ICH E6 R3 Updates for the Reference Model

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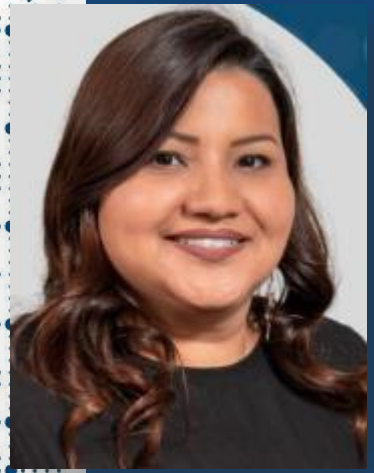
Meet the Speakers

Dawn Niccum

Title: Executive Vice President, Quality Assurance

Organization: inSeption Group

Insert your short bio here as text in sentence form or use notes space below and delete this text.



Jennifer Escobar, MS

Title: Director, Clinical Operations

Organization: Alkeus Pharmaceuticals

Clinical Operations professional with 18+ years of experience leading global, multi-phase clinical development programs, with expertise in project planning, execution, and implementation. For the past 6 years, role has focused heavily on TMF management and oversight.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

1. ICH E6(R3) Guidance and the TMF Reference Model
2. Project Background
3. Purpose & Key Priorities
4. Process & Examples
5. Outputs of Exercise
6. Discussion

Audience Poll

Have you read ICH E6 R3?

a) Yes, completely

b) Yes, only Appendix C

c) Yes, skimmed it

d) Yes, opened it

e) No, haven't had time

f) What is E6 R3?

Background

ICH E6(R3) “Good Clinical Practice” Guideline was released on 6-Jan-2025

- EU (EMA) adopted R3 in July 2025
  - Annex 1 + principles adopted; Annex 2 still under consultation
- FDA published R3 guidance in Sep 2025
  - No official implementation date set yet

To prepare for the impact of E6(R3) on the TMF Reference Model, a team of global GCP experts was convened to expand the model and ensure industry alignment on inspection readiness and TMF expectations in line with the updated guidance.

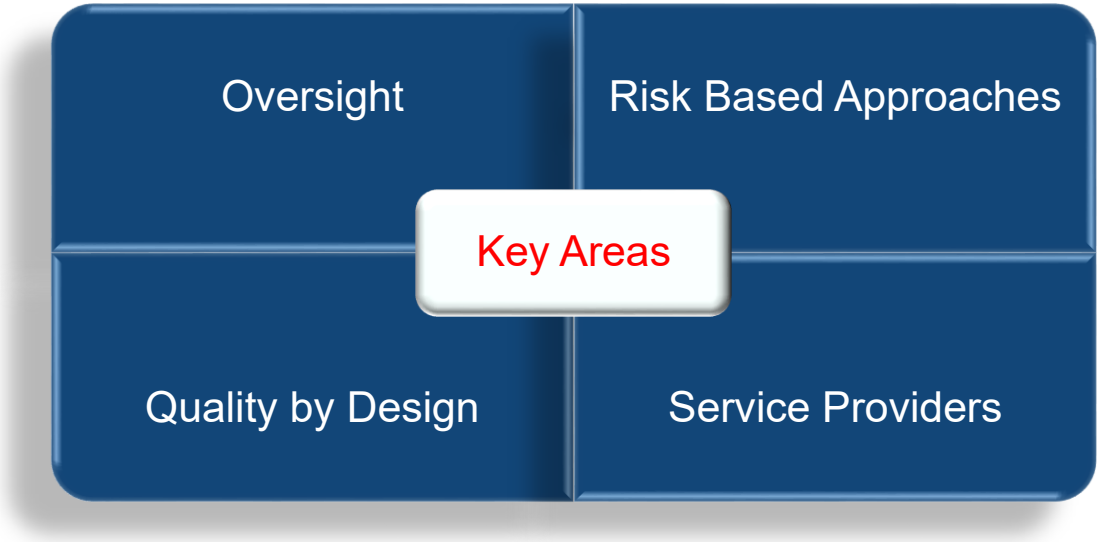
Purpose

This group's efforts focused on adapting the TMF Reference Model to E6(R3), with four key objectives:

Align the TMF Structure with E6(R3)	Strengthen Inspection Readiness	Promote Industry Harmonization	Support Continuous Compliance
Define filing locations that **capture** the **evidence** sponsors must generate **to demonstrate compliance**	Map TMF content to regulatory expectations to **ensure evidence is consistent, organized, and accessible**	Establish a shared framework that **reduces variability** and supports **clear, aligned TMF practices** under the new guidance	Provide a model that can **adapt to evolving guidance** and **ensure long-term sustainability** of inspection readiness

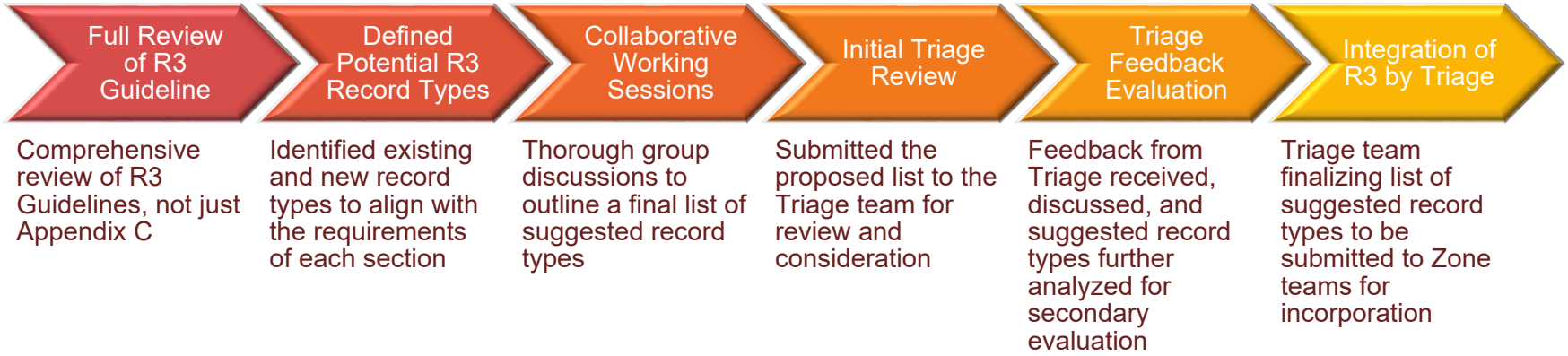
Focus of Key Areas

This initiative centered on tailoring the TMF Reference Model to E6(R3) and identifying critical areas of focus.



Process

Implemented the process strategy outlined below to assess, identify, classify, and manage the anticipated R3-related TMF content effectively.

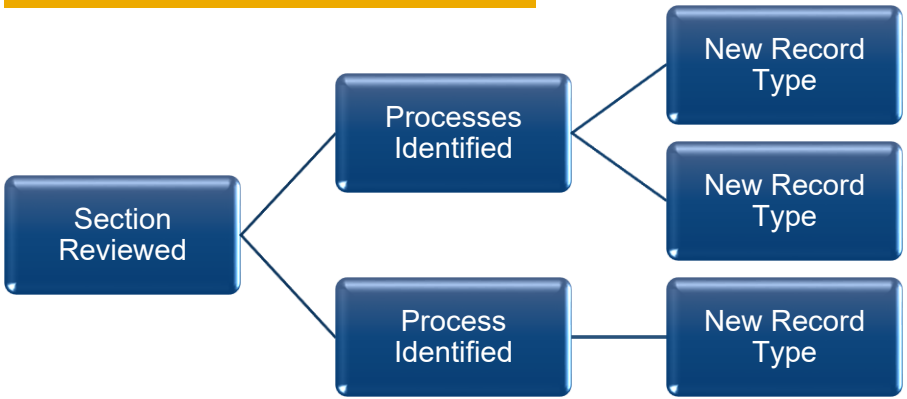


How Suggested Record Types were Identified

Upon review of all sections of R3:

- Identified current artifacts that aligned with the update
- Identified additional record groups/types to include in v4.0

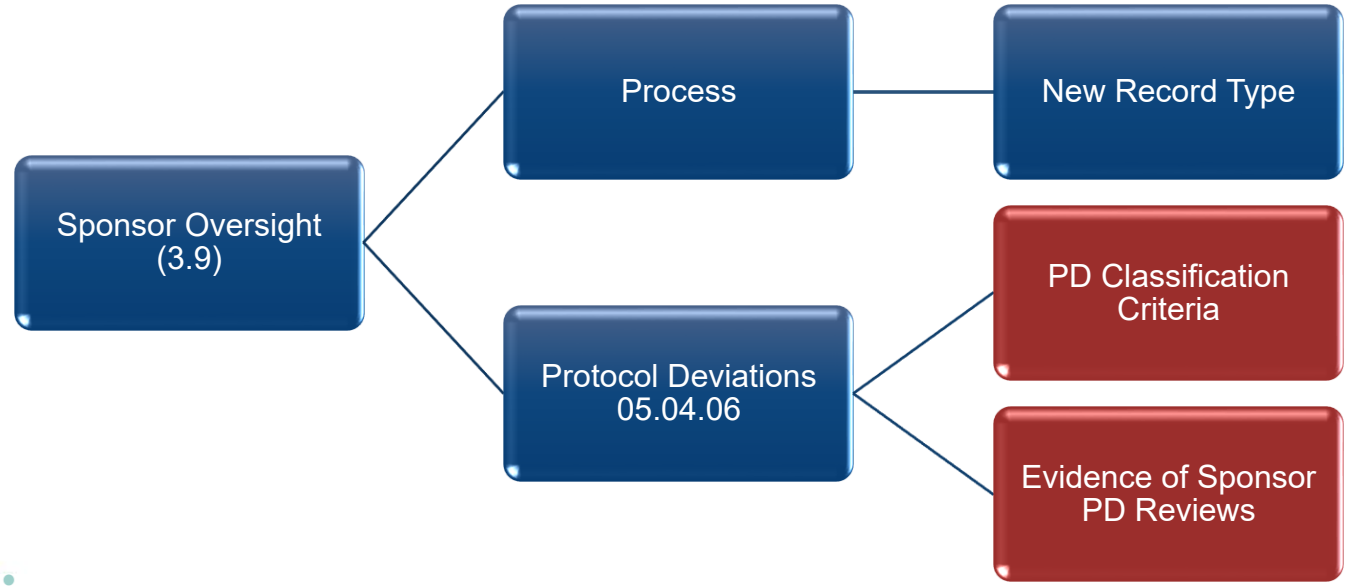
Strategic Framework



ICH E6(R3) Section	
1	IRB/IEC
2	Investigator
3.1	Trial Design
3.2	Resources
3.3	Allocation of Activities
3.4	Qualification & Training
3.5	Financing
3.6	Agreements
3.7	Investigator Selection
3.8	Comm w/IRB/IEC & Reg Authorities
3.9	Sponsor Oversight
3.10	Quality Management
3.11	Quality Assurance & Quality Control
3.12	Noncompliance
3.13	Safety Assessment & Reporting
3.14	Insurance/Indemnification/Compensation
3.15	Investigational Product(s)
3.16	Data and Records
3.17	Reports
Appendix C	Essential Records

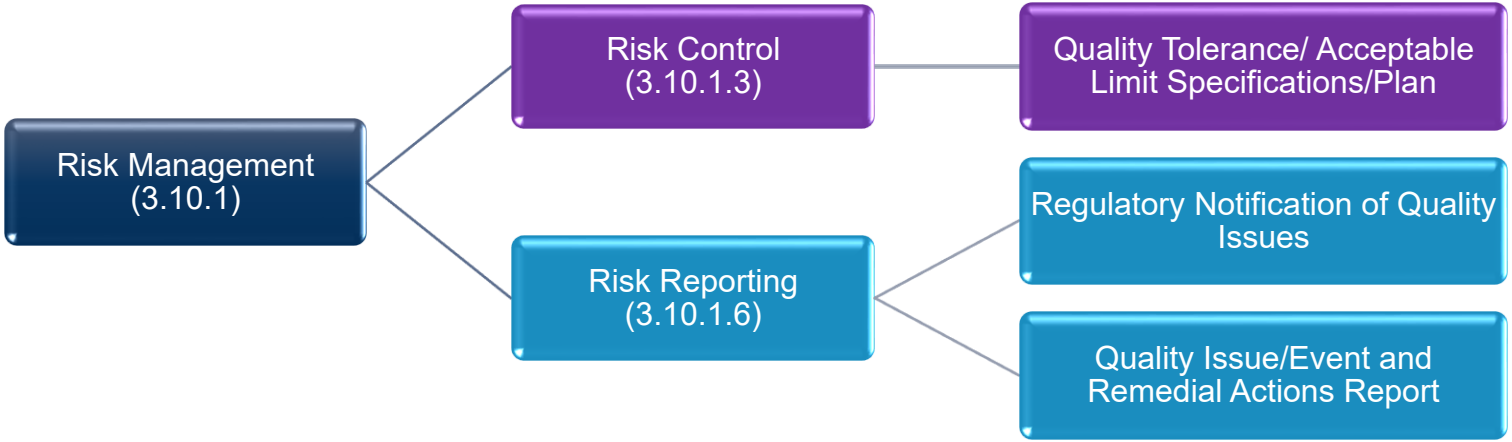
Example: Section 3.9 Sponsor Oversight

3.9.3 The sponsor should determine necessary trial-specific criteria for classifying protocol deviations as important. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or wellbeing.



Example: Section 3.10.1 Risk Management

3.10.1.3 …Where relevant, the sponsor should set pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors. These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed.



3.10.1.6 The sponsor should summarize and report important quality issues (including instances in which acceptable ranges are exceeded, as detailed in section 3.10.1.3) and the remedial actions taken and document them in the clinical trial report (see ICH E3).

Outputs of Exercise

- Originally identified ~50 new suggested record types were sent to Triage
  - Examples:
    - Evidence of Risk Review
    - Oversight Plan
    - Regulatory Notification of Quality Issues
- Common themes – "**Show me the Evidence**"
- The suggested record types are under review by the Triage team, with final recommendations to be submitted to the Zone teams for incorporation into TMF RM v4.0.

Thank You!