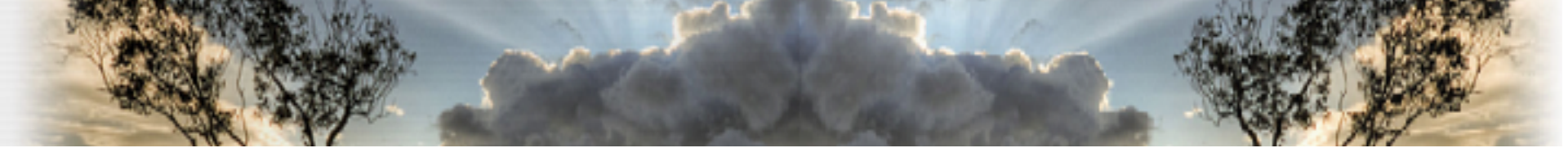


Context of Use principles for biomarker assay validation and sample analysis

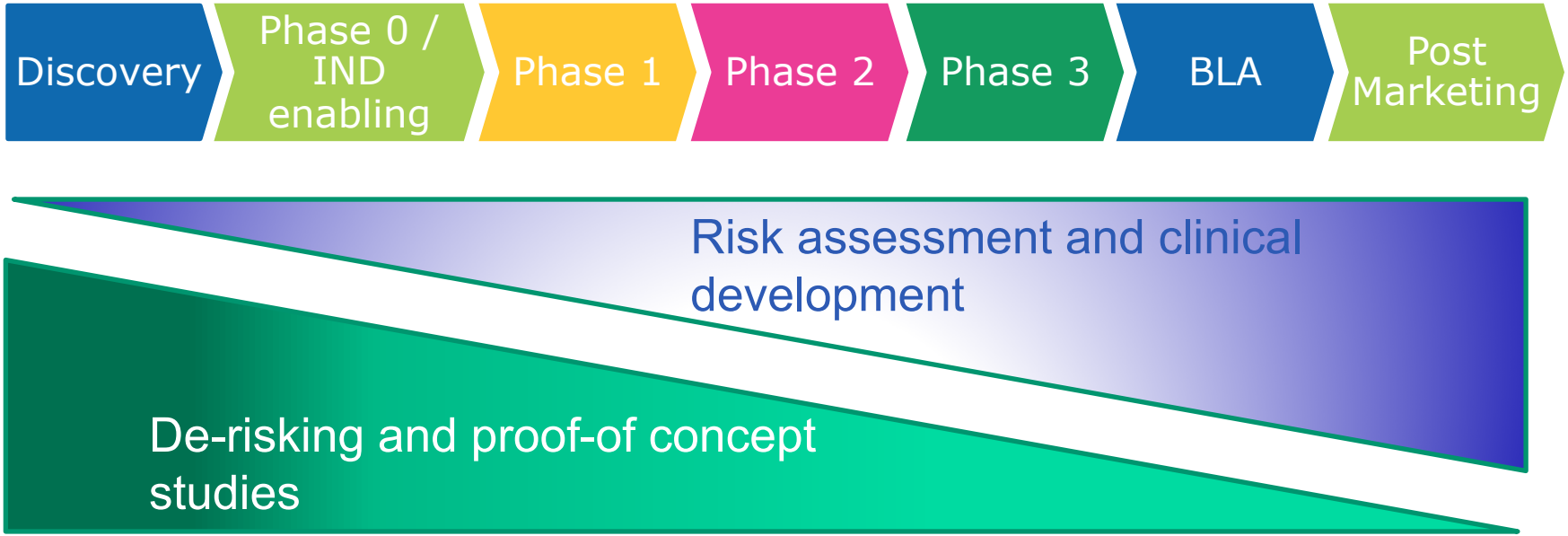
Kyra Cowan, on behalf of the EBF

May 19th, 2022

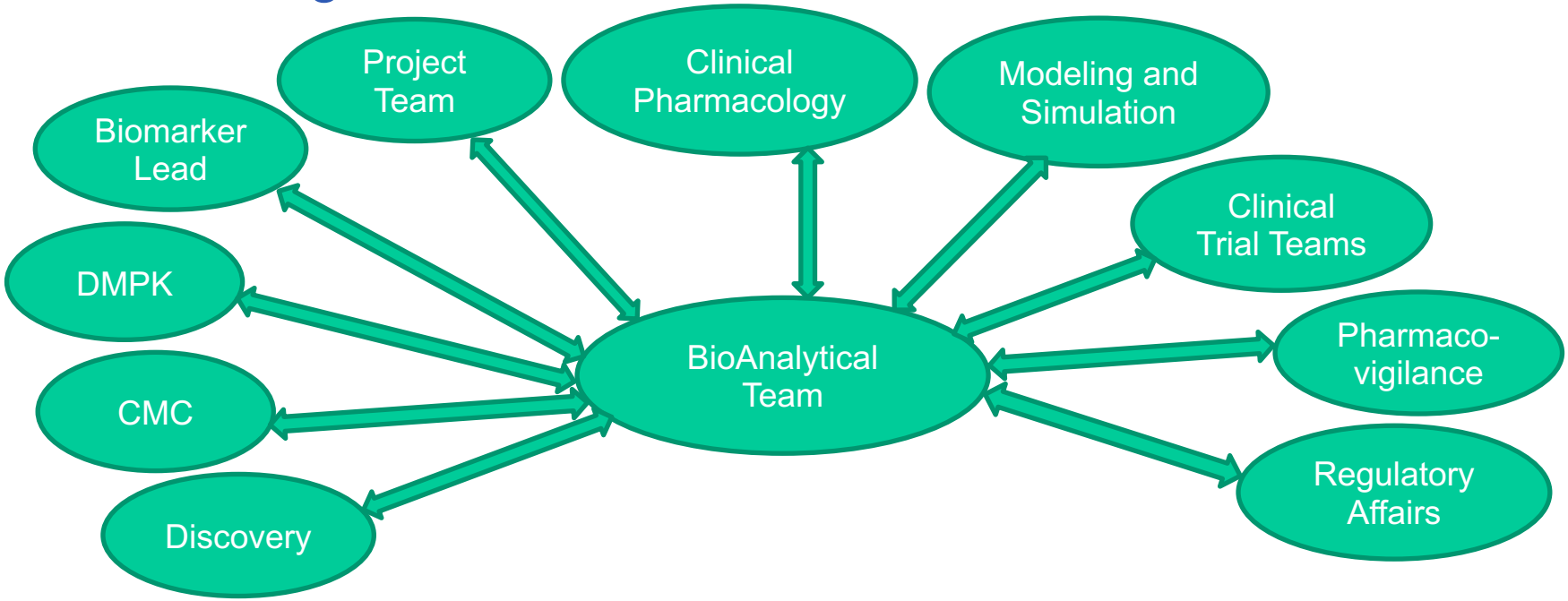
Some thoughts

- Drug development and biomarker strategies
- Our impact as bioanalytical scientists on molecule teams
- Biomarker strategies: how we influence the outcome
- Context-of-Use (CoU) for biomarkers
- Implementing CoU
  - Why it is important
  - How we can make it happen

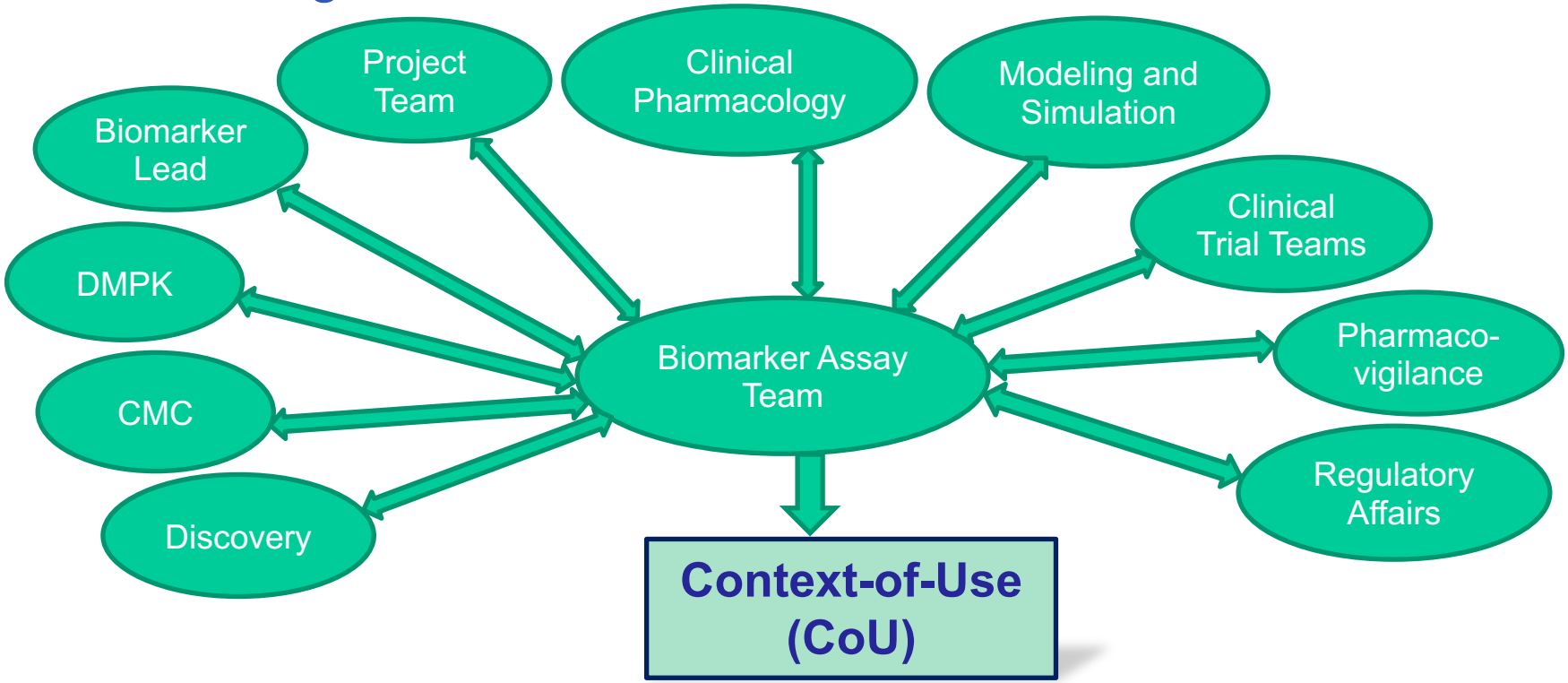
Drug Development Strategies



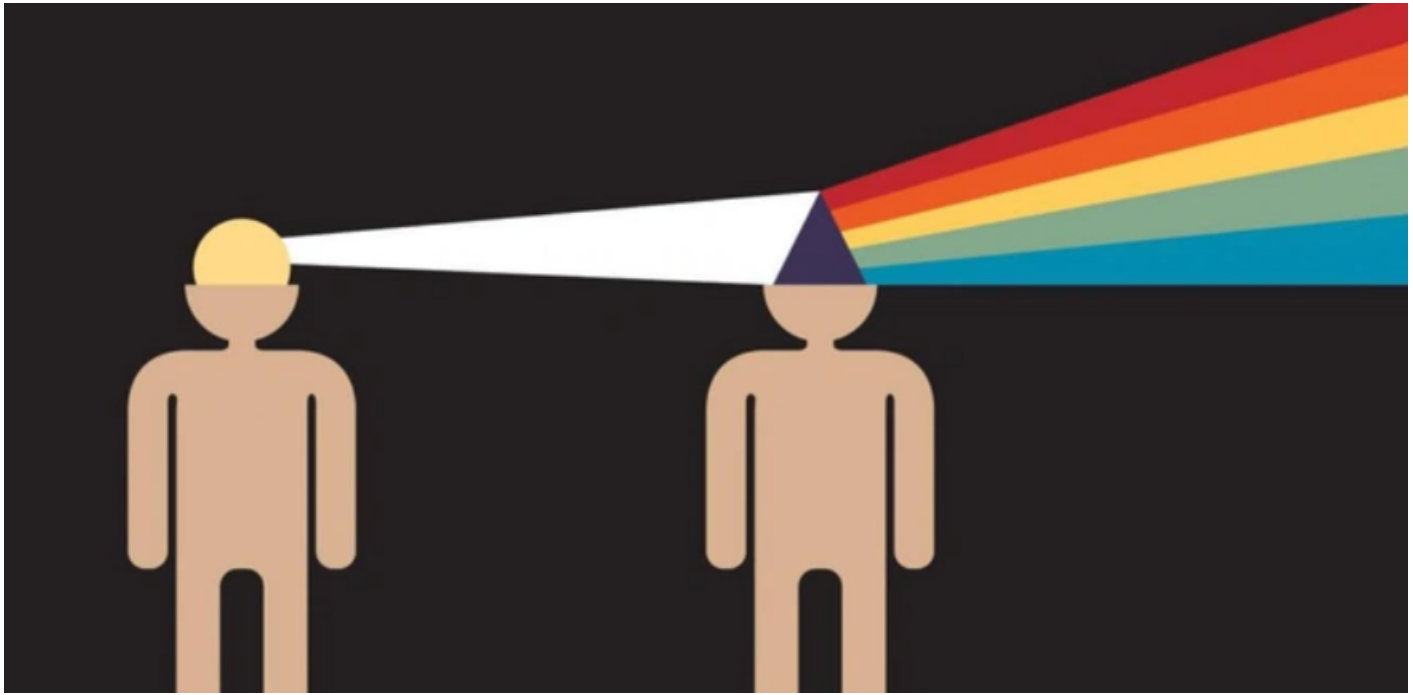
Drug development strategies require informed dialogue across cross-functional molecule teams



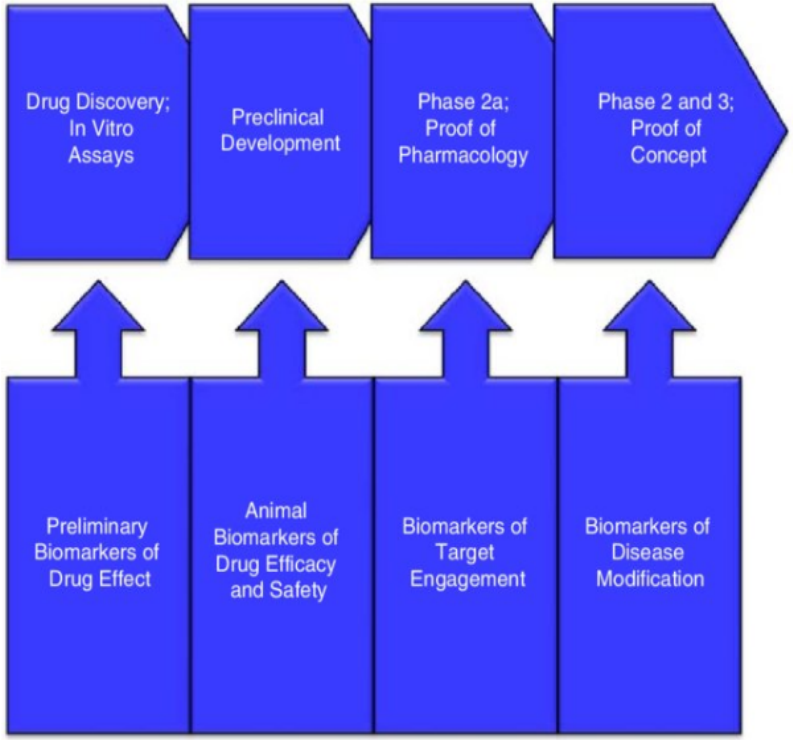
Just as much, biomarker strategies require informed dialogue across cross-functional molecule teams



Opportunity to Influence as Bioanalytical Scientists



Opportunity to Influence as Bioanalytical Scientists on Biomarker 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

- Need to ask the right questions.
- Need to know the biology.
- Need to know 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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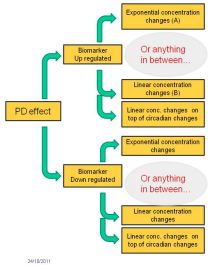
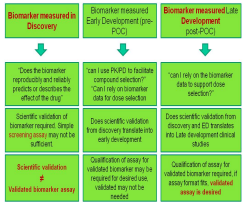
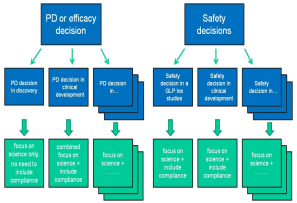
The Principles of Biomarker Assay CoU

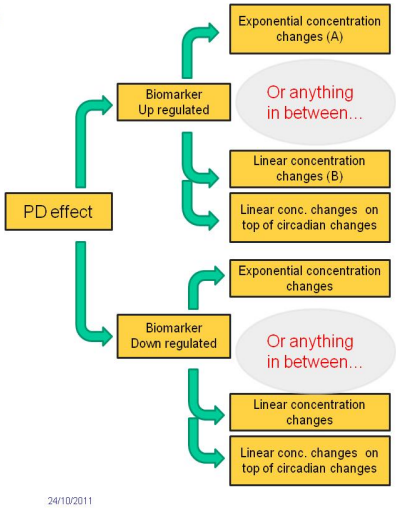
- **Understand what it is**
- **Understand why it is critical**
- **Understand how to implement it, considering the many challenges**
  - Scientific
  - Analytical
  - Stakeholder management

EBF recommendation (2012) – 4 pillars

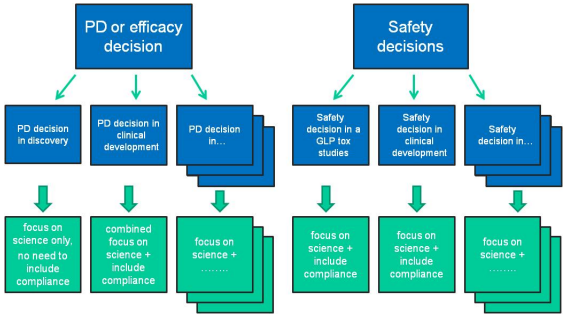




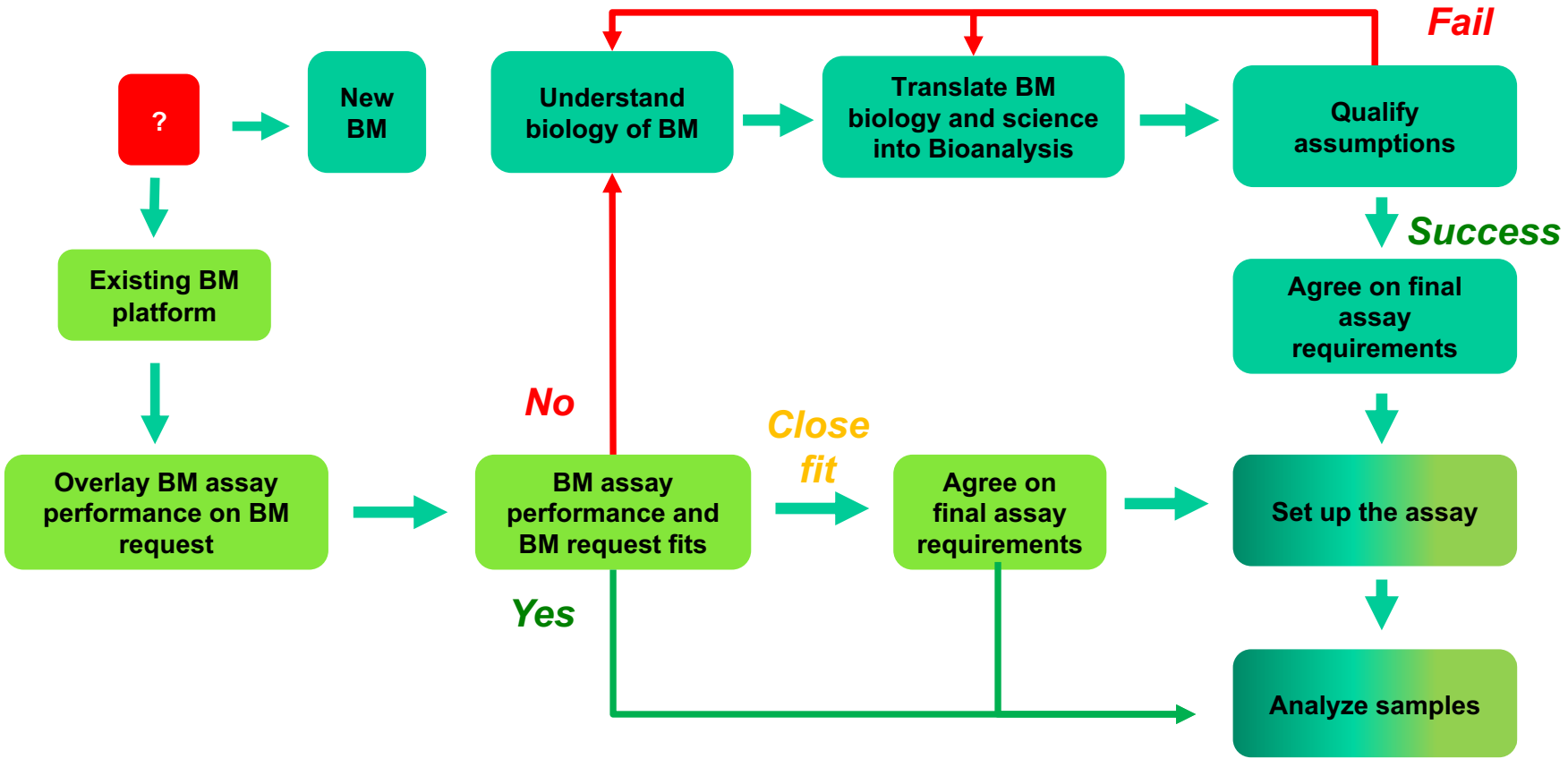


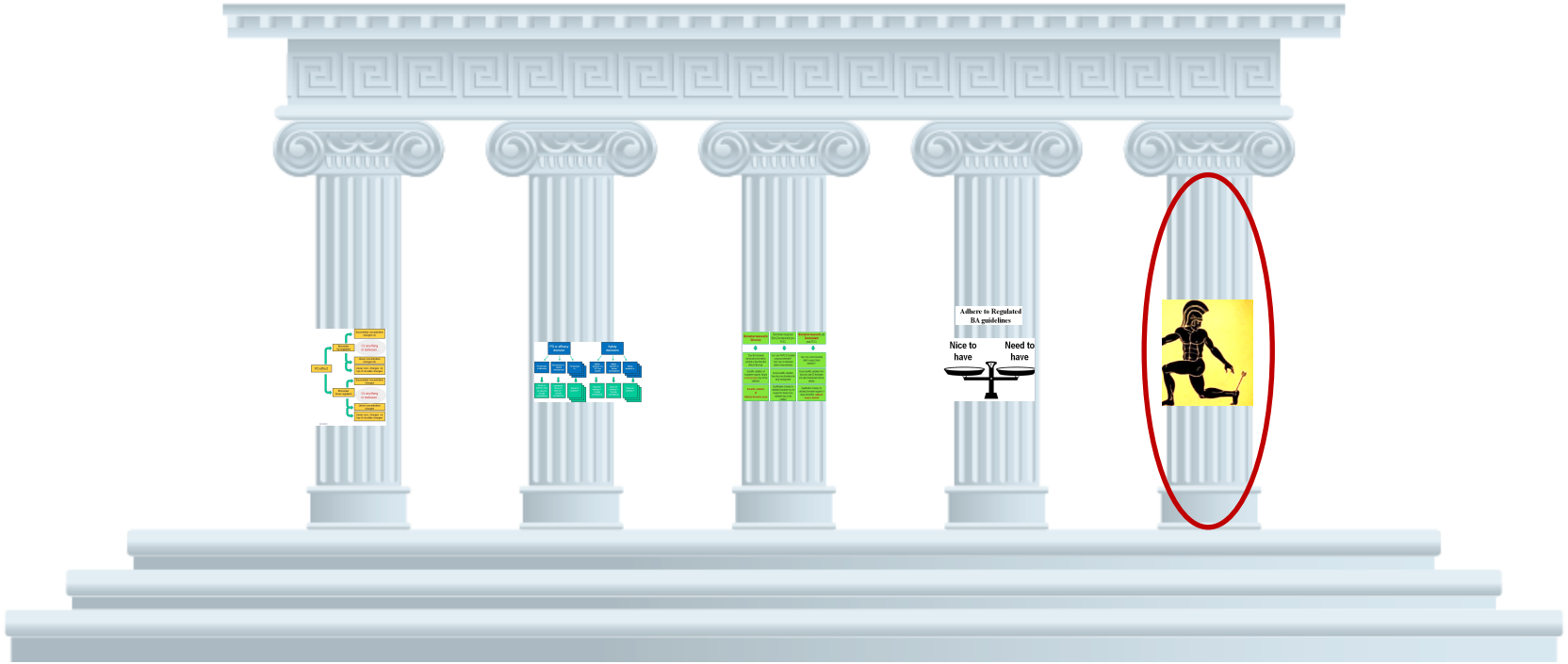


Biomarker measured in Discovery	Biomarker measured Early Development (pre-POC)	Biomarker measured Late Development post-POC)
"Does the biomarker reproducibly and reliably predicts or describes the effect of the drug"	"can I use PK/PD to facilitate compound selection?" "Can I rely on biomarker data for 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

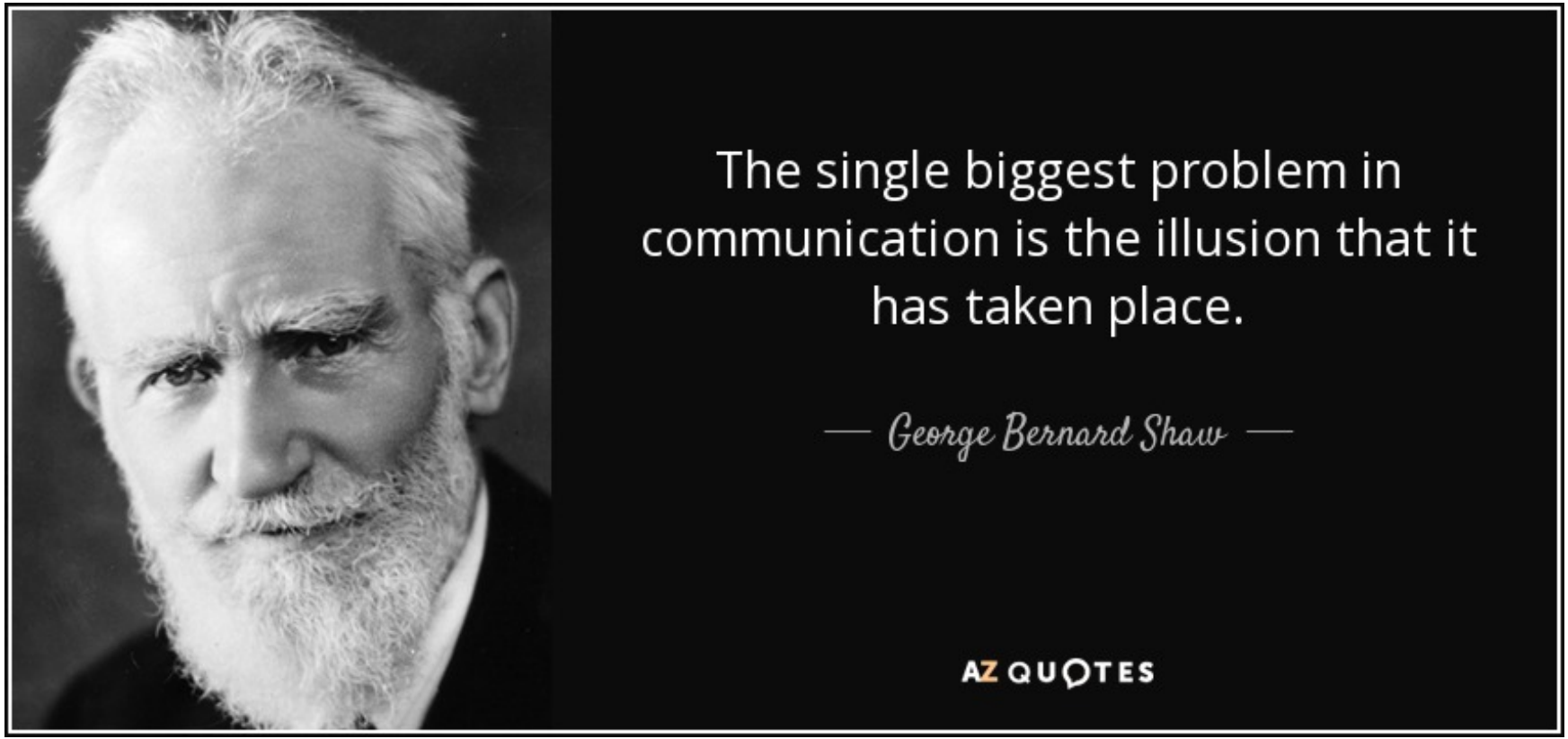



Adhere to Regulated BA guidelines
Nice to have
Need to have

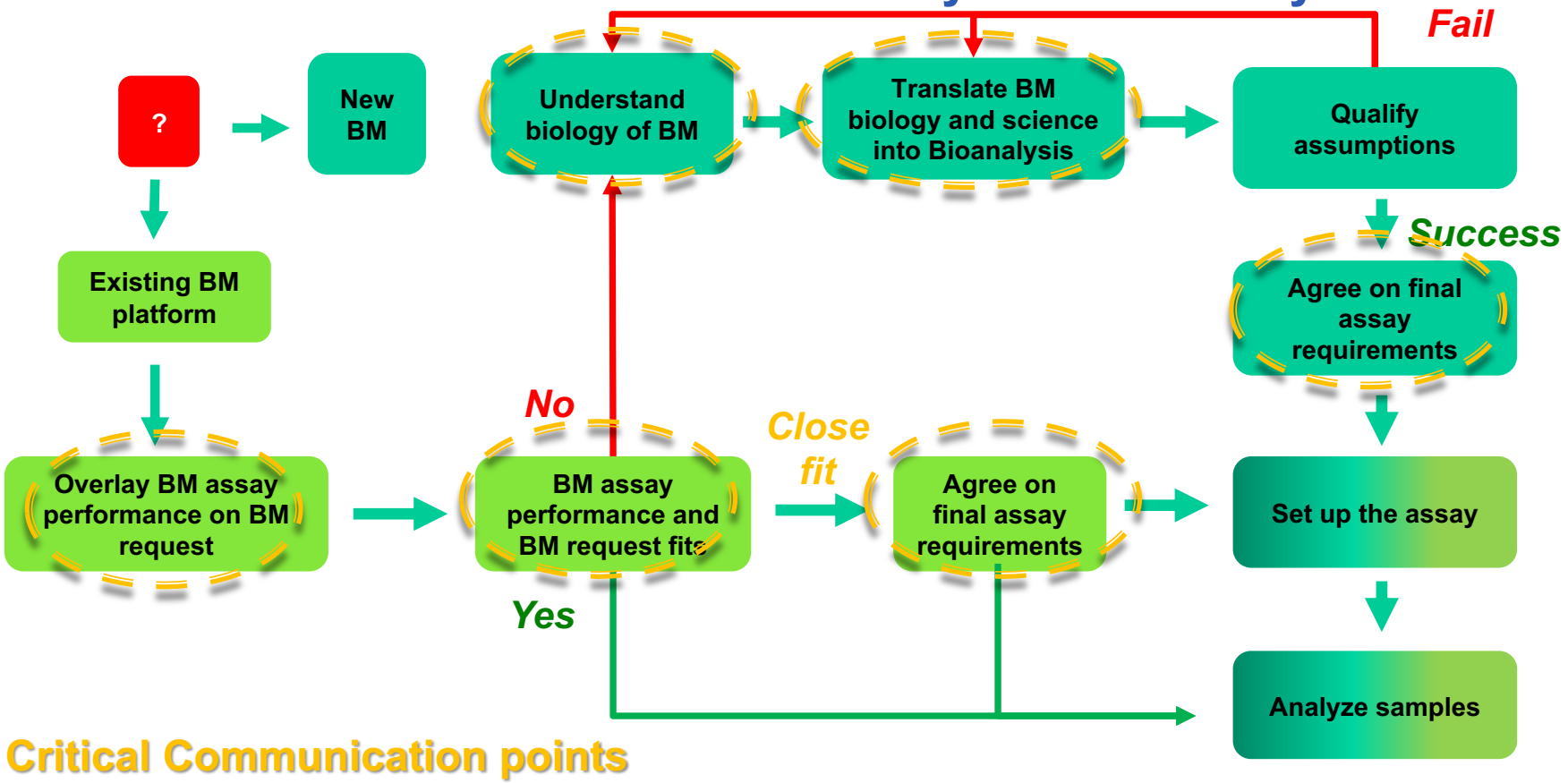
The 5th pillar - COMMUNICATION

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 = **Context of Use for BM Assays**

- **Detailed definition of the purpose of the assay for each analyte**
  - **Understood and agreed upon by all stakeholders**
  - **Documented in method summaries, validation plans, validation reports**

- CoU statement: A few sentences defining biomarker
  - This leads to the appropriate assay, characterisation, and acceptance criteria.
- For example, the biology, pharmacological effect
  - What the data will be used for, eg. scientific or safety decisions taken
- Then consider what is possible from a BA perspective
  - To understand biological, analytical variability…

Most important: To ensure the appropriate interpretation of data to serve patients.

Importance of Documenting Context of Use 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
  - Leads to incorrect data and decisions, negatively impacting patients

- **Institutional knowledge may change:** new team members, people leaving

Bottom Line: Bioanalytical scientist takes ownership to communicate with their stakeholders and 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

1/2: 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

2/2: 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.

- **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.**

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.

CoU principles being talked about, but: Quotes from Stakeholders

- I believe that we, as assay developers 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.
- 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**
  - **YSS, the rest of the EBF Community, and beyond:**
    - You are the multipliers of the message for CoU throughout industry, to drive the topic internally and externally
    - How do we avoid inappropriate guidance from HAs, inappropriate implementation of BMV guidance on BM assays in general
    - How do we change the way of thinking
  - **Clarity and alignment across industry…**

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.
  - 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 scientific rationale, discussion; being beholden to HA BMV

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 to implement BM strategy.
  - Implementation and documentation of Purpose (CoU) for each set of BM data
    - In method summaries, in validation plans, in assay specification document or online „living document“, etc., for each purpose for each BM

Proposed structure, starting at Lead Optimisation

Discovery Team

DMPK

Research

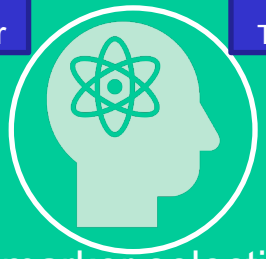
Nonclinical safety

Bioanalytical PK/ADA

BM Team

BM Integrator

BM Technology



Biomarker selection, strategy

Analytical, Operations

Data Interpretation

CoU statement per analyte, Documentation

Development Team

Medical

Drug Safety

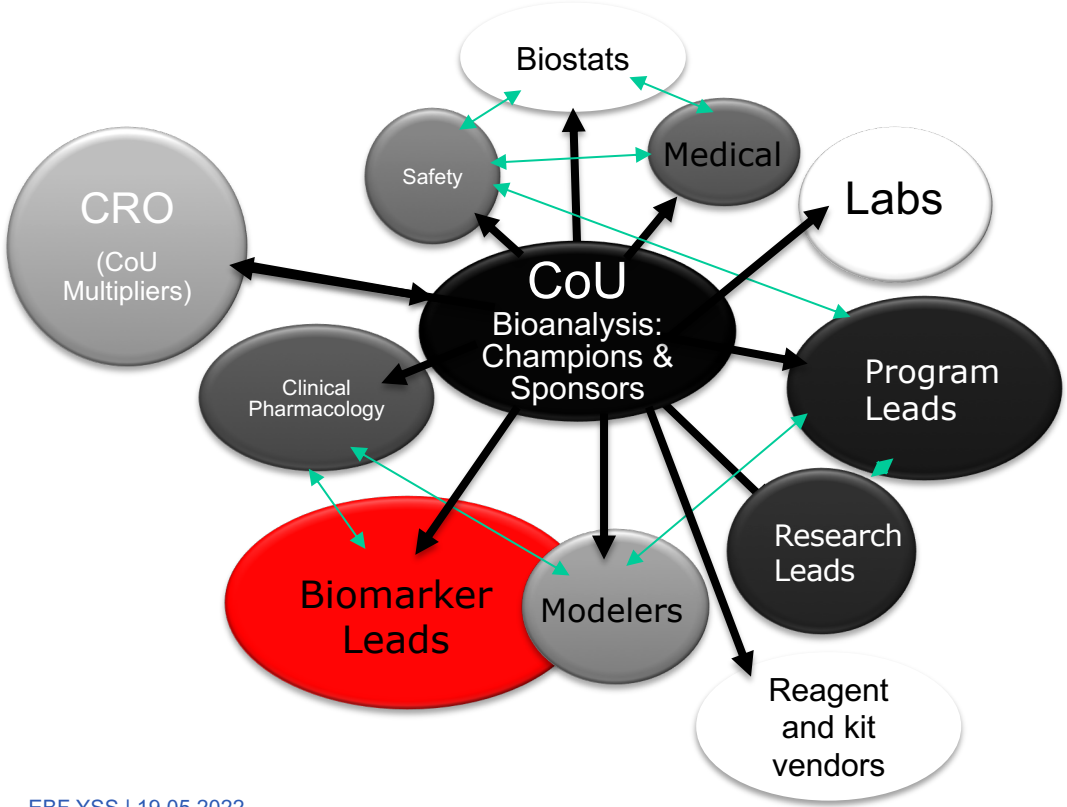
Pharmacometrics

Clinical Pharmacology

Touchpoint Meetings*

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

How do we ensure CoU is implemented appropriately?



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?

High Level Example

- **Ask the question:** Focus on the purpose of the assay, and any information that is known about the biomarker
- **Then:** Consider the potential technologies, platforms, and assay (kits and reagents) that could be used
- **Goal:** To develop a valid assay for sample analysis, a method appropirately validated for that CoU

Example:

- **Information from stakeholder:** Biomarker (BM) of interest, domain of interest, matrix, patient indication, whether it‘s a PD BM, phase of clinical trial (questions being asked, design of trial), literature information on BM including disease state levels relative to healthy and biological variability, expected changes if PD.
- **Additional information found in literature by BA scientist:** isoforms – need total or specific assay?
- **CoU statement:** A potential PD BM being explored in a phase X clinical trial in patients with disease Y, to be measured in Z matrix where total levels are expected to change from disease levels to levels in healthy volunteers (potentially A-fold at maximum). A proximal BM to confirm response to drug and potentially lead to decisions (but not necessarily).
- **Bioanalytical strategy** is born out of this: sensitivity needs (less than expected healthy levels), do not need an isoform-specific assay, relative quantitative assay (parallelism, precision), long-term stability.

Development and Validation

Parameter	Approach	Acceptance Criteria
Parallelism	10 healthy and 10 disease-state samples, at least 3 dilutions in quantitative range	Evaluate and define acceptance criteria for validation
Precision	5 QC pools (endogenous analyte, 2 days, 2 runs	Evaluate and define acceptance criteria for validation
Sensitivity	Defined by parallelism	100% healthy individual above LLOQ
Specificity	Pull-down experiment	Pass
Stability	Benchtop 4 and 24 h, F/T 3X, -20/-70 6 mos	Within B-fold precision

- Asked the questions
- CoU statement
- Technology, assay/reagents, development parameters
- Characterisation of the assay
- Acceptance criteria, Validation (rubber stamp)

Focus Workshop

BM CoU: Sharing Experience through Examples

Live in Malaga: September 29-30

Agenda planning has begun:

Building the workshop around representative examples of biomarker assays.
As examples, they are validated (or not) in line with CoU principles.
Examples selected for the workshop will have been discussed within the EBF Biomarker team.
Each presentation will be selected to ensure maximum fit with the workshop goals.

Abstracts still being accepted until June 1st.

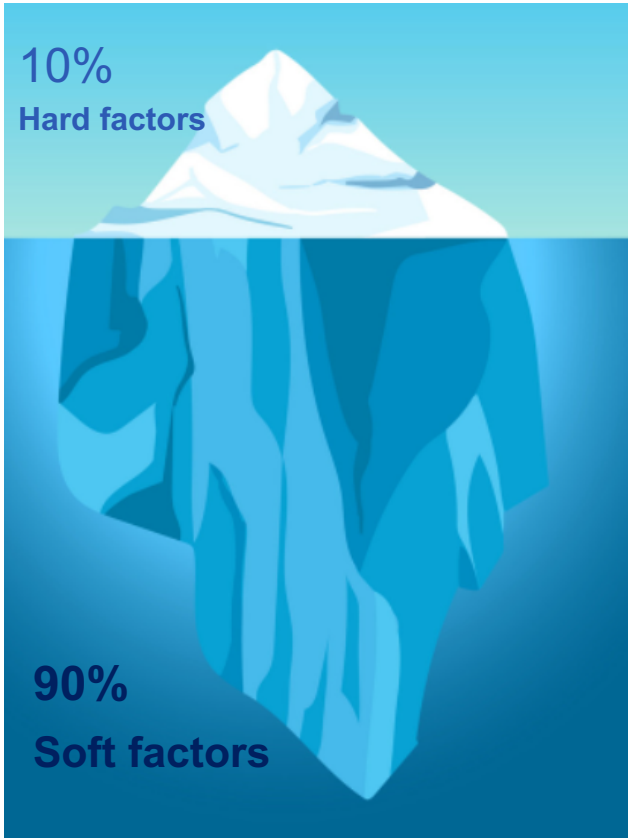
EBF

The iceberg model

What are key factors for implementing change successful?

- 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 your project.
- Develop an understanding of the situation, risks, impact and activities in the change process.

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 for your project.

5 **Empower Action**

- Win-Win-Strategy: make your stakeholders to your partners.
- **Involve your stakeholders e.g. your colleagues 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**

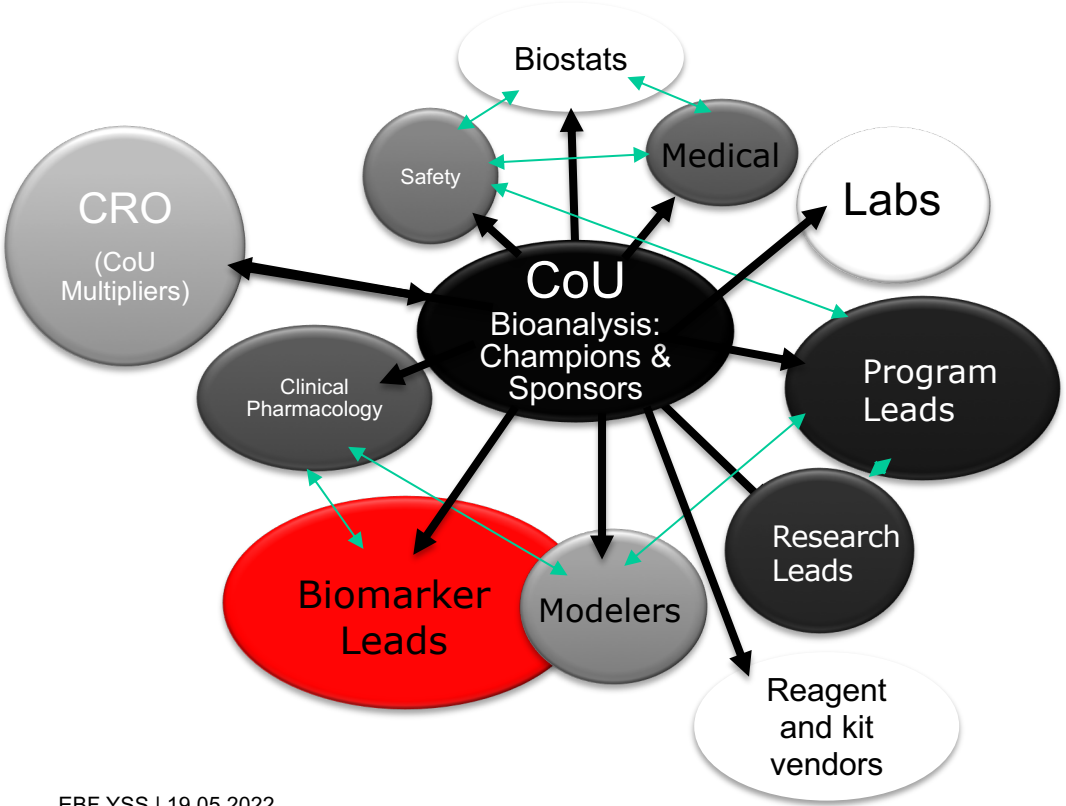
- Use the energy from the quick wins to drive your change initiative forward.

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.

Changing the mindset

Be the voice on your teams



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Acknowledgements

EBF Biomarker Teams:
Jo Goodman, AstraZeneca;
Michaela Golob, Nuvisan;
Anna Lauren, Novo Nordisk;
Philip Timmerman, EBF

Organisers of EBF YSS 2022!

Thank you!!

EBF Biomarker Team Members:
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