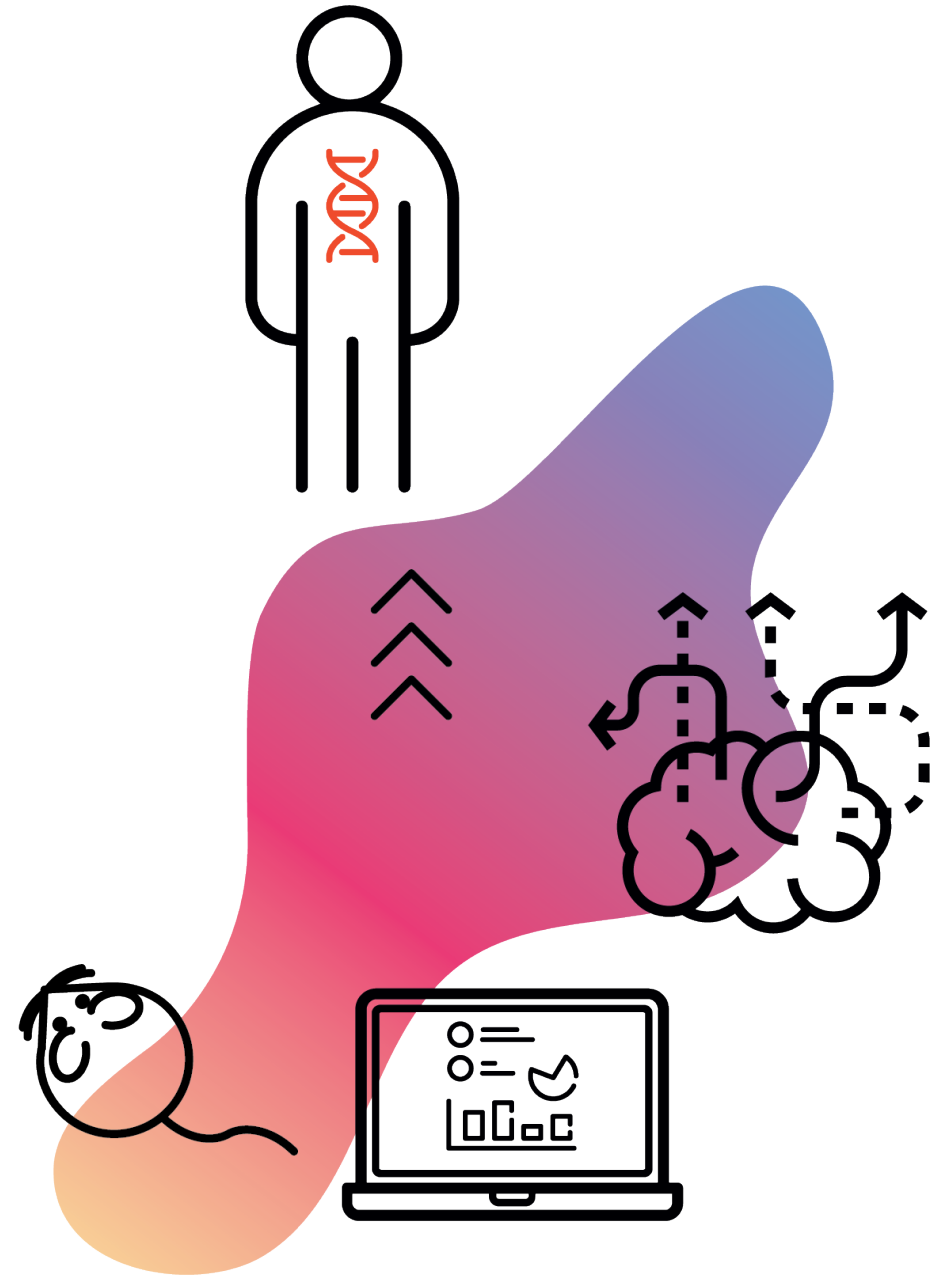




Biomarker as a “question-based approach” embedded in Idorsia’s R&D

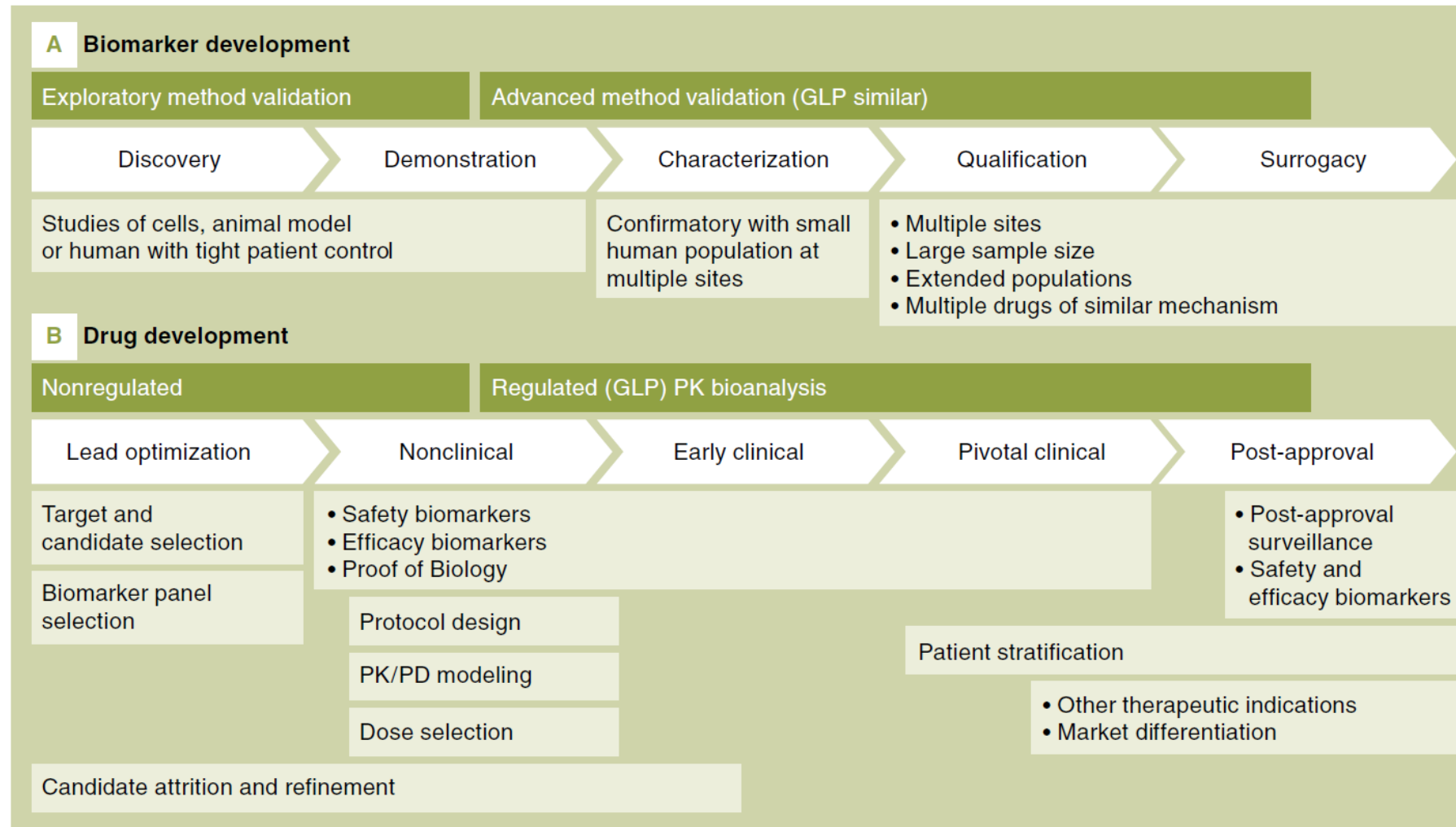
EBF – 14th EBF Open Symposium – 24 November 2021



Biomarkers are an integral part of biopharmaceutical R&D

- Biomarker utility is greatly hampered by the lack of standardizations, unclear guidances and mis concepts of utility
- Biomarker interests have increased since the release of the FDA Critical Path Report in 2004 but have been used for more than 2000 years!
- Utility of a biomarker is determined by rigor in which it was discovered and developed
- Our biopharmaceutical R&D is data driven and based on asking the right questions
- As we progress our projects, we keep asking critical questions
- It is of great importance that with the handovers, the continuity of the biomarker strategy is guaranteed. A good biomarker strategy starts with the inception of the project in early discovery!

Consider the analogies between Biotherapeutics and Biomarker development

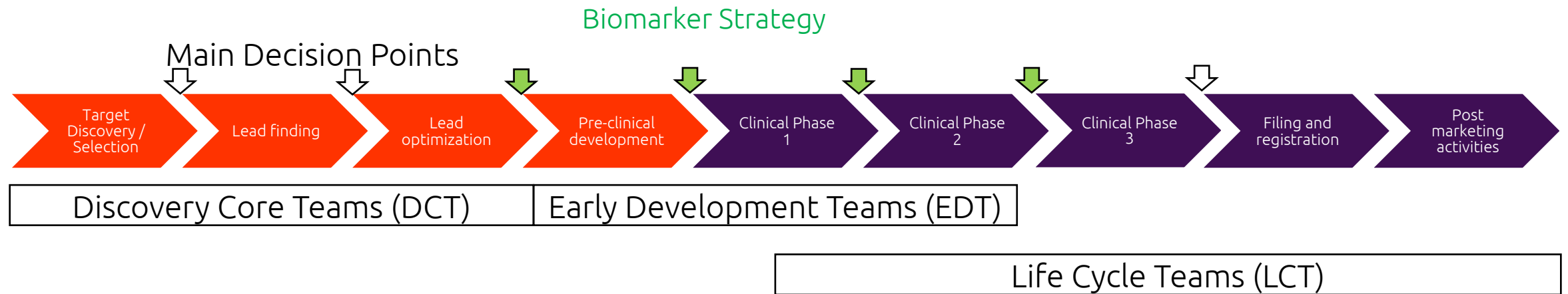


From Lee JW, Bioanalysis 2009

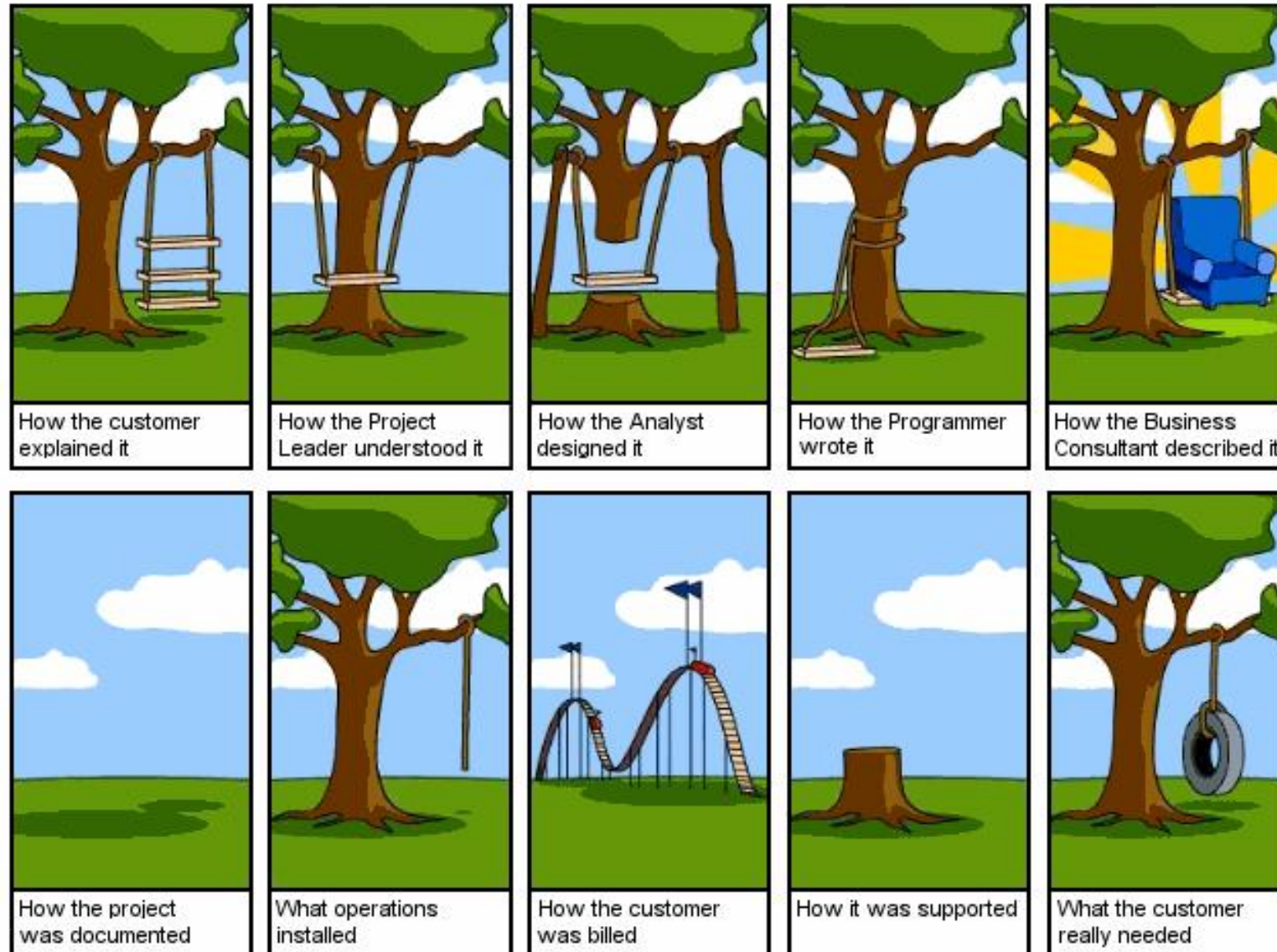
Solution: an Integrated Biomarker Approach

General R&D structure

- Translational Biomarker Representatives are part of the Early Development Teams (EDT) and Life Cycle Teams (LCT)



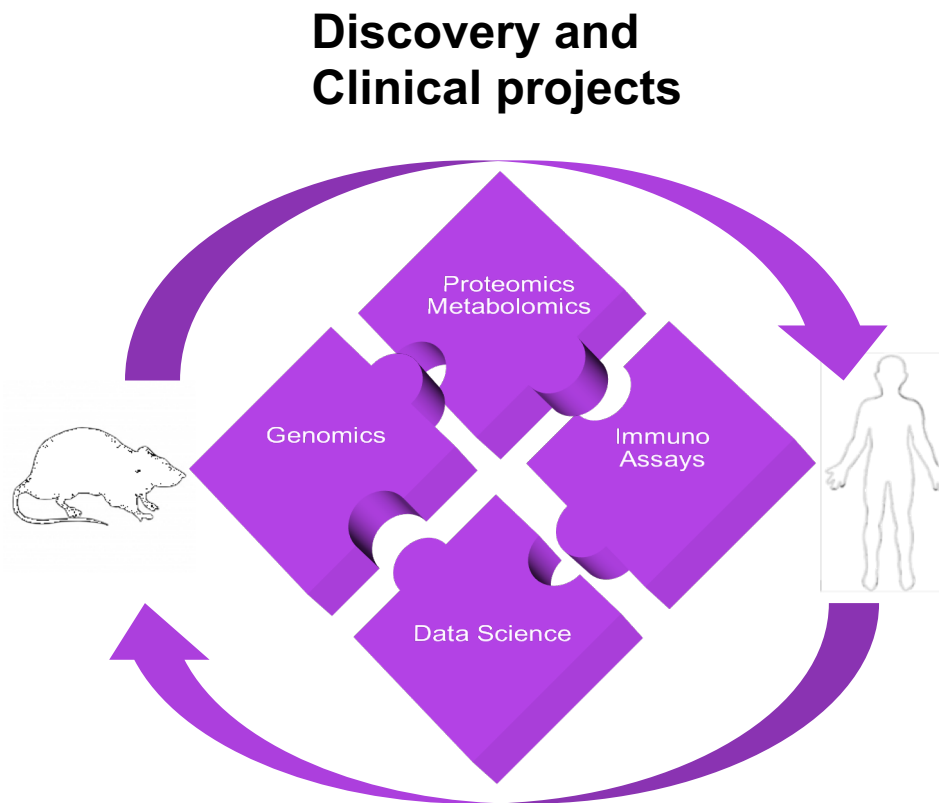
The Context of Use Paradigm shift



Translational Biomarker Group: bench to bedside and back

Biomarkers / Mechanistic studies / Translational Studies

- *In vitro* / *ex vivo* / *in vivo* preclinical models
- Retrospective sample analyses
- Prospective Studies
- Phase I and II exploration
- Phase II and Phase III consulting



**Biomarker data for
exploration and
decision-making!**

Selection of

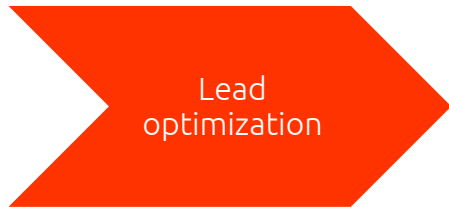
- Drugs
- Dose
- Indications
- Patients

Biomarker Discovery and Development is Question driven not Technology driven!
We evaluate the best possible options once the question is clearly defined.

Process

LO: start of the biomarker strategy: Question Based Approach

- A TBG Member is appointed to a core team and supports indication selection and biomarker strategy



Biomarkers are addressed using a Question Based Approach (alternative for Context of Use)

The Biomarker Guidance Table (BiGT): An electronic “living” document with time stamped revisions

Question Category Biomarker “readiness” Assay Assay validation level

Category	Question	Biomarker	Stage	Work
Diagnostic in human	How is the disease (stage) diagnosed?	NT, CT, MRI, PET, etc.	✓	✓
Diagnostic in animal model	Does it translate into pre-clinical models?	CT, MRI, PET, etc.	✓	✓
Exposure	Can we detect the compound in a) blood? b) tissue?	CT, MRI, PET, etc.	✓	✓
Drug-target interaction (Target engagement)	Does the compound directly interact with the target?	CT, MRI, PET, etc.	✓	✓
Target modulation	Does activation / inactivation of the target elicit measurable effects in known downstream pathways? (proof of biology)	CT, MRI, PET, etc.	✓	✓
Pharmacology	Does the compound elicit its required pharmacological effect? (pharmacodynamic)	CT, MRI, PET, etc.	✓	✓
Efficacy (early decision)	Does the treatment result in reaching an early decision endpoint? (proof of concept I)	CT, MRI, PET, etc.	✓	✓
Efficacy (regulatory)	Does the treatment result in reaching a regulatory endpoint? (proof of concept II)	CT, MRI, PET, etc.	✓	✓
Safety	What markers allow monitoring safety aspects?	CT, MRI, PET, etc.	✓	✓
Stratification	Does variability in the target population result in variable efficacy and side effects? Does a hypothesis allow for prospective biomarker segmentation studies?	CT, MRI, PET, etc.	✓	✓

Preclinical Development

- TBG representative becomes team member of EDT

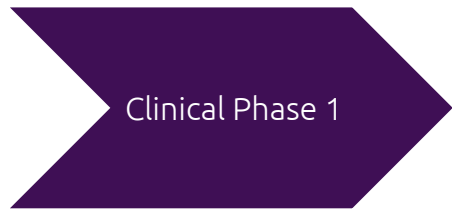


- Biomarker strategy refinement, focus on feasibility and assay development for First in Human (FiH)
- CoU central to biomarker development
- Decision on in- or out-sourcing
- Updates IB with relevant biomarker parts
- Biomarker implementation into Phase 1 clinical protocol:
 - Biomarker Validation Plan formalized
 - Biomarker Validation report formalized
 - Biomarker Analysis Plan formalized

Confidential	
Research Report B-15.010	
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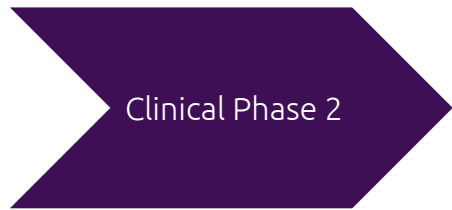
- Biomarkers deployed



- CoU definition for internal decision-making biomarkers: mostly target engagement and pharmacodynamics
- Coordinate the sampling logistics with the Idorsia Research Bio Repository (IRBR)
- Biomarker measurements : TBG or outsourced
- Biomarker data analysis : Clinical Pharmacology / biometrics
- Clinical Biomarker reports

Clinical Phase II, PoC

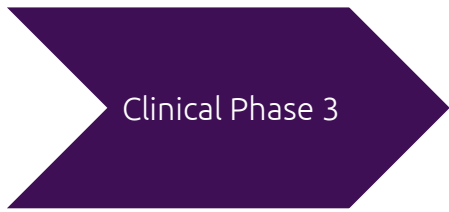
- Biomarker addendum to the clinical development plan



- Biomarker strategy further refined
- Shift CoU towards disease relevant biomarkers
- Clinical protocol writing biomarker relevant parts
- Coordinate the sampling logistics with the Idorsia Research Bio Repository (IRBR)
- Biomarker measurements : TBG or outsourced
- Biomarker data analysis : Biometrics

Clinical Phase III

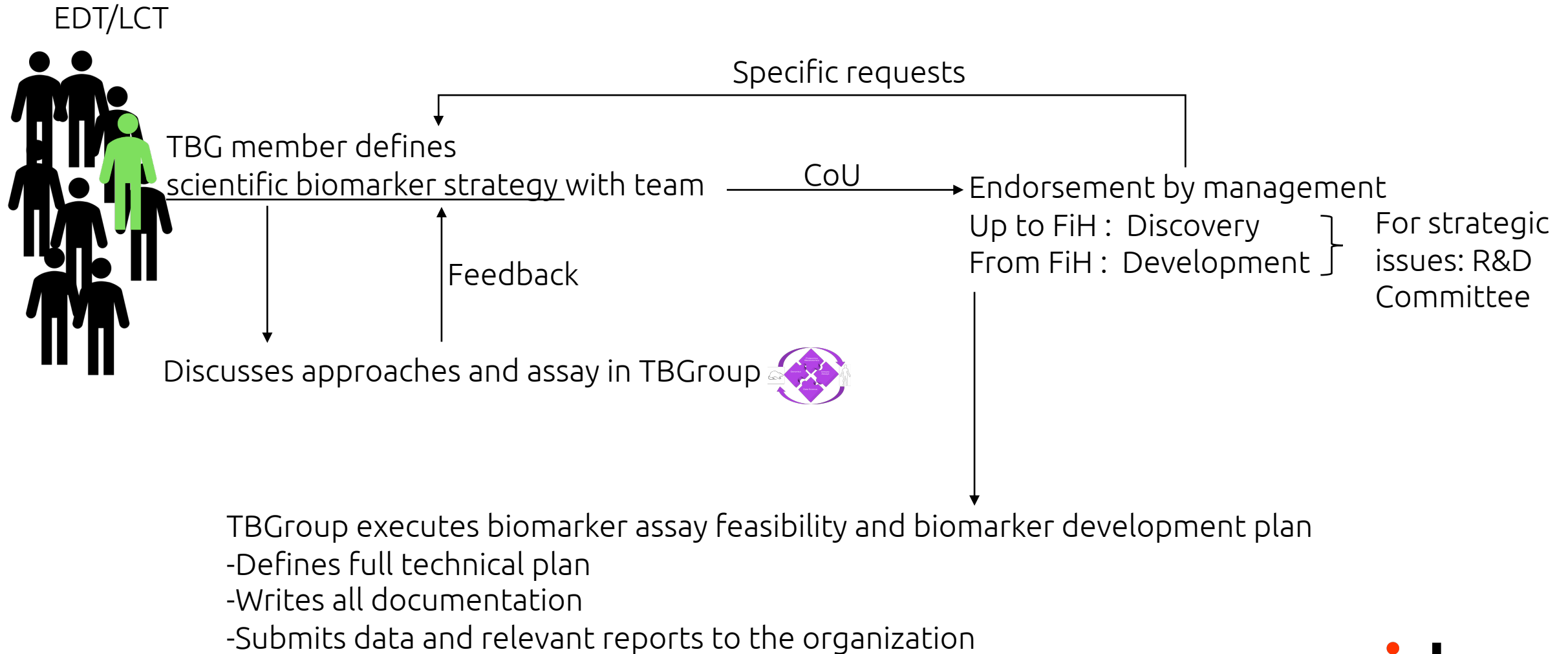
- Final biomarker strategy refinement



- CoU definitions for exploratory biomarkers (sometimes endpoints) all other biomarkers are either part of standard clinical assessments or diagnostic and monitoring
- Exploratory biomarkers measured in-house or outsourced
- All other biomarkers outsourced
- TBG members remain to consult the LCT and management on “regulatory defined” biomarkers. Also responsible for interaction with CRO central labs on quality control before, during and after study.

TBG Biomarker Expert Roles

Biomarker expert have multiple roles as they also run labs or conduct experiments

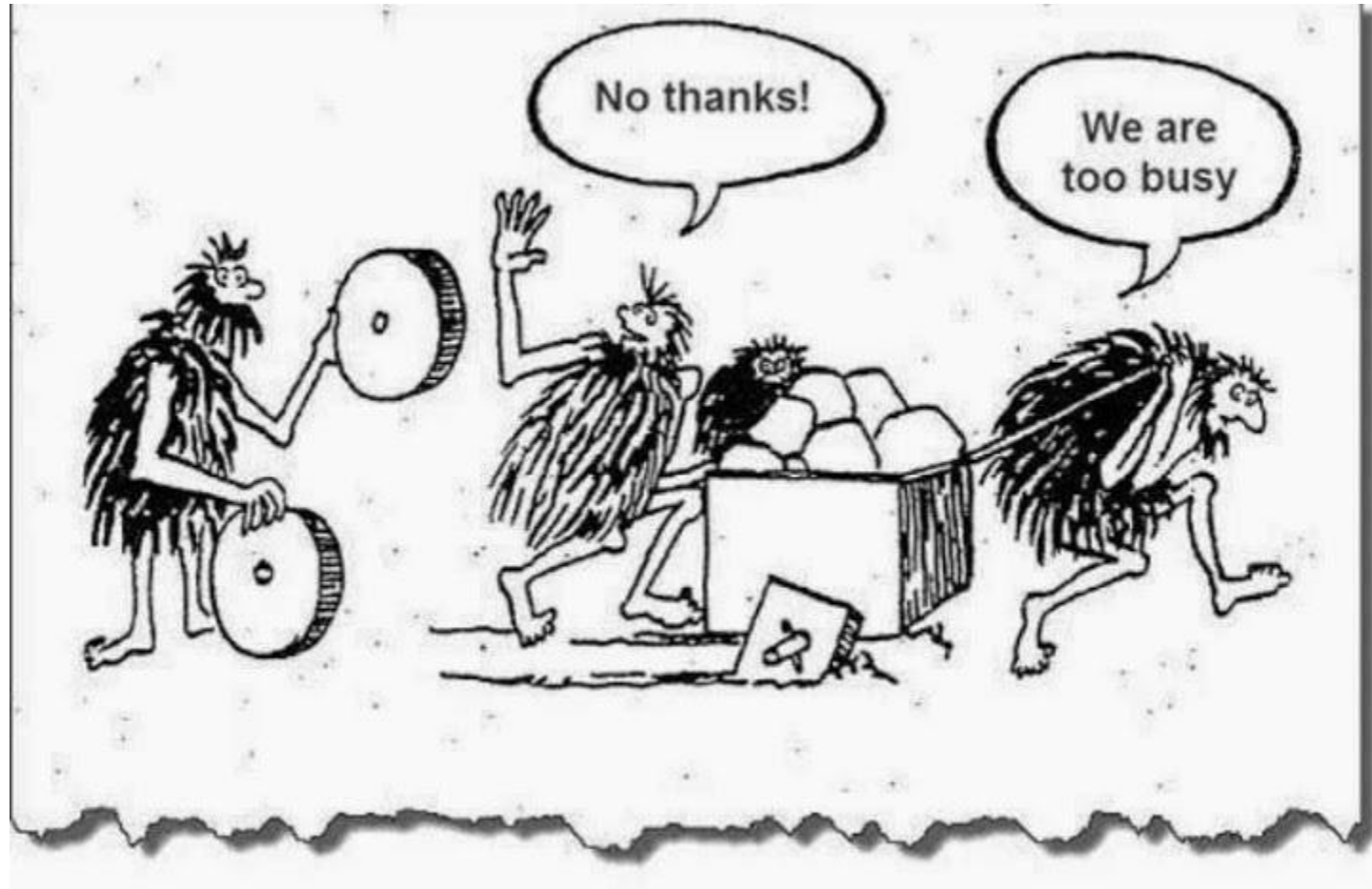


Summary Idorsia biomarker strategy

Key aspects

- Structured translational biomarker activities start in LO phase
- The Translational Biomarker Group is specialized function in the research organization that covers all aspects of biomarkers from **strategy** to **development** and **implementation** and **contextual analyses**
- The Bioanalytical Group, also in discovery is only involved in PK measurements (cross talks exist on technical aspects for LCMS based biomarker assays)
- TBG experts are **responsible** for guiding strategy in teams and **accountable** for assay development and clinical implementation. Outsourcing in partnership with clinical organization
- TBG has implemented the **Question Based Approach** but is now adopting the **CoU** which is captured in the biomarker validation report
- **IMPORTANT:** TBG is **part of the project team** and wherever applicable part of the management decision meetings, this has a big impact on the CoU!

Reality is sometimes hard to accept for a biomarker scientist

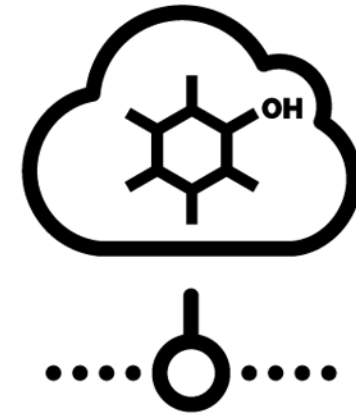


idorsia

Less
is more...

Creativity and Simplicity

Thank you for Listening!



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