M11
Clinical Electronic Structured Harmonised Protocol

cdisc

2023
EUROPE
INTERCHANGE
COPENHAGEN | 26-27 APRIL

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
M11 - Clinical Electronic Structured Harmonized Protocol (CESharP)

Panagiotis Telonis, Scientific Administrator, EMA
Jimita Parekh, VP Medable

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

Meet the Speakers

Panagiotis Telonis

Title: Scientific Administrator, Chief Information Office

Organization: European Medicines Agency

Panagiotis is a University of Athens graduate, School of Mathematics (1986), with postgraduate expertise at Research Center for Astronomy and Applied Mathematics of Academy of Athens (1987-1988), and at National Centre for Scientific Research DEMOKRITOS (1989-1990) where he served as elected researcher until 2008. He participated in many EU funded and GR national R&D projects, in the Internet development for the Greek Academic Community (NIC Handle PT81), national delegate in European Networking and Telematics fora (IXI–Cosine, EMPB, EuropaNET, DANTE, EMA TIGs), and ICT advisor of the Aegean University, University of Thessaly, War Games Division of the Ministry of Defense, Office of the Minister of Health and Welfare.

He joined EMA in June 2008 served at the Pharmacovigilance and Risk Management Sector /Data Collection and Management, at Business Data and Support Department /Data Standardisation and Analytics, and at Chief Information Office contributing to international data standards development in the context of ISO, HL7, ICH M2/M11, EMA-FDA Collaboration Framework on IDMP, Clinical Trial Navigator initiative, and to Global Identification Working Group for scaling ISO IDMP for global use cases.

Meet the Speakers

Jimita Parekh

Title: Vice President, Growth & Strategy

Organization: Medable, Inc.

Jimita is an experienced leader motivated to further the needle on patient inclusivity in clinical trials. She has been a change leader within the Drug Development Ecosystem, especially Clinical Operations, and Regulatory Innovation space for ~20 years. Jimita's leadership experience and focus have been on Data Standards & Governance, Technology, and Innovation through strategic planning and execution across biopharma. In her current role as Vice President, Growth she partners with biopharma, academia, and regulatory policy makers to accelerate therapies to patients through the adoption of digital solutions.
Jimita's experience includes Oncology, Ophthalmology, and Metabolic Diseases. She believes that innovations in clinical trial execution technology can provide "access" and "enhance the patient experience" which in turn will help us build a faster information highway to bring therapies to patients faster.

Topics

- Introduction to ICH M11
- Value of a Structured Harmonized Protocol
- Scope and Breadth of M11's Work Plan
- Deliverables-The Guideline & Template
- Deliverables-The Technical Specification & Artefacts
- Next Steps

Introduction (ICH)

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

- Unique harmonisation initiative for regulators and pharmaceutical industry
- Originally founded in 1990
- Reformed as a non-profit legal entity under Swiss Law on 23 October 2015

Members and Observers

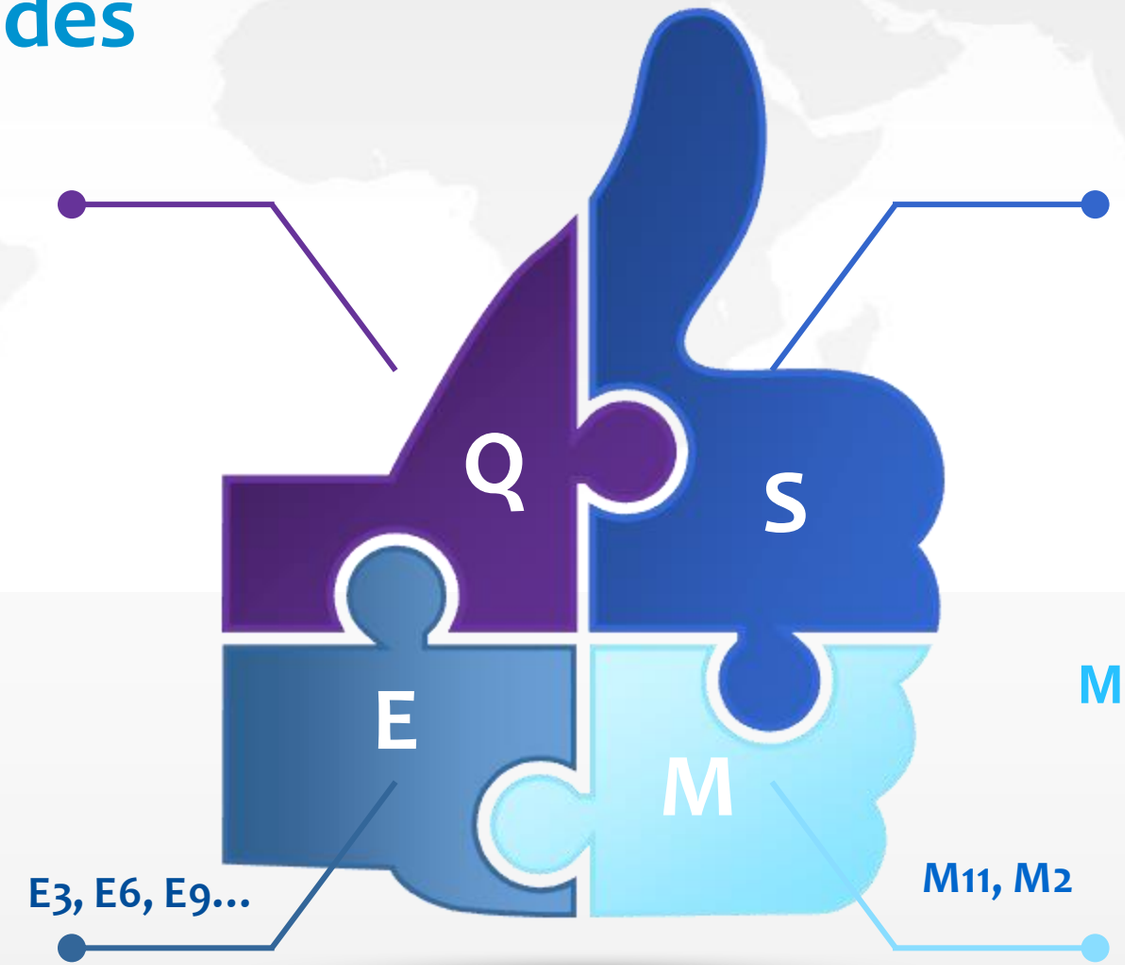
- **Founding Regulatory Members**
  - EC (Europe), FDA (US), MHLW/PMDA (Japan)
- **Founding Industry Members**
  - EFPIA, JPMA, PhRMA
- **Standing Regulatory Members**
  - Health Canada (CA), Swissmedic (CH)
- **Regulatory Members**
  - ANVISA (BR), COFEPRIS (MX), HSA (SG), MFDS (KR), MHRA (UK), NMPA (CN), SFDA (SA), TFDA (Chinese Taipei), TITCK (TR)
- **Industry Members**
  - BIO, Global Self-Care Federation, IGBA
- **Standing Observers**
  - IFPMA, WHO
- **Legislative or Administrative Authorities**
  - AEC (AZ), ANMAT (AR), ANPP (DZ), CDSCO (IN), CECMED (CU), CPED (IL), DPM, Tunisia (TN), EDA (EG), Indonesian FDA (ID), INVIMA (CO), JFDA (JO), MMDA, Moldova (MD), MOPH (LB), National Center (KZ), NPRA (MY), NRA (IR), Roszdravnadzor (RU), SAHPRA, South Africa (ZA), SCDMTE (AM), SECMOH, (UA), TGA (AU)
- **Regional Harmonisation Initiatives (RHIs)**
  - APEC, ASEAN, EAC, GHC, PANDRH, SADC
- **International Pharmaceutical Industry Organisation**
  - APIC
- **International Organisation regulated or affected by ICH Guideline(s)**
  - Bill & Melinda Gates Foundation, CIOMS, EDQM, IPEC, PIC/S, USP

Introduction (ICH Guidelines)

Topics and Codes

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).

Clinical Electronic Structured Harmonized Protocol (CESharP) M11

01 | No internationally harmonized standard template for the format and content to support consistency across sponsors and exchange of protocol information.

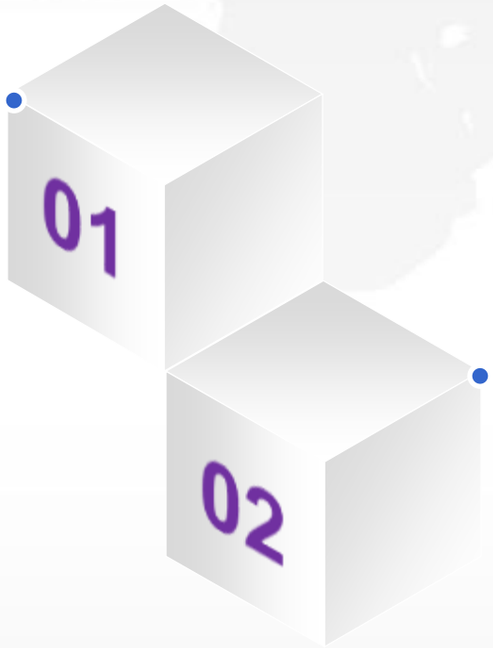
02 | Lack of harmonization contributes to inefficiencies and difficulties in reviewing and assessing clinical protocols by regulators, sponsors, ethical oversight bodies, investigators, and other stakeholders

ICH M11-M2 Deliverables

ICH M11 developed a new harmonized guideline on the clinical protocol that specifies comprehensive organization with standardized content

D1: Template

Includes identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange



D2: Technical Specification

Uses an open, non-proprietary standard to enable electronic exchange of clinical protocol information

5 Steps in ICH Process

Implementation

National or regional procedures for Implementation

Step 5

Adoption of an ICH Harmonized Guideline

Sign-off by Regulatory Topic Leads

Step 4

We are here:

- **Working towards Step 3**
- **Signoff in 2023/24**

Regulatory Public consultation, Reconciliation, and Sign-off

Sign-off by Regulatory Topic Leaders

Step 3

a. ICH Parties consensus on Technical Document
b. b. Draft Guideline adoption by Regulators

Endorsement
a. by Assembly
b. by Regulators

Step 2

Consensus building - Technical Document

Sign-off by Topic Leaders

Step 1

Sign-off, endorsement and adoption can be achieved at a face-to-face meeting or electronically.

Topics

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- Scope and Breadth of M11's Work Plan
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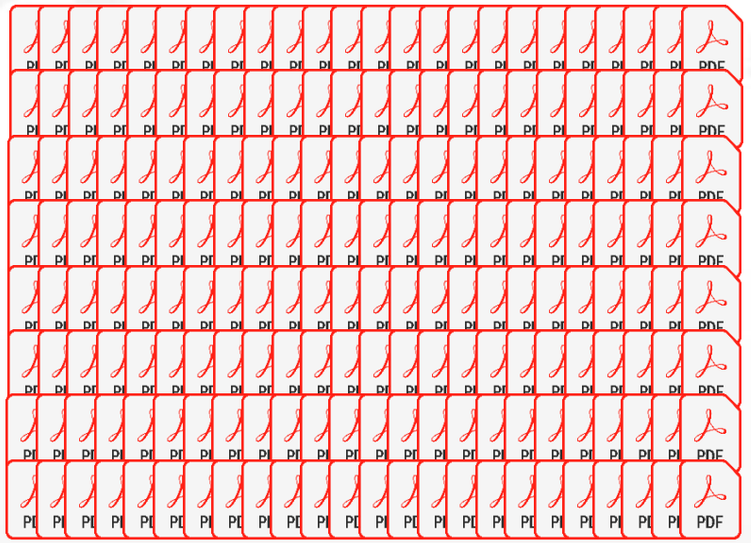
Why Clinical electronic Structured Harmonized Protocol (CeSHarP)?

- **Paper Submissions… Not like this anymore…**

- **…but this isn't much better!**



Value of an Electronic, Structured Protocol Template

Value of an ICH Protocol Template

- Predictable
  - Structure
  - Content
  - Level of detail
  - Presentation (of some content)
- Provides flexibility where needed
- Common instructions
- Consistent with all other relevant ICH Guidelines
- Acceptable in all ICH countries

+

All of the benefits of a traditional template, PLUS

Searchable content and metadata, for example:

Tailored experience

- Side-by-side comparison of fields or sections
- Task- or role-based views
- Custom views

Collaboration and Continuity

- Transition of molecules via mergers/acquisitions
- Multi-sponsor studies
- Data integration

Downstream Automation

- Population of CT Registry
- Content reuse to SAP, CSR, other protocols

Future standardization and automation

Topics

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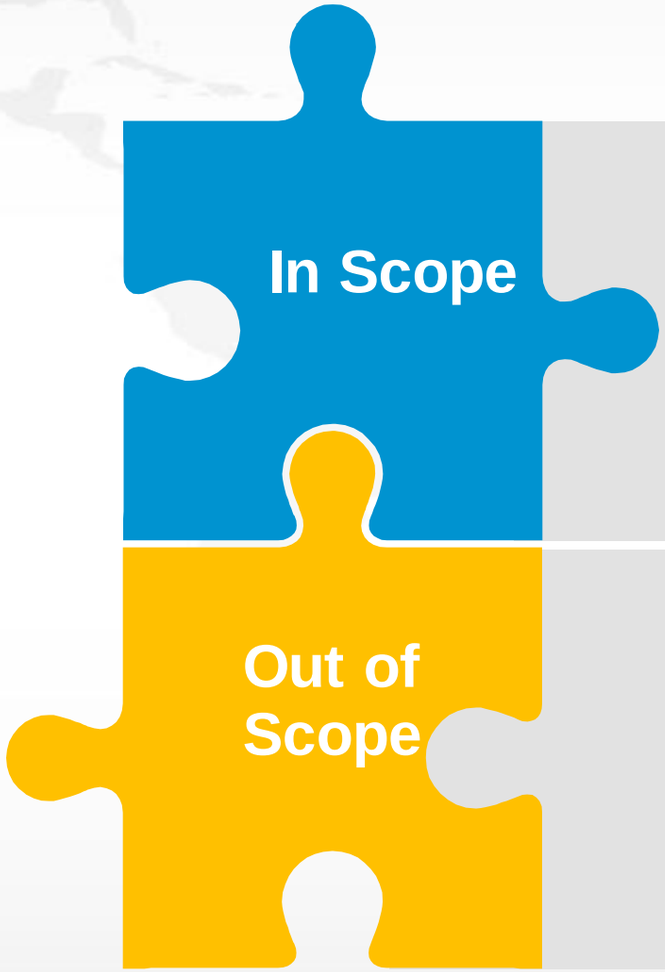
Scope



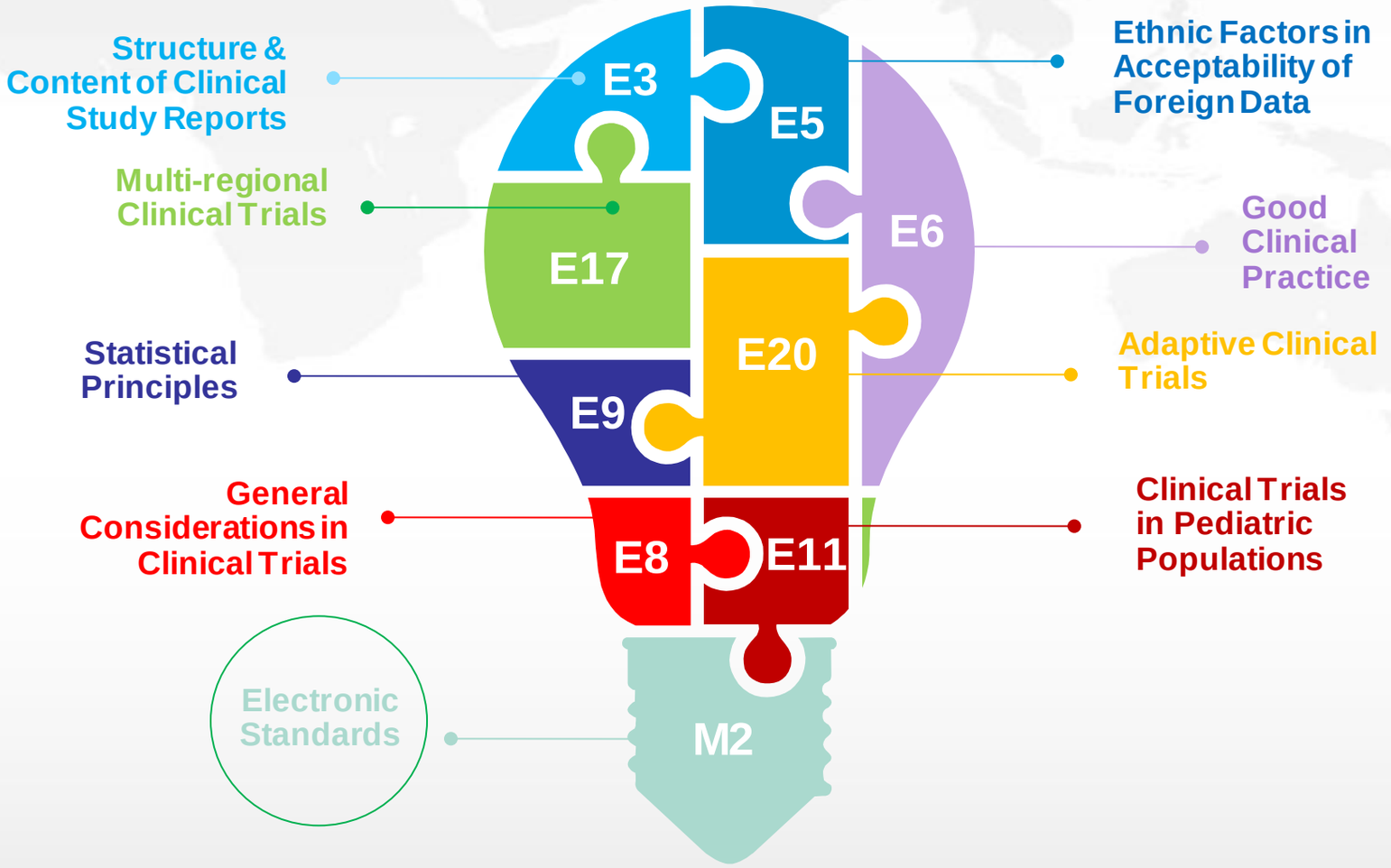
- The Template and Technical Specification are applicable to interventional clinical trials of medicinal products across all phases and therapeutic areas of clinical research

- Neither the Guideline nor the Template or Technical Specification are intended to specify processes related to development and maintenance of a protocol.
- They do not supersede or negate other guidelines that establish requirements for protocol content.
- They do not provide instruction on the development of a well-designed trial or characterize a well-crafted final protocol

ICH M11 EWG

- **Regulatory Members**
  - ANVISA, Brazil
  - COFEPRIS, Mexico
  - EC, Europe
  - FDA, United States
  - HSA, Singapore
  - MFDS, Republic of Korea
  - MHRA, UK
  - MHLW/PMDA, Japan
  - NMPA, China
  - TFDA, Chinese Taipei
  - Health Canada, Canada
  - SFDA, Saudi Arabia
  - Swissmedic, Switzerland
  - TITCK, Turkey
- **Industry Members**
  - EFPIA
  - JPMA
  - PhRMA
  - BIO
  - Global Self-Care Federation
  - IGBA

Source: https://ich.org/page/members-observers



How to Think About the M11 Documents

- **Guideline** is like a container
  - Not expected to change over time
- **Template** and **Technical Specification** are like ice and water
  - Different forms of the same matter
  - Will change over time

Topics

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ICH M11 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

ICH M11 Guideline

ICH HARMONISED GUIDELINE

STRUCTURE AND CONTENT OF A CLINICAL PROTOCOL

M11

ICH Consensus Guideline

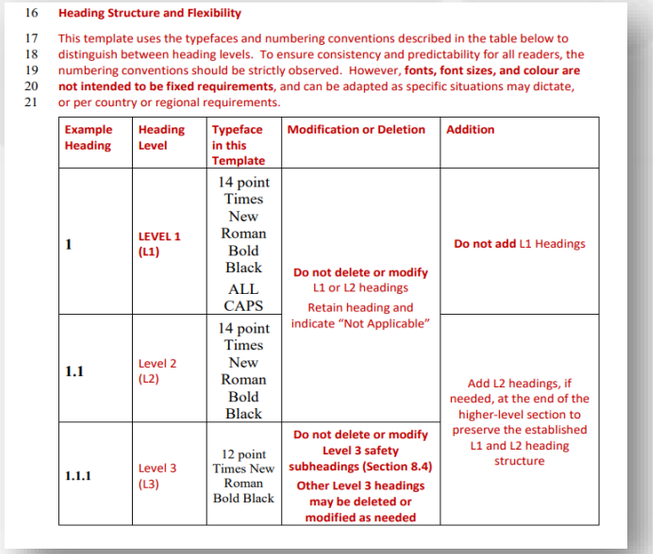
TABLE OF CONTENTS

Guideline describes approach used to develop the two other deliverables:

- Background
- Purpose
- Scope
- General design principles, e.g.,
  - Avoid unnecessary duplication of content
  - Use cross-referencing
  - Avoid multiple terms for the same thing
  - Introduce more structured content, where possible
  - Used established terms / definitions

ICH M11 Protocol Template

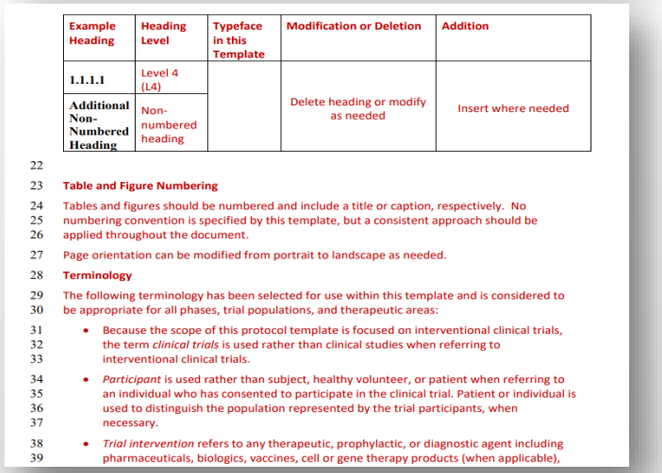
- Principles for Development
  - Build common core content
  - Serve the needs of stakeholders
  - Define content for electronic exchange
  - Design for content re-use
  - Maintain flexibility



Heading Structure and Flexibility

This template uses the typefaces and numbering conventions described in the table below to distinguish between heading levels. To ensure consistency and predictability for all readers, the numbering conventions should be strictly observed. However, **fonts, font sizes, and colour are not intended to be fixed requirements**, and can be adapted as specific situations may dictate, or per country or regional requirements.

Example Heading	Heading Level	Typeface in this Template	Modification or Deletion	Addition
1	LEVEL 1 (L1)	14 point Times New Roman Bold Black ALL CAPS	**Do not delete or modify** L1 or L2 headings Retain heading and indicate "Not Applicable"	**Do not add** L1 Headings
1.1	Level 2 (L2)	14 point Times New Roman Bold Black		Add L2 headings, if needed, at the end of the higher-level section to preserve the established L1 and L2 heading structure
1.1.1	Level 3 (L3)	12 point Times New Roman Bold Black	**Do not delete or modify Level 3 safety subheadings (Section 8.4)** **Other Level 3 headings may be deleted or modified as needed**	



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),

- Preamble to the ToC
  - Conventions
  - General header & structure guidance
  - Explanation of terms

Topics

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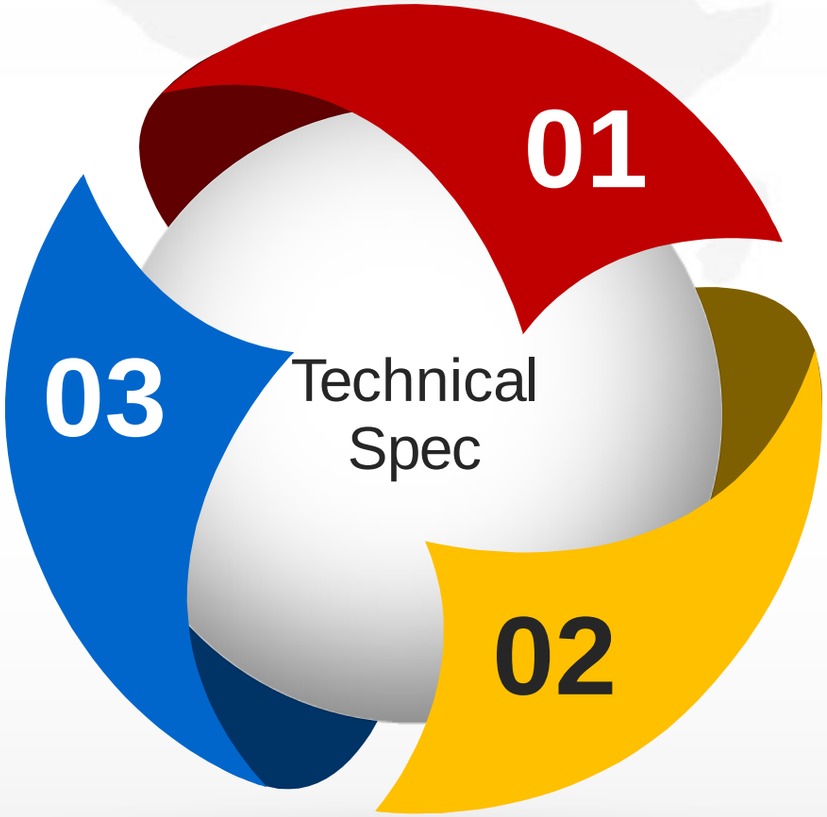
The Tech Specification includes (1/2)



Business requirements and common structured protocol content components – *the data and metadata*.

An open, non-proprietary standard for electronic exchange enables development of interoperable electronic tools to facilitate exchange, review, and execution of protocols.

Conformance, cardinality, and other technical attributes that enable the electronic exchange of protocol content.

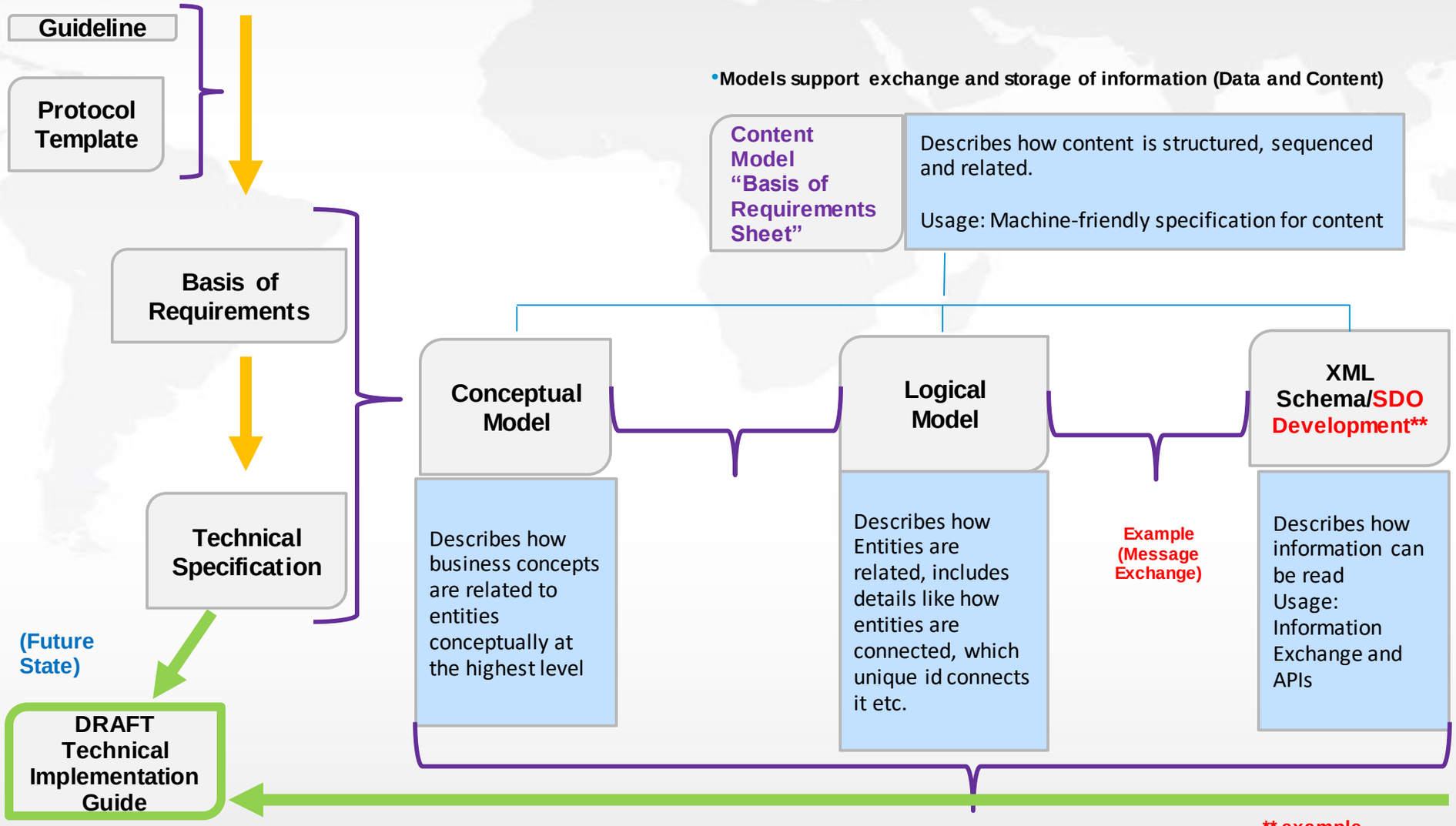
The Tech Specification includes (2/2)

- Detailed descriptions of the structured content components
- Specific data fields
- Blocks of text-based content
- Other defining attributes
- Business rules as established in the Template

Overall Rules

Term (Variable)	Overall rules
Data Type	Text
Topic, Value or Header	H
Definition	
User Guidance	
Conformance	Rules
Cardinality	
Relationship content from ToC 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	

M11-M2 Technical Development Process



Artefacts

Technical Specifications

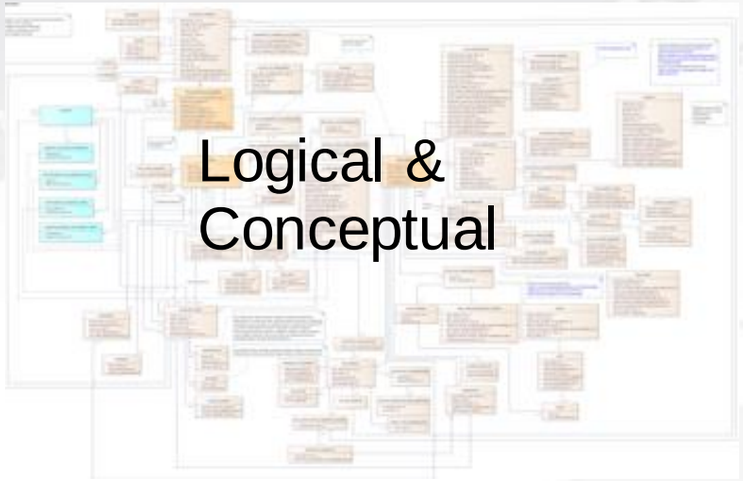
Overall Rules

Term (Variable)	Overall rules
Data Type	Text
Topic, Value or Header	H
Definition	
User Guidance	
Conformance	Rules
Cardinality	
Relationship content from ToC 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	

Basis Of Requirements+ Controlled Terminology+ Code list

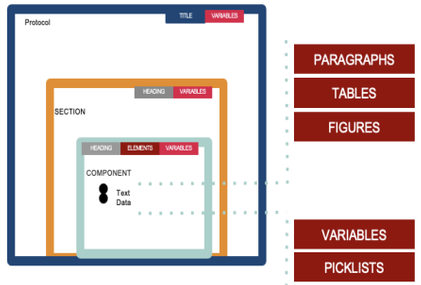
A	B	C	D	E	F	G	H	I
Field Identification								
Field ICH, EU, US, JP	Included in POC search	Repeatable section	DATA ELEMENT	HEADER Element	FIELD NAME	MAX LENGTH	DATA TYPE	VALUES
ICH	Yes		A.1	Protocol Full Title	Protocol Title		Text	
ICH			A.2	Sponsor Confidentiality Statement	Sponsor Confidentiality Statement		Text	
ICH	Yes		A.3	Protocol Number	Protocol Number		Text	
ICH			A.4	Version	Version		Number	N
ICH			A.5	Amendment Number	Amendment Number		Number	N
ICH			A.6.1	Amendment Scope	Amendment Scope		Pick List	
ICH			A.6.2		Country/Region Identifier	2	Text	AN
ICH			A.7	Compound Number	Compound Number		Text	
-	-	-	-	**Compound Name(s)**	-	-	-	-
ICH			A.7.1	Compound Name(s)	Nonproprietary Name		Text	
ICH			A.7.2		Proprietary Name		Text	
ICH			A.7.3		Additional Proprietary Name		Text	
-		-	-	-	-	-	-	-
ICH	yes		A.8.1	Trial Phase	Trial Phase	1	Pick List	N
ICH			A.8.2		Description of Trial Phase Other		Text	

Models



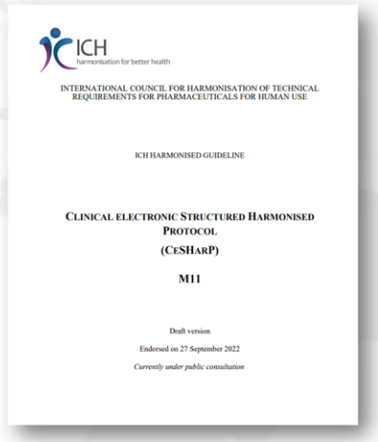
Content Model Example - Protocol

The content model identifies each piece of content and defines relationships (hierarchy) to enable information exchange at different levels of granularity.



Artefacts

Guideline & **Template** → **Technical Specification**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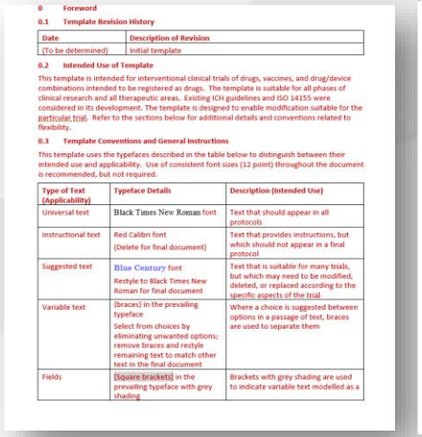

0 Foreword

0.1 Template Revision History

Date	Description of Revision
(To be determined)	Initial template

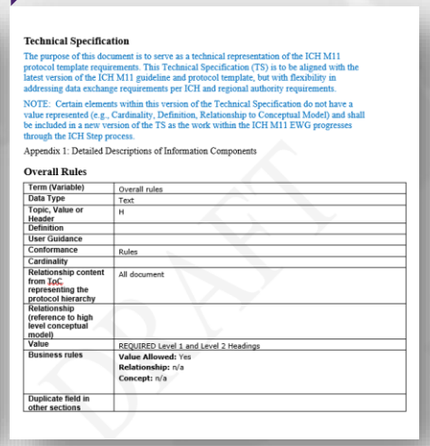
0.2 Intended Use of Template

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 ToC 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	

FHIR Profiles

Electronic Document
Human Readable Form

Machine-Readable Form

Per ICH Regional Requirements

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

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Joint international collaboration on ICH M11 CeSharP

- HL 7 Vulcan (https://hl7vulcan.org/) and CDISC (https://www.cdisc.org/about) are announcing a project that will deliver an electronic exchange standard for the ICH M11 Clinical electronic Structured Harmonised Protocol (CeSharP).
- HL 7 is a not-for-profit organization focused on providing standards for the exchange, integration, sharing and retrieval of health information.
- CDISC is a nonprofit standards development organization that develops standards that support acquisition, exchange, submission, and archive of biopharmaceutical data.
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (https://www.ich.org/) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH Guidelines.
- M11's deliverables include a guideline, a clinical protocol template, and an electronic exchange standard

CDISC M2/M11 potential engagement

01 Controlled terminology, code lists, content nomenclature.

02 Define Content model to represent content agnostic of exchange standard.

03 Determine conformance rules for M11 model.

04 Collaborate with ICH M2/M11 on defining mappings between M11 model and CDISC Standards and Artifacts.

05 Joint project with Vulcan FHIR accelerator to deliver an electronic exchange standard for the ICH M11.

FHIR Accelerators / What

- Designed to assist communities and collaborative groups across the global health care spectrum in the creation and adoption of high quality FHIR IGs and other standard artifacts to move toward the realization of global health data interoperability.
- HL7 help convene and work with communities and implementers with an interest in using FHIR to address common use cases.
- HL7's Accelerators help such communities initiate and efficiently navigate through the standards development process by providing:
  - Guidance on how to navigate and work with HL7 work groups, product families and project teams.
  - Basic team collaboration infrastructure tools.
  - A range of other optional support services for Accelerator groups based on their own needs, ranging from self-service guidelines, to contracted project and/or financial management, contracting with SMEs, and other project and infrastructure services

Ref: https://www.hl7.org/about/fhir-accelerator/

VULCAN Vision statement

Why Vulcan?

Fully integrate research into the delivery of healthcare by streamlining data collection and exchange into a singular process.

What are we doing to reach that vision?

- Collaborating with the international research community to align clinical data and clinical research data at the point of collection.
- Developing out the HL7 FHIR standard to support the bidirectional flow of data.

How will we accomplish this?

- Bridge existing gaps
- Strategically connect industry collaborations
- Maximize collective resources
- Deliver integrated tools and solutions

The Convening Members of Vulcan

Represent a Wide Variety of Expertise

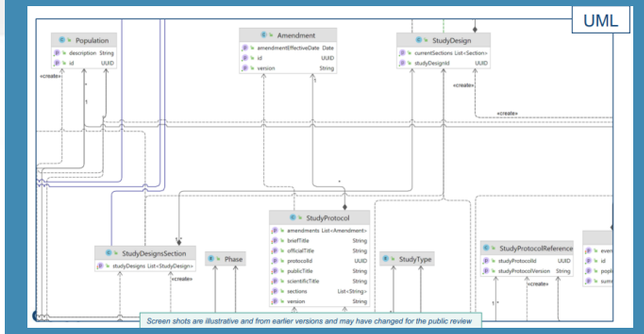
Vulcan Projects (as of March 2023)

Project	Objectives	Vulcan Lead
Schedule of Activities (SoA)	Represent the schedule of activities in FHIR from a spreadsheet. Enable the consistent description, timing and identification of each activity in a study	***Mike Ward*** (TransCelerate) ***Geoff Low*** (PHUSE)
Real World Data (RWD)	Extract data from EHRs in a standardized format to support clinical research and especially submission to Regulators	***Scott Gordon*** (FDA) [Open Position]
Phenotypic Data	To increase the availability of high-quality standardized phenotypic information for genomic research and genomic medicine.	***Anita Walden*** (University of Colorado Anshutz) ***Shahim Essaid*** (University of Colorado Anschutz)
Electronic Product Information (ePI)	Define a common structure for product information (monographs) that supports cross-border exchange of data for patients	***Craig Anderson*** (Pfizer) ***Catherine Chronaki*** (Secretary General at HL7 Europe)
Adverse Events (AE)	Support standardizing the reporting and format of an adverse event. Improve the maturity of the relevant FHIR resources	***Michelle Casagni*** (MITRE) ***Ed Millikan*** (FDA)
FHIR to OMOP	Support the development of FHIR to OMOP data transfer for better analysis of clinical data for research	***Davera Gabriel*** (Johns Hopkins) ***Catherine Diederich*** (Duke)

NEW: Vulcan SC meeting (19 Apr 2023): announcement of the ICH MC decision on a joint ICH M2/M11, HL7 Vulcan, and CDISC collaboration project to deliver an electronic exchange standard for the ICH M11 Clinical electronic Structured Harmonised Protocol (CeSharP).

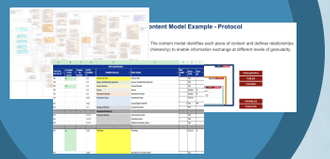
Stay tuned!

DDF (CDISC/TransCelerate)

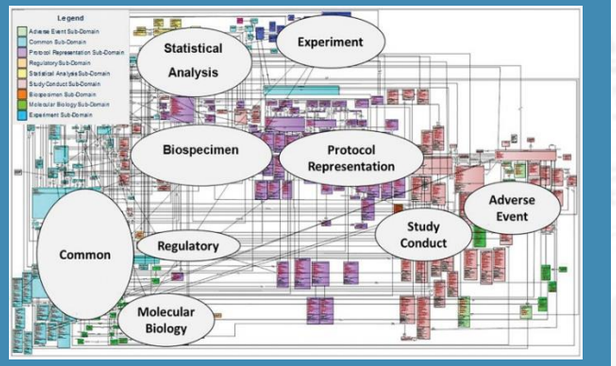


https://www.cdisc.org/ddf

Basis of Requirements

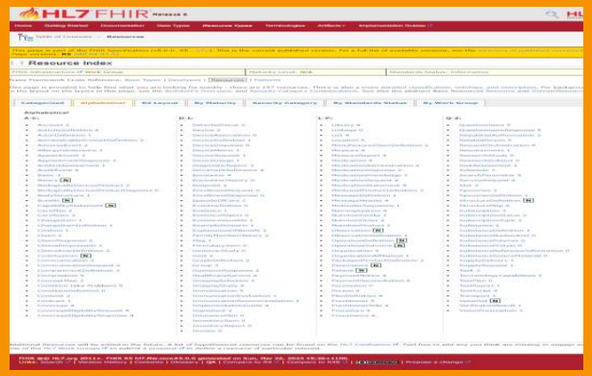


CDISC/HL7/ISO BRIDG



https://bridgmodel.nci.nih.gov/

FHIR



https://build.fhir.org/

https://hl7vulcan.org/)

Terminology in the Context

Thank You!