How organizational design influences the analytical clinical biomarker process at BI

A case study

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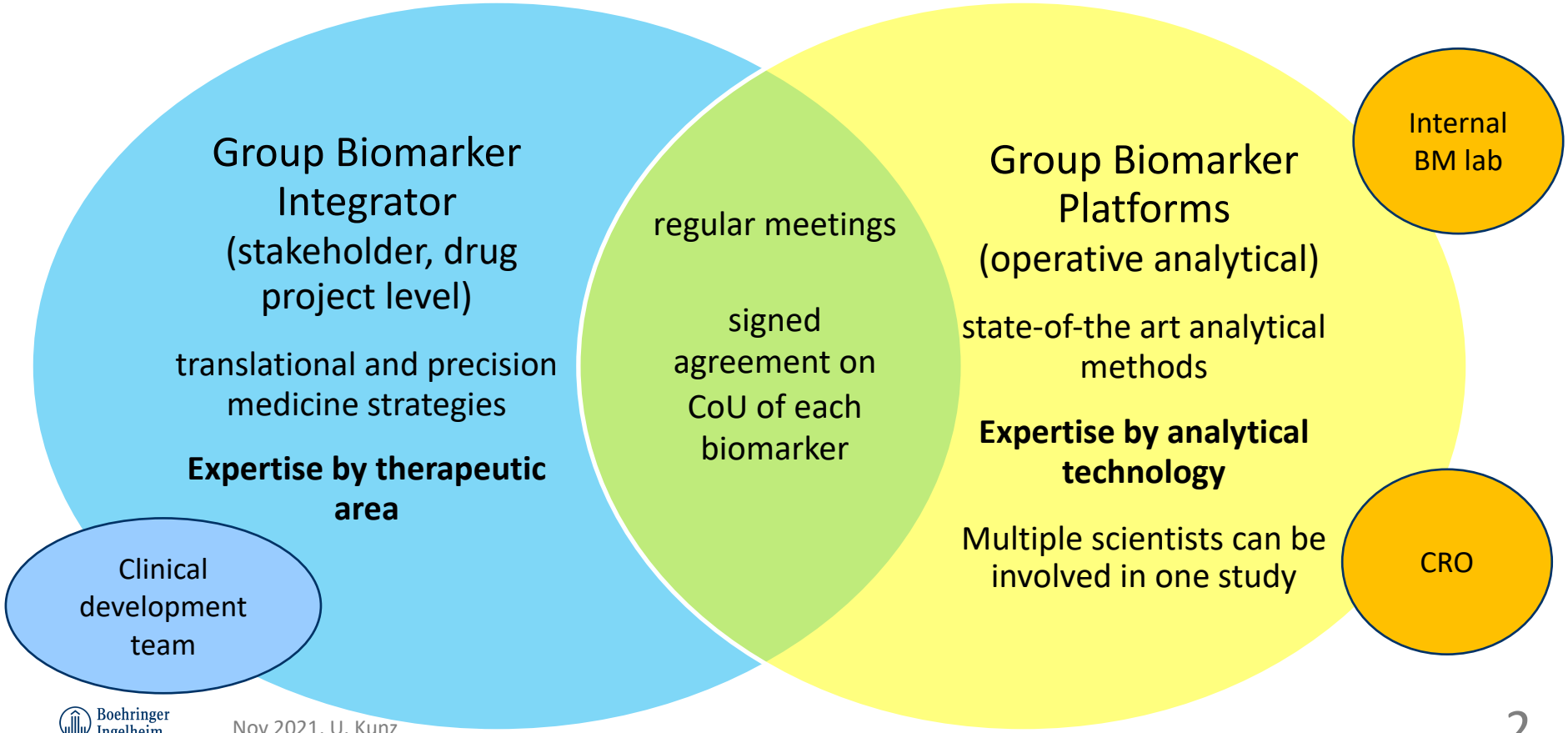

case study – 1. the request for analytical support

- stakeholder -> biomarker platforms group (analytical experts)
  Basic information about planned study and biomarker package
  „A First–in-human Phase I, multicenter, dose escalation trial of DRUG administered in patients with tumour expressing TARGET“

Planned biomarker	Suggested technique
Target expression on tumour (patient selection BM)	IHC
apoptosis	IHC
T-cell activation	FACS
Soluble target	Immunoassay
Cytokine release	Multiplex Immunoassay
…	

Colour code:
Blue = stakeholder
Yellow = analytical expert
Red text = case study

- Nomination of analytical experts for study

2. The kick-off meeting (s)

- Stakeholder invites all analytical experts
  - Details of drug development program and planned clinical study
  - Reason for the biomarkers in the request list,
    how they would support the study and the drug development (**CoU**)
  - Timelines and logistical aspects of the study (e.g. soluble target data after each dose cohort)
- Analytical expert asks for detailed information about each BM
  - Sharpening the CoU (expected range of sol. target level slightly higher than healthy volunteers, expected increase during treatment, ….)
  - Sources of further information (publications about soluble target, assay/antibody available in research, pre-clinical data, competitor projects?)
- Analytical expert:
  - translates CoU into an **analytical strategy**
  - suggests **analytical method** suited for the CoU (MSD due to need for high sensitivity)

Biomarker Intended Use and Implementation Statement and Translation of the CoU into a bioanalytical strategy

Stakeholder (CoU)

Exploratory surrogate target engagement PD biomarker modulation in blood: changes during drug administration.

Hypothesis:

- Do the baseline levels influence PK of drug?
- Do the total **soluble target concentrations** reach a level that might neutralize the drug efficacy?
- Increase of total target level by prolongation of half-life due to complex formation with drug?

Results after each dose cohort necessary to support decisions on further dosing

100 patients, 3 samples per patient

PLANNED STATISTICAL ANALYSIS

- Concentration data for **pk/pd modelling**
- **% change from baseline** or absolute change from baseline

Analytical expert (analytical strategy)

MATRIX/METHOD/ASSAY

- Matrix: EDTA Plasma (if no differences plasma vs. serum)
- Method: BI **MSD assay using BI antibodies** from research and **commercial recombinant standard**
- Sensitivity: proposed **LLOQ < 1. quartile** healthy volunteer level, min. 50pg/mL (info from modelling)
- Specificity: **total soluble target**, interpreted as shedded extracellular domain of target receptor
- **Parallelism: mandatory** due to use of data in pk/pd modelling
- **Precision: no target** as treatment effect is unknown

Huge number of QC aliquots (incl. endogenous plasma)

RISK ASSESSMENT (patient, business, regulatory, questionnaire)

- Overall **risk is considered low**. Long term comparability of results would require **additional validation and assay monitoring effort**.

Stakeholder and all analytical experts agree on the content by signature.
Afterwards the analytical experts are accountable for the method development/selection and validation

Continous interaction prior, during and after clinical study

- Follow up meetings
  - to update stakeholder about status/performance of analytical methods and interim results
  - to update analytical experts about status of clinical trial and development project

- Inclusion of biostatistics, pk, modelling and data management to discuss data transfer and evaluation (review of trial statistical analysis plan)
  - limitations of analytical method
    - e.g. relative quantitative target assay not absolute quantitative (ngEq/L instead of ng/L)
    - imprecision of method vs. biological variance
  - what kind of interpretation would be covered by the method validation and what not (e.g. exact molecular weight of endogenous analyte is unknown)

What would have happened without the IUIS/CoU

Missing information about	Possible consequence in assay validation	Possible consequences on data interpretation
required specificity (e.g. **total** target)	Commercial kit instead of homebrew assay (not total, not free but something in between)	Misleading data interpretation (failed pk/pd model verification
Required sensitivity	Wrong assay range	Below lower limit of quantification results only
Data evaluation	Maybe a quasi-quantitative assay would have been accepted	No valid concentration data, not useful for modelling.
Frequent need for interim data	Storage of insufficient aliquots of reagents and QCs	Frequent bridging of lots may cause additional bias on data
Treatment effect on BM	Wrong assay range, insufficient precision	Treatment and biological effect masked by analytical error
Duration of trial, need for long term comparability of data	Lack of stability information, insufficient method robustness	Additional bias on data, risk of non-comparable results or even not valid results

General consequences of lack of CoU

- Blaming the analyst for data that is not useful 
- Misleading PD or patient selection BM data may cause development of a less effective drug, risk of late failure in phase III or application 
- A good drug killed early during development for the wrong reasons 

Advantages of a pre-defined detailed CoU

- No waste of human specimen (GCP)
- No delays in studies due to missing data for milestone decisions
- Protects from the changing minds of stakeholder(s) during an ongoing study
- Stronger position of the analytical expert in the biomarker/translational medicine process/organization and even in drug development
- High likelihood of useful and valid data
- Smarter decisions and more successful drug development