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Biotechnology — Predictive computational models in personalized medicine research —

Part 2: Requirements and recommendations for implementing computational models in clinical integrated decision support systems

Biotechnologie — Modèles informatiques prédictifs dans la recherche sur la médecine personnalisée —

Partie 2: Exigences et recommandations pour la mise en œuvre de modèles informatiques dans les systèmes d'aide à la décision clinique intégrés

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Foreword

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This document was prepared by Technical Committee ISO/TC 276, *Biotechnology*.

A list of all parts in the ISO 9491 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The combination of patient-derived data, such as genomics and lifestyle information, with patient registries and databases holds immense potential for improving medical care. One such potential lies in computer-based personalized models capable of providing precise, patient specific, predictions. Predictive and prognostic models hold great potential to support clinical decision making in personalized medicine and could ultimately facilitate a paradigm shift to a more personalized form of treatment.[1] Various computational models (see 3.10) have been devised to assist with the decision-making process.

Prognostic models are mathematical tools that relate a person's current characteristics and individual risk factors to the likelihood of a particular future outcome or disease course. Examples include estimating the probability of disease progression in an already ill patient or predicting whether an individual is likely to develop a disease in the future based on its own risk profile (risk stratification). Prognostic models can incorporate one or many current characteristics (multivariable). When validated, these models provide clinicians with objective estimates of the probability of treatment response, possible complications or quality-of-life-evolution that complements other clinical information.

Predictive modelling, on the other hand, uses available data to forecast likely future responses and effects of a specific treatment or intervention. This can be used to identify patients at high risk for adverse events (such as hospital re-admission) as well as those with a high probability of responding positively to a specific treatment. By providing individualized information on prognosis and potential response to therapy, predictive models are increasingly valuable tools for personalized, patient-centred medicine. Examples include identifying patients at high risk of readmission after a particular treatment or in silico modelling of therapy effects in specific patients or cohorts[1].

The assessment of computational models (e.g., statistical models, mechanistic models, machine learning and deep learning models) is done in the context of clinically driven research studies. Nevertheless, these studies are complex and challenging both from the clinical and the technological side. For complex diseases, such as certain cancer types, very often, only a few prognostic bioprofiles and even fewer, if any, multiscale prognostic models (models that include biological data ranging from the molecular scale to the entire organs and human organism, such as multi-scale models) are available on which to base personalized treatment decisions.

In most cases, available models lack robust validation in which: a) the predicted risks are compared to the actual observed outcomes in a patient population, and b) the model is validated in patient cohorts different from those used for developing the model and quality controls.[2] These controls include the internal and external validation of the computational models. Internal validation is needed during the model development to quantify any optimism in the predictive performance whereas external validation is needed for model generalization and require new data sets.[3] This causes a gap where important information becomes unavailable for optimal treatment decision making.

More prognostic predictions than those available from current clinical guidelines-based systems (such as Tumor-Lymphnode-Metastasis staging for cancer) are often needed to implement the first-line treatment that maximizes the therapeutic result and minimizes the impacts of therapy in terms of functional impairment and toxicity. Providing clinicians with the prognostic and predictive models supporting clinical decisions and providing all the necessary information to tailor treatment and care delivery pathways to each patient during their usual practice, in contrast to the current "one-size-fits-all approach", is an unmet need.

The development of clinical decision support system (CDSS)[4][5][6] could be achieved by combining "traditional" statistical models[5] [6] with artificial intelligence (AI) algorithms[7] driven by the manifold of health and other person-related data (big data) collected from patients,[1] as well as the integration of big data results with the statistical models. Moreover, it is necessary to validate the existing and newly developed models in different individuals and several populations and either adjust the person-related models accordingly or develop generally applicable models.[1] This process will create a virtuous cycle of learning between research and clinical practice, through the mutual feeding of external population data and patient-specific clinical data.

Improving the clinical decision process by implementing a prognostic system based on personalized computational models that increases the accuracy and reinforcement of a multidisciplinary decision-making would help define the optimal treatment for a particular patient. In addition, uncovering patient-specific and

population-related patterns can improve care and pave the way for better-tailored treatment guidelines, by assessing the importance (scoring) of new prognostic markers for outcome prediction, finally improving the patient's quality of life.

Biotechnology — Predictive computational models in personalized medicine research —

Part 2:
Requirements and recommendations for implementing computational models in clinical integrated decision support systems

1 Scope

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. This document also specifies how to integrate these rules 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 standard clinical practice, outside of a formal research or investigational setting.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 9491-1, *Biotechnology — Predictive computational models in personalized medicine research — Part 1: Constructing, verifying and validating models*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
artificial intelligence
AI
<discipline> research and development of mechanisms and applications of *AI systems* (3.2)

Note 1 to entry: Research and development can take place across any number of fields such as computer science, data science, humanities, mathematics and natural sciences.

[SOURCE: ISO/IEC 22989:2022, 3.1.3]

3.2
artificial intelligence system
AI system
engineered system that generates outputs such as content, forecasts, recommendations or decisions for a given set of human-defined objectives

Note 1 to entry: The engineered system can use various techniques and approaches related to artificial intelligence to develop a model to represent data, knowledge, processes, etc. which can be used to conduct tasks.

Note 2 to entry: AI systems are designed to operate with varying levels of automation.

[SOURCE: ISO/IEC 22989:2022, 3.1.4]

3.3
big data
extensive datasets — primarily in the data characteristics of volume, variety, velocity, and/or variability — that require a scalable technology for efficient storage, manipulation, management, and analysis

Note 1 to entry: Big data is commonly used in many different ways, for example as the name of the scalable technology used to handle big data extensive datasets.

EXAMPLE High volume, high diversity biological, clinical, environmental, and lifestyle information collected from single individuals to large cohorts, in relation to their health and wellness status, at one or several time points

[SOURCE: ISO 9491-1:2026, 3.3, modified — "(see reference [8] for additional information)" in EXAMPLE removed.]

3.4
bioprofile
objective 'fingerprint' or 'pattern' in the *data* (3.12) that provides phenotypic information, e.g. about a complex underlying disease that evolves with time

3.5
black box
idealized mechanism that accepts inputs and produces outputs, but is designed such that an observer cannot see inside the box or determine exactly what is happening inside that box

[SOURCE: ISO/IEC 18367:2016, 3.4, modified — Note 1 to entry removed.]

3.6
clinical decision support
type of service that assists healthcare providers in making medical decisions, which typically require input of patient-specific clinical variables and provide patient-specific recommendations

[SOURCE: ISO/TR 14639-2:2014, 2.8, modified — "system" replaced by "service"; Note 1 to entry removed and "which typically require input of patient-specific clinical variables and provide patient-specific recommendations" from Note 1 added to the definition]

3.7
clinical decision support system
CDSS
software designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base, whereafter patient-specific assessments or recommendations are presented to the clinician or the patient to aid in the process of making evidence based clinical decisions

Note 1 to entry: This definition was derived from Reference [26].

Note 2 to entry: In this document, we use “system” as an abbreviation of clinical decision support system.

[SOURCE: ISO/TS 22756:2020, 3.2, modified — “CDSS“ and Notes 1 and 2 to entry added.]

3.8
clinical study
any investigation in relation to humans intended:

a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

b) to identify any adverse reactions to one or more medicinal products; or

c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining the safety or efficacy, or both of those medicinal products

Note 1 to entry: This definition is derived from Article 2(2) (2) of the European Union Clinical Trials Regulation[20].

3.9
clinical trial
clinical study (3.8) which fulfils any of the following conditions:

a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the country concerned;

b) the decision to prescribe that the investigational medicinal product is taken together with the decision to include the subject in the clinical study; or

c) have diagnostic or monitoring procedures in addition

Note 1 to entry: In general, a clinical trial is a research investigation involving human subjects that is designed to answer specific questions about the safety and efficacy of a biomedical intervention (drug, treatment, device) or new ways of using a known drug, treatment, or device) (see [28])

Note 2 to entry: In this document we refer to *interventional clinical performance study* (3.16) for the first design purpose, and observational study for the second design purpose (see [29]).

Note 3 to entry: An observational (non-interventional) study refers to a study in which test results obtained during the study are not used for patient management and do not impact treatment decisions (see [29]).

Note 4 to entry: This definition is derived from Article 2(2) (2) of the European Union Clinical Trials Regulation[20].

3.10
computational model
in silico model
description of a biological system in either a mathematical expression or graphical form, or both, that is implemented and studied with a computer highlighting objects and their interactions

[SOURCE: ISO 9491-1:2026, 3.5, modified — Note 1 to entry removed.]

3.11
computational modelling
setting up, developing, formatting, refining, parameterizing, validating, handling, simulating and analysing *computational models* (3.10)

Note 1 to entry: Simulation-based analysis to test hypotheses within in silico experiments, providing predictions to be tested by in vitro and in vivo studies

3.12
data
reinterpretable representation of information in a formalized manner suitable for communication, interpretation or processing

Note 1 to entry: Data can be processed by humans or by automatic means.

[SOURCE: ISO/IEC 2382:2015, 2121272, modified — Notes 2 and 3 to entry removed.]

3.13
data integration
systematic combining of data from different independent and potentially heterogeneous sources, to create a more compatible, unified view of these data for research purpose

[SOURCE: ISO 5127:2017, 3.1.11.24]

3.14
deviation
departure from an approved *standard operating procedure (SOP)* (3.32) or established standard

[SOURCE: ISO 15378:2017, 3.7.5]

3.15
interoperability
ability of two or more systems or components to exchange information and to use the information that has been exchanged

[SOURCE: ISO/TS 27790:2009, 3.39]

3.16
interventional clinical performance study
study in which test results obtained during the study can influence patient management decisions and might be used to guide treatments

EXAMPLE Studies for companion diagnostics.

[SOURCE: ISO 20916:2019, 3.21]

3.17
machine learning
ML
computer technology with the ability to automatically learn and improve from experience without being explicitly programmed

EXAMPLE Speech recognition, predictive text, spam detection, or optimizing model parameters through computational techniques, such that the model's behaviour reflects the data or experience.

[SOURCE: ISO 9491-1:2026, 3.12]

3.18
model
abstract description of reality in any form (including concepts, *data* (3.12) elements, terms, and their relationships, statistical, theoretical, mathematical, physical, symbolic, graphical or descriptive form of a domain) that presents a certain aspect of that reality

Note 1 to entry: It is often further specified to distinguish between conceptual, logical and *computational models* (3.10).

[SOURCE: ISO/TR 23087:2018, 3.5, modified — "concepts, *data* (3.12) elements, terms, and their relationships, statistical, theoretical" and Note 1 to entry have been added.]

3.19
modelling
construction of abstract representations in the course of design, for example, to represent the logical structure of software applications before coding

[SOURCE: ISO 13972:2022, 3.1.6]

3.20
model validation
validation
comparison between the output of the calibrated model and the measured data, independent of the data set used for calibration

[SOURCE: ISO 14837-1:2005, 3.7, modified — Synonym 'validation' added]

3.21
natural language
language which is or was in active use in a community of people, and the rules of which are mainly deduced from the usage

[SOURCE: ISO/IEC 15944-8:2012, 3.82]

3.22
natural language generation
NLG
task of converting *data* (3.12) carrying semantics into *natural language* (3.21)

[SOURCE: ISO/IEC 22989:2022, 3.6.8]

3.23
natural language processing
NLP
information processing based upon *natural language understanding* (3.24) or *natural language generation* (3.22)

[SOURCE: ISO/IEC 22989:2022, 3.6.9, modified — "<system>" removed from entry]

3.24
natural language understanding
NLU
natural language comprehension
extraction of information, by a functional unit, from text or speech communicated to it in a *natural language* (3.21), and the production of a description for both the given text or speech and what it represents

[SOURCE: ISO/IEC 22989:2022, 3.6.11]

3.25
personal data
any information relating to an identified or identifiable natural person

[SOURCE: ISO 22857:2013, 3.9]

3.26
personal health data
any *personal data* (3.25) relevant to the health of an identified or identifiable natural person

[SOURCE: ISO 22857:2013, 3.10]

3.27
personalized medicine
precision medicine
medical *model* (3.18) using characterization of individuals' phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention

Note 1 to entry: Examples for individuals' phenotypes and genotypes are molecular profiling, medical imaging and lifestyle *data* (3.12).

Note 2 to entry: Medical decisions, prevention strategies and therapies in personalized medicine are based on this individuality.

[SOURCE: ISO 9491-1:2026, 3.18]

3.28
registry
information system for registration

[SOURCE: ISO/IEC 11179-1: 2023, 3.2.34]

3.29
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[SOURCE: ISO/IEC Guide 51:1999, 3.10]

3.30
risk assessment
overall process comprising a *risk analysis* (3.29) and a *risk evaluation* (3.31)

[SOURCE: ISO/IEC Guide 51:1999, 3.12]

3.31
risk evaluation
procedure based on the *risk analysis* (3.29) to determine whether the *tolerable risk* (3.34) has been achieved

[SOURCE: ISO/IEC Guide 51:1999, 3.11]

3.32
standard operating procedure
SOP
authorized, documented procedure or set of procedures, work instructions and test instructions for production and control

[SOURCE: ISO 15378:2017, 3.7.10]

3.33
statistical method
statistical technique
methodology for the analysis of quantitative *data* (3.12) associated with variation in products, processes, services and phenomena under study to provide information on the object of the study

[SOURCE: ISO 10017:2021, 3.1]

3.34
tolerable risk
risk which is accepted in a given context based on the current values of society

[SOURCE: ISO/IEC Guide 51:1999, 3.7]

3.35
usability
extent to which a system, product or service can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use

Note 1 to entry: The "specified" users, goals and context of use refer to the particular combination of users, goals and context of use for which usability is being considered.

Note 2 to entry: The word "usability" is also used as a qualifier to refer to the design knowledge, competencies, activities and design attributes that contribute to usability, such as usability expertise, usability professional, usability engineering, usability method, usability evaluation, usability heuristic.

[SOURCE: ISO 9241-11:2018, 3.1]

4 Fundamental requirements

4.1 General

Clinical decision support systems (CDSS) are software tools including algorithms that link together and analyse multisource and multiscale patients' data from Electronic Health Records (EHRs) including laboratory data, patient history, risk factors, behavioural data and socio-economic indicators if available, multi-omics (e.g. genomics, transcriptomics, radiomics, metabolomics, etc.), pathology, and imaging data, with available multiscale prognostic models and graphical visualization tools that assist healthcare providers in clinical decisions. CDSS may also include population-based epidemiologic, behavioural and environmental data. CDSS aid physicians in integrating almost all-available information to allow the best possible treatment and therapy decisions. To support healthcare professionals in their daily practice, aggregated knowledge shall be displayed in user-friendly formats so that physicians, non-technical laboratory personnel, nurses, data/research coordinators, and end-users can enter data, access information, and understand the output in the clinical setting. CDSS are tools that incorporate established clinical knowledge and updated patient information to enhance patient care; they encompass an array of strategies supporting a variety of topics. [9] Patient data require sequential processing to reach correct clinical conclusions, and then to become knowledge. EHR-based CDSS promise to translate clinical data into knowledge that can be readily used by physicians for decision-making and that can decrease the incidence of errors.

The system should intrinsically allow collaborative analysis, enabling multiple users to work on the same research objects and studies, reinforcing multidisciplinary decision-making. Insights from different collaborators shall be visible to all other cooperation partners to be used, for instance, for other studies focused on different cancer types. Users shall be able to define their role and activities assignments, being managed for the principal investigator of each study.

Data collection functionality shall be readily available when new data is collected, following the Clinical Record Forms (CRF), defined in the data layer. Data quality reports shall also be accessible from this functionality, and data correction shall be allowed. The user should access the data by selecting it following the standard nomenclature defined in the data layer. Data queries should be delivered through an understandable and easy-to-use interface, enabling the management of extensive heterogeneous data. The

users shall be able to export the data and visualize it. For each individual patient's EHR, direct visualization and a descriptive way to allow first data exploration should be provided.

Population data or other public data should be delivered - whenever available - to provide context and reference indicators. Existing preliminary analysis, evidence criteria and researchers' insights shall be available when accessing a particular manuscript.

4.2 Standardization requirements for clinically driven research studies

4.2.1 General

Scientific managers and clinical trials responsible are experiencing increasing regulations such as Good clinical practice (GCP) regulations or some European and international guidelines and directives. Still, limited discussions have been conducted to formalize and define the adequate quality of a standard operating procedure (SOP) system.

Since data represent a key aspect for sound and trustable research in clinical trials and digital health studies, data sharing and (re)use procedures are fundamental. Consequently, a high level of rigorous standards and semantic specificity is required not just for humans, but also for computational analysis. In particular, standardization can improve clinical research through increased data quality, better data integration and reusability, facilitation of data exchange with collaborating institutions, increased use of software tools, improvements in team communication, and simplification of regulatory reviews and audits. Similarly, trial execution procedures, processes, documentation, and reporting shall be ruled by well-defined SOPs relying on acknowledged standards and guidelines.

The user should not need to search for relevant standards or guidelines to select the appropriate ones, as this is time-consuming and error prone. On the contrary, the system shall propose the necessary information and the appropriate SOPs to guide the research and elaborate on the reporting results. Annex A includes a map of the existing guidelines to report clinical trial results when dealing with personalized systems and computational models. Considering these guidelines in Annex A and the Good Clinical Practice recommendations, Figure 1 represents the clinical research process. First, a CDSS should collect from the clinical researchers and provide the rational, goals and setting of the study. If the study is interventional, then details on the intervention (whether it is a drug administration or a computational model-driven intervention) shall be provided by the clinical researchers. Then, in all studies, clinical researchers and their teams should perform and document carefully data collection and data management processes to make sure that the data quality is sufficient to allow performing modelling (either standard statistics or computational models) and ensure interpretability of the results.

Limitations of the clinical research study shall be reported and taken into account, including:

a) populations representativeness: inclusion criteria limiting the population of interest to specific subgroups (e.g., non-considering gender/ethnicity/etc. in the study as compared to real-world prevalence fractions);

b) selection bias: systematic differences between baseline characteristics of the compared groups;

c) performance bias: systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest;

d) detection bias: systematic differences between groups in how outcomes are determined;

e) attrition bias: systematic differences between groups in withdrawals from a study.

Methodologies and guidelines exist to address such biases, which shall be implemented and reported with the study results.

Ethical and legal considerations applied in the trial shall also be considered, addressed, and reported by the study team as they can influence study subject inclusion criteria and/or data collection.

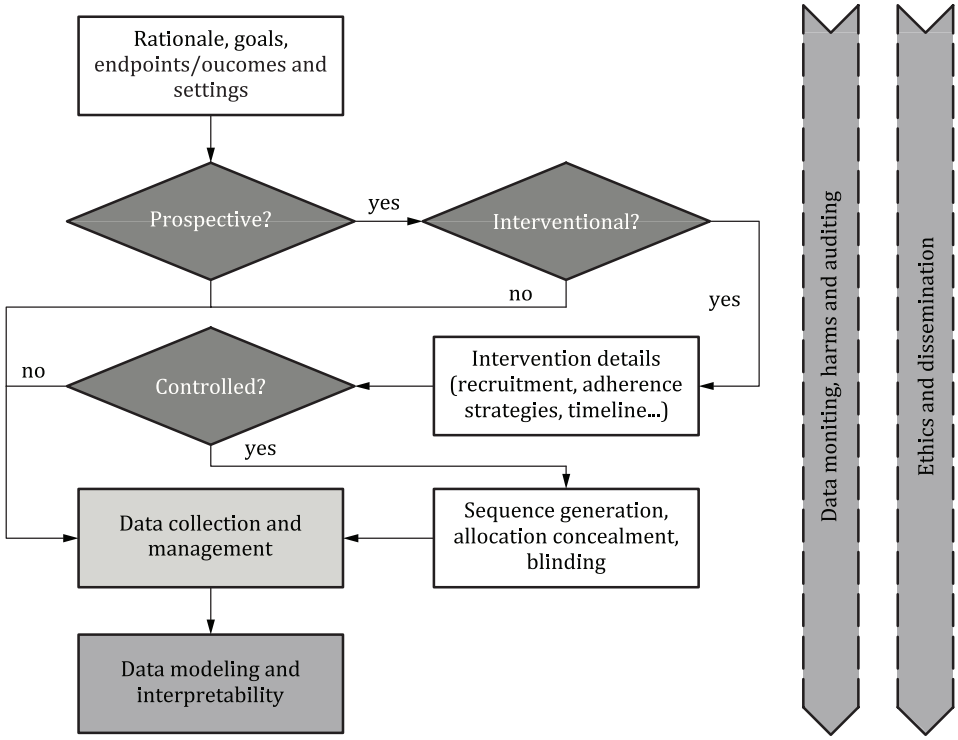

Figure 1 — Overview of the clinical trial process

4.2.2 Reference standards to be considered in the relevant SOPs

Any developed and implemented IT solutions in the healthcare delivery pathway should conform with reference standards, including but not limited to:

a) ISO/IEEE 11073[42];

b) ISO 13119[29];

c) ISO 22857[43];

d) ISO/IEC 22989[44];

e) ISO 23903[45];

f) ISO 30401[46];

g) ISO/IEC 38500[47];

h) ISO 80000[48];

i) ISO 9001[49];

j) ISO/TS 22756[50];

k) ISO/TS 5346[51];

l) ISO 9491-1;

m) ISO 29585[52].

4.2.3 Basic requirements and conditions for in silico models for clinical decision support systems

In silico models and associated CDSS shall be flexible and adaptable to the specific clinical care workflows to which they are applied.