Avicenna Alliance Glossary

Terms for Computer Modelling and Simulation

Introductory Remark

*There are occasional confusions and diverging opinions possibly leading to misunderstanding in the use of some in silico concepts in the literature. To clarify **our** message, a team of academic and industry members of the Avicenna Alliance is proposing a definition of words regularly used in the 'in silico' literature. The definitions in this glossary, results of a consensus within our members, clarify the meaning of the terms we are using in our publications. We understand that different definitions may exist and we welcome any comment as these definitions may evolve.*

This Glossary is a second release with an extended list of definitions; more concepts will be defined and existing definitions may be adjusted in future updates/releases of this document. Therefore, comments and inputs are welcome to enrich this glossary. You are encouraged to share your comments or suggestions for modification with Roberta Maggi, manager@avicenna-alliance.com .

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DEFINITIONS:

Absolute benefit
Difference between the rate or risk of event between the untreated / control individuals and the corresponding treated individuals in the same group or cohort. Instead of the event rate, it can also be the value of a marker.

Adequacy assessment
Process of evaluating the evidence in support of credibility of a computational model, for a given context of use, and making a determination on whether the evidence is sufficient.

Agent-Based models (ABM)
Computational representation of a physical reality that utilizes a large number of autonomous discrete particles (called Agents) that move in space and time, interact with each other and change their internal state according to a set of rules. ABMs are capable of re-creating macro-level phenomena by the actions and interactions of micro-level individual agents (emergence).
Example: "A multi-step and multi-scale bioinformatic protocol to investigate potential SARS-CoV-2 vaccine targets", Briefings in Bioinformatics, Volume 23, Issue 1, January 2022, bbab403,
https://doi.org/10.1093/bib/bbab403

Applicability
Relevance of the credibility assessment of the computational model (e.g. verification and validation activities, uncertainty quantification) for a given context of use. (Adapted from FDA, source "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions - Draft Guidance for Industry and Food and Drug Administration Staff", https://www.fda.gov/media/154985/download.

Assertion
Principal feature (e.g., Chemical or biological entities and their functional relation(s) between these entities) of a piece of knowledge (scientific extract, Figure, Table) that carries scientific information in the form of plain language that will be assembled into a Knowledge Model.

Base model
Hypothetical, abstract representation of the object's properties, in particular, its behaviour, which is valid in all possible contexts, and describes all the object's facets. (H. Vangheluwe, McGill University, 2001).

Calculation verification (i.e. solution verification)
The process of estimating the numerical error in the output of a computational model due to the use of numerical methods to solve the mathematical model (including the post-processing) specific to the context of use. It aims to estimate the magnitude of the numerical errors in the estimated solutions. (Based on M. Viceconti et. al.).

Calibration (Model) (i.e. tuning or fine-tuning)
The process in which a priori unknown and estimated parameters are refined through a numerical procedure in order to achieve a desired behavior of the model regarding given criteria.

Clinical outcome
Measurable change in patient's health, function or quality of life at specific time point.

Clinical score
A standardized quantitative or qualitative indicator of the severity of a disease, or other variables for a particular patient, at a particular instant in time. The clinical score may be obtained on the basis of a series of clinical and/or biological and/or imaging and/or pathological factors.

Code verification
The process of ensuring the quality (including correctness, reproducibility and good standards practices) of the algorithm and its source code via minimization of weaknesses and errors, when translating the chosen mathematical model.

Comparator
Test data that are used for comparison with computational results as part of the validation, which may be data from bench testing or *in vitro*, *ex vivo*, *in silico*, and *in vivo* studies.

Compartment
Specific subsection or structure of a biological system in a computational model. The level of granularity depends on the Context of Use. Compartment may be also called "**part**" depending on the field of application.

Computational modelling
Numerical representation of the mathematical model performed by means of computational implementation in order to simulate and study complex systems. (Based on FDA: Frontiers in Medicine, September 2018, Volume 5, Article 241 by Tina Morrison (FDA) et. al.)

Computational modelling and simulation (CM&S) in healthcare
Computational modelling and simulation (CM&S) makes use of programming languages, numerical methods, high-performance computing, to create numerical representations of first-principles equations, to reduce, refine or even replace experimental and clinical research.
(Reference: National Institute of Biomedical Imaging and Bioengineering (NIBIB). Computational Modeling. 2020 [cited 2020 12 Nov 2020]; Available from: https://www.nibib.nih.gov/science-education/science-topics/computational-modeling.)

Context of Use (CoU)

Defines the specific role and scope of the computational model used to address the question of interest. It should include a detailed statement of what will be modelled and how the outputs from the computational model will be used to answer or inform the question of interest. It is important to note that the CoU is distinct from the "indications for use" or "intended use" of a medical device, which are descriptions of how a device is intended to be used in clinical practice. [Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices V&V 40 – 2018. ASME, 2018. 60p. ISBN: 9780791872048.]

Credibility

Represents the belief in the predictive capability of the computational model for the context of use (COU) applying engineering judgement based on the available evidence. (Reference: ASME V&V 40 - 2018). See "Model credibility".

Decision consequence

The significance of an adverse outcome resulting from an incorrect decision concerning the question of interest, i.e., the severity of the adverse outcome if the decision based on the model is incorrect.

Descriptors

Descriptors are all the associated values (depending on research area), varying from one patient to another (e.g., that could be associated with model inputs or outputs).

Digital Evidence (i.e., *in silico* evidence)

Results of computational modelling and simulation submitted as part of a (regulatory) evaluation process provided in a prescribed format, that encompass *in silico* trials and *in silico* tests.

Digital twin

A computational model of physical assets (or processes or systems) that learns and is updated from multiple sources, in real time or not, depending on the context of use. It acts as a bridge between the physical and virtual world, allowing analysis (e.g. simulations) that can help to anticipate problems and plan for the future.

In silico

In silico means carried out in the computer (i.e., the silica), which is analogous to *in vitro* (in the glass), *ex vivo* (outside the living organism), or *in vivo* (inside the living organism).
References: Chiavaroli C, Rousseau CF, Voisin EM. *In Silico* Approach: From Computer To Patient? Advantages and Limits of Toxicology Prediction in the Current Regulatory Environment. Voisin Consulting Life Sciences 2017 White Paper.

In silico trials (IST)

Use of computational modelling and simulation (CM&S) for testing treatments (drugs and/or medical devices) to mimic both bench testing (in vitro, ex vivo) and animal / human experimentation (in vivo) with the goal of providing digital evidence for regulatory evaluation process, under well-defined conditions, ideally described in standard. Also known as *in silico* experiments.

The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention - from a published article 10.1177/0954411917702931

In silico clinical trial (ISCT)

Use of computational modelling and simulations to mimic the human experimentation required in the regulatory evaluation process of a medicinal (including medical devices) product or intervention, under well-defined conditions using verified and validated models. It requires the definition of virtual patients or virtual populations of patients.

Reference: "Use of disease models and virtual patients to run computer-simulated clinical trials" - Novadiscovery definition

In silico evaluation

Evaluation performed via computational modelling & simulation outside the traditional clinical settings; e.g. *in silico* evaluation can involve computational models to predict the behaviour of a molecule in a biological system, or to simulate the performance of a new material in various environmental conditions. This type of evaluation can be a cost-effective and time-efficient way to test and optimise new products, without the need for expensive and time-consuming physical experiments. These examples are not exhaustive.
Reference: Vasey, B., Nagendran, M., Campbell, B. et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. Nat Med 28, 924–933 (2022). https://doi.org/10.1038/s41591-022-01772-9.

In silico method (ISM)

Are procedures to conduct experiment, evaluation or analysis, using computer-based tools. *In silico methods* comprise utilisation of mechanistic and phenomenological models.

The three types of *in silico* evaluation methodologies considered here are:
○ *in silico* test (or experiment or study) refers to the execution of an in vitro or ex vivo experiment in the computational environment
(Ref: Viceconti, M., A. Henney, and E. Morley-Fletcher, *In silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. Research and Technological Development Roadmap. 2016, Avicenna Consortium: Brussels (Chapter I, page 11))
○ *in silico* medicine refers to the use of individualised computational modelling in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of diseases.
○ *in silico* trial (see above definition on "*In silico* Trial")
Reference: Viceconti, M., et al., *In silico* trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods, 2020.

Knowledge model

The founding literature describing the knowledge upon which the Formal Model is implemented. It includes assertions, data, the associated knowledge gaps, a graphical representation, and a list of model components.

Mathematical model

"*The mathematical equations, boundary conditions, initial conditions, and modelling data needed to describe a conceptual model*" (ASME V&V 40-2018).

Measurable variable

The variable of the model that can be quantified.

Mechanistic model

Model aimed at describing causal relationships (i.e., carried by knowledge) based on scientific laws, typically simplified in terms of cause-effect actions, as opposed to a correlational, data driven model.

Model

A representation of a system that we observe, try to understand, and/or create. It may imply a simplification of a real system. (See "Base model")

Model credibility

Refers to the trust in the predictive capability of the computational modelling and simulation for the COU. Trust can be established through the collection of verification and validation (V&V) evidence and by

demonstrating the applicability of the V&V activities to support the use of the computational model for the COU.

Reference: ASME V&V 40-2018.

To demonstrate the credibility, it is recommended to identify the credibility factors (e.g., goodness of fit, input parameters) for which it will be defined prospective credibility goals, (e.g., low/medium/high equivalency).

Reference : FDA draft guidance - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions.

Model falsification

Activity that challenges the validity of the model within its Context of Use. Once the model cannot be falsified after several independent attempts, the model can be considered valid within its Context of Use. Falsifiability is an important characteristic of the model that represents the capacity for the model to be proven wrong. See also "Validation".

Model influence

It is the contribution of the computational model to the decision, addressing the question of interest in relation to other available evidence.

Model output

Describes the value (e.g., time series) of a model variable resulting from a simulation of the model provided with a set of model inputs.

Model risk

Model risk is the possibility that the use of a *in silico* method leads to a decision that results in patient harm and/or other undesirable outcomes. It reflects the risk the decision-maker incurs when using a computational model to support a decision.

References: ASME V&V 40 - 2018, Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices.
And,
Horner M, Reiterer M, Rousseau C.F. Ensuring the Quality of *in silico* Evidence: Application to Medical Devices. Avicenna Alliance 2021, Position Paper. https://avicenna-alliance.com/publications/

Model scope:

Extent of applicability of the model to biological/physiological/clinical systems, implied by the question of interest.

Model specifications

Qualitative or quantitative requirements (implicit or explicit) the model must meet.

Modelling

The process of representing a system with a specific computational tool.

Parameter

A quantitative entity within a Formal Model whose value is set to remain constant in a particular given context. Its value might be derived from a piece of knowledge or adjusted during the Formal Model calibration phase.

Personal Digital Avatar (PDA)

Digital twin of a specific human connected with its physical counterpart (physical twin) to regularly collect data about his/her evolution and predict likely evolution of his/her health.

Pharmacokinetic model
A simple and usually phenomenological mathematical model used for predicting the active concentration of a bioactive molecule at the site of action.

Prognostic model
Statistical or non-statistical mathematical model that predicts the probability of occurrence of a clinical event/outcome over time at the patient level as a function of the initial state of the patient (e.g., clinical, biological, physiological).

Question of interest
It describes the specific question, decision or concern that is being addressed (at least in part) based on the results of a computational model. It is "*the calculated or measured result from a computational model or comparator, respectively*" (ASME V&V 40-2018).

Reference: Horner M, Reiterer M, Rousseau C.F. Ensuring the Quality of *in silico* Evidence: Application to Medical Devices. Avicenna Alliance 2021, Position Paper. https://avicenna-alliance.com/publications/

Risk analysis
Analysis based on a combination of a model influence and decision consequence.

Scorings
Scorings are quantitative evaluations of closeness of an obtained behaviour to an expected behaviour of the model for a given set of input parameters. It is used during model calibration.

Sensitivity
Measure of the magnitude of influence of a given parameter, assumption, or variable on the model output/s. High sensitivity to a particular variable means a small change in that variable could lead to a substantial change in model output.

Strength of evidence:
Defines the confidence that can be put on the reliability of an assertion used in the model (or any evidence or knowledge).

Submodel
A model may be divided into submodels during the model development process.
Submodels can be of the following types:
- **Disease submodel**: Model of the (electro)physiology and/or pathophysiology and/or geometry of distinct sub-parts (cells, tissues, organs or processes) of biological system. It is connected to other submodels by its inputs and outputs.
- **Clinical submodel**: Part of the model that links the evolution of disease (components of disease model) to clinical outcome.
- **Treatment** or **medical device submodel**: Describes the disposition and the action of a health product on its target(s) within the organism. In some cases this may be simply represented by a change of parameter in the pathophysiological or disease submodel. For drugs, it may include a PK-PD model predicting the amount of drug at the site of action as well as its effect.

System
A well-defined object or group of objects (e.g., organs) in the real world that are joined together in some regular interaction or interdependence toward the accomplishment of some purpose, under specific conditions, only considering specific aspects of its/their structure and behaviour. (based on H. Vangheluwe, McGill University, 2001; & A. Juan Perez, UOC, ISBN: 978-84-692-9597-7)
A system can be continuous or discrete depending on the time point under consideration.

Uncertainty
Potential deficiencies in any phase or activity of modelling, computation, or experimentation process that is due to inherent stochasticity (aka aleatoric uncertainty), lack of knowledge or unreliable knowledge (aka epistemic uncertainty).
References: ASME V&V 40-2018

Validation
Activity demonstrating that the underlying mathematical model correctly represents the reality of interest within the Context of Use. "The process of determining the degree to which a model or a simulation is an accurate representation of the real world". See also "Model Falsification"
Reference: ASME V&V 40-2018

Variability (Patient related)
Inter-individual differences between patients due to differences in diet, genetics or immune status or intra-individual differences in the same subject over time due to diurnal cycles and other rhythms, biological repair mechanisms, dietary variables, ageing, changes in environment, etc.
Reference: Inspired by "*Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: Building model credibility*", Flora T. Musuamba et al., https://doi.org/10.1002/psp4.12669.

Variables
Quantitative entity within a model, whose value depends on parameters/data on other variables and is expected to vary along the course of simulation.

Verification (Calculation)
Calculation verification ensures the accurate reproducibility of the mathematical solutions of the model equations. It mainly aims at evaluating the approximation errors and ensuring the correctness of solving the equations, i.e., the quantification of the error caused by the approximated solution of the mathematical model, vf(I).
Reference: Based on ASME V&V 40-2018 and M. Viceconti et all.

Verification (Code)
Code verification is essentially a quality assurance practice for the software we use to solve the model, and a stability check for the numerical algorithms it implements. Software quality assurance is done with methods typical of software engineering, such as regression tests, or unit tests. Numerical solvers implementations are tested to check their stability, their rates of convergence, their computational efficiency, etc. Commercial codes tend to have their own extensive code verification.
Reference: M. Viceconti, M. A. Juárez, C. Curreli, M. Pennisi, G. Russo and F. Pappalardo, "Credibility of *In Silico* Trial Technologies—A Theoretical Framing," in *IEEE Journal of Biomedical and Health Informatics*, vol. 24, no. 1, pp. 4-13, Jan. 2020, doi: 10.1109/JBHI.2019.2949888.

Verification (Model)
Model verification corresponds to the activity demonstrating the capability of solving the mathematical model correctly. It is usually separated into "code verification" and "calculation verification". "*The process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modelling and simulation*".
Reference: Based on ASME V&V 40 - 2018) See "Code Verification" and "Calculation verification".

Virtual cohorts
A library of multiple parameters (e.g., geometries) sets that represent a defined population under study for the context of use and the clinical intended population. It could be either statistical representation of the clinical intended population (e.g., epidemiology) or a subject-specific representation of patients. It may be

used to support the development, and evaluation (i.e., the testing, the safety and/or efficacy) of new drugs or new medical devices."

Reference: Based on C. Miller et al, *In silico* trials for treatment of acute ischemic stroke: Design and implementation, https://doi.org/10.1016/j.compbiomed.2021.104802; and F. Pappalardo, M. Viceconti et al, *In silico* clinical trials: concepts and early adoptions, Briefings in Bioinformatics, Volume 20, Issue 5, https://doi.org/10.1016/j.compbiomed.2021.104802.

Virtual patient

A virtual patient can be considered as a computational model and simulation that represents the peculiar characteristics of one human subject (e.g., anatomy, (patho) physiology and/or lifestyle) and his/her interaction with the medicinal product of interest; and predicts (as opposed to measuring experimentally) quantities of interest necessary to support decision-making within a specific context of use.

Virtual patient can result from statistical process, for instance by using methodological heterogeneity assessments." (Reference: reference: Kononowicz AA, Woodham L, Georg C, Edelbring S, Stathakarou N, Davies D, Masiello I, Saxena N, Tudor Car L, Car J, Zary N. Virtual patient simulations for health professional education. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD012194. DOI: 10.1002/14651858.CD012194.)

Virtual population

Subset of plausible population generated based on the variability applied on subjects descriptors.

Reference: "*Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models*", RJ Allen et al. 10.1002/psp4.12063.

Uncertainty Quantification (UQ):

Activity to determine how the uncertainty in the model inputs (e.g., parameters, initial conditions) propagates into uncertainty in the model outputs; it is the process of identifying, characterising, and quantifying those factors that could affect the accuracy of computational results (based on FDA definitions in several guidances).

"The three sources of computational model uncertainty are uncertainties due to modelling assumptions and approximations, uncertainties resulting from the numerical solution of the governing equations, and uncertainties in the model input parameters." See "uncertainty"

Reference: M. Viceconti et al.