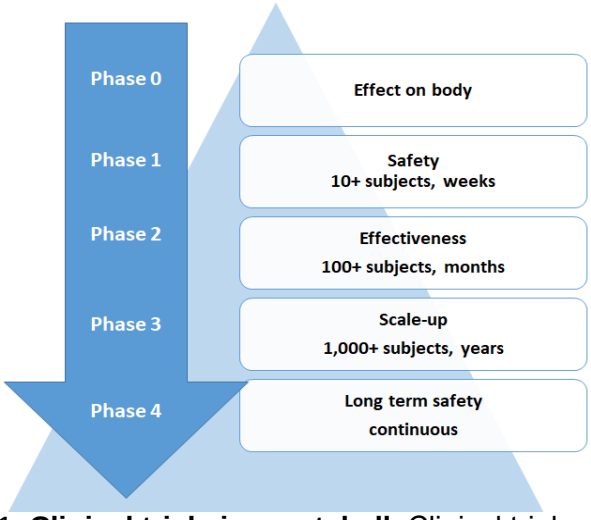
PDS: High Level Architecture

To streamline a clinical innovation pipeline from peer-reviewed research to safe, effective, validated, evidence-based and personalized clinical decision support, we developed a framework and application programming interface (API) specifications that we simply call *PDS*.

Here, we outline problems that guided the development of this generalized framework, which can provide solutions across multiple domains. We also show how *PDS* can be used for precision dosing, describe the architecture and detail the anticipated impact. After completing this document, consider reading the High-Level Design (HLD) document.

Problem Statement

The promise of precision medicine is to bring the right drug to the right patient at the right time. However, the clinical trials necessary for realizing that promise are costly in both time and resources (Figure 1). Innovative analytical models can identify biomarkers that predict outcome, thereby matching patients to treatments with the lowest risk of adverse events to improve safety and efficacy.



Phase	Approximate Success Rate
1	70%
2	33%
3	25-30%
Phase1-3:	6-7%

Figure 1: **Clinical trials in a nutshell**. Clinical trials validate a drug's safety (Phase 1) and effectiveness (Phase 2) at scale (Phase 3) and over time (Phase 4). Pre-clinical Phase 0 enrolls no human patients, conducting tests *in vitro* and on animal models while thousands of people are enrolled by Phase 3. Trials are time consuming, lasting approximately 10 years, and costs up to $1 billion, with only 6-7% of new drugs typically making it past phase 3.

The innovation pipeline required to advance precision medicine (Figure 2) often starts with data generated by *practice* that drives hypothesis-driven *research*, which in turn leads to

development of new therapies that require *validation* before implementation in *practice*. However, moving peer-reviewed models from the *research* phase into the *validation* phase is fraught with social and technological obstacles. Although the biomedical domain is replete with community standards, there are currently no standards that can be used to program a peer-reviewed, *research* analytical model that can be deployed unchanged to a *development* context followed by a *validation* context and, finally, into clinical workflows.

Standards defining model inputs and outputs (APIs) can enable connectivity between multiple frameworks, and consequently, reusability within multiple steps of the innovation pipeline. Such API standards would ease the burden of validating modeling software because no refactoring would be required as the program moved through the innovation pipeline with the same API. In addition to reusability of software throughout the innovation pipeline, analytical model API standards would enable interoperability, meaning that a single, peer-reviewed model could be used across multiple pharma, CROs, and healthcare providers without any modification or refactoring.

Figure 2: **Precision medicine innovation pipeline**. Most precision medicine is practiced in the clinic (bottom left quadrant), where the goal is to provide the right drug for the right patient at the right time. Practice informs research via retrospective studies, which are primarily conducted in academia (upper left quadrant). Academic activities also generate and test hypotheses that lead to drug target, biomarker and companion diagnostic development (upper right quadrant). Development activities are often conducted by pharmaceutical companies, which may hire a Contract Research Organization (CRO) to run clinical trials and validate findings (lower right quadrant). All these activities require modeling and analytics.

Furthermore, a framework devised to integrate with analytical model API standards and patient data server standards could connect novel, innovative models with real and simulated data. This would allow the models to be used to solve multiple decision support problems across

various therapeutic areas and intervention types. As an exemplar, we describe the use case of precision dosing to show how the PDS framework and standards can provide solutions to some of these problems.

Use Case: Precision Dosing

Figure 3 is borrowed from the 'Precision Dosing Initiative' page on the UNC Eshelman School of Pharmacy website and depicts a 'precision dosing development and evaluation "engine"'. RENCI's Translational Science team fits into this engine by architecting novel and disruptive middleware to accelerate the injection of validated dosing tools directly into clinical workflows for pilot trials.

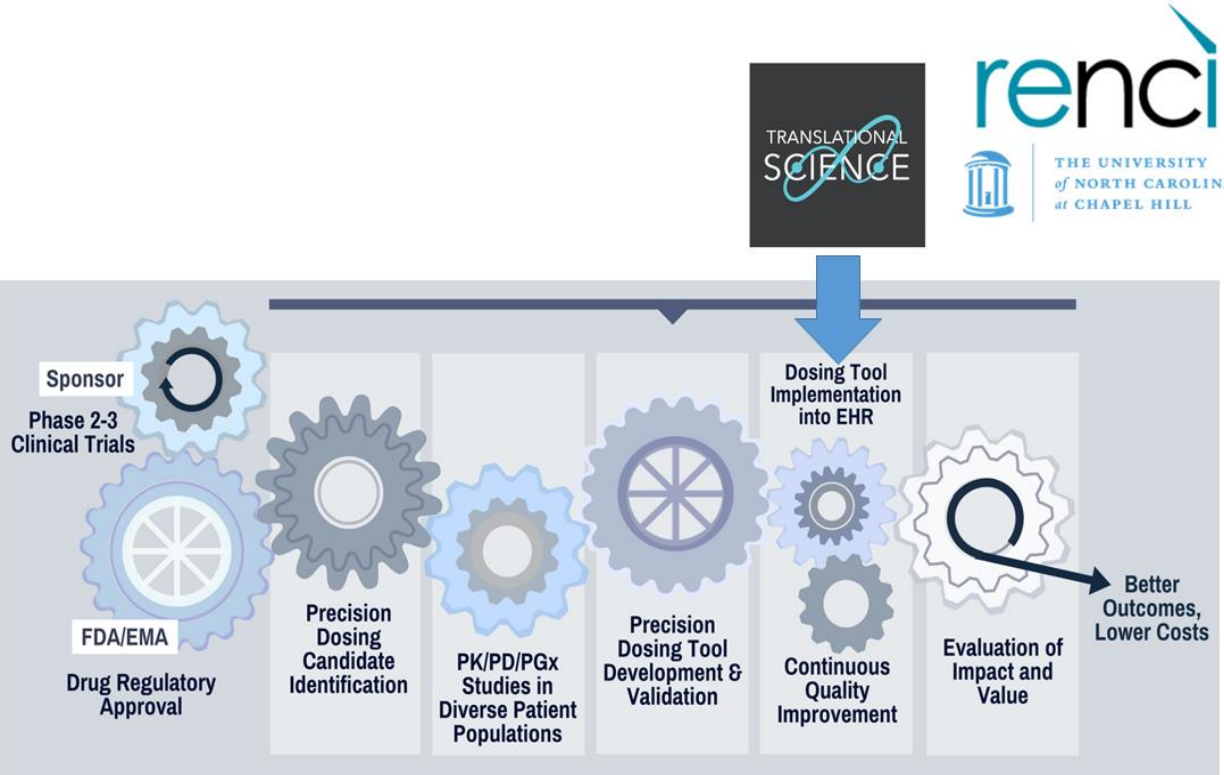


Figure 3: **Precision dosing development and evaluation "engine"**. This figure is borrowed from the 'Precision Dosing Initiative' page of the UNC Eshelman School of Pharmacy website.

With funding from Eshelman Institute of Innovation (EII) and help from the UNC Eshelman School of Pharmacy, we interviewed focus groups and found the top two barriers to precision dosing were lack of extensibility and interoperability of current systems. Hence, we architected a novel system that allows for interoperability (Figure 4) with any patient data server, real or simulated, and supports the FHIR patient data record standard. We embraced a "bring your own models" philosophy that can support cutting-edge AI-based implementations as well as

traditional NONMEM implementations, and even DILI-sym models. If you know the patient variables required, if you can describe how they are used your model, run the model, and update the outputs, then you can implement it and plug it in.

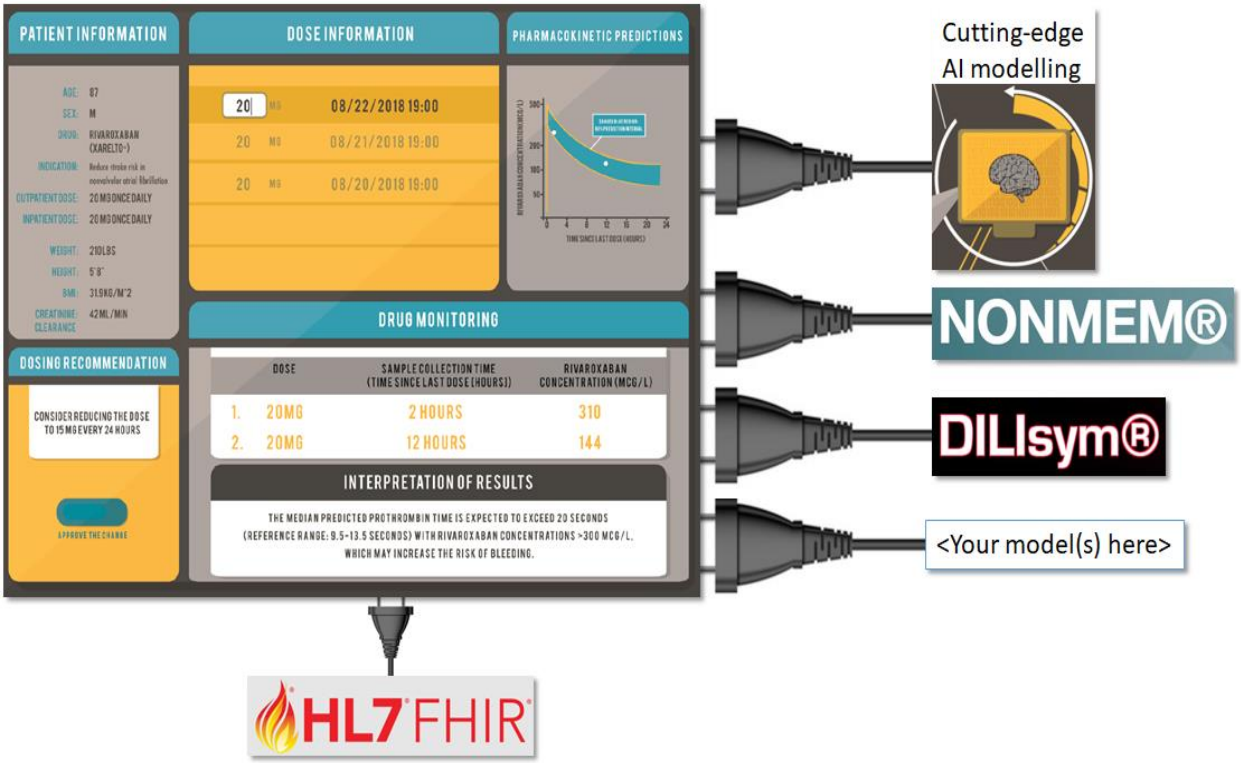


Figure 4: **Precision dosing dashboard for interoperability**. The dashboard can pull patient data from a FHIR server, map it to clinically relevant variables, and query analytical models with that data to get well-formatted guidance. Analytical models are containerized behind RESTful interfaces and can be implemented in any language using any computational resources.

In addition to facilitating and listening to the focus groups, we evaluated vendor software systems that were identified by the UNC STAR Team as software aimed at answering some of the same precision dosing questions. We did not find any vendors providing software with the same flexibility in terms of healthcare record interoperability or model plugin flexibility. In fact, the use cases in Figure 5 depict some of the barriers a dosing model developer might face when attempting to use some of the current vendor-supplied software on the market.

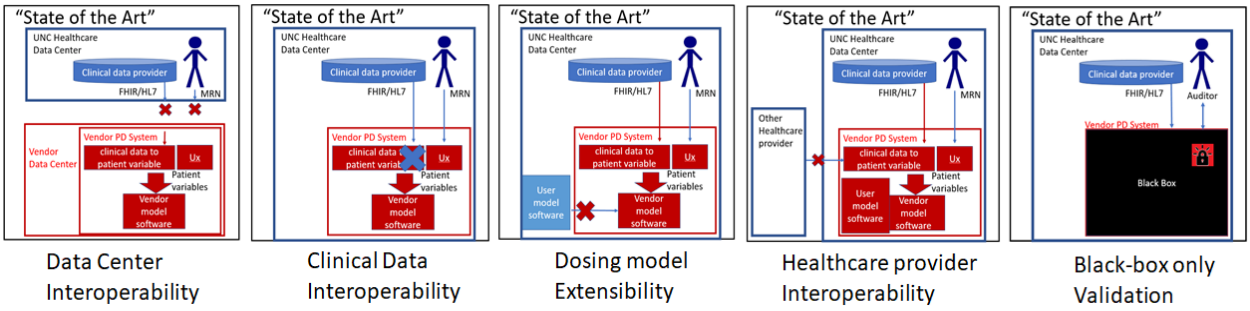


Figure 5: **Interoperability and extensibility barriers to precision dosing**. Left to right: (1) Real patient data providers (like hospitals) have security rules that prohibit export of their clinical data, barring integration with a SaaS vendor platform hosted in a cloud, (2) If the FHIR-enabled vendor platform can be hosted within a hospital's data center, it still needs to be customized to interpret the unique methods that hospital uses for encoding patient variables. (3) With a customized vendor system hosted inside the hospital, additional customizations are needed to extend the vendor software for use with any newly emerging, validated dosing model. (4) Once an emerging dosing model has been integrated into the vendor system, the same customization efforts must be repeated because that validated model cannot "just plug-in" to other hospital workflows. (5) Closed systems must be validated as "black box," and the vendor must be trusted to have a full quality assurance plan including unit, system, and integration testing of their unpublished code

Solution: PDS, a FUSE Architecture

Our architecture (Figure 6) includes the ability to plug in a FHIR server (bottom left) as well as a patient variable mapper. The FHIR specification doesn't require specific encoding for the clinical data or even that the data are present. A large part of electronic health record (EHR) data are collected more for reimbursement and less for research or even clinical utility. Thus, a plug-in can be implemented by a data provider to map EHR data to values and variables that meaningful to model developers and prescribing clinicians. For example, there may not be a recently measured body mass index (BMI) LOINC code, but there may be recent values for body height and body weight LOINC codes from which the "mapper" may infer BMI. Note that the "Presentation Layer" (at the top) contains "Model View" for the model developer and "Clin View" for the prescribing clinician. The "Clin View" is mostly subsumed by the clinical workflow software. It relies on the hospital's IT integration team to make a simple call for guidance to the PDS system and only raises alerts if there is a discrepancy with the configured model. By adding no extra steps to current workflows, the PDS can remain out of the way unless the clinician needs decision support.

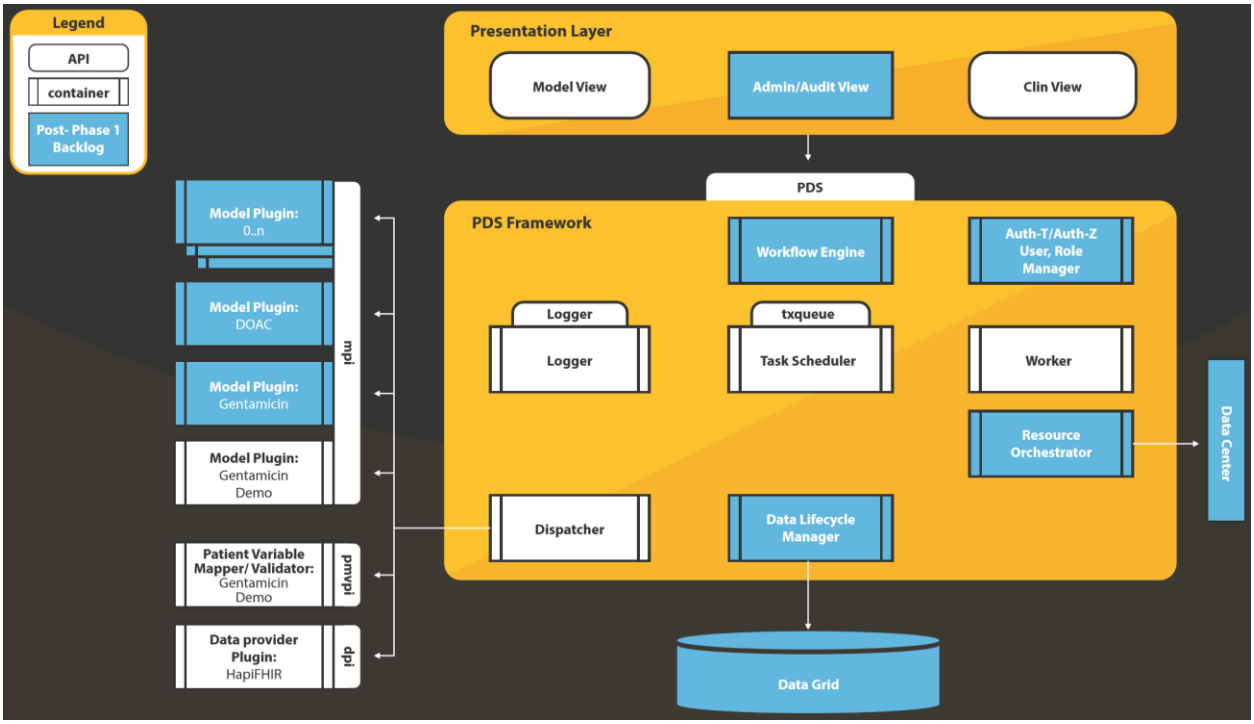


Figure 6: **PDS FUSE Architecture**. The architecture uses the FAIR principles, in addition to principles for Usability, Sustainability/Scalability, and Extensibility.

Impact

By including both standards and a deployment framework, PDS allows the research-use-only (RUO) development environment to mirror the clinical-use environment. This environmental symmetry is designed to accelerate innovations in pre-clinical research and expedite translation to healthcare provider. New interoperability standards could also empower the expansion of a global dosing model catalog because there is no vendor lock-in. Such standards could allow knowledge from powerful public data commons and platforms to be integrated into the analytical models. These standards can likewise provide integrative support for prehospital patient care (e.g., Ambulance-ESO Suite integration). Furthermore, there is a bright future for collaborations in precision medicine because developers can easily share models on this platform. This framework creates disruptive innovation for defining patient variables, with applications in pharmacogenomics where it offers a new path for integrating biomolecular knowledge. We expect it to drive better patient stratification and improved clinical trial outcomes.

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