De-risking Pipeline Economics and Market Access with Computational Modelling

To combat escalating R&D costs, high clinical attrition and stringent global pricing pressures, the biopharmaceutical industry is on a quest to find the best uses for AI and computational modelling. Increasingly, Bayesian digital twins and in silico trials are used to expedite and de-risk drug development. By combining multi-omic and real-world data, these computational models generate next-gen Digital Controls capable of managing biological uncertainty, reducing reliance on human subjects and streamlining trial design, particularly for rare diseases. This paradigm shift not only compresses development timelines to safeguard pipeline economics against policies like the US MFN but also delivers the robust, patient-level evidence necessary to satisfy modern regulatory and HTA mandates, including the FDA Modernization Act 2.0 and the EU Joint Clinical Assessment.

R&D Productivity Crisis

The biopharmaceutical industry is intimately familiar with "Eroom's Law", the opposite of Moore's Law, where drug discovery is becoming exponentially slower and more expensive over time, despite remarkable, concurrent improvements in technology and an increase in the volume of research data. The financial reality of bringing a novel therapeutic to market is staggering; costs frequently exceed $2.5 billion, and the development timeline routinely stretches over a decade. This crisis is most acutely felt in complex disease areas like oncology, where the clinical trial failure rate for novel therapeutics routinely hovers above 95%.

With the rise of AI, the drug discovery process has been transformed, with faster timelines and drugs for previously undruggable targets now possible. Increased efficiency of this process, however, hasn't yet translated into novel targets, with most "AI-generated" drugs developed for existing and previously reported targets. Furthermore, while the progress in drug discovery is commendable and promising, it is relatively cheap to fail in the discovery stages. It is very expensive to fail in late-phase clinical trials. Given the industry's current attrition rates, translating promising in vitro results into patient benefit remains a challenge, which this new wave of drugs is now facing.

For decades, the standard drug development paradigm has relied heavily on traditional in vitro assays and in vivo animal models to predict human responses. Utilising these models possesses inherent translational limitations, as they frequently fail to capture the immense, multi-scale complexity and heterogeneity of human biology. But, as with every model, it is not the real thing. It captures some elements, but not others. Combining the knowledge across those models together with patient clinical responses and outcomes, however, could break this cycle of late-stage attrition and unsustainable costs.

Closing the Translational Gap with Computational Biology

To bridge the translational gap, often referred to as the "Valley of Death", the industry is increasingly turning to New Approach Methodologies (NAMs) and computational biology. NAMs represent modern laboratory techniques, such as cell-based assays, organ-on-a-chip platforms and computer-based pharmacological models. They are designed to mimic human tissues and organs directly. The regulatory momentum behind this shift is accelerating. In April 2025, the U.S. Food and Drug Administration (FDA) announced immediate plans to phase out animal testing requirements for monoclonal antibodies and other drugs, signalling a definitive transition toward human-centred evidence generation. This announcement builds upon the FDA Modernization Act 2.0 of 2022, which legally authorised drug sponsors to use non-clinical tests to investigate drug safety and effectiveness prior to human trials.

Among the most promising NAMs are *in silico* (computer-based) models. By integrating datasets generated by simpler NAMs with human clinical data, computational models can evaluate biological processes with direct human relevance, offering high-throughput screening that predicts drug behaviour, therapeutic effects and toxicities much faster and safer than animal testing. Several technologies like these are now commercially available for research use only.

While individual NAMs and basic computational models excel at predicting drug effects on isolated biological systems, they inherently fragment human biology. They struggle to model the complex, integrated coordination of molecular signalling pathways across interconnected tissues. Many continue to rely on population-level information rather than focusing on individual patients who drive heterogeneity of clinical response and outcome. The ultimate evolution to bridge this gap would be the ability to model an individual patient's biology via their "digital twin".

Digital twinning is a concept that has been used for decades in engineering and other complex industries to run multiple simulations and scenarios before committing to real-world implementation. A human digital twin is a dynamic, data-driven computational representation of an individual, but unlike engineering, some of the modelling components are invisible and uncertain. Crucially, they move beyond static precision medicine like baseline biomarker measurements (e.g., HER2 or BRCA mutations) to incorporate dynamic, high-dimensional multi-modal data. By integrating genomics, transcriptomics, proteomics and Real-World Data (RWD) such as electronic health records and patient registries, digital twins allow researchers to simulate dynamic, systems-level cancer adaptations under the selective pressure of multi-agent therapies.

The Bayesian Advantage

Integrating massive volumes of multi-omic data presents a profound dimensionality problem. Human biology is

Feature	Cell models (2D/3D)	Animal models (incl. PDX)	*In silico* models (incl. digital twins)
Key strengths	Provides direct human relevance using human cells; allows for mechanistic evaluation of specific biological systems	Provides integrated physiology; capable of evaluating systemic effects and interactions across interconnected tissues simultaneously	Dynamically synthesises fragmented multi-omic data to predict systemic human response
Throughput	High	Low	Extremely High
Heterogeneity	Moderate Reflects human tissue, but lacks system-wide diversity	Limited Often doesn't reflect human genetic diversity	High Simulates vast human genetic diversity and creates heterogeneous virtual populations
Adaptability	Static New variables require new cultures	Static New variables require new animals	Dynamic Parameters can be updated in real-time
Ethical burden	Low Reduces the reliance on animals for early-stage screening	High Entails extensive reliance on animals for every variable	Low Drastically reduces the need for both animals and human trial participants for placebo/ standard treatment arms
Limitations	Susceptible to phenotypic drift, culture conditions, passage, and biological fragmentation	Prone to severe translational failures due to interspecies differences	Accuracy is entirely dependent on the quality of the underlying data, requires validation

Table: Models used to bridge the translation gap in drug development

notoriously stochastic, and biological data is frequently sparse, noisy, highly variable and subject to batch effects. Standard deep learning algorithms often struggle in this environment, unable to scale to more than a few dozen features and prone to overfitting, with a lack of scientific transparency demanded by medical regulators.

Bayesian probabilistic frameworks are explicitly designed to navigate uncertainty. Rather than providing a rigid, unexplainable, binary decision, a Bayesian model calculates the probability of a clinical outcome based on biological first principles and continuously updates its internal beliefs as new real-world clinical evidence is introduced. This continuous updating provides researchers and regulators with scientifically rigorous, biologically interpretable confidence intervals. In complex conditions like oncology, having a model that manages uncertainty with mathematical soundness is a critical advantage, generating the clinical trust necessary for regulatory and commercial success.

REAL-WORLD APPLICATION:

In Silico Trials and n-of-1 Simulations

Examples of Model-Informed Drug Development (MIDD) for clinical stage de-risking are growing, and one of the practical applications of digital twins is computationally simulating how an investigational drug will perform across patient populations through *in silico* trials. These trials are deployed in two primary mutually inclusive formats to tangibly accelerate clinical research: by simulating hundreds of trial designs and inclusion/ exclusion criteria, and/or augmenting a specific trial with digital (sometimes referred to as 'synthetic') controls aggregated into a digital comparator arm.

Fully *In Silico* Trials using Virtual Patients Only

Fully *in silico* trials rely exclusively on patient simulations without concurrent human subjects. These virtual cohorts allow drug developers to evaluate multiple dosing regimens, eligibility criteria, drug combinations and outcome measures in hours to days, identifying optimal therapeutic windows before a single human is exposed. Select Clinical Research Organisations (CROs) provide these services, but increasingly, there are specialised companies dedicated to modelling *in silico* clinical trials using RWD alone, or in combination with AI to expand digital patient populations.

Furthermore, fully *in silico* trials possess unique ethical utility; they permit researchers to test scenarios that are practically or ethically impossible to conduct in the real world. For example, modelling foetal drug exposure during pregnancy, evaluating therapies in neonates where controlled trials pose unacceptable risks, or testing extreme dosing limits.

Modelling response to standard-of-care therapy is more robust than predicting how a novel drug will behave, so of course, this approach has limitations. As with any model, it is most applicable to reducing the vast uncertainty of clinical response based on historical data and predictive analytics, not an exact forecaster of future events.

Hybrid *In Silico* Trials and Digital (Synthetic) Controls

Hybrid trials supplement physical human clinical trials with historical patients or digital twins of real participants, ranging from specific individuals to entire subpopulations. Their most critical application is the generation of Digital Control Arms, which are frequently highlighted for their ability to make rare

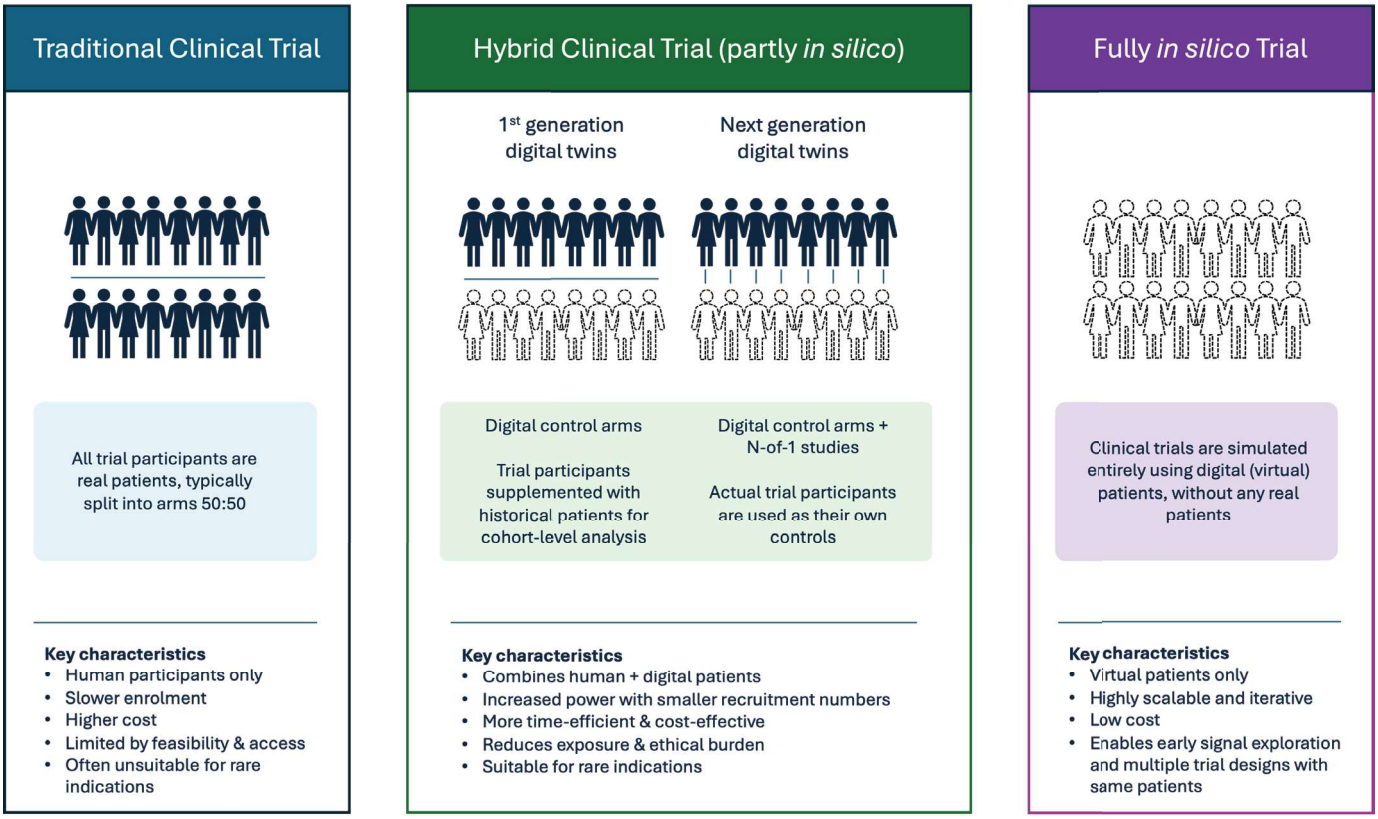

Figure 1: Clinical trials augmentation with in silico modelling and digital twins

disease and orphan drug studies viable. However, their utility extends significantly beyond ultra-rare conditions. Digital controls provide critical comparator information across broader clinical applications by supplementing or partially replacing traditional control arms. In many complex fields like oncology, assigning terminal patients to a placebo or standard-of-care arm is increasingly viewed as ethically fraught.

How does it work? First-generation digital twins enabled researchers to match historical patients to the active treatment cohort based on clinical baseline variables to simulate the control group's outcomes. In other words, they asked the question "how did patients with these characteristics respond to standard therapy in the past?" This provides developers with a robust computational baseline to rapidly evaluate drug efficacy without the time and expense of recruiting a full physical control cohort. Regulatory agencies are already accepting such evidence in drug submissions. The FDA has granted drug approvals based on real-world evidence and external control arms for not only rare conditions, but also more common indications such as non-small-cell lung cancer.

The main limitation of the first generation of digital twins is reliance on historical data and its availability. It also gave a very specific and static snapshot of patients' disease state. In contrast, Bayesian digital twins unlock the most advanced iteration of the control arm, the highly personalised "n-of-1" trial design. In an n-of-1 approach, a patient's own virtual counterpart serves as their direct control comparator. Rather than relying on empirical population averages to gauge efficacy, researchers can use Bayesian-powered platforms to generate detailed, patient-level simulated evidence. This allows clinical researchers to precisely model how a specific individual's unique molecular pathology would evolve under the standard-of-care versus any investigational precision therapy.

The potential of this approach has already been recognised and encouraged by the FDA and EMA, with draft guidance issued by both regulators. But the impact extends beyond just scientific evidence. Integration of Bayesian digital twins into the clinical development process represents a profound commercial imperative for biopharmaceutical developers.

Commercial and Market Access Imperative of Digital Twins

The global pharmaceutical industry is facing unprecedented pricing pressures, heavily driven by Most Favoured Nation (MFN) policies and tightening margins in the United States. The ripple effects of these policies are fundamentally altering the viability of European market launches, exemplified by recent UK deals involving heavy net price adjustments in exchange for tariff relief.

To protect launch economics and ensure European market viability in this climate, R&D costs must be drastically reduced. Digital twins transition from scientific novelties to protective commercial tools by heavily compressing R&D timelines. Through *in silico* trials and virtual control arms, developers can identify risks before costly late-stage trials, streamline development and accelerate time to market. This allows the enormous capital savings to offset pricing pressures and be passed on to patients, ensuring equity of access.

Furthermore, digital twins are becoming essential for satisfying payers and Health Technology Assessment (HTA) bodies. The implementation of the EU-level Joint Clinical

Assessment (JCA) has significantly raised evidentiary standards for clinical proof and reimbursement across member states. Pharmaceutical companies must provide deeper justifications for therapeutic value. Bayesian-powered digital twins provide a highly efficient solution, generating robust, patient-level simulated evidence. By bridging the gap between clinical trial data and real-world efficacy at a fraction of the cost, these models generate the high-resolution, predictive evidence required by HTA bodies to confidently justify reimbursement decisions.

Concluding Remarks

Digital twins and *in silico* trials are not poised to completely replace human clinical trials in the near term. Rather, their strategic purpose is to aggressively de-risk them. By leveraging uncertainty-aware Bayesian algorithms, the biopharmaceutical industry can ensure that only the safest, most effective therapeutics advance to human clinical trials. Realising the full potential of this technological paradigm shift will require robust cross-disciplinary collaboration among biopharma companies, data scientists and global regulatory agencies to standardise multi-omic data and break down fragmented silos. Ultimately, the true beneficiary of this transition is the patient, as the industry becomes equipped to deliver highly personalised, life-saving precision treatments faster, safer and at a fraction of the historical cost.

Dr. Irina Babina

Dr. Irina Babina is the CEO of Concr, a deeptech company that applies astrophysics computational models to solve translational challenges in cancer treatment and care. Trained as a geneticist, Irina spent over 12 years as a cancer scientist, developing targeted breast and gastric cancer therapies and researching mechanisms of cancer resistance at the Royal College of Surgeons and the Institute of Cancer Research in London. Seeing the lack of translation of promising science, she turned to funding management and investing, helping other researchers with the development of their healthcare innovations, deploying over £120m of public and VC funds into innovation. Irina continues to work with scientific founders to help improve the lives of patients with cancer.