR+PR and PFS at 6 months.

Secondary objectives include toxicity evaluation.

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Case 2

- Inclusion/Exclusion criteria
  - Patients must have recurrent or persistent ovarian carcinoma which is refractory to curative therapy or established treatments..
  - Patients must have a documented FGFR2 activating mutation either on primary, recurrent or metastatic biopsy. Activating mutations are defined as the known FGFR2 hotspots at S252W, P253R, S373C, Y376C, C383R, N550K, N550H, K660E.
  - Patients must have had at least one prior chemotherapeutic regimen for management of endometrial carcinoma; this includes prior use of adjuvant chemotherapy.
  - Usual other stuff….

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Case 2

- Eligible patients will be identified from patients in which mutation testing was performed by the clinician as part of clinical care.
- Is there an investigational IVD being used in this study protocol?
  - Yes
  - No

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Case 2

- Samples must also be sent to the central laboratory for confirmatory testing. Presence of a qualifying mutation must be verified by central lab prior to randomization.
- Is there an investigational IVD in the study?
  - Yes
  - No

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Case 2

- The central lab will determine the mutation status by NextGen sequencing. The result will be reported back to the site PI and participant, and will be used to determine if the participant is eligible to continue in the trial and receive the study drug.
- Is the IVD exempt?
  - Yes
  - No

Known adverse effects of ponatinib

- **WARNING: VASCULAR OCCLUSION, HEART FAILURE, and HEPATOTOXICITY**
- Vascular Occlusion:
  - Arterial and venous thrombosis and occlusions have occurred in at least 27% of Iclusig treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events (5.1).
  - Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion. A benefit-risk consideration should guide a decision to restart Iclusig therapy (5.1).
- Heart Failure:
  - Heart failure, including fatalities, occurred in 8% of Iclusig-treated patients. Monitor cardiac function. Interrupt or stop Iclusig for new or worsening heart failure (5.2).
- Hepatotoxicity:
  - Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor hepatic function. Interrupt Iclusig if hepatotoxicity is suspected (2.3, 5.3).

Case 2

- What is the risk determination?
  - NSR
  - SR
  - > minimal risk

Case 3

- Patients with metastatic NSSCA of the lung will be enrolled in a phase 1 trial comparing new tyrosine kinase inhibitor 123ABC in combination with SOC drugs to SOC alone. All patients will have whole exome sequencing performed on samples of tumor collected prior to initiation of therapy (may be from original diagnostic w/u), and again after 3 cycles of chemotherapy, to detect any specific genotypes or acquired changes that may be associated with response or resistance to treatment.
- To date, 25 patients have been treated with the drug. AE's included leukopenia, nausea/vomiting and loss of appetite. None occurred more frequently than placebo.

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Case 3

- Is there an investigational IVD in this study?
  - Yes
  - No

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Case 3

Early phase 1 data and preclinical data suggest that patients with a specific mutation A54P in gene RFP were more likely to respond to treatment than others.

Therefore, after the first 30 patients are enrolled, an expansion cohort will be opened in which only patients with mutation A54P will be enrolled.

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Case 3

- As the test will now be used to determine treatment, and there is no medically established confirmatory test, there is now a non-exempt investigational IVD being used. Given that, what factors should the IRB consider in determining whether the IVD is NSR or SR?
  - A. The procedure used to collect the specimen for testing
  - B. The toxicity associated with the SOC chemotherapy regimen.
  - C. The toxicity of the investigational drug
  - A and C
  - All of the above

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Thank you!

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