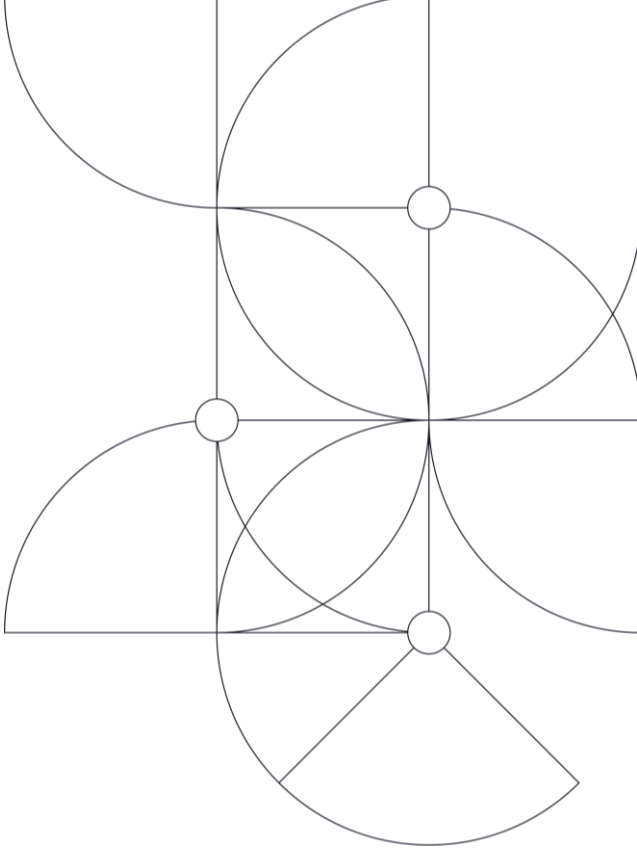

In-Silico Clinical Trials
A Blueprint for the Future

Prepared for EFSPI

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Impact where it matters.

Why In-Silico Trials?

In-silico clinical trials are emerging as an important innovation to address the limitations of traditional clinical trials. Conventional trials are expensive and time consuming, contributing to high drug development costs and delays in bringing therapies to market. Additionally, ethical concerns arise when testing experimental treatments on human subjects, particularly in vulnerable populations or for rare diseases where patients are limited. In-silico trials address these challenges by leveraging computational models to simulate clinical trials, enabling researchers to test hypotheses, optimize trial designs, and predict outcomes before or instead of running an actual trial.

In-silico methods are not new. Manufacturing, aerospace, and automotive industries have been using digital twins for many years to optimize production and accelerate product development. Closer to home, Medical Device organizations have seen significant adoption of digital twins in product design, and they are increasingly using in-silico trials for regulatory submissions. In pharma, in-silico methods are most heavily adopted in Discovery, with several TechBio companies emerging with a predominately in-silico approach. Now we are seeing in-silico move "downstream" with rapid adoption in pre-clinical and emerging (yet still limited) adoption in clinical trials.

What are In-Silico Trials?

In-silico clinical trials are computer-based simulations that replicate traditional clinical trials using virtual patients instead of real human subjects. These virtual patients are digital representations of diverse populations, constructed using many data sources (clinical trials, RWD, genomic data, etc.). Through a combination of modeling approaches, in-silico trials simulate the administration and effects of a treatment on these virtual patients and predict clinical outcomes to evaluate the efficacy and safety of treatments in a virtual environment. In-silico trials can thereby evaluate a large volume of synthetic protocol designs and virtual cohorts before enrolling a single patient.

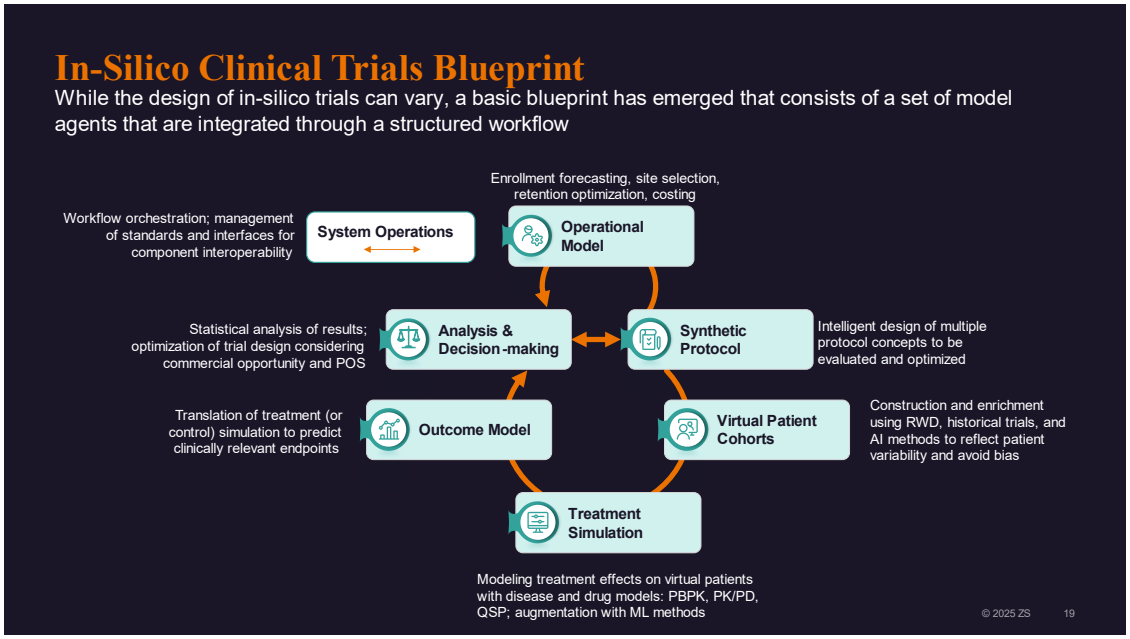

Figure 1: In-Silico Trials Blueprint

While the design of in-silico trials can vary, a basic blueprint has emerged that consists of a set of models that are integrated through a structured workflow (Figure 1).

- **Synthetic Protocol Management** – develop many protocol design options for each study, and then model, evaluate, optimize, and catalogue selected protocols for future use

- **Virtual Patient Cohort Generation** – create virtual patient cohorts (based on protocol IE criteria) using RWD and/or historical trial data leveraging AI foundation models (e.g., variational autoencoders or GANs) to reflect real-world patient variability and avoid bias
- **Treatment Simulation** – model the administration and effects of the treatment on virtual patients, based on PBPK models to simulate ADME, PD models to link drug concentration to pharmacological effect, QSP models to assess the interactions at the system level, and ML models to complement/improve these mechanistic models by learning from large datasets.
- **Outcomes Prediction** – predicts clinical outcomes, by applying statistical or ML techniques to map treatment simulation outcomes to clinically relevant endpoints (refining the model by comparing predictions with actual data), using disease progression models to translate mechanistic signals into how disease evolves over time
- **Operational Simulation** – simulates operational elements (sites, enrollment, cost, quality, timeline) based on analysis of protocol, cohorts, and predicted outcomes, for a balanced protocol assessment/optimization based on both scientific and operational considerations.
- **Analysis & Decision-Making** – compiles and analyzes trial results to adapt/optimize the trial using optimization algorithms and assess trial success via statistical analysis techniques to calculate confidence intervals against pre-defined criteria. Provide visualization and reports to inform and recommend decisions to key stakeholders.
- **System Operations** – the in-silico system also requires many operational components to work efficiently, including a user interface and workflow; an integrated data ecosystem; interoperable libraries for models, protocols, cohorts, and scenarios; validation module for regulatory acceptance, & documentation

How will in-silico trials be used?

While the use of in-silico trials is emerging, there is a **progressive cascade of use cases that build off each other** from pre-clinical to registrational trials and beyond (Figure 2).

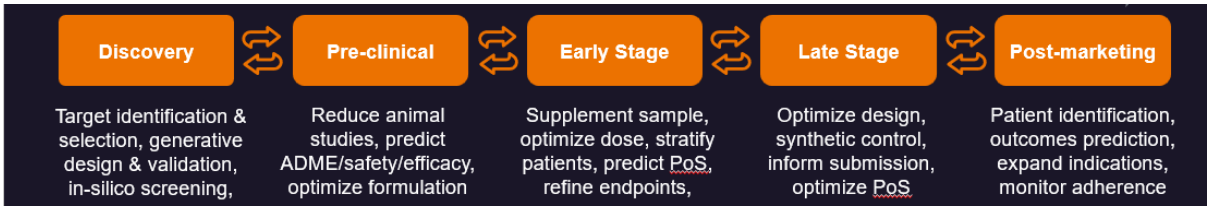

Figure 2: Progressive Cascade of Use Cases

In **pre-clinical** development, in-silico trials can reduce or supplement animal studies and help optimize formulation and delivery. In **early development**, in-silico trials can supplement (or reduce) small sample sizes and model the diversity of patient populations in the real world to optimize dose, mitigate risk, refine endpoints, stratify patients, and refine protocols. In **registrational studies**, in-silico trials can optimize design and operations, provide synthetic controls, help assess/understand trial results, and inform submission. **Post approval**, in-silico trials show promise in assessing long-term treatment affects and informing new indications and label expansion with synthetic data. Moreover, the methods developed via in-silico trials may also serve as the foundation for clinical decision-support models and tools to inform patient diagnosis and treatment selection.

What is the maturity and adoption of in-silico trials?

We consider in-silico trials to be an emerging capability that is still in its infancy, although the components and use cases described above have varying degrees of maturity across disease areas. We are not aware of any pharma company that has anything close to a comprehensive in-silico trials capability as defined in this document, however, several large pharma companies are highly focused on building an in-silico trials future.

Most of the advancement we have seen on in-silico trials is occurring in the broader Digital/AI marketplace outside of large pharma. We recommend large pharma companies monitor and engage these companies as partners, vendors, or investors, similar to how research organizations are building their in-silico discovery capabilities through a mix of internal and external investments.

One of the most common questions is whether regulatory agencies will support the use of in-silico trials or serve as a barrier. Thus far the FDA has given the industry plenty of 'runway' to expand its use of models and AI to support drug development. This includes providing helpful guidance for MIDD and AI and facilitating open dialogue in the form of meetings and published perspective. Having said this, we also have seen a gap between the vision and policies of senior leadership in regulatory agencies and the actions of 'on-the-ground' regulatory staff.

What are the critical in-silico capabilities?

Most pharmaceutical organizations will require significant advancements in their data, modeling, and technology capabilities for in-silico trials:

- **Multi-modal data** (bench, pre-clinical, clinical, RWD, omics, imaging) that is FAIR (Findable, Accessible, Interoperable, Reusable) and available compliantly as analysis ready datasets not constrained by "functional ownership" to design, train and inform in-silico models
- **Advanced analytics** (Generative AI, ML, digital twin, simulation) talent needs to be added to current functional capabilities. Also, existing PK/PD and biostatistical methods will need to improve and/or new AI/ML methods will need to be adopted or developed
- **High-performance in-silico system** environment that is fit-for-purpose to in-silico trials and enables multiple functions to support the progressive cascade of use cases, along with the supporting engineering, productization and user adoption capabilities

While the in-silico system, models and data are essential, it is just as important to consider 'softer' capabilities required to realize value from the in-silico approach, such as organization design, operating model, leadership and trust:

- **T-shaped professionals** that have deep expertise in their discipline, but more importantly and E2E view across the progressive cascade of models, data, and use cases
- **Organizational design** that de-emphasizes the current "function-first" model in most large pharmaceutical organizations, enables shared capabilities, and collaborative work
- **Integrated trial design operating model** (governance, process, roles, etc.) that is fit-for-purpose to in-silico trials but also appropriately integrated with traditional trials
- **Trust framework** for validation, verification, uncertainty, traceability, data integrity, bias mitigation, and risk assessment to ensure trust among internal and external stakeholders
- **In-Silico Leadership** vision from senior drug development leadership, with functional leaders pulling through changes in culture/mindset, operating model, and org design

What is the road ahead?

Because in-silico trials represent a substantial departure from the existing paradigm, pharma companies need strong leadership commitment and a unified in-silico vision. A clear in-silico strategy should create focus and define the most important outcomes to pursue. For example, a focused in-silico strategy might be to elevate PTRS in an Alzheimer's disease portfolio by improving Phase 2 success rates. Even with a focused strategy, the investment and change required is still significant and full of risks. Organizations should look at alternative models of innovation adoption, such as a 'skunk works venture' that sits outside the 'performance engine' of the company with an incentive to do things differently and learn through failure. Regardless of the model used, it's important to recognize that the organizational changes to people and operating model will be substantial during the in-silico revolution, but we believe this change is necessary, considering the substantial promise that in-silico trials may bring.

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