

Standards for virtual human twins

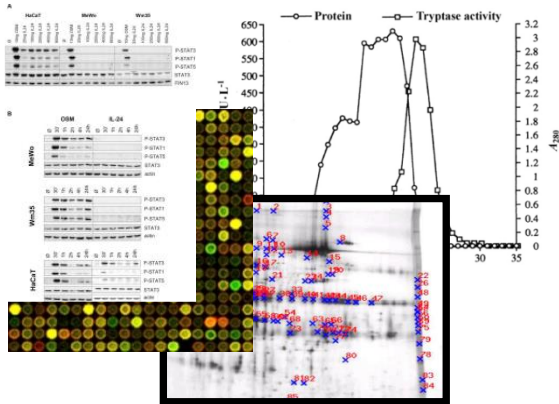
and their implementability

Gerhard Mayer and Martin Golebiewski

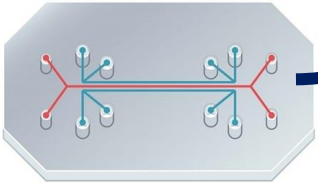
Heidelberg Institute for Theoretical Studies

Data Integration for the VHT

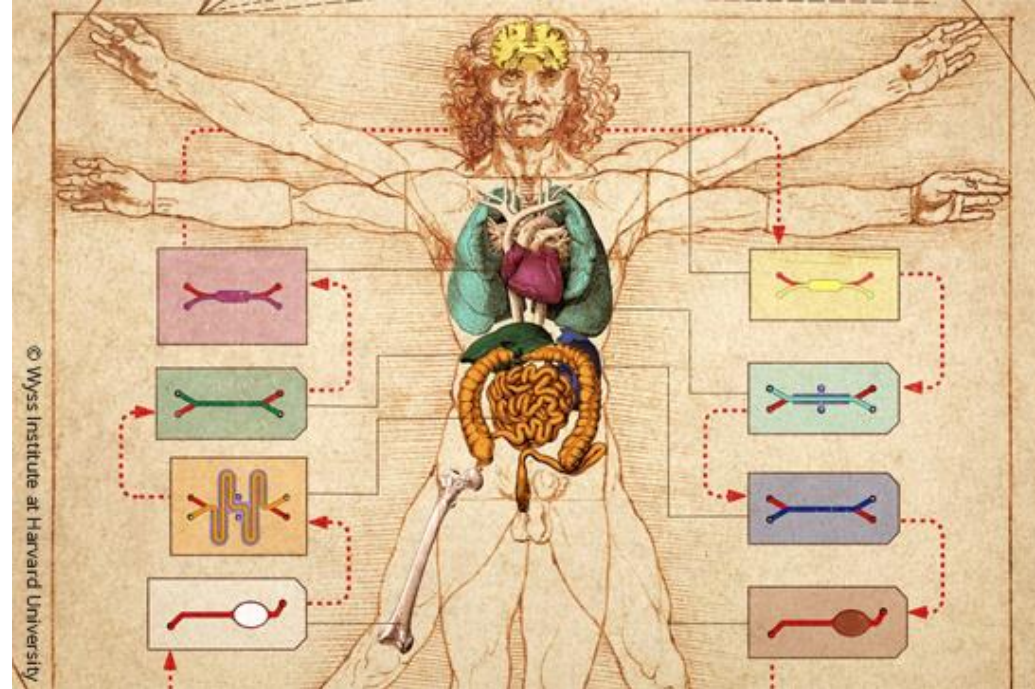
Data from the donor



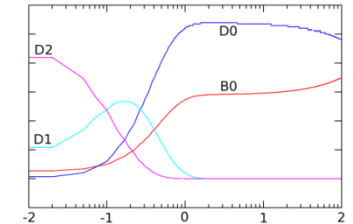
Process Data
& SOPs



collect &
integrate

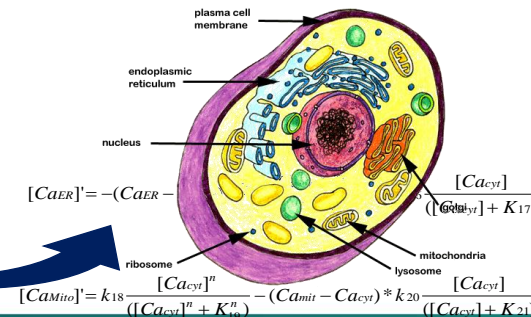


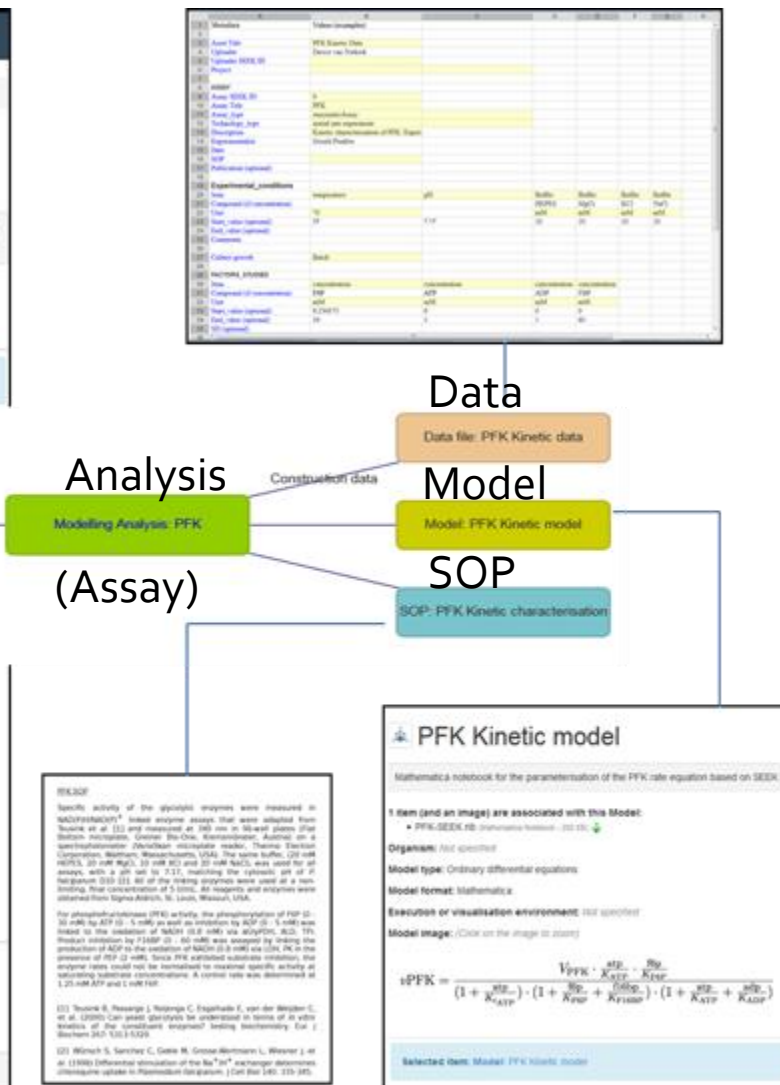
Simulation



simulate

Model



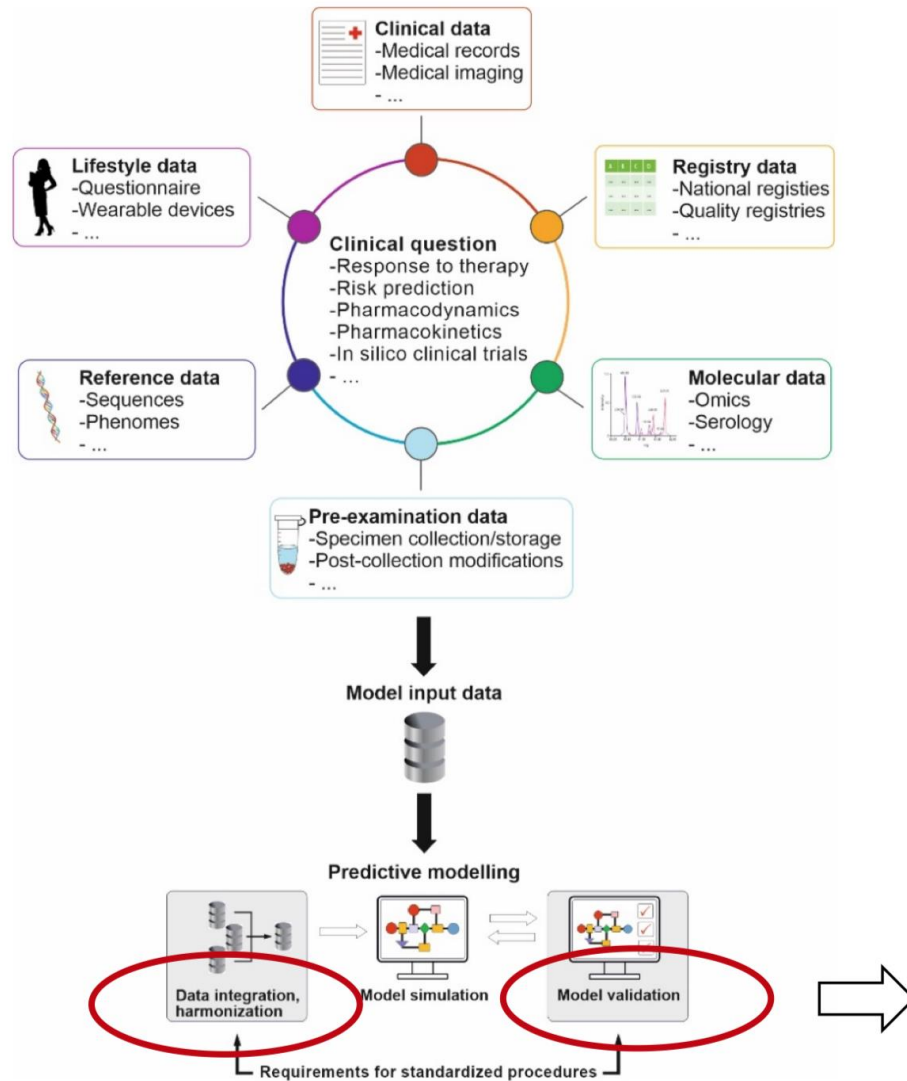


Integrative Data Management Systems: e.g. FAIRDOM SEEK

Wolstencroft K, Krebs O, Snoep JL, Stanford NJ, Bacall F, Golebiewski M, Kuzyakiv R, Nguyen Q, Owen S, Soiland-Reyes S, Straszewski J, van Niekerk DD, Williams AR, Malmström L, Rinn B, Müller W, Goble C: **FAIRDOMHub: a repository and collaboration environment for sharing systems biology research.** *Nucleic Acids Research* 45(D1): D404-D407 (2017). DOI: 10.1093/nar/gkw1032

Wolstencroft K, Owen S, Krebs O, Nguyen Q, Stanford NJ, Golebiewski M, Weidemann A, Bittkowski M, An L, Shockley D, Snoep JL, Mueller W, Goble C:
SEEK: a systems biology data and model management platform. *BMC Systems Biology*, 9: 33 (2015).
DOI: 10.1186/s12918-015-0174-y

Standardization Requirements for the VHT



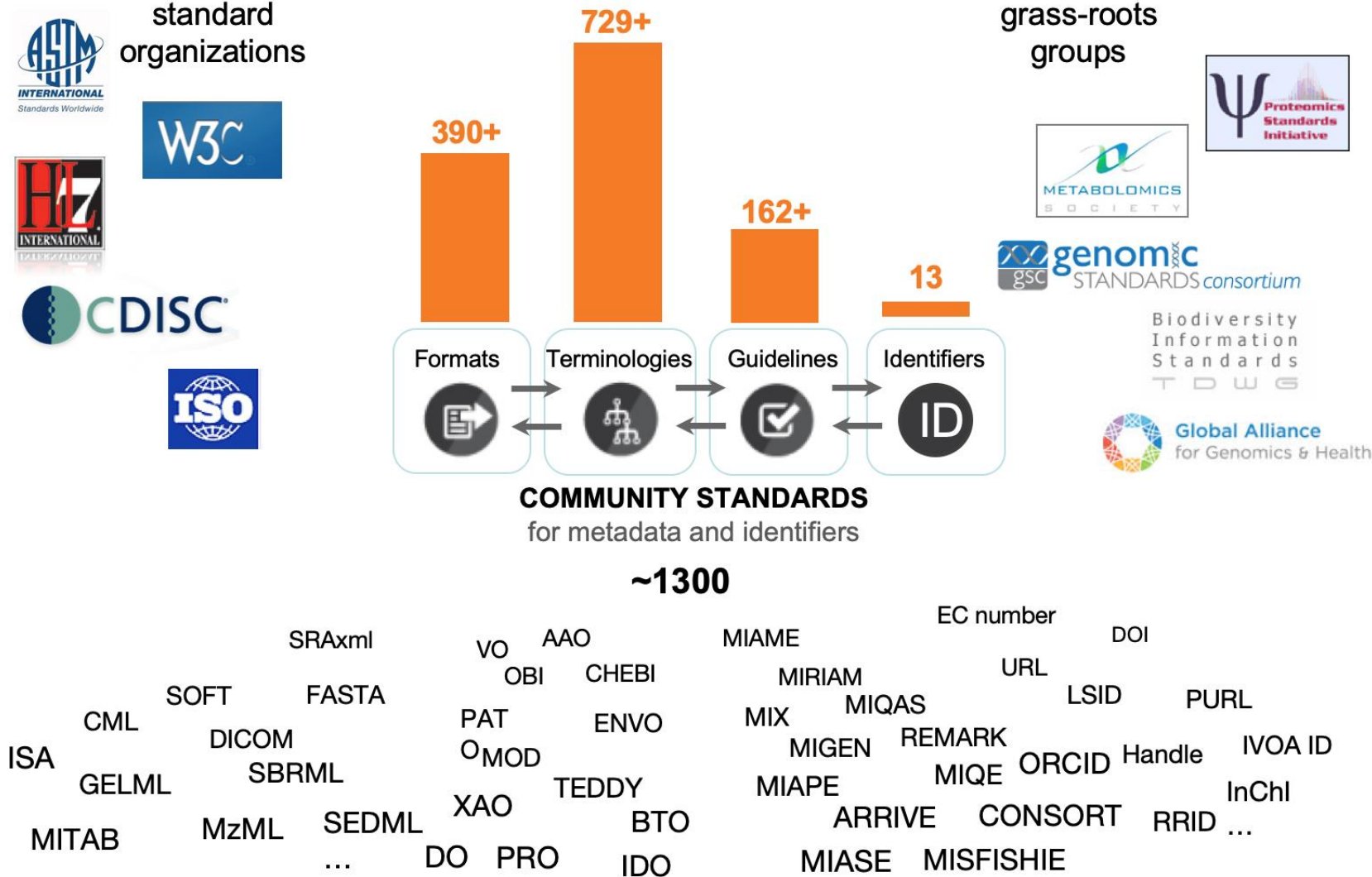
Recommendations and standards for

- ⇒ Data integration
- ⇒ Model validation
- ⇒ Legal/ethical issues (e.g. patient rights, GDPR)

e.g.

- **ISO 20691:2022** Requirements for data formatting and description in the life sciences
- **ISO TS 9491:2023** Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research — Part 1: Guidelines for constructing, verifying and validating models
Part 2: Guidelines for implementing computational models in clinical integrated decision support systems
- **ISO 23494 series: Biotechnology — Provenance information model for biological material and data**
- **ISO 4454:2022** Genomics informatics — Phenopackets: A format for phenotypic data exchange
- **ASME VV40:** Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices
- **Community standards:** e.g. COMBINE, GA4GH, etc.

The Forrest of Standards in the Life Sciences



For modelling standards see review:
 Golebiewski M: **Data Formats for Systems Biology and Quantitative Modeling**,
 In: Ranganathan S., Nakai K., Schönbach C. and Gribskov M. (eds.) **Encyclopedia of Bioinformatics and Computational Biology**, Volume 2, 2019, Pages 884-893

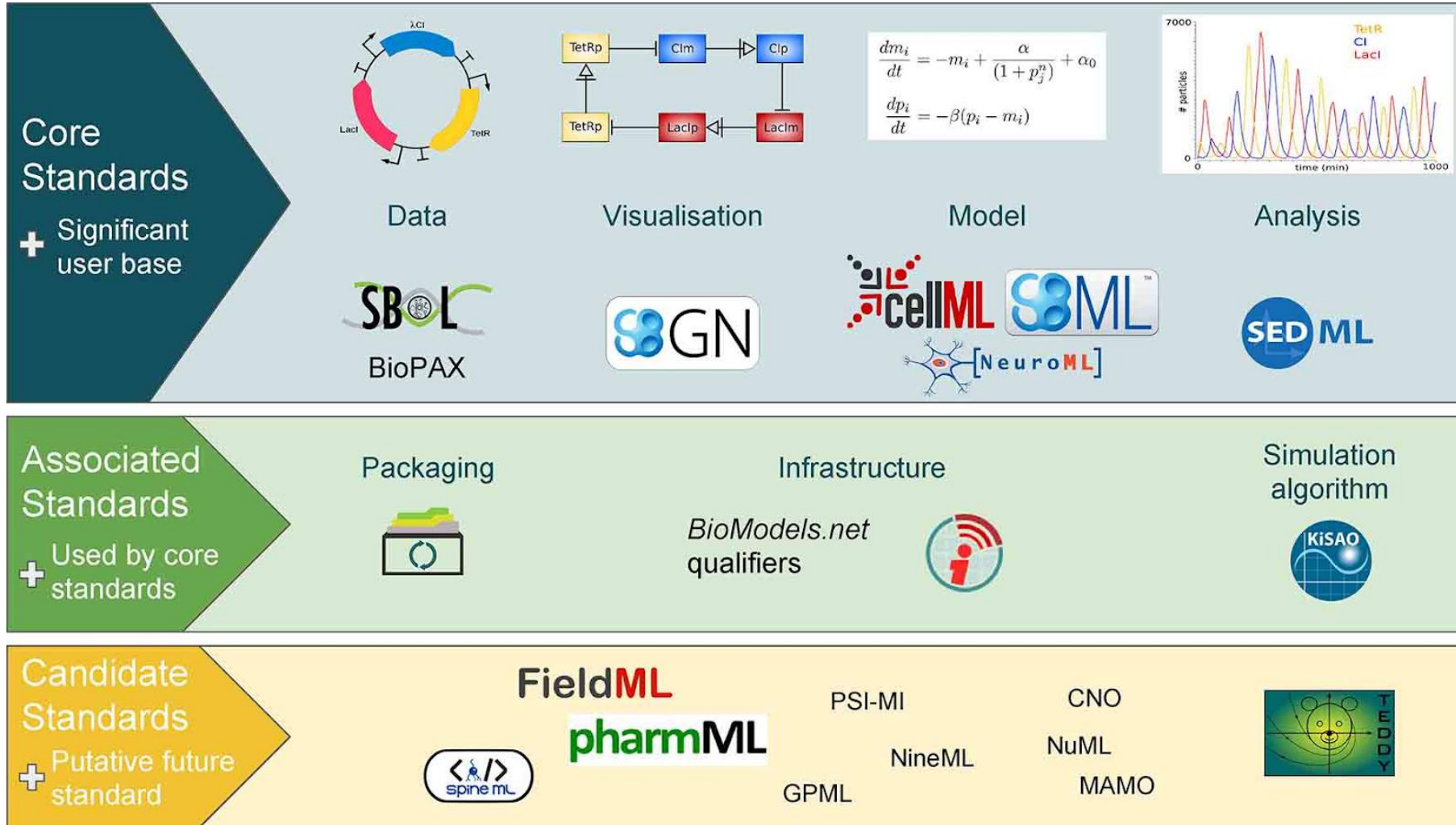
FAIRsharing.org
 standards, databases, policies

Source: Susanna-Assunta Sansone
 (University of Oxford, UK)

COMBINE Community Standards for Computational Modelling in Biology



<http://co.mbine.org>



Schreiber et al (2020).

DOI:

<https://doi.org/10.1515/jib-2020-0022>




Ecosystem
for Digital Twins
in Healthcare




COMBINE Standards for Computational Modelling in Biology

FAIRsharing.org  Collections


 Computational Modeling (COMBINE)

doi:10.25504/fairsharing.9qv71f






 **Systems Biology Markup Language**
Abbreviation: SBML

General Information



The Systems Biology Markup Language (SBML) is a machine-readable exchange format for computational models of biological processes. Its strength is in representing phenomena at the scale of biochemical reactions, but it is not limited to that. By supporting SBML as an input and output format, different software tools can operate on the same representation of a model, removing chances for errors in translation and assuring a common starting point for analyses and simulations.

Homepage <http://sbml.org>
Countries that developed this resource [Worldwide](#)
Created in 1999
Taxonomic range
 All



Knowledge Domains

 Enzymatic Reaction  Mathematical Model  Molecular Entity  Network Model  Pathway Model


Subjects

 Life Science  Systems Biology

In the following recommendations:

 EMBOpress 








How to cite this record FAIRsharing.org: SBML; Systems Biology Markup Language; DOI: <https://doi.org/10.25504/FAIRsharing.9qv71f>; Last edited: April 10, 2019, 10:49 a.m.; Last accessed: Dec 04 2019 4:52 p.m.

This record is maintained by [skeating](#) 

Record added: May 14, 2015, 11:14 a.m.
Record updated: April 10, 2019, 10:47 a.m. by [The FAIRsharing Team](#).

[Show edit history](#)

Legend

-  DATABASE
-  POLICY
-  COLLECTION
-  TERMINOLOGY ARTIFACT
-  MODEL/FORMAT
-  IDENTIFIER SCHEMA
-  REPORTING GUIDELINE

Implementing Databases (17)

MetaCrop 2.0

The MetaCrop resource contains information on the major metabolic pathways mainly in crops of agricultural and economic importance. The database includes manually curated information on reactions and the kinetic data associated with these reactions. Ontology terms are used and publication identification available to ease mining the data.

Integrated Pathway Analysis and Visualization System

iPAVS provides a collection of highly-structured manually curated human pathway data, it also integrates biological pathway information from several public databases and provides several tools to manipulate, filter, browse, search, analyze, visualize and

Related Standards

Reporting Guidelines

[Minimal Information Required In the Annotation of Models](#)

Terminology Artifacts

[Open Food Safety Model Ontology](#)

[Systems Biology Ontology](#)

Models and Formats

[CellML](#)

[Systems Biology Graphical Notation](#)

[Simulation Experiment Description Markup Language](#)

[Open Modeling EXchange format](#)

[Extensible Markup Language](#)

<https://fairsharing.org/collection/ComputationalModelingCOMBINE>

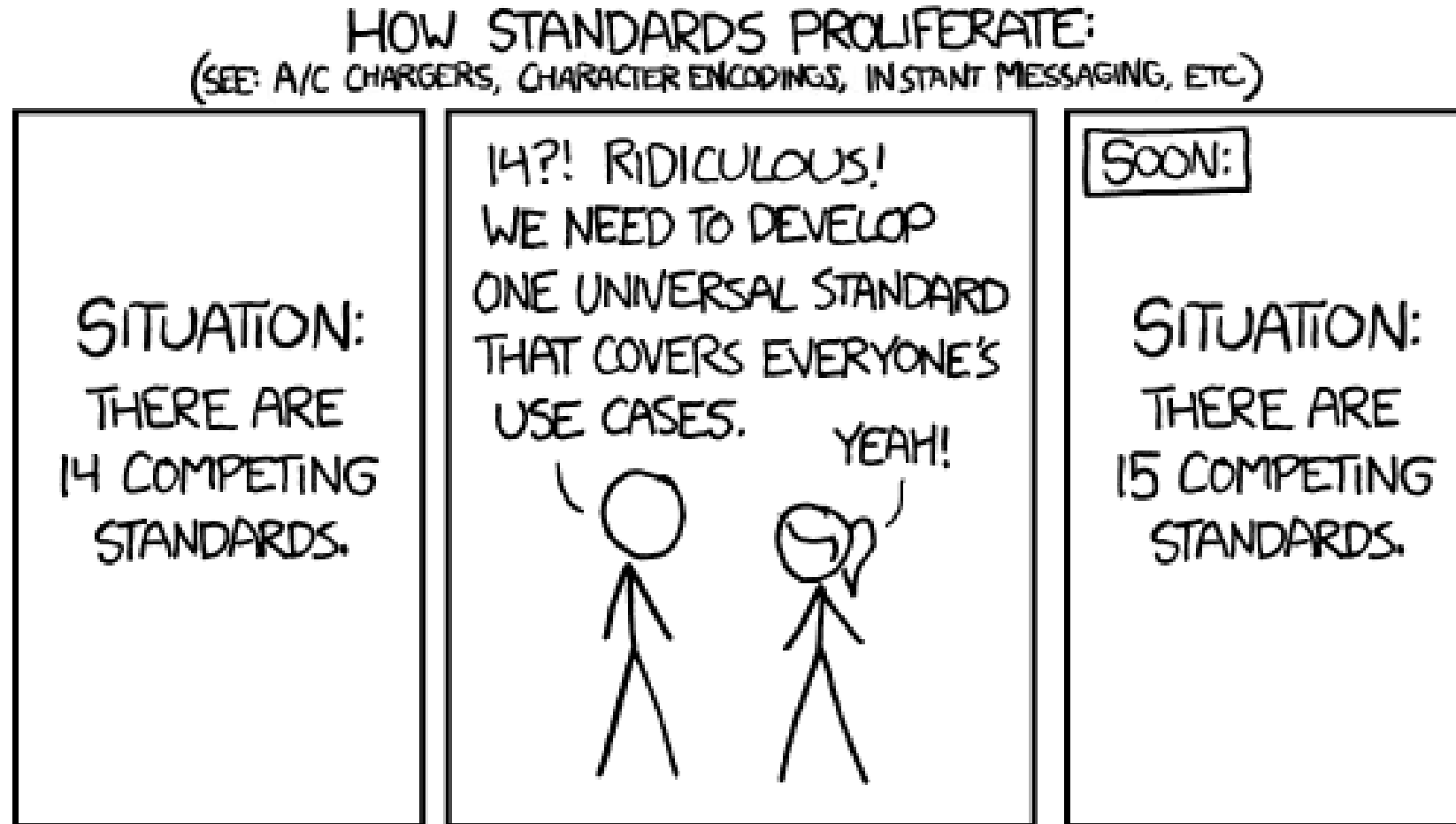


Ecosystem
for Digital Twins
in Healthcare



Community (de-facto) standards in life sciences

So many standards...



Standardized and Harmonized Data Sharing: **ISO 20691:2022**

Requirements for data formatting and description in the life sciences



Reference framework („hub“) standard for data standards

- Requirements and rules for the concerted application of (community) standards for formatting, description and documentation of datatypes in the life sciences
- Catalogue of criteria and requirements for interoperable life science data formats and semantic data description standards

SCOPE:

- **Guidance** on rendering data in the life sciences findable, accessible, interoperable and reusable (FAIR)
- **Requirements for the consistent formatting and documentation of data and metadata** in the life sciences (experimental and procedural data obtained manually, as well as machine derived)
- **Requirements for storing, sharing, accessing, interoperability and reuse of data and metadata** in the life sciences
- Applicable to manual or computational workflows that systematically capture, record or integrate data and corresponding metadata
- Applicable to many domains in biotechnology and the life sciences (including the domains relevant for VHTs)

Standardized and Harmonized Data Sharing: ISO 20691:2022 Requirements for data formatting and description in the life sciences



Annex A (informative)

Recommended formats for life science data

A.4 Formats for computer models of biological systems

A.4.1 CellML

CellML is a machine-readable, XML-based^[23] model description and exchange format for computer-based mathematical models^{[85][86]}. CellML is a description language to define models of cellular and subcellular processes. It defines lightweight XML constructs that group mathematical relationships within modules. The variables used in the mathematics are defined within each module, and connections between variables in different modules can be specified. CellML supports component-based modelling, allowing models to import other models, or subparts of models, therefore strongly encouraging their reuse and facilitating a modularized modelling approach. A CellML model typically consists of components, which can contain variables and mathematics that describe the behaviour of each component. The format provides means to reuse and group components into hierarchical structures. All entities (elements) carry an identifier and mathematical definitions are encoded using MathML. The mathematical model is considered to be the primary data, and biological context is provided by annotating the variables and equations with metadata using the Resource Description Format (RDF) ^{[9][87]}.

A.4.2 Systems Biology Markup Language (SBML)

SBML is a machine-readable, XML-based^[8] model description and exchange format for computational models of biological processes^{[88][85]}. Its strength is in representing phenomena at the scale of biochemical processes, but it is not limited to this only. The evolution of SBML proceeds in stages in which each “Level” is an attempt to achieve a consistent language at a certain level of complexity. Since SBML Level 3 the format is modular, with the core usable in its own right and packages being additional “layers” adding features to the core. By itself, SBML core is suited to representing such things as classical metabolic models and cell signalling models involving well-defined substances and entities homogeneous

Annex B (informative)

Minimal reporting standards for data, models and metadata

B.2 Minimum information standards

Table 3 — List of minimum information standards

Acronym	Name	Description and Homepage
CIMR	Core Information for Metabolomics Reporting	Minimal requirements for metabolomics experiments http://www.metabolomics-msi.org
MIABE	Minimum Information about Bioactive Entities	Reporting requirements for the publication of data on one or a series of bioactive entities, such as pharmaceuticals and pesticides http://mibbi.sourceforge.net/projects/MIABE.shtml
MIACA	Minimum Information About a Cellular Assay	Information guideline and a modular Cellular Assay Object Model (CA-OM) that can cover the range of cellular assays possible and which is the basis for efficient data exchange http://miaca.sourceforge.net
MIAME	Minimum Information About a Microarray Experiment	Information needed to enable the interpretation of the results of the experiment unambiguously and potentially to reproduce the experiment http://fged.org/projects/miame
MIAPAR	Minimum Information About a Protein Affinity Reagent	Guideline for experimentalists who wish to unambiguously describe protein affinity reagents and their protein targets



Standardized and Harmonized Data Sharing: ISO 20691:2022 Requirements for data formatting and description in the life sciences



Annex A (informative)

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MIACA	Minimum Information About a Cellular Assay	Information guideline and a modular Cellular Assay Object Model (CA-OM) that can cover the range of cellular assays possible and which is the basis for efficient data exchange http://miaca.sourceforge.net
MIAME	Minimum Information About a Microarray Experiment	Information needed to enable the interpretation of the results of the experiment unambiguously and potentially to reproduce the experiment http://fged.org/projects/miame
MIAPAR	Minimum Information About a Protein Affinity Reagent	Guideline for experimentalists who wish to unambiguously describe protein affinity reagents and their protein targets



Search through current results.

MATCH ALL TERMS		MATCH ANY TERM	
	MAINTAINED	NOT MAINTAINED	
	RECOMMENDED	NOT RECOMMENDED	
	READY	DEPRECATED	UNCERTAIN IN DEV.

Registry

APPLY

Record Type

APPLY

Subjects

APPLY

Domains

APPLY

Licence(s)

APPLY

Organisation(s)

APPLY

Countries

APPLY

Species

APPLY

User defined tags

APPLY

<https://fairsharing.org/3533>

LOINC



Logical Observation Identifier Names and Codes

LOINC is a common language (set of identifiers, names, and codes) for clinical and laboratory observations. LOINC is a catalog of measurements, including laboratory tests, clinical measures like vital signs and anthropomorphic measures, standardized survey instruments, and more. LOINC enables the exchange and aggregation of clinical results for care delivery, outcomes management, and research by providing a set

[Life Sci...](#) [Biomed...](#) [Preclin...](#) [Genetic ...](#) [Assay](#) [Phenoty...](#) [Homo s...](#) [+2 more tags](#)

Related Standards 7
Implementing Databases 0
Endorsing Policies 0

ISO 20691:2022 Online FAIRsharing Collection

SBOL Visual



Synthetic Biology Open Language Visual

Synthetic Biology Open Language Visual (SBOL Visual) is an open-source graphical notation that uses schematic "glyphs" to specify genetic parts, devices, modules, and systems.

[Life Sci...](#) [Syntheti...](#) [Data Vis...](#) [DNA Se...](#) [Sequen...](#) [Nucleic ...](#) [All](#) [one more tag](#)

Related Standards 2
Implementing Databases 1
Endorsing Policies 0

→ Will be constantly updated and maintained

MINI



Minimum Information about a Neuroscience Investigation

This module represents the formalised opinion of the authors and the CARMEN consortium, which identifies the minimum information required to report the use of electrophysiology in a neuroscience study, for submission to the CARMEN system

[Life Sci...](#) [Electrop...](#) [Neuron](#) [Assay](#) [Brain](#) [All](#)

Related Standards 0
Implementing Databases 0
Endorsing Policies 0

PharmML



Pharmacometrics Markup Language

PharmML is an exchange format for non-linear mixed effect models used in pharmacometrics and provides means to encode models, trial designs, and modelling steps. This standard allows for a smooth exchange of models between different software tools used in population pharmacokinetics/pharmacodynamics.

[Bioche...](#) [Biomed...](#) [Reactio...](#) [Modellin...](#) [Verkehr...](#)

ISO 23494 series

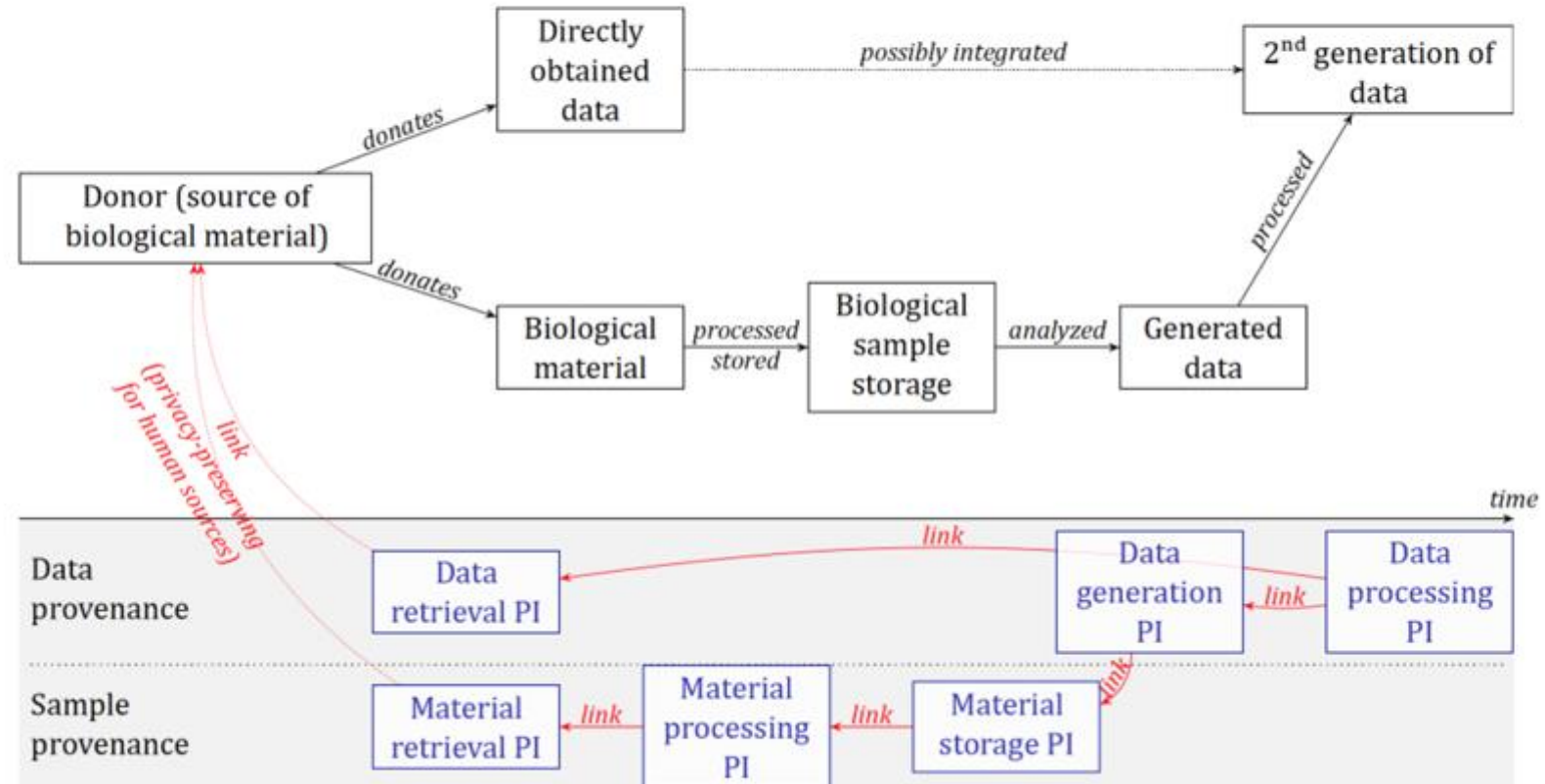
Provenance information model for biological specimen and data



Scope:

- **History of biological samples:**
 - acquisition
 - processing
 - transportation
 - storage
 - retrieval ...
- **Data history:**
 - generation of datatypes
 - processing
 - storage
 - validation ...
- **Based on W3C Prov**

PROVENANCE COVERAGE



Holub P. • ISO/PWI 23494-1 & BBMRI-ERIC Liaison Report • ISO TC 276 WG 5, Tokyo, 2019-06-13

Standards for model quality, verification and validation

- ASME V&V 40: Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices (→ currently under development as ISO/IEC standard)
- GSP (good simulation practice initiative by Avicenna Alliance, VPHi & ISW project)
- ISO TS 9491-1:2023 Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research — Part 1: Guidelines for constructing, verifying and validating models (initiated by EU-STANDS4PM)
- ISO TS 9491-2 Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research — Part 2: Guidelines for implementing computational models in clinical integrated decision support systems (initiated by EU-STANDS4PM)

Implementation guide and standards document

- Standards document

<https://zenodo.org/uploads/10492796>

- Implementation guide

<https://zenodo.org/records/10524795>

- FairSharing collection

<https://fairsharing.org/4787>

The screenshot displays the FAIRsharing.org website interface. At the top, there is a navigation bar with the FAIRsharing.org logo and a search bar. Below the navigation bar, there are several tabs: STANDARDS, DATABASES, POLICIES, COLLECTIONS, ORGANISATIONS, ADD CONTENT, and STATS. The main content area is titled "GENERAL INFORMATION" and features a large header for the "EDITH standards collection for Virtual Human Twins in Health". The header includes the EDITH logo and three circular icons: a green circle with a white 'R', a grey circle with a white person icon, and a grey circle with a white document icon. Below the header, there is a table with the following information:

Type	Collection
Registry	Collection
Description	Collection of standards recommended by the European EDITH (Ecosystem Digital Twins in Healthcare) consortium for virtual human twins (VHTs) in health.
Organisations	Heidelberg Institute for Theoretical Studies , EDITH consortium , VPHI - Virtual Physiological Human Institute
Homepage	https://www.edith-csa.eu

EDITH

Standards Implementation

Guide for VHTs in Health

Implementation guide - Introduction

Resources:

- EDITH-T2.3 document “[Analysing current landscape of standards, identifying needs and gaps](#)”
- EDITH-T4.2 document “[EDITH standards implementation guide \(IG\)](#)”
- [EDITH Fairsharing collection](#) of standards, terminologies and guidelines (<https://fairsharing.org/4787>)

Best practices:

- [Toward Good Simulation Practice \(GSP\)](#) guidelines of the [Avicenna Alliance](#): risk-informed credibility assessment of *in silico* simulation models
- [Modelling Good Research Practices](#) defined by ISPOR and SMDM

Recommended standards for Europe:

- [European Electronic Health Record Exchange Format \(EEHRxF\)](#)
- [IEEE P7003](#) Standard for **Algorithmic Bias** Considerations
- [IEEE P7001/D4](#) Draft Standard for **Transparency** of Autonomous Systems
- [IEEE 7000](#) Standard Model Process for Addressing **Ethical Concerns** during System Design
- ...

Implementation guide – Data handling

Data preparation ([ISO 20691:2022](#) and [ISO/TS 9491-1:2023](#))

- **sampling** the data.
- **data formatting and harmonization**, e.g., lab value concentrations must have a **unit** associated with them. This unit can either be mass/volume or mol/volume. Therefore, the values shall be converted to a unique scale. For that the molecular weight of the analyte must be known.
- data description by **descriptive metadata**, describing for example the context of the datasets.
- **semantic annotation** of the data, e.g., by annotating genes and proteins with ontology terms.
- definition of a data **interoperability framework** (e.g. [BRIDG](#), [FHIR](#), ...)
- **data integration**, either on the personal or on the variable level → use of persistent identifiers.
- adding data **provenance information**.
- defining who can **access** the data.
- → **FAIR data**

Implementation guide - Schemas

Input and output interfaces should avoid **unstructured** .csv or .txt data

- Use of **schemas** for describing the data formats, e.g.
 - [JSON schema](#)
 - [XML schema](#) (.xsd)
 - [ObjTables](#) for describing the content of .csv files
 - Own clearly documented “schema” for .csv files uniquely describing the used cells (values and units)
- Standardized **serialization formats** for binary data
 - [Apache Avro](#)
 - Google [protobuf](#)

Implementation guide – Data integration and metadata

- Use of persistent identifiers like [compact Uniform Resource Identifiers](#) (CURIEs). General form “**prefix:local unique identifier**”, where the prefix encodes the resource; [Bioregistry](#) for resolving the CURIEs
- Data interoperability frameworks like e.g. [Biomedical Research Integrated Domain Group](#) (BRIDG)

Metadata standards:

- [Dublin Core Metadata](#) (DC): set of 15 basic metadata elements
- [Data Catalog Vocabulary](#) (DCAT): interoperability between catalogues
- [MetaData Registry](#) (MDR, ISO/IEC 11179:2023): how to maintain database of metadata
- [Open Archives Initiative Protocol for Metadata Harvesting](#) (OAI-PMH): set of 6 HTML verbs

Use of ontologies:

- [Systems Biology Ontology](#) (SBO)
- [Terminology for Description of Dynamics](#) (Teddy)
- [Kinetic Simulation Algorithm Ontology](#) (KiSAO)
- [Provenance, Authoring, and Versioning](#) (PAV)
- ...

Implementation guide – Metadata annotation

Metadata annotation:

- Triplet phrases: *subject – predicate – object*
- the recommended predicates are mostly 'is' or 'isVersionOf' (see Table 2 in ISO 20691 for other predicates)
- done by embedding RDF <annotation> elements into XML-based data files

Example:

```
<rdf:Description rdf:about="./MyModel.xml#meta2">  
  <dcterms:description>Cardiomyocyte cytosolic ATP concentration</dcterms:description>  
</rdf:Description>
```

Checks for data quality:

- Completeness (missing values)
- Plausibility (range checks, cross-reference checks)

Implementation guide – Executing models

Model parameterization:

- In SBML: *'Parameter'* and *'Constraint'* components
- SED-ML: Parameter class
- Other: [tabular parameter estimation](#) (PETab) format encoding the model parameter information

Model execution:

- **readers** for SED-ML, unzipper for OMEX , ... must be present in the execution environment

Depending on the model type, a proper **model solver** for running the simulation must be available

- for **deterministic** SBML models: [RoadRunner](#), [CellDesigner](#), [Copasi](#), [Morpheus](#), the [SBMLToolbox](#) or the [systems biology simulation core algorithm](#)
- **Gillespie algorithm** for **stochastic** simulations, discrete-event simulations (DES) and multi-agent-based simulations (MABS).

Implementation guide – Verification and validation

Proposal is to follow the procedure described by the **ASME V&V 40** standard, see the [Toward Good Simulation Practice \(GSP\)](#) book.

Table 1: Terminology used by the [ASME V&V 40](#) standard for quality assessment

Quality Term	Description	Evidence Type
Verification	Did you solve the underlying mathematical model correctly?	Mathematical Evidence
Validation	Does the underlying mathematical model correctly represent the reality of interest?	Experimental Evidence
Uncertainty Quantification	What is the uncertainty in the inputs (e.g., parameters, initial conditions), and what uncertainty in the outputs results from that?	Statistical Evidence
Applicability	How relevant is the validation evidence to support using the model in the context of use?	Engineering Judgement
Credibility	Based on the available evidence, is there trust in the predictive capability of the computational model for the context of use (CoU)?	Engineering Judgement

Implementation guide – Verification and validation

- Definition of the scientific / medical **question of interest (QoI)** and the **context of use (CoU)**:
The CoU is a complete description of the planned modelling use and defines the role and scope of the model used to address the question of interest
- **model risk** (with its two components **model influence** and **decision consequence**) - the possibility that the results of the model simulation are wrong and lead to negative consequences for the patient - must be assessed
- **applicability** of a model is given by the evidence to support the use of the model in the defined CoU
- **risk-informed credibility assessment** is performed which encompasses the **three credibility factors**
 - model **verification** with the two factors **code verification** (source code or algorithmic errors) and **calculation verification** (discretization or iterative errors)
 - model **validation** asks if the model can correctly simulate reality, e.g., the correctness of the underlying model assumptions and approximations
 - **uncertainty quantification (UQ)**: sensitivity analysis to determine how sensitive the model output reacts to uncertainties in the model assumptions and input parameters

Implementation guide – EHR data and CDS

Electronic Health Record (EHR) data:

- should follow the [European Electronic Health Record Exchange Format](#) (EEHRxF) recommendations; can be implemented as
 - HL7 [Fast Healthcare Interoperability Resources](#) (FHIR) profiles
 - [Integrating Healthcare Enterprise](#) (IHE) profiles
 - [Open Electronic Health Record](#) (OpenEHR) format
 - For integrating EHR data with research data, the [Biomedical Research Integrated Domain Group](#) (BRIDG) standard can be used.

Clinical decision support (CDS) systems:

- knowledge representation the [Arden syntax](#) 3.0
- encoding of clinical decision support logic by
 - [Clinical Quality Language](#) (CQL) using **clinical quality measures** (CQM): measures performance on population health in response to the delivery of health care services
 - [Clinical Decision Support Hooks](#) (CDS Hooks)
 - [Substitutable Medical Applications and Reusable Technology](#) for CDS (SMART on FHIR)

Implementation guide – Building an approved model

- The general **model building process** should be done according to the [ISO/TS 9491-1:2023](#) (“Predictive computational models in personalized medicine research – Part 1: Constructing, verifying and validating models”) standard respecting the model formatting rules described in [ISO 20691:2022](#) (“Requirements for data formatting and description in the life sciences”).
- Iterating the **model execution cycle** consisting of the steps
 - model building/adaption
 - parametrization
 - execution
 - validation, verification and uncertainty quantification (VVUQ) → credibilityuntil the model credibility is high enough to get regulatory approval by **FDA** or **EMA** or an official **Health Technology Assessment (HTA)** admission office.
- Execute the approved model on the targeted execution environment. Before execution, the used patient data must be prepared according to the description in section *"Data handling"*.

Missing standards still under development

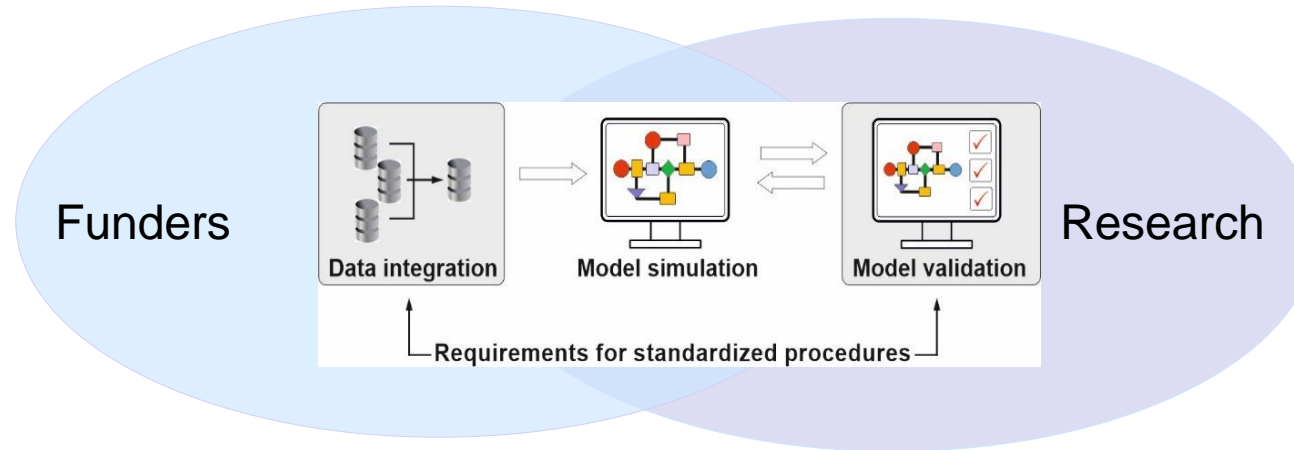
- **Adaption of ASME V&V-40:2018 standard**
 - Adaptation of the ASME V&V-40 medical device standard for the risk-informed credibility assessment of biochemical models.
 - Should include the assessment of agent-based models (AGM's) as well as data-driven (AI/ML) models.
 - Joint IEC TC 62 / ISO TC 276 working group (lead: Ch. Danielson)
- **Standardization for agent-based modeling: openVT (Virtual Tissue)**
 - Development of a multi-scale agent-based standard subsuming MorpheusML, MultiCellDS, MultiCell3D standards and the proprietary CompuCell3D format.
 - This standard is currently under discussion in the COMBINE network (lead: J. Glazier)
- **Standard for the semantic description of virtual twins in healthcare**
 - Standard currently under discussion in the COMBINE network (lead: R.S.M. Sheriff)
 - several levels of metadata describing a VHT (biological, technical, legal and descriptive metadata).
- **Development of a new workflow standard for the VHT's**
 - Decided at the Paris meeting (A. Hoekstra).
 - which features and concepts are missing in the current CWL (Common Workflow Language) standard and what are the expected additional features?

ISO TS 9491 Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research

Standards for model quality, verification and validation

- ASME V&V 40: Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices (→ currently under development as ISO/IEC standard)
- GSP (good simulation practice initiative by Avicenna Alliance, VPHi & ISW project)
- ISO TS 9491-1:2023 Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research — Part 1: Guidelines for constructing, verifying and validating models (initiated by EU-STANDS4PM)
- ISO TS 9491-2 Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research — Part 2: Guidelines for implementing computational models in clinical integrated decision support systems (initiated by EU-STANDS4PM)

Rationale to develop an ISO Technical Specification for modelling in personalised medicine



Before ISO TS 9491:

- ⇒ No broadly accepted standards for health & disease data integration for predictive modelling
- ⇒ Many grass root but non-binding standards

ISO TS 9491-1 defines rules for

- ⇒ for data integration into models and VHT components
- ⇒ model setup, validation, simulation description & handling
- ⇒ adaptation of community standards for VHT and modelling processes in health and clinical research

ISO TS 9491 Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research — Part 1: Guidelines for constructing, verifying and validating models

Scope

This document specifies requirements and recommendations for:

- Design, development and establishment of predictive computational models
- Set-up, formatting, validation, simulation, storing and sharing of computational models
- Data used to construct or required for validating such models
- Formatting, descriptions, annotations, interoperability, integration, access and provenance of such data for research purposes in the field personalised medicine.

Computational models used in routine clinical, diagnostic or therapeutic purposes are excluded.

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ISO TS 9491 Content example: Models in personalised medicine

4.2.2 Cellular systems biology models

4.2.2.1 General

Simulation of complex dynamic biological processes and networks. Models can be either data-driven ("bottom-up") or mechanism-based ("top-down").

Mechanism-based concepts aim for a structural representation of the governing physiological processes based on model equations with limited amount of data, which are required for the base model establishment [16] or, alternatively, on static interacting networks [17, 18]. Data-driven approaches ([4], [19]) require, as the name implies, sufficiently rich and quantitative time-course data to train and to validate the model. Due to its often black-box nature, the model validation process in data-driven approaches relies on performance tests against known results.

4.2.2.2 Challenges

- Creation of models that balance the level of abstraction with comprehensiveness to make modelling efforts reproducible and reusable (abstraction vs size).
- Development of prediction models that can be adopted easily to individual patient profiles.
- Efficient parameter estimation tools to cope with population and disease heterogeneity.
- Overfitting of the model to the experimental/patient data and optimization methods for model predictions in a realistic parametric uncertainty.
- Flexibility in models to cope with missing data (e.g., diverse patient profiles).
- Scaling from cellular to organ and to organism levels (e.g., high clinical relevance, high hurdles for regulatory acceptancy).

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ISO TS 9491-1 Content example: Data preparation

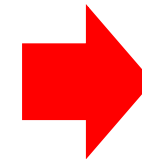
4.4 Data preparation for integration into computer models

4.4.1 General

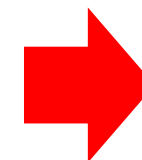
Computational models in the life sciences in general and in personalised medicine research specifically are increasingly incorporating rich and varied datasets to capture multiple aspects of the modelled phenomenon. Data types are encoded in technology and subdomain specific formats and the variety and incompatibility, as well as lack of interoperability of such data formats have been noted as one of the major hurdles for data preparation.

To allow for seamless integration of data used for the construction of predictive computational models in personalised medicine these data shall:

- include or be annotated with sampling and specimen data that follow the recommendations and requirements as specified by the relevant domain-specific standards;
- be formatted using generally accepted and interoperable standard data formats commonly used for the corresponding data types (as specified by ISO 20691);
- include or be annotated with descriptive metadata that consider generally accepted domain-specific Minimum Information guidelines and describes the metadata attributes and entities using semantic standards, such as standard terminologies, controlled vocabularies and ontologies (as specified in Annex B of ISO 20691:20XX);
- follow best practice recommendations and requirements of generally accepted domain-specific data interoperability frameworks;
- structured in a way that allows integration of the data into a model, together with other data;
- include or be annotated with data provenance information that allows for tracking of the data and source material throughout the whole data processing and modelling;
- be made accessible via harmonized Data Access Agreements (hDAAs) for controlled access data, if open access to the data is not possible.



ISO 20691:2022
as normative
reference



Link to data
provenance
(ISO 23494)

© ISO



ISO TS 9491-1 Content example: Sampling data

4.4.2 Sampling data

Dedicated measures need to be taken for collecting, stabilizing, transporting, storing and processing of biological specimen/samples, to ensure that profiles of analytes of interest (e.g. gene sequence, transcript, protein, metabolite) for examination are not changed ex vivo. Without these measures, analyte profiles can change drastically during and after specimen collection, thus making the outcome from diagnostics or research unreliable or even impossible, because the subsequent examination will not determine the situation in the patient, but an artificial profile generated during the pre-examination process. Important measures include for example times and temperatures of sample transportation not exceeding the specifications provided in ISO standards (ISO 20916:2019 as well as ISO 20186-1:2019) and ISO technical specifications (e.g. ISO/TS 20658:2017), giving guidelines on all steps of the pre-examination workflow. Conditions applied to specimen shall be documented in addition to other important metadata, including but not limited to the following Table 1.

Table 1 — Examples of important metadata collected during pre-examination workflows

Metadata relevant in pre-examination processes	
Specimen collection	– ID of responsible person
Information about specimen donor	– ID – Health status (e.g. healthy, disease type, concomitant disease, demographics [e.g. age and gender]) – Routine medical treatment and special treatment prior to specimen collection (e.g. anaesthetics, medications, surgical or diagnostic procedures, fasting status) – Appropriate consent compliant with EU and national law from the specimen donor/patient
Information about the specimen, collection from the donor or patient and processing	– Type and the purpose of the examination requested – Specimen collection technique used (e.g. surgery, draw, flush) – Time and date when the specimen is removed from the body – Documentation of any additions or modifications to the specimen after removal from the body (e.g. addition of reagents)
Specimen storage and transport	– Temperatures of the collection device's surroundings
Specimen reception	– ID or name of the person receiving the specimen – Arrival date, time and conditions (e.g. labelling, transport)

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ISO TS 9491 Content example: Model formatting

4.5 Model formatting

4.5.1 General

If feasible (e.g. for mechanistic models), the encoding of a predictive computational model in personalised medicine shall be formatted using generally accepted, appropriate and interoperable standard model formats commonly used for the corresponding data types (as specified by ISO 20691 with extensive examples of standard formats recommended in annex A.3). The used data format and its version shall be unambiguously documented with the data to allow for later decoding of the data. The corresponding scientific communities have defined many grassroots standards to consistently structure and format data, models and their metadata for modelling [38] and simulation [31] in the life sciences. These standardization efforts are driven by standardization initiatives, such as the Computational Modelling in Biology Network (COMBINE)¹⁷ ([39], [40]). For providing the potential users with an overview and comparable information about such standards, web-based information resources have been developed and are publicly available, such as the NormSys registry¹⁸ for modelling standards.

Examples of established model formats mainly used for models consisting of molecular entities and describing their interactions and dynamical interplay include:

- SBML (Systems Biology Markup Language) as standardized interchange format for computer models of biological processes [41];
- CellML, a standard format to store and exchange reusable, modular computer-based mathematical models;
- NeuroML (Neural Open Markup Language), which allows standardization of model descriptions in computational neuroscience;
- SBOL for synthetic biology models;
- BioPAX for biological/biochemical pathway models [42].

ISO TS 9491-2 Biotechnology - Recommendations and requirements for predictive computational models in personalised medicine research - Part 2: Guidelines for implementing computational models in clinical integrated decision support systems

This document specifies requirements and recommendations for designing, developing, and establishing integrated clinical decision support systems (CDSS) for research purposes in personalized medicine.

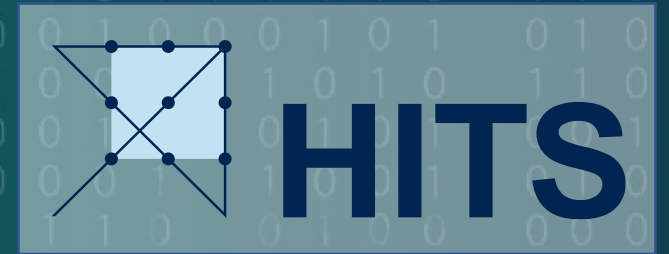
This document can be used as an implementation guideline for setting up computational modelling workflows to enable such systems. It addresses data quality, formatting and handling, as well as the processes generating such data, and the set-up, validation, simulation, storing and sharing of computational models used for this specific purpose in personalized medicine. This includes recommendations and rules for configuration, descriptions, annotations, interoperability, integration, access and provenance of such data and derived models in an interpretable and evidence-based manner. It also specifies how these rules should be integrated with clinical trials execution applying standard operating procedures. Furthermore, requirements and recommendations for data used to construct or required for validating such models are addressed.

This document does not apply for computational models used for diagnostic or therapeutic purposes in the clinical routine.

→ **Accepted as ISO Committee Draft in ISO/TC 276 Biotechnology**

→ **Revised version currently drafted for final ISO DTS (ISO Draft Technical Specification) ballot**

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EDITH - European Virtual Human Twin

<http://www.edith-csa.eu>

Deliverables available under the tab 'Dissemination/Materials':

<https://www.edith-csa.eu/materials/>

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Breakout Session

Standards for human digital twins

and their implementability

Gerhard Mayer Martin Golebiewski

Heidelberg Institute for Theoretical Studies

SDBV (Scientific DataBases and Visualization) group

Implementation guide and standards document

- Standards document

<https://zenodo.org/uploads/10492796>

- Implementation guide

<https://zenodo.org/records/10524795>

- FairSharing collection

<https://fairsharing.org/4787>

The screenshot displays the FAIRsharing.org website interface. At the top, there is a search bar with the text "search through all content" and a "SEARCH" button. Below the search bar, there are navigation tabs: STANDARDS, DATABASES, POLICIES, COLLECTIONS, ORGANISATIONS, ADD CONTENT, and STATS. The "COLLECTIONS" tab is currently selected. The main content area shows the "GENERAL INFORMATION" for the "EDITH standards collection for Virtual Human Twins in Health". The collection is identified by a green circular icon with a white 'R' and the text "EDITH". The "Type" is listed as "Collection", and the "Registry" is also "Collection". The "Description" states: "Collection of standards recommended by the European EDITH (Ecosystem Digital Twins in Healthcare) consortium for virtual human twins (VHTs) in health." The "Organisations" listed are "Heidelberg Institute for Theoretical Studies , EDITH consortium , VPHI - Virtual Physiological Human Institute". The "Homepage" is linked to "https://www.edith-csa.eu". On the right side of the collection card, there are three circular icons: a green circle with a white 'R', a grey circle with a white person icon, and a grey circle with a white document icon.

Implementation guide - Introduction

Resources:

- EDITH-T2.3 document “[Analysing current landscape of standards, identifying needs and gaps](#)”
- EDITH-T4.2 document “[EDITH standards implementation guide \(IG\)](#)”
- [EDITH Fairsharing collection](#) of standards, terminologies and guidelines (<https://fairsharing.org/4787>)

Best practices:

- [Toward Good Simulation Practice](#) (**GSP**) guidelines of the [Avicenna Alliance](#): risk-informed credibility assessment of *in silico* simulation models
- [Modelling Good Research Practices](#) defined by **ISPOR** and **SMDM**

Recommended standards for Europe:

- [European Electronic Health Record Exchange Format](#) (**EEHRxF**)
- [IEEE P7003](#) Standard for **Algorithmic Bias** Considerations
- [IEEE P7001/D4](#) Draft Standard for **Transparency** of Autonomous Systems
- [IEEE 7000](#) Standard Model Process for Addressing **Ethical Concerns** during System Design
- ...

Implementation guide – Data handling

Data preparation ([ISO 20691:2022](#) and [ISO/TS 9491-1:2023](#))

- **sampling** the data.
- **data formatting and harmonization**, e.g., lab value concentrations must have a **unit** associated with them. This unit can either be mass/volume or mol/volume. Therefore, the values shall be converted to a unique scale. For that the molecular weight of the analyte must be known.
- data description by **descriptive metadata**, describing for example the context of the datasets.
- **semantic annotation** of the data, e.g., by annotating genes and proteins with ontology terms.
- definition of a data **interoperability framework** (e.g. [BRIDG](#), [FHIR](#), ...)
- **data integration**, either on the personal or on the variable level → use of persistent identifiers.
- adding data **provenance information**.
- defining who can **access** the data.
- ➔ **FAIR data**

Implementation guide - Schemas

Input and output interfaces should avoid **unstructured** .csv or .txt data

- Use of **schemas** for describing the data formats, e.g.
 - [JSON schema](#)
 - [XML schema](#) (.xsd)
 - [ObjTables](#) for describing the content of .csv files
 - Own clearly documented “schema” for .csv files uniquely describing the used cells (values and units)
- Standardized **serialization formats** for binary data
 - [Apache Avro](#)
 - Google [protobuf](#)

Implementation guide – Data integration and metadata

- Use of persistent identifiers like [compact Uniform Resource Identifiers](#) (CURIEs). General form “**prefix:local unique identifier**”, where the prefix encodes the resource; [Bioregistry](#) for resolving the CURIEs
- Data interoperability frameworks like e.g. [Biomedical Research Integrated Domain Group](#) (BRIDG)

Metadata standards:

- [Dublin Core Metadata](#) (DC): set of 15 basic metadata elements
- [Data Catalog Vocabulary](#) (DCAT): interoperability between catalogues
- [MetaData Registry](#) (MDR, ISO/IEC 11179:2023): how to maintain database of metadata
- [Open Archives Initiative Protocol for Metadata Harvesting](#) (OAI-PMH): set of 6 HTML verbs

Use of ontologies:

- [Systems Biology Ontology](#) (SBO)
- [Terminology for Description of Dynamics](#) (Teddy)
- [Kinetic Simulation Algorithm Ontology](#) (KiSAO)
- [Provenance, Authoring, and Versioning](#) (PAV)
- ...

Implementation guide – Metadata annotation

Metadata annotation:

- Triplet phrases: ***subject – predicate – object***
- the recommended predicates are mostly 'is' or 'isVersionOf' (see Table 2 in **ISO 20691** for other predicates)
- done by embedding **RDF <annotation> elements** into XML-based data files

Example:

```
<rdf:Description rdf:about="./MyModel.xml#meta2">  
  <dcterms:description>Cardiomyocyte cytosolic ATP concentration</dcterms:description>  
</rdf:Description>
```

Checks for data quality:

- Completeness (missing values)
- Plausibility (range checks, cross-reference checks)

Implementation guide – Executing models

Model parameterization:

- In SBML: **'Parameter'** and **'Constraint'** components
- SED-ML: **Parameter** class
- Other: [tabular parameter estimation](#) (**PETab**) format encoding the model parameter information

Model execution:

- **readers** for **SED-ML**, unzipper for **OMEX**, ... must be present in the execution environment

Depending on the model type, a proper **model solver** for running the simulation must be available

- for **deterministic** SBML models: [RoadRunner](#), [CellDesigner](#), [Copasi](#), [Morpheus](#), the [SBMLToolbox](#) or the [systems biology simulation core algorithm](#)
- **Gillespie algorithm** for **stochastic** simulations, discrete-event simulations (**DES**) and multi-agent-based simulations (**MABS**).

Implementation guide – EHR data and CDS

Electronic Health Record (EHR) data:

- should follow the [European Electronic Health Record Exchange Format \(EEHRxF\)](#) recommendations; can be implemented as
 - HL7 [Fast Healthcare Interoperability Resources \(FHIR\)](#) profiles
 - [Integrating Healthcare Enterprise \(IHE\)](#) profiles
 - [Open Electronic Health Record \(OpenEHR\)](#) format
 - For integrating EHR data with research data, the [Biomedical Research Integrated Domain Group \(BRIDG\)](#) standard can be used.

Clinical decision support (CDS) systems:

- knowledge representation the [Arden syntax](#) 3.0
- encoding of clinical decision support logic by
 - [Clinical Quality Language \(CQL\)](#) using **clinical quality measures (CQM)**: measures performance on population health in response to the delivery of health care services
 - [Clinical Decision Support Hooks \(CDS Hooks\)](#)
 - [Substitutable Medical Applications and Reusable Technology](#) for CDS (**SMART on FHIR**)

Implementation guide – Building an approved model

- The general **model building process** should be done according to the [ISO/TS 9491-1:2023](#) (“Predictive computational models in personalized medicine research – Part 1: Constructing, verifying and validating models”) standard respecting the model formatting rules described in [ISO 20691:2022](#) (“Requirements for data formatting and description in the life sciences”).
- Iterating the **model execution cycle** consisting of the steps
 - model building/adaption
 - parametrization
 - execution
 - validation, verification and uncertainty quantification (**VVUQ**) → credibilityuntil the model credibility is high enough to get regulatory approval by **FDA** or **EMA** or an official **Health Technology Assessment (HTA)** office.
- Execute the approved model on the targeted execution environment. Before execution, the used patient data must be prepared according to the description in *section "Data handling"*.

Missing standards still under development

- **Adaption of ASME V&V-40:2018 standard**
 - Adaptation of the ASME V&V-40 medical device standard for the risk-informed credibility assessment of biochemical models.
 - Should include the assessment of agent-based models (AGM's) as well as data-driven (AI/ML) models.
 - Joint IEC TC 62 / ISO TC 276 working group (lead: Ch. Danielson)
- **Standardization for agent-based modeling: openVT (Virtual Tissue)**
 - Development of a multi-scale agent-based standard subsuming MorpheusML, MultiCellDS, MultiCell3D standards and the proprietary CompuCell3D format.
 - This standard is currently under discussion in the COMBINE network (lead: J. Glazier)
- **Standard for the semantic description of virtual twins in healthcare**
 - Standard currently under discussion in the COMBINE network (lead: R.S.M. Sheriff)
 - several levels of metadata describing a VHT (biological, technical, legal and descriptive metadata).
- **Development of a new workflow standard for the VHT's**
 - Decided at the Paris meeting break-out (A. Hoekstra).
 - which features and concepts are missing in the current CWL (Common Workflow Language) standard and what are the expected additional features?

Implementation guide – Verification and validation

Proposal is to follow the procedure described by the **ASME V&V 40** standard, see the [Toward Good Simulation Practice \(GSP\)](#) book.

Table 1: Terminology used by the [ASME V&V 40](#) standard for quality assessment

Quality Term	Description	Evidence Type
Verification	Did you solve the underlying mathematical model correctly?	Mathematical Evidence
Validation	Does the underlying mathematical model correctly represent the reality of interest?	Experimental Evidence
Uncertainty Quantification	What is the uncertainty in the inputs (e.g., parameters, initial conditions), and what uncertainty in the outputs results from that?	Statistical Evidence
Applicability	How relevant is the validation evidence to support using the model in the context of use?	Engineering Judgement
Credibility	Based on the available evidence, is there trust in the predictive capability of the computational model for the context of use (CoU)?	Engineering Judgement

Implementation guide – Verification and validation

- Definition of the scientific / medical **question of interest (QoI)** and the **context of use (CoU)**:
The CoU is a complete description of the planned modelling use and defines the role and scope of the model used to address the question of interest
- **model risk** (with its two components **model influence** and **decision consequence**) - the possibility that the results of the model simulation are wrong and lead to negative consequences for the patient - must be assessed
- **applicability** of a model is given by the evidence to support the use of the model in the defined CoU
- **risk-informed credibility assessment** is performed which encompasses the **three credibility factors**
 - model **verification** with the two factors **code verification** (source code or algorithmic errors) and **calculation verification** (discretization or iterative errors)
 - model **validation** asks if the model can correctly simulate reality, e.g., the correctness of the underlying model assumptions and approximations
 - **uncertainty quantification (UQ)**: sensitivity analysis to determine how sensitive the model output reacts to uncertainties in the model assumptions and input parameters

Joint IEC TC 62 / ISO TC 276 working group

- Assessment of credibility of computational models used in the field of medical devices
- CM&S: Software as *in silico* Medical Device (SaMD)
- including knowledge-based, data-based and hybrid models
- complementary to traditional verification methods like bench testing, animal testing, and human clinical trials
 - aligned with **ASME V&V 40** standard
 - quantitative risk-based credibility assessment framework
 - Verification, Validation and Uncertainty Quantification
- **FDA guidances:**
 - “Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions”
 - “Reporting of Computational Modeling Studies in Medical Device Submissions”
- **ISO 9491-1/2:** personalized models / CDS

Definition of needed standards

Adaption of **ASME V&V 40:2018**:

- Joint IEC/ISO group to adapt ASME V&V-40:
- should not only be applicable for medical devices, but also for systems medicine models:
 - physics/knowledge-based (ODE, PDE, ABM, ...)
 - data-based (AI/ML)
 - hybrid models
- should be compatible with already existing standards for
 - personalized models (**ISO TS 9491-1:2023**)
 - medical decision support systems (**ISO/AWI 9491-2**).

AI/ML models continuously learn and are adapted to actual and newly added data

→ specified in a Predetermined Change Control Plan (**PCCP**) to handle this “drift” and meet the requirements of FDA/EMA regulations.

The END – Questions, Comments, Remarks, Ideas, ...

EDITH - European Virtual Human Twin

<http://www.edith-csa.eu>

Deliverables available under the tab 'Dissemination/Materials':

<https://www.edith-csa.eu/materials/>

Question to the audience: Implementability

Do you see any problems for the **implementability** of the presented standards on the **EDITH simulation environment**, especially with respect to the

- Catalogue / Repository
- Simulation platform
- Workflow execution engines

Questions to the audience: Missing standards, terminologies or services

- How can SDOs and standardization initiatives help to build a standard based VHT infrastructure?
- Are there relevant standards existing, but missing in our standards document?
- Are there domains for which proper standards or terminologies are still not defined?
- Is there a need for basic services, e.g., for a dedicated terminology service for VHTs?