EBF

14th EBF Open Symposium

Science – Our Universal Language

Feedback from 14th EBF Open Symposium

& recent EBF Discussions

Kyra Cowan, on behalf of the EBF

3 December 2021, Cyberlona

2021 Objectives	Biomarker Strategy Subteam
Project Title:	Biomarker CoU: Implications for the assay
Team Leader:	Kyra Cowan, Merck KGaA
Team *(from organizing committee)*	Jo Goodman, AstraZeneca; Michaela Golob, Nuvisan; Anna Lauren, Novo Nordisk; Philip Timmerman, EBF
Team	Laetitia Sorde, Sobi; Peter Groenen, Idorsia; Ulrich Kunz, Boehringer-Ingelheim; James Lawrence, F-Star; Lien Dejager, UCB; Alessandra Vitaliti, Novartis; Laurent Vermet, Sanofi; Lene Andersen, Orphazyme; Marianne Fjording, Bioagilytix; Mario Richter, Abbvie; Matti Kimberg, Synexa; Mike Wright, GSK; Nicole Justies, Roche; Philip De Decker, argenx; Radboud van Trigt, PRAHS; Renaud Jasnowski, Active-Biomarkers;
Goals *(for this year)*	**First: battle for industry-wide implementation of CoU**

Biomarker Strategy Team 2021

- Building from BM FW April 27-28 on CoU
  - We need to keep the momentum going
  - Still have issues with understanding/alignment within BA space
  - **To our EBF Community:**
    - You are the multipliers, the sponsors, the champions of the message for CoU throughout industry, to drive the topic internally and externally
    - We need to avoid inappropriate guidance from HAs, inappropriate implementation of BMV guidance on BM assays in general
    - How do we change the way of thinking? – this is not repackaging of the Jean Lee or subsequent FFP papers – rather diving deeper into the strategy and the science that supports CoU implementation.
  - Clarity and alignment across industry
- **First team meeting: What works, doesn't work, in organisational structures**
  - **Volunteers** to describe their organisations
  - **Agreed:** BA scientist is in the driver's seat, and it's critical that BA scientists are considered integral on the core team, for example.
  - **Agreed:** CoU should be discussed early, and confidence needs to be built in what we have to offer, so that the importance of CoU is convincing.

Summary on Common Ground

- **What works:**
  - Clear and documented BM strategy and integrated BM approach.
    - Ensure that the biology is discussed and understood.
  - Clearly defined, centralised BM group that covers BM assay, operational, and BM strategy expertise and corresponding responsibilities.
    - Overarching view on CoU, all BM activities (assays, samples, data analysis, CoU).
    - High functioning matrix work environment with clear R&Rs and close collaborations.
    - Ideally, operational separation of decision-making BM assays from PK/ADA BA team.
      - Depending on CoU, separate processes for PK v BM
  - If not one BM group:
    - Close collaboration between BA and BM leads, if separate functions.
      - Co-location of these groups preferred.
    - Close collaboration with all stakeholders, including outsourcing, to implement BM strategy.
  - Implementation and documentation of Purpose (CoU) for each BM data
    - In method summaries, in validation plans, in SAPs, in assay specification document or online „living document“, etc., for each purpose for each BM
  - Inclusion in clinical protocol review

Summary on Common Ground

- **What doesn‘t work:**

  - Lack of Biomarker assay expertise, or relying on PK assay experts.
  - Siloed operational teams, or complex team organisation, and/or gap in communication btw Sponsor/CRO, so that BA input and involvement is lost.
  - Fractioned responsibilities across functions without single BM lead with overarching investment in all BM deliverables.
  - Applying the wrong regulations and check boxes (eg. PK SOP, QA vs independent QC, etc.).
  - Lack of a possibility to have scientific rationale, discussion, and therefore being beholden to BMV.

Simple Structure, starting at Lead Optimisation

Discovery Team

DMPK

Research

Nonclinical safety

Bioanalytical PK/ADA

Translational BM Lead

BM Integrator

BM Techno

Biomarker selection, strategy

Analytical, Operations

Data Interpretation

CoU statement per analyte, Documentation

Development Team

Medical

Drug Safety

Pharmacometrics

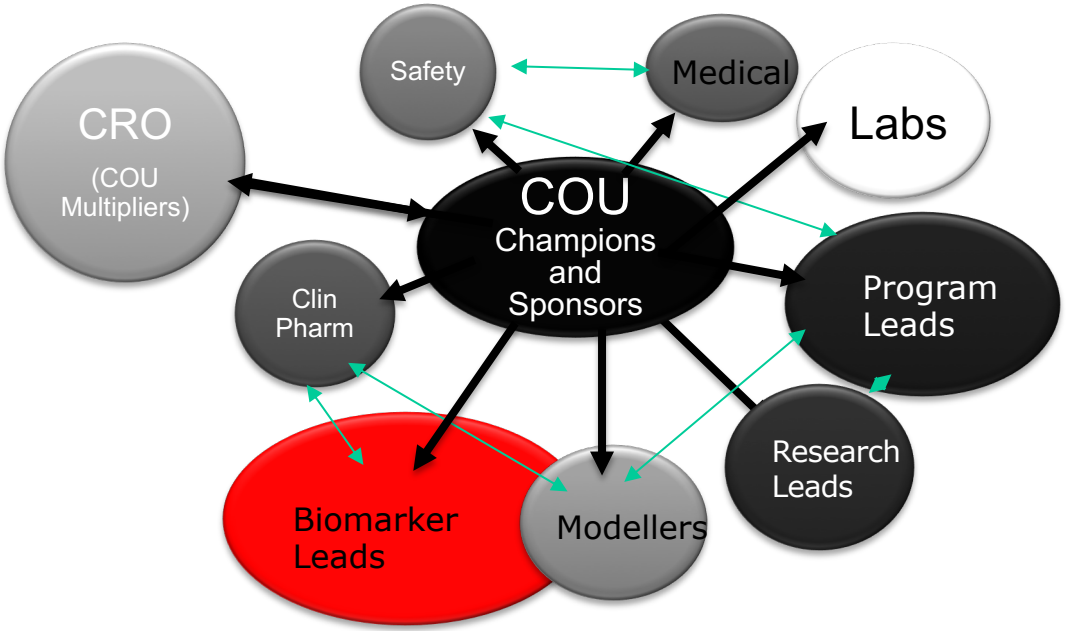
Clinical Pharmacology

Touchpoint Meetings*

*Touchpoint meetings with BM Lead would need to involve all relevant functions

Changing the mindset with defined responsibilities and documented communications

Truly matrix approach to communication for simplified org:



Stakeholder Management is key:

- How can we ensure COU is implemented and communicated?
- What is missing in the communication?
- How can we best educate/train?
- How can we make sure we are relaying the right message?
- How do we relay a sense of urgency for COU?
- How do we ensure consistent buy-in?

How to make CoU implementation successful?

1 **Create awareness**
- Create a feeling for urgency for CoU.
- Develop an understanding of the situation, risks, impact and activities in implementing CoU (train and explain).

2 **Win supporters**
- Get top management commitment.
- Build a team that supports the message.

3 **Develop a vision**
- Make it clear and understandable what's being implemented and why.
- Explain the outcome of using CoU.

4 **Communicate the vision**
- Provide timely and honest information.
- Get buy-in for CoU.

5 **Empower Action**
- Win-Win-Strategy: make your stakeholders to your partners.
- Involve your stakeholders e.g. the employees in decisions.

6 **Create short-term wins**
- Get change blockers or neutral people on your side by showing successes of the project.
- Communicate about your wins.

7 **Leverage wins to drive change**
- Use the energy from the quick wins to drive your change initiative forward.

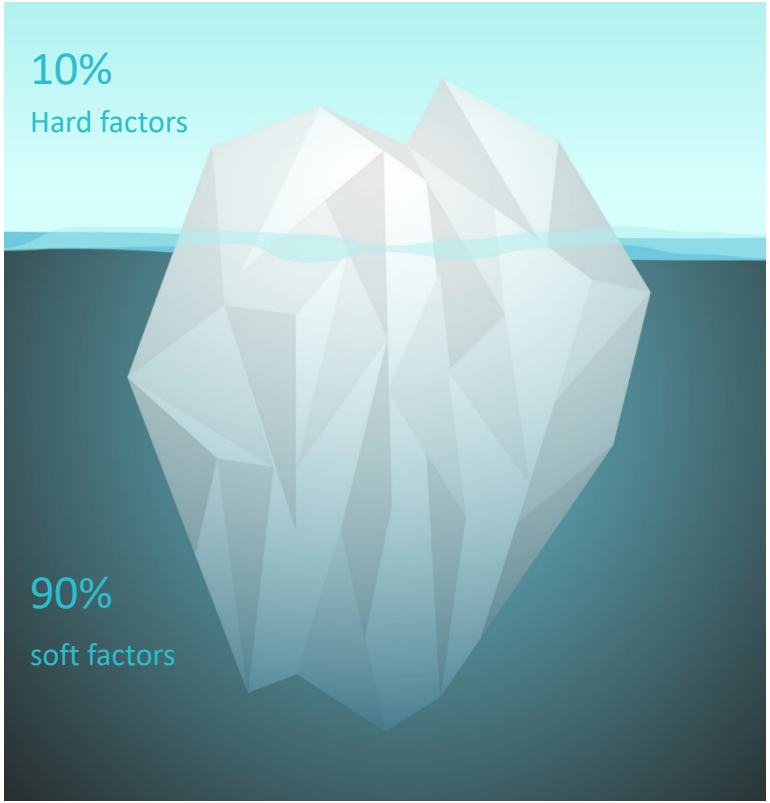
8 **Embed in culture**
- Stabilize the situation again and develop attitudes and behaviors which embed the changes in the culture and daily work.
- Make long-term objectives measurable.

The iceberg model

What are key factors that will make implementing COU successful?

- Training programs
- Costs
- Timeline
- Organisational structure
- Available technologies
- Regulatory domain knowledge

- **Involving the employees/stakeholders**
- **Honest and timely communication**
- **Normal routines, habits**
- **Top management commitment**
- **Motivating organizational culture**
- **Change promoters (those willing and understanding CoU)**
- **Corporate culture of continuous change**



Conclusion

The base of change management lies below the surface of the iceberg.

Involving the stakeholders in an honest and timely communication is key to successful and regular implementation of CoU principles for all biomarkers

QUESTIONS: EBF, recent discussions

Four Questions, 40 minutes:

1. In my company/organisation, we actively apply the principles of CoU for BM assays, with CoU summarised in one sentence as:

Building the BM assay on decision taken by the data, (i) having informed the end user of the data (stakeholder) of what the assay can do, and (ii) being informed by the end user of the data (stakeholder) what the assay should do to allow valid decision to be taken by the data. CoU is not copying PK-assay criteria (i.e. from BMV guideline) as a starting point for the assay performance

a. Yes
b. Partly: please comment of what you apply/don't apply:
c. No
d. I do not sufficiently understand CoU principles
e. I understand CoU differently: please comment

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a. **Yes: 12**
b. **Partly: please comment of what you apply/don't apply: 34**
c. **No: 6**
d. **I do not sufficiently understand CoU principles**
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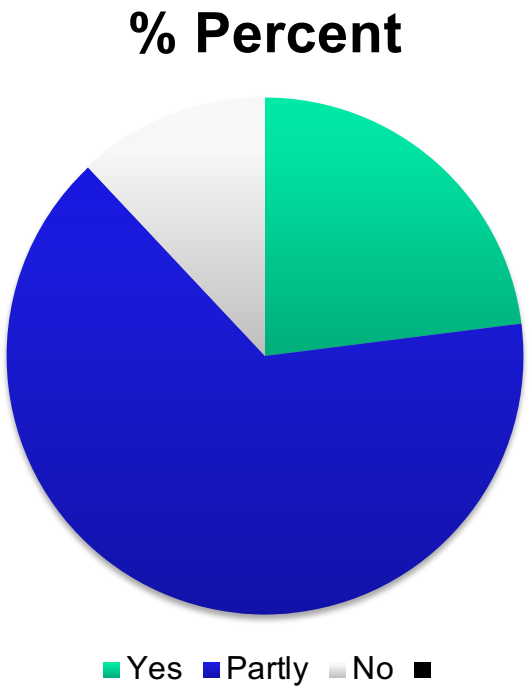

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- Project dependent. More and more people are more educated and understand what is COU.
- It is not totally completely documented. From CRO point of view, 80% of BM are validated as PK assay as no COU information available.
- For CRO's the stakeholder/client can be a limiting factor in the application of the CoU. CRO's are limited by the clients decision, the CRO can try and convince client to carefully consider the CoU but at the end the decision point is defined by the clients final decision making. This can be difficult especially with exploratory BM.
- Could help to send a questionnaire in order to achieve a good perspective on the CoU.
  - Would be helpful for some guidance on developing an appropriate questionnaire.
- B – depends on the stage of the project – different groups between preclin and clinical. In preclin, infomation around biology, etc provided so context of use.
- CRO – struggle to implement context of use – hard to find the correct people to talk to at the client – client is king so in the end have to do what they want. Biotech don't have the experience so its easier to do context of use but difficult to find the infomation. Smaller companies treat them as PK but can be convinced. Pharma generally hold on to PK criteria – some stricter than others
- For sponsors hurdles remain: internal communication, knowledge of CoU and aligment on the concept for a given BM
- These hurdles vary by size, complexity and expertise of a given sponsor
- Responsiblity for CoU is rightfully in the BA Lab as they are responsible for the data.

QUESTIONS: EBF, recent discussions

2. What is the analytical process that your organisation applies for BM assays?
    a. BMV principles as per EMA/FDA Guideline, i.e. we use our PK SOP
    b. Diagnostic principles as for central labs (CLSI/CLIA)
    c. An internal guideline/SOP that defines in detail the validation strategy for Biomarkers, dependent on the analytical technology but independent from the CoU.
    d. I do not follow any guideline or SOP
    e. Other…

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c. **An internal guideline/SOP that defines in detail the validation strategy for Biomarkers, dependent on the analytical technology but independent from the CoU.: 19**
d. **I do not follow any guideline or SOP: 3**
e. **Other…**

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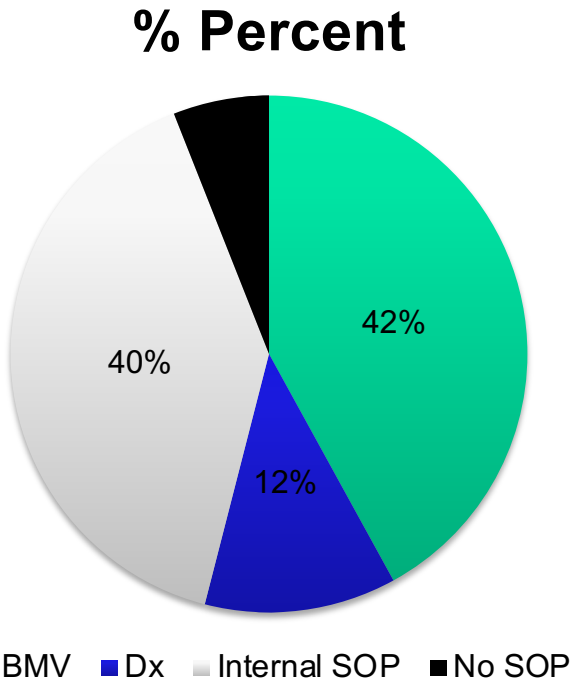

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- SOP for Biomarker, but flexibly used more as a guidance refrring to guideline, details documented in the bioanalytical plan (extend of validation, references to be used, acceptance criteria etc.)
- SOP specific for analytical technology (but freedom in the CoU)
- PK SOP and take as template but delete what is not relevantB/C, in the past BMV was used but have been moving towards CoU.
- Qualification is performed “in the spirit” of the BMV
- It is very difficult to write an SOP for a BM, sometimes there is a process to map out the potential options. Another preference would be to make additional comments to the PK SOP stating of how the SOP can be differently applied to BM.

QUESTIONS: EBF, recent discussions

3. In my company/organisation, the team(s) involved in BM assay validation and analysis is organised within:

a. Same scientists also dealing with PK/ADA assays
b. Dedicated and Integrated in the bioanalytical department (PK/ADA)
c. Dedicated Biomarker team not involved in PK/ADA assays (e.g. part of pharmacology, translational medicines team,…but not a regulated BA team)
d. Other or if more answers apply: please specify.

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3. In my company/organisation, the team(s) involved in BM assay validation and analysis is organised within:

a. **Same scientists also dealing with PK/ADA assays: 34**
b. **Dedicated and Integrated in the bioanalytical department (PK/ADA): 10**
c. **Dedicated Biomarker team not involved in PK/ADA assays (e.g. part of pharmacology, translational medicines team,…but not a regulated BA team): 5**
d. **Other or if more answers apply: please specify.**

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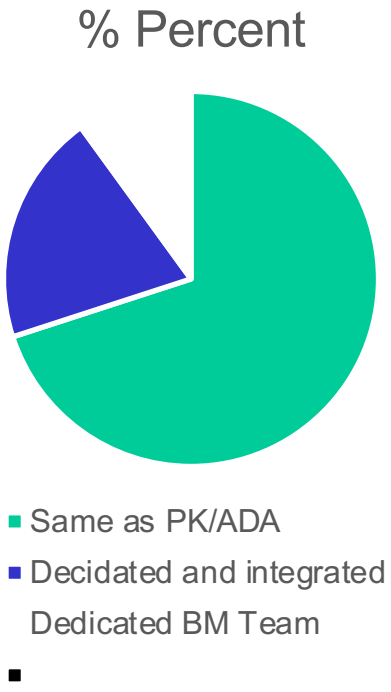

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   d. Other or if more answers apply: please specify.

- Not easy in small structures to have separate teams ; depends also on repartition of the activities
- In general, try to have analytical scientists who can do BM and PK/ADA, however not always possible. Having scientists who can do both allow for more flexibility and personal fulfillment for the scientists. One CRO has Client dedicated teams so means the scientists are responsible to the client itself, and hence should be able to cover both.
- Can be risky to only have single dedicated experts, is often limited by the size of the lab.
- Pharma company 1: Same scientists also dealing with PK/ADA assays
- Pharma company 2: Dedicated and Integrated in the bioanalytical department (PK/ADA) - You have to be strict on training the scientists/lab techs. They may some times fall back on PK criteria. Using checklists to define criteria.

QUESTIONS: EBF, recent discussions

4. Who should be responsible/accountable for the validity/usefulness of the requested Biomarker data?

a. The stakeholder/sponsor who requested the BM analysis in a particular trial/project (= end user of data)
b. The bioanalytical expert who selects the BM assay based on input from stakeholder and requests assay validation inhouse or external (CRO)
c. The Lab Head/Scientist of internal lab or CRO who performs assay validation/sample measurement according to a validation plan/analytical work plan
d. Someone else – please comment

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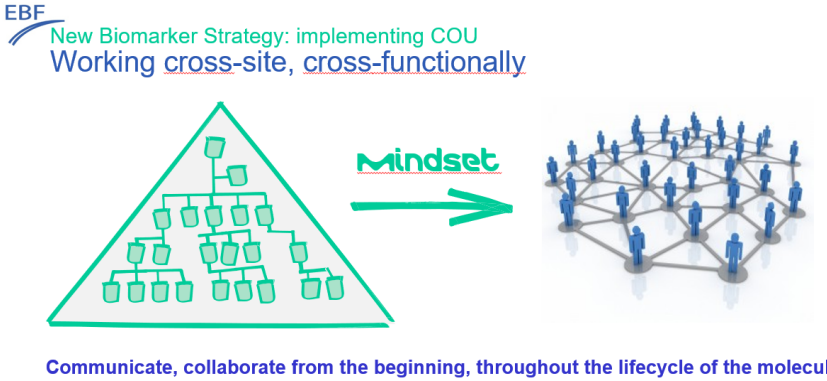
d. Someone else – please comment

Question 4

Question 8: **Bonus question** Who should be responsible/accountable for the validity/usefulness of the requested Biomarker data?	
The stakeholder/sponsor who requested the BM analysis in a particular trial/project (= end user of data)	**Accountable – for "Usefulness"**
The bioanalytical expert who selects the BM assay based on input from stakeholder and requests assay validation inhouse or external (CRO)	**Responsible – for "Validity"**
The Lab Head/Scientist of internal lab or CRO who performs assay validation/sample measurement according to a validation plan/analytical work plan	**Responsible – for "Validity"**
Someone else – please comment	

Acknowledgements



EBF Community, AAPS collaborations
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