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Designing Individualized Dosing Regimens under Pharmacokinetic Variability, Incomplete Patient Information, Uncertain Exposure–Response Relationships, and Competing Safety Objectives

Noah Williams[1]*, Grace Collins[1], Ethan Brooks[2], Daniel Green[3]

[1] Department of Individualized Dosing and PK Variability, Faculty of Pharmacy, University of Sydney, Sydney, Australia.
[2] Department of Exposure–Response Uncertainty, Faculty of Pharmacy, University of Queensland, Brisbane, Australia.
[3] Department of Safety Objectives and Dosing Optimization, Faculty of Pharmacy, University of New South Wales, Sydney, Australia.

***Email:** noah.williams@sydney.edu.au*

ABSTRACT

Individualized dosing is frequently presented as a problem of estimating an appropriate dose from patient covariates, drug concentrations, and population pharmacokinetic or pharmacodynamic models. This framing is incomplete when patient information is missing or delayed, exposure–response relationships are uncertain, efficacy and toxicity objectives conflict, and treatment must be revised as the patient's condition changes. This article develops an original decision-theoretic framework for organizing individualized dose selection under these conditions. The proposed architecture represents available observations, missingness, measurement quality, adherence information, and time-varying characteristics as an evolving patient-evidence state rather than a fixed covariate profile. Candidate regimens are evaluated through predictive distributions for exposure, efficacy-related response, toxicity-related response, and clinically relevant outcomes. Safety constraints are considered separately from preference-sensitive benefit–harm comparisons so that a predicted efficacy advantage cannot automatically compensate for an unacceptable probability of serious harm. Additional monitoring is treated as valuable only when the information is expected to alter the decision sufficiently to justify its burden, delay, and cost. Sequential dose adaptation incorporates predefined continuation, modification, stopping, abstention, and escalation rules. Decision-focused simulation is proposed to examine calibration, unsafe regimen selection, constraint violations, decision regret, inappropriate abstention, model misspecification, and performance under changing patient states before prospective clinical evaluation. Clinical governance requires transparent model scope, traceable data, version control, equity assessment, documented human override, and clear accountability. The framework is an original conceptual synthesis rather than a validated dosing method. Its use remains conditional on drug-specific evidence, defensible safety boundaries, externally evaluated predictive performance, prospective patient-outcome validation, and implementation studies within the intended clinical context.

Key words: *Clinical pharmacokinetics, Pharmacodynamics, PK/PD, Dose–exposure–response, Population modelling, Precision dosing*

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INTRODUCTION

Individualized dosing seeks to select a regimen that is appropriate for a particular patient rather than relying exclusively on a standard dose derived from population averages. Population pharmacokinetic models, therapeutic drug monitoring, exposure–response analyses, and Bayesian forecasting have created increasingly sophisticated

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means of estimating individual exposure. Nevertheless, the availability of pharmacometric models has not made model-informed dosing routine because technical performance must be connected to clinical workflow, interpretable evidence, suitable monitoring, implementation capacity, and a clearly defined decision purpose [1].

A broader precision-dosing perspective recognizes that dose selection depends on more than a model-generated exposure estimate. Patient characteristics, disease state, organ function, concomitant treatments, adherence, assay information, drug properties, and clinically meaningful outcomes may all affect the action that should be considered. These inputs must be linked within an explicit framework that explains how information is transformed into a treatment decision and how the decision will be revised when new evidence becomes available [2]. Treating these components as independent technical tasks risks producing a numerically precise answer to an incompletely specified clinical question.

The prevailing framing is especially insufficient when information is missing, covariates change over time, predictive models disagree, or exposure is an imperfect surrogate for efficacy and toxicity. Under these conditions, individualized dosing is not simply the calculation of a patient-specific parameter. It is a decision under uncertainty among competing actions whose consequences are incompletely known. Model-informed precision dosing therefore requires validation and implementation evidence proportional to its intended use, including evidence that the complete decision pathway—not merely the underlying model—is suitable for the population, setting, and clinical objective [3].

This Original Decision-Theoretic Framework Article proposes a conceptual architecture for organizing that pathway. The contribution integrates patient-state representation, probabilistic exposure–response prediction, explicit efficacy–toxicity utility, non-compensatory safety constraints, information-sensitive monitoring, sequential adaptation, abstention, and accountable human override. These relationships are proposed as an original synthesis of established pharmacometric and clinical decision concepts. The framework does not identify a universally preferred regimen, provide drug-specific safety thresholds, establish clinical effectiveness, or constitute a validated prescribing system. Its purpose is to clarify the information, reasoning, validation, and governance required before an individualized dosing recommendation can be considered decision-ready.

Individualized dosing as a decision under uncertainty

Digital precision dosing is often described through its component technologies, including population models, electronic health records, concentration measurements, clinical decision-support software, and computational prediction. Their combination, however, creates a multidisciplinary decision problem rather than a purely technical calculation. Data quality, model assumptions, workflow timing, professional interpretation, and the relationship between the predicted quantity and the intended clinical outcome jointly determine whether a model output can support an action [4]. A prediction may be statistically credible yet operationally irrelevant if it arrives after the treatment decision, depends on unavailable measurements, or addresses exposure while the unresolved concern is toxicity.

The central decision is therefore not “What dose does the model predict?” but “Which available regimen is most defensible for this patient, at this time, given the current evidence and the consequences of error?” Population-level recommendations remain essential starting points, but they may behave as blunt instruments when variability in clearance, susceptibility, disease trajectory, or response makes the consequences of a standard regimen uneven across patients [5]. Individualization does not reject population evidence; it uses that evidence as a prior structure that must be updated, qualified, or sometimes left unchanged according to the reliability and relevance of patient-specific information.

The proposed framework defines a dosing decision through six connected elements: the current patient-evidence state, a set of clinically feasible regimens, predicted consequences under each regimen, safety conditions that cannot be traded away, a benefit–harm valuation for the remaining options, and an action rule that includes treatment, monitoring, stopping, or escalation. The evidentiary requirements of each element depend on context of use. A tool intended to assist an experienced pharmacologist with a narrow therapeutic decision requires different validation and interface safeguards from a system expected to generate recommendations across institutions or patient groups [6]. Decision readiness must therefore be claimed for a specified use, not for a model in the abstract.

Uncertainty within this architecture has several sources. Pharmacokinetic variability concerns differences in exposure-generating processes; parameter uncertainty concerns limited knowledge of those processes; residual variability represents unexplained deviations; measurement uncertainty concerns the reliability of observed data; model uncertainty concerns competing structural explanations; and decision uncertainty concerns whether these

uncertainties could change the preferred action. The framework proposes that uncertainty should be evaluated according to its decision consequence. Uncertainty that does not alter regimen ranking may be tolerable, whereas apparently modest uncertainty may be unacceptable when it places a patient near a serious-toxicity boundary. This interpretation is conceptual and requires drug- and context-specific validation before clinical use.

Patient-state and evidence representation

Individualized dose selection begins with a representation of what is known about the patient, how it became known, and what remains uncertain. Electronic health record integration can connect demographic characteristics, laboratory results, medication history, dosing records, concentration measurements, and clinical observations to model-informed decision support [7]. Yet an electronic record is not itself a reliable patient state. Values may be outdated, copied forward, recorded in incompatible units, obtained after the relevant dose, or disconnected from adherence and sampling-time information. A usable evidence representation must therefore preserve timestamps, measurement provenance, units, assay context, and the relation of each observation to treatment history.

The framework distinguishes the observed evidence state from the underlying patient state. The observed evidence state contains available measurements, documented treatments, missingness indicators, adherence information, and data-quality attributes. The underlying patient state refers to the biological, behavioral, and clinical conditions that influence exposure and response but may be only partially observed. Examples include current renal function, inflammatory status, absorption behavior, organ reserve, pathogen susceptibility, treatment adherence, and evolving toxicity. This distinction prevents an estimated or imputed characteristic from being treated as equivalent to a directly measured and verified observation.

Missing information requires particular caution because the reason a value is absent may itself be clinically informative. Evaluations of covariate imputation in pharmacometrics show that performance depends on the structure and extent of missingness, the relationships among variables, and the method used to recover unavailable covariates [8]. A single substituted value can create an appearance of certainty and may distort an individualized prediction when the missingness mechanism is related to disease severity, clinical workflow, or treatment response. The proposed architecture therefore requires missingness to remain visible within the evidence state rather than being silently removed during preprocessing.

Multiple imputation provides one means of propagating uncertainty from missing covariates through a pharmacometric analysis instead of basing the decision on one completed dataset [9]. Within the proposed framework, this principle is extended beyond a specific imputation technique. Alternative plausible patient states should be carried into the predictive stage whenever their differences could change exposure, response, safety classification, or regimen ranking. This representation cannot recover unmeasured biology or eliminate bias from non-ignorable missingness. It instead makes uncertainty explicit, allows sensitivity analysis, and supports abstention or additional monitoring when the available information cannot justify a stable decision.

Predictive distributions for exposure and response

A decision architecture requires more than a single predicted concentration, clearance estimate, or probability of target attainment. Point predictions conceal the range of outcomes that may occur and can make two regimens appear equivalent even when one carries substantially greater uncertainty. Pharmacometric confidence and prediction intervals address different sources of uncertainty and must be interpreted according to the predicted quantity and intended decision [10]. For individualized dosing, the relevant output is therefore a distribution of plausible consequences under each regimen, accompanied by a clear account of the uncertainties included and excluded.

Model-selection uncertainty is especially important when several population models are plausible for the same drug and patient group. Predictive performance may vary according to model structure, covariate relationships, estimation data, and the characteristics of the patient being assessed. Model averaging or structured model selection can improve forecasting in some settings by avoiding complete dependence on one apparently preferred model [11]. This evidence does not establish that averaging is always superior. It supports the broader requirement that alternative models should be examined when structural choice could alter the dose decision.

External challenge is also necessary because acceptable fit in a development dataset does not establish transportability. Published voriconazole models, for example, have shown materially different behavior when evaluated with real-world clinical data, illustrating how population composition, clinical practice, sampling, and model assumptions can affect predictive adequacy [12]. A model may consequently describe its original data while providing poorly calibrated or clinically misleading predictions in another setting. The proposed framework

treats external evaluation as part of defining the valid decision domain rather than as an optional confirmation after implementation.

Predictive distributions should connect candidate regimens to exposure, efficacy-related response, toxicity-related response, and patient-relevant outcomes where those relationships can be supported. They should also distinguish parameter uncertainty, residual variability, measurement error, missing-covariate uncertainty, model disagreement, and possible population shift. Decision-ready prediction therefore requires explicit interval characterization, consideration of model-selection uncertainty, and external challenge within the intended clinical domain [10–12]. Even a well-calibrated distribution does not establish that the modeled relationship is causal, that exposure is an adequate surrogate for outcome, or that selecting a regimen from the distribution improves patient care. Those questions require separate decision-focused and clinical validation.

Utility functions for efficacy and toxicity

Exposure–response models describe anticipated consequences, but they do not determine how competing outcomes should be valued. A decision requires an explicit account of efficacy, toxicity, treatment burden, and patient preferences. Preference-informed clinical utility methods demonstrate how exposure–response evidence can be connected to the relative importance assigned to different outcomes [13].

A clinical utility index can combine several attributes to compare candidate doses, making the assumptions behind dose selection more visible than an isolated efficacy or safety endpoint [14]. Its conclusions nevertheless depend on the selected attributes, predictive models, scaling choices, and importance weights. A favorable score is therefore conditional rather than an objective property of a regimen.

Multiattribute utility approaches can structure benefit–risk comparison when several efficacy and toxicity dimensions matter simultaneously [15]. They are particularly useful when no dose dominates every alternative. They should not conceal disagreement among outcomes, convert weak evidence into apparent precision, or allow a composite score to replace examination of clinically serious harms.

The proposed architecture separates evidence-derived predictions from value judgments. Patient preferences may influence trade-offs among acceptable options, whereas predicted outcome distributions must remain evidence-constrained. Sensitivity analysis should show whether reasonable changes in preferences or assumptions alter the preferred regimen. Utility organizes a decision; it does not validate the underlying exposure–response model.

Competing safety constraints and unacceptable-risk thresholds

Dose optimization should not be equated with selecting the highest tolerated or most pharmacologically active dose. Contemporary oncology dose-optimization arguments emphasize preserving meaningful benefit while reducing avoidable toxicity and treatment burden [16]. This principle is relevant whenever greater exposure may increase both therapeutic effect and clinically important harm.

Therapeutic drug monitoring becomes decision-relevant only when a measurement is connected to a validated model, an interpretable target, and an action that can improve the treatment pathway [17]. Concentration measurement alone does not establish that a dose should be increased, reduced, or maintained, particularly when response varies independently of exposure.

Population concentration targets may also be inadequate when individual response biomarkers, vulnerability, or treatment objectives differ [18]. The proposed framework therefore distinguishes preference-sensitive trade-offs from non-compensatory safety constraints. A serious risk should not automatically become acceptable because another outcome receives a high utility weight.

A defensible dose-selection process must connect dose optimization, model-informed interpretation of monitoring data, and individual response-relevant safety objectives rather than maximize dose or target attainment in isolation [16–18]. Candidate regimens should first undergo a safety-feasibility assessment. When none is acceptably supported, the architecture proposes abstention, stopping, additional investigation, or escalation instead of forced selection.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in designing individualized dosing regimens under pharmacokinetic variability, incomplete.

Table 1. Definitions, components, relationships, and intended uses in Designing Individualized Dosing Regimens under Pharmacokinetic Variability, Incomplete.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Patient-evidence state	Fragmented or incomplete information	Measurements, timing, provenance, missingness, adherence	**Proposed:** preserve observed and uncertain information separately	More transparent decisions	Data-quality and missingness validation	False certainty from incomplete records	Does not recover unobserved biology
Predictive distribution	Point estimates conceal possible outcomes	PK, PD, covariates, model and residual uncertainty	**Proposed:** compare distributions across regimens	Uncertainty-aware ranking	Calibration and external evaluation	Miscalibration or transport failure	Prediction does not prove causation
Efficacy–toxicity utility	Competing outcomes lack a common decision structure	Outcome predictions and defensible preferences	**Proposed:** compare acceptable regimens across multiple attributes	Explicit benefit–harm reasoning	Preference and sensitivity studies [13]	Arbitrary weights or unstable rankings	Utility is not clinical validation
Safety-feasibility screen	Benefit may conceal unacceptable harm	Toxicity distributions and justified boundaries	**Proposed:** exclude unacceptable options before utility ranking	Prevent compensatory treatment of severe risk	Drug- and context-specific safety evidence [16]	Unsupported or poorly calibrated thresholds	No universal threshold is supplied
Model-informed monitoring	Measurements may not change action	Forecasting model, assay, timing, response target	Evidence-supported measurement-to-decision link [17]	More purposeful monitoring	Predictive and workflow validation	Burden without decision benefit	Measurement alone is insufficient
Individual response target	Population targets may not reflect patient needs	Biomarkers, vulnerability, treatment objective	Evidence-supported shift toward response-relevant interpretation [18]	Better alignment with individual objectives	Prospective outcome evidence	Unvalidated surrogate or biomarker	Individualization does not remove uncertainty
Abstention and escalation	No regimen may be acceptably supported	Safety status, uncertainty, model domain	**Proposed:** permit no-dose-selection outcome	Avoid forced recommendations	Decision-focused simulation and prospective evaluation	Excessive or insufficient abstention	Not a validated clinical rule

Value of additional monitoring information

Additional monitoring is useful only when it can improve the decision. Evaluations of Bayesian forecasting show that the value of a concentration measurement depends on the predictive performance and suitability of the model used to interpret it [19]. A technically accurate assay may provide little value when the result cannot distinguish among competing actions.

Monitoring can also improve pharmacometric target attainment without necessarily improving patient outcomes. A multicentre trial of model-informed antibiotic dosing illustrates the need to distinguish successful target control from demonstrated clinical benefit [20]. The proposed framework therefore treats target attainment as an intermediate result rather than proof of therapeutic value.

The value of additional information is defined conceptually as the expected improvement in decision quality after receiving new evidence, weighed against delay, cost, sampling risk, and patient burden. Monitoring is favored when it is likely to change the selected action or materially reduce uncertainty near an important safety boundary. **Figure 1** presents the original conceptual synthesis for decision-theoretic architecture for individualized dose selection, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

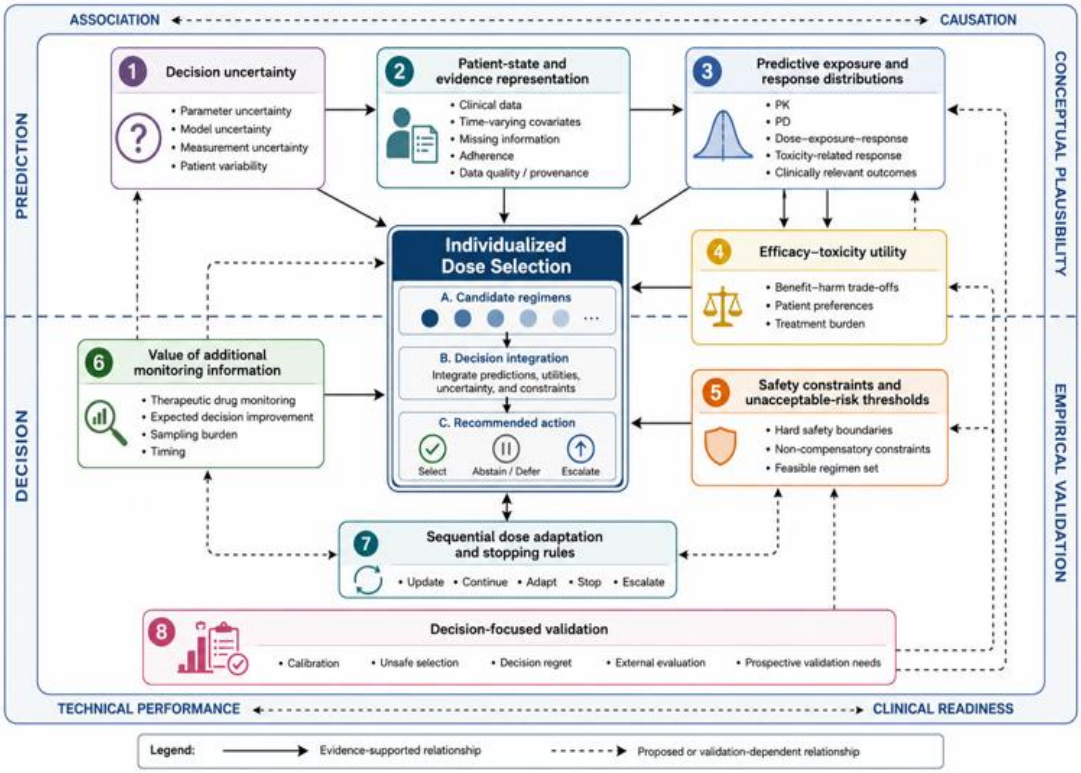

Figure 1. Decision-Theoretic Architecture for Individualized Dose Selection.

The figure is an original conceptual synthesis developed for "Designing Individualized Dosing Regimens under Pharmacokinetic Variability, Incomplete Patient Information, Uncertain Exposure–Response Relationships, and Competing Safety Objectives." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

Sequential dose adaptation and stopping rules

Individualized dosing is usually sequential rather than final. Bayesian updating and reinforcement-learning methods show how new observations can be incorporated into repeated dosing decisions while representing future consequences [21]. Their use remains conditional on credible transition models, clinically defensible objectives, and safeguards against unsafe exploration.

Continued-learning approaches further recognize that population models may require revision as clinical data accumulate [22]. Updating, however, is not automatically beneficial. Uncontrolled learning can amplify documentation errors, treatment-selection bias, population shift, or feedback created by earlier model recommendations.

The proposed architecture distinguishes patient-level updating from model-level updating. Patient-level updating revises the current individual state after new measurements. Model-level updating changes the underlying population or response model and should require separate governance, version control, retrospective testing, external challenge, and authorization.

Continuation, adaptation, stopping, abstention, and escalation rules should be prespecified conceptually before implementation. **Table 2** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for designing individualized dosing regimens under pharmacokinetic variability, incomplete..

Table 2. Testable propositions, evidence requirements, and validation criteria for Designing Individualized Dosing Regimens under Pharmacokinetic Variability, Incomplete.

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
State updating	Revise patient representation	New observations enter the evidence state	Changes predictive distributions	Calibration after updating	Delayed, incorrect, or biased data	Verify timing, provenance, and relevance	Updating alone does not validate action
Sequential action selection	Compare current and future consequences	State and predictions inform the next regimen	Uses utility and safety constraints	Lower unsafe-selection and decision-regret rates	Unstable dose oscillation	Predefine permissible actions	Simulation success is insufficient
Monitoring trigger	Determine whether more data are worthwhile	Expected information gain versus burden	Can delay or change action	Monitoring changes decisions appropriately	Repeated low-value testing	Define assay and turnaround requirements	No universal monitoring schedule
Stopping rule	End or suspend an unsafe or futile pathway	Toxicity, non-response, or uncertainty signal	Overrides utility ranking	Timely recognition of stopping conditions	Delayed stopping or premature discontinuation	Establish clinical escalation authority	Requires indication-specific evidence
Continued model learning	Revise population-level model	Accumulated clinical data enter controlled update [22]	Affects future patient predictions	Stable performance across versions	Drift, feedback bias, subgroup harm	Independent review and version control	Not routine self-modification
Human override	Permit accountable deviation	Clinician rationale returns to audit layer	May interrupt any automated pathway	Appropriate, traceable overrides	Automation bias or undocumented discretion	Record reasons and consequences	Human presence does not cure invalid design
Abstention	Decline unsupported selection	Excess uncertainty or no feasible regimen	Triggers monitoring or escalation	Reduced unsafe forced recommendations	Excessive or inadequate abstention	Define escalation and fallback care	**Proposed; requires prospective validation**

Validation through decision-focused simulation

Simulation can compare dosing policies before prospective clinical use by exposing them to varying patient trajectories, observation schedules, model errors, and treatment histories [23]. Its purpose should extend beyond reproducing concentrations to examining how uncertainty affects actions and consequences.

Decision-focused evaluation should assess calibration, inappropriate regimen selection, constraint violations, decision regret, delayed stopping, unstable adaptation, subgroup performance, and abstention behavior. Stress tests should include missing information, measurement error, misspecified covariate relationships, population shift, competing models, and delayed monitoring.

Simulation can reject unsafe assumptions or reveal failure modes, but it cannot establish patient benefit. Clinical value ultimately requires evidence that the complete decision pathway improves outcomes relevant to patients rather than only model fit or target attainment [24].

Validation should therefore proceed from technical and computational testing to external pharmacometric evaluation, prospective workflow testing, and clinical outcome assessment. The relevant comparator may be standard care, an established dosing protocol, or a simpler model. Acceptance criteria must be prespecified for the intended drug, population, and decision context.

Clinical governance and human override

Clinical governance begins with a defined context of use, named professional responsibilities, data provenance, software version control, and transparent limitations. Evaluations of model-informed dosing software show that available tools differ in functionality and may not satisfy all scientific, technical, and workflow requirements [25].

Governance must also address equity. Precision-dosing decision support can reproduce unequal representation, measurement access, data quality, or interface usability, producing different performance across patient groups [26]. Subgroup evaluation should therefore examine both predictive behavior and access to the information required by the model.

Clinical governance must connect patient-outcome validation, fit-for-purpose software controls, and equitable human decision-support design [24–26]. Human override should be available when relevant information lies outside the represented state, but each override should be reason-coded, traceable, and reviewed for recurring model, data, interface, or workflow failures.

Human supervision does not automatically make an invalid architecture safe. Clinicians may accept erroneous recommendations through automation bias or reject appropriate recommendations because uncertainty is poorly communicated. Accountability should therefore be distributed explicitly among model developers, data stewards, software owners, clinical services, and authorized decision-makers.

Limitations and research priorities

The framework remains limited by the distinction between prediction and intervention. Adaptive titration can create treatment–response feedback, time-dependent confounding, and selection effects. Causal claims about what would occur under an alternative titration strategy may require assumptions beyond ordinary predictive fit [27].

Emerging foundation models may help integrate heterogeneous clinical information, but they also introduce problems of calibration, provenance, interpretability, fabrication, domain shift, and accountability [28]. They should not be treated as substitutes for drug-specific PK/PD evidence or as mechanisms for recovering information that is absent or unidentifiable.

Further research should establish methods for representing non-ignorable missingness, uncertain adherence, changing covariates, competing models, unstable preferences, and rare serious toxicity. Comparative studies should test when constrained utility, information-sensitive monitoring, sequential adaptation, and abstention improve decisions over simpler rules.

Prospective evaluation must also identify when the framework should not be used. Important boundaries include poorly characterized exposure–response relationships, unreliable measurements, absence of feasible alternatives, unsupported safety thresholds, unrecognized population shift, and clinical situations in which delayed action creates greater risk than additional modeling can resolve.

CONCLUSION

This article proposes an original decision-theoretic architecture that connects patient-state representation, predictive exposure–response distributions, explicit efficacy–toxicity utility, non-compensatory safety constraints, value-based monitoring, sequential adaptation, stopping, abstention, and accountable human override. Its principal contribution is to reframe individualized dosing as a transparent action-selection problem under incomplete information rather than as dose calculation alone. The framework remains conceptual and requires drug-specific calibration, external evaluation, decision-focused simulation, prospective clinical validation, equity assessment, and implementation governance. It does not provide universal thresholds, validated treatment recommendations, regulatory conclusions, or a deployment-ready system.

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