Companion Diagnostic IUO Studies in a CLIA-certified Laboratory

Mort Minaee LPD, RAC
VP Regulatory Affairs
October 4, 2019

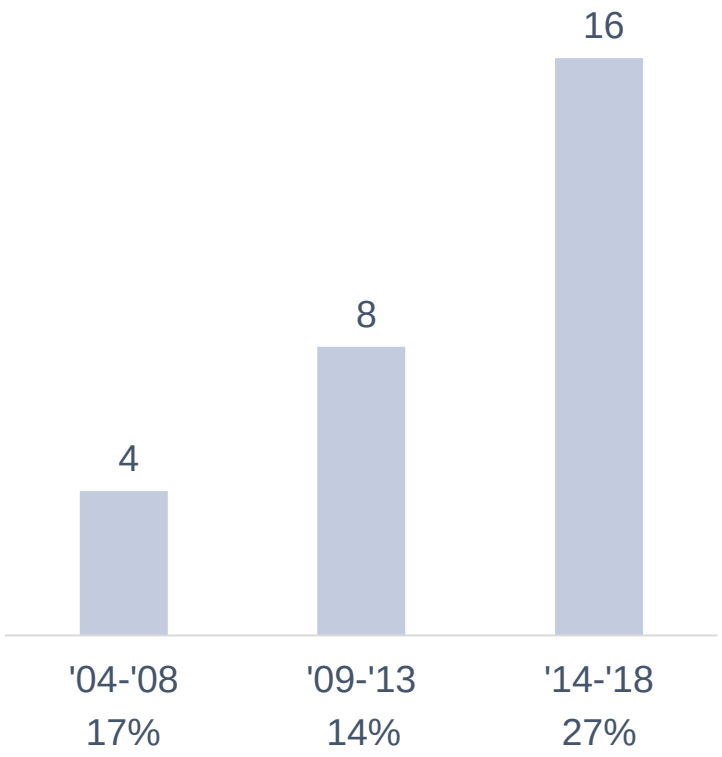
GUARDANT

Overview

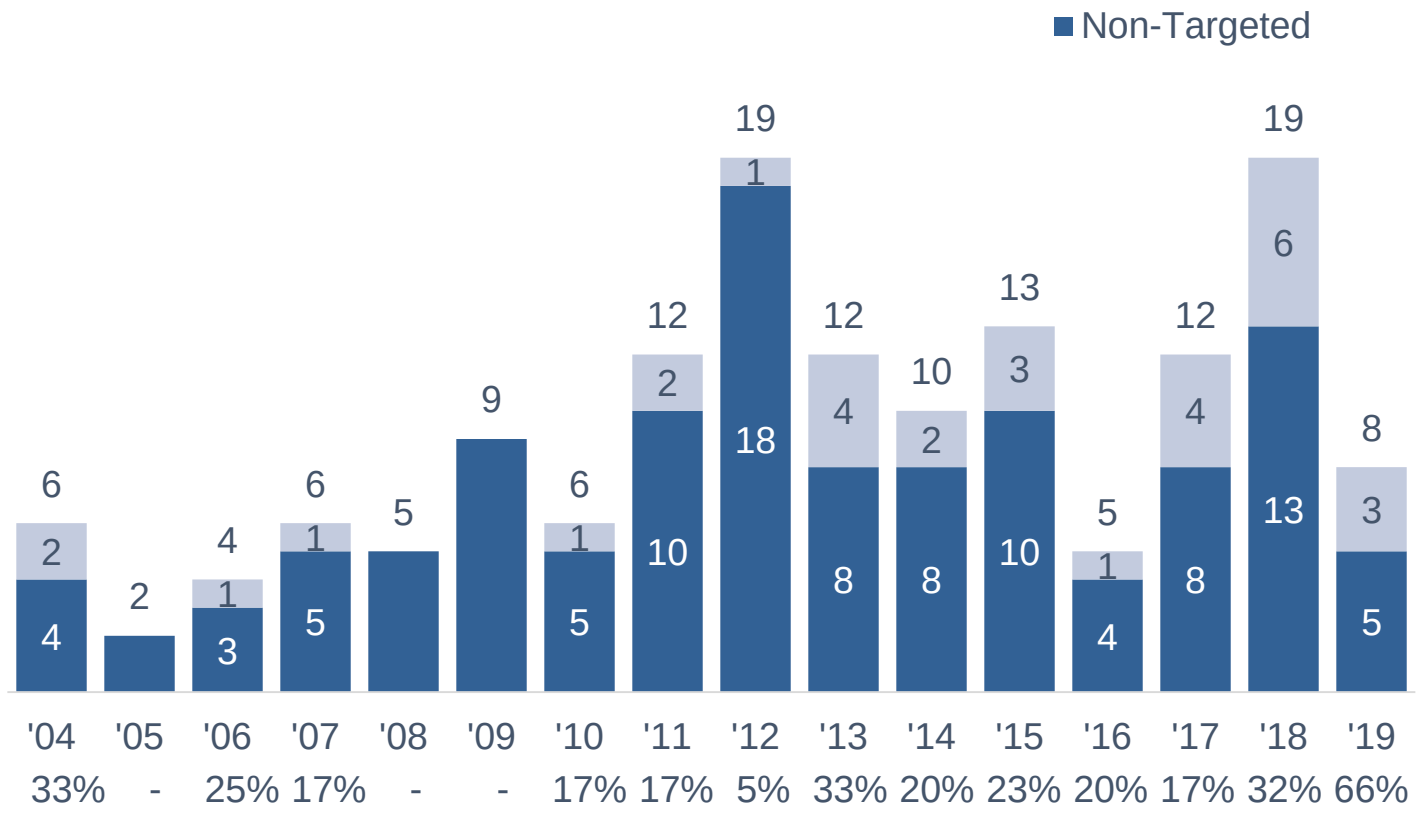
- Important considerations for Companion Diagnostics
- Basic CDx IDE Study Requirements
- IDE Study Risks Management
- IDE Study Planning

Targeted therapy drug approvals have doubled every five years

Targeted Tx Approvals, Nos., % Onc.



Oncology Approvals, Nos., % of Oncology

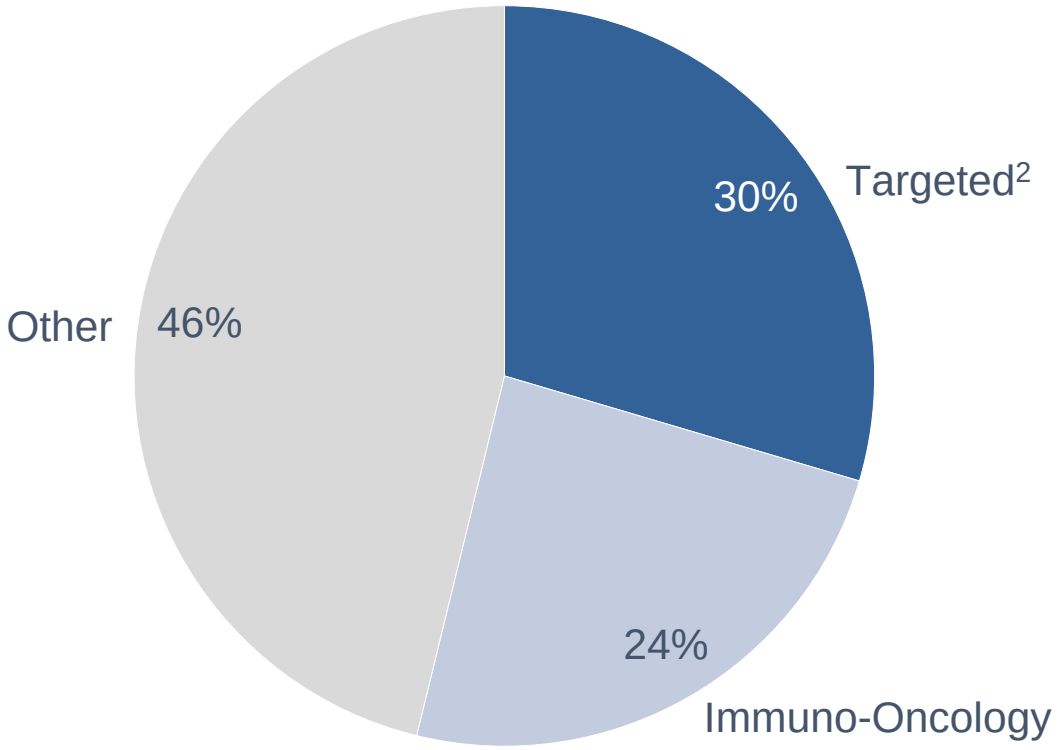


2018 Targeted Tx approvals: Larotrectinib, Lorlatinib, Talazoparib, Dacomitinib, Encorafenib, Binimetinib
2019 Targeted Tx approvals: Alpelisib, Erdafitinib, Entrectinib
Source: FDA approvals; Guardant analysis (LRP Situation Analysis, August 25th 2019)

Industry pipeline drives size of market opportunity. Targeted therapies account for 30% of pipeline

Solid Tumor Oncology Clinical Pipeline

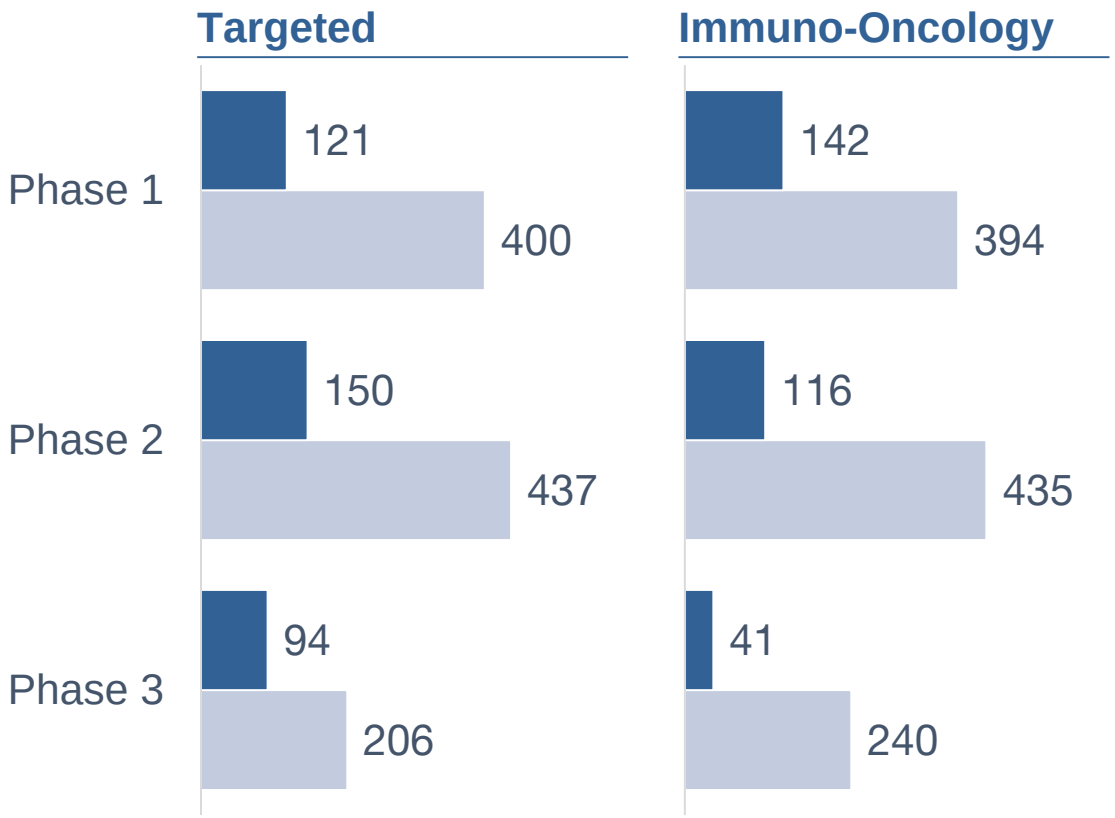
100% = 1,234 Programs[1]



Solid Tumor Oncology Clinical Pipel

Programs Trials

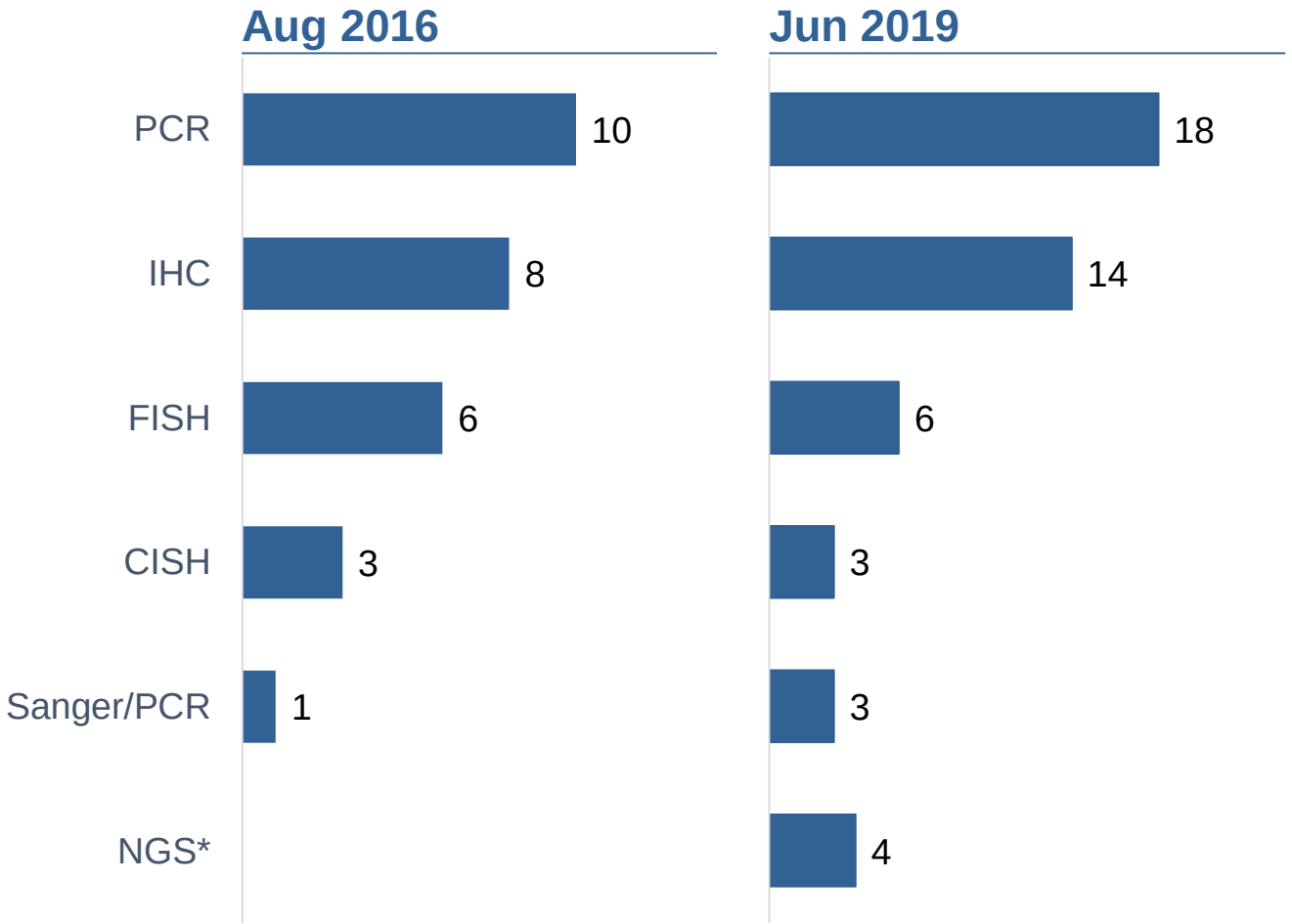
Count, by Phase



1 Excludes programs owned and in development by universities and hospitals
2 Targeted where mutation found in gene or other selected compound of pathway
Source: Kantar Database, August 2019

NGS and Liquid Biopsy CDx are becoming a reality

CDx Count by Technology



Solid Tumor Biomarkers

BCR-ABL, BRAF, EGFR, FGFR3, FLT3, IDH1, IDH2, KIT, KRAS, PIK3CA	
ALK, EGFR, ERBB2, KIT, PD-L1	
ALK, ERBB2, PDGFRB, TP53	
ERBB2	Three PCR based LBx for EGFR, one for PIK3CA
BRCA1/2	
ALK, BRAF, BRCA1/2, EGFR, ERBB2, KRAS, NRAS, ROS1	

* 4 NGS-based CDx across 23 markers. FoundationOne, FoundationFocus BRCA, Oncomine Dx, illumina's RAS Praxis
Source: FDA approvals

GUARDANT

Important Considerations for CDx Studies

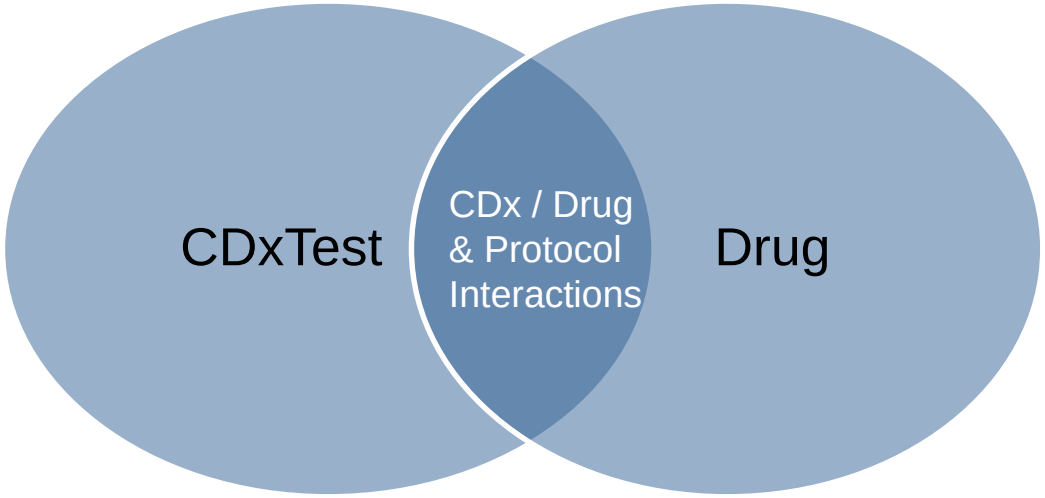
- New forms of risks to study subjects
- New potential regulatory risks to Sponsors, Labs and Dx manufacturers
- Potential impacts might include:
  - Study subject injury
  - Invalidation of clinical data
  - Loss of certification for CLIA labs

What is Unique about CDx Tests?

- Diagnostic method consists of a combination of one or more devices and a process to achieve a desired diagnostic output
- Can be used to include / exclude study subjects, determine the dosage or dosage range of a drug, track subject responses to companion drugs, determine the likelihood of a positive subject response to a drug, or for other purposes of determining drug safety or efficacy
- CDx tests combined with sample collection / processing and a test method form the “Test System”
- The ”system” view is made because study subject risks can be presented by each component of the test system:
  - Sampling and sample handling procedures
  - Test measurements
  - Test method and data analysis procedures

Risks to Study Subjects

- Incorrectly adjusted drug dosages due to erroneous CDx Test results
- Erroneous exclusion of subjects from the treatment they need or the wrong treatment given
- Delayed subject treatment because CDx Test results are not available or results are questioned by clinical investigators



Basic CDx IDE Study Requirements

GUARDANT

Good Clinical Practice per ICH E6 and FDA GCP

- Appropriate controls over the procedures and equipment used in a study
- Procedures for equipment operation and for conducting test methods
  - IQ, OQ, PQ (as appropriate) equipment validations at the site(s) of usage
  - Validation of the test method(s) in the lab it is being used in, including verification of assay or system performance
  - Tracking of equipment and design controls for equipment changes
- Training and demonstrated proficiency of lab technicians on equipment usage and test method procedures

CLIA Requirements

- Per §42 CFR 493.3(b)(2), a laboratory that tests human specimens is not exempt from CLIA certification requirements
  - unless the testing "do[es] not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients"
- Per §42 CFR 493.1253 a laboratory must establish performance specifications for the accuracy, precision, and reportable range of test results for the test system
- As applied to CDx studies this means that if the results of the laboratory testing are to be reported to a Clinical Investigator or treating physician for any form of patient management, a CLIA-certified laboratory must establish CDx test performance specifications at each of its laboratories that perform such testing

CLIA & GCP: Common Grounds

- IUO CDx must meet its performance specs (“analytical validation”) in the hands of those using them in a clinical trial
- Changes to IUO CDx tests in clinical trials should consider and may require design controls
- Design controls apply to ensure the safety of a CDx test being used in a clinical trial
- This means AV (sample collection and processing methods, equipment and test method validations) and laboratory technician training before the study starts
- Re-validation and retraining at various times throughout the study
- Records of these activities by the CDx provider and the Sponsor throughout the study

Study Risks Management

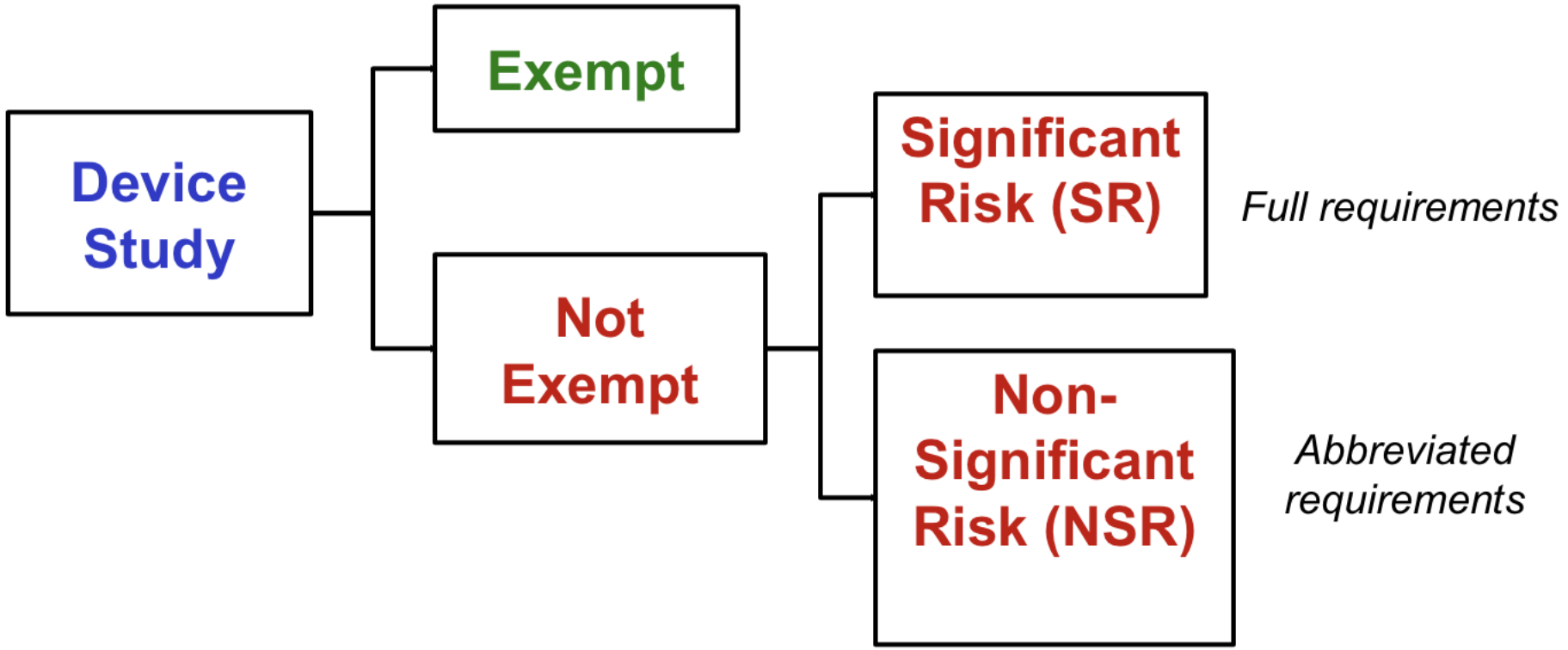
GUARDANT360

Different Kinds of Risks

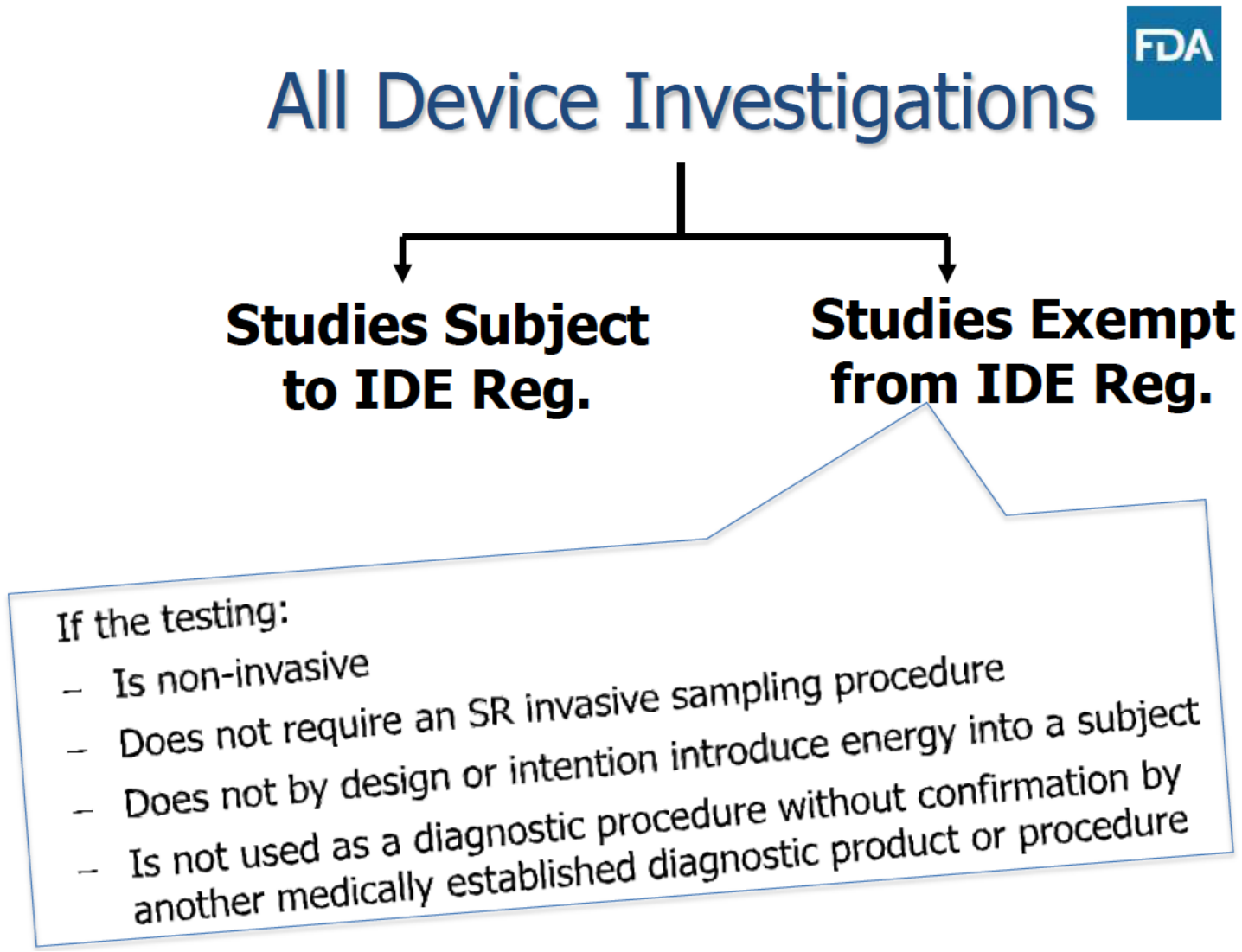
- Risks to Study Subjects

- Other Regulatory Risks
  - Sponsor risks: invalidation of study data
  - Dx manufacturer risks: lack of an IDE when the study is a Significant Risk study
  - CLIA lab risks: loss of CLIA certification for noncompliance with Part 493

When is an IDE needed?

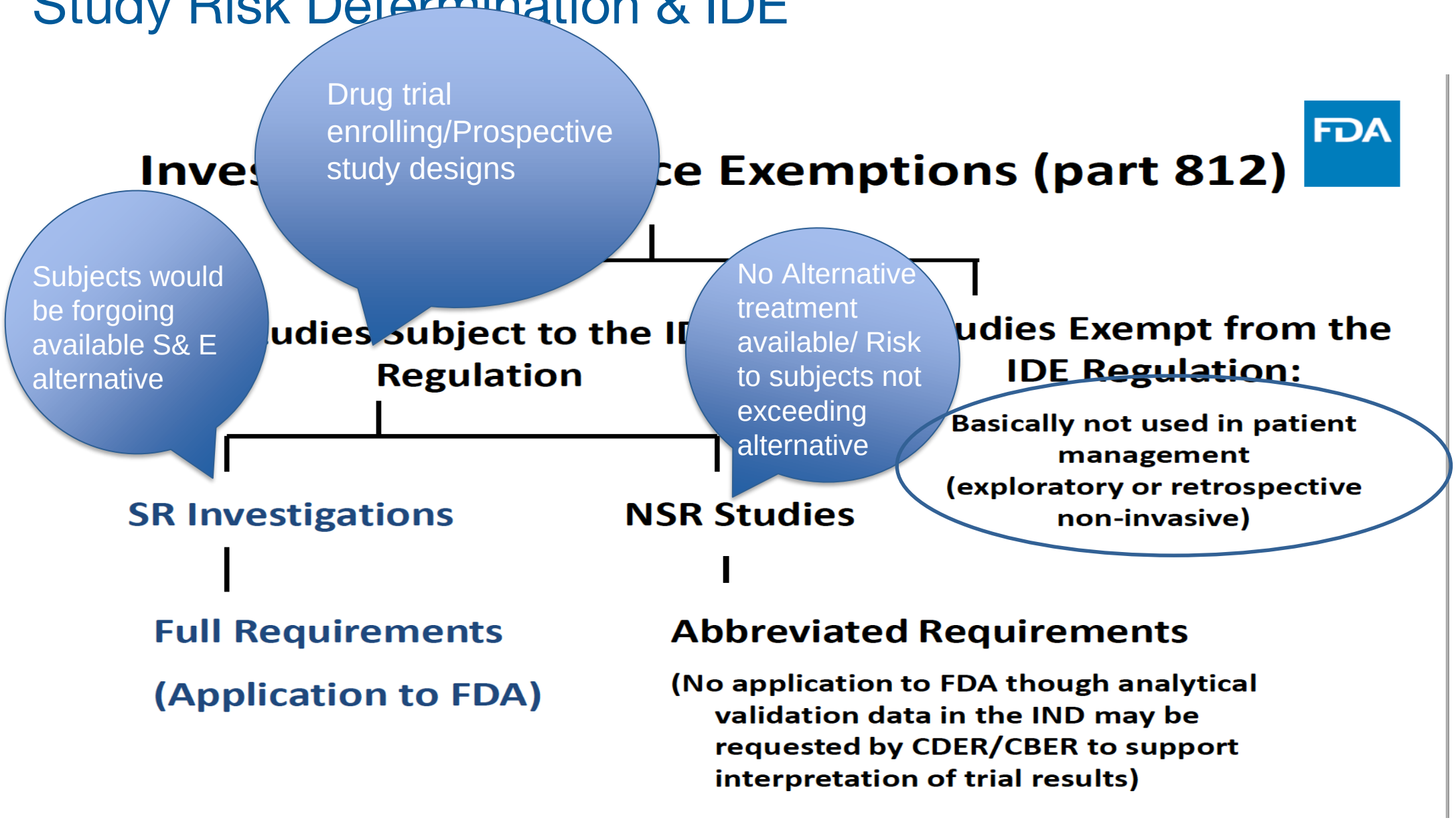


Which Studies are Exempt from IDE Reg.?



www.fda.gov

Study Risk Determination & IDE



Regulatory SOPs- Study Risk Determination

GUARDANT	Regulatory Risk Determination of Clinical and Research Studies	
Document ID: SOP-REG-000001	Revision Number: 1.0	Page: 1 of 13

1. PURPOSE

The purpose of this document is to define the procedure for determining the regulatory risks of studies and outline the FDA and EU regulatory requirements for conducting clinical and research studies.

2. SCOPE

The scope of this document includes regulatory risk determinations for all clinical and research studies regardless of sponsor, clinical trial phase, CDx status, or use of the data generated in the study. These instructions should be followed as a planning activity prior to the initiation of a new clinical or research study or when changes are proposed for an existing clinical or research study.

Observational clinical studies are out of scope for this SOP.

3. REFERENCES

3.1 FRM-REG-000016, *Internal Regulatory Risk Determination Worksheet*

3.2 POL-CDV-000001, *Clinical Development Clinical Trial Program*

3.3 SOP-CDV-000010, *Procedure for Companion Diagnostic Studies*

3.4 SOP-CDV-000002, *Companion Diagnostic Trial Monitoring Plan*

3.5 SOP-BDV-000003, *KickOff Procedure for BioPharma Exploratory Studies*

3.6 SOP-QUA-000001, *Control of Documents*

3.7 SOP-QUA-000002, *Control of Records*

3.8 SOP-QUA-000019, *Design and Development*

3.9 Directive 98/79/EC of the European Parliament of the Council of 27 October 1998 on in vitro diagnostic medical devices

3.10 Guidance for Clinical Investigators, Industry, and FDA Staff – Financial Disclosure by Clinical Investigators

3.11 Investigational IVDs Used in Clinical Investigations of Therapeutic Products; Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards

3.12 Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies

3.13 Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices; Guidance for Industry and Food and Drug Administration Staff

Key Factors in Determining Study Risk

1. Will patients be foregoing or delaying standard of care 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. Will the subject need to undergo an additional procedure of significant risk as part of the investigational study that they would have not otherwise been subject to with the standard of care?
5. Is there information that outcomes with the therapeutic are worse in a subset of patients defined by the test?

CDx IDE Studies- Regulatory Considerations

- Is the study really non-significant risk?
- What controls will be required over the study and the CDx components?
- Is CLIA compliance required?
- What records will be required to demonstrate regulatory compliance during the study and where should these records reside?
- What are the risks to the Sponsor if these regulatory risks are not managed?

IDE Study Planning

GUARDANT360

CDx Study Planning Components

Study Risk Management Plan

- Developed jointly by the Sponsor, CDx provider(s)/the clinical lab
- Risk assessment and control applied at the protocol level (top-level risk assessment) looking for CDx-created hazards
- Risk controls applied to each clinical process (e.g. sample acquisition) and to each CDx test component

Regulatory Compliance Plan

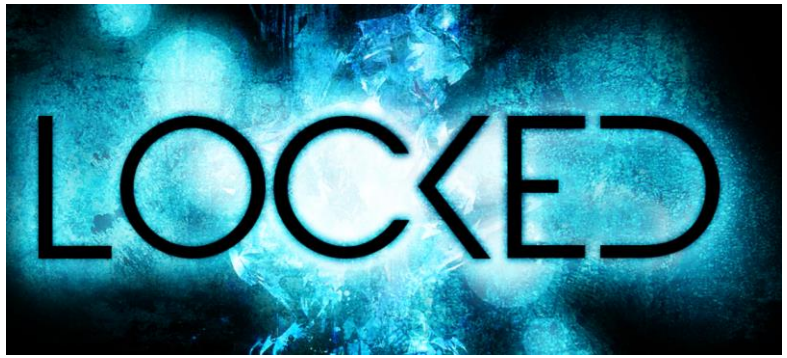
- SR or NSR study based on the risk assessments
- IRB, IDE or IND
- CLIA compliance requirements
- Relevant controls (e.g. design controls / validations)

Source: Guardant Health analysis

CDx Development Challenges

- Business issues
  - CDx manufacturers: CDx IVD development, validation, investigational testing, submission, compliance with device regulations
  - Rx manufacturers: Assuring availability of a CDx essential for the safe and effective use of their drug
    - Uncertainty of the CDx needs (e.g., adaptive trials)
    - Underestimate of CDx development efforts
    - Common use of lab developed tests
- Use of one or more clinical trial assays (CTAs) for patient enrollment (partly or completely)

Practical Considerations

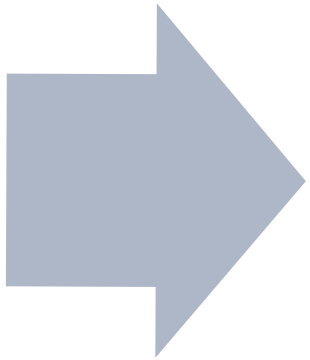


- Assay cutoff
  - Define cutoffs and lock down prior to the initiation of the analytical and clinical validation studies
  - Determination of the cutoff should be part of the assay development

- Changes to the product
  - Changes to the product can be significant enough to require that study subjects treated with different versions of the test be considered as separate strata and analyzed separately,
  - **calling into question whether the data can be pooled across strata**

Practical Considerations (cont'): From the CTA version to the CDx Test

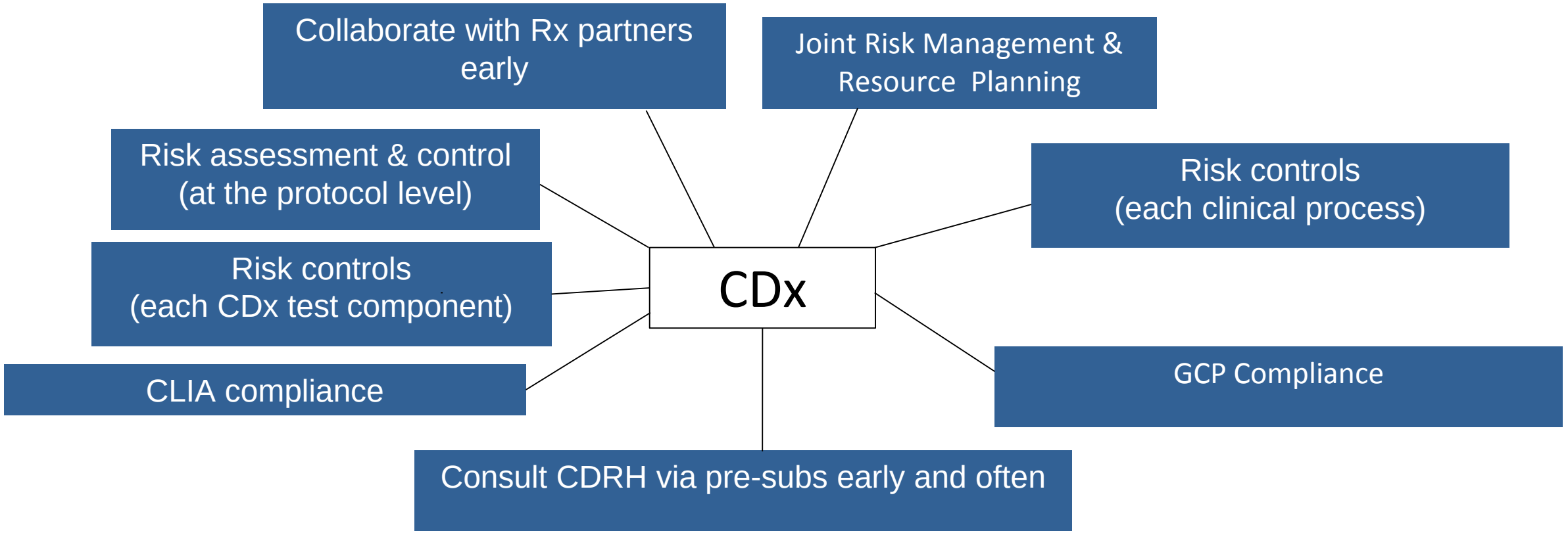
CTA
Clinical Trial Assay Version



CDx
The specific CDx Test Version (the final to-be-marketed device)

- Sample Requirements
  - All screened samples for the trial (marker-positive and marker-negative) by an earlier CTA version should be collected and banked under appropriate conditions for re-testing with the specific CDx test, as needed
- Bridging study
  - With all marker-positive samples and a random subset of marker-negative samples from the clinical trial with the final assay configuration
  - Consider detailed methods for sensitivity analyses of the missing test results
  - Seek FDA feedback on the bridging study protocol and the statistical analysis plan

Key success factors




GUARDANT™