CoU statement at Boehringer Ingelheim

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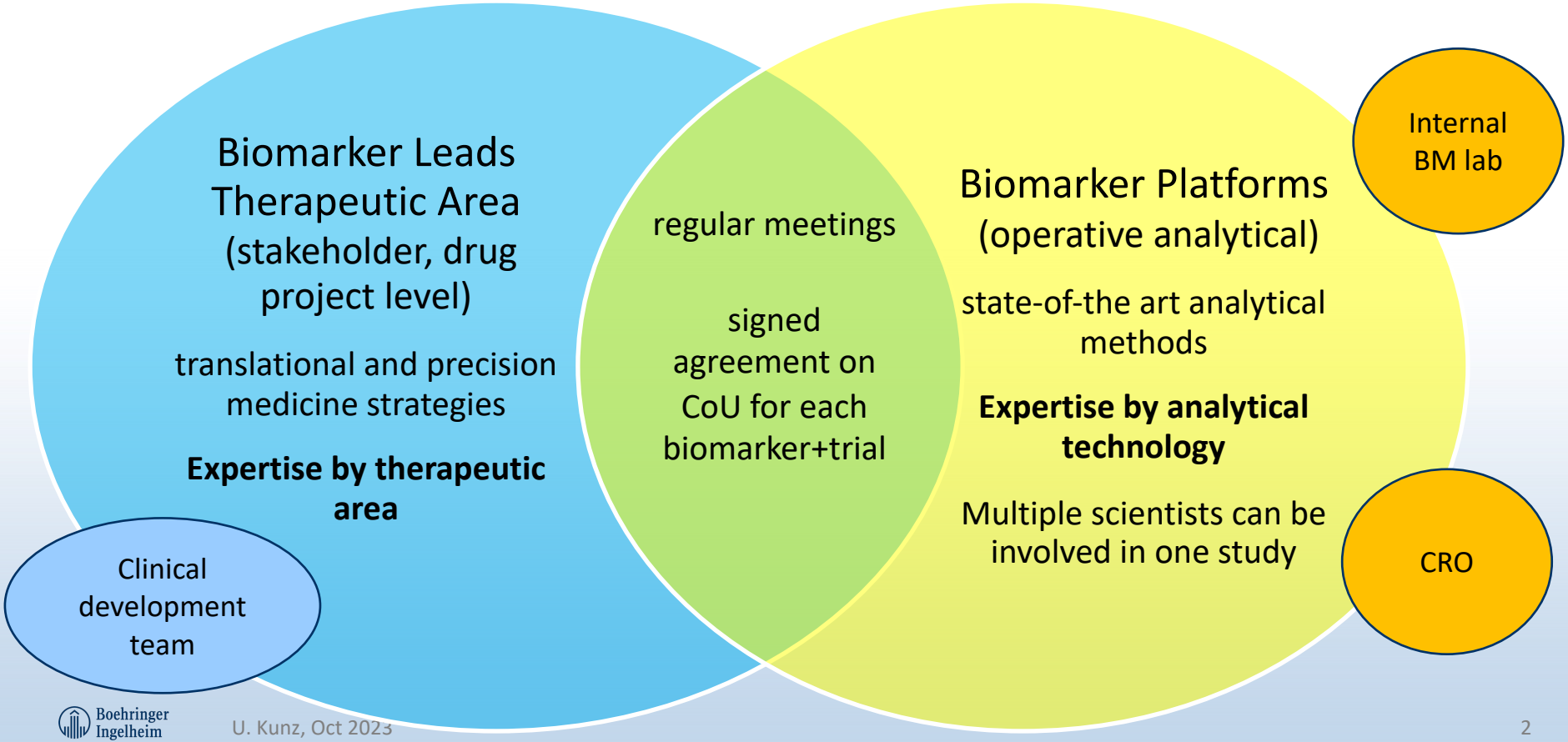
Boehringer Ingelheim

Who is involved?



How is it done and when?

1. Stakeholder invites all analytical experts
   - Prior to the 1. draft of the Clinical Trial Protocol
   - Details of drug development program and planned clinical study
   - Rough CoU of all the biomarkers requested
   - Timelines and logistical issues of the study
2. Analytical expert asks for detailed information about each BM
   - Sharpening the CoU
   - Sources of further information
3. Analytical expert:
   - translates CoU into an **analytical strategy**
   - suggests **analytical method** suited for the CoU

Where do we capture it?
Biomarker Intended Use and Implementation Statement

Content	Comments
Trial number	One document per trial (covering all BM, 3-30 pages)
Document version, history	All document versions to be archived, It should be clear whether changes affect the intended use of a BM
Authors	Stakeholder **and** all Bioanalysts
General Information about trial	Drug development project, clinical phase, population, # of subjects, rough planned timelines
List of all BM	
Operational details	Blinding, priority, reporting, frequency of interim evaluations
Risk assessment	Patient, regulatory, business
Detailed description of CoU	**one section per BM**

Stakeholder and all analytical experts agree on the content by **signature**.

Afterwards the analytical experts are accountable for the method development/selection and validation

What is discussed? Intended Use (CoU)

- ✓ the **exact analyte** (e.g. incl. uniprot#, isoform, "free" vs. total)
- ✓ the **biological context**/function of the BM in the matrix (relevant reference if available, biological variance, circadian rhythm)
- ✓ the **hypothesis or function** of the BM with regard to treatment/disease (incl. baseline level and expected change during treatment) (relevant reference if available)
- ✓ the **purpose** of BM measurement in the study
- ✓ the possible **impact** on decisions (incl. possible cut-off or decision points/trees)
- ✓ an **outlook** on possible future use of this BM (incl. need for comparable concentration results)
- ✓ Specification of method and **matrix** (if already fixed)
- ✓ Description of **planned data evaluation/statistics**

Case study - CTGF as disease modulating pd biomarker

CTGF is a marker of tissue fibrosis. Serum levels of CTGF_Q5M8T4, N-terminal fragment, are elevated about 1.5-2 fold (50-100 ng/mL, intra- and inter-subject biological variance known, Lit1) in patients with systemic sclerosis and associated with extent of skin sclerosis and severity of pulmonary fibrosis. It is a hypothesis that CTGF levels will decrease after treatment with drug over x month to an unknown extent as a disease modulating biomarker, although already described for another drug in the same indication (lit2).

The assay will be accepted as it has performed in a previous trial. The significance between the average relative change from baseline of about 100 patients vs. placebo will be calculated.

Same case study - CoU summary for translation into the bioanalytical strategy

Analyte Specificity	CTGF_Q5M8T4, N-terminal fragment + full length (research, reference literature) in serum
Trial population (phase)	patients with systemic sclerosis (phase II)
BM category	Disease modulating pd biomarker (explorative = not clinically qualified)
BM purpose	Hypothesis testing: is CTGF a suitable BM in this indication?
Position of the BM in the biological context	CTGF is a marker of tissue fibrosis. Serum levels of CTGF are elevated 1.5-2 fold in patients with systemic sclerosis and associated with extent of skin sclerosis and severity of pulmonary fibrosis. Very low biological intra-subject variance.
Expected magnitude of biomarker change to affect decisions	Slight decrease after treatment, unknown extent, maximal down to healthy volunteer level (0 - 50%)
BM impact on drug development	supportive disease modulating BM, test whether hypothesis is true, not solely used for any decisions
Risk (patient, regulatory, business)	No patient risk, no regulatory risk, low business risk
Data evaluation	average relative change from baseline (> 100 patients) vs. placebo, descriptive statistics and significance test
Data comparability	within this study only (about 3a), within subject 48 weeks

Supportive information: any literature/data/previous experience about BM