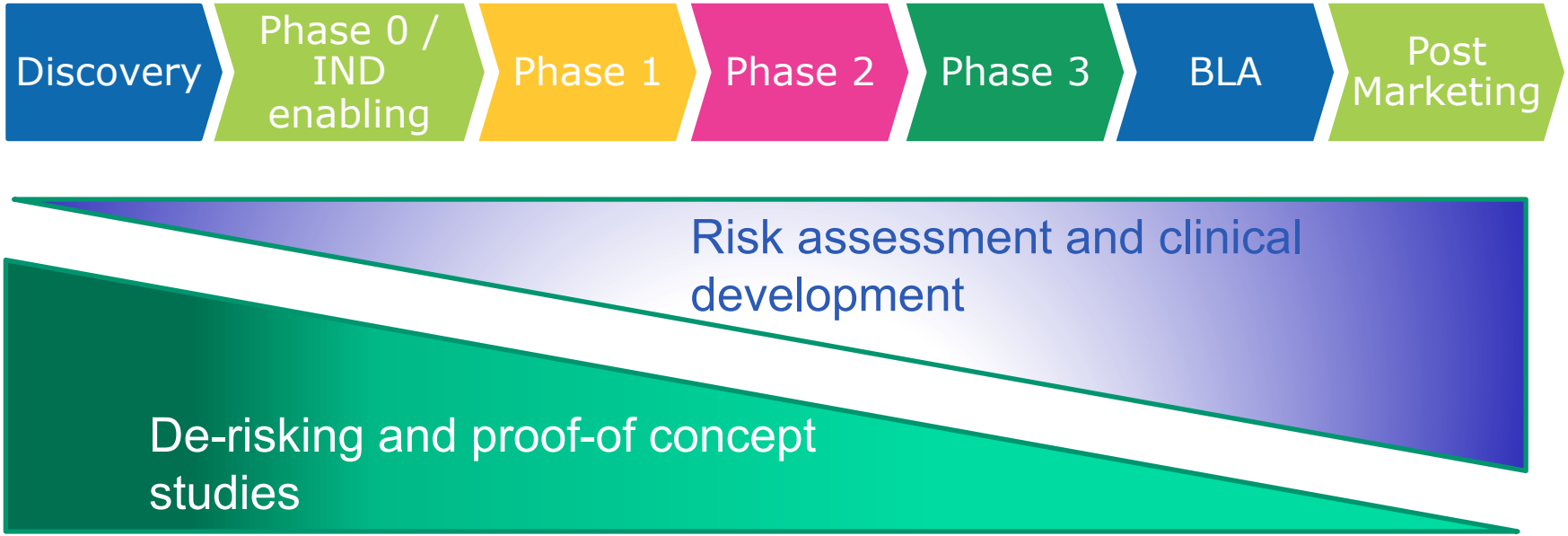
Autumn Focus Workshop
Biomarkers/CoU - Sharing Experience through Examples

Feedback from BM team discussions on organisational design driving CoU principles

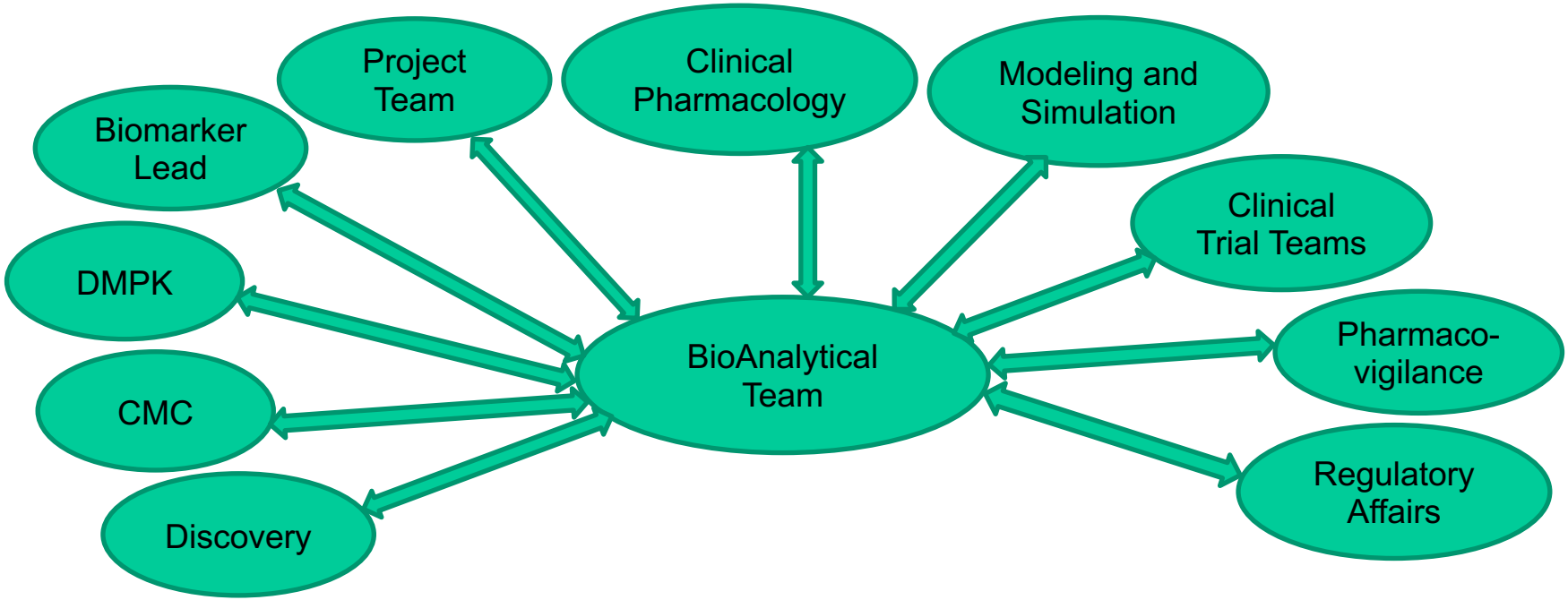
Kyra Cowan, on behalf of the EBF

29-30 September 2022 – Malaga, Spain

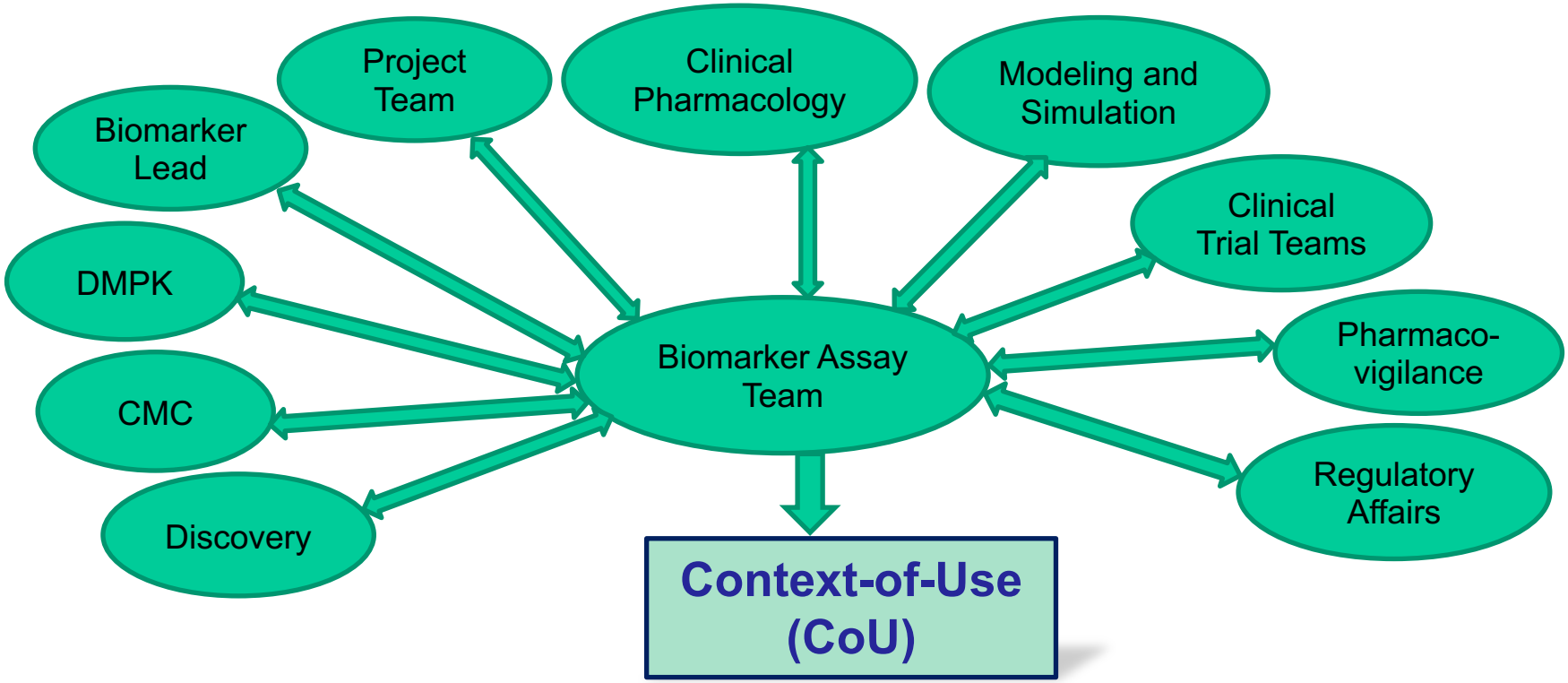
Drug Development Strategies



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



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



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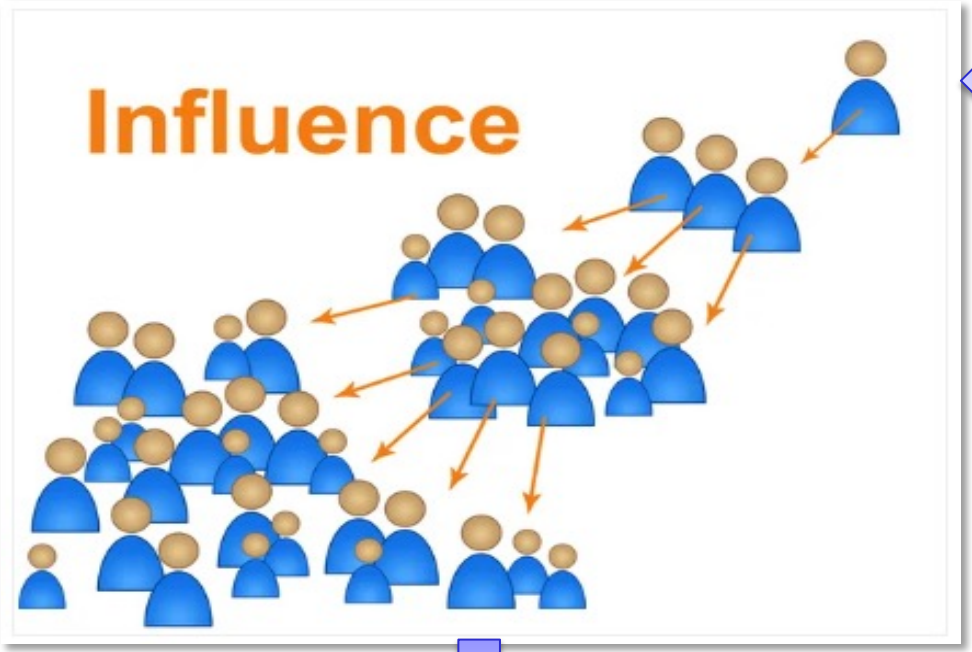
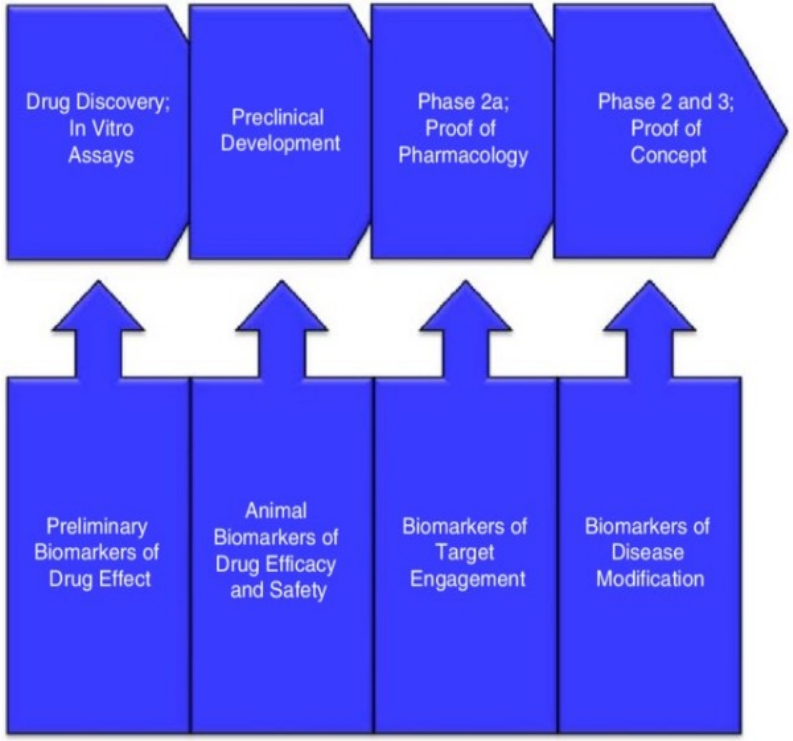
CoU:
THE KEY opportunity to Influence as Bioanalytical Scientists



Optimised Drug Development

Opportunity to Influence as BA Scientists on BM Strategies, key to 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.

Cummings JL, CNS Spectrums, 2013

Bioanalytical Scientists: Our Impact

- Criticality of how we understand the science underlying our deliverables
- Imperative that we know our science and 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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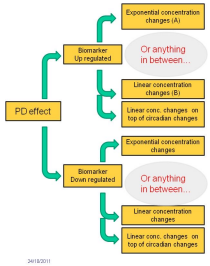
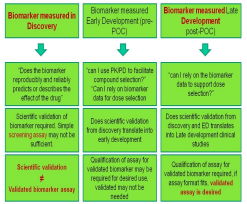
  Followed by:
  - **How?**
    - **Assay technology type, platform, format, reagents, assay characterisation, etc.**

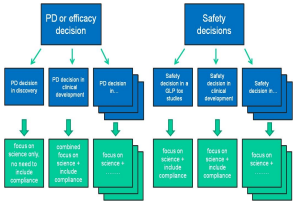
Biomarker Assay CoU: The Game-Changer for Many

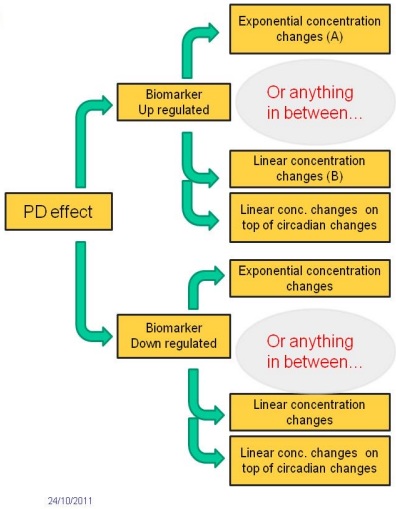
- **Understand what it is**
- **Understand why it is critical**
- **Understand how to implement it, considering the many challenges**
  - Scientific
  - Analytical
  - Strategic: communication, stakeholder management, operational

EBF recommendation (2012) – 4 pillars

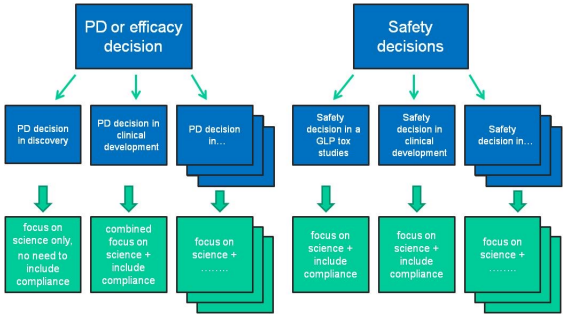




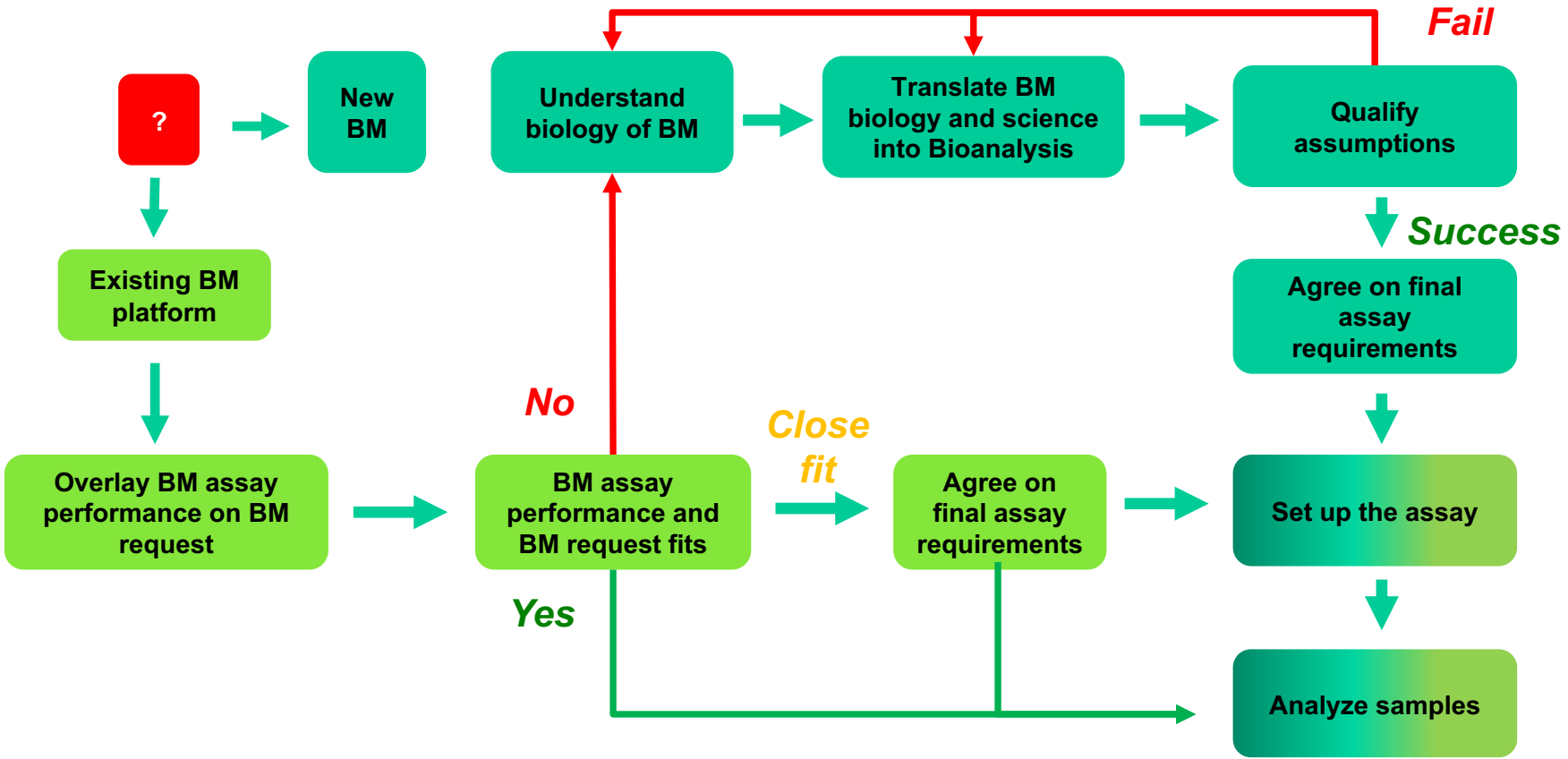


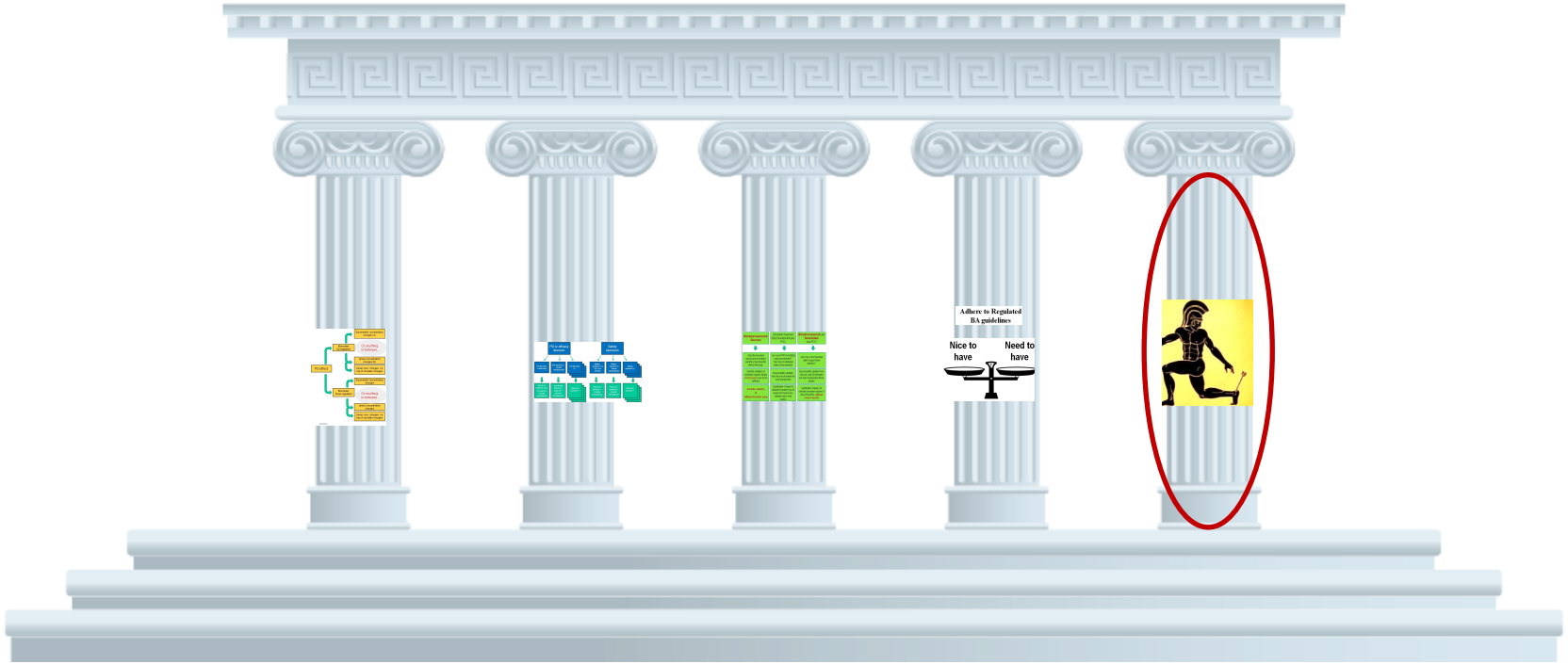


Biomarker measured in Discovery	Biomarker measured Early Development (pre-POC)	Biomarker measured Late Development post-POC)
"Does the biomarker reproducibly and reliably predicts or describes the effect of the drug"	"can I use PK/PD to facilitate compound selection?" "Can I rely on biomarker data for dose selection	"can I rely on the biomarker data to support dose selection?"
Scientific validation of biomarker required. Simple screening assay may not be sufficient.	Does scientific validation from discovery translate into early development	Does scientific validation from discovery and ED translates into Late development clinical studies
Scientific validation ≠ Validated biomarker assay	Qualification of assay for validated biomarker may be required for desired use, validated may not be needed	Qualification of assay for validated biomarker required, if assay format fits, validated assay is desired



Combined flowchart

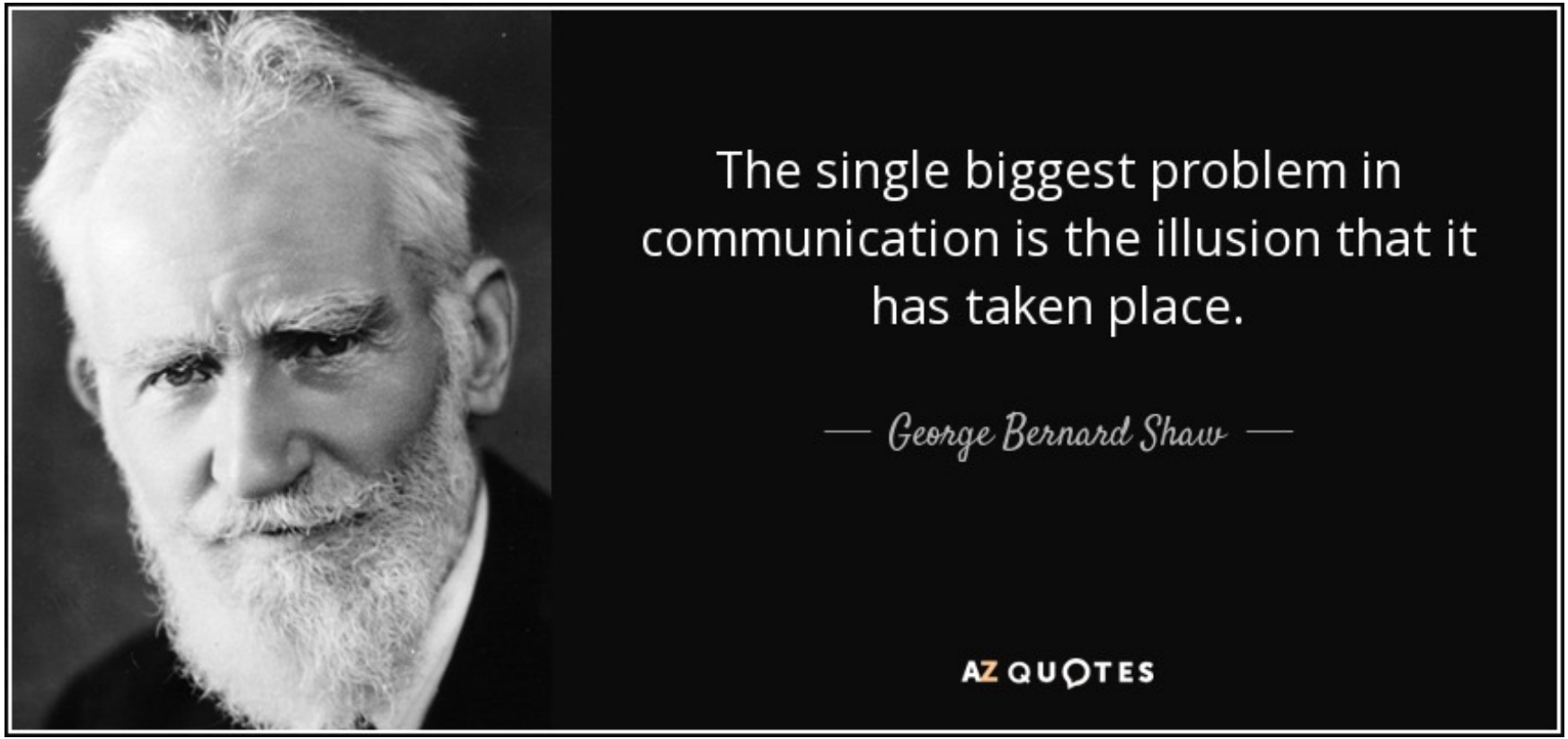



Adhere to Regulated BA guidelines
Nice to have
Need to have

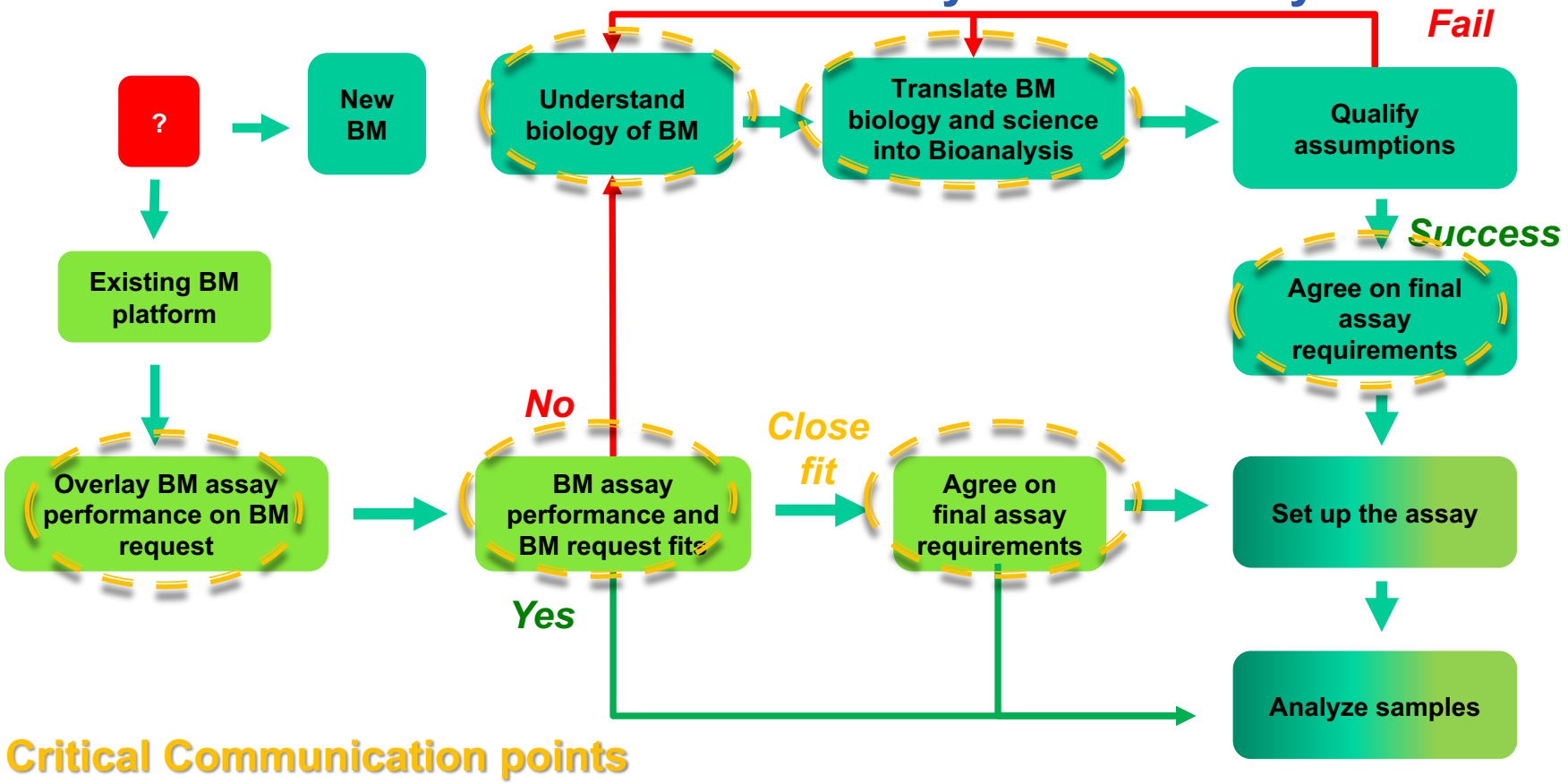
The 5th pillar - COMMUNICATION

Communicate, communicate, communicate:

- To understand the biology, pharmacological effect... of the BM
- To understand what the data will be used for
  - Scientific decisions taken
  - Safety decisions taken
  - Other?
- To share what is possible from a BA perspective (can be more or less)
- To share what is not realistic from a BA perspective
- To ensure optimal cost/benefit


The single biggest problem in communication is the illusion that it has taken place.
— George Bernard Shaw —
AZ QUOTES

(Lack of) Communication – the Achilles' heel of any success story



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

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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

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

- **The identified questions would then address:**
  - **Type of assay** required (e.g. free or total, in-house assay, commercial kit, single analyte, multiplex, research use, diagnostic)
  - **Format** of the assay and critical reagents
  - **Technology** choice, with pros and cons
  - Access to appropriate **biomarker samples**

1/3: Highlights from the EBF 2020 Recommendations: CoU Principles

- **Communication is KEY, and must be sustained.**
  - Major challenge, given organisational structures and perceptions
- **Know your stakeholders and involve them.**
  - Understanding the complexity of matrix environment, mapping is critical
    - Program Leads, Project Managers, Safety, Pharmacologists, Modelers, etc.
- **Agree on and document the CoU.**
  - Implement the right assay for the right data and the right decisions
  - May require some high level, appropriate training to gain common ground

2/3: Highlights from the EBF 2020 Recommendations: CoU Principles

- **A BM Assay is NOT a PK Assay: Why Not?**
  - Challenges, both scientific and analytical
  - Scientific: expression levels, endogenous forms, variability, sample collection
  - Analytical: Technological advances, platforms available, kits or de novo, PK or biomarker assay expertise or

  Plus: Analytical variability and the achievable precision for an assay will be affected by assay platform and reagent choices.

3/3: Highlights from the EBF 2020 Recommendations: CoU Principles

- **Differences from PK assays include:**
  - Infinite CoU‘s
  - Starting material (Endogenous vs. Recombinant, Platforms, reagents, kit);
  - Development and Validation: Parameters, Acceptance criteria
  - Regulatory Guidances: Limited

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.**

Summary: Cross-Industry Implementation of CoU is 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.**

- **CoU may change over time**
  - Diversity and complexity of biomarker assays is wide, a framework may stifle the crucial conversations that are needed for defining the assay purpose.

  Therefore: default to the misapplication of PK approaches and criteria is wrong.

Yet Still: quoting from our BA community and stakeholders:

- I believe that we understand and apply this principle to our development and degree of validation efforts, but I don't think the rest of the world is aligned to this.
- Often I feel that people cite CoU without understanding what boundaries are defined.
- There is a misunderstanding from high stakeholders on CoU.
- I guess I know what it is but not sure I fully understand what it involves.

Biomarker Strategy Team 2021-2022 (Parts I & II)

- Our learnings continue:

  - **Still have issues with understanding/alignment within BA space of what COU is, how to get the CoU information right, and how that directly affects what is done in the lab, let alone stakeholder management.**
    - Every BM assay is “fully validated” for the CoU: need for harmonisation
  - **We need to keep the momentum going**

  - **You, the rest of the Bioanalytical Community, and beyond:**
    - You are the multipliers of the message for CoU throughout industry, to drive the topic internally and externally

  - **Clarity and alignment across industry…**

EBF

White Paper

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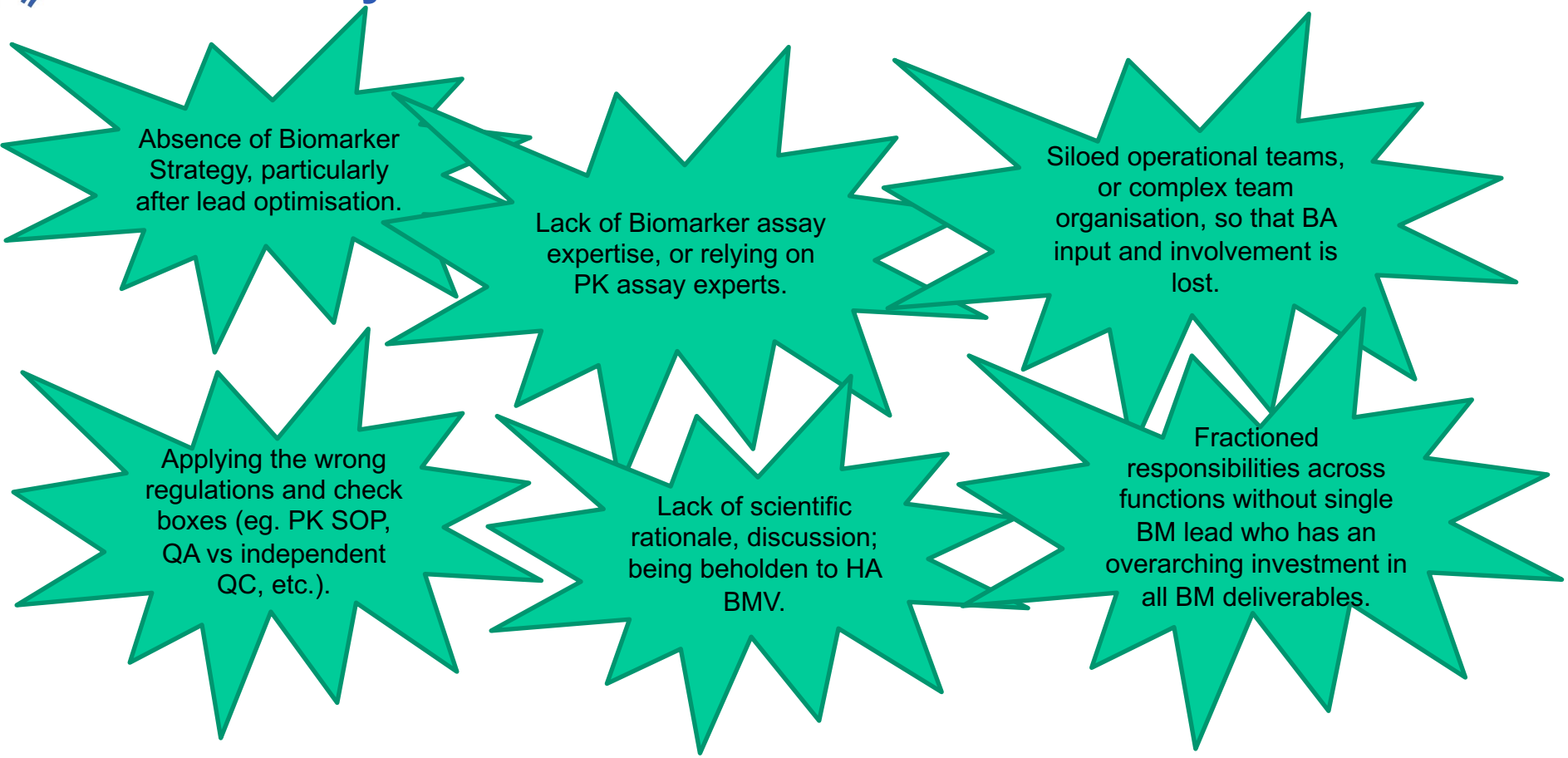
Bioanalysis

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]

Bioanalysis (2022) ePub ahead of print, https://doi.org/10.4155/bio-2022-0143

Summary on Common Ground: What doesn‘t work

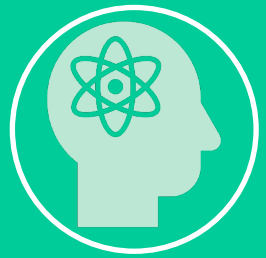


Summary on Common Ground: What WORKS

- 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

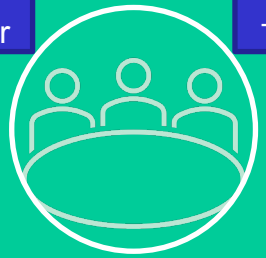


DMPK
Research
Nonclinical safety
Bioanalytical PK/ADA

BM Team

BM Integrator

BM Technology



BM selection, strategy
Analytical, Operations
Data Interpretation
CoU statement per analyte, Documentation

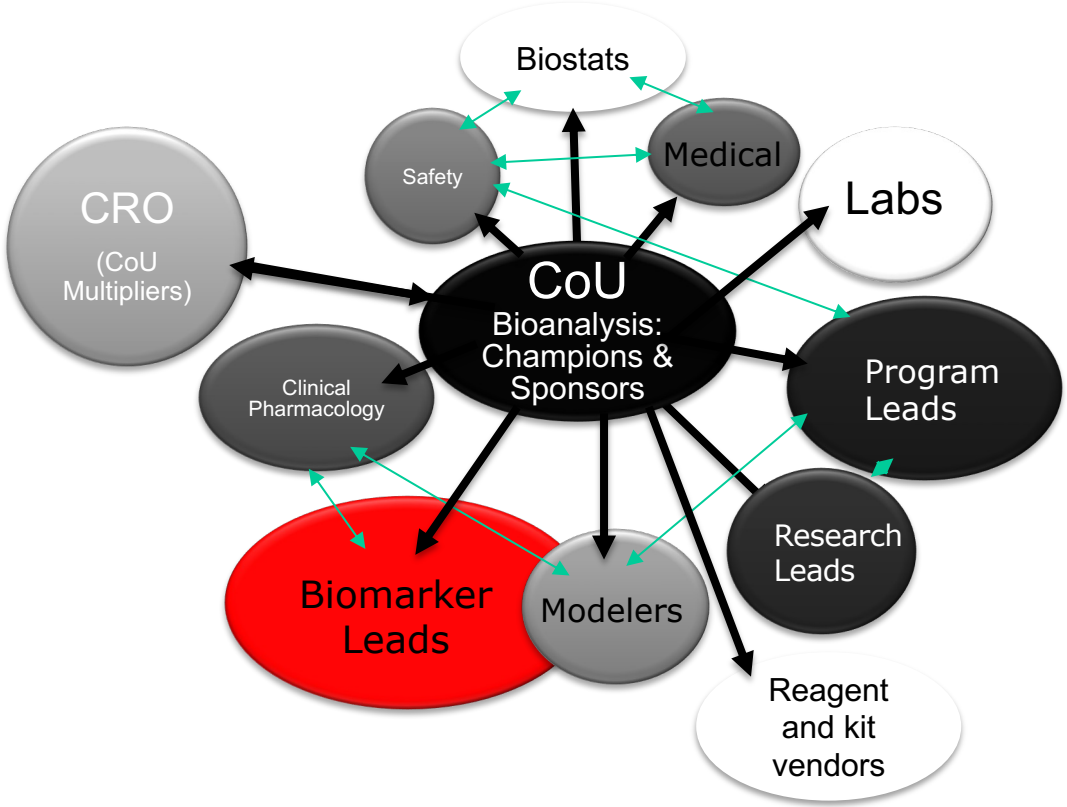
Development Team

Medical
Drug Safety
Pharmacometrics
Clinical Pharmacology

Touchpoint Meetings*

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

Proposed structure, starting at Lead Optimisation



Stakeholder Management:

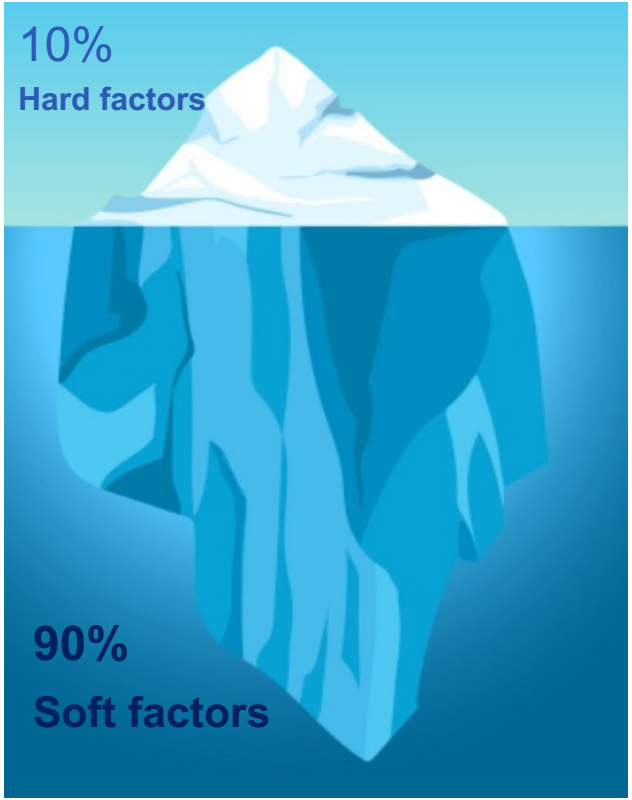
- Who are our stakeholders (list)?
- What is missing in the communication?
- How can we best educate/train?
- How can we make sure we are relaying the right message?
- How do we relay a sense of urgency for CoU?
- How do we ensure consistent buy-in?

The iceberg model

What are key factors for implementing change (CoU)?

- Training programs
- Costs
- Timeline
- Organizational structure

- **Involving stakeholders**
- **Honest and timely communication**
- **Motivating organizational culture**
- **Change promoters (Multipliers)**
- **Corporate culture of continuous change**
- **Top management commitment**



Conclusion

The base of change management lies below the surface of the iceberg. Involving the stakeholders and an honest and timely communication is key to make a change project successful.

EBF

8 steps to success

How can I contribute to make CoU implementation successful?

1 **Create awareness**

- Create a feeling for **urgency** for implementation of CoU.
- **Develop an understanding of the situation, risks, impact and activities in the change process (needing CoU principles).**

2 **Win supporters**

- Get top management commitment.
- Build a guiding team.

3 **Develop a vision**

- **Make it clear and understandable what's changing and why.**
- Explain the outcome of your project.

4 **Communicate the vision**

- **Provide timely and honest information.**
- Get buy-in.

5 **Empower Action**

- Win-Win-Strategy: turn your stakeholders into your partners.
- **Involve your stakeholders 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.

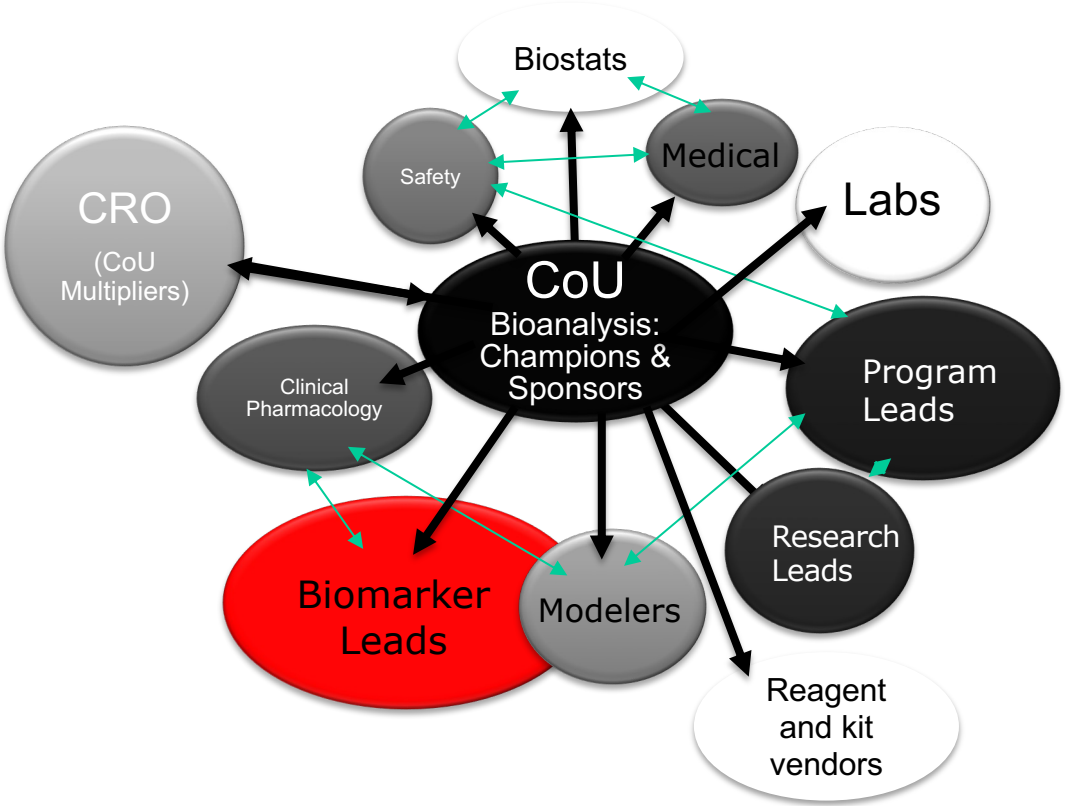
7 **Leverage wins to drive change**

- Use the energy from the quick wins to drive CoU implementation 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.

Be the voice on your teams!



Acknowledgements

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Philip Timmerman, EBF

And Rob…

Current EBF Biomarker Team Members:

= ← + Laetitia Sorde, Sobi; Ulrich Kunz, Boehringer-Ingelheim; Peter Groenen, Idorsia; James Lawrence, F-Star; Mario Richter, Abbvie; Philip De Decker, Argenx; Lien Dejager, UCB; Richard Hughes, DDS; James Beecroft, Roche; Daniel Thwaites, Labcorp.

+

And from previous EBF BM teams from 2012

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