What Does the CIOMS WG XII Benefit-Risk Assessment (BRA) Report Say?

EFSPI/PSI Benefit-Risk Assessment ESIG

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Key Takeaways

Lifecycle approach to benefit-risk assessment:

- Transitioning benefit-risk evaluation from a post-hoc analysis to an integral part of clinical trial design and conduct.
- This shift emphasizes the need for developing patient-centric benefit-risk endpoints alongside traditional efficacy and safety endpoints.
- Introduction of BRAD [Benefit-Risk Assessment Document]

Patient-Centric Approach:

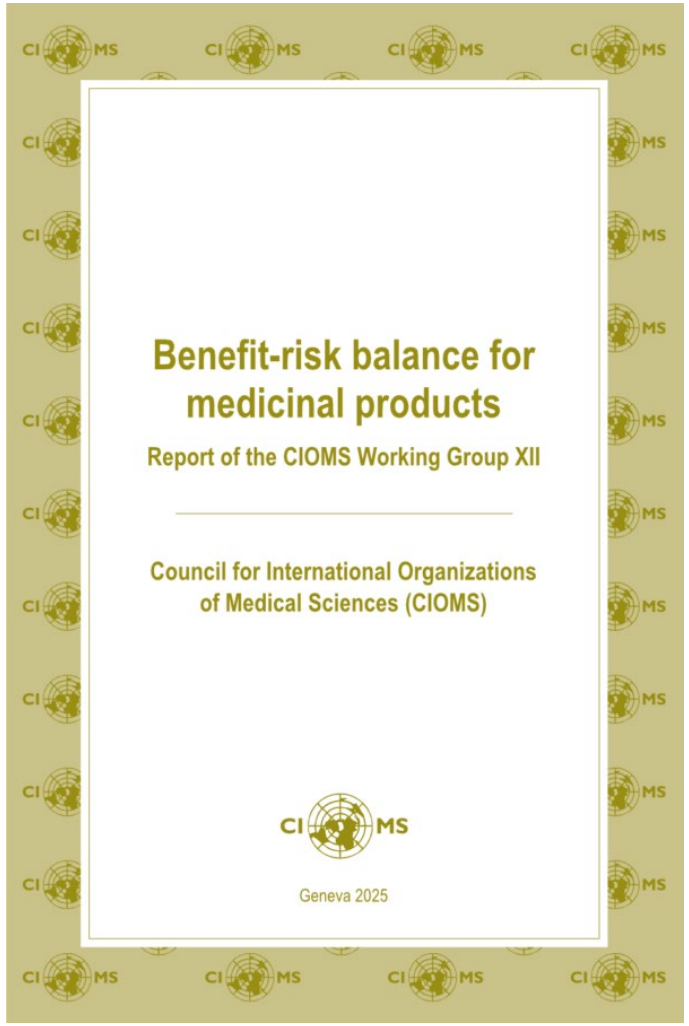
- A focus on how benefits and harms are experienced by patients, leading to a more holistic understanding of treatment impacts.
- Offers a more complete picture of the patient response than marginal analyses of efficacy and safety

Potential implications

- May influence protocol development and reporting/publishing standards.
- The report's recommendations are poised to shape the evolution of existing guidelines (e.g. SPIRIT, CONSORT, PRECIS), making them more relevant to current clinical practices and patient needs.

Benefit-risk Balance for Medicinal Products

NEW! 27.May.2025



The CIOMS Working Group XII aims to put forward:

- a life-cycle based Benefit-Risk Assessment (BRA) approach
- to support decision making and transparent communication

- Chapter 1: Benefit-risk landscape
- Chapter 2: Structured benefit-risk approach/framework
- Chapter 3: Benefit-risk assessment methodology considerations
- Chapter 4: Specificities of benefit-risk assessment methods for special situations
- Case Studies

https://cioms.ch/working-groups/working-group-xii/

https://doi.org/10.56759/gwfz1791

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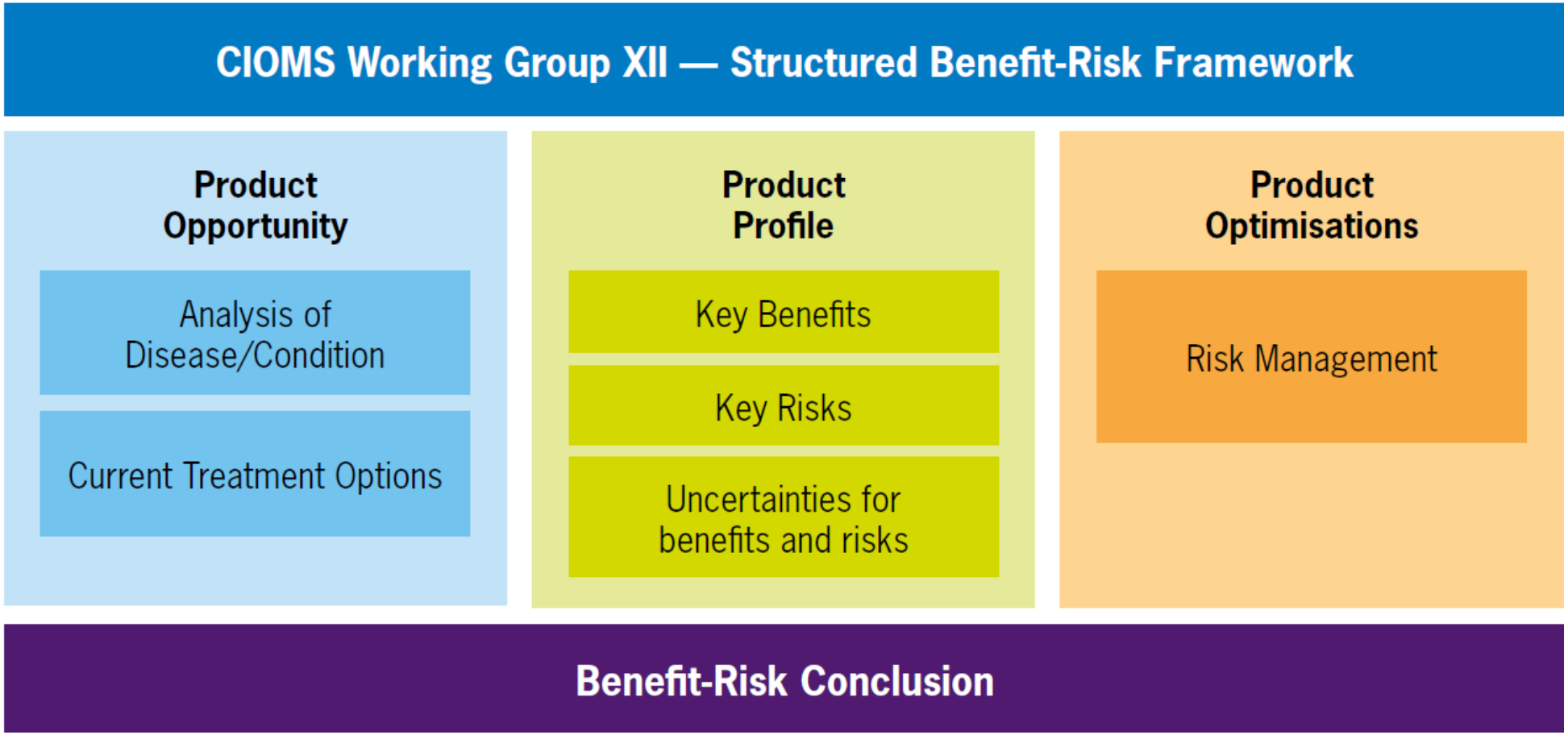
Transformation of the Perspective of BRA

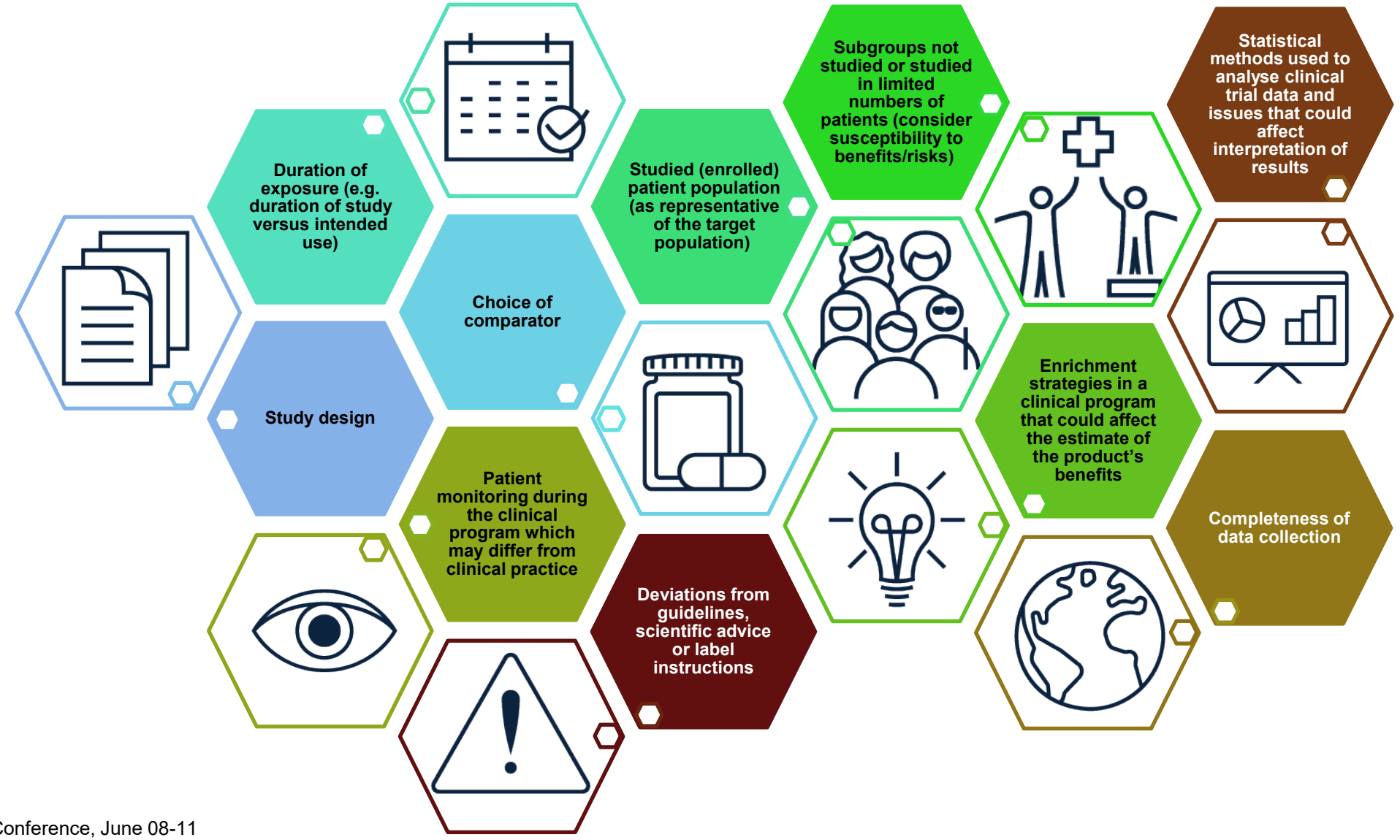
- Supersedes the CIOMS Working Group IV report
- Take a lifecycle approach starting benefit risk assessment as early as possible in early drug development and maintained continuously through the life-cycle
- Evolve from a post-hoc to a pro-active approach including diligent forethought and integration of benefit-risk assessment into clinical trial design, conduct, analyses, and reporting
- Include patient perspective, including pragmatic patient-centric methodologies, in the benefit-risk assessment
- Involve multidisciplinary teams, including perspectives of key stakeholders
- Enhance transparency of the decision-making process

Components of a Structured Benefit-Risk Framework

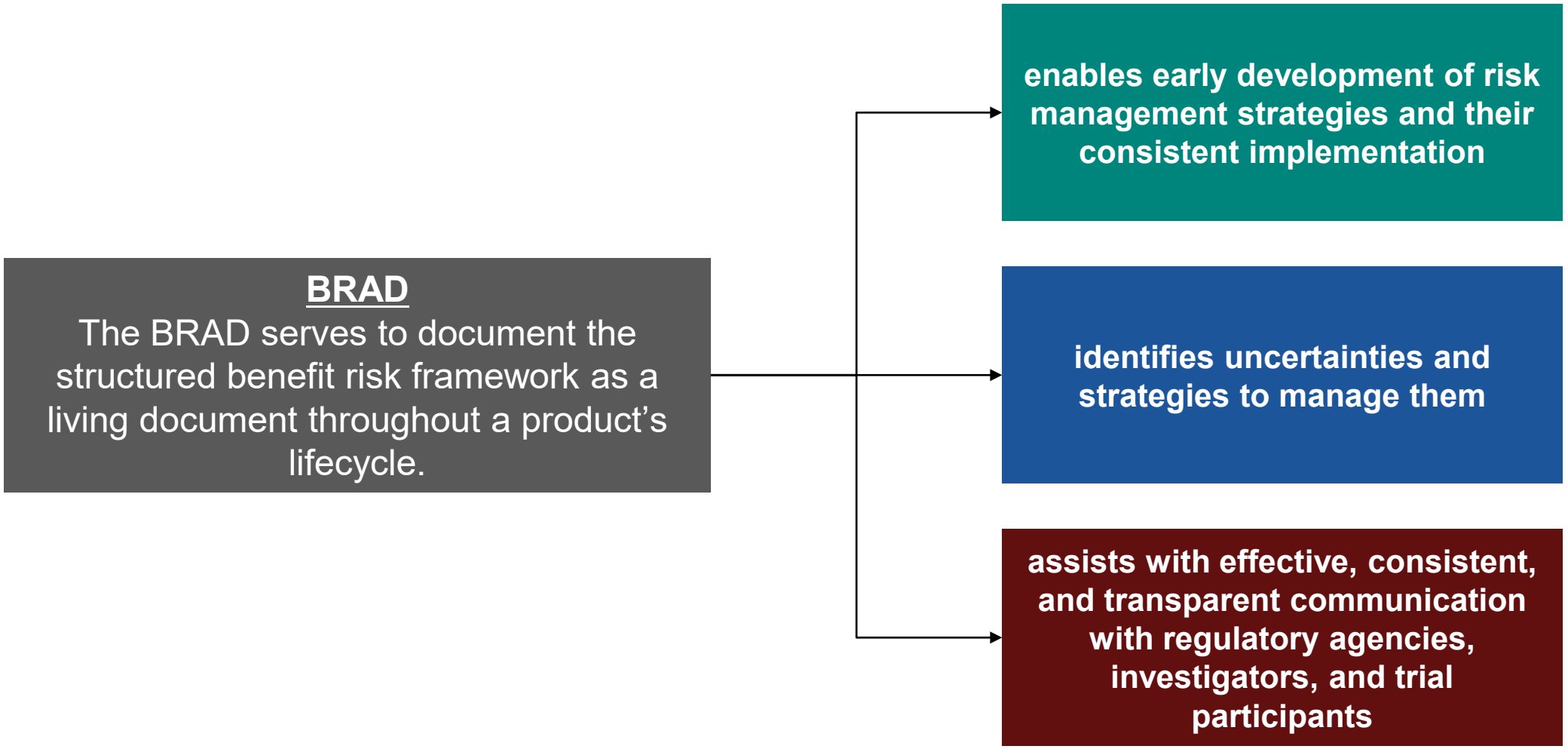


- Reflects perspective of CIOMS WG XII
- Based on ICH M4E(R2), EMA PROACT-URL, and other BR frameworks

Sources of Uncertainties in SBRF

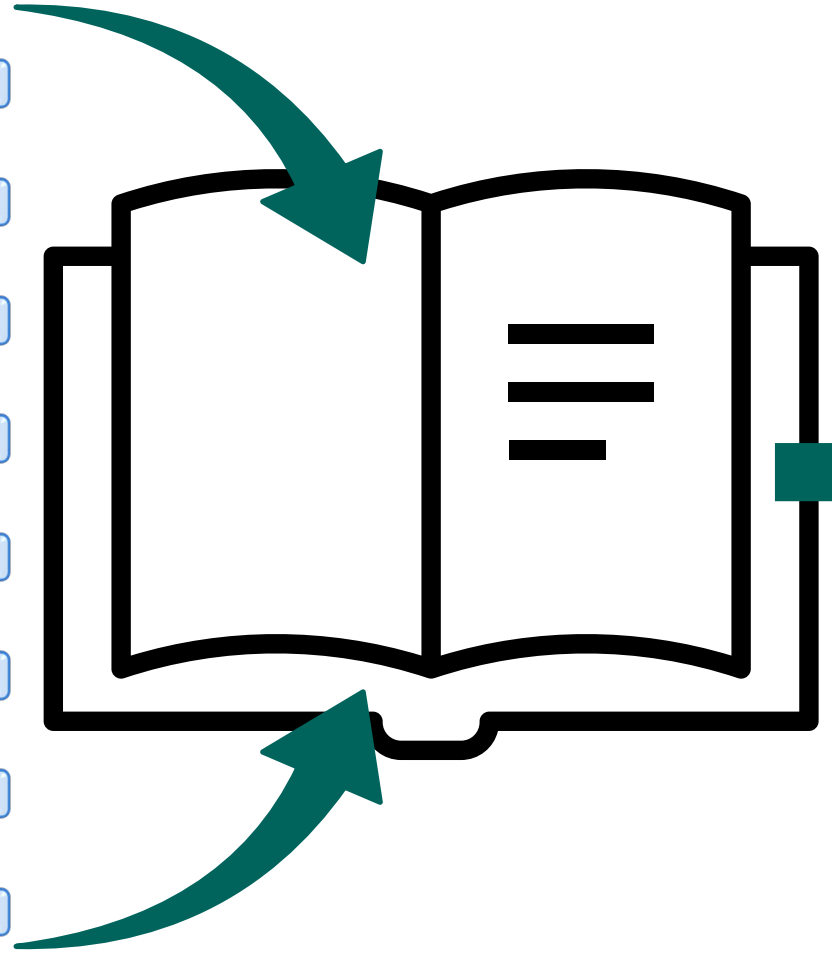


The Benefit-Risk Assessment Document (BRAD)



Source and impacted document of a BRAD

- Toxicology reports
- Patient journey
- Characterisation of the disease state and unmet need
- Disease treatment guidelines
- Target product profile or claims
- IND / NDA / MAA / BLA†
- Clinical Development Plan/Asset Plan
- Investigator Brochure (IB)
- PRO/QoL instruments and domains
- Product Safety Plan / Developmental RMP / RMP
- Regulatory Documents (including Briefing Books
- DSUR / PSUR / PBRER
- CSRs
- Epidemiologic study data
- SAP for a product submission
- Product Label/Company Core Data Sheet (CCDS)
- Real-world evidence

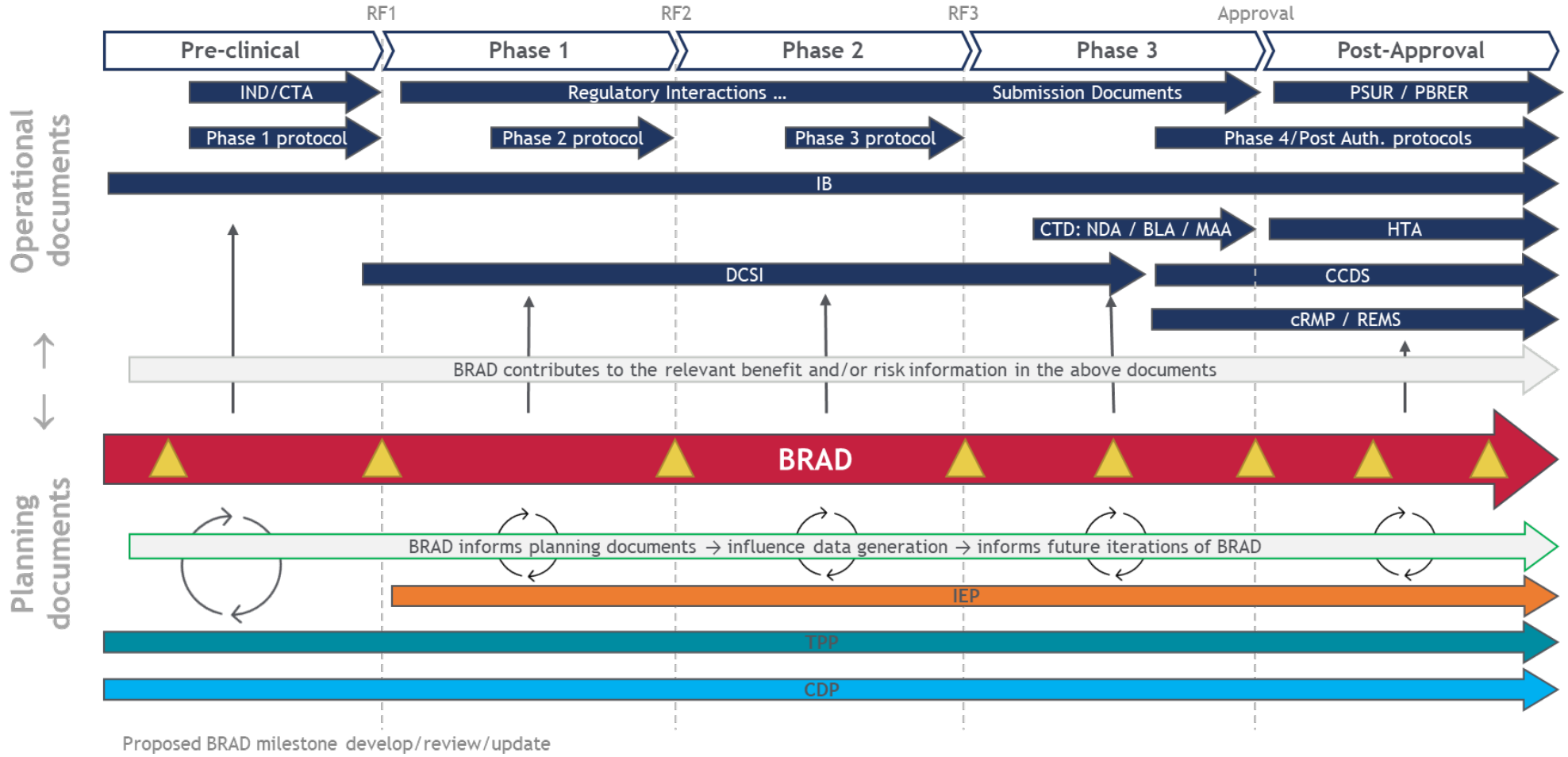


- NDA / MAA / BLA
- Regulatory documents including Briefing Books
- PSUR / PBRER

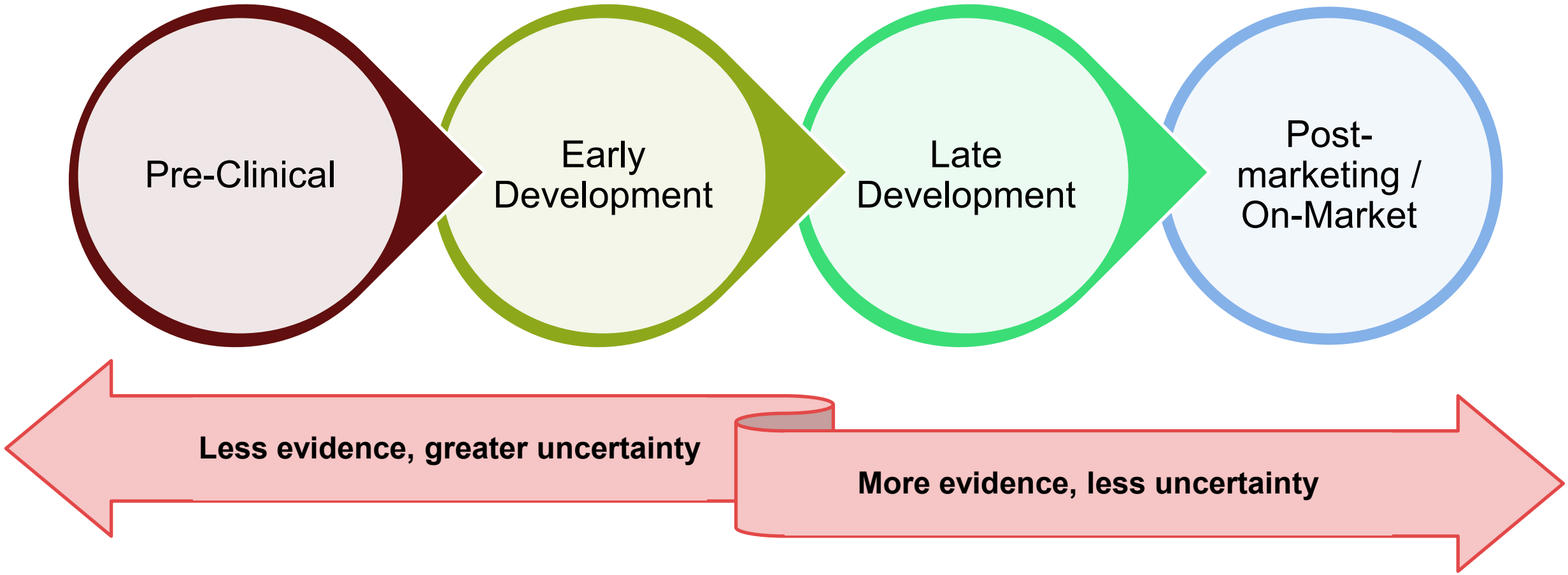
† Investigational New Drug (IND) for drugs which *are not yet approved* and New Drug Application (NDA)/ Marketing Authorisation Application (MAA)/Biologic License Application (BLA) for *previously approved drugs*

The BRAD

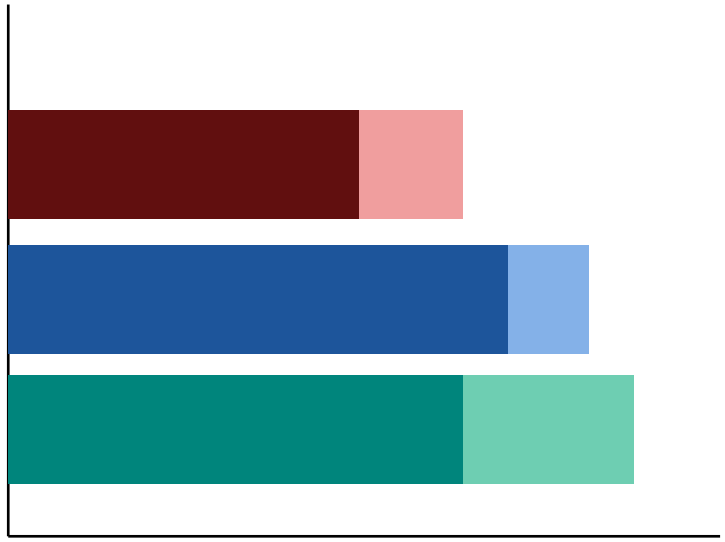
Leveraging the Benefit-Risk Considerations Throughout Product Development and Beyond



Lifecycle Approach to Benefit-Risk Assessment



Importance of Incorporating Patient Perspective



- Trt 1, without patient input
- Trt 1, patient input
- Trt 2, without patient input
- Trt 2, patient input
- Trt 3, without patient input
- Trt 3, patient input

Benefit of involving patients throughout product lifecycle

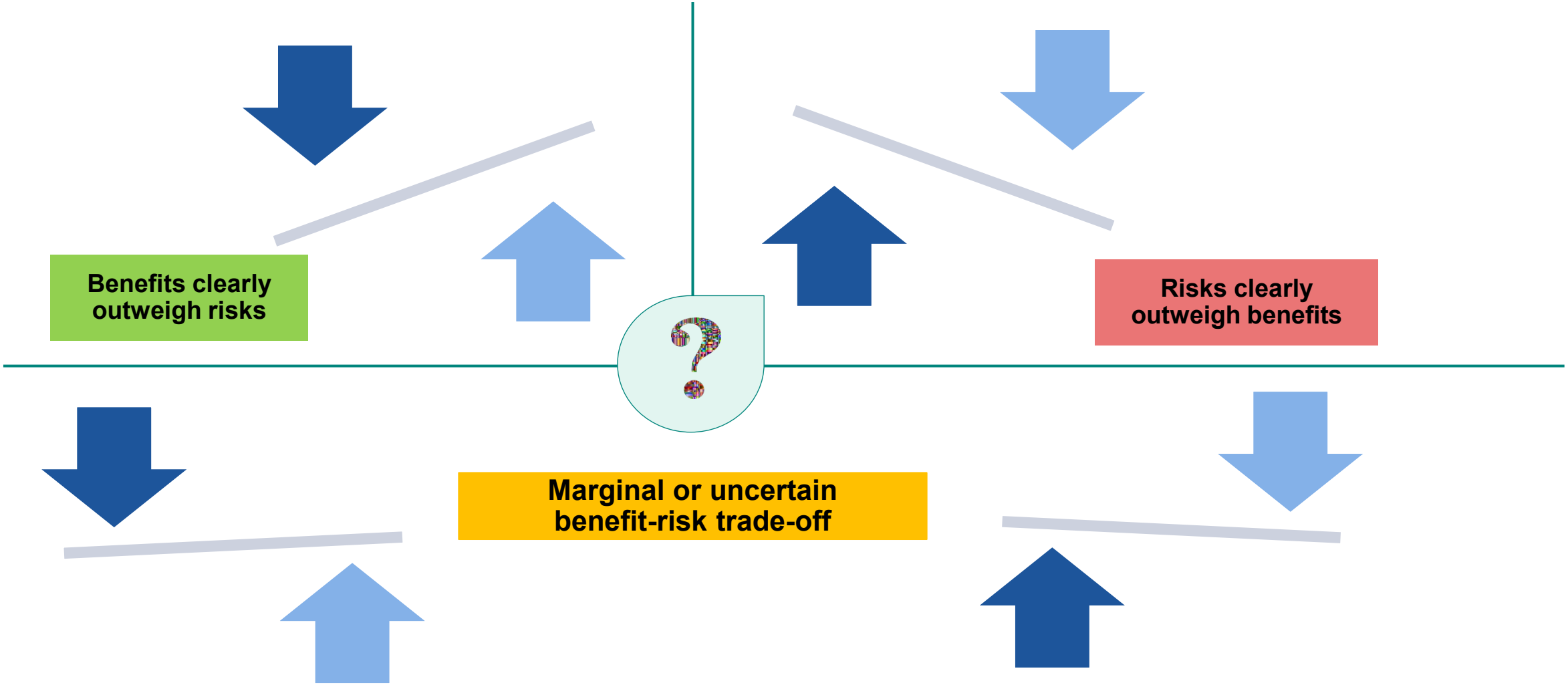
- Improve the quality of the evidence and decision making
- Increase transparency
- Support trust and mutual respect between stakeholders
- Aid effective communication

Value of patient input

- Most important benefits and risks
- Relative importance of clinical outcomes and safety concerns
- Relative importance of different BR attributes
- Impact on quality of life
- Acceptable or unacceptable risks
- BR trade-offs for maximum acceptable effect size

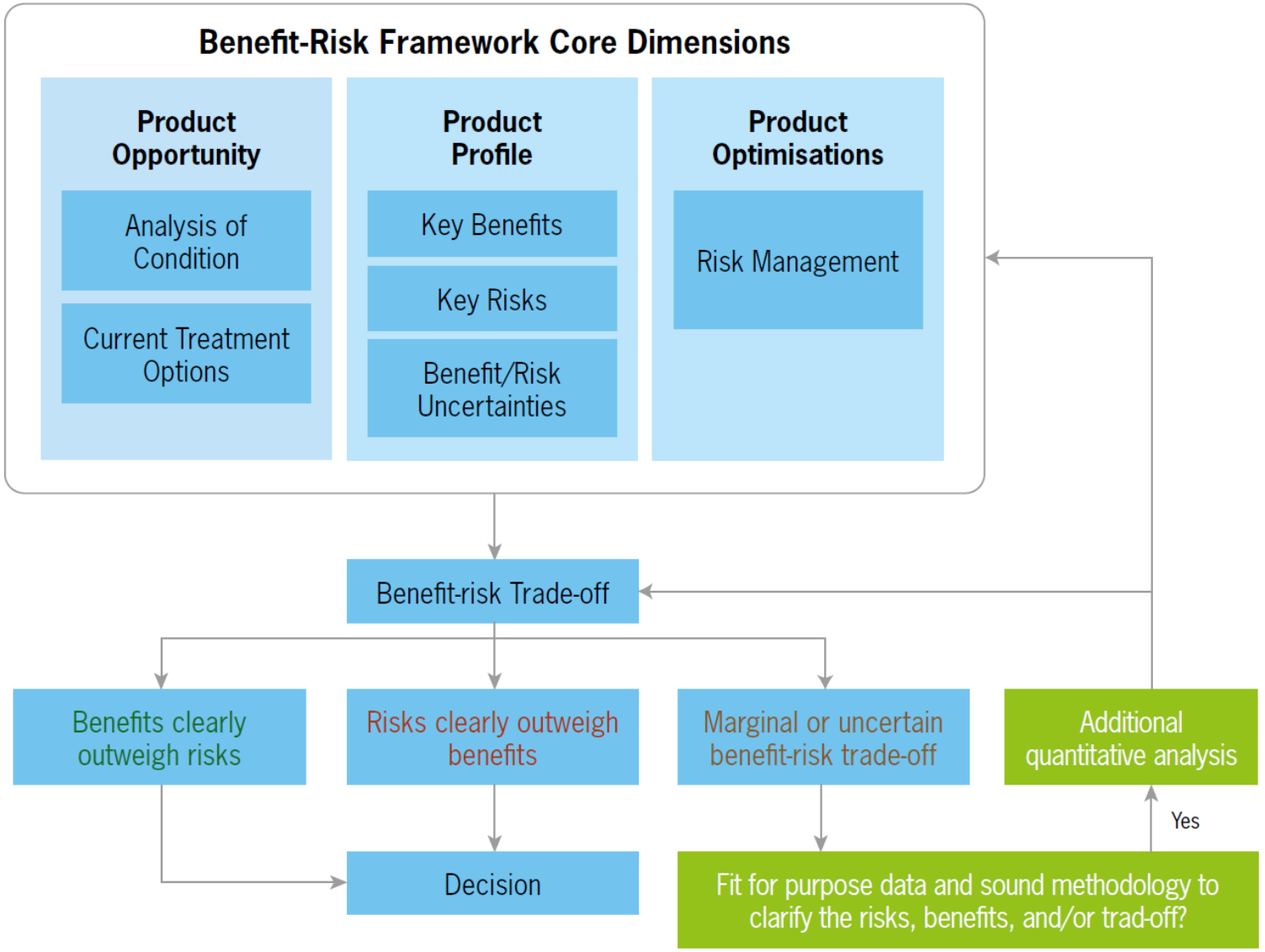
Homogeneous patient population vs specific subgroups vs “vocal minority”

Possible Outcomes of a Benefit-Risk Assessment



Decision Tree for Additional Quantitative Analysis in BRA

The benefit-risk decision is a judgement call and should be made based on the totality of evidence.



BRA Methodology Considerations

- Study designs and statistical approaches to generate data that inform the benefit-risk assessment
- Methodological considerations to gain patient insights
- Methodological considerations for addressing uncertainties in benefit-risk assessment
- Approaches to visualisation of benefit-risk assessment
- The multidisciplinary Benefit-Risk Management Team

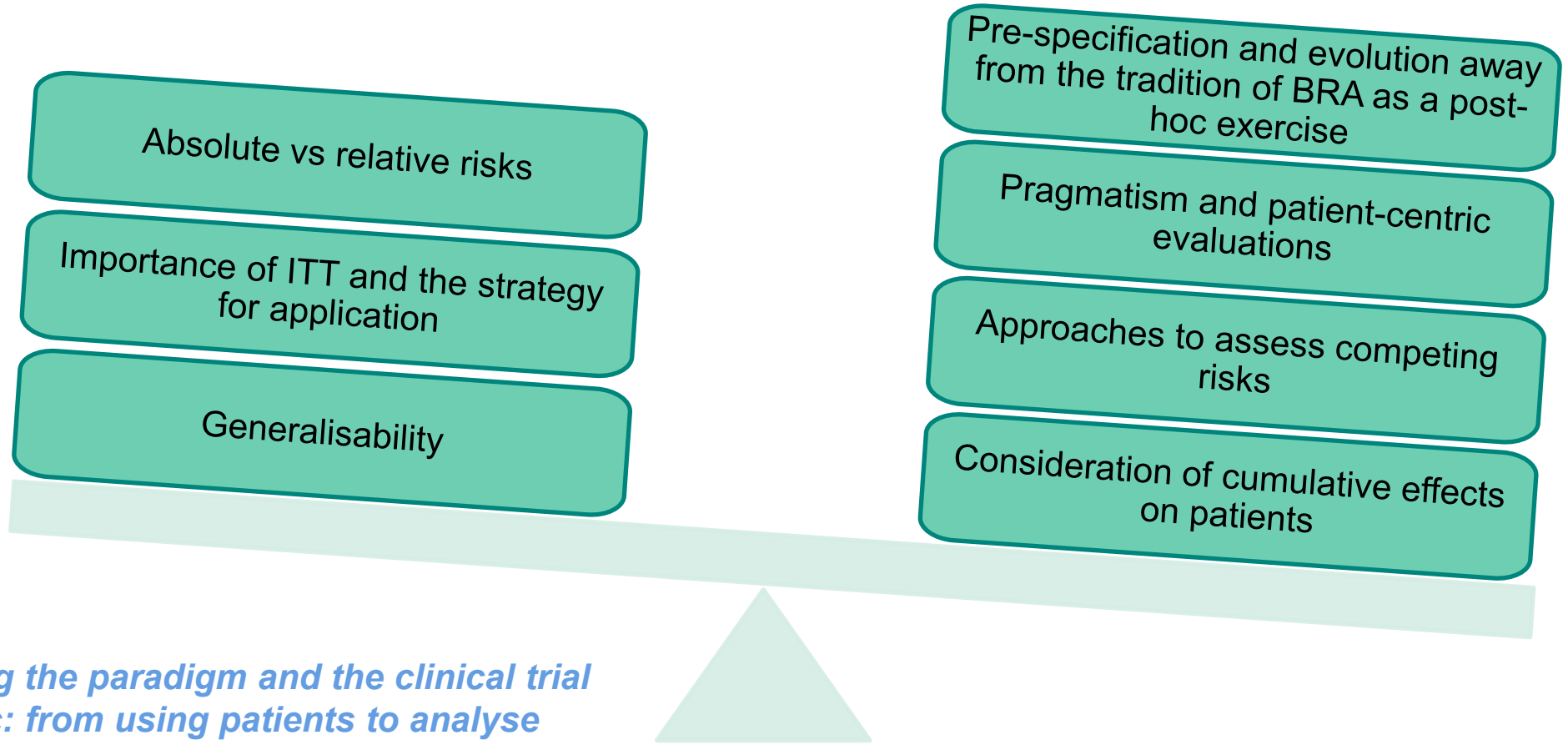
Patient-Level BRA – a Novel Lifecycle Paradigm

- Conventional approaches synthesise information using separate marginal analysis of the benefit outcome(s) and the risk outcome(s) ➔ not patient-centric
- Challenges:

01	02	03	04
Associations between the positive and negative outcomes	**Cumulative nature of outcomes in individual patients**	**Competing risk complexities during the interpretation of component outcomes**	**Unclear generalizability to patient populations**

- Novel paradigm focus: questions of a pragmatic origin ⇒ clinical importance
  - Transforming BRA from a post-hoc exercise to one that is thoughtfully integrated into clinical trial design, conduct, and analyses; and
  - Adding patient-centric BR analyses.

Methodological Issues to Consider



"Changing the paradigm and the clinical trial arithmetic: from using patients to analyse outcomes to using outcomes to analyse patients"

Acknowledgments

CIOMS Working Group XII

experts from drug regulatory authorities, including ICH founding members, industry and academia

The Working Group (WG) XII started its work in September 2019, worked through the COVID-19 pandemic, adjusting its work pace as needed, and completed its work in 2025. The continued dedication of the WG members, despite added challenges of the COVID-19 pandemic, is highly appreciated.

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Thank you!