VULCAN
HL7 FHIR

HL7 Working Group Meeting
Europe

HL7 FHIR MARATHON

HOSTED BY
HL7 Hellas

EuroVulcan 2
18th January 2024
Royal Olympic Hotel, Athens

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Q3 Panel: Vulcan Utilizing the Digital Protocol / ICH M11 CeSHarP: Focus on Mission, Plans, Key Challenges, European Involvement

Session Chair: Panagiotis Telonis, European Medicines Agency

January 18, 2024

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Q3 Panel: Vulcan Utilizing the Digital Protocol / ICH M11 CeSHarP

ATHENS DIGITAL HEALTH WEEK
15-19th January 2024 | Royal Olympic Hotel

Panelists

1. History of Clinical Research Protocol Standardization: *Rebecca Kush, Vulcan Advisory Council co-Chair*
2. ICH M11 Clinical Protocol Template and Exchange Standard: *Ron Fitzmartin **(online)**, PhD, MBA, ICH M11 Rapporteur, U.S. FDA*
3. The perspective of CROs in Europe: *Yoani Matsakis, EUCROF*
4. The perspective of Academic Centers: *Meletis Dimopoulos, National and Kapodistrian University of Athens*
5. Decentralized clinical trials (or elements in clinical trials): *Christos Lionis, University of Crete*
6. ICH M11, Digital Protocols: A Pharma Perspective: *Rob DiCicco **(online)**, TransCelerate BioPharma*
7. The Vulcan UDP Project: Hugh Glover, Vulcan Technical Director

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Q3.1 History of Clinical Research Protocol Standardization

Rebecca D Kush, PhD
Chair, Vulcan Advisory Council
Founder and President Emeritus, CDISC
President, Catalysis

January 18, 2024

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Protocol Representation Group (PRG)

- The PR Group was formed as a volunteer organization of domain experts representing the stakeholders of the biopharmaceutical industry, NCI/NIH, and FDA with specific expertise in developing and/or conducting regulated clinical trials with regulated protocols.

•PR Group is both:

  - A CDISC Team
  - A Project Team of the Health Level 7 (HL7) Regulated Clinical Research and Information Management (RCRIM) – now BR&R

- Contributors

•Bayer Healthcare
•Beardsworth Consulting
•Boehringer-Ingelheim
•Booz Allen Hamilton
•CDISC
•City of Hope
•Digital Infuzion
•Eli Lilly and Company
•EMEA
•FDA
•GlaxoSmithKline
•HP
•IBM
•Intrasphere
•J&J PRD
•Medidata (Fast Track)
•Memorial Sloan Kettering
•Merck
•NIH, NCI, caBIG
•Novartis
•Novo Nordisk
•Octagon Research
•Omnicare
•Oracle
•Pfizer
•PHT
•Quintiles
•SAIC
•Sanofi-Aventis
•Sanofi-Synthelabo
•SAS
•Seattle Children's
•TAP Pharmaceutical Products
•UCB Group
•UCSF Med Ctr
•University of Pittsburgh
•USF
•WHO
•Wyeth
•Zurich Biostatistics

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Protocol Representation Project Description

Protocol Representation will identify **standard elements** of a clinical trial protocol that can be further elucidated and codified to facilitate study design, regulatory compliance, project management, trial conduct and data interchange among consumers and systems.

This work will be based upon the needs of protocol consumers, which may include regulatory authorities, IRBs, statisticians, project managers, site personnel and users of any downstream systems for the **management of clinical trial information**.

Project Objective(s): Publication of a standard, machine-readable model for protocol representation that will enable interchange of this data among systems and stakeholders.

PR Group April 2002

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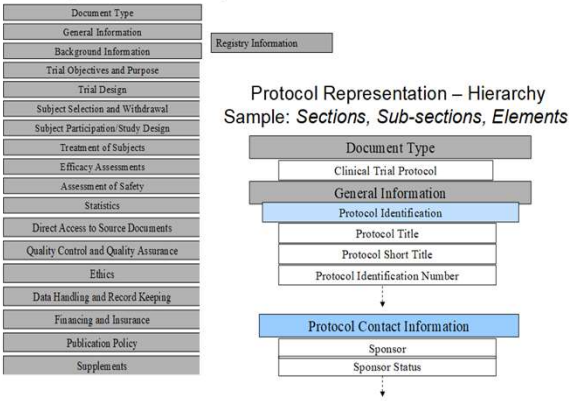
PRG Approach

- Development should concentrate on content first and implementation second
- Elements must be defined in a glossary, since the industry uses multiple definitions for the majority of protocol elements
  - CDISC Glossary, Applied Clinical Trials, published yearly
- Identify core set of elements initially, expand with further details as needed
- Initially based on
  - ICH E6 - Basis for the development and organization
  - ICH E3 - Terms & definitions
  - EudraCT (EMEA) - Key words and Protocol description
  - Specific topics (e.g. IRB, SAP-E9)



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2004: How did BRIDG get started?

- Four important streams of development came together:
  - **CDISC**: In early 2004, CDISC started constructing a Domain Analysis Model to support harmonization of their standards for clinical research as well as with the Health Level Seven (HL7) healthcare standard.
  - **NCI**: In late 2004, NCI's Cancer Biomedical Informatics Grid (caBIG™) initiative joined the CDISC BRIDG efforts to construct a structured protocol representation for its Clinical Trials Management Systems (CTMS) Workspace, in order to further interoperability among clinical trials research in cancer.
  - **HL7**: In 2005, the BRIDG model was adopted by the HL7 Regulated Clinical Research Information Management (RCRIM) Technical Committee as the RCRIM Domain Analysis Model.
  - **FDA**: In 2007, the US Food and Drug Administration included BRIDG in their draft 5 year PDUFA IV IT Plan as a foundation for several projects.

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*Biomedical Research Integrated Domain Group (BRIDG) Model

The BRIDG Model*

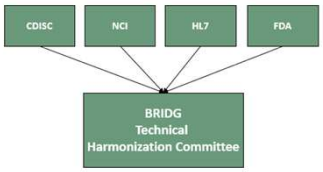
BRIDG Model:
- ***HL7 Standard***
- ***CDISC Standard***
- ***ISO Standard***

A clinical research domain analysis model (UML) initiated by CDISC, BRIDGing
- *Organizations (CDISC, HL7, FDA, NCI)*
- *Standards*
- *Research and Healthcare*

Towards semantic interoperability; a Portal to Healthcare

Open source ; Collaborative Project
- *See BRIDG Model on CDISC website or www.bridgmodel.org*

Organization of the BRIDG THC



- **Technical Harmonization Committee (THC)**
  - Responsible for ongoing model maintenance
  - Harmonizes subdomain projects into the main model

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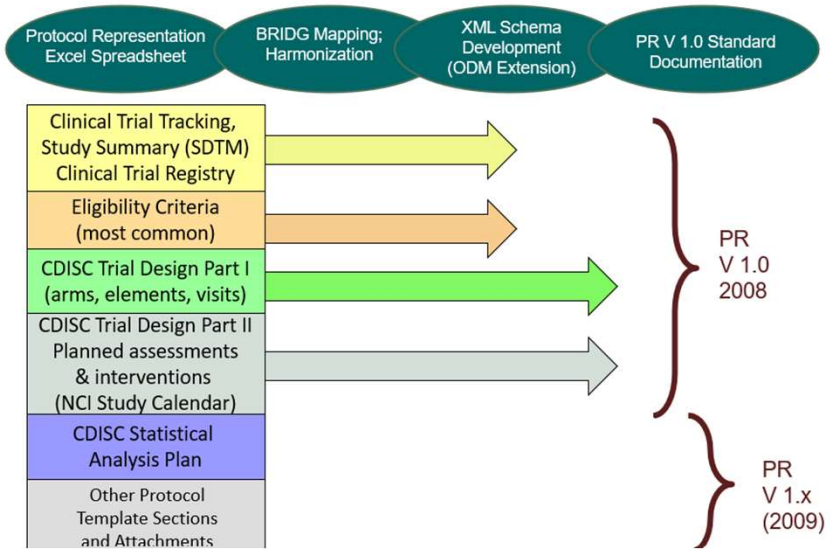
CDISC-HL7 Protocol Representation Standard - Development



BRIDG SCOPE:

Protocol-driven research and its associated regulatory artifacts*, i.e. the data, organization, resources, rules, and processes involved in the formal assessment of the utility, impact, or other pharmacological, physiological, or psychological effects of a drug, procedure, process, or device on a human, animal, or other biologic subject or substance plus all associated regulatory artifacts required for or derived from this effort.*

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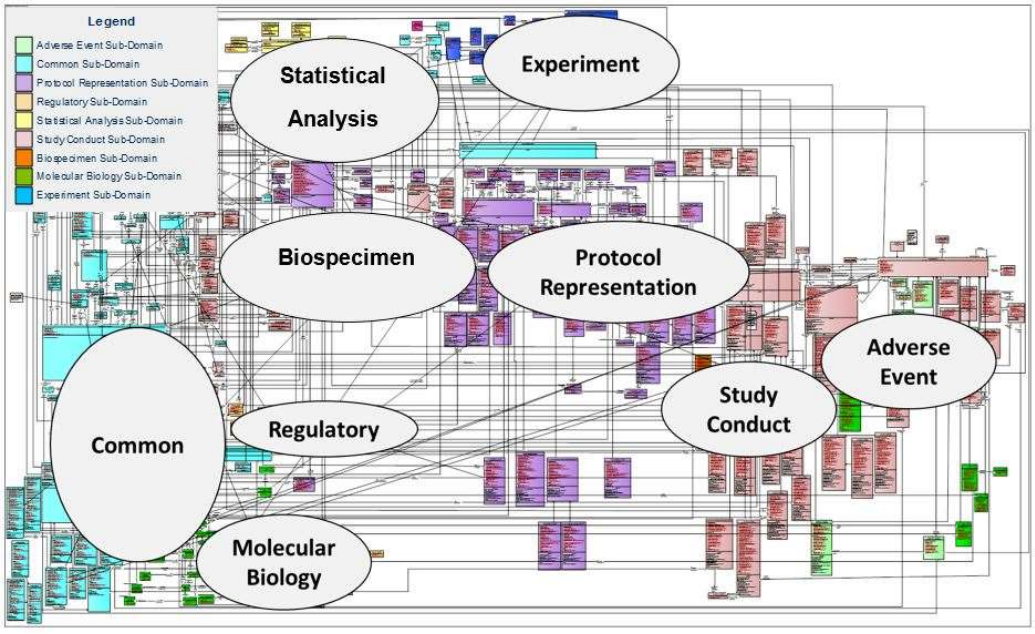
BRIDG and Subdomains



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CDISC Protocol Representation Model

V 1.0 Now Available! (Year: 2010 – CDISC Education)

Protocol Section	CRF Develop-ment	Data Collection	Data Analysis	Report or eSubmission
Info for Trial Registration				Study Summary
Eligibility Criteria				Eligibility Criteria
Study Design: Arms, Epochs				Study Design: Arms, Epochs
Study Design: Planned Events				Study Design: Planned Events
	CDASH CRFs	Data Collection	Data Tabulation	SDTM Data
Statistical Analysis Plan			Data Analysis	***ADaM*** Datasets
Appendices, etc.				Appendices, etc.

PR Version 1.0

Information Re-Use
Improved Quality and Efficiency

SDTM

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Early Implementers (2010)
- **Genzyme (now Sanofi)**
- **Medidata (Designer)**
- **City of Hope (ASPIRE)**

Study Design Elements required by FDA

Terminology supported by NCI EVS

Clinical Trial Registry (CTR) ODM XML supports:
- **WHO ICTRP (International Clinical Trial Registry Platform)**
- **NLM Clinicaltrials.gov**
- **Japan's CTR**

IHE Integration Profile:
- **Retrieve Protocol for Execution (RPE)**

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The Problem with the BRIDG Model: *SME Perspective (examples)*

- BRIDG Model has become 'too complicated' for most SMEs to easily understand
  - "Where are my words?"
    - E.G. "An Adverse Event is a type of Observation"
    - "We don't use the word 'arm'"
    - "That's not what we call it on submission"
  - SMEs tend to be focused on a particular 'sub-domain'
    - Adverse Events
    - Trial Design
    - Regulatory Reporting
- Certain constructs in the current model have little relevance to the average SME
  - Data Type bindings

CDISC

Source: Charlie Mead

HL7

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TransCelerate and Protocol-Related Activities

- TransCelerate (collaborative biopharma industry initiative) launched in 2012:
  - Common Protocol Template (CPT) initiative to develop a machine-readable AND human-readable protocol template; TCB worked with FDA and CDISC on this initiative
  - TCB also worked with CDISC on therapeutic area data standards content and the CDISC Library (formerly SHARE)
- Current CPT Information from TransCelerate:

  "The Clinical Content & Reuse (CC&R) Initiative, formerly known as Common Protocol Template (CPT), aims to enhance clinical trial processes by developing common content for reuse across clinical trial documents in the Clinical Template Suite (CTS)." (TransCelerate website)
- See also TransCelerate's Digital Dataflow Initiative.
- TransCelerate Members are in ICH.

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2017 NIH-FDA Release Standard Protocol Templates

NIH and FDA Release Protocol Template for Phase 2 and 3 IND/IDE Clinical Trials

Notice Number: NOT-OD-17-064

Key Dates

Release Date: May 2, 2017

Related Announcements

NOT-OD-18-167
NOT-OD-16-043
NOT-OD-19-092
NOT-DA-23-033

Issued by

National Institutes of Health (NIH)

Clinical Trial E-Protocol Tool and Template Documents

The electronic protocol writing tool aims to facilitate the development of two types of clinical trials involving human participants. The first type of trials are Phase 2 and 3 clinical trial protocols that require a Food and Drug Administration (FDA) Investigational New Drug (IND) or Investigational Device Exemption (IDE) application.

NIH developed a second protocol template to help behavioral and social science researchers prepare research protocols for human studies measuring a social or behavioral outcome or testing a behavioral or social science-based intervention.

Both templates found in the electronic protocol tool meet the standards outlined in the *International Council on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (ICH-E6)*. These are international standards of good clinical practice that apply to all clinical trials, and their goals are to ensure research integrity and protect human subjects. In addition, use of the electronic protocol tool allows researchers to interface directly with clincialtrials.gov.

Purpose

The National Institutes of Health (NIH) and Food and Drug Administration (FDA) developed a clinical trial protocol template with instructional and example text for NIH-funded investigators to use when writing protocols for phase 2 and 3 clinical trials that require Investigational New Drug application (IND) or Investigational Device Exemption (IDE) applications. In March 2016 a draft template was released for public comment generating nearly 200 comments from 60 respondents. All comments were carefully considered and many were incorporated into the final template. The agencies goal is to encourage and make it easier for investigators to prepare clinical trial protocols that are organized consistently and that contain all of the information necessary for the review of the protocol. The template follows the International Conference on Harmonisation (ICH) E6 (R2) Good Clinical Practice and is available as a Word document

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-064.html

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Thank You …

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ONLINE

Q3.2 ICH M11 Clinical Protocol Template and Exchange Standard

Ron Fitzmartin, PhD, MBA, ICH M11 Rapporteur, U.S. FDA

January 18, 2024

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U.S. FDA Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

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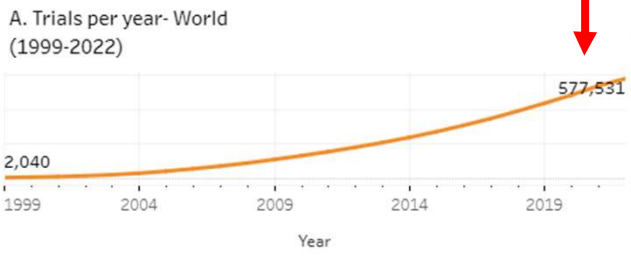
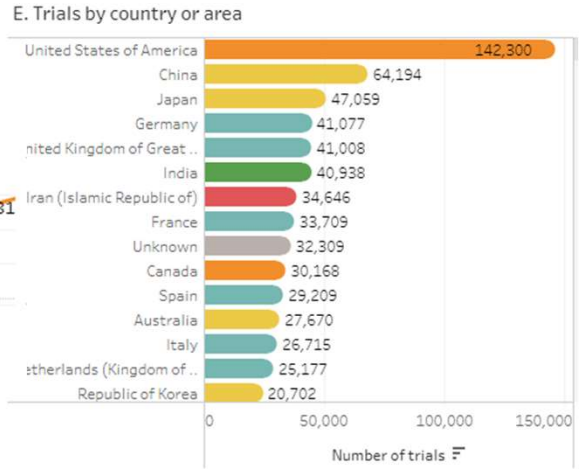
Number of Interventional Clinical Trials in 2022

577,531





That's a lot of protocols!

Number of trial registrations by location, disease, phase of development, age and sex of trial participants (1999-2022) (who.int)

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Why we need a standardized protocol template

U.S. FDA*	Est. # Unique Protocols Submitted Annually
CDER	4294
CBER	590
Est. Total	4884

* Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research -period 2018/2019

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ICH M11 Expert Working Group

- ICH M11 has three deliverables…
  1. **Guideline is a high-level document that:**
     - Provides the background on why a harmonized clinical protocol template is needed, and
     - Describes how the template and technical specification were developed.
  2. **Template**
     - Includes identification of headers, common text, instructions, data fields and terminologies.
  3. **Technical Specification**
     - Serves as a technical representation of the ICH M11 protocol template.
     - Aligns with the latest version of the ICH M11 guideline and template standard to enable electronic exchange of the clinical protocol information.

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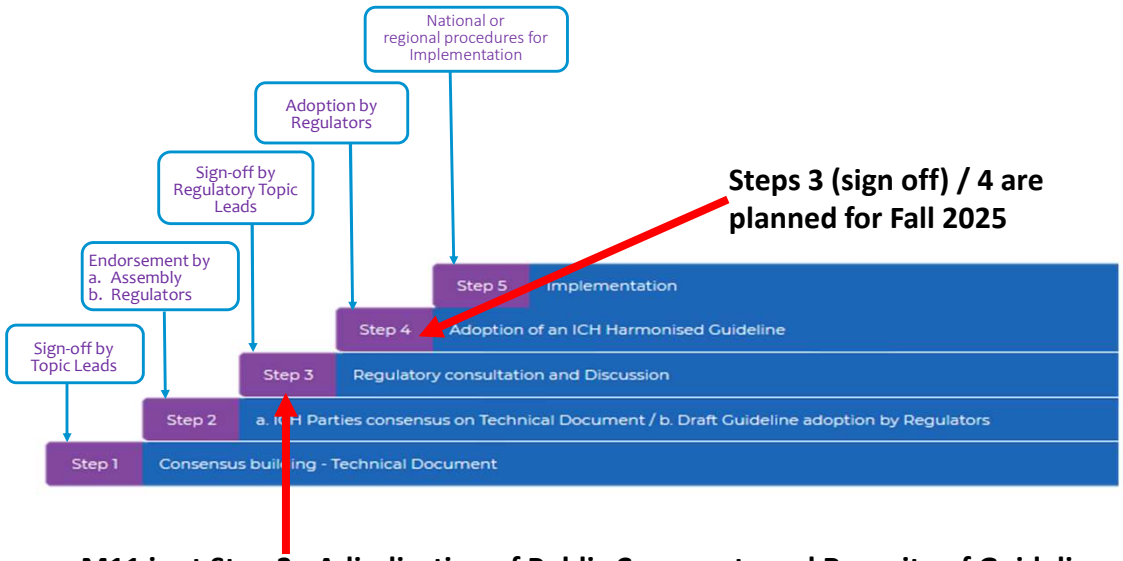
ICH Step Process



Steps 3 (sign off) / 4 are planned for Fall 2025

M11 is at Step 3 - Adjudication of Public Comments and Re-write of Guideline, Template and Technical Specification

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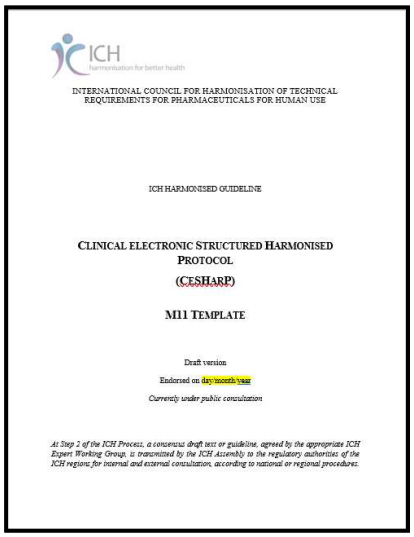
ICH M11 Terminology

- M11 / M2 collaborating with HL7 Vulcan / CDISC project to create draft semantics for the *Protocol Template / Tech Specification*
  - 257 Data Elements
  - 22 Valid Value Sets comprising 112 terms
- Plan to have CDISC curate the terminology
- CDISC will use their public review process prior to and regulatory public consultation later in year.



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 TEMPLATE

Draft version

Endorsed on day/month/year

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.

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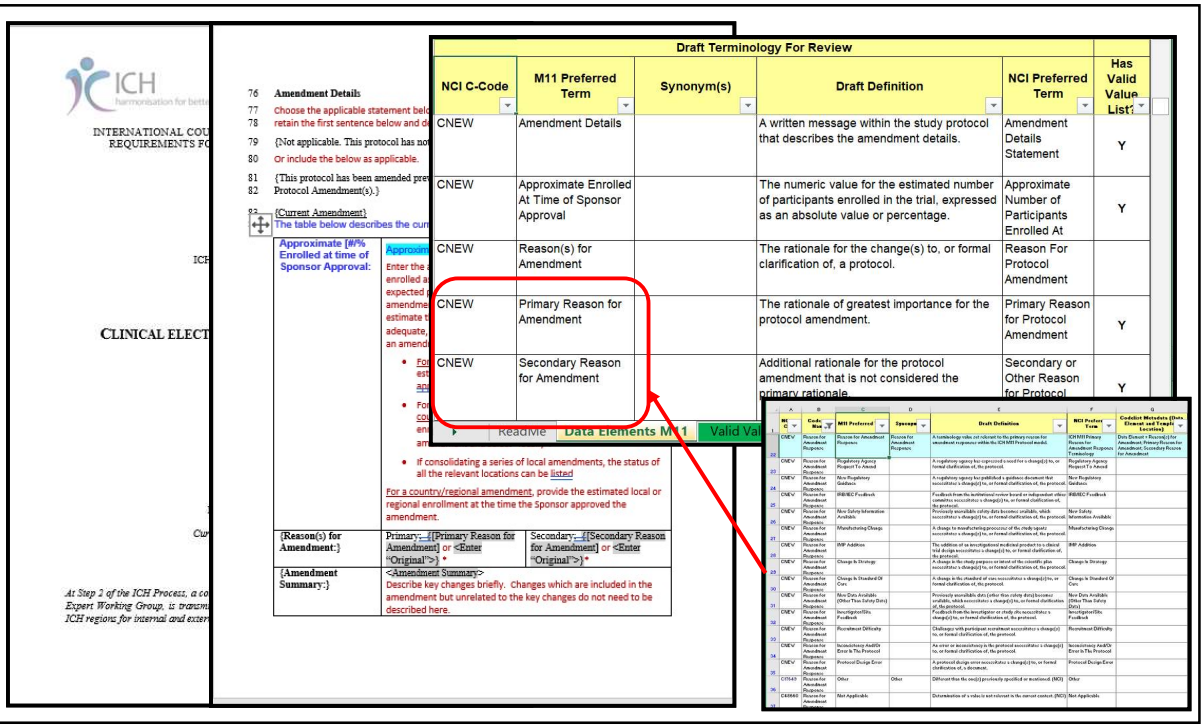

Draft Terminology For Review

NCI C-Code	M11 Preferred Term	Synonym(s)	Draft Definition	NCI Preferred Term	Has Valid Value List?
CNEW	Amendment Details		A written message within the study protocol that describes the amendment details.	Amendment Details Statement	Y
CNEW	Approximate Enrolled At Time of Sponsor Approval		The numeric value for the estimated number of participants enrolled in the trial, expressed as an absolute value or percentage.	Approximate Number of Participants Enrolled At	Y
CNEW	Reason(s) for Amendment		The rationale for the change(s) to, or formal clarification of, a protocol.	Reason For Protocol Amendment	
CNEW	Primary Reason for Amendment		The rationale of greatest importance for the protocol amendment.	Primary Reason for Protocol Amendment	Y
CNEW	Secondary Reason for Amendment		Additional rationale for the protocol amendment that is not considered the primary rationale.	Secondary or Other Reason for Protocol	Y

Readme | Data Elements M11 | Valid Val

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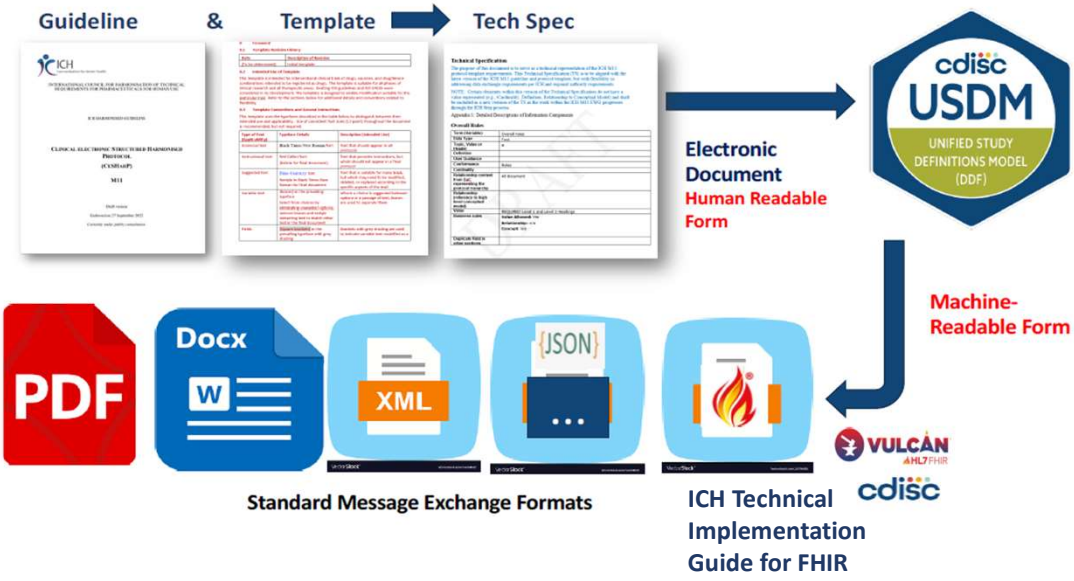
M2/M11 Technical Development Process



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PROJECT PRISM

(PrecisionFDA Regulatory Information Service Module)

- Joint FDA / Industry Research Collaborative to demonstrate the feasibility of
  - Interactive and collaborative regulatory and scientific review and
  - Submission validation
- Utilizing FDA's production regulatory cloud platform, known as PrecisionFDA
- Utilizing actual regulatory-grade data provided by PRISM Industry partners, as well as third-party tools FDA currently uses for eCTD and study data review / validation.
- Various use cases will be evaluated, including *standardized clinical protocol*.

Note: Regulatory data that is under official regulatory review will not be used in this research

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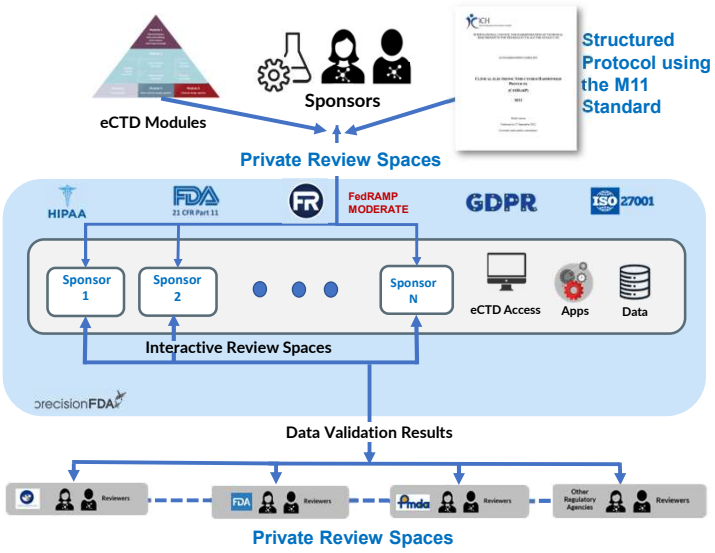
Implementation of the M11 Protocol Standard for Interactive Activities in the Cloud



M11-conformed eProtocols…

- Use a common data model & standards (e.g., CDISC)
- Can be exchanged using multiple standards: FHIR, XML, MS Word, PDF
- Can use common tools to access data repositories
- Can be real-time quality-checked
- Ensure consistency across protocol sections
- Ensure line of sight of trial objectives, endpoints, procedures and design.
- Facilitate downstream processes, e.g., SAP, CSR, Registries

Note: This is only an example, the regulatory agencies noted above does not imply their participation

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Thank You

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Q3.3 The perspective of CROs in Europe

Yoanni Th. MATSAKIS – European CROs Federation (EUCROF)

January 18, 2024

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A few words about

EUCROF
European CRO Federation

www.eucrof.eu
https://conference.eucrof.eu/

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EUCROF : the mission

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- EUCROF is a legal non-profit entity founded in 2005 and representing the interests of CROs in Europe towards
  - Regulatory bodies
  - Pharmaceutical, biotech, medical device industry
  - Healthcare related industry within the field of clinical research
  - Patients' associations
- EUCROF's goal is to promote Clinical Research by improving the knowledge, competence and skills of CROs

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An international representative corporate organisation

ATHENS DIGITAL

MEMBERS : National Associations

1. ACCSCR	Romania	17
2. ACRO-CZ	Czech Republic	16
3. ACRON	The Netherlands	41
4. AECIC	Spain	29
5. AFCROs	France	100
6. AICRO	Italy	30
7. ASCRO	Sweden	17
8. BeCRO	Belgium	52
9. BVMA	Germany	46
10. CCRA	United Kingdom	28
11. GCP&RA	Lithuania	5
12. HACRO	Greece	16
13. POLCRO	Poland	5
14. SACROP	Slovakia	16
15. SAKDER	Turkey	24

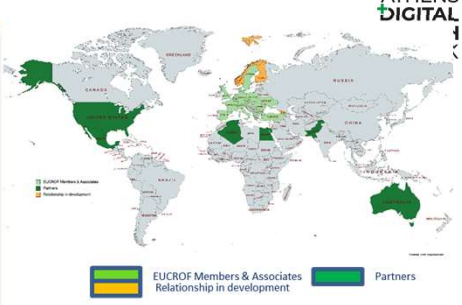
- Members & Associate Mbs: legal entities registered in Europe
- Partners: legal entities registered outside Europe

Associate Members

1. Albania
2. Bulgaria
3. Croatia
4. Denmark
5. Latvia
6. Portugal
7. Slovenia
8. Spain
9. Switzerland (4)
10. Ukraine
11. United Kingdom (2)

Partner Members

1. Algeria
2. Australia
3. Egypt
4. Israel
5. Mexico
6. Pakistan
7. USA



- **31 Countries**
- 450+ Affiliated CROs
- +90% are SMEs
- ~ 30 000 professionals

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Governance - Organization

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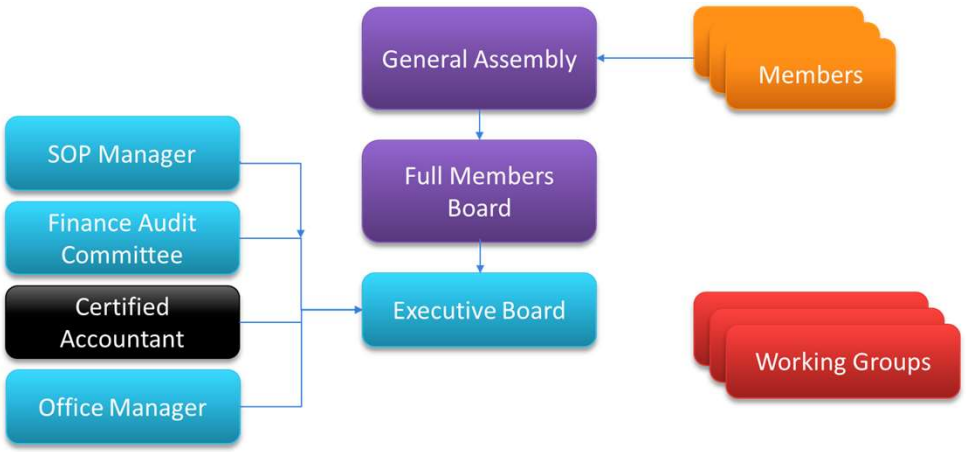

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Governance - Organization

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- Executive Board
  - Elected, 2 years mandate
  - Monthly meetings
  - Proposes Policy / Coordinates / Day to day management
  - 1 x half time permanent office manager (Assia Rosati)
  - Subcontracted accounting office
- Full Member Board
  - Every Member Represented
  - Decision Making – Votes (members only)
  - Monthly meetings
- General Assembly
  - Decision Making - Votes
  - Bi-annual meetings
- Financial Auditing Committee
- Working Groups


President
Martine DEHLINGER-KREMER


Vice-President
Stefano MARINI


Secretary
Simon LEE


Treasurer
Yoanni Th. MATSAKIS


Member
Christophe GOLENVAUX

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Working groups

Working Group	Chair
Clinical Trial Centres	Antoinette van Dijk
Clinical Trials Legislation	Dagmar Chase
Clinical Trials Logistics	Michael Shumilin
Communication	Christophe Golenvaux
Early Phase	---
Events and Training	Donato Bonifazi
Innovative Medicines	Dolores Pérez Méndez
Medical Devices	Şebnem Yaşaroğulları
New Technologies	Fiona Maini
Paediatrics	Martine Dehlinger-Kremer
Patients' Associations	Jean-Sébastien Gosuin
Pharmacovigilance	Nicolas Tsiakkas
Real World Data & Digital Health	Alexandre Malouvier

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Ongoing initiatives and accomplishments (1/5)

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- Active Stakeholder of the EMA

EMA EUROPEAN MEDICINES AGENCY

  - EU Clinical Trial Information System (CTIS)
    - Involved from the start in 2014: Dossier set up; User Acceptance Testing off site;
    - Two Product Owners and the Industry Training representative.
    - Participate to the regular CTIS stakeholder meetings
    - Participate in the CTR and CT transitions initiative to identify a solution
  - Member of Industry Stakeholders, Quarterly meetings
  - Member of ACT EU Multi-Stakeholder Platform (KOM in June 2023)
  - Contributed actively to EU DCT project: Workshop at EMA in October 2022
  - European Network of Paediatric Research (Enpr-EMA)
  - Pharmacovigilance
  - GCP Inspection Working Group
  - COVID-19 pandemic & new rules - Collaboration with EMA and EU Commission for new guidelines

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Ongoing initiatives and accomplishments (2/5)

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- Specific positions with the EMA
  - Member European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) WG2, since February 2018: Xavier Fournie
  - Observer Member Coordinating Group of European Network of Paediatric Research at EMA (Enpr-EMA) since April 2018: Martine Dehlinger-Kremer

- GDPR Code of Conduct for CROs
  - Approved by the 27 EU DPA and EDPB, CNIL is the coordinating DPA. Collaboration with Industry, Patient Organisations, Academics & ECs
  - Will be first International GDPR CoC in the health area.
  - Approval expected mid 2024.

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Collaborations with other stakeholders (3/5)

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EMA EUROPEAN MEDICINES AGENCY
European Commission
World Health Organization
ENEPP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EPF European Patients Forum
efpia European Federation of Pharmaceutical Industries and Associations
EUCOPE European Confederation of Pharmaceutical Entrepreneurs AISBL
ACRO
JCROA Japan CRO Association
WORLD DUCHENNE ORGANIZATION UPPMD
EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy
EnprEMA
ACRP
EuropaBio
leem LES ENTREPRISES DU MÉDICAMENT
SCRS Society for Clinical Research Sites
A NETWORK POWERED BY PEERS eClinical forum

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Ongoing initiatives and accomplishments (4/5)

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- Remote SDV/SDR
  - Position paper endorsed by EFPIA, reviewed by EMA. Final version with EMA
- EU CRO Benchmarking
  - Position of CROs in clinical research environment
  - Article published pharma journal in Sweden
  - New benchmarking in 2023
- Clinical Research Barometer
- Publications & Posters
  - Poster presentation, ISPOR, Boston, USA, 9 May 2023 on " *The Importance of Clinical Research Organizations (CRO) in Clinical Research and Impact of COVID-19 Pandemic*"
  - Publication of abstract in Health Value, June 2023 "*The current status of European research related to COVID-19*": Published in Applied Clinical Trial (on-line), 26 Jan 2021
  - Pharmacovigilance (PV) in 2020: *Boldly Shaping the Future*-Part I and II in Applied Clinical Trials

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Ongoing initiatives and accomplishments

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EUCROF24
19-20 FEBRUARY | PRAGUE

https://conference.eucrof.eu/

7TH EUROPEAN CONFERENCE ON CLINICAL RESEARCH: PUSHING BOUNDARIES AND ACCELERATING INNOVATION

EUCROF24 will bring together pharma, biotech, medical device companies, CROs and other service providers, technology providers, regulators, patients, and academia, to discuss the current challenges, and future direction of Clinical Research across Europe. EUCROF24 is the 7th running of the EUCROF Clinical Research Conference that attracts a diverse range of speakers and attendees from functions including clinical operations, regulatory, data management, statistics, medical and safety, digital health technology, quality assurance, as well as patient groups and regulators.

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Participation in xShare

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SHARE
EHR Xchange Format

- A HORIZON-HLTH-2023-IND-06-02 project led by HL7 Europe
- WP5 - European EHRxF in Clinical Research: Core Set and IPS-R
  - Develop harmonized data formats starting from Business use cases using HIDs listed in EHDS draft regulation aligning them across health care, population health, and clinical research **(WP**2-3-4-**5)**
  - Open call for implementation of the IPS-R
  - A 120 000 EUR budget to help and attract candidates for implementation
  - An introductory presentation at the 7th European Conference on Clinical Research
  - A full presentation in 2026 at the 8th European Conference on Clinical Research

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Expectations

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- Full Digital Data Flow for Clinical Research
  - From protocol to submission, including data collection (HL7, FHIR, CDash & ODM), data management (SDTM) and stat (ADAM)
  - Data collection can be done directly from the EHR (where HL7 and FHIR have a key role)
- EUCROF affiliates are fully aligned with the objectives
  - Reduce manual curation of protocol information
  - Automated setup of systems to execute a study (e.g. EDC, CTMS, HER, DCT software)
  - Advanced analytics : smart study design, predictive risk modelling, feasibility …
  - Reduction in cost and time for bespoke integration
- Data Protection rights (principle of minimization …)
- Transform data into knowledge : use of AI based tools, set-up tasks automation

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What EUCROF can do ?

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- Contribute to ICH M11 CeSHarp : data managers, subject matter experts (business domain, standards ...)
- Business cases : implementation in processes and tools, develop new solutions and offers
- Awareness & experience sharing: working groups, webinars, conference …

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Thank You …

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Q3.4 The perspective of Academic Centers

Meletis Dimopoulos, National and Kapodistrian University of Athens

January 18, 2024

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Vulcan Utilizing the Digital Protocol / UDP Project (was ICH M11):
Focus: Mission, Plans, Key Challenges, European Involvement
The perspective of Academic Centers

Meletios-Athanasios Dimopoulos, MD
Professor and Chairman

Department of Clinical Therapeutics, Alexandra Hospital
National and Kapodistrian University of Athens,
School of Medicine, Athens, Greece

Athens Digital Health Week, 15-19 January 2024

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The perspective of Academic Centers

Benefits for Academic Centers (1/6)

- Enhanced collaboration and knowledge sharing
  1. Academic centers are often hubs of interdisciplinary collaboration, bringing together researchers, clinicians, and students from various disciplines.
  2. The implementation of the Digital Protocol Project fosters seamless communication and knowledge sharing among these diverse stakeholders.
  3. Researchers can access and exchange standardized protocol information, promoting collaboration on a global scale.

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The perspective of Academic Centers

Benefits for Academic Centers (2/6)

- Efficient protocol development
  1. The Digital Protocol significantly accelerates the protocol development process.
  2. Academic centers can benefit from streamlined and standardized templates, reducing the time and effort required to create protocols.
  3. This efficiency allows researchers to focus more on the scientific aspects of their studies and accelerates the overall pace of research within academic settings.

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The perspective of Academic Centers

Benefits for Academic Centers (3/6)

- Interoperability and data integrity
  1. The alignment of CeSHarP with CDISC standards ensures interoperability and data integrity throughout the research lifecycle.
  2. Academic centers can seamlessly exchange protocol information with other institutions, ensuring consistency and reliability in data interpretation.
  3. This interoperability is crucial for multi-center trials and collaborative research initiatives.

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The perspective of Academic Centers

Benefits for Academic Centers (4/6)

- Adherence to regulatory standards
  1. Compliance with regulatory standards is paramount in clinical research.
  2. The Digital Protocol Project aligns with international regulatory expectations, ensuring that academic centers adopting this standard adhere to the highest quality and ethical standards.
  3. This not only expedites regulatory approvals but also enhances the credibility of research conducted within academic institutions.

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The perspective of Academic Centers

Benefits for Academic Centers (5/6)

- Resource optimization
  1. Academic centers often face resource constraints, including time, personnel, and funding.
  2. The Digital Protocol Project optimizes these resources by offering standardized templates and guidelines.
  3. This minimizes the need for redundant work and allows academic institutions to allocate resources more efficiently, thereby maximizing the impact of research initiatives.

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The perspective of Academic Centers

Benefits for Academic Centers (6/6)

- Educational opportunities
  1. The implementation of a standardized digital protocol provides unique educational opportunities for students within academic centers.
  2. By utilizing cutting-edge technologies and adhering to global standards, students gain valuable experience that aligns with industry practices.
  3. This exposure enhances their preparedness for careers in clinical research and strengthens the academic institution's reputation.

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The perspective of Academic Centers

University Community – Potential Perspectives (1/6)

- Research excellence

1. The Digital Protocol Project positions academic institutions at the forefront of research excellence.
2. By adopting standardized digital protocols, universities demonstrate a commitment to leveraging innovative technologies for the advancement of science.
3. This, in turn, attracts top-tier researchers, funding opportunities, and collaborative partnerships, enhancing the overall research ecosystem.

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The perspective of Academic Centers

University Community – Potential Perspectives (2/6)

Global collaboration and networking

1. The interoperability facilitated by the Digital Protocol Project opens doors for global collaboration.
2. Academic centers can engage in international research initiatives, exchange data with global partners, and contribute to the collective knowledge base.
3. This fosters a sense of community within the university ecosystem and provides students and researchers with exposure to diverse perspectives.

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The perspective of Academic Centers

University Community – Potential Perspectives (3/6)

- Competitive advantage in grant applications

1. Funding agencies increasingly prioritize research projects that demonstrate alignment with international standards and innovative methodologies.
2. Academic centers utilizing the Digital Protocol Project gain a competitive edge in grant applications.
3. The standardized approach enhances the credibility of proposed research, making it more appealing to funding bodies seeking projects with a high likelihood of success and impact.

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The perspective of Academic Centers

University Community – Potential Perspectives (4/6)

Cross-disciplinary synergy

1. The Digital Protocol Project encourages cross-disciplinary collaboration within the university community. Researchers from diverse fields can converge around standardized protocols, fostering synergies that lead to novel insights and breakthroughs.
2. This interdisciplinary approach aligns with the evolving nature of modern research, where complex problems often require multifaceted solutions.

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The perspective of Academic Centers

University Community – Potential Perspectives (5/6)

- Alumni and industry collaboration
  1. Graduates from academic institutions adopting the Digital Protocol Project enter the workforce with a unique skill set that aligns with industry standards.
  2. This not only enhances their employability but also establishes stronger connections between academia and industry.
  3. Industry collaborations and partnerships become more seamless, creating a mutually beneficial relationship between academic centers and the private sector.

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The perspective of Academic Centers

University Community – Potential Perspectives (6/6)

Contribution to scientific knowledge

1. The implementation of standardized digital protocols contributes to the broader scientific knowledge base.
2. As academic centers adopt these protocols and conduct research in alignment with global standards, they contribute valuable data to larger datasets.
3. This collective contribution enhances the overall understanding of diseases, treatments, and healthcare practices, benefiting the global scientific community.

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The perspective of Academic Centers

Take Home Message

- The Digital Protocol Project (ICH M11) represents a paradigm shift in the way clinical trials are conceptualized and conducted.
- For academic centers, this initiative offers a myriad of benefits, ranging from enhanced collaboration and efficiency to global recognition and educational opportunities.
- The potential perspectives for the university community extend beyond individual institutions, influencing the broader research landscape and contributing to the advancement of science on a global scale.
- As academic centers embrace the Digital Protocol, they position themselves as leaders in research innovation, paving the way for a more interconnected and impactful future in the field of clinical trials and medical research.

- ICH: International Committee on Harmonisation

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The perspective of Academic Centers

References

- https://www.ema.europa.eu/en/ich-m11-guideline-clinical-study-protocol-template-and-technical-specifications-scientific-guideline
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m11-clinical-electronic-structured-harmonised-protocol
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Q3.5 Decentralized clinical trials (or elements in clinical trials)

Christos Lionis MD PhD FRCGP(Hon) FESC FWONCA
Emeritus Professor of General Practice and Primary Health Care School of Medicine, University of Crete, Greece
Former EC Expert Panel on Effective Ways of Investing in Health
EMA SAG Vaccines
WONCA Working Party on Mental Health (Chair)
University of Crete

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Acknowledgements:

This presentation is based on a collaborative work carried out at the School of Medicine, University of Crete and it was my privilege working and learning from the work of many colleagues, including Dr. Marilena Anastasaki, Dr. Sophia Papadakis and Dr. Elena Petelos

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CONTENTS

Definition of concepts

EC/EMA Recommendation paper, General considerations

Specific considerations and experiences gained from studies carried out in Crete, Greece

Conclusive remarks

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A Definition

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / News & Events for Human Drugs / The Evolving Role of Decentralized Clinical Trials and Digital Health Technologies

The Evolving Role of Decentralized Clinical Trials and Digital Health Technologies

"Decentralized clinical trials and digital health technologies are gaining momentum in medical research, allowing research participants to partake in trials remotely using state-of-the-art digital health technologies.

https://www.fda.gov/drugs/news-events-human-drugs/evolving-role-decentralized-clinical-trials-and-digital-health technologies#:~:text=In%20a%20decentralized%20clinical%20trial,facility%2C%20or%20a%20nearby%20laboratory

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Why Decentralised Clinical Trials

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1. They are important for access and accessibility, compared with traditional clinical trials.
2. They bring new challenges and new opportunities for healthcare professionals and allied professions involved in trial conduct.
3. They are suitable for primary health care essential

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General considerations

HMA Heads of Medicines Agencies | European Commission | EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Recommendation paper on decentralised elements in clinical trials

TABLE OF CONTENT

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- Protection of rights, safety, dignity and well being of participants
- Adherence to EU, national laws, regulations etc
- Participatory process
- Involvement in the design, development and implementation
- Transfer of burden be weighed against the potential benefits
- A summary of the decentralized elements in the cover letter
- Risk benefit assessment
- Outside of the traditional patient centers
- To be designed to generate reliable and robust data
- IT devices/ technologies to be fit for reliable data collection
- Contingency plan
- Medical devices, including in vitro diagnostics, to be compliant with the applicable medical device legislation

- *Well-being*

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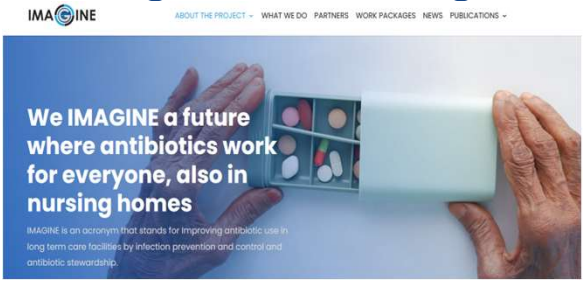
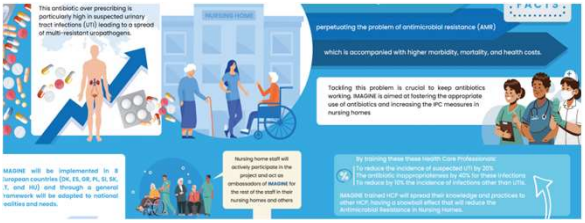
Consideration on keeping oversight on incoming data

- Trial participants, investigators, and service providers should receive training on how to use digital tools to ensure proper data collection, review, and transmission.
- A review of safety data should be planned with a high-risk perspective.
- Digital tools need to transmit the required alerts as planned.
- Trial participants should be fully informed in advance on how the information is transmitted via digital tools.





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Informed consent process

- In a remote manner.
- Digital information leaflets to be used.
- Informed consent interview (on-site or a digital/virtual meeting, the trial participant's preferences)
- Use of electronic methods for the consent signature
- Provision of adequate and sufficient information, including the trial design, the target population, the risks, burdens, and potential leaflet.

diseases | MDPI

Article

A Mixture of Essential Oils from Three Cretan Aromatic Plants Inhibits SARS-CoV-2 Proliferation: A Proof-of-Concept Intervention Study in Ambulatory Patients

Christos Lionis [1,2,*,†], Elena Petelos [1,3], Manolis Linardakis [1], Athanasios Diamantakis [1], Emmanouil Symvoulakis [1], Maria-Nefeli Karkana [1], Marilena Kampa [4], Stergios A. Pirintsos [5,6], George Sourvinos [7] and Elias Castanas [4,†]

- Data were collected on Day 1, Day 7, and Day 14.
- Following the initial face-to-face consultation, data collection and consultations were performed by trained medical personnel either remotely (by phone) or via home visits.
- The severity of symptoms was assessed through the utilization of a five-point Likert scale, starting from 0 (no severity),1 (very mild), 2 (mild), 3 (moderate), and 4 (severe).
- Data were recorded on Day 1 and taken as the baseline.

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Informed consent interview

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- To be remotely
- **Vulnerable patients**
- Trial participant's preferences

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Digital information leaflets

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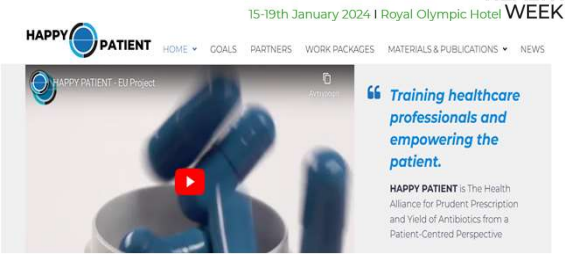
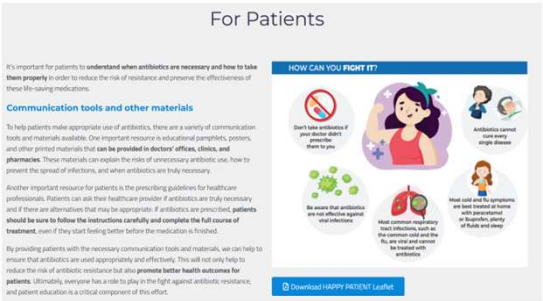
- The trial participant's capacity and preferences.
- To serve a double target, trial participant's information and informed consent interview.
- In alignment with the protocol and the clinical trial application.





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Delivery of investigational medicinal products and administration at home

•Considerations of IMP delivery direct to trial participants

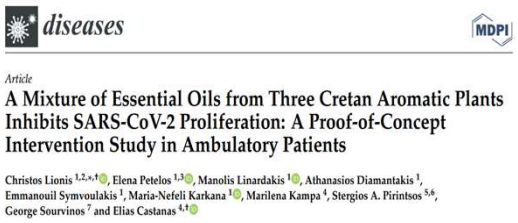
-Who will be responsible for the delivery to the participant (to distribute or dispense)

-Who remains responsible for the decision of treatment

-The presence and involvement of caring services

-Alignment with ethical approval and protocol

•Consideration on IMP storage and administration at the trial participants' home



diseases

MDPI

Article

A Mixture of Essential Oils from Three Cretan Aromatic Plants Inhibits SARS-CoV-2 Proliferation: A Proof-of-Concept Intervention Study in Ambulatory Patients

Christos Lionis [1,2,*,†], Elena Petelos [1,3], Manolis Linardakis [1], Athanasios Diamantakis [1], Emmanouil Symvoulakis [1], Maria-Nefeli Karkana [1], Marilena Kampa [4], Stergios A. Pirintsos [5,6], George Sourvinos [7] and Elias Castanas [4,†]

- The CAPeo mixture, in the form of two 0.5 mL soft capsules, in a concentration of 15 mL/L, was administered per os daily for two weeks (14 days) to the subjects who were allocated in the IG.
- The subjects in the CG received usual care, including instructions for monitoring the progress of the illness and for taking analgesics if needed.

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Trials related procedures at home

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- Home situation and appropriateness
- Set of inclusion and exclusion criteria regarding the adequacy of trial's participant home
- Do not harm or cause additional risk to the trial participant
- Compliance monitoring
- Training of the people involved in the procedures of the trial at home
- An opportunity to meet the PI in person
- Assessment of adverse events
- Alternatives provision

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Data collection and management

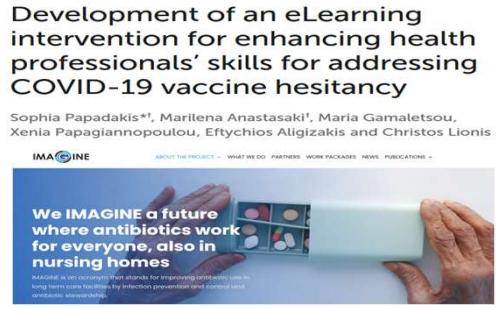
An extensive shift of data collection from the investigator site to:

- the trial participant
- Care givers
- Caring Services
- Other people involved

Digital training of the people involved in the data collection.

Quality assessment of all decentralised procedures.

Alignment with the protocol and ethical approval.



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Trial monitoring

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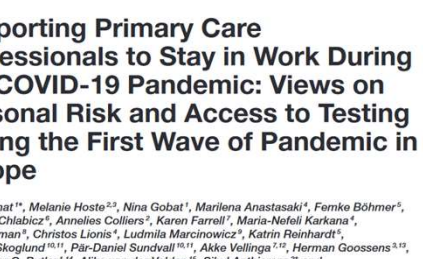
- Usually, a combination of centralized and site monitoring procedures.
- Risk associated with decentralised process, tools, locations, and people involved in the trial monitoring.
- Accountable team and its training.



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Concluding remarks

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- There are numerous reasons to implement decentralized clinical trials.
- Decentralized clinical trials can facilitate the integration of primary healthcare, enhancing not only research but also the quality of patient care.
- The existing legislation and regulatory framework necessitate a comprehensive revision.

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ONLINE

Q3.6 ICH M11, Digital Protocols: A Pharma Perspective

Rob DiCicco, TransCelerate BioPharma

January 18, 2024

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TransCelerate was conceived to improve the health of people around the world by accelerating and simplifying the research and development of innovative new therapies

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TransCelerate BIOPHARMA INC.
Accelerating Answers.

In 2012, after several years of discussion, R&D Leaders formed a non-profit to collaborate using the words "**Transform**" and "**Accelerate**" to create TransCelerate.

Member driven mission to collaborate across the global biopharmaceutical research and development community to **identify, prioritize, design, and facilitate** the implementation of solutions designed to drive the **efficient, effective and high-quality delivery of new medicines.**

TransCelerate has grown from **10 pioneering companies** to **22 Member Companies** working towards improvement in key value drivers in clinical research.

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Since 2012, we have been on a journey to advance data utilization/reuse *in partnership with CDISC, Regulators and Technology Companies*

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- Clinical Data Standards
- Common Protocol Template
- FDA-NIH Leadership Council
- Automation PoC
- Digital Data Flow
- ICH M11 CeSHarp
- ACRO and EU PEARL Collaborations
- Vulcan

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Where are we now ?

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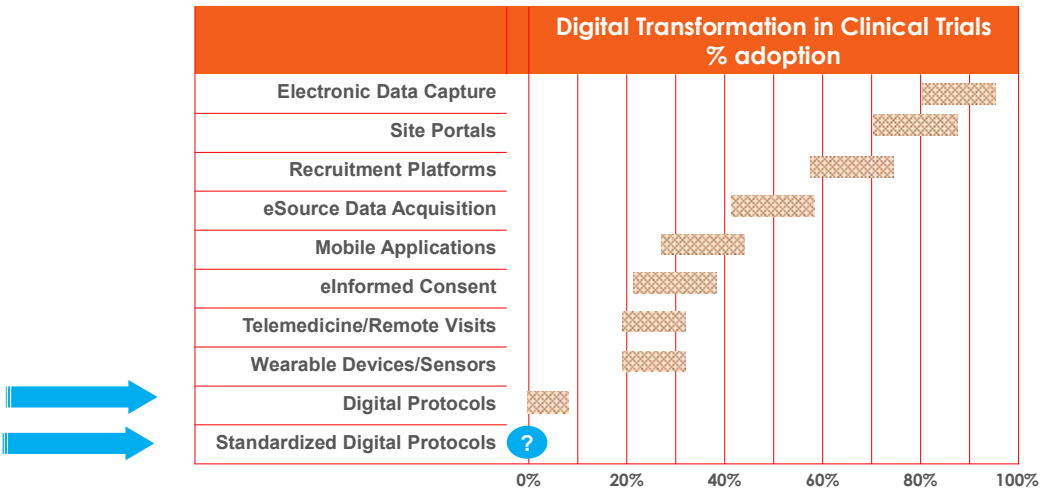

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Digital Data Flow At-a-Glance

Digitizing clinical study design components to enable interoperability and reuse

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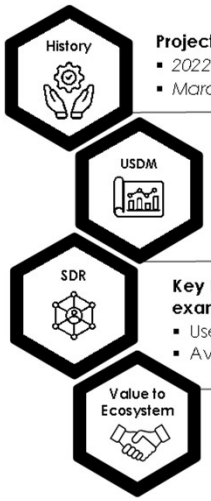

Project sponsored by TransCelerate and solutions developed in close collaboration with CDISC
- *2022*: Minimum Viable Product proved out EDC set-up use case
- *March 2023*: v2.0 release proved out additional downstream automation & analytics use cases

Key Deliverable: CDISC Unified Study Definitions Model (USDM) specifies the structured components of a clinical study design / clinical protocol
- Structure for biomedical concepts and advanced timepoints support automated set up of Schedule of Activities and more complex study design types

Key Deliverable: Study Definitions Repository (SDR) Reference Implementation acts as a functioning, example approach to connect systems using protocol info
- Used to input, export and store study definitions in a USDM-conformant format
- Available as downloadable open-source code or accessible via a shared sandbox environment

Solutions create new sources of value for sponsors, sites & patients through digitization
- Data interoperability, automation & analytics minimize time to start-up & improve quality by design
- Digital protocols enable assisted study design, automated feasibility, eligibility matching, etc.
- Ability to plug-and-play across clinical systems in IT landscape

https://transcelerate.github.io/ddf-home/

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Collaboration to amplify value of multiple initiatives

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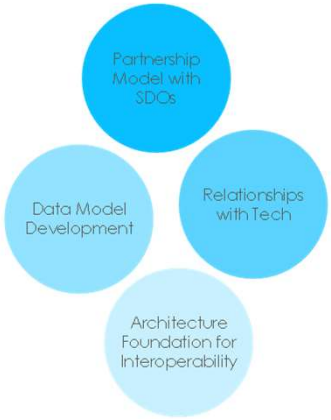
Capabilities, expertise, and relationships built to date across multiple projects



collaborating to maximize synergies & collective resources

will extend the value of multiple initiatives across the ecosystem

- Regulatory-driven implementation of Harmonized Protocol Guideline
- Regulator Receipt of Digitized Protocol (USDM + FHIR)
- Operational & EHR-related Uses of Digitized Protocols

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What, **How and Why?**

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CONVENE STAKEHOLDERS TO READY THE ECOSYSTEM FOR CLINICAL TRIALS AT THE POINT OF CARE

ENABLE COMPLETE DIGITIZATION & INTEROPERABILITY OF THE STUDY PROTOCOL ACROSS RESEARCH & CARE

Ecosystem collaboration is fundamental to these goals

- TransCelerate Members
- HCPs / Clinicians
- Community Care
- Patient Groups
- Regulators
- Policy Makers / Agencies
- Technology Community
- Standards Setting Org's
- Other Consortia

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Q3.7 The Vulcan UDP Project

Hugh Glover, Vulcan Technical Director

January 18, 2024

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UDP Project Deliverables

CeSHarP

- Tech Spec
- Template
- Guideline
- FHIR –Technical Guide

USDM and Terminology

- USDM
- M11/USDM Terminology
- USDM JSON API
- USDM Conformance Rules
- USDMIG

Utilizing the Digital Protocol – UDP

- Use Cases
- Implementation Guide(s)
- Reference Application
- Connectathon

Shared

- Maintenance Plan
- Communications Strategy

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Talking Points:

- 4 Organisations, 3 projects, 14 Deliverables
- Deliverables have interdependencies
- ICH asked Vulcan to help develop the FHIR Implementation Guide
- By going beyond the original ICH objectives CDISC, TransCelerate and Vulcan make the CeSHarP TechSpec and Template more widely applicable and useable.

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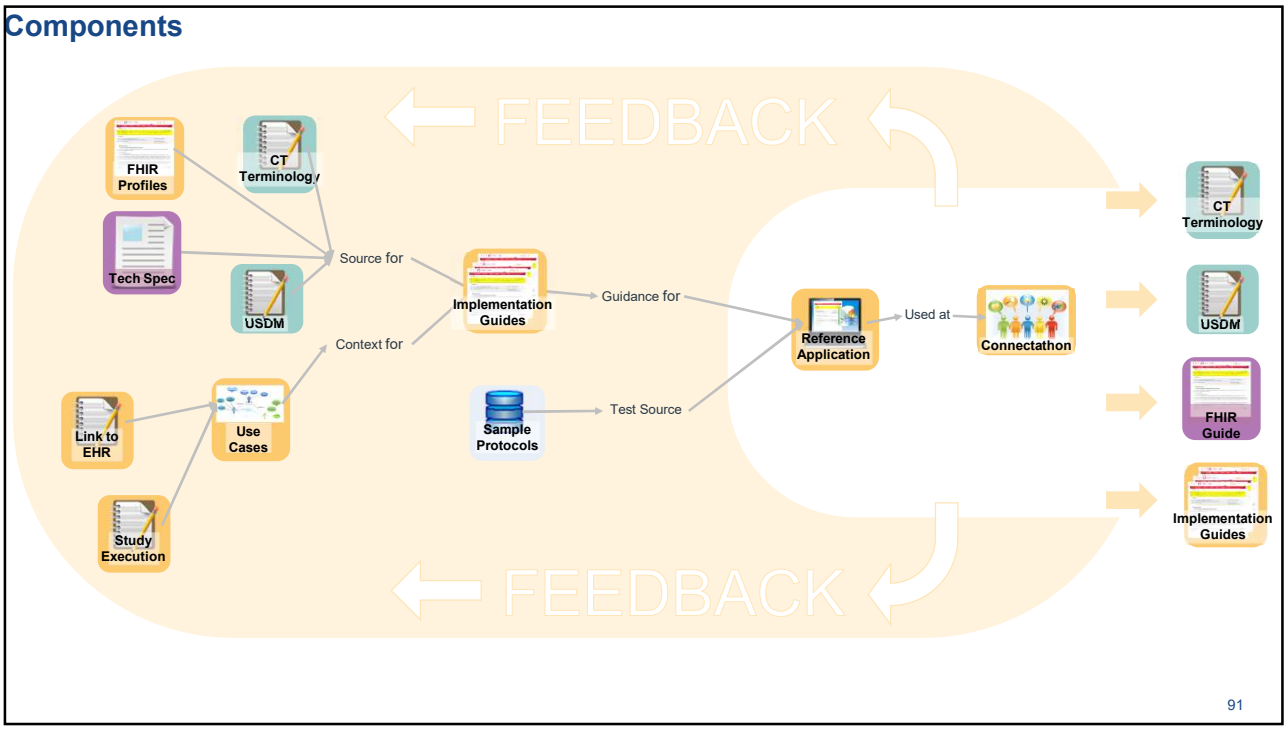
Components
FEEDBACK
FHIR Profiles
CT Terminology
Tech Spec
USDM
Source for
Context for
Implementation Guides
Guidance for
Reference Application
Used at
Connectathon
Link to EHR
Use Cases
Study Execution
Sample Protocols
Test Source
CT Terminology
USDM
FHIR Guide
Implementation Guides
FEEDBACK
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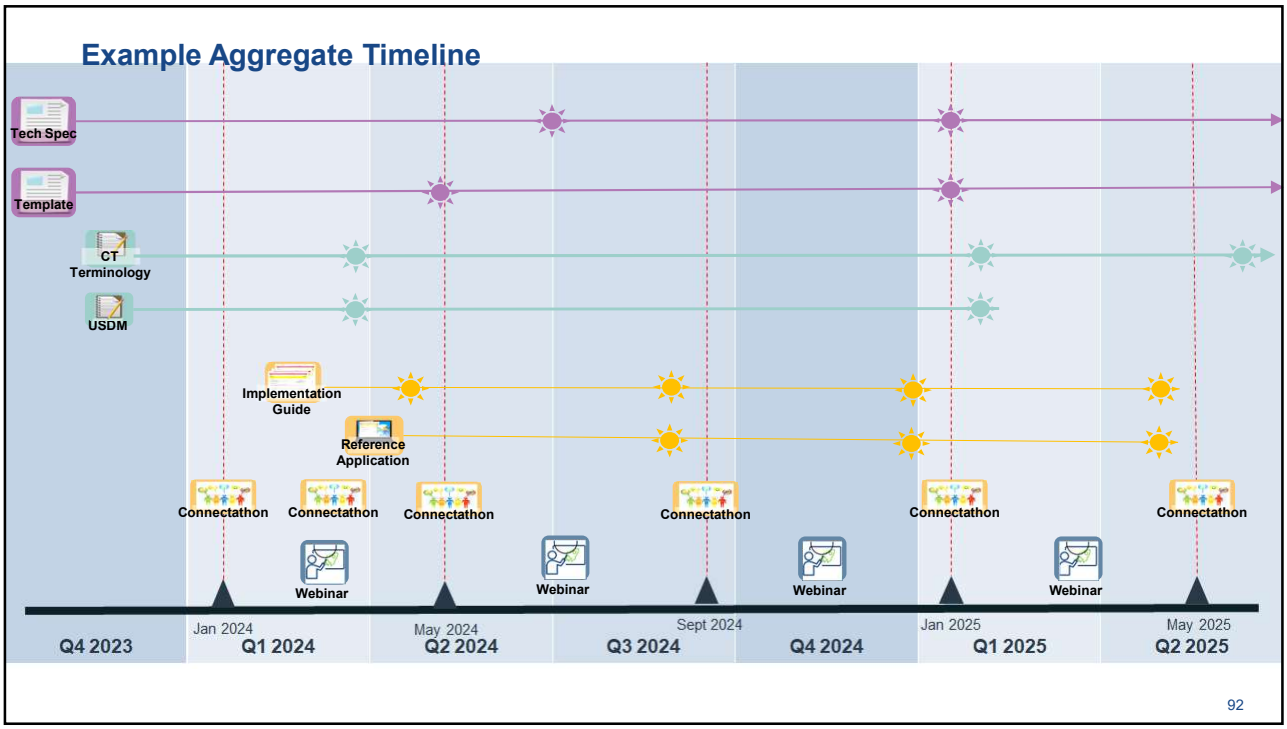
Example Aggregate Timeline
Tech Spec
Template
CT Terminology
USDM
Implementation Guide
Reference Application
Connectathon
Connectathon
Connectathon
Connectathon
Connectathon
Connectathon
Webinar
Webinar
Webinar
Webinar
Jan 2024
May 2024
Sept 2024
Jan 2025
May 2025
Q4 2023
Q1 2024
Q2 2024
Q3 2024
Q4 2024
Q1 2025
Q2 2025
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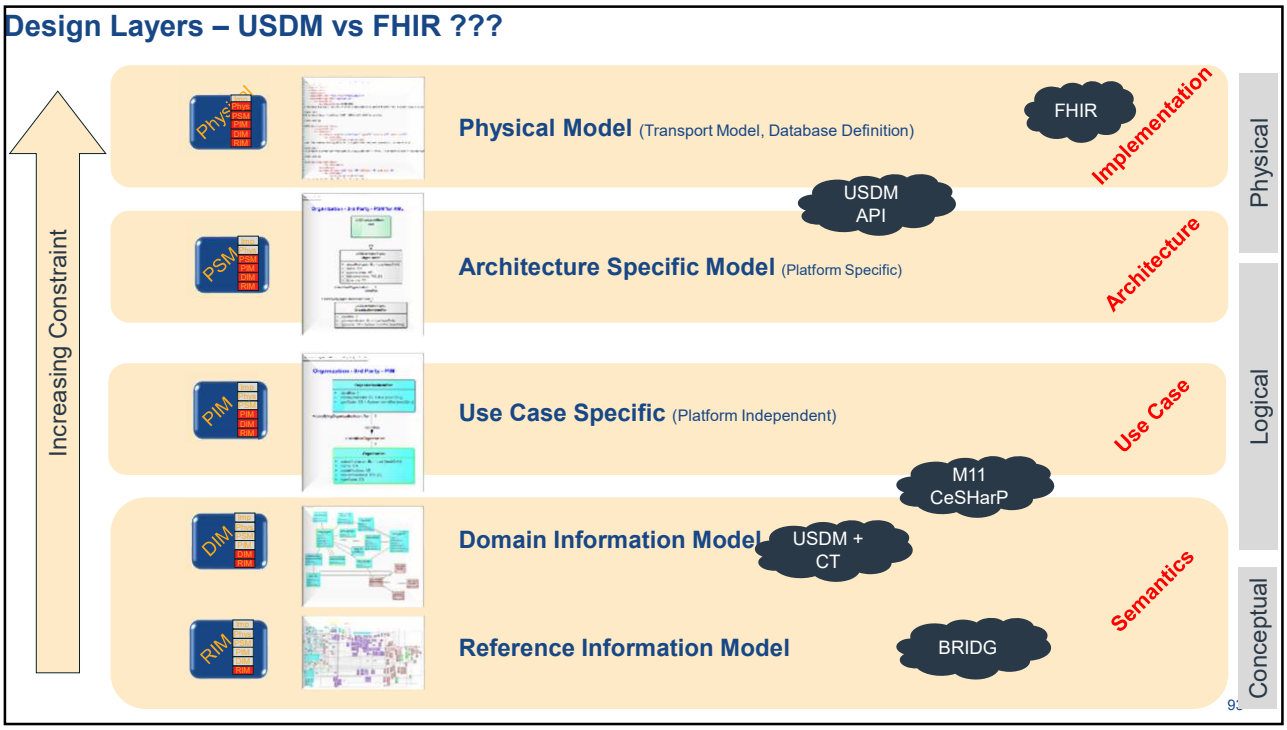
Design Layers – USDM vs FHIR ???



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Use Cases

Make protocols usable by regulators
- **Sponsor to Regulator**
- **Regulator to Regulator**

Accelerate Study Start-up and lay foundation for other downstream uses of protocol information
- EDC set up

Make protocols usable in FHIR for study execution
- **SoA for a Subject (update existing IG)**
- *Integration with EHR*
- *Representation of Eligibility Criteria / Automated subject identification*
- *Study feasibility analysis*
- *Study cost estimation*

...

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Developing Use Cases
Suggestions

- **Sponsor to Regulator Protocol Transmission (ICH)**
- **SoA for a Subject (update existing IG) (Vulcan)**

1. Version management (e.g, difference simplification and participant correlations)
2. Study estimated cost analysis
3. Site-level qualifications (e.g., specialty, medical resources, etc.)
4. Cohort identification / Eligibility / Capability
5. Study feasibility (e.g., running SoA on sample data)
6. Using a digital protocol as a single source of truth
7. Harmonising Definitions of Terminology and Process
8. Structured Data Capture derived from Protocol Definitions



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Developing Use Cases
Summary and Discussion

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Leading choices
- Cohort Identification
- SDC from Protocol

Second Tier
- Source of Truth
- Harmonisation

Third Tier
- Study feasibility

Comments
1. The second tier are in some ways actually pre-cursors for the leading choices
2. We now have a manageable number of potential projects to consider

Next Steps
1. Begin to expand the very simple statements we currently have
2. Look at the dependencies
3. Continue discussions

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Thank You …

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Q3 Panel: Vulcan Utilizing the Digital Protocol / ICH M11 CeSHarP

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Panelists

1. History of Clinical Research Protocol Standardization: *Rebecca Kush, Vulcan Advisory Council co-Chair*
2. ICH M11 Clinical Protocol Template and Exchange Standard: *Ron Fitzmartin (online), PhD, MBA, ICH M11 Rapporteur, U.S. FDA*
3. The perspective of CROs in Europe: *Yoani Matsakis, EUCROF*
4. The perspective of Academic Centers: *Meletis Dimopoulos, National and Kapodistrian University of Athens*
5. Decentralized clinical trials (or elements in clinical trials): *Christos Lionis, University of Crete*
6. ICH M11, Digital Protocols: A Pharma Perspective: *Rob DiCicco (online), TransCelerate BioPharma*
7. The Vulcan UDP Project: Hugh Glover, Vulcan Technical Director

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Networking Break

15:15 – 15:45

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