EMA
EUROPEAN MEDICINES AGENCY

Clinical electronic Structured Harmonised Protocols – How is ICH M11 supporting trial design and reporting?

CDISC EU Interchange 2025 – 14 May 2025

Presented by Nick Halsey

Data Analytics and Methods Task force, European Medicines Agency

Disclaimer and Acknowledgements

Disclaimer

The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the EMA, or its scientific committees, or reflecting the position of the EMA. In addition, I am not presenting on behalf of ICH.

Acknowledgements

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M11 EWG

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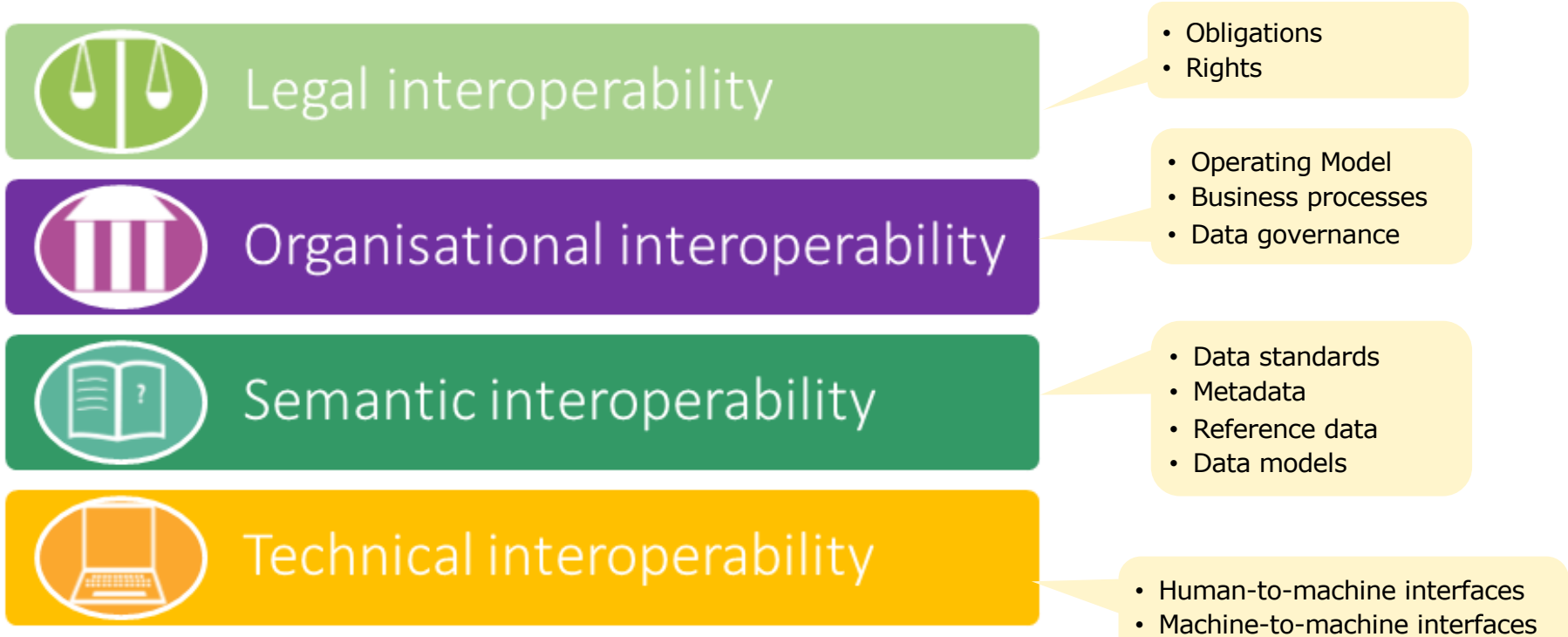
- ICH background
- What is M11 about? Motivation, content and operational considerations.
- Links to CDISC, HL7 Vulcan & CTIS

POLAND25.EU

European Interoperability Framework
-
A common approach for interoperability

EIF - 4 inter-linked interoperability layers

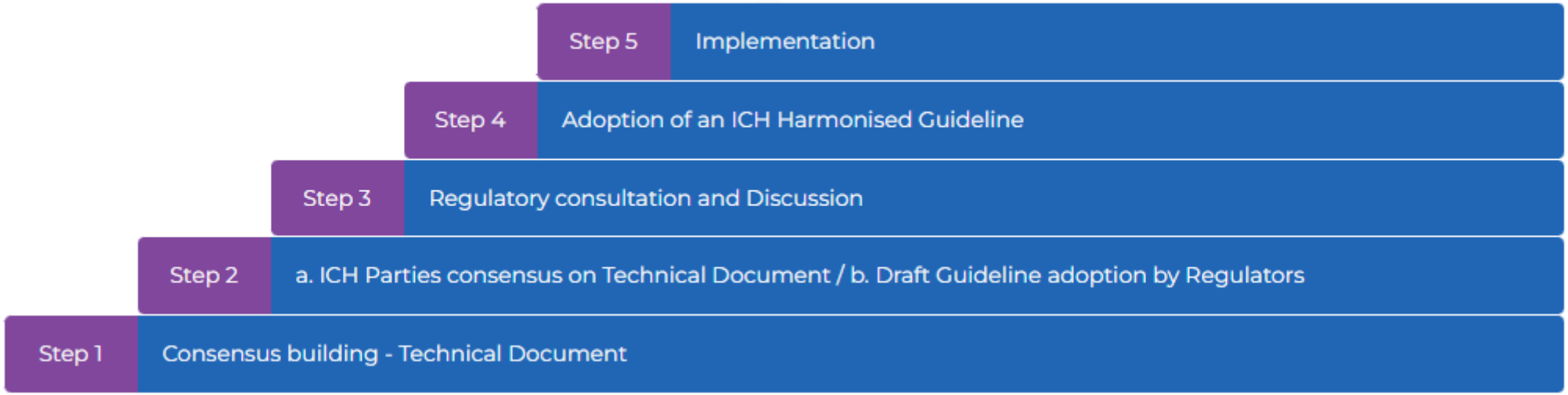


International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

About ICH

- Bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH Guidelines.
- **ICH's mission** is to achieve greater harmonisation worldwide to ensure that safe, effective and high- quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards
- As of November 2021, **67 state of-the-art technical ICH Guidelines** and standards have been produced spanning the pharmaceutical products lifecycle, with further guidelines under development

Formal ICH Procedure



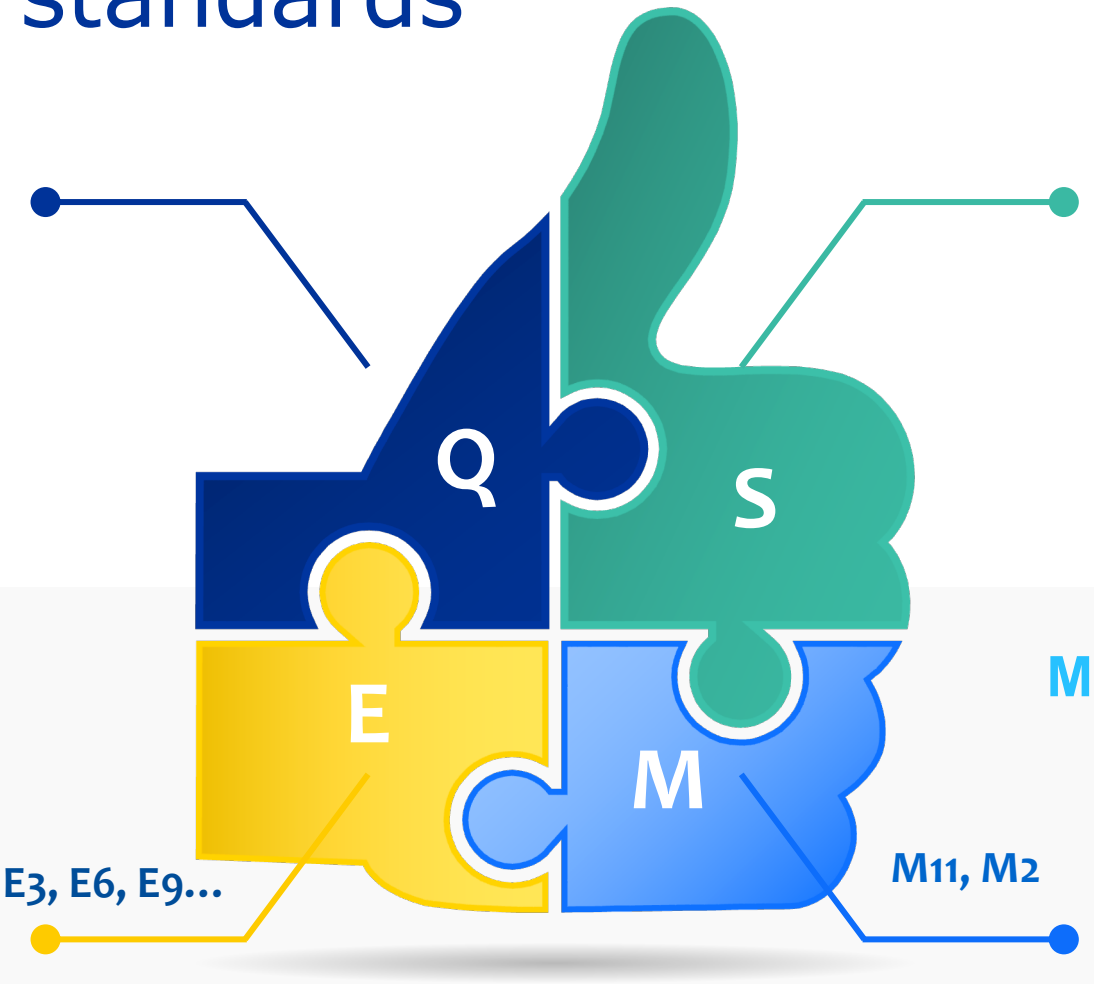
Source: https://www.ich.org/page/formal-ich-procedure

ICH Work Products

Guidelines / standards

Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.



Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

Benefits of a structured, harmonized document

- Difference between a PDF (electronic paper) vs. a truly electronic document, where important data elements can be captured automatically.
- Some advantages…
  - Efficient searching of information
  - Searchable content and metadata
  - Machine-readable
  - Content reuse
  - Makes documents easily accessible for years to come

Regulators receiving documents…

Chemist Lee Geismer looking over an NDA in the 1960s. Source: https://www.fda.gov/about-fda/histories-fda-regulated-products/summary-nda-approvals-receipts-1938-present

EMA archives

Why Clinical electronic Structured Harmonised Protocol (CeSHarP)?

Protocols

- The clinical protocol is an important document that describes the processes and procedures directing the conduct and analysis of a clinical study.
- Format and core content of study protocols vary from sponsor to sponsor, making interpretation difficult for:
  - Medical Writers,
  - Study Sites,
  - IRBs,
  - Regulators,…
- Regulators receive protocols in many different formats
- Approx. 4900 unique protocols received by FDA*

Problem

- No internationally harmonized standard template for the format and content to support **consistency** across sponsors and **exchange of protocol information**.
- Lack of harmonization contributes to **inefficiencies** and **difficulties** in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders.

*Estimated annual number based on 2018-2019 data from CDER and CBER

M11 is not just *one* document

Guideline

Provides background, purpose, and scope as a guideline


ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11

Draft version

Endorsed on 27 September 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Template

Provides written format for the Interventional Clinical Trial Protocol Template


ICH harmonisation for better health

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M11 TEMPLATE

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Technical Specifications

Provides technical representation aligned with the guideline and template


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M11 TECHNICAL SPECIFICATION

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Guideline

- Explains the need, outlines development

Template

- Specifies headers, common text, instructions, data fields, and terminologies.

Technical Specification

- open, nonproprietary standard to enable electronic exchange of clinical protocol information

ICH M11 Protocol Template

Structure

- Preamble to the TOC
  - Conventions
  - General header & structure guidance
  - Flexibility
  - Abbreviations
- Explanation of terms
- Document has more than 50 pages

Preamble

Example Heading	Heading Level	Typeface in this Template	Modification or Deletion	Addition
1.1.1.1	Level 4 (L4)		Delete heading or modify as needed	Insert where needed
Additional Non-Numbered Heading	Non-numbered heading			

Table and Figure Numbering

Tables and figures should be numbered and include a title or caption, respectively. No numbering convention is specified by this template, but a consistent approach should be applied throughout the document.

Page orientation can be modified from portrait to landscape as needed.

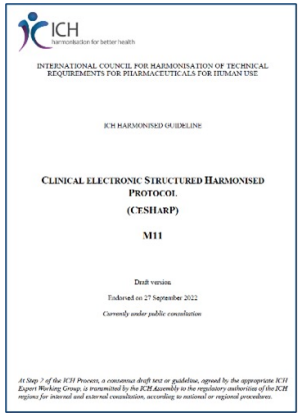
Terminology

The following terminology has been selected for use within this template and is considered to be appropriate for all phases, trial populations, and therapeutic areas:

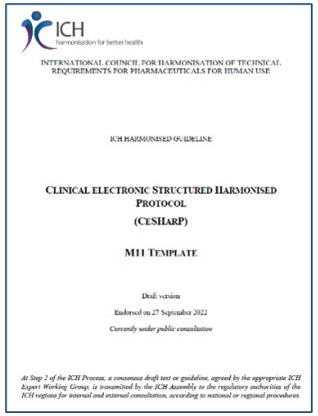
- Because the scope of this protocol template is focused on interventional clinical trials, the term *clinical trials* is used rather than clinical studies when referring to interventional clinical trials.
- *Participant* is used rather than subject, healthy volunteer, or patient when referring to an individual who has consented to participate in the clinical trial. Patient or individual is used to distinguish the population represented by the trial participants, when necessary.
- *Trial intervention* refers to any therapeutic, prophylactic, or diagnostic agent including pharmaceuticals, biologics, vaccines, cell or gene therapy products (when applicable),

M11 interdependencies

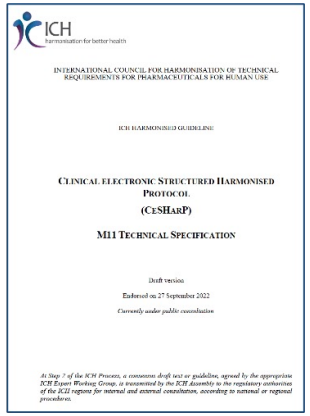
- M11 artefacts



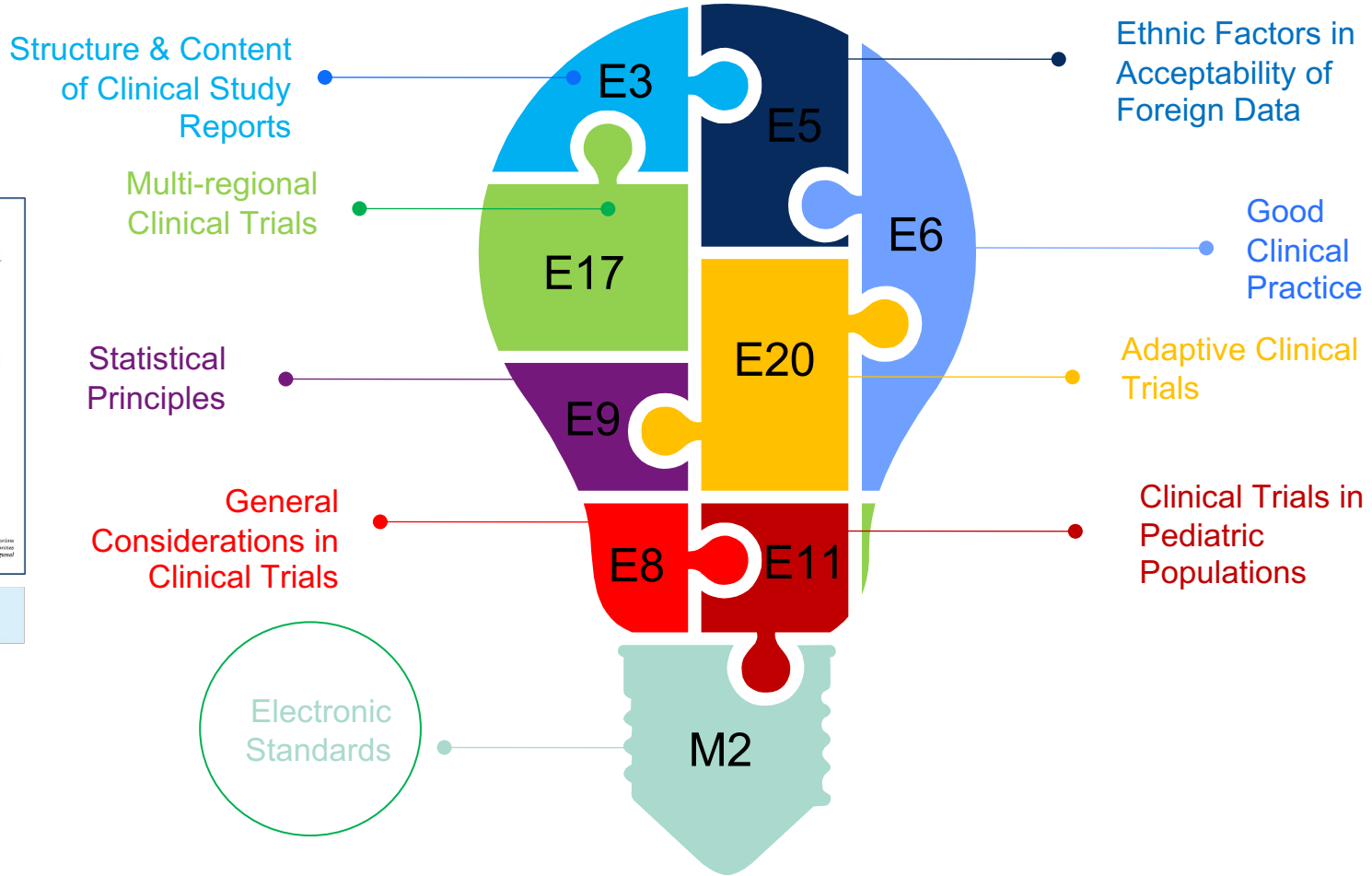
Provides background, purpose, and scope as a guideline



Provides the written format for the Interventional Clinical Trial Protocol Template



Provides the technical representation aligned with the guideline and protocol template

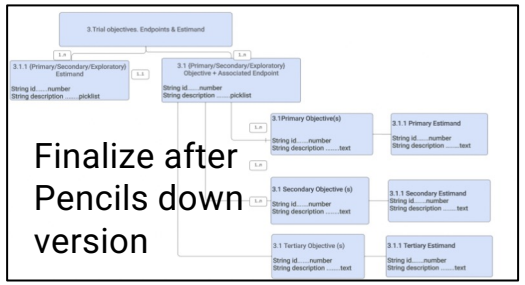


Complexity - Challenge 3: Models Over Time

2023-2025

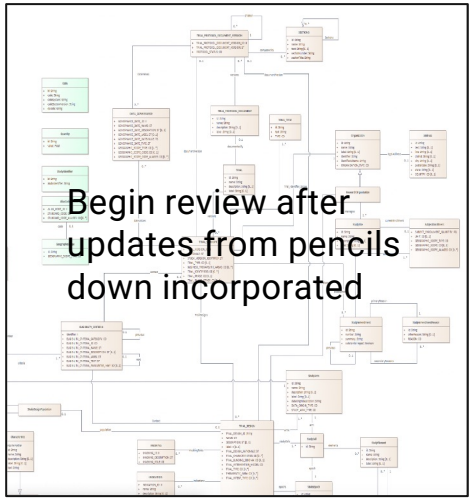
2023 2024 2025

Document Centric ViewTech spec Visuals)



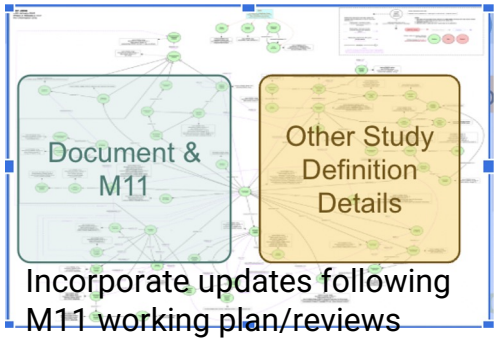
Finalize after Pencils down version

ICH M11 Conceptual Model



Begin review after updates from pencils down incorporated

ICH M11 View in CDISC USDM



Incorporate updates following M11 working plan/reviews

FHIR Transport Model

Technical Specifications Phase

Document Centric View to explain relationships to authors /medical Writers

Conceptual model provides the ability to store information in a standardized fashion, useful for technical and data personnel

Technical Implementation Guide Development Phase

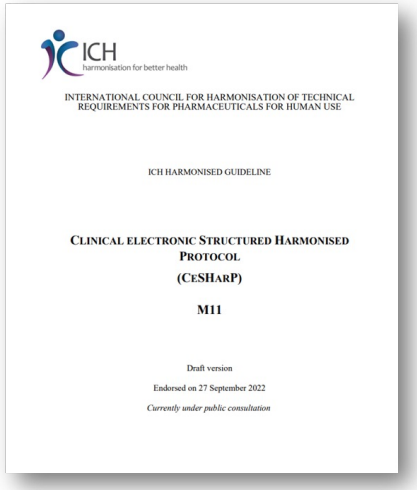
CDISC USDM accommodates the M11 elements and their semantics and create an ICH M11 model specific view

FHIR Transport Model will house everything required for technical exchange, storage and transport of the protocol Information

EMA

M11 Template can be exchanged using many formats

Guideline & **Template** → **Tech Spec** → **Technical Implementation Guide** → **FHIR Profiles**



ICH
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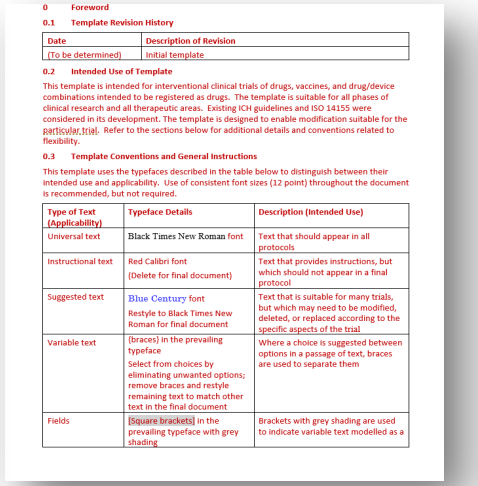


0 Foreword

0.1 Template Revision History

Date	Description of Revision
(To be determined)	Initial template

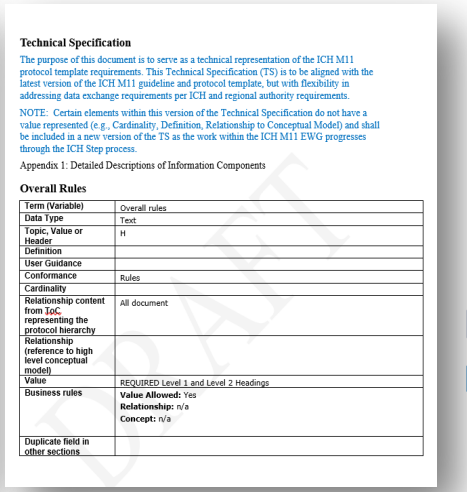
0.2 Intended Use of Template

This template is intended for interventional clinical trials of drugs, vaccines, and drug/device combinations intended to be registered as drugs. The template is suitable for all phases of clinical research and all therapeutic areas. Existing ICH guidelines and ISO 14155 were considered in its development. The template is designed to enable modification suitable for the particular trial. Refer to the sections below for additional details and conventions related to flexibility.

0.3 Template Conventions and General Instructions

This template uses the typefaces described in the table below to distinguish between their intended use and applicability. Use of consistent font sizes (12 point) throughout the document is recommended, but not required.

Type of Text (Applicability)	Typeface Details	Description (Intended Use)
Universal text	Black Times New Roman font	Text that should appear in all protocols
Instructional text	Red Calibri font (Delete for final document)	Text that provides instructions, but which should not appear in a final protocol
Suggested text	Blue Century font Restyle to Black Times New Roman for final document	Text that is suitable for many trials, but which may need to be modified, deleted, or replaced according to the specific aspects of the trial
Variable text	(braces) in the prevailing typeface Select from choices by eliminating unwanted options; remove braces and restyle remaining text to match other text in the final document	Where a choice is suggested between options in a passage of text, braces are used to separate them
Fields	[Square brackets] in the prevailing typeface with grey shading	Brackets with grey shading are used to indicate variable text modelled as a



Technical Specification

The purpose of this document is to serve as a technical representation of the ICH M11 protocol template requirements. This Technical Specification (TS) is to be aligned with the latest version of the ICH M11 guideline and protocol template, but with flexibility in addressing data exchange requirements per ICH and regional authority requirements.

NOTE: Certain elements within this version of the Technical Specification do not have a value represented (e.g., Cardinality, Definition, Relationship to Conceptual Model) and shall be included in a new version of the TS as the work within the ICH M11 EWG progresses through the ICH Step process.

Appendix 1: Detailed Descriptions of Information Components

Overall Rules

Term (Variable)	Overall rules
Data Type	Text
Topic, Value or Header	H
Definition	
User Guidance	
Conformance	Rules
Cardinality	
Relationship content from IoC representing the protocol hierarchy	All document
Relationship (reference to high level conceptual model)	
Value	REQUIRED Level 1 and Level 2 Headings
Business rules	**Value Allowed:** Yes **Relationship:** n/a **Concept:** n/a
Duplicate field in other sections	

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Electronic Document
Human Readable Form

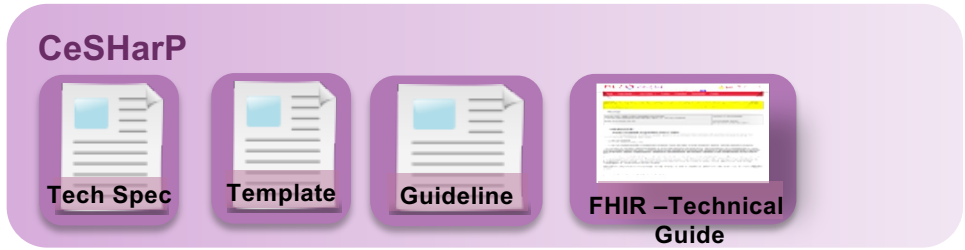
Standard Message Exchange Formats*

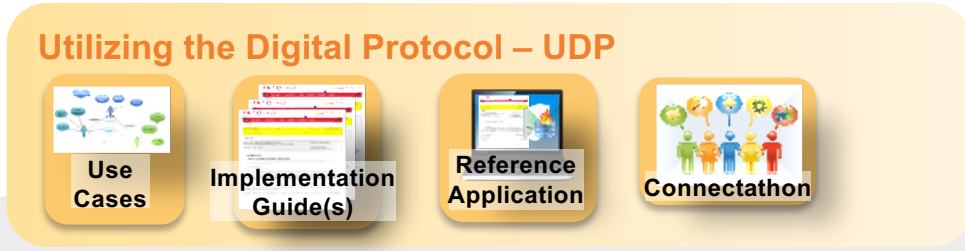
Machine - Readable Form

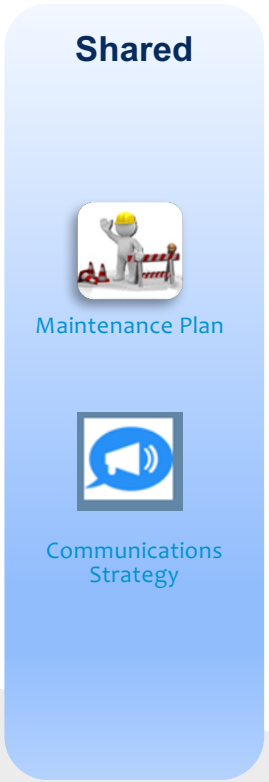
Per ICH Regional Requirements

*** Technical Implementation Guides may be needed for various use cases**

Coordination efforts



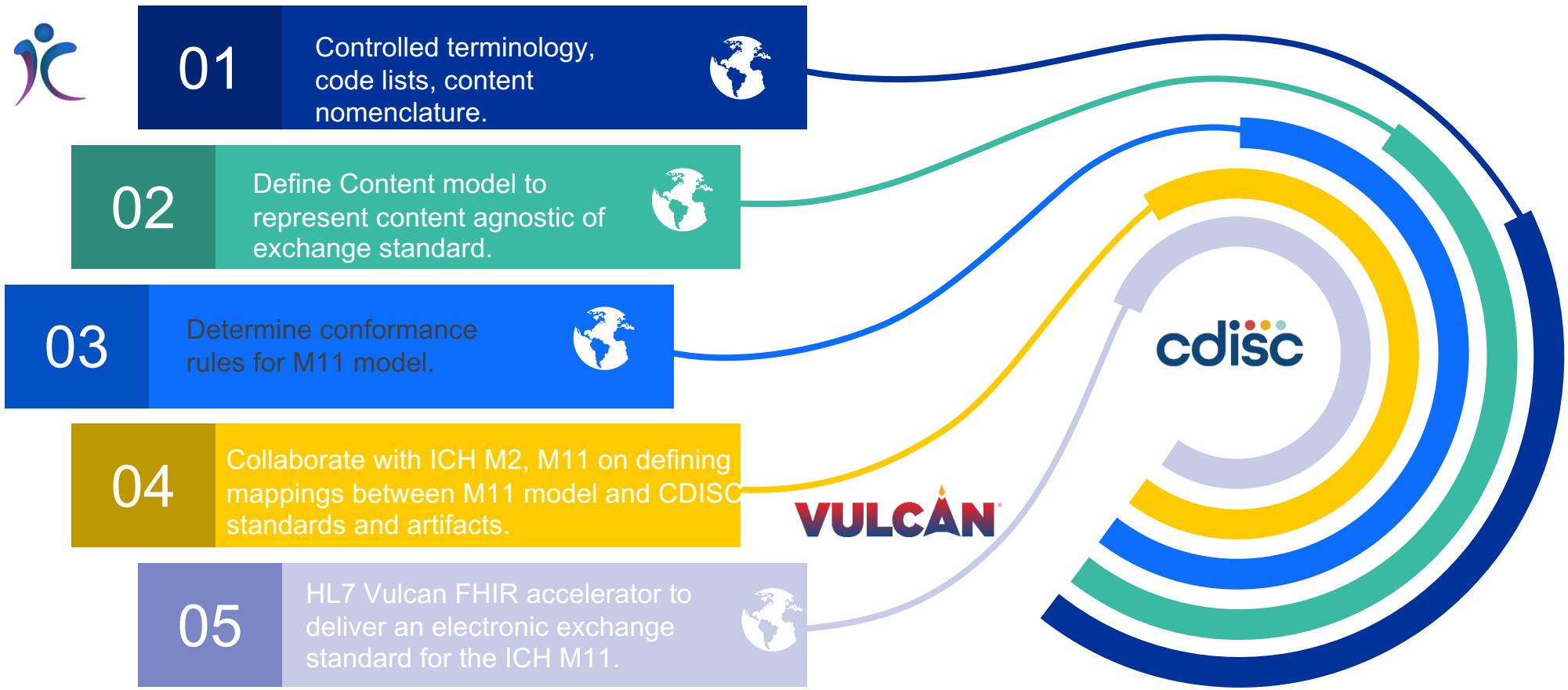




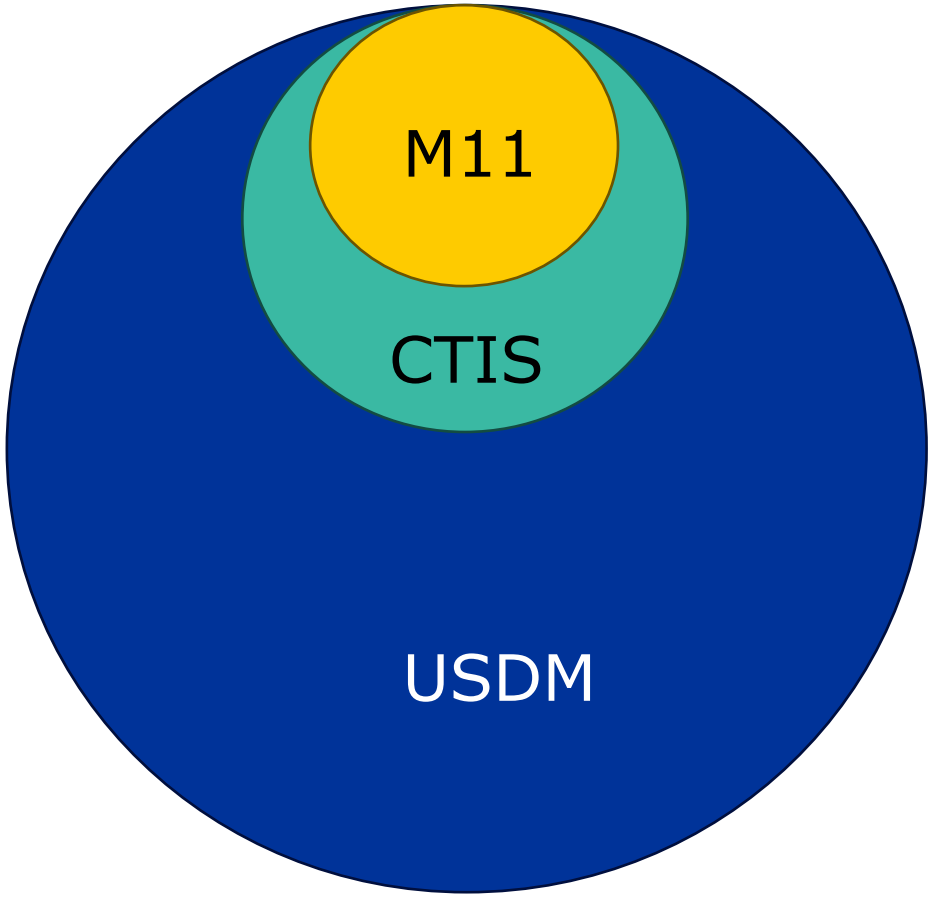
Key Points

- 4 Organizations
  - 3 Projects
  - 14 Deliverables
- Deliverables have interdependencies
- Inputs:
  - ICH M11 template
  - ICH M11 technical specification
  - Models, definitions
- Initial outputs:
  - FHIR IG will allow the exchange of ICH M11 protocols that leverage the M11 technical specification and will carry the CDISC CT and USDM to enable structured, digitized content.
- Expanded:
  - UDP will allow for Implementation Guides for additional use cases while maintaining the harmonization and connectivity.

ICH M2, M11, CDISC, HL7 Vulcan engagement (high level)



Link Between USDM, M11 & CTIS Data



- Areas to be aligned
  - Data elements
  - Definitions
  - Code lists
- EU CTIS has data requirements in addition to M11
- In the future structured study results

M11 - Next steps

1.c. Future anticipated key milestones

Expected future completion date	Milestone
Feb. 2025	*Step 2 approval of the draft updated Technical Specification*
Apr. 2025	*Regional Public Consultation on the draft updated Technical Specification*
Jul. 2025	*Adjudication of Public Comments on the Technical Specification*
Oct. 2025	*Updated Guideline, Template and Technical Specification*
Nov. 2025	*Step 3 Sign-off & Step 4 adoption of the Guideline, Template and Technical Specification*
Jan. 2026	*Final versioned training materials*
Feb. 2026	*Step 2 (Testing) of the ICH Technical Implementation Guide for Fast Healthcare Interoperability Resources (FHIR)*
May 2026	*Step 4 adoption of ICH Technical Implementation Guide for FHIR*

ICH_M11_EWG_WorkPlan_2025_0214.pdf

Take-home messages

- M11 will provide a new structure for protocols (truly electronic and in terms of content)
- Better exchangeability and information retrieval
- Efficiency gains through harmonization

Next steps:

- Revised Protocol Template published 03/2025 (for reference only).
- Revised Technical Specifications for public consultation until 22/04/2025.
- Sign-off Step 3 in 2025 and move to ICH member adoption at Step 4

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SCIENCE MEDICINES HEALTH

Thank you

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