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Biomarker Access and Quality

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EBE-EFPIA Personalised Medicine Working Group

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

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

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)

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	Prospective	Yes
	Stratification		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

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

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.

Clincal 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 is 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 de well documented and archived
  - Depending on the intended use different validation levels are applied (see next slide)

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	--		✓

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

Conclusion

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