Statistical Issues and Methods for the Clinical Validation of Follow-On Companion Diagnostic Devices

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Follow-On (Me-too) CDx

- Definition: A Follow-On companion diagnostic (denoted as FCD) is an in vitro companion diagnostic device as having the same therapeutic indication as a FDA-approved companion diagnostic (i.e. comparative companion diagnostic CDx, denoted CCD)
  - information provided by FCD is essential for the safe and effective use of the corresponding therapeutic product in CCD.

- Other considerations
  - Biological Target: e.g. BRAF V600E gene
  - Analyte type: DNA vs. protein
  - Methodology: PCR vs. sequencing
  - Specimen types: formalin-fixed paraffin-embedded (FFPE) vs. plasma

Follow-on CoDx Approval

	First-of-a-Kind /Original	"Follow-on"
Sponsor	**QIAGEN**	**Roche Molecular System**
Device	***therascreen* KRAS RGQ PCR Kit**	**cobas KRAS Mutation Test**
Intended Use (IU)	The *therascreen* KRAS RGQ PCR Kit is a real-time qualitative **PCR** assay used on the Rotor-Gene Q MDx instrument for the detection of **seven somatic mutations** in the human KRAS oncogene, using DNA extracted from formalin **fixed paraffin-embedded (FFPE) colorectal cancer (CRC)** tissue. The *therascreen* KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with **Erbitux (cetuximab) and Vectibix (pantitumumab)** based on a KRAS no mutation detected test result.	The cobas KRAS Mutation Test, for use with the cobas 4800 System, is a real-time **PCR** test for the detection of **seven somatic mutations** in codons 12 and 13 of the KRAS gene in DNA derived from **formalin-fixed paraffin-embedded human colorectal cancer (CRC)** tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with **Erbitux (cetuximab) or with Vectibix (panitumumab)** may be indicated based on a no mutation detected result.

FCD Validation Studies

- **Measurement Performance Studies:** parameters associated with the measuring capability of a test
  - **Pre-analytical:** related to specimen collection (including timing, technique (aliquoting, pipetting, and retrieval), and processing), as well as handling and storage (including time, temperature, humidity, and volume)
  - **Analytical:** related to the precision, accuracy of the test method and factors which may interfere with a particular assay (LoB/LoD, precision, analytical accuracy etc.)
  - **Post-analytical:** related to data entry and calculations by laboratory staff, result validation, interpretation of the result, data transfer and the method used to report the results (electronic, paper or telephone)

- **Clinical Studies:** parameters associated with the capability of a test for predicting treatment responses [predictive tests] or parameters associated with the capability of a test for identifying/selecting patients for a specific therapeutic treatment [selection tests]

This talk will focus on clinical validation studies

FCD Clinical Performance Validation

The safety and effectiveness of FCD for its therapeutic indication in its intended use as that of a CCD is supported if

- Therapeutic efficacies in FCD intended use population are comparable between FCD and CCD [*ideal and recommended*]
  - For selection tests: the efficacy of the therapeutic product in selected patients by FCD is comparable to that in patients selected by CCD
  - For predictive tests: therapeutic product by FCD interaction is comparable to therapeutic product by CCD interaction
- Agreements between FCD and CCD are sufficiently high

FCD Clinical Validation Study Designs

Design	Original clinical trial			New clinical trial		External concordance study	
	Drug	CCD	FCD	Drug	FCD	CCD	FCD
1	✓	✓		✓	✓		
2	✓	✓	✓				
3	✓	✓				✓	✓
4	✓	✓				✓	✓

- Direct estimate of drug efficacy*:* design 1
- Direct estimate of drug efficacy and agreement: design 2 (same as bridging study)
- Indirect estimate of drug efficacy and agreement: design 3
- Agreement from the concordance study: design 4

This talk will focus on the agreement from external concordance study design 4

Clinical Validation of FCD

- Therapeutic product efficacy in FCD intended use population
  - Direct estimate:
    - Conduct a new clinical trial using FCD and the therapeutic product, and estimate the drug efficacy directly from observed clinical and FCD results (*ideal not practical*)
    - Retest the samples of the original clinical trial conducted to evaluate the CCD and the drug by FCD, and estimate the drug efficacy directly from observed clinical and FCD results

      (*ideal if no sample stability issue and % of retesting by FCD is about 100%*)
  - Indirect estimate: using statistical modelling to provide hypothetic drug efficacy estimate based on (1) clinical and CCD test results from the original clinical trial and (2) agreement between FCD and CCD obtained in an external concordance study
    - model assumptions should be detailed, justified e.g. is the agreement in the concordance study really transportable to the original clinical trial?
    - limitations of modelling will need to be stated.
    - Inappropriate study design or conduct of the concordance study can invalidate the indirect estimates

FCD Clinical Validation via an External Concordance Study

- Reference standard is available
  - Each enrolled sample will be tested by the reference standard, FCD, and CCD

- Reference standard is NOT available
  - Each enrolled sample will be tested by FCD once and twice CCD (denoted as CCD1 for the 1st replicate and CCD2 as the 2nd replicate)

External Concordance Study when Reference Standard is Available

- Each enrolled sample will be tested by the reference standard, FCD, and CCD

- Primary analysis:
  - Positive predictive values are comparable between FCD and CCD i.e. Pr.(Reference Standard Pos | FCD Pos) and Pr.(Reference Standard Pos |CCD Pos) are comparable
  - Negative predictive values are comparable between FCD and CCD i.e. Pr(Reference Standard Neg |FCD Neg) and Pr(Reference Standard Neg |CCD Neg) are comparable

Table 1: External concordance study when reference standard is available

	Reference Standard						total
	G Positive			G Negative			
	CCD Pos	***CCD Neg***	***total***	***CCD Pos***	***CCD Neg***	***total***	
FCD Pos	a_1	b_1	m_1	a_0	b_0	r_1	(m_1+r_1)
FCD Neg	c_1	d_1	m_0	c_0	d_0	r_0	(m_0+r_0)
$Total$	n_{11}	n_{10}	n_1	n_{01}	n_{00}	n_0	n

**: $(m_1 + r_1) + (m_0 + r_0) = n_1 + n_0 = n$

$(n_{11} + n_{01}) + (n_{10} + n_{00}) = n_1 + n_0 = n$

External Concordance Study when Reference Standard is Available

Study Designs:

- Design 4.11: a random sample of n representative subjects from FCD intended use population are enrolled
  - Assume $\Pr(G\ Pos|sampled) = \Pr(G\ Pos)$ in FCD intended use (IU) population
  - Each enrolled subject is tested once by FCD, CCD, and reference standard
  - No enrichment

- Design 4.12: the concordance study is sized and patients are enrolled based on reference standard results, i.e.

  n_1 of G Pos and n_0 of G Neg are enrolled.
  - Assume $\Pr(G\ Pos|sampled) > \Pr(G\ Pos)$
  - **Positive patients are enriched**

Study Designs

- Design 4.13: the concordance study is sized and patients are enrolled based on FCD test results i.e. $(m_1 + r_1)$ FCD Pos and $(m_0 + r_0)$ FCD Neg are enrolled. [***not recommended***]
  - Assume $\Pr(G\ Pos|sampled) > \Pr(G\ Pos)$
  - $(m_1 + r_1) + (m_0 + r_0) = n$
  - **Positive patients are enriched**

- Design 4.14: the concordance study is sized and patients are enrolled based on CCD test results i.e.

  $(n_{11} + n_{01})$ CCD pos and $(n_{10} + n_{00})$ CCD neg are enrolled
  - Assume $\Pr(G\ Pos|sampled) > \Pr(G\ Pos)$
  - $(n_{11} + n_{01}) + (n_{10} + n_{00}) = n$
  - **Positive patients are enriched**

Estimation and Hypothesis Testing

- The estimates of positive (or negative) predictive values and their confidence intervals for FCD or CCD are study design dependent!

  ***Ref: Li, Meijuan**, Statistical methods for clinical validation of follow-on companion diagnostic devices via an external concordance study, Statistics in Biopharmaceutical Research (to appear)*

- The study design is a paired sample design

- Positive and negative predictive values are correlated

- The study acceptance criteria needs clinical and statistical justification and will vary case by case

External Concordance Study when Reference Standard is Not Available

- Each enrolled sample will be tested by FCD once and by CCD twice (denoted as CCD1 and CCD2, respectively)

- Primary analysis:
  - Agreement between FCD and CCD is comparable to the agreement between two replicates of CCD (*i.e.* CCD1 and CCD2)
    - The positive (PPA) and negative (NPA) percentage agreements between FCD and CCD1 are comparable to PPA, NPA between CCD2 and CCD1
    - The positive (PPA) and negative (NPA) percentage agreements between FCD and CCD2 are comparable to PPA, NPA between CCD1 and CCD2

Table 2: External concordance study when reference standard is Not available

	$CCD1Pos$			CCD_1Neg			
	CCD2 Pos	**CCD2 Neg**	*total*	**CCD2 Pos**	**CCD2 Neg**	*total*	***total***
FCD Pos	a_1	b_1	m_1	a_0	b_0	r_1	(m_1+r_1)
FCD Neg	c_1	d_1	m_0	c_0	d_0	r_0	(m_0+r_0)
total	n_{11}	n_{10}	n_1	n_{01}	n_{00}	n_0	n

**: $(m_1 + r_1) + (m_0 + r_0) = n_1 + n_0 = n$

$(n_{11} + n_{01}) + (n_{10} + n_{00}) = n_1 + n_0 = n$

External Concordance Study when Reference Standard is not Available

Study Designs

- Design 4.21: a random sample of n representative subjects from FCD intended use population are enrolled
  - Assume $\Pr(G\ Pos|sampled) = \Pr(G\ Pos)$ in FCD intended use (IU) population
  - Each enrolled subject is tested once by FCD and twice by CCD
  - **No enrichment**

- Design 4.22: the concordance study is sized and patients are enrolled based on FCD results i.e. $(m_1+\mathrm{r}_1)$ FCD Pos and $(m_0+\mathrm{r}_0)$ FCD Neg are enrolled. The sample of each enrolled FCD pos or FCD neg is tested twice by CCD. [***not recommended***]
  - Assume $\Pr(FCD\ Pos|sampled) > \Pr(FCD\ Pos) \rightarrow \Pr(G\ Pos|sampled) > \Pr(G\ Pos)$
  - **Positive patients are enriched**

Study Designs

- Design 4.23: the concordance study is sized and patients are enrolled based on the 1st replicated results of CCD i.e. n_1 CCD1 pos and n_0 CCD1 neg are enrolled. The sample of each enrolled CCD1 pos or CCD1 neg is tested by FCD and CCD again (i.e. CCD2).
  - Assume $\Pr(CCD1\ pos|sampled) > \Pr(CCD1\ pos) \rightarrow \Pr(G\ pos|sampled) > \Pr(G\ pos)$
  - **Positive patients are enriched**

Estimation and Hypothesis Testing

- The estimates of positive (or negative) percentage agreements and their confidence intervals are study design dependent!

  ***Ref: Li, Meijuan**, Statistical methods for clinical validation of follow-on companion diagnostic devices via an external concordance study, Statistics in Biopharmaceutical Research (to appear)*

- The study design is a paired sample design

- Estimated positive (or negative) percentage agreements are correlated

- The study acceptance criteria needs clinical and statistical justification and will vary case by case

Concluding Remarks

- The lack of (or no access to) the therapeutic sponsor's clinical trial samples, manufacturer of a follow-on companion diagnostic is challenged with how to demonstrate clinical performance of FCD, the agreements between FCD and CCD (or standard) from an external concordance study may be used for the clinical validation of FCD.

- Even though the talk focus on the agreement of an external concordance study, the sponsors are encouraged to directly estimate therapeutic efficacy in its IU population through a randomized clinical trial of the therapeutic product and the follow-on device when possible.

- The extent of analytical and clinical studies needed to support regulatory approval of a follow-on companion diagnostic will likely vary on a case-by-case basis

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Thanks

Questions?

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