

Biomarker Assays in Clinical Trials



Tricia Carrigan, Ph.D.
Member, EFPIA Personalized Medicine Working Group
Head, Translational Molecular Biomarkers and Companion Diagnostics,
MSD, Kenilworth, NJ., USA

1

Considerable Uncertainty and Variability For Investigation Use Requirements of Biomarker Tests in the Context of Clinical Trials in EU

- For use of a biomarker test in the context of pharmaceutical trials, regulatory requirements apply
- In the EU, there is considerable variability in requirements, frequently requiring exhaustive validation, for support of CE marking of tests used in early phase trials
- EBE EFPIA PMWG proposes a risk-based approach, with assay validation appropriate for the context of use within the clinical trial



2

2

A requirement for CE-mark for use of a biomarker assay in interventional studies may not be appropriate & poses challenges

- It is agreed that CE marking must be performed prior to assay commercialisation

However

- Requiring a CE-mark for assays intended exclusively for deployed in early clinical trials may misrepresent the identity/purpose of the trial assay and cause later confusion
 - Different patient population (i.e. disease stage) in early clinical trials compared to final companion diagnostic (CDx) indication
 - Different indications (i.e. all-comers) in early clinical trials compared to final CDx indication
 - Different treatment options (i.e. last line versus 2nd line) in early clinical trials compared to final CDx indication
- It is agreed that analytical validation and demonstration of assay suitability is needed prior to use of a clinical trial assay (CTA), but these factors are independent of having a CE mark



3

Intended use and assessment of risk should determine requirements for assay validation prior to use

- A CTA in clinical trials can be applied for very different intended uses (or context of use). This includes:
 - retrospective exploratory analysis
 - pharmacodynamic analysis
 - prospective analysis for patient management (including patient selection)
- Prospective testing for patient management in clinical trials may be driven by:
 - A strong responder hypothesis based on preclinical data
 - The biomarker molecule itself is the target of a given drug

Propose for the assay applied in these studies to be validated according to certain standards, with performance requirements depending on the risk associated to the intended use (see next slide)



4

Different biomarkers have different intended uses; validation requirements should be in line with **context of use** and risk

Type	Intended Use	Timepoint of analysis	Impact on patient treatment?
Exploratory	Hypothesis Generation	Retrospective	No
Pharmacodynamic	Dose-finding Hypothesis testing (Mode of action)	Retrospective	No
Predictive	Enrichment/Selection Stratification	Prospective	Yes No

- In general, retrospective analyses are mostly not related to a risk to the patient (exception: invasive/high-risk sample collection)
- Analysis for patient management may be associated with a higher risk, depending on how the assay is being used and the clinical setting of the study



5

Assessment of risk is critical to determining validation requirements; harmonization with other global regulations may simplify processes

US FDA uses 4 key questions to determine risk of an investigational device

(see FDA draft guidance „Investigational IVDs Used in Clinical Investigations of Therapeutic Products”, December 18, 2017)

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?

Yes to any of the above results in the study being Significant Risk (SR)

No to all is Non Significant Risk



6

Proposed questions to assess risk could aid determination of validation requirements & simplify the process

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?

If the answer to all questions above is „NO“ the use of a trial assay is not associated with an increased risk to trial subjects. Such assay shall be technically validated based on a fit-for-purpose approach.



7

Clinical Trial Assays (CTA) for low risk early clinical trials should be validated using a fit-for-purpose approach

- Validation of assay in early drug development shall follow the concept of “Fit-for-Purpose”:
 - Fit: Biomarker assay must be reliable and produce reproducible and accurate data
 - Purpose: Biomarker assay must be suitable for the specified intended use
- Fit-for-Purpose is a strategy which allows for continuous and evolving validation process of biomarker assays in course of drug development
- Where assays deployed in early clinical trials (even selection assays) pose a low risk to trial subjects a technical validation based on fit-for-purpose approaches is sufficient
 - Performance of Fit-for Purpose validation shall follow international/harmonized standards (i.e. CLSI, NCCLS etc.)
 - Results of assay validation shall be well documented and archived
 - Depending on the intended use different validation levels are applied (see next slide)



8

Defining the minimal analytical validation criteria for a CTA (prototype assay) follows a risk based approach

	Biomarker Assay in/for Clinical Trials = Clinical Trial Assay (CTA)		For Reference (Commercialised assay meeting CE-IVD Requirements)
Context of Use	Exploratory (retrospective; not for patient selection)	Selection or Enrichment	Commercial / EU
Utilization in Study Phase	I, II	I, II, III	
Sample Types	Contrived samples, spike-ins acceptable	Clinical samples matching tissue/disease type	Clinical samples matching target population
Range/Sensitivity	(✓)	✓	✓
Specificity	(✓)	✓	✓
Robustness	-	(✓)	✓
Stability - Sample/specimen	✓	(✓)	✓
Stability - Reagent	-/(✓)	(✓) within period of trial	✓
Stability - Onboard (for instruments)	-/(✓)	(✓) within period of trial	✓
Shipping stability	-	(✓) within context of trial	✓
Accuracy (trueness & precision)	✓	✓	✓
Repeatability	✓	✓	✓
Reproducibility	-/(✓)	(✓) within context of trial	✓
Cut-off	-	✓	✓
Interferences	-	(✓) within context of specimen	✓
Cross reactions	-/(✓)	(✓) within context of specimen	✓
Clinical performance	-		✓
Full scientific validity	-		✓

9

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9

Additional Considerations

- Additional elements that should be in line with the test's context of use:
 - Sample identity: Use of contrived or spiked samples rather than patient specimen should be acceptable for low risk applications
 - Data depth should also correlate with the context of use

10

Conclusion

The proposed strategy results in data packages consistent with the role of the test in the context of the clinical investigation.



11

11

Name: Tricia Carrigan, Ph.D.
Email Address: tricia.carrigan@merck.com

12

Backup

13

Application of CTA in early drug development is a research tool covered by clinical trial regulation rather than IVD regulations; pivotal trials require performance evaluation of the diagnostic

- In early clinical trials biomarker testing is mostly based on RUO reagents, RUO products/tests without involvement of a diagnostic partner. Tests are either performed locally at clinics or centrally in analytical labs (CROs)
- Development of IVD products including a diagnostic partner starts after successful proof of concept of an IND (after phase 1b or phase 2) informed by exploratory data that allows for assay definition (e.g. cut-off)
- In early (Ph 1/2) clinical trials clinical trial assays (CTAs) have no proven medical purpose → CTAs do not meet definition of medical device/IVD → CTAs are (clinical) research tools covered by the clinical trial regulation rather than in vitro diagnostic directive (IVDD)
- Biomarker testing is not performance evaluation of the trial assay and therefore utilization of the assay is outside of the scope of in vitro diagnostic regulations (IVDR) or other national IVD regulations
- In pivotal trials that include prospective testing with a future companion diagnostic the assay will be undergoing performance evaluation for that intended use

14

14

Examples of intended use cases provide indication that such an approach is feasible

Type	Intended Use	Timepoint of analysis	Impact on patient treatment?
Explorative	Hypothesis Generation	Retrospective	No
Pharmacodynamic	Dose-finding Hypothesis testing (Mode of action)	Retrospective	No

- Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?
 - NO for exploratory and pharmacodynamic assays as no impact on patient treatment
- 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?
 - NO for exploratory and pharmacodynamic assays as no impact on patient treatment
- 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?
 - NO for exploratory and pharmacodynamic assays as no impact on patient treatment
- Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?
 - NO for most exploratory and pharmacodynamic assays as archived material and/or non/minimal invasive sampling (i.e. blood collection) is used



15

15

Examples of intended use cases provide indication that such an approach is feasible

Type	Intended Use	Timepoint of analysis	Impact on patient treatment?
Predictive	Enrichment/Selection	Prospective	Yes
Predictive	Stratification		No

- Will use of the investigational test results lead to some trial subjects foregoing or delaying a treatment that is known to be effective?
 - NO for stratification assays as no impact on treatment (negative and positive patients are treated the same way)
 - NO for enrichment/selection assays in early clinical trials in oncology where there is no known effective treatment for last line patients
 - YES (potential) for enrichment/selection assays in late stage trials as there may be a standard of care treatment available
- 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?
 - NO for many trials as safety profile of drug is well characterized and benefit/risk is calculated
- 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?
 - NO for many early clinical trials as effectiveness of investigational treatment is not demonstrated and no known effective alternative treatment
 - YES (potential) for registrational trials
- Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?
 - NO for most selection assays archived material and/or non/minimal invasive sampling (i.e. blood collection) is used



16

16