# Navigating the Transition from ISO 14155:2020 to ISO 14155:2025

## Changes and Challenges

# Agenda

- ISO 14155 Implementation & Timelines

- Risk Management in Clinical Investigations

- Suspension and Termination of Clinical Investigations

- ICH E9 (R1) – Estimand Framework in the Context of ISO 14155

- Summary: Transitioning to ISO 14155:2025

# IMPLEMENTATION TIMELINES

**1993**

EN 540: First harmonised guidance for device investigations in the EU

**1996**

ISO 14155:1996: Transfer of EN 540 principles to ISO platform

**2003**

ISO 14155-1 / -2:2003: Detailed trial planning and documentation

**2011**

ISO 14155:2011: Alignment with ICH GCP and global regulations

**2020**

ISO 14155:2020: Harmonisation with EU MDR/IVDR and FDA

**2025**

ISO 14155:2025: Future adaptation to MDR and global trends

## Implementation – next steps

- Final draft registered for formal approval since March 24th, 2025
  - Expected to come into effect in 2025, with transition periods applying

# RISK MANAGEMENT

## Device & Procedure

- Additional clarity around risk assessment of the **medical device** & **study-related procedures**
  - Only procedures **beyond clinical standard** need to be considered (Section 6.2.1)
  - **Risk acceptability thresholds** to be estimated based on the expected incidence of harm
  - Risk management for the clinical investigation **differs from ISO 14971**
  - Risks also to be evaluated for **required procedures** (Section 7.4.5)

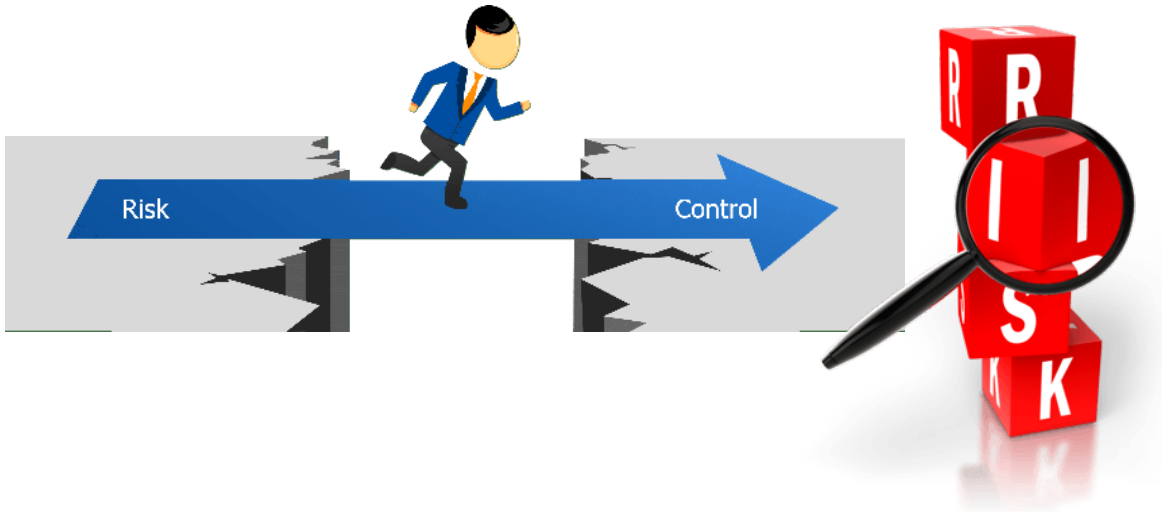
> […] a clinical investigation of an investigational medical device requires that the **residual risk(s) related to its use**, as identified in the risk analysis, as well as risk(s) to the subject associated with the **clinical procedure** required by the CIP **that are additional to normal clinical practice** […] be balanced against the anticipated benefits to the subjects.

ISO 14155:2025 – Section 6.2.1

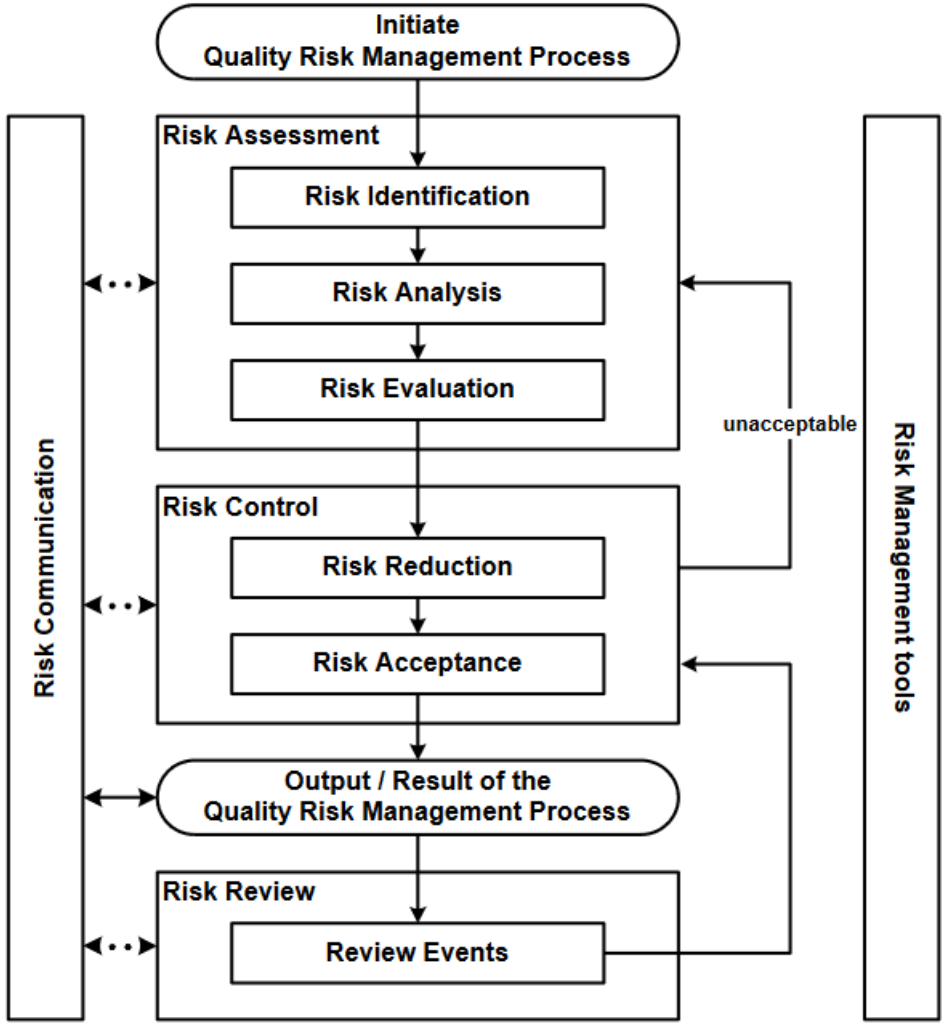
# RISK MANAGEMENT

## RISK MANAGEMENT PROCESS

- Identify critical **processes**/**data**
- Identify **risks** to these processes/data
- Evaluate risk based on **likelihood**, **impact** and **detectability**
- **Control** or **accept** risks
- **Communicate** risks and **review** continually
- Update risk review **periodically**
- Report deviation from **tolerance limits**

# RISK MANAGEMENT

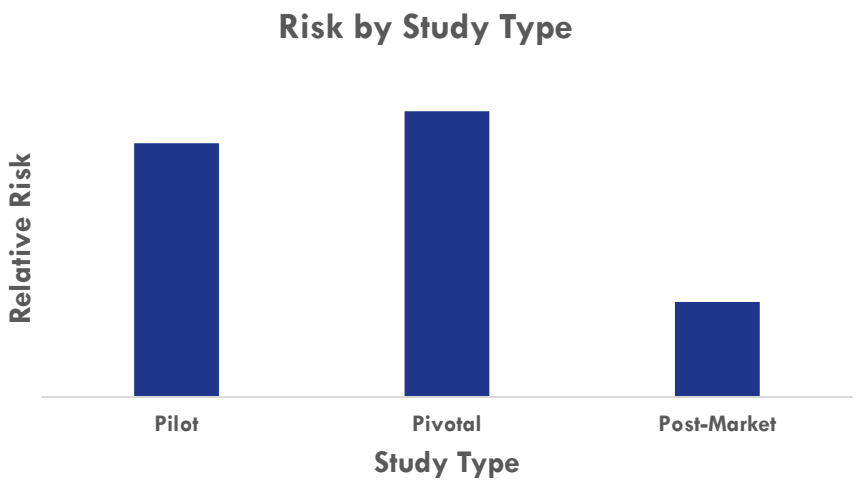


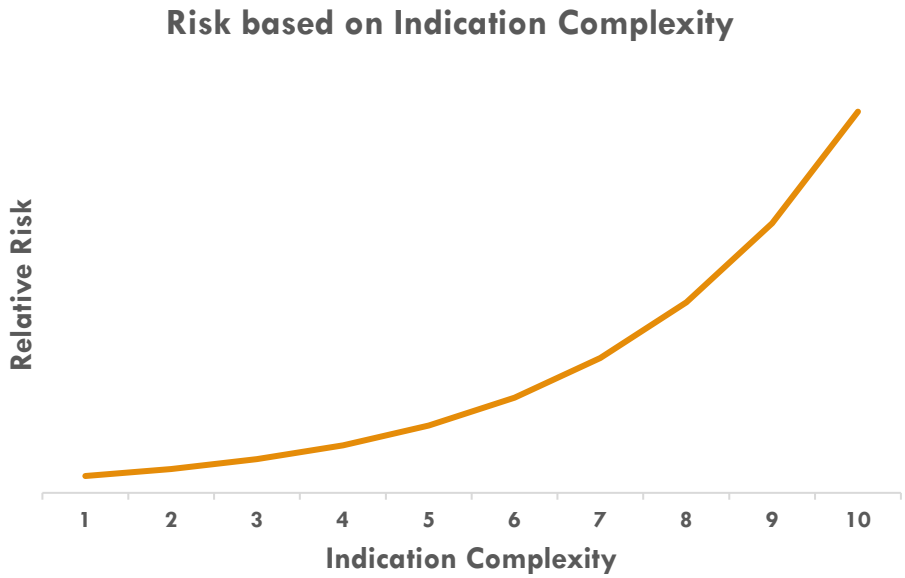

ICH Q9 – Quality Risk Management

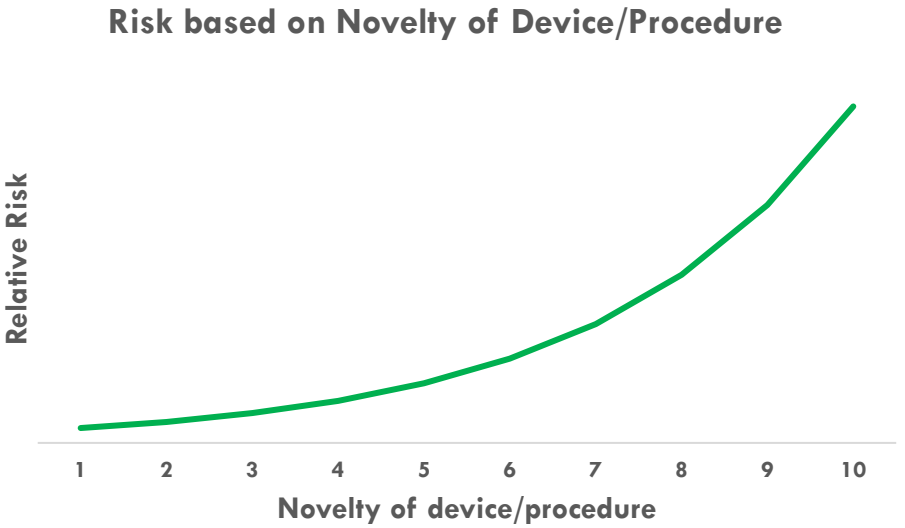
# RISK MANAGEMENT

The **level of** effort, formality and documentation of the quality risk management **process** should be **commensurate** with the **level of risk**.

**Risk-Based Approach**



# RBQM DOCUMENTATION

| | RACT version | <enter RACT version number> | <enter RACT version date> | | | | | Overall Risk Level: | #N/A | #N/A | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Category Number | Category | Objective | Questions for Discussion | Considerations | Impact 3 point scale (blue line = category | Probability 3 point scale (blue line = category | Detectability 3 point scale (blue line = category | Total Category Risk Score | Category Weighting 0.1 - 1.0 (summary | Program/protocol risk | Rationale for category risk level assessment | Functional Plan(s) Impacted | Examples for considering high risk | Examples for considering medium risk | Examples for considering low risk | Mitigation/Comments - possible examples are given in the tab |
| **1** | **Safety** | **Determine any known risks for subject safety** | **If your company has standard processes for determination of potential or identified safety risks, then this can serve as input to the overall risk category** | | | | | **#N/A** | **1.00** | | | | | | | |
| 1.1 | Safety | | Per the Medial Surveillance Team (MST) Chair with Medical Leader confirm what is the safety risk to the subject? | Identified risks from the Medical Surveillance Team which have predetermined rules for determining safety risk with confirmation from the Medical Leader | | | | #N/A | | | | | Identified risks per MST | Potential risks per MST | no potential or identified risks | |
| 1.2 | Safety | | Is the compound a marketed product? | | | | | #N/A | | | | | The compound is not a marketed product | The compound is a marketed product but is being studied in an unapproved indication | The compound is a marketed product and is being studied in an approved indication | |
| 1.3 | Safety | | Is the risk greater than or less than the Standard of Care(SOC)? | | | | | #N/A | | | | | Markedly higher than the risk of SoC – Trials involving IP not authorized by local regulatory authority (a grading lower than HIGH may be justified if there is extensive class data or pre-clinical and clinical | Somewhat higher than the risk of SoC – authorized by local regulatory authority, but using for new indication, studying substantial dosing modifications, or use in combinations where interactions are suspected | No higher than the risk of SoC - using authorized (local regulatory authority) range of indication, dosage and form, or off-label use that is established in practice and supported by published evidence | |
| 1.4 | Safety | | Is this compound/class known to have any serious side effects/toxicity? Have events of special interest been identified? | Consider any protocol-specific reporting requirements for (S)AEs and endpoints | | | | #N/A | | | | | Yes more than X? | Between X and Y | Less than Y | |
| 1.5 | Safety | | Are there any specific Health Authority (HA) requirements/ commitments? | e.g. Special Protocol Assessment, Post Marketing Requirement | | | | #N/A | | | | | Incorrect application of feedback | Timelines and protocol are taking specific HA requirements/commitments into account | There are no specific HA requirements/commitments | |
| 1.6 | Safety | | Is the compound known to have any significant interactions with other medications? | | | | | #N/A | | | | | Interaction may cause SAES | Interactions are related to Cytochrome P450 induction or inhibition | No drug-drug interactions have been identified | |
| **2** | **Study Phase** | **Factor the risks inherent in the study** | | | | | | **#N/A** | **1.00** | | | | | | | |
| 2.1 | Study Phase | | Does the Phase of the trial increase the risk? | A small sample size (Phase 1) means a lower acceptable error rate | | | | #N/A | | | | | Phase IIA | Phase IIB-IIIB | Phase IV | |
| 2.2 | Study Phase | | Is this a pivotal trial? | | | | | #N/A | | | | | Original application for marketing authorization | Supplemental/new indication for an approved product requiring a Phase III | Supplemental application not requiring a Phase III clinical trial (e.g., post marketing commitment) | |

TransCelerate Risk Assessment Categorization Tool

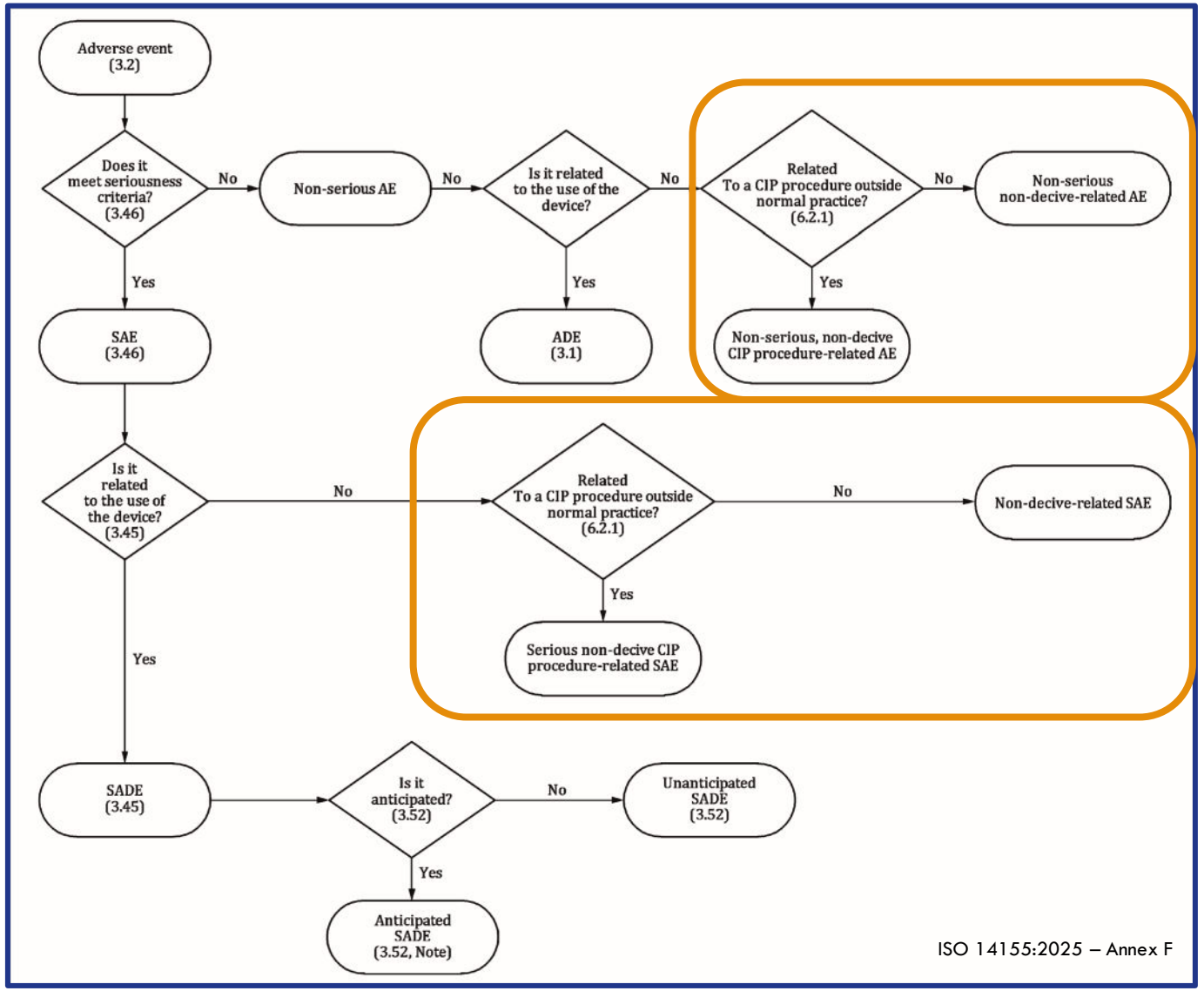
# RBQM DOCUMENTATION

| Key Risk | Key Risk Indicator | KRI Information Source | Imp. | Likeli. | Detect. | Lower Limit | Upper Limit | Limit Calculation | Comment |
|---|---|---|---|---|---|---|---|---|---|
| **4.1.1 High number of delayed SAE reports leading to risk for patient safety** | Number of delayed SAE reports | Date of knowledge of SAE and date of SAE entry in EDC system | 4 | 2 | 2 | 5% | 10% | (Number of delayed SAE reports at study site) / (Number of SAEs at study site)*100% | SAEs are considered delayed if they have not been reported within 24 hours of awareness. |
| **4.1.2 High frequency of eye-related adverse events indicating systematic issues** | Number of eye-related AEs | AE eCRF in EDC system | 4 | 3 | 1 | 1 | 3 | ((Number of eye-related AEs at study site) / (Number of patients at study site)) | |
| **4.1.3 High frequency of intraoperative events indicating systematic issues** | Number of intra-operative events | intraoperative complications eCRF in EDC system | 3 | 3 | 1 | 25% | 50% | ((Number of patients with at least 1 intraoperative event at study site) / (Number of patients at study site)) *100% | |

# ADVERSE EVENT REPORTING

## AE Reporting & Assessment Requirements

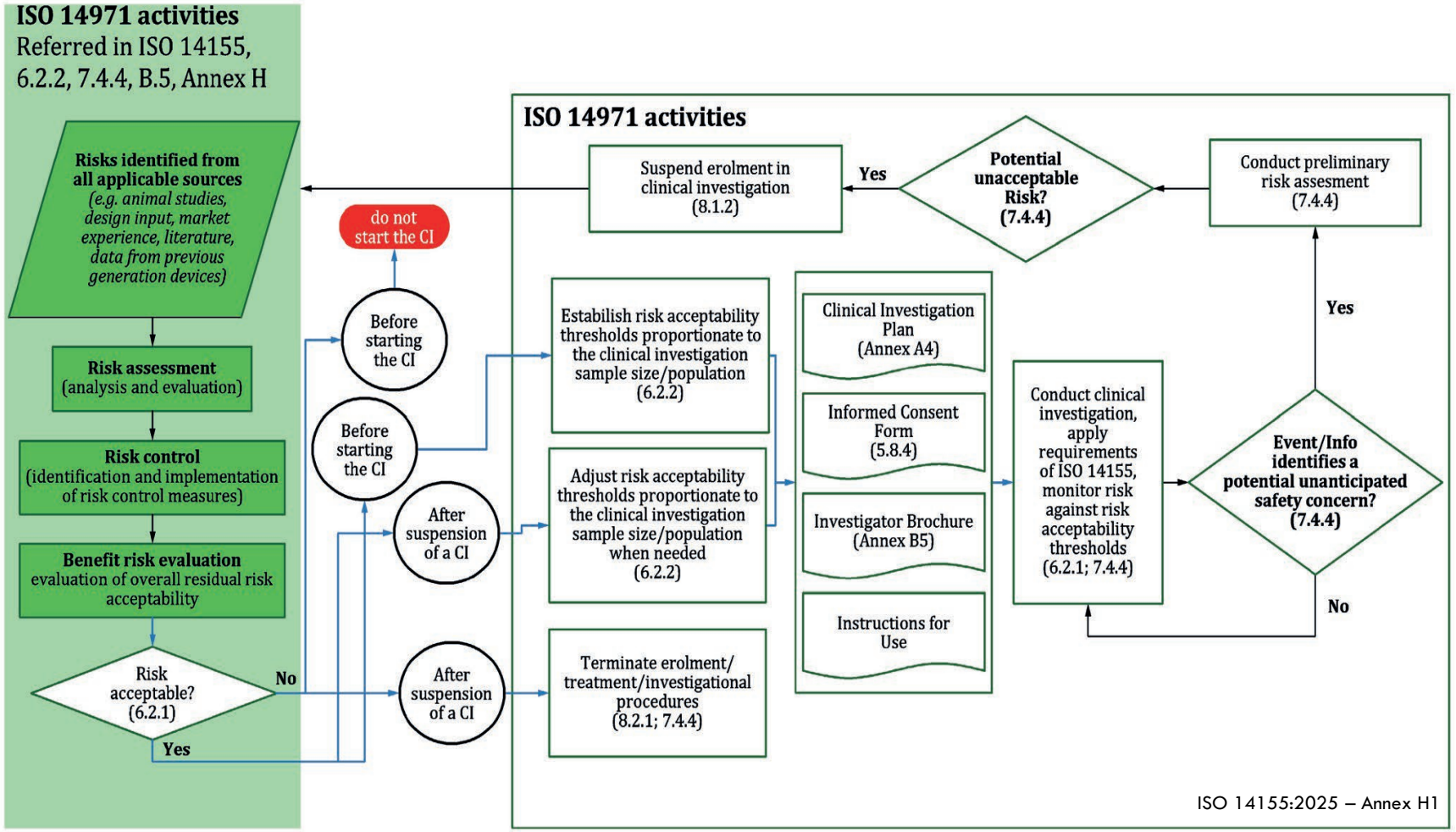
- **Update risk assessment** in case safety profile **deviates from expectation** (Section 7.4.4)
- AE assessment overview updated (Annex F)
- Opportunity for **reduced AE recording and reporting** (Section 7.4.2)
  - Rationale to be provided within the CIP



# TERMINATION & SUSPENSION

## Termination & Suspension

- Clear distinction and flow-chart
  - Connected to Risk assessment and observation (thresholds)
- Consider input from independent committees
  - **DMC** responsibility extended to termination & suspension decisions
  - Consider if CEC (**new – Section 6.12**) input impacts benefit assessment



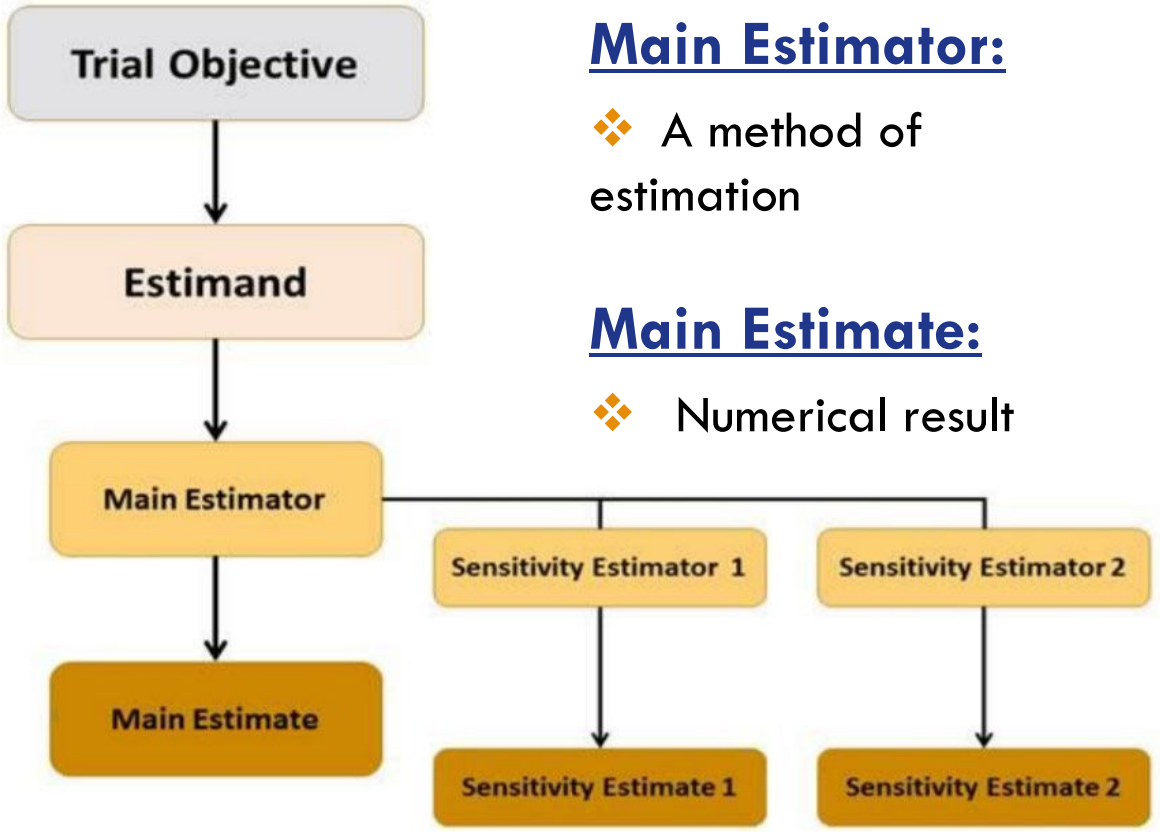
# STATISTICAL CONCEPTS ISO 14155:2025

## Expansion of statistical requirements

- **Performance** now strongly tied to **clinical benefit** (Section 3.12)
- Non-inferiority margins need to be **clinically justified** (Section A.7)
  - Must be **smaller than effect size**
- Justification for methods to adjust for **missingness**
  - Address **bias** from **imputation** (Section A.7)

## Standardizing Statistical Descriptions

- Call for utilization of the **Estimand framework** (ICH E9 (R1); Section A.7 and Annex K.2)
  - Includes the description of **intercurrent events** and their proposed analysis




## Estimand:

- What is to be estimated?

## Main Estimator:

- A method of estimation

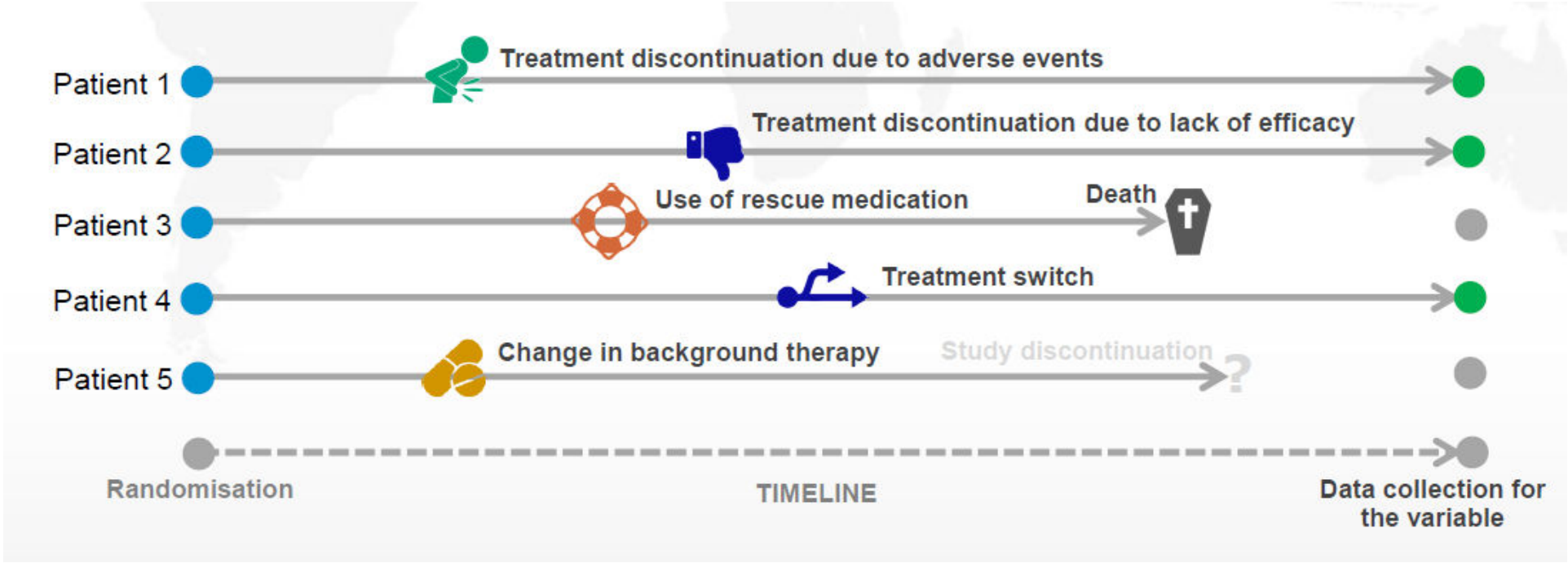
## Main Estimate:

- Numerical result

# ESTIMANDS & INTERCURRENT EVENTS

"Events occurring after treatment initiation that affect either the **interpretation** or the **existence** of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to **precisely define the treatment effect** that is to be estimated."

(p.19, Glossary ICH E9 (R1), Intercurrent events)




EMA/CHMP/ICH/436221/2017

# PREPARING FOR ISO 14155:2025

## How to prepare for the ISO update?

- Understand that **ISO 14155 and ICH GCP** get more and more **similar**
- **Perform gap analysis**
  - Many of the changes are **insignificant** – reinforce existing requirements
  - Still, many companies have **not adequately implemented ISO 14155:2020**
- Use chance to **streamline** and create opportunity to **simplify**
  - Risk-based quality management strongly encouraged

# You have questions around the conduct of clinical investigations and the impact of ISO 14155?

## We are here to help!

❖ **Connect after the event!**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❖ **Meet us later!**

**Booth #21!**