15th Open Symposium

The Bioanalytical Compass

Navigating to our True North

Past, current, and future of EBF discussions:

Challenges and recommendations on Biomarker CoU

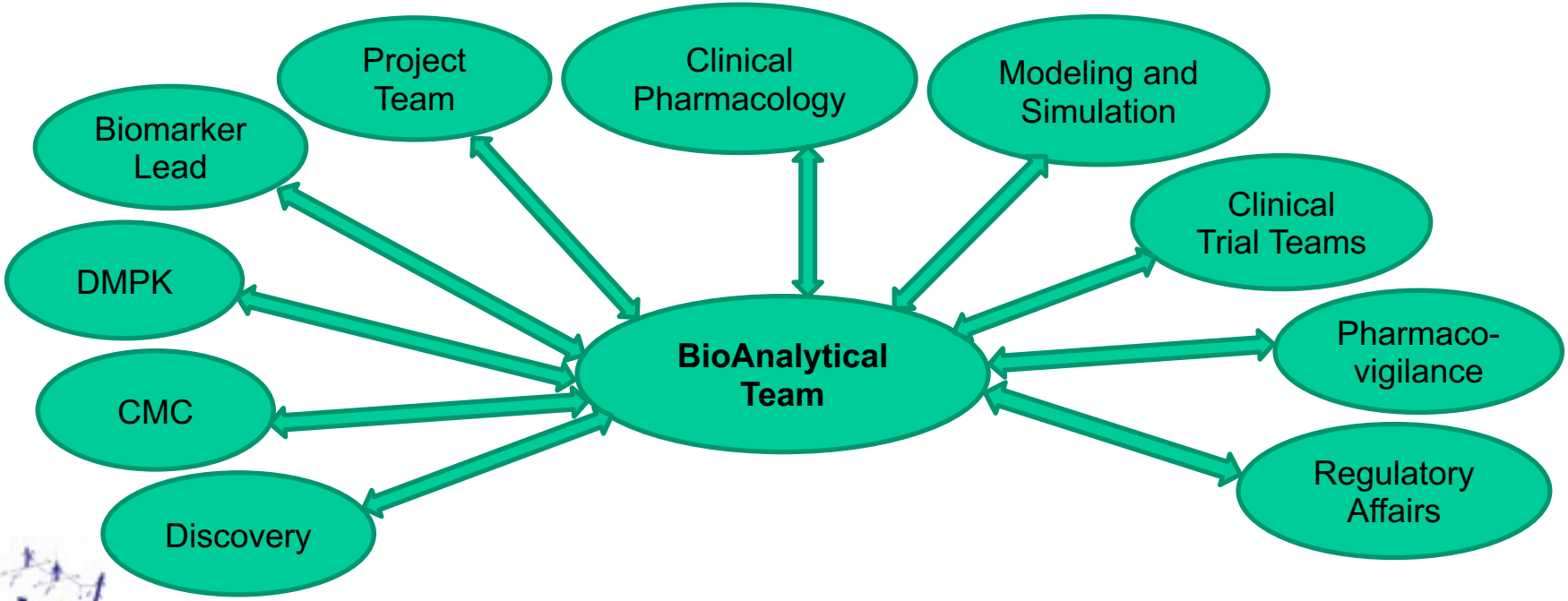
Kyra Cowan, on behalf of the EBF

16-18 November 2022, Barcelona

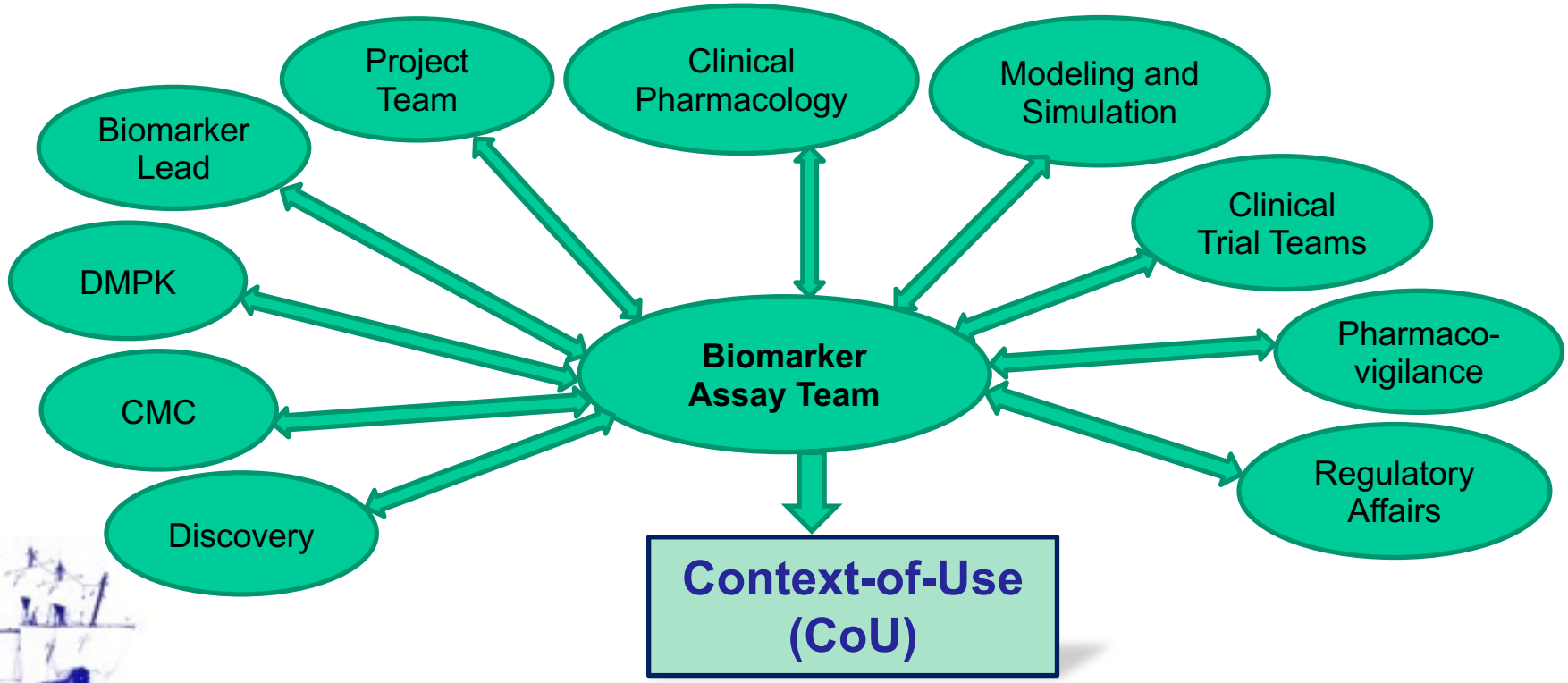
Content

- Quick recap: CoU and the rationale
  - Why are we talking about this, and the history of the discussion
- Recent deliverables from the EBF BM Teams
  - Publications, presentations, workshops
- Highlights from the Autumn FW on CoU: Shared Experiences
- What‘s next

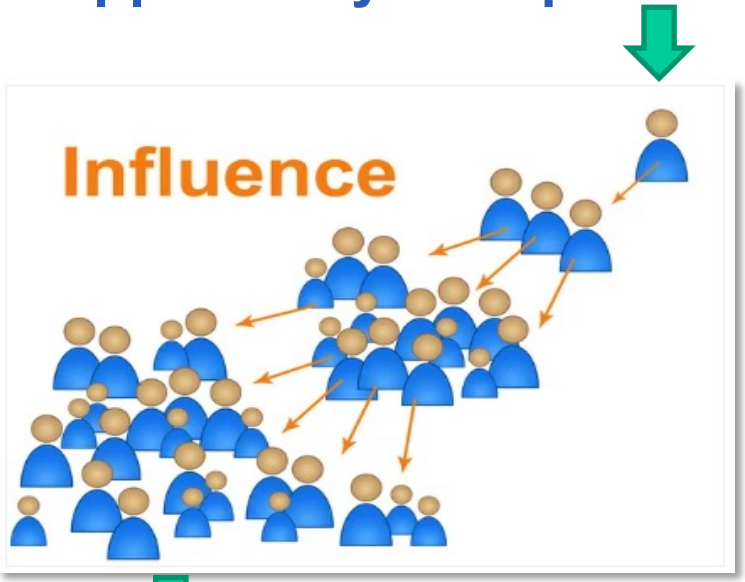
Drug development strategies require informed dialogue across cross-functional molecule teams



Just as much, biomarker strategies require informed dialogue across cross-functional molecule teams



BA Scientists on BM Strategies, key to Drug Development: Opportunity to Impact



Optimised Drug Development

- **The biomarker strategy is as important as drug development strategy**
  - Given attrition rates
  - Given need for quantitative predictions, translatability of preclinical and clinical data, and holistic data interpretation

First:

- Need to ask the right questions.
- Need to know the biology.
- Need to understand the impact of molecule design.

Then:

- Need to know how each biomarker can be measured appropriately.

Bioanalytical Scientists: Our Impact

- We must understand the science underlying our deliverables
- Imperative that we know how important it is that we influence molecule teams in R&D.
- Every assay begins with a question: Why?
  - What is the scientific rationale to measure this, i.e. The purpose??

  Followed by:
  - Full, documented definition of the purpose (context of use) of the biomarker in question.

  Followed by:
  - How?
    - Assay technology type, platform, format, reagents, characterisation, etc.

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  Followed by:
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Biomarker Assay CoU: The Game-Changer for Many

- **Understand what it is**
- **Understand why it is critical**
- **Understand how to implement it, considering the many challenges:**
  - Scientific
  - Analytical
  - Strategic:
    - communication, stakeholder management, operational

<u>Bottom Line:</u> Bioanalytical scientist takes ownership to communicate with their stakeholders and provide adequate rationale and education.

Over a decade of debate, discussion, and scientific rationale through case studies:

Future Science Ltd
Bioanalysis
Volume 4, Issue 15, August 2012, Pages 1883-1894
https://doi.org/10.4155/bio.12.164

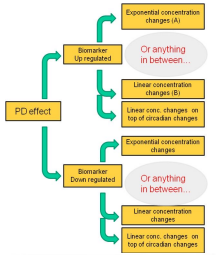
Bioanalysis

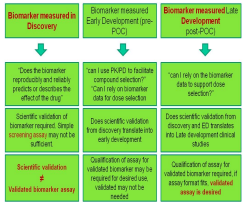
General content - White Paper

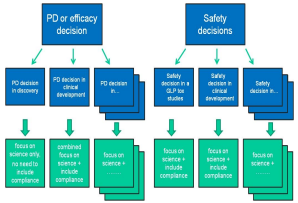
European Bioanalysis Forum recommendation on method establishment and bioanalysis of biomarkers in support of drug development

Philip Timmerman[1,*], Christian Herling[2], Daniela Stoellner[3], Birgit Jaitner[3], Susanne Pihl[4], Karen Elsby[5], Neil Henderson[5], Begona Barroso[6], Stephanie Fischmann[7], Arjen Companjen[8], Amanda Versteilen[8], Stewart Bates[9], Clare Kingsley[10] & Ulrich Kunz[11]

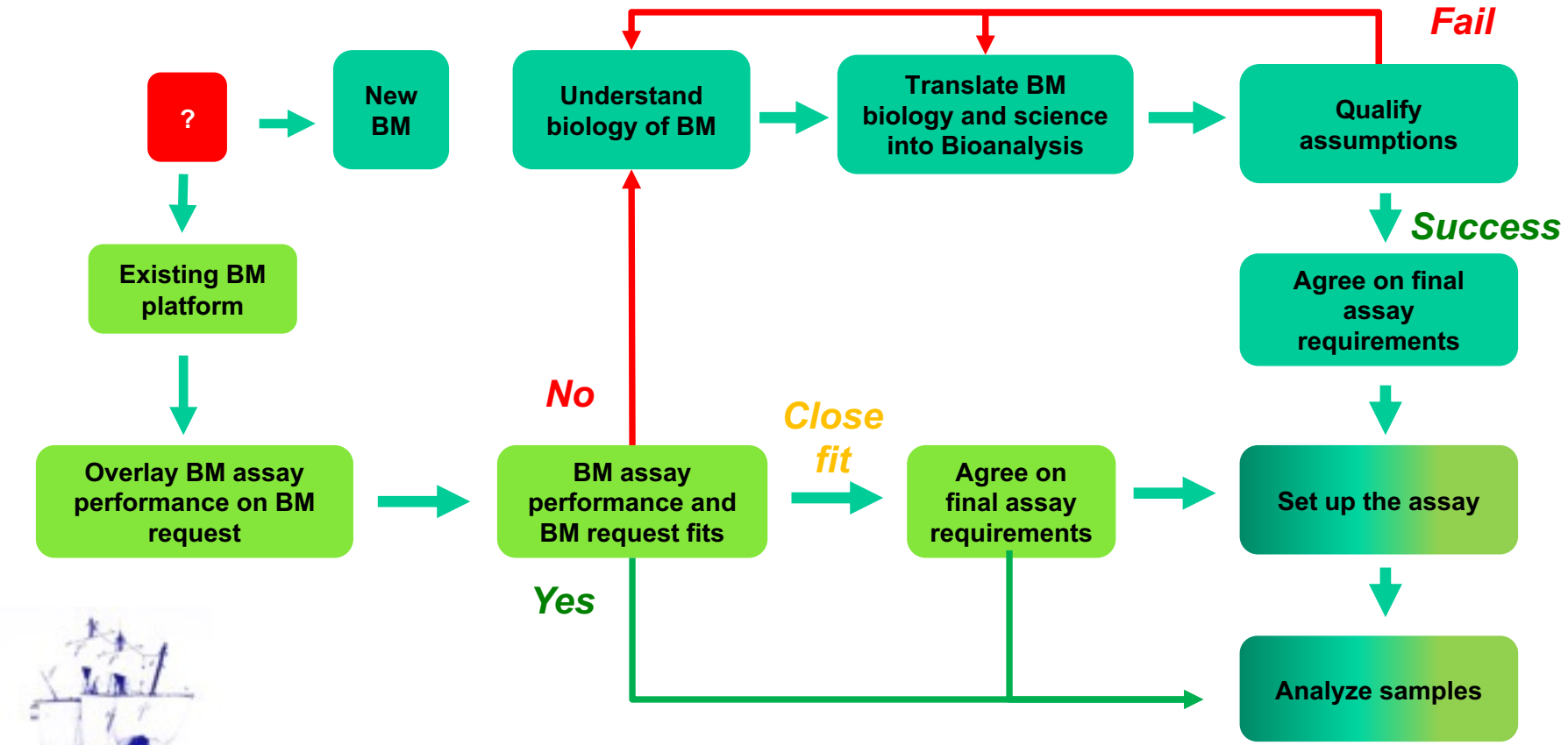
EBF recommendation paper (2012) – 4 pillars



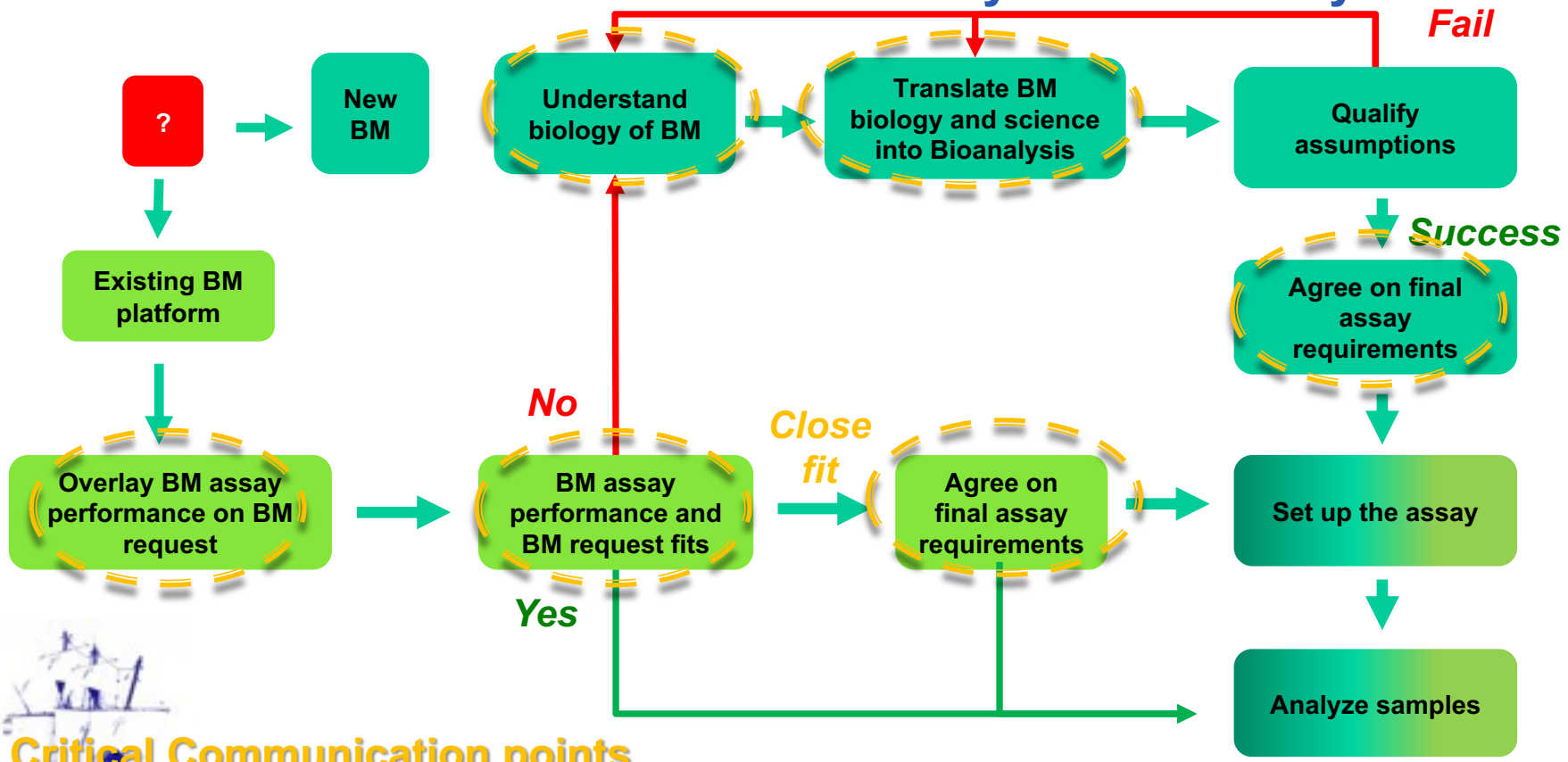




Combined flowchart



(Lack of) Communication – Can lead to downfall of any success story

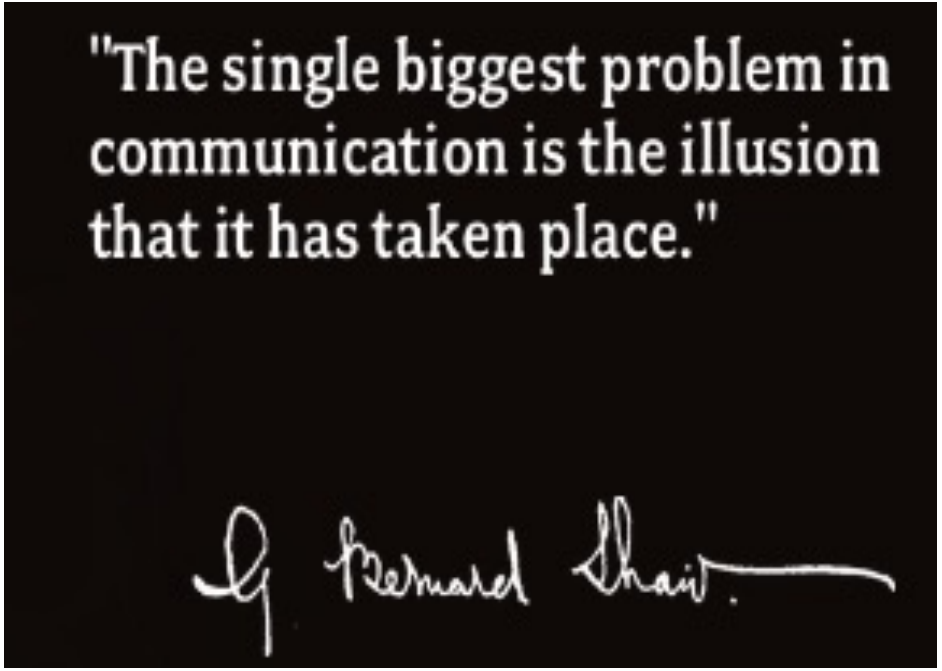


Critical Communication points

The 5th pillar - COMMUNICATION

- To understand the biology, pharmacological effect... of the biomarker
- To understand what the data will be used for
  - Scientific decisions taken
  - Safety decisions taken
  - Other?
- To share what is possible and what is not realistic from a BA perspective

- **To ensure optimal drug development for patients…**



These critical points= **CoU Statement for BM Assays**

- A few sentences, detailed enough to define the purpose of the assay for each analyte

Eg. the biology, pharmacological effect, what the data will be used for, eg. scientific or safety decisions taken, and to understand the biological, the analytical variability, etc.

- **Understood and agreed upon by all stakeholders**
- **Documented in method summaries, validation plans, validation reports**

- Then consider what is possible from a BA perspective:

This leads to the appropriate assay, characterisation, and acceptance criteria.

IMPACT: ensure the appropriate interpretation of data for the best drug development strategy, ultimately to serve patients.

Rationale for Documenting CoU for BM Assays

The purpose of the assay may change from one study to the next

The types of decisions being made based on the results may vary and should be communicated each time

Without an agreed CoU there is a risk of implementing the wrong assay, with inappropriate characterizations and therefore validation…

…Leading to incorrect data and decisions, negatively impacting patients

Institutional knowledge may change: people leaving, new team members...

Bottom Line:

Bioanalytical scientist takes ownership:

- **Communicate with stakeholders,**
- **Provide adequate education.**

White Paper

For reprint orders, please contact: reprints@future-science.com

Bioanalysis

Update to the European Bioanalysis Forum recommendation on biomarkers assays; bringing context of use into practice

Joanne Goodman[1], Kyra J Cowan[2], Michaela Golob[3], Lars Karlsson[4], Ulrich Kunz[5], Robert Nelson[6], Hans Ulrichts[7], Lauren Stevenson[8], Linda Terry[9] & Philip Timmerman*,[10]

Bioanalysis (2020) 12(20), 1427–1437

EBF Recommendations on BM Assay Characterisation

(1) **CoU must first be defined and agreed upon by <u>all stakeholders</u>:**
- **EBF recommends** this to fully understand what question(s) the biomarker data will address.

(2) **CoU can then serve to identify:**

a. **Type of assay** required (e.g. free or total, in-house assay, commercial kit, single analyte, multiplex, research use, diagnostic)

b. **Format** of the assay and critical reagents

c. **Technology** choice, with pros and cons

d. Access to appropriate **biomarker samples**

Highlights from the EBF 2020 Recommendations: CoU Principles

- **Communication is KEY, and must be sustained.**
- **Know your stakeholders and involve them.**
- **Agree on and document the CoU.**

A BM Assay is NOT a PK Assay, different challenges:

- **Infinite CoUs** for BM assays
- **Scientific:** expression levels, endogenous forms, variability, sample collection
- **Analytical:** Technological advances, platforms available, kits or de novo, PK or biomarker assay expertise, starting material (recombinant)
- **Limited** regulatory guidance
- Plus: **Analytical variability and the achievable precision** for an assay will be affected by assay platform and reagent choices.

A BM Assay is NOT a PK Assay: Development and Validation?

The context is ever-changing…

…but key concepts stay the same:

- **Development (new assay), Characterisation (existing assay), Feasibility (testing with known COU)**: more or less constant experiments (depending on analytical technique), independent of COU:
  - Parallelism (Selectivity, MRD, LLOQ)
  - Specificity
  - Detectability in target matrix

- **Validation:** a "**rubber stamp**", based on previous assay characterization, and not equal to development.
  - **Validation purely confirms, in a controlled environment, what is already known from the experiments conducted in method development.**

Change is not easy; Communication is not easy...

Biomarker Team 2021-2022 (Parts I & II)

Overarching Question:

- **What is slowing the implementation of CoU for Biomarkers?**
  - Issues with understanding/alignment within BA space of what CoU is
  - Issues with how to get the CoU information right
  - Issues with how CoU directly affects what is done in the lab
  - Issues with stakeholder management.

- **We need to keep the momentum going for clarity and alignment across industry.**

Biomarker Team Part I

Newlands Press Ltd
Bioanalysis
Volume 14, Issue 13, July 2022, Pages 911-917
https://doi.org/10.4155/bio-2022-0143

Bioanalysis

White Paper

Biomarker context-of-use: how organizational design can impact the implementation of the appropriate biomarker assay strategy

Kyra J Cowan[1], Michaela Golob[2], Joanne Goodman[3], Anna Laurén[4], Lene Andersen[5], Philip De Decker[6], Lien Dejager[7], Marianne Scheel Fjording[8], Peter Groenen[9], Renaud Jasnowski[10], Nicole Justies[11], Matti Kimberg[12,‡], Ulrich Kunz[13], James Lawrence[14], Mario Richter[15], Laetitia Sordé[16], Radboud van Trigt[17], Laurent Vermet[18], Alessandra Vitaliti[19], Michael Wright[20] & Philip Timmerman[21,*]

Summary on Common Ground: What doesn‘t work

Absence of Biomarker Strategy, particularly after lead optimisation.

Lack of Biomarker assay expertise, or relying on PK assay experts.

Siloed operational teams, or complex team organisation, so that BA input and involvement is lost.

Applying the wrong regulations and check boxes (eg. PK SOP, QA vs independent QC, etc.).

Lack of scientific rationale, discussion; being beholden to HA BMV.

Fractioned responsibilities across functions without single BM lead who has an overarching investment in all BM deliverables.

Summary on Common Ground: What WORKS

- Clear, documented BM strategy and integrated BM approach.
- Clearly defined, centralised BM group that covers BM assay, operational, and BM strategy expertise.
- Ideally, operational separation of decision-making and processes of BM assays from PK/ADA.
- Close collaboration between BA and BM leads, if separate functions, and with stakeholders
- Implementation and documentation of Purpose (CoU) for each set of BM data
- High-functioning matrix work environment with clear R&Rs and close collaborations.

Proposed structure, starting at Lead Optimisation

Discovery Team

Biomarker selection, strategy

Analytical, Operations

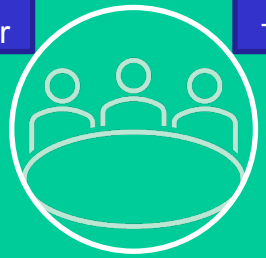
Data Interpretation

CoU statement per analyte, Documentation

BM Team

BM Integrator

BM Technology



Medical

Drug Safety

Pharmacometrics

Clinical Pharmacology

Development Team

DMPK

Research

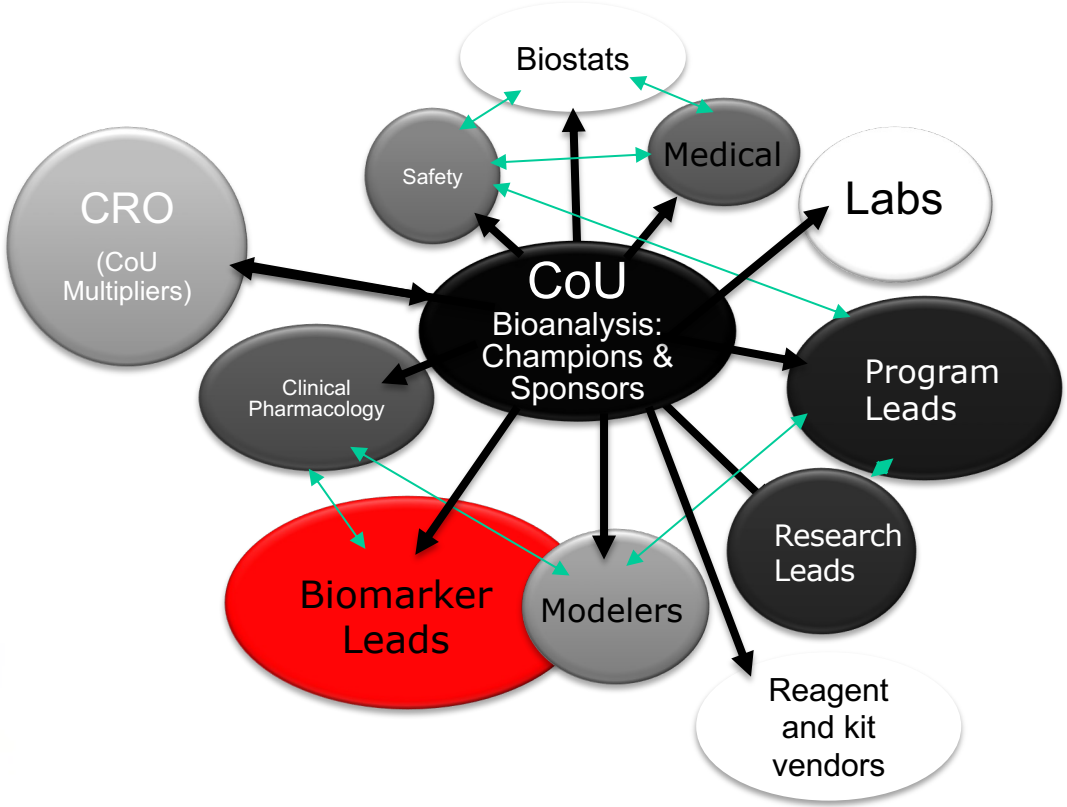
Nonclinical safety

Bioanalytical PK/ADA

Touchpoint Meetings*

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

Proposed structure, starting at Lead Optimisation



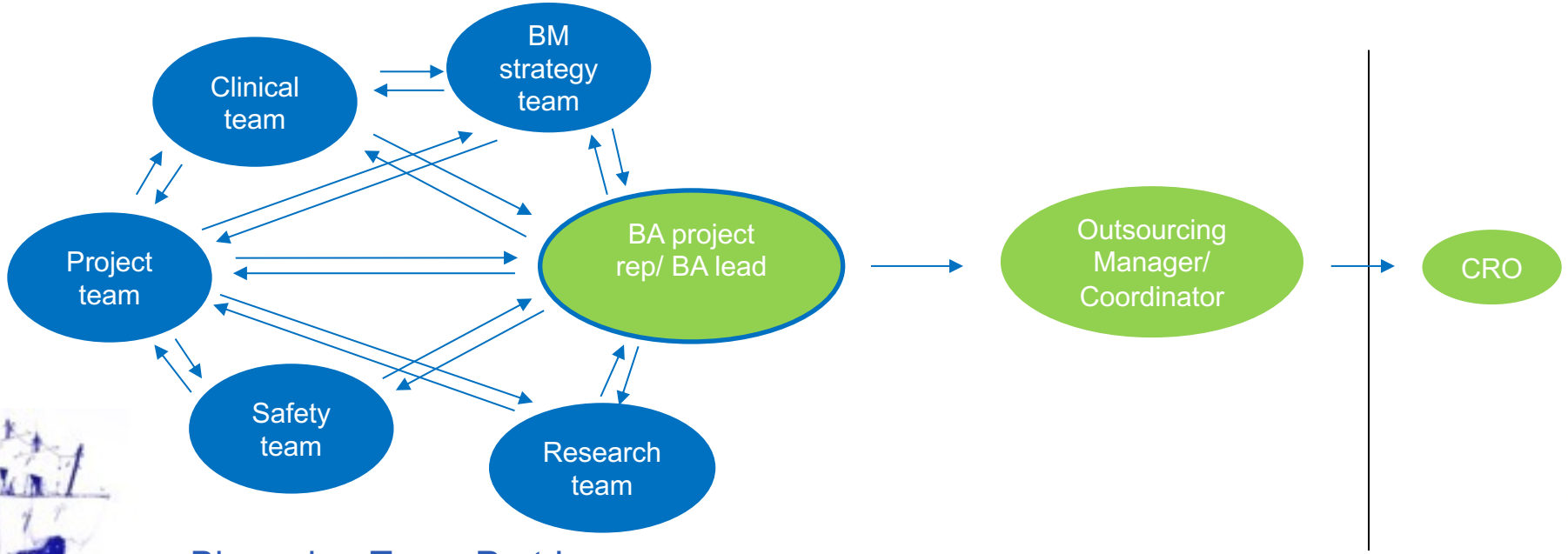
Stakeholder Management:

- Who are our stakeholders (list)?
- 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?

CoU: From a CRO Perspective | What is key

"Communication is key"

….and this is often already one of the biggest issues within pharma/sponsor companies:



CoU: From a CRO Perspective | How it should be

Expected procedure based on state-of-the-art BA community discussion/ agreement

Sponsor

Sponsor/ Sponsor & CRO/ CRO

Discussion on BM - Definition of CoU

Selection of analytical technology to answer specific question

Definition of Fit-for-Purpose validation parameters

Analytical work at the CRO

CoU: From a CRO Perspective | Reality

Expected procedure based on state-of-the-art BA community discussion/ agreement

Sponsor

Sponsor/Sponsor & CRO/CRO

Discussion on BM - Definition of CoU

Selection of analytical technology to answer specific question

?

Maybe internally in Pharma – often no info to CRO

Definition of Fit-for-Purpose validation parameters based on CoU

Large / Small Molecule BM?

"There should be a commercial LBA kit available"

"your standard LCMS"

Full Validation "to be on the safe side"

Biomarker Team Part I

CoU: From a CRO Perspective | When we ask… and how we react…

What we get, if we ask first time for a CoU:

- Exploratory
- Primary Endpoint
- Secondary Endpoint
- I have this list of BM to be analysed
- Requested by our clinicians
- CoU will be shared before sample analysis
- Not clear yet
- Determination of BM XY
- Result of a BM search

No clear CoU ….in the BA teams – CRO & Sponsor:

- “Do I really need to ask back for CoU?”
- “It’s a BM, let’s widen up the acceptance criteria – we always did it like that”
- “Come on, the request is “determination of BM xy” and we have the method up and running – no need for CoU discussion”
- “Why do you need a CoU, your BD mentioned you have analysed this BM before”
- “Perfect there is a commercial kit on the market, no need for any assay development/ transfer”
- “Full validation to be on the safe side”

What we do in the contract process:

Request to BD for a BM assay validation and clinical sample analysis of a clinical study: **Cost Proposal**

Cost Proposal: Part of a “price grid” for validation and sample analysis

Contract signed: Agreement in contract specifically followed

CoU: From a CRO Perspective | How it could be

Our idea of how it could/ should work at the CRO:

1. Getting the request for a proposal/service estimate
2. Please fill in our BM questionnaire
3. Selection of possible method (already clear or discussed)
4. Proposal of fit-for purpose validation parameters
5. Agreement on fit-for purpose validation parameters
6. Prep of proposal/service estimate for the client

Fear there is no time/ energy to go through this discussion and other CROs just do it

Need to insist on a documented, scientifically sound CoU statement for each analyte.
Then the assay chosen can be validated for its purpose.
Only when the CoU is clear can the data be fit-for-purpose.

Autumn Focus Workshop
Biomarkers/CoU - Sharing Experience through Examples

29-30 September 2022 – Malaga, Spain

Biomarker Team Part II

BM CoU FW Case Studies Summary

- Cross-industry workshop
- Pharma, biotech, and CROs
- 14 Case Studies showing the implementation of CoU on Biomarkers
  - BI, UCB, Fstar, Idorsia, argenx, LabCorp, Novo Nordisk, Merck KGaA, Abbvie, Sobi, LGC, IRBM
  - CROs, Biotech, Pharma; BA community, BA stakeholers
  - Technology agnostic

- Available slides will be posted on EBF website

BM CoU FW Case Studies Summary (cont'd)

- Take-Home Messages:
  - All BM assay should have: The What, The Why, and then The How
  - Acceptance criteria: depends on CoU! Choose the appropriate
  - Stakeholder management key, need to understand BM biology
  - Push back if no CoU, or ask clarifying questions
  - CROs – more challenging – often no formal process for CoU
  - CROs: require culture change, tend towards templates and SOPs
  - Consider the world of CLIA and IVDR

Biomarker Team Next Steps

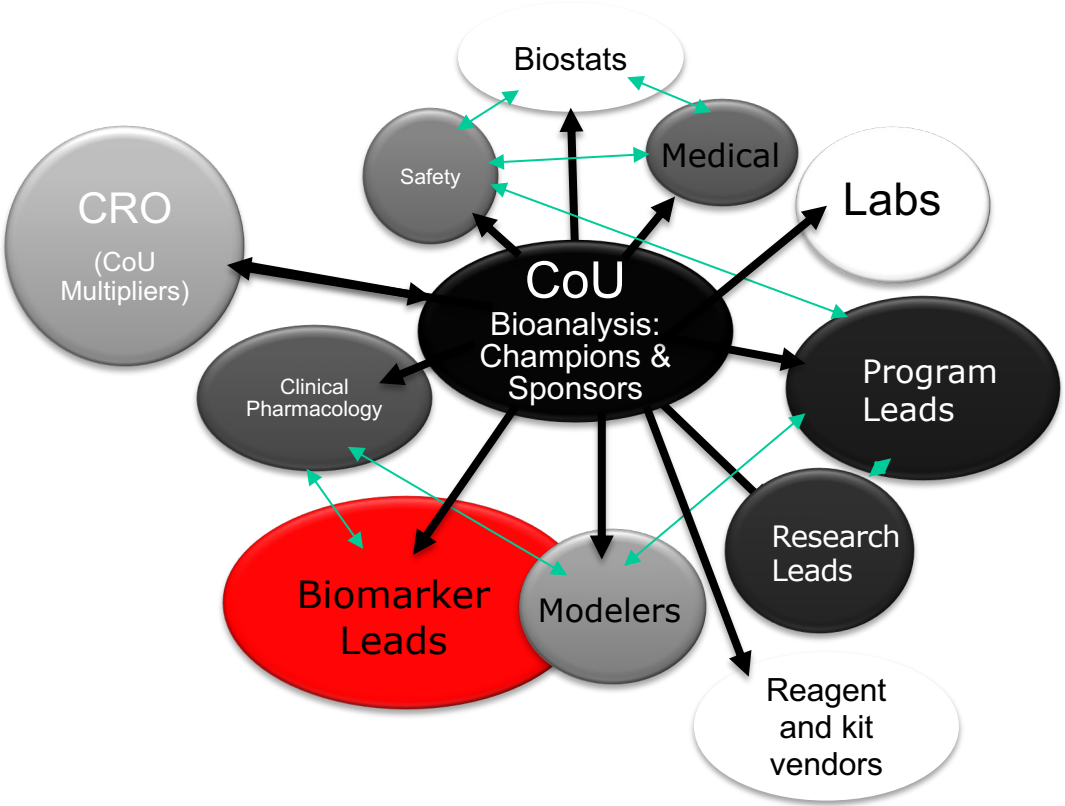
- **Feedback and regrouping for biomarker team:**
  - Continuing the momentum
    - Cyberevent „Roadshow“ – bring the case studies closer to the scientists and stakeholder
  - **Increase our focus on the strategic values CRO can bring**
    - CROs are at the crossroad and can be empowerment to faciltate the change, e.g.the benefit of a CRO saying „No“
    - Can be the theme for a FW in 2023?
  - **Focus on case studies – the „what ifs“**
    - Case studies generalised
    - Suggestions for hypothetical situations
    - Potential or real consequences of missing the ball
    - Publication non-IP, finding common ground on ways to implement (communication)

Ultimate Goal: Cross-Industry Implementation of CoU for patients

- **Ommission of CoU** for Biomarker Assays is Dangerous
  - **Wrong CoU**: inappropriate acceptance criteria, poor use of resources and time, wrong decisions, **failed drug development.**
  - **CoU must be re-evaluated** as the „purpose“ changes, will dictate assay characterization and much later validation.
    - **Decisions need to be driven by the science, not a framework or categories.**

- **Diversity and complexity of biomarker assays is wide.**
  - **Therefore:** default to the misapplication of PK approaches and criteria is wrong, as is a framework or tiers, which may stifle the crucial conversations that are needed for defining the assay purpose.

Be the voice for CoU on your teams!



Acknowledgements

EBF Biomarker Team Parts I and II!

...And from previous EBF BM teams from 2012

Jo Goodman, AstraZeneca
Michaela Golob, Nuvisan
Anna Lauren, Novo Nordisk
Philip Timmerman, EBF

Organisers of EBF OS 2022!

Thank you!!

Contact Information

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