White paper

Model-informed Drug Development (MIDD) at NOVA



nova DISCOVERY

NOVA's modeling and simulation approach combines mathematical models of diseases and treatments with virtual patients into an integrated clinical trial simulation platform called Jinkō®. NOVA builds disease and treatment computational models based on knowledge extracted from literature and data. To simulate a trial, we run those models on virtual patients with appropriate simulated scenarios (*in silico* experimental protocols) to predict the clinical efficacy of new drugs at the population level before in-human trials take place.

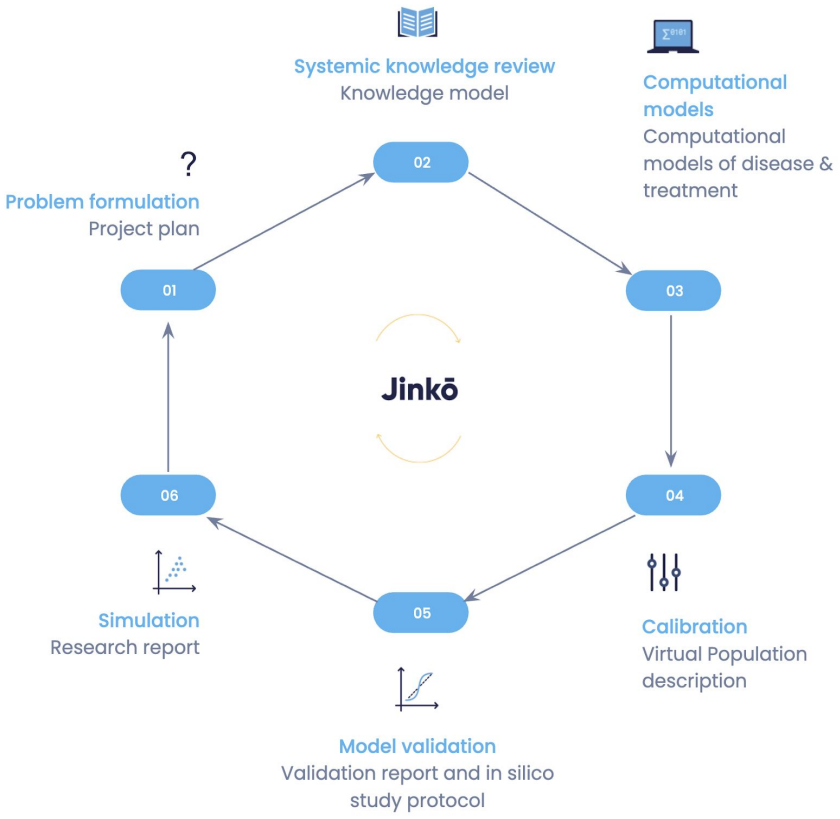
Various applications of the NOVA methodology

NOVA's Model-informed Drug Development (MiDD) approach yields applications spanning the entire R&D spectrum, from systematic target combination exploration to value demonstration to payers:

- Discovery (streamline target identification & secure proof of concept)
  - Explore efficacy between various targets
  - Explore efficacy of various combinations of targets/treatments
  - Explore transability from animal models to humans
- Clinical development
  - Explore various regimens (dose, number of administration(s) per day, time between administrations, duration of treatment, time of administration vs time of meals)
  - Identify subgroups of optimal responders/theranostics biomarkers
  - Reduce sample size and follow-up duration
  - Reduce the risk of protocol amendments and delays
  - Optimize trial design
- Pricing and Market access:
  - Demonstrate value to payers by predicting the real life drug related benefit and the optimal target population
  - Transpose Phase 3 trial results into a virtual representative population of specific geographies and context
  - Benchmark competing treatments

Standard *in silico* project workflow

NOVA's 6 step approach to *in silico* workflow



Step 1

Upon agreement with the sponsor on the problem formulation (*i.e.* questions that should be addressed *in silico*), the pathophysiology of interest is broken down into submodels and for each submodel a level of granularity is set (molecular, cellular or organ).

Step 2

For each submodel, a Knowledge Model (KM) is developed, including all the biological entities involved in a given submodel as well as the functional relationships between these entities. This step leverages our Jinkō platform as a way to increase efficiency and improve ease of access to the data and results that form the basis of the model.

Step 3

A graphical representation of the biological system is then converted into mathematical equations to produce the Computational Model (CM). Input parameters are adjusted in order to optimize the agreement between actual observed data and the model's outputs. This step benefits from Jinkō's speed, certainty, check, and communication.

Step 4

A Virtual Population (VP) is created. A VP is defined as a set of virtual patients, where each virtual patient is a vector of descriptors. Generating a virtual patient consists of sampling sets of descriptors based on their co-distribution laws. Those laws are adapted and inferred so that the resulting model inputs (linked functionally to patient descriptors) fall within calibrated ranges.

Step 5

The model is validated following published US FDA guidelines and using additional methods implemented in Jinkō. The validation plan consists in simulating real-life trials, while attempting to follow the protocol applied by the Sponsor as closely as possible.

Step 6

Simulations to answer the batch of questions initially asked in Step 1. An *in silico* clinical trial can explore new prospective scenarios, or reproduce the protocol of an existing *in vivo* trial (*e.g.* same dose, same regimen). By virtue of its simulation-based approach, NOVA's platform provides possibilities that do not exist in a real-life drug trial: for instance, each virtual patient is its own control, as it can be run through as many different simulation scenarios as necessary (*e.g.* control, dose A, dose B).

Deliverables

NOVA's 5 key deliverables

- Deliverable 1 - Knowledge models: Summary of the review of literature in text and graphic form, containing all the pieces of knowledge necessary to build the computational model, as well as a list of knowledge gaps and an associated modeling strategy.
- Deliverable 2 - Validation protocol: Protocol defining the simulations to be run for the validation, the data to be used ("validation dataset") and the endpoints to be met for the validation.
- Deliverable 3 - Simulation protocol: Protocol defining the simulation to be run and the analyses necessary to answer the questions. This can be seen as the *in silico* equivalent to the clinical trial protocol.
  - For example, simulating a control arm, a QD treated arm, and a BID treated arm, with the same virtual population, in order to rank the regimens according to a given endpoint.
  - Identifying a subset of responders to the treatment and their common characteristics, to find biomarkers of response.
- Deliverable 4 - Validation report: Report on the validation phase, describing which endpoints were met, and a conclusion.
- Deliverable 5 - Final report: Report answering the research questions, using the model outputs from the different simulations and analyses defined in the Simulation protocol.

Regulatory

NOVA supports its sponsors' strategies and discussions with regulatory authorities to include modeling and simulation in their global clinical plan in view of increasing the probability of success, reducing costs and accelerating treatment delivery time to patients.