Navigating ICH E6(R3): Tools and Resources for Understanding Changes and Supporting Adoption

March 4, 2025 9:00 AM EST

Using TransCelerate's tools to help interpret and implement updated Good Clinical Practice Guideline ICH E6(R3)

Welcome

Ground Rules

- **We want to make this discussion helpful and answer as many of your questions as we can, so here are some quick ground rules:**
  - Participation is voluntary, as is using TransCelerate assets/tools
  - The responsibility for compliance with laws and regulations is owned by the solution adopter.
  - You don't have to identify what company you work for
- **Things we would ask you not to discuss:**
  - What vendors/sites/CROs you are using or not using
  - Any issues you have with any vendors/sites/CROs
  - Your long-term development plans
  - Anything related to costs or pricing
- **We can't answer questions about:**
  - Vendors
  - Costs of using/implementing TransCelerate assets/tools
  - Which member companies are using the assets/tools

TransCelerate is a Not-for-Profit Entity Created to Foster Collaboration

Our mission is to collaborate across the global biopharmaceutical R&D community to identify, prioritize, design, and facilitate the implementation of solutions designed to drive the efficient, effective, and high-quality delivery of new medicines.

A Member-Driven Mission

Experts from across our participating Member Companies dedicate their time to TransCelerate.

TransCelerate **identifies the issues and challenges** facing our industry.

TransCelerate **designs and delivers practical solutions** for global adoption by any stakeholder.

Who are our Members?

View a full list of our members

Membership* is available to biopharmaceutical research and development organizations that engage in innovative discovery, development and manufacturing of new medicines

* to be eligible for membership, companies must meet specified eligibility criteria.

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Today's Expert Panelist and Guest Speakers

Panelists:

Madeleine Whitehead, RBQM Product & People Lead, Roche

Tashan Mistree, Senior Director, Business Operations, Office of Chief Medical Officer, GSK

Shilpa Lewandowski, Director, Study Management, AstraZeneca

Arlene Lee, Director, Product Management, Data Quality and Risk Management Solutions, Medidata representing ACRO

Guest Speakers:

Rebecca (Harrison) Stanbrook, GCP Strategic Lead, Process & Risk Surveillance, Novartis

David Nickerson, Head of Clinical Quality Management, EMD Serono/Merck KGaA

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We want to hear from you?

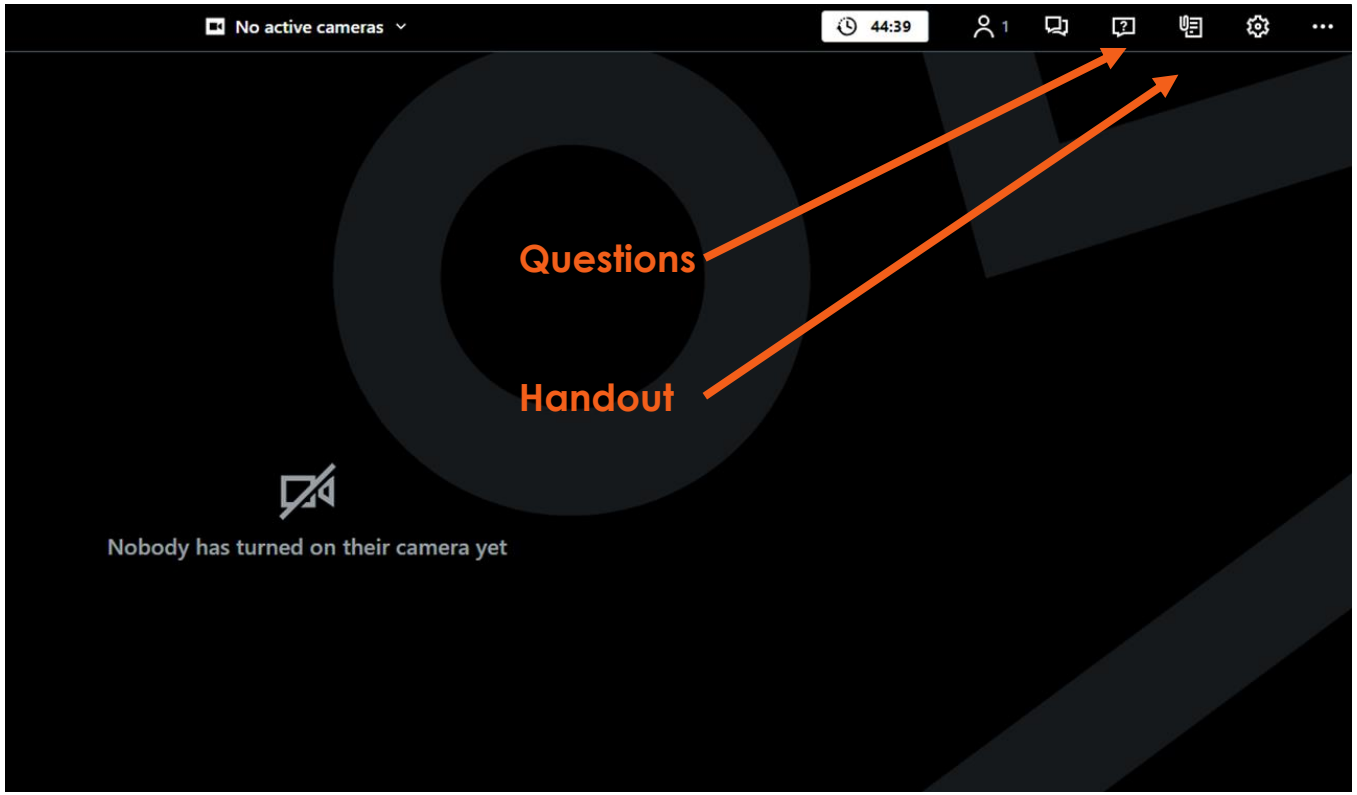
TransCelerate thanks the Association of Clinical Research Organizations (ACRO) for their partnership in developing nine adoption tools and solutions across **Risk Management** and **Data Governance** focus areas.

Agenda

- Welcome
- ICH E6(R3) Executive Summary
- Importance of ICH E6(R3) and E8(R1) Working Together
- Deeper Dive - What's New in ICH E6(R3)
- Demonstration of Published Tools and Solutions
- Q&A

Logistics for the Webinar

- **All participants will be muted for this call.**
- **For audio**: Connect to audio to listen to presentations via your computer or phone
- **To submit a question to the presenters**:
  - Type your question in the Questions panel and click Send.



Reminder: This webinar may be recorded in whole or in part.

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Scope for Today

- Thank you for all the questions that have come in advance of the Webinar. Your interest is appreciated and has helped us craft the presentation.
- The solutions we will discuss today are a result of the work of TransCelerate member company Subject Matter Experts, experts from ACRO and input from a Site Advisory Group conducted by SCRS.
- There are theoretical case studies presented to demonstrate context for the usefulness of the solutions. Specific examples and real-life case studies are not available. TransCelerate members will work to identify success stories and share externally when/if possible.
- Specific documentation or company processes (ICFs, EMR use, deviations) for audits, specific stakeholder impact, or regional impact/implementation was not in scope of this effort.
- Each company is responsible for its own ICH E6(R3) compliance, as well as compliance with any relevant laws or regulations.

Disclaimer

- The views presented are the views of the presenters, and not necessarily those of their employers, EFPIA, PhRMA or the EWG
- These slides are intended for discussion purposes only and for the personal use of the audience. These slides are not intended for wider distribution outside the intended purpose without approval of the presenters.
- The content of this slide deck is accurate to the best of the knowledge of the presenters at the time of production

ICH E6(R3) Executive Summary

David Nickerson, (EDM Serono) PhRMA Topic Lead ICH E6(R3)
Rebecca Stanbrook, (Novartis) EFPIA Topic Lead ICH E6(R3)

Topics

- Background to the GCP Renovation
- Structure of R3
- Scope of R3
- Points to consider

Good Clinical Practice – ICH E6 (R3)

Step 4

Step 4 document – to be implemented

ICH training library

6 January 2025

Good Clinical Practice – ICH E6 (R3)

Legal Notice

Background to the Renovation

ICH-E6(R3): Background to this Revision

E8 – integrating QbD into study design and conduct

↕

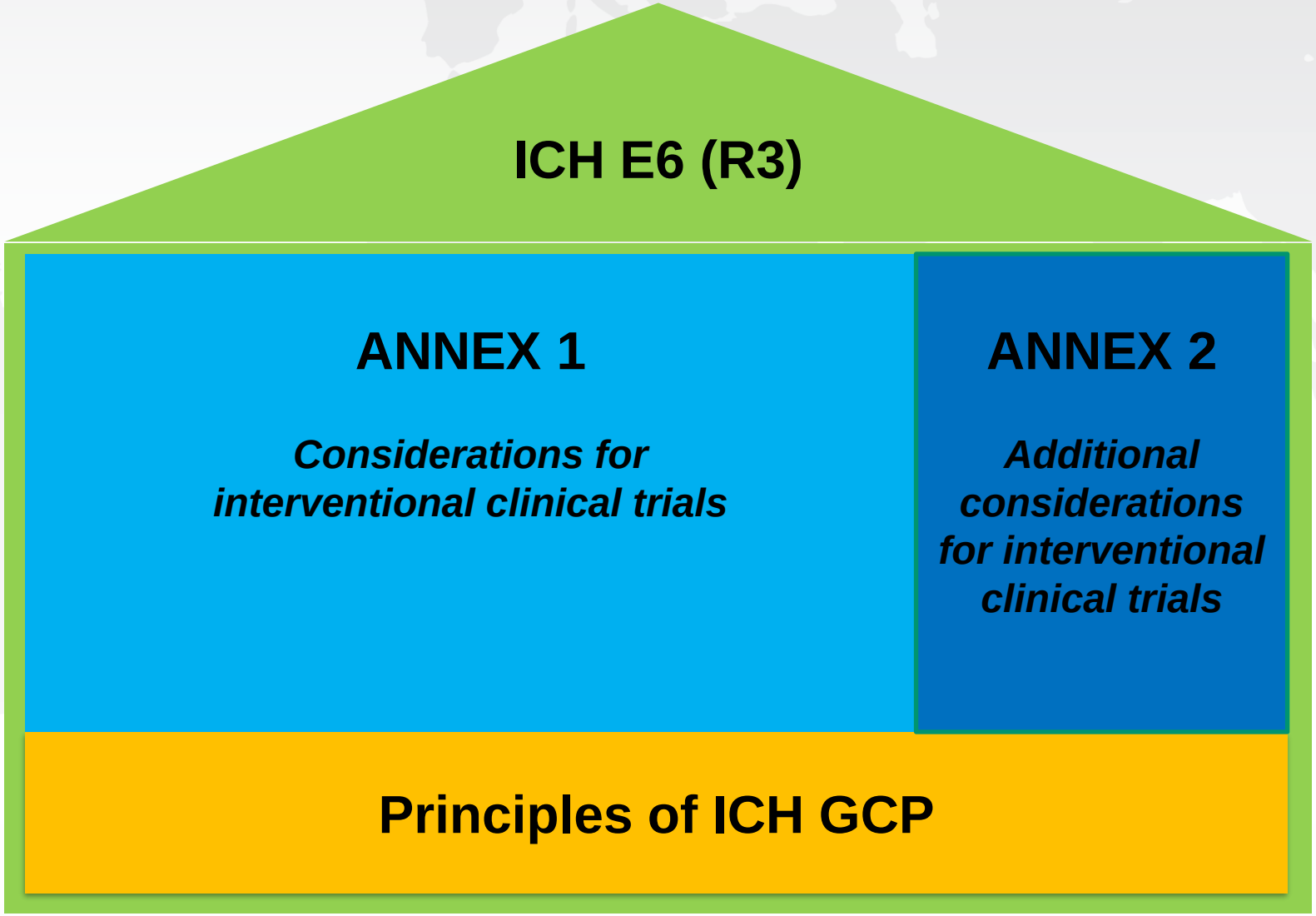
E6 – Applying the foundation of E8 to the conduct of clinical trials

Do not read E6(R3) in isolation

- **E6: Good Clinical Practice (GCP) – finalised in 1996**
  - Described the responsibilities of investigators and sponsors and expectations of interested parties in the conduct of clinical trials;
  - Covered aspects of monitoring, reporting, and archiving of clinical trials; and
  - Included sections for essential documents and investigator brochures
- **E6 (R2) – finalised in 2016**
  - Included integrated addendum to encourage implementation of improved and more efficient approaches to GCP, while continuing to ensure human subject protection; and
  - Updated standards for electronic records.
- **E6 (R3) – finalised in 2025**
  - Grounded in the foundational principle of Quality by Design (QbD)
  - Involves critical thinking
  - Utilises proportionate, risk-based approaches
  - Recognises that a one size does not fit all.

Structure of the Guideline

OVERVIEW OF ICH E6 (R3)



Revised Structure

E6(R3) Guideline

E6(R3) Principles and Annex 1 replacing E6(R2)

I. INTRODUCTION

II. PRINCIPLES OF ICH GCP

III. ANNEX 1

1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
2. Investigator
3. Sponsor
4. Data Governance – Investigator and Sponsor

APPENDICES

Appendix A. Investigator's Brochure
Appendix B. Clinical Trial Protocol and Protocol Amendment(s)
Appendix C. Essential Records for the Conduct of a Clinical Trial

GLOSSARY

ANNEX 2 – *under public consultation from November 2024 to March 2025*

Scope of the Document

Scope

- This guideline applies to interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities. The Principles of GCP in this guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorisation applications in accordance with local requirements.
- The Annexes provide the basis for the appropriate interpretation and application of the principles and should therefore be appropriately considered; however, various approaches to the provisions in the Annexes may be considered provided they are justified and achieve the intended purpose of the application of the principles.
- This guideline encourages a risk-based and proportionate approach to the conduct of a clinical trial.

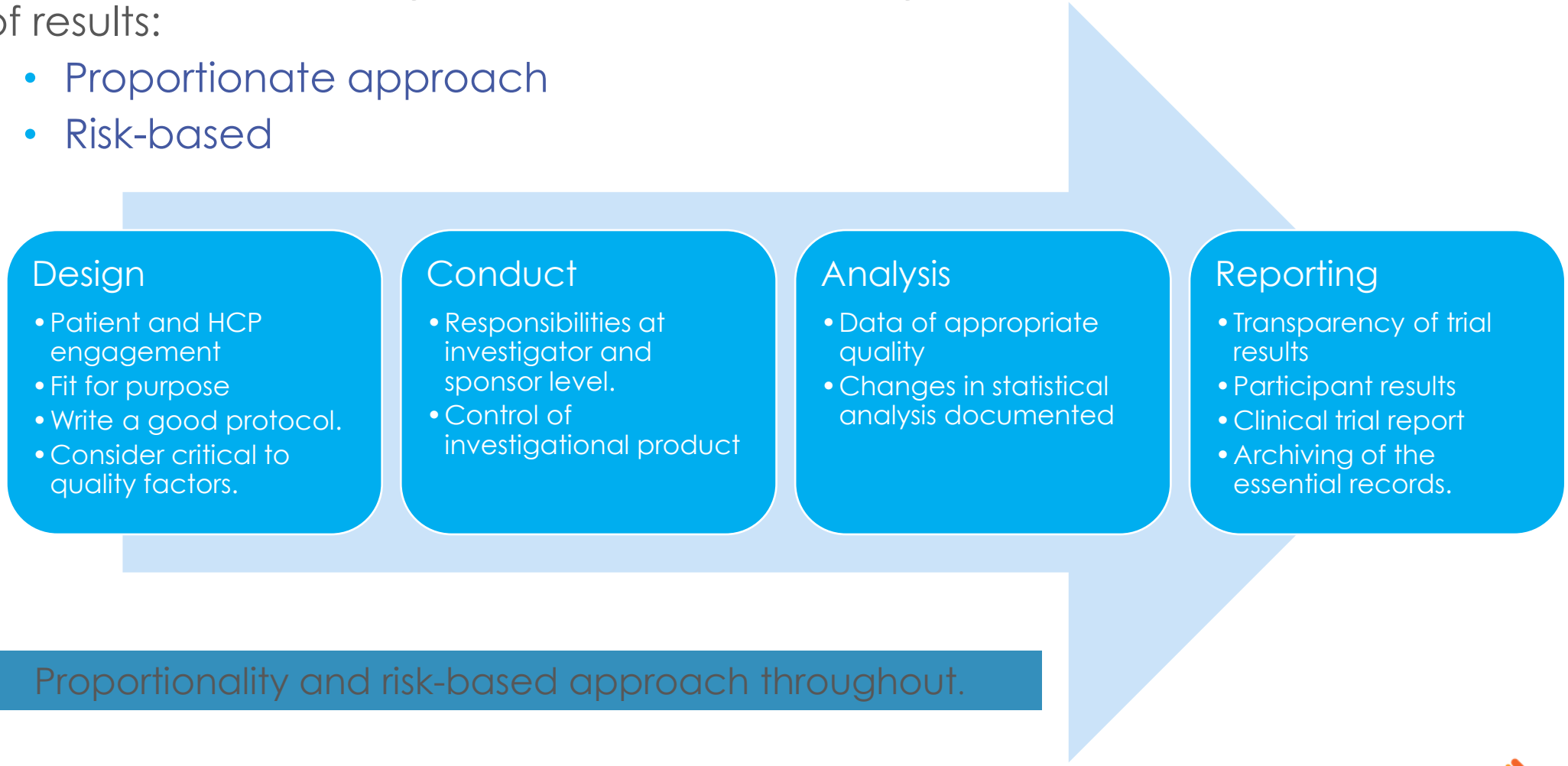
Innovation, Efficiency & Engagement

- Encouraging the exploration of technology:
  - The principles are intended to support efficient approaches to trial design and conduct. For example, innovative digital health technologies, such as wearables and sensors may expand the possible approaches to trial conduct.
  - Such technologies can be incorporated into existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials.
  - The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design.
- Encouraging engagement and inclusivity:
  - The use of innovative trial designs and technologies may enable the inclusion of a wider and more diverse population of participants and thereby broaden the applicability of trial outcomes.
  - The design and conduct of the clinical trial may be supported by obtaining the perspectives of interested parties, such as patients and their communities, patient advocacy groups and healthcare professionals. Their input can help to reduce unnecessary complexity, improve feasibility and increase the likelihood of meaningful trial outcomes.

Points to Consider

Points to consider

- Think – participant's rights safety and well-being and the reliability of results:
  - Proportionate approach
  - Risk-based

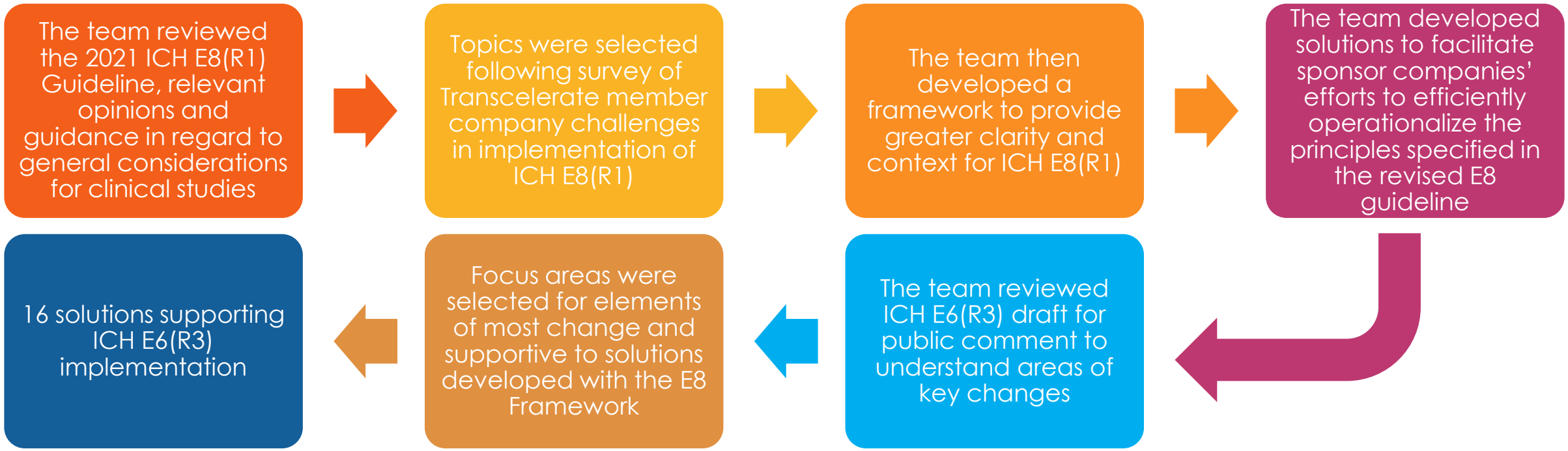


Importance of ICH E6(R3) and E8(R1) Working Together

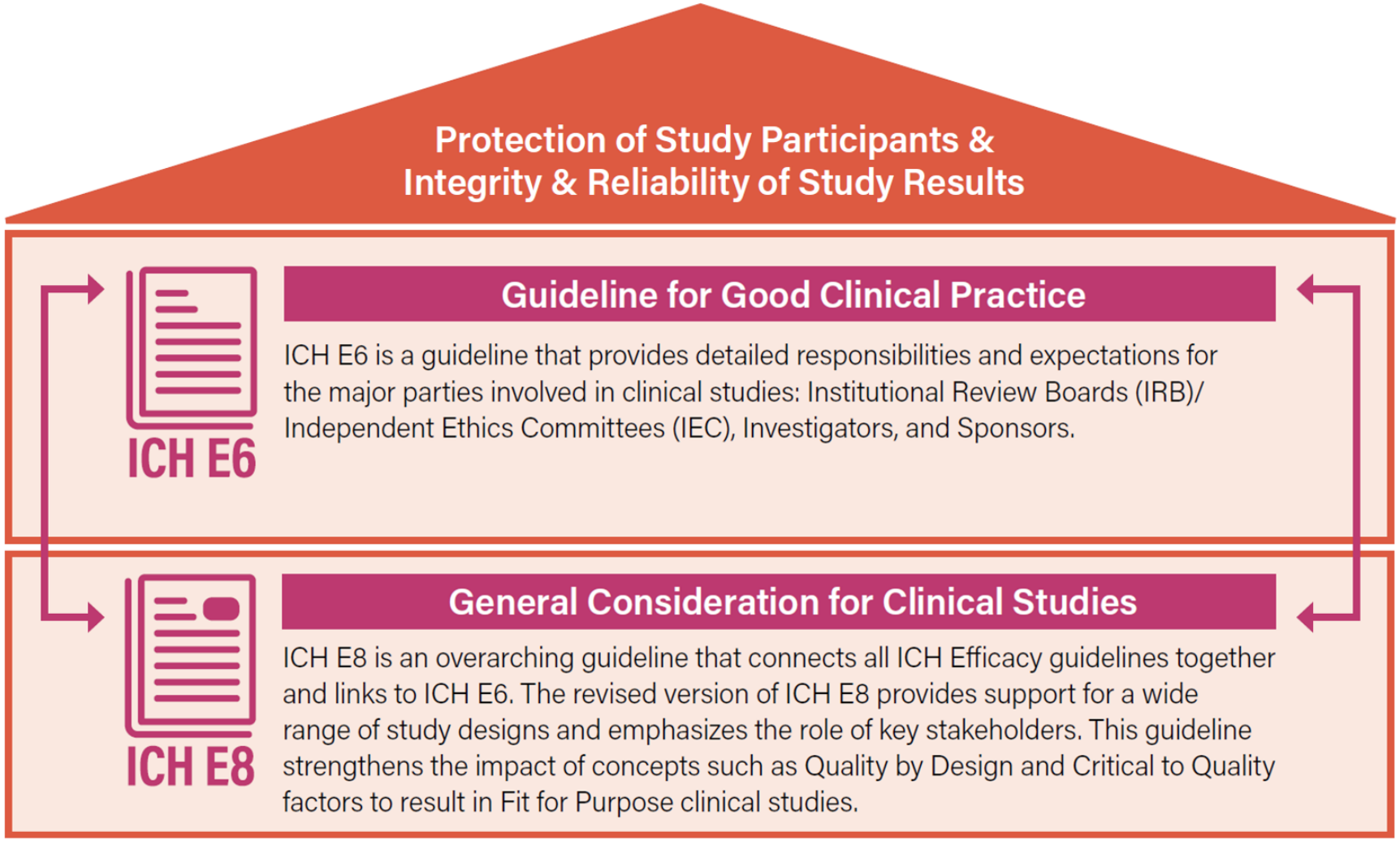
TransCelerate's Journey from ICH E8(R1) to E6(R3)

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been revising their Good Clinical Practice (GCP) Guidelines to provide updated guidance to address the increasing diversity of study types and data sources being employed to support regulatory and other health policy decisions. Sponsors of clinical studies face challenges in operationalizing these new guidelines.

The goal of the Interpretation of Clinical Guidance and Regulations (IGR Clinical) workstream has been working to provide solutions to give clarity on key concepts from ICH E8 (R1) and ICH E6(R3).



WHAT IS ICH E8?



Source: What You Need to Know About ICH E8 – Infographic

Source: What You Need to Know about ICH E8 (R1): Using TransCelerate's Tools to Help Interpret and Implement - YouTube

WHAT IS ICH E8?

- ICH E8(R1) is an overarching guideline that partners with ICH E6(R3) & connects other Efficacy guidelines
- ICH E8(R1) has been updated to reflect the increasing complexity of clinical study designs

- ICH E8(R1) provides guidance for a wide range of study designs and highlights the role of key stakeholders (e.g., Healthcare Professionals, Study Participants)
- ICH E8(R1) reinforces the concept of proactively building quality into the design of clinical studies. Strengthening components such as Quality by Design (QbD), and Critical to Quality Factors (CtQs)
- ICH E8(R1) aims to support clinical studies that are fit for purpose

Source: What You Need to Know About ICH E8 – Infographic

How the Guidelines Support Each Other

Overview: ICH E6(R3) and ICH E8(R1) are complementary guidelines that enhance the quality and efficiency of clinical trials.

- ICH E8(R1) provides general considerations for clinical studies, promoting Quality by Design (QbD) and identifying Critical to Quality (CtQ) factors
- ICH E6(R3) focuses on Good Clinical Practice (GCP), emphasizing a risk-proportionate approach and quality management throughout the clinical trial lifecycle.

Integration:

- Both documents advocate for robust processes to ensure data integrity and participant safety, with E6(R3) building on the principles set out in E8(R1).
- Both guidelines stress the importance of involving all stakeholders, including patients, in the trial design and execution.
- Together, they aim to make clinical trials more adaptable and efficient, accommodating ongoing innovations and technological advancements.

Together, ICH E6(R3) and ICH E8(R1) ensure clinical trials are well-designed, ethical, and produce reliable results for regulatory decisions and better patient outcomes.

Deeper Dive – What's new in ICH and the TransCelerate Tools

What's new about E6(R3) content?

- Encourage **fit-for-purpose** and **quality by design** approaches.
  - **Proportionality and risk-based** approaches with a focus on the clinical trial's critical-to-quality factors whose integrity is fundamental to safety of participants and the **reliability of trial results;**
  - Builds on key concepts outlined in ICH E8(R1), which includes **fostering a quality culture** and proactively designing quality into clinical trials and drug development planning, identifying **factors critical to trial quality**.

- **Language to facilitate innovations in clinical trial design, technology and operational approaches.**
  - Facilitate innovative clinical trial designs, for example, clinical trials utilizing Decentralised Clinical Trial (DCT) elements and pragmatic elements, reflecting trials that closely resemble routine clinical practice.
  - Facilitate the use of Digital Health Technologies (DHTs), healthcare infrastructure, and other tools to facilitate enrollment and retention, capture data, monitor, and to analyse results.
- **Set a foundation for practical/feasible expectations around the responsibilities of sponsor and investigator in a digital ecosystem.**

Source: ICH Step 2 Presentation 22MAY2023; ICH Step 4 Presentation 23JAN2025

TransCelerate ICH E6(R3) Solutions

Building on the foundation of the E8(R1) solutions

Solutions to 1) help interpretation of ambiguous areas of the ICH E6(R3) guidelines, and 2) aid industry in operationalization of ICH E6/E8.

ICH E6(R3) Focus Areas

- Risk Proportionality
- Monitoring (Sponsor Quality Management)
- Investigator
- Trial Design
- Risk Management (ACRO Co-developed)
- Data Governance (ACRO Co-developed)

ICH E8(R1) Solutions

- ICH E8 Landscape Assessment
- ICH E8 Infographic
- Stakeholder Engagement Tool
- Culture & Engagement Resource Pack
- CtQ Tool and Resources
- ICH E8 Case Studies
- ICH E8 Publication

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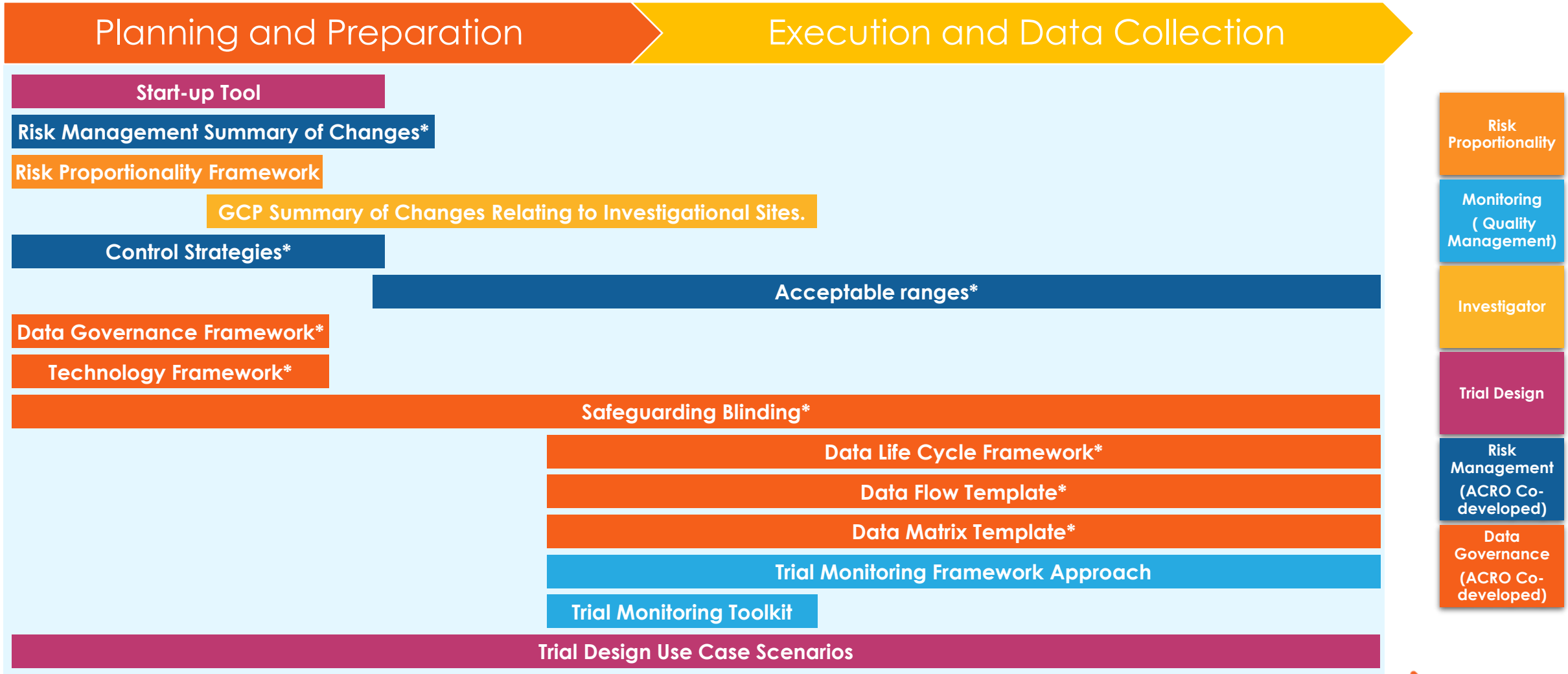
E6 Suite of Solutions



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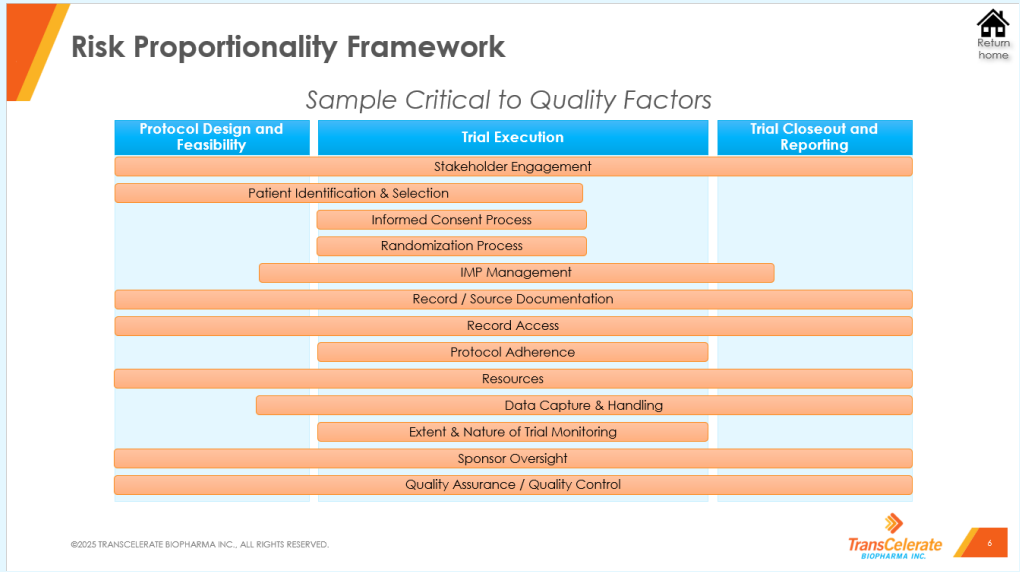
Risk Proportionality Framework

Toolkit Value

Interactive PowerPoint that provides examples of critical to quality factors and potential elements of a proportionate, risk-based approach as outlined in ICH E6(R3). This framework will **support industry in understanding a risk-based and proportionate approach** in the conduct of a clinical trial encouraged by ICH.



- **Risk Proportionality**
- Monitoring (Quality Management)
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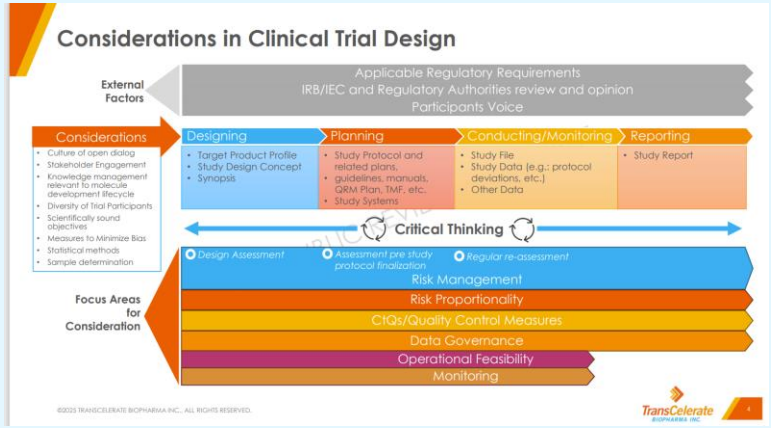
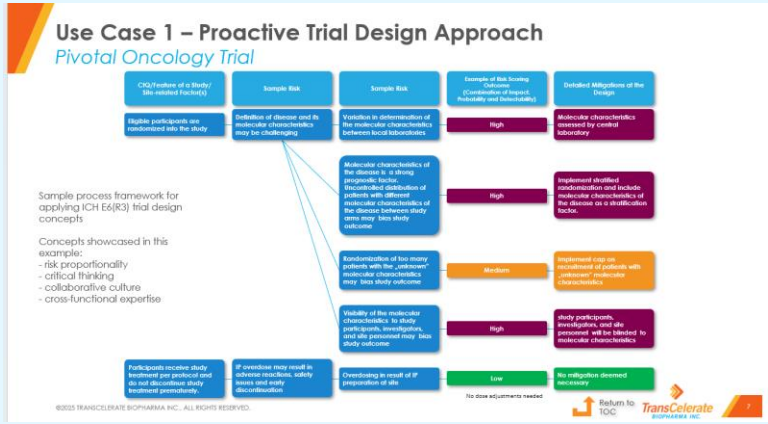
Trial Design Start-up Considerations Tool
(currently accepting public comment)

Toolkit Value

The Trial Design Starter Toolkit **fosters critical thinking** for robust and compliant trials aiding GCP stakeholders in management of ICH E6(R3) requirements by supporting **Quality by Design (QbD) and risk-based approaches**. It supports the transition to **a proactive quality culture**, guiding stakeholders through risk assessments and emphasizing early risk identification and mitigation.





Trial Design Use Case Scenarios

- Risk Proportionality
- Monitoring (Quality Management)
- Investigator
- **Trial Design**
- Risk Management (ACRO Co-developed)
- Data Governance (ACRO Co-developed)

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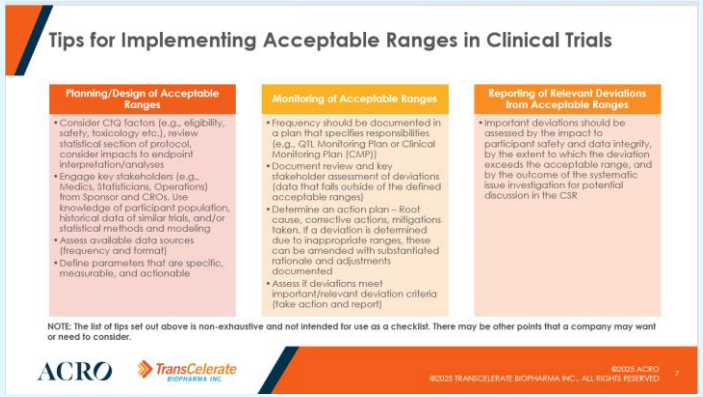
Risk Management Summary of Changes*

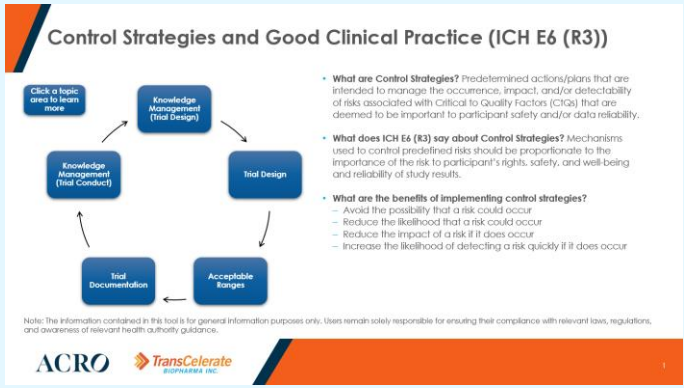
Control Strategies*

Acceptable ranges*

Toolkit Value

The toolkit aims to focus on assessing the state of control for important risks with the potential to significantly impact the critical to quality factors. The consideration tools, co-developed with ACRO, **supports the implementation of control strategies to ensure participant protection and enhance study reliability** in clinical trials. In ICH E6(R3), the **acceptable ranges** concept was established to **enable clinical trial innovation**.





- Risk Proportionality
- Monitoring (Quality Management)
- Investigator
- Trial Design
- **Risk Management (ACRO Co-developed)**
- Data Governance (ACRO Co-developed)

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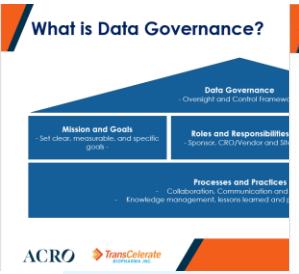

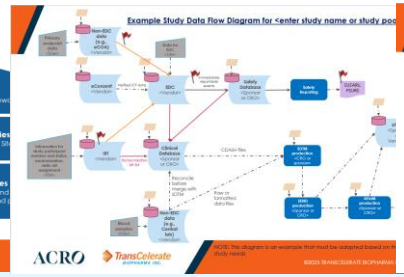

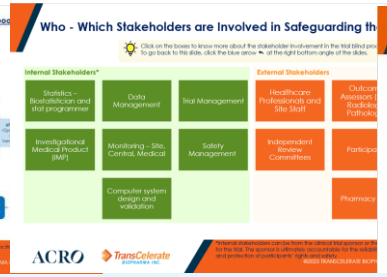

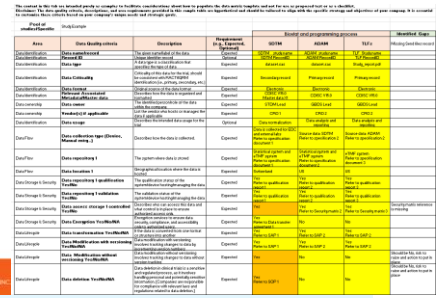

- **Data Governance Framework***
- **Technology Framework***
- **Safeguarding Blinding***
- **Data Life Cycle Framework*** **(currently accepting public comment)**
- **Data Flow Template***
- **Data Matrix Template***

Toolkit Value

These tools, developed jointly with ACRO, collectively seek to enhance data management in clinical research by improving clarity, coordination, and data quality. They provide frameworks and templates for data governance, data lifecycle management, safeguarding blinding, and utilizing computerized systems to adhere to requirements outlined in ICH E6(R3) **to support effective data handling and integrity throughout the study process**

- Risk Proportionality
- Monitoring (Quality Management)
- Investigator
- Trial Design
- Risk Management (ACRO Co-developed)
- **Data Governance (ACRO Co-developed)**

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Risk Proportionality

Monitoring (Quality Management)

Investigator

Trial Design

Risk Management (ACRO Co-developed)

Data Governance (ACRO Co-developed)

GCP Summary of Changes Relating to Investigational Sites

Toolkit Value

A collated summary of changes to Annex I Section II. The information may support in development of training materials on ICH GCP E6(R3) updates and **enhancing understanding of the changes to the investigator responsibilities section**.

Pillar	Topic	ICH E6(R3) Section (Annex I)	Prior Text in ICH E6(R2)	New or Updated Text	Summary of Change
Communications	IRB/IEC	2.4.1	4.4	New	It is now specifically stated that "submission to the IRB/IEC can be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements"
Communications	IRB/IEC	2.4.4	4.4.3	New	It is now specifically stated that "as the trial progresses, the investigator/institution or sponsor should provide any updates to the participant information to the IRB/EC in accordance to applicable regulatory requirements"
Communications	IRB/IEC	2.4.5	4.10.2	New	It is now specifically stated that "the investigator or the sponsor should submit documented summaries of the trial status to the IRB/IEC in accordance with local regulatory requirements or upon request."
Communications	IRB/IEC	2.4.6	4.10.2	New	It is now specifically stated that the "investigator or the sponsor should promptly communicate to the IRB/IEC and where applicable, the institution about any changes significantly affecting the conduct of the trial and/or increasing the risk to participants"
Communications	IRB/IEC	2.6.3	4.12.2	Updated	If the sponsor prematurely terminates or suspends the trial, the investigator or sponsor should promptly inform the IRB/IEC and regulatory authorities.
Communications	Medical Care of Participants	2.7.1 (d)	4.3.3	Updated	The investigator should inform the participants primary physician about the participants involvement in the trial if the participant agrees. Previously it was only recommended to inform.
Communications	Medical Care of Participants	2.9.3	4.3	New	New language that the investigator should inform the participant as per their preference of the trial results and treatment received (after blinding).
Communications	IRB/IEC	1.1	3	New	A new section has been added providing global guidance on communication with IRB/IEC and regulatory authorities.
General	Principles of ICH GCP	II	2	Updated	The thirteen principles of ICH E6 R2 have been reorganized into eleven more detailed principles, each including a main statement and accompanying sub-points.
Operations	Unblinding	2.11	4.7	Updated	A new requirement in unblinding: In the case of an emergency, to protect patient safety, the investigator should be prepared and capable from the start of the trial to perform unblinding.
Operations	Reporting	2.12.1	4.9	New	There is a new expectation that the Investigator should ensure data integrity when generating, recording and reporting trial data under their responsibility
Operations	Reporting	2.12.5	4.9.1	Updated	New language on the expectation for Investigators to review and endorse reported data at milestones agreed with the Sponsor. The investigator should ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools provided by the sponsor.

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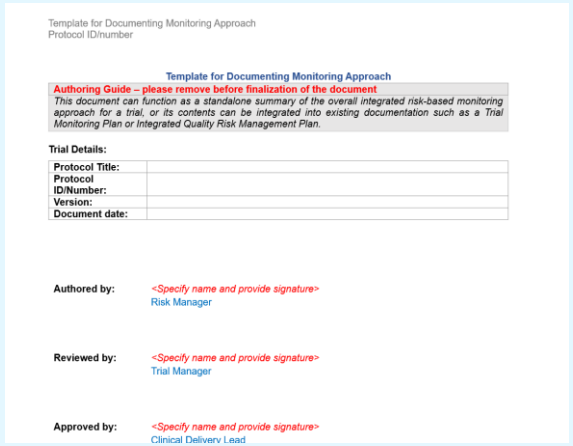

Template for Documenting Monitoring Approach
Protocol ID/number

Template for Documenting Monitoring Approach

Authoring Guide – please remove before finalization of the document

This document can function as a standalone summary of the overall integrated risk-based monitoring approach for a trial, or its contents can be integrated into existing documentation such as a Trial Monitoring Plan or Integrated Quality Risk Management Plan.

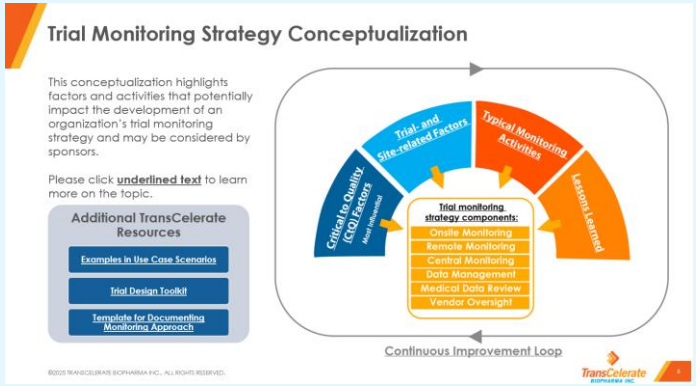
Trial Details:

Protocol Title:	
Protocol ID/Number:	
Version:	
Document date:	

Authored by: *<Specify name and provide signature>* Risk Manager

Reviewed by: *<Specify name and provide signature>* Trial Manager

Approved by: *<Specify name and provide signature>* Clinical Delivery Lead



Toolkit Value

The monitoring toolkit reflects the ICH E8(R1) and ICH E6(R3) principles and emphasizes tailoring a trial monitoring strategy to ensure participant safety and data reliability, and customization incorporating various activities and technologies in individual trials. The provided template helps sponsors document their risk-based monitoring approaches, **supporting the development of flexible and responsive strategies**.

Trial Monitoring Template Approach

Trial Monitoring Toolkit

- Risk Proportionality
- **Monitoring (Quality Management)**
- Investigator
- Trial Design
- Risk Management (ACRO Co-developed)
- Data Governance (ACRO Co-developed)

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Demonstration of Published Tools and Solutions

Use Case 1 - Proactive Trial Design Approach

Pivotal Oncology Trial

Trial Characteristic

- Indication: first-line metastatic cancer stage IV disease
- Key eligibility criteria:
  - Histologically confirmed metastatic cancer
  - Ability to provide adequate tissue sample,
  - Available central test results for biomarkers (tumor mutational status)
  - ECOG Performance status of 0 or 1
- Design details: a phase III, double-blind, multicenter trial
- Intervention: chemotherapy + placebo vs chemotherapy + investigational drug, treatment to be continued until objective progression
- Storage conditions: 2-8 °C, no dose adjustments needed
- Primary endpoint: Progression free survival (PFS) assessed by Blinded Independent Central Review (BICR) using imaging only
- Secondary endpoint – PFS assessed by Investigator, Overall survival
- Number of trial participants – 500 in the trial
- Global trial involving 14 countries and ~150 investigational sites
- Recruitment period: 1 ½ years
- Duration of trial: 3 years until primary read out, 5 years for final OS

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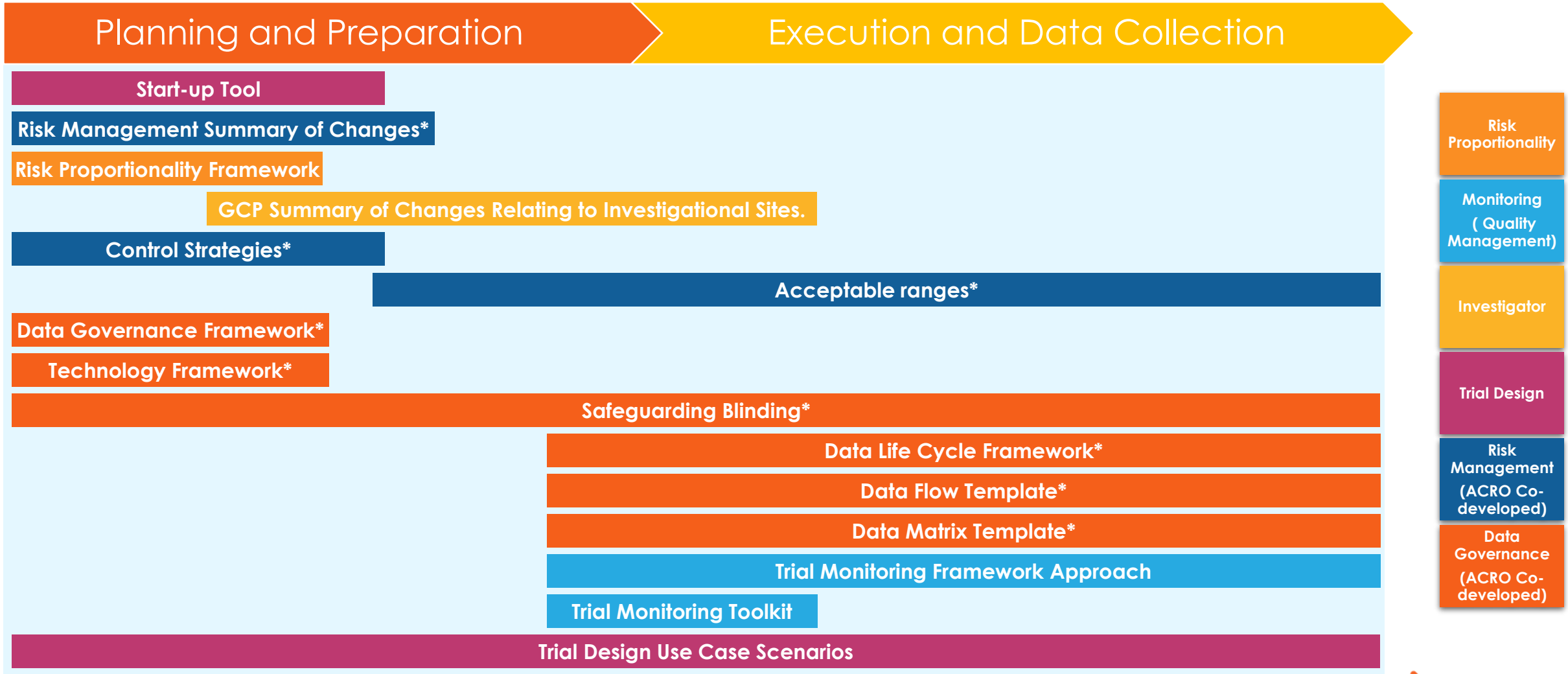
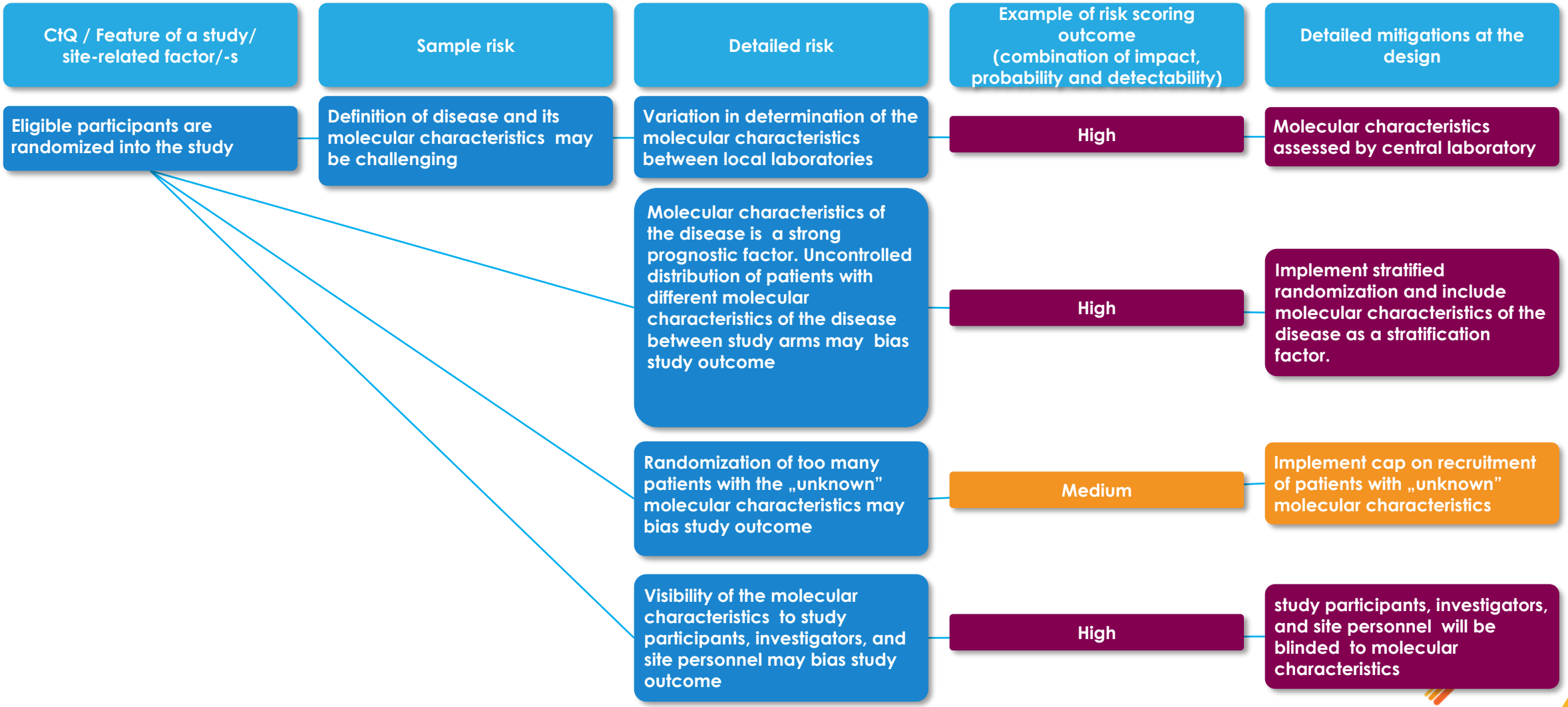


* = Co-developed with ACRO

CTQs in Action Use Case Example

Proactive Trial Design Approach of a Pivotal Oncology Trial



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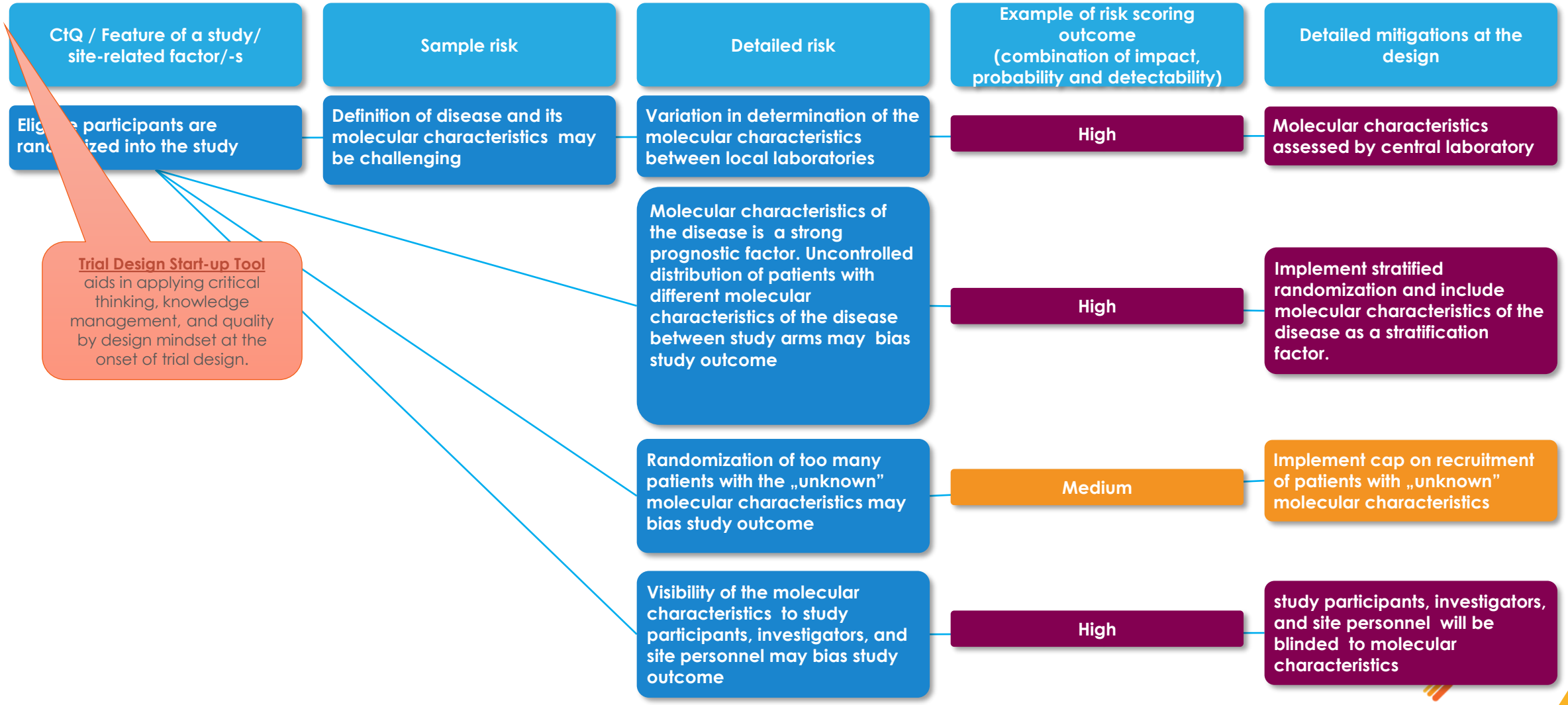

CTQs in Action Use Case Example

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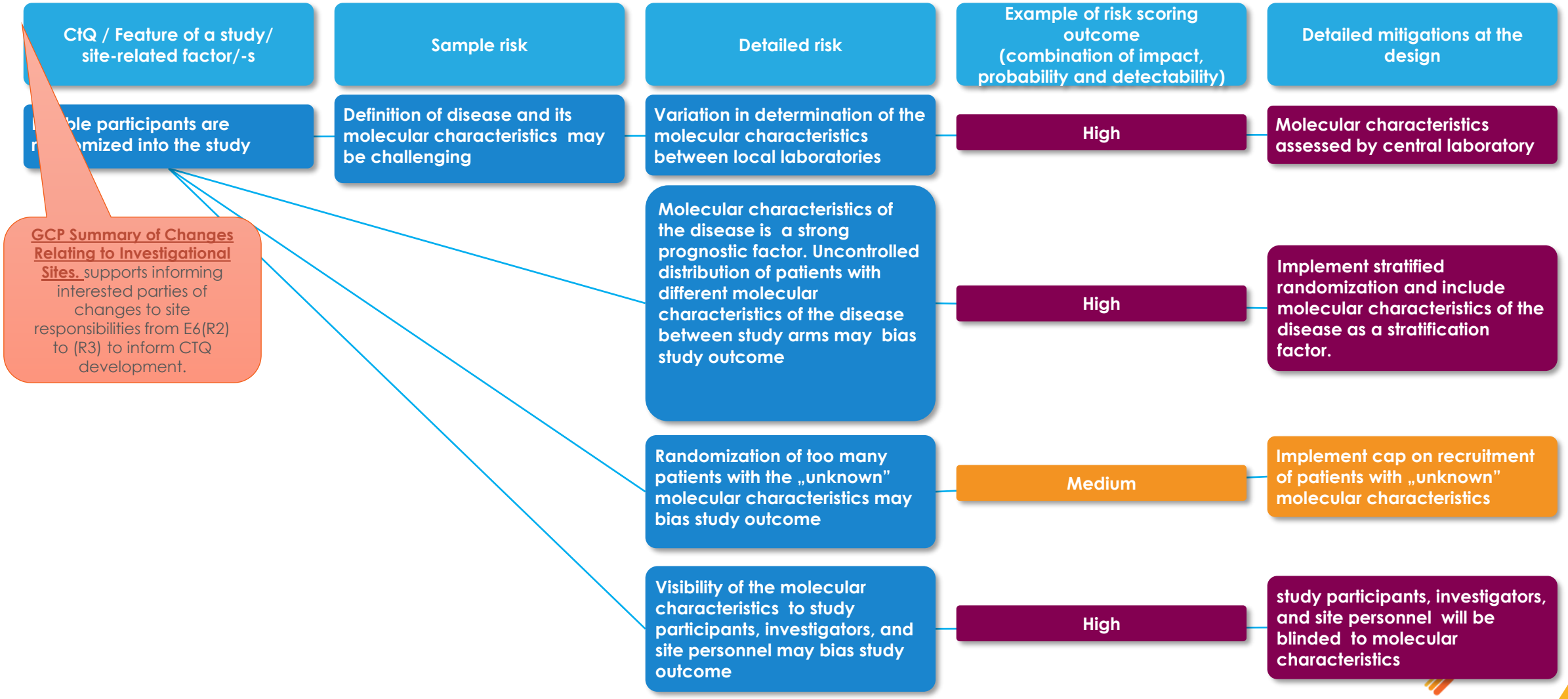

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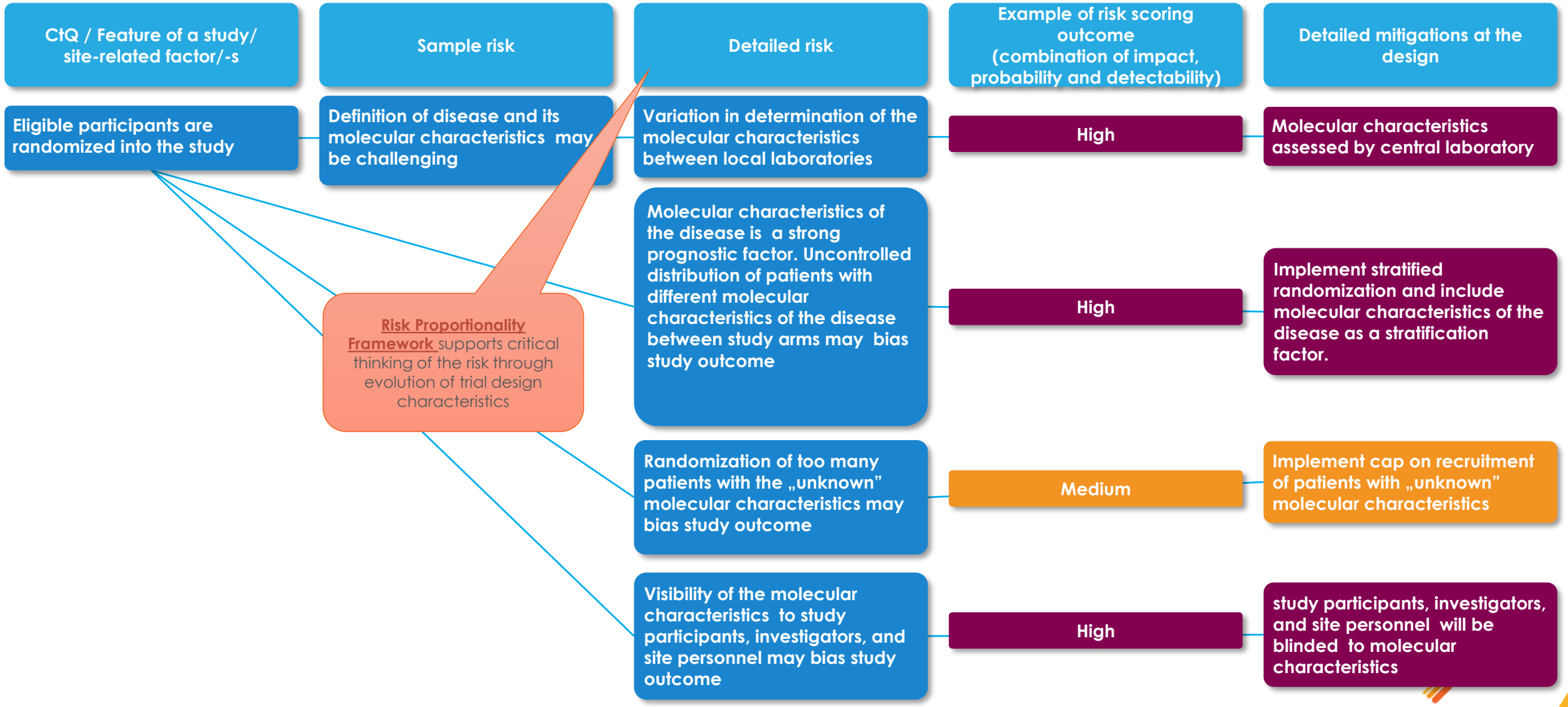
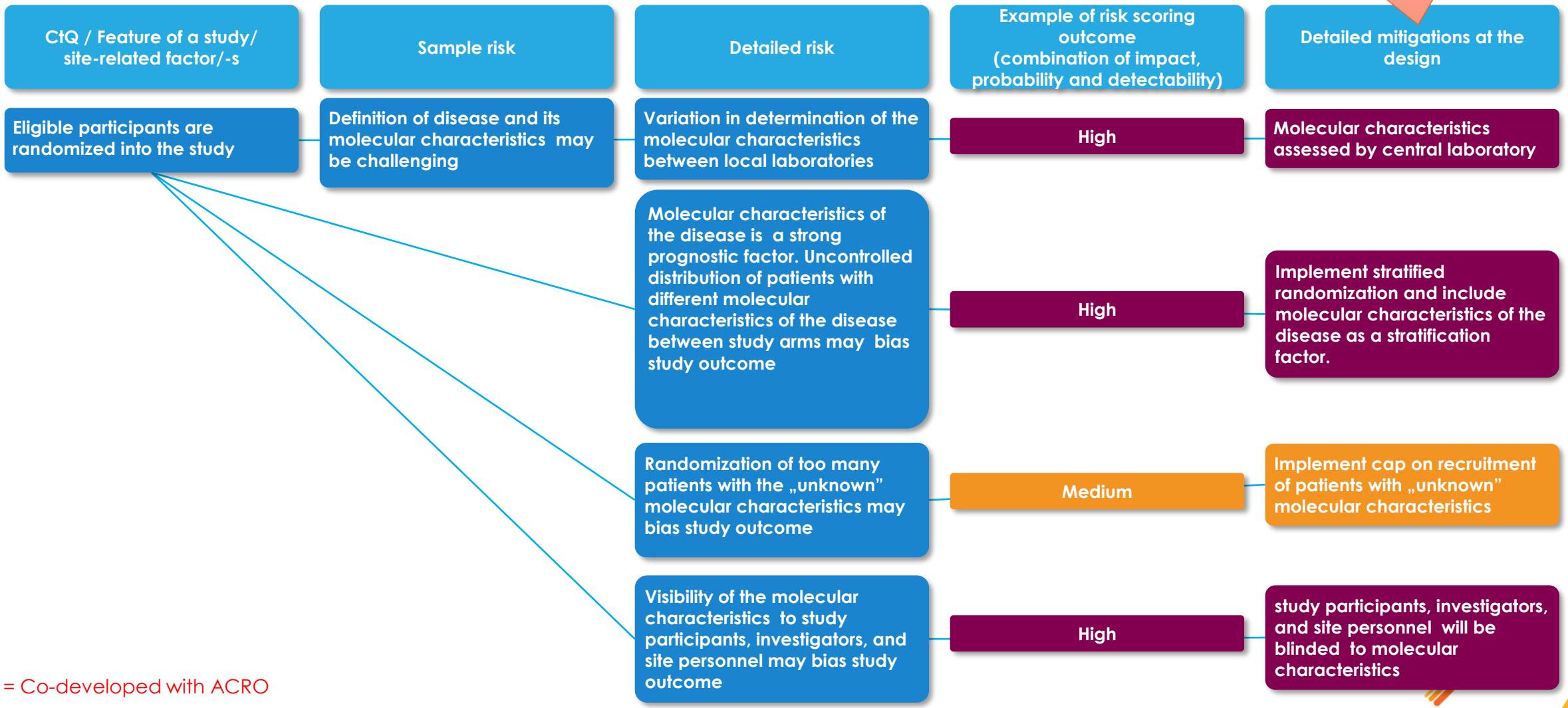


CTQs in Action Use Case Example

Proactive Trial Design Approach of a Pivotal Oncology Trial

Control Strategies Tool* supports critical thinking to predefine appropriate mitigations to risk associated to CtQs



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CTQs in Action Use Case Example

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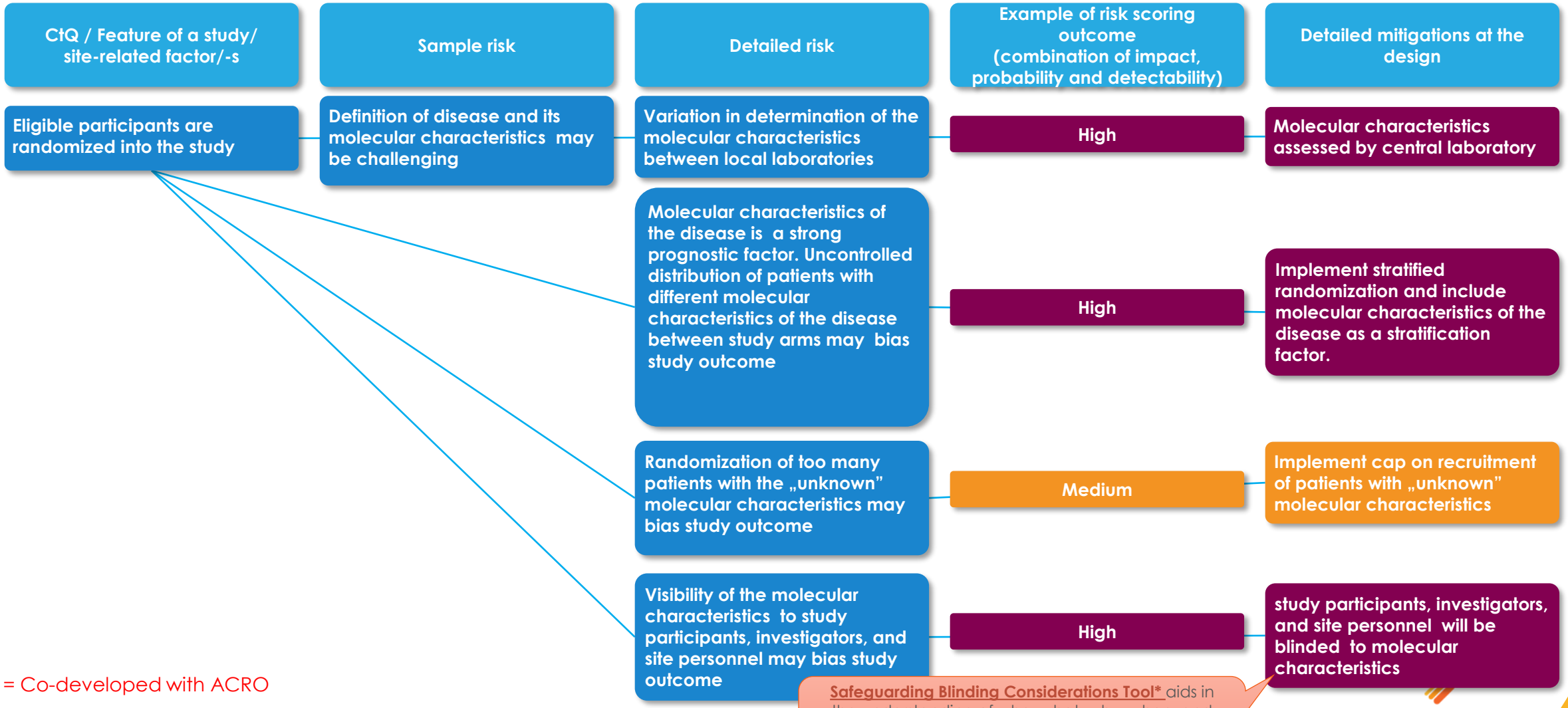

Safeguarding Blinding Considerations Tool* aids in the understanding of who, what, why, when, and how to safeguard the study blind from start-up to reporting

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Hypothetical Use Case for Monitoring Components & Activities

Potential Options in a Pivotal Oncology Trial

CtQ / Feature of a trial-/ site-related factor	Feature: Location of primary endpoint data	CtQ: Tumor assessment data is complete, consistent and of quality allowing for robust PFS	CtQ: Tumor assessment data is complete, consistent and of quality allowing for robust PFS
Monitoring strategy component	Onsite monitoring	Remote monitoring	Central monitoring
Activity	Source Data Verification (SDV)	Review of critical data	Review of data visualization
Potential Consideration	No SDV of efficacy data	To include: follow up for PFS with a focus on continuation of scans until BICR-confirmed progression, BICR process compliance and BICR issue resolution	Review of aggregated data/visualization showing sites/countries having patients at risk of premature PFS censoring, i.e., patients w/o baseline scan, patients with baseline scan who: 1) missed two consecutive follow-up scans, 2) initiated subsequent anticancer therapy prior to progression, 3) terminated from the trial before progression due to any reason apart from death Complemented with a QTL to monitor trial level
Rationale	Critical data (primary endpoint data) is not collected in eCRF	Continuation of scans and timely transfers needed to avoid PFS censoring.	To support primary endpoint data

Hypothetical Use Case for Monitoring Components & Activities

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Data Governance Framework* provides some possible approaches for compliance with ICH E6(R3) new data governance section.

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Hypothetical Use Case for Monitoring Components & Activities

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Technology Framework*
Outlines Computerized Systems requirements of ICH E6(R3) and supports the understanding of the roles and responsibilities of those involved.

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Hypothetical Use Case for Monitoring Components & Activities

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Study Data Flow template* supports the creation of data flow diagrams that maps clinical trial data from its capture, review, finalization and archiving.

Data Matrix Template* supports the creation of holistic overview on study data provenance/ collection method, data transformation, reviews techniques. It can help to detect potential risk and to implement mitigations actions

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Hypothetical Use Case for Monitoring Components & Activities

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Acceptable Ranges Tool* dives into the introduction of acceptable ranges and comparison to E6(R2), implementation, and potential use case.

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Interpretation of Guidances & Regulations Clinical: ICH E6/E8

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Question & Answer

We want to hear from you?

Thank you!

Contact Us!

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Link to ICH E8 Tools