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Risk-based approach for biomarker assay deployment in clinical trials as an alternative to CE marking

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EBE-EFPIA Personalised Medicine Working Group

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 placing a commercial assay on the EU market

However, under the IVD Directive

- Requiring a CE-mark for clinical trial assays (CTA*) 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 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, but this does not mean that a CE mark is needed

**CTA is an assay which is part of a drug clinical trial and is not meant for commercialisation*

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

- In early clinical trials biomarker testing is often 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 manufacturer starts after successful proof of concept of an IVD (often after phase 1b or phase 2) informed by exploratory data that allows for assay definition (e.g. cut-off)

- Many early (Ph 1/2) CTAs have no proven medical purpose → Many CTAs do not meet definition of medical device/IVD → Many CTAs are (clinical) research tools covered by the clinical trial regulation rather than the in vitro diagnostic directive (IVDD)

- Biomarker testing <u>is not</u> performance evaluation of the trial assay and therefore utilisation of the assay is outside of the scope of in vitro diagnostic directive or other national IVD legislations

- By the time of undertaking a pivotal trial, that include prospective testing with a future companion diagnostic, the assay will be undergoing performance evaluation for that intended purpose

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

- In clinical trials, a CTA may be intended for very different purposes (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

Even in these cases the purpose of the analysis is not performance evaluation of the assay. In none of these examples, is the purpose to generate data for the performance evaluation of the assay as such. However, before an assay can be used in studies, it should meet a predefined set of performance requirements. These should be adapted to the risk associated with the intended purpose (see next slide).

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

Type	Intended purpose	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 rarely pose 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 performed and the clinical setting of the study

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

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 (NSR)

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 considered to be associated with an increased risk to trial subjects. Such assay shall be technically validated based on a fit-for-purpose approach

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

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

1. **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
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?**
   - **NO** for exploratory and pharmacodynamic assays as no impact on patient treatment
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?**
   - **NO** for exploratory and pharmacodynamic assays as no impact on patient treatment
4. **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

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

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

1. **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
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?**
   - **NO** for many trials as safety profile of drug is well characterized and benefit/risk is calculated
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?**
   - **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
4. **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

Clinical Trial Assays 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 purpose

- 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 purpose different validation levels are applied (see next slide)
  - Notion mentioned in “EMA Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle”* EMA/CHMP/800914/2016

When/how can we define minimal analytical validation criteria for a CTA (prototype assay), following a risk-based approach ?

Preliminary draft for discussion

	Biomarker Assay in/for early clinical trials		For reference
			Commercialised assay
Context of Use	Exploratory (including retrospective; not for patient selection)	Selection or Enrichment E.g. BRAF	Commercial / EU
Typically used 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 use on instruments)	-- /(✓)	(✓) preliminary	✓
Shipping stability	--	(✓) within context of trial	✓
Accuracy (results from trueness and precision)	✓	✓	✓
Repeatability	✓	✓	✓
Reproducibility	-- /(✓)	(✓) within context of trial	✓
Cut-off	--	✓	✓
Interferences	--	(✓) within context of specimen & technology	✓
Cross reactions	-- /(✓)	(✓) within context of specimen & technology	✓
Clinical performance	--	--	✓
Scientific validity	--	Scientific rationale	✓

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