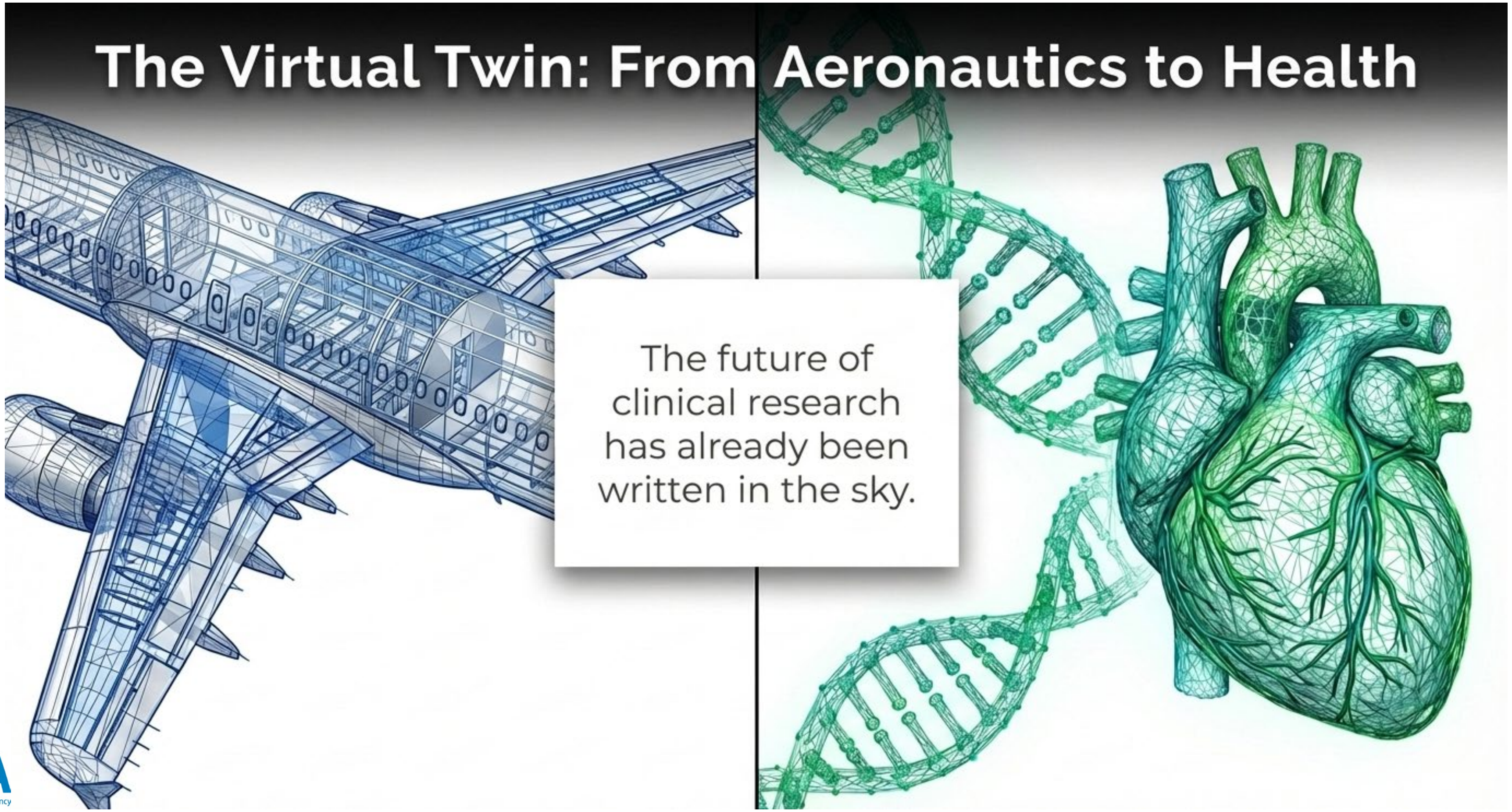
Emerging approaches to clinical research:

from emulated trial to *In Silico* method

www.biotrial.com/

What if we started by looking outside of the drug industry...

Inspiration from Aeronautics



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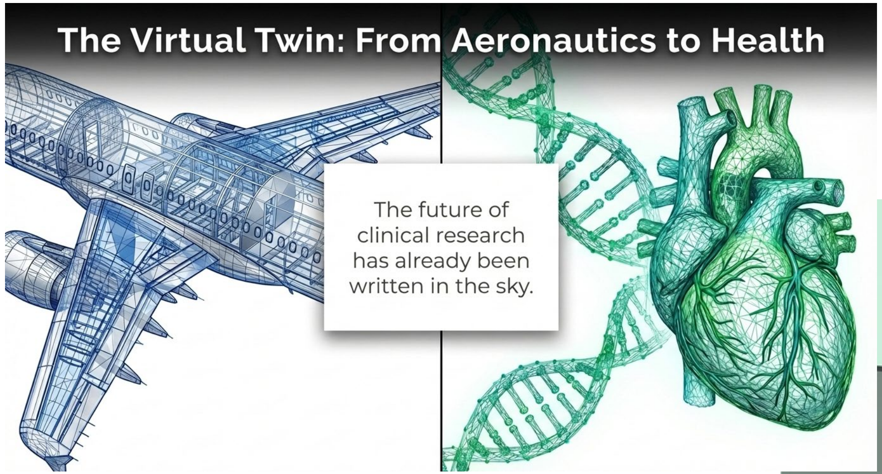

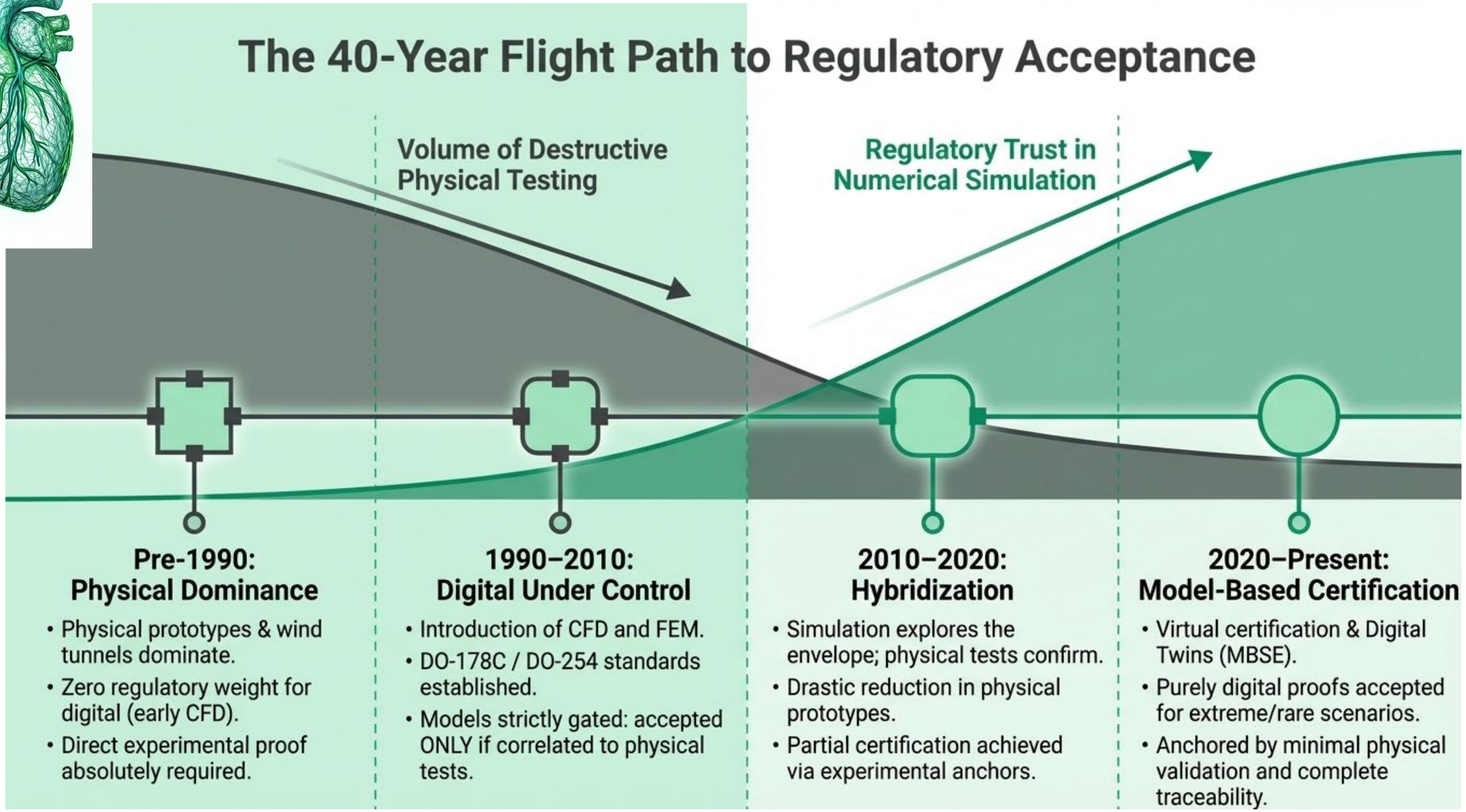

What if we started by looking outside of the drug industry...

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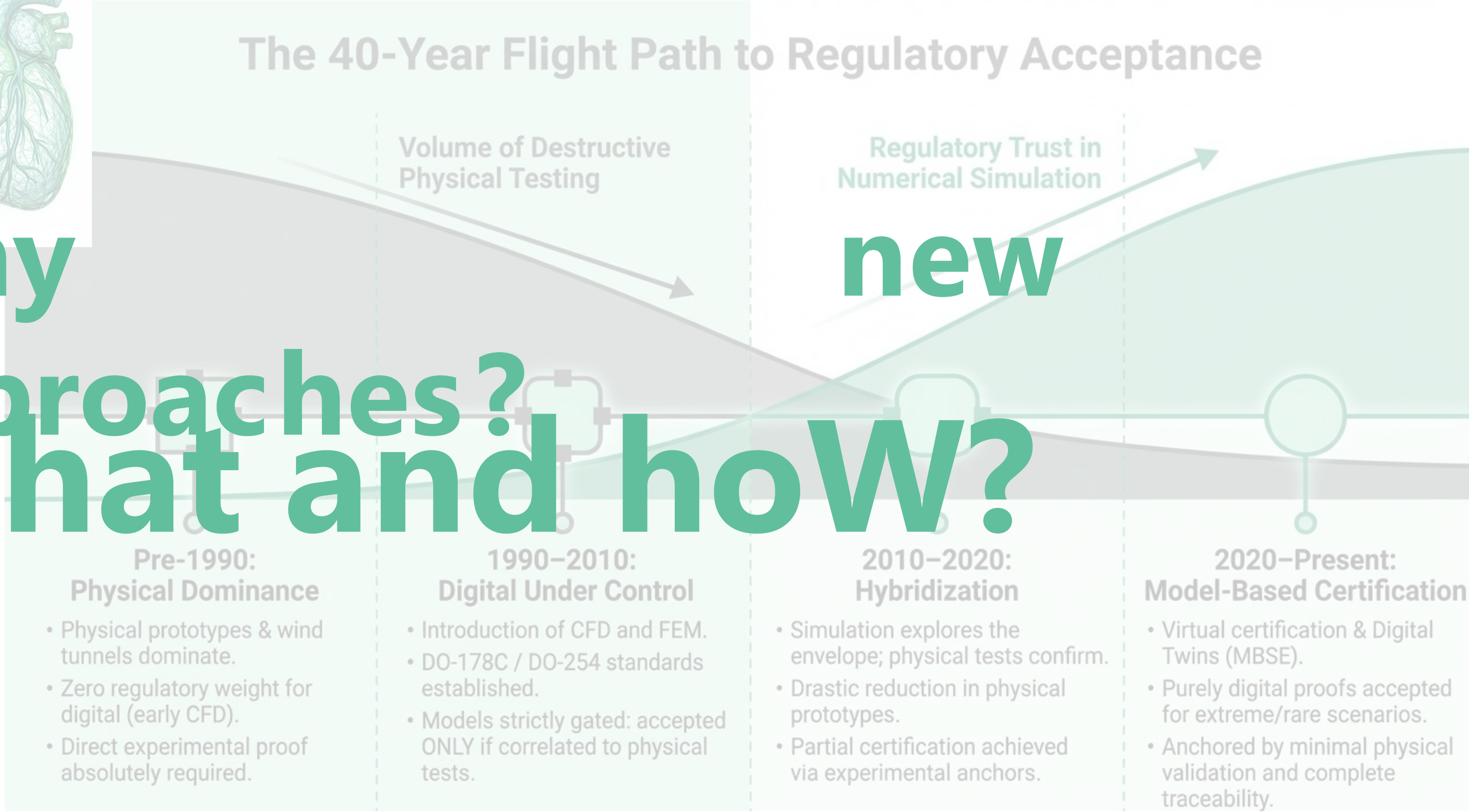


Why new approaches?

What and hoW?

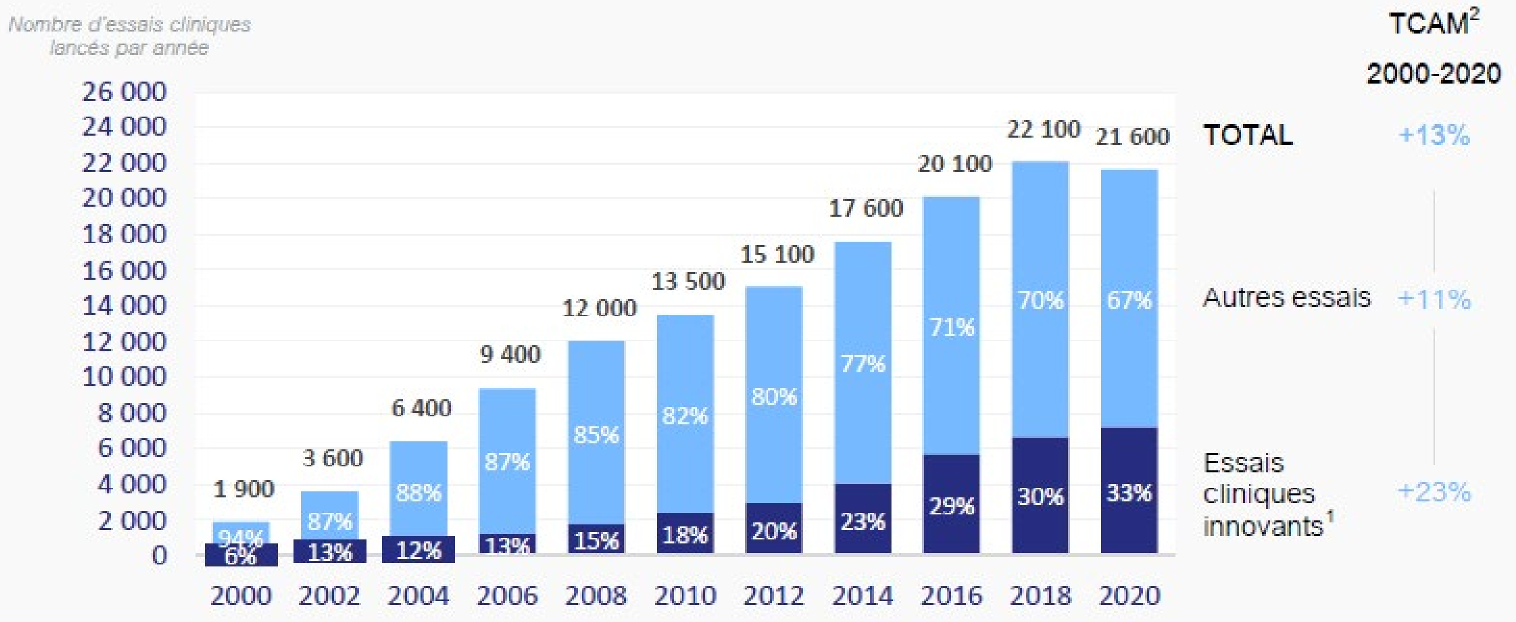
Current Challenges in Clinical Research

Moving beyond traditional approach

leem

« Essais cliniques 2030 »

Evolution des essais cliniques dits innovants[1] vs. autres essais, 2000-2020[(1)]



[1] Les essais cliniques dits innovants incluent l'un des types de technologies suivants :

> Technologies **d'analyse** (intelligence artificielle, blockchain, biomarqueur[3], etc.) – 55% des essais cliniques dits innovants[4]

> Technologies **connectées** (smartwatches, applications mobiles, etc.) – 39% des essais cliniques dits innovants[4]

> Technologie de **télémédecine** (téléconsultations, homecare, surveillance à distance, etc.) – 5% des essais cliniques dits innovants[4]

> Technologies de **pilotage** (formulaires électroniques de rapport de cas e-CRF, e-consentement, etc.) – 1% des essais cliniques dits innovants[4]

Innovation in clinical research

Six key innovation pillars identified by the LEEM

Decentralized & Digital Clinical Trials

Remote patient participation, digital tools, and hybrid trial models

Real-Word Data (RWD) Integration

Use of real-world evidence to complement clinical trial data

In Silico Methods

Computational modeling and simulation to support drug development

Biomarker-Driven Trials

Patient stratification and precision medicine approaches

Innovative Therapeutics

Advances therapies (e.g., gene therapy, cell therapy, RNA-based drug)

Drug-Device Combinaison Products

Integrated therapeutic solutions combining drugs and medical devices

Innovation in clinical research

Six key innovation pillars identified by the LEEM

Synthetic patient

Modeling and simulation

Artificial Intelligence

Evidence Synthesis

RWD

Synthetic arms

Virtual Trials

Digital Twin

In Silico Trial

Model Informed Drug Development

External Control Arm

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Drug-Device Combinaison Products

Integrated therapeutic solutions combining drugs and medical devices

Trend of AI risk prediction for clinical trials (cut-off date - 15.07.2024)

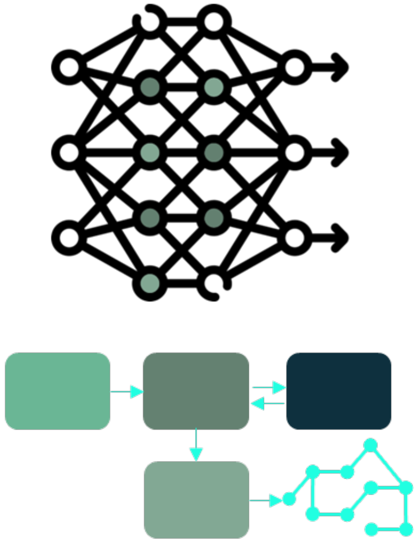
Let’s make it clear

Two ways to create a synthetic cohort: EMULATION & SIMULATION

Statistics *versus In silico*

Emulation of a cohort using **Advanced Statistics**

OR



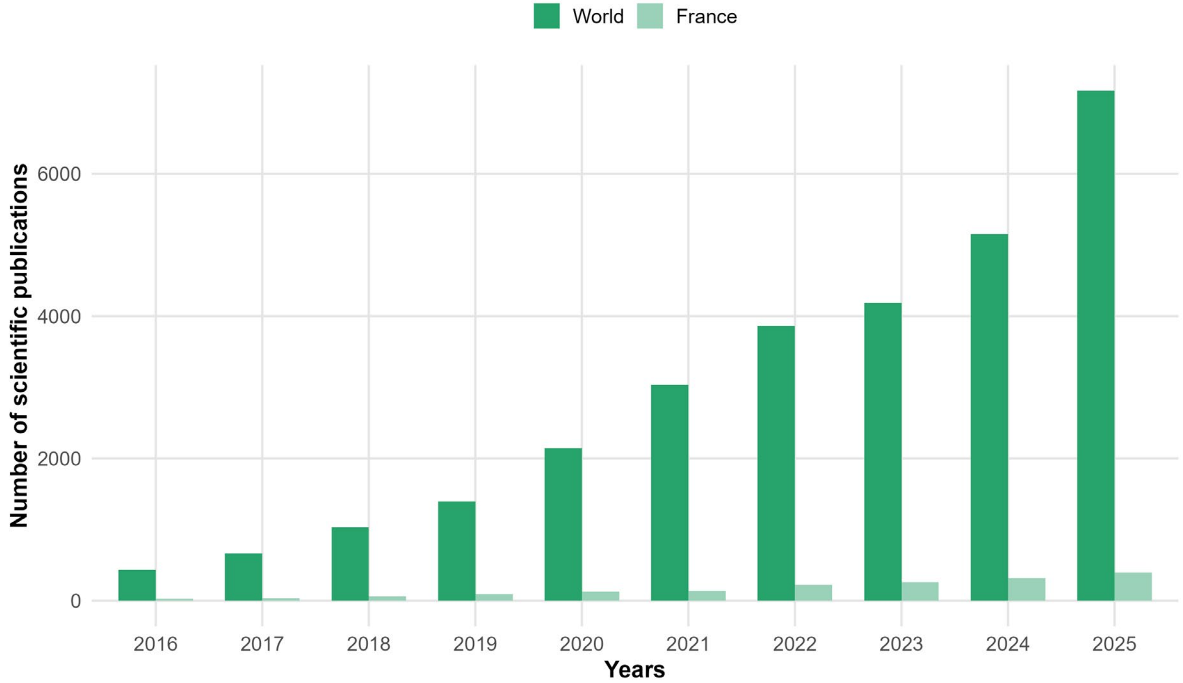
Simulation of a cohort using **Machine Learning** or **Mechanistic Modeling** (PKPD, QSP)

Synthetic cohort

Emulated trials

Emulated Trial & In-Silico Methods: Both Based on Secondary Data Source

Growing interest in Real-World Data (RWD)*



* Extracted from PubMed using "real world data“ or “real-world data“ or "real world evidence“ or "real-world evidence“ or “RWD” or “RWE”

Secondary data sources

RWD sources[1]

« Routinely collected data »

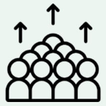
Electronic Health Records

Medical claims data

Product and Digital Health Technologies

Disease registries

Other sources



Cohort studies

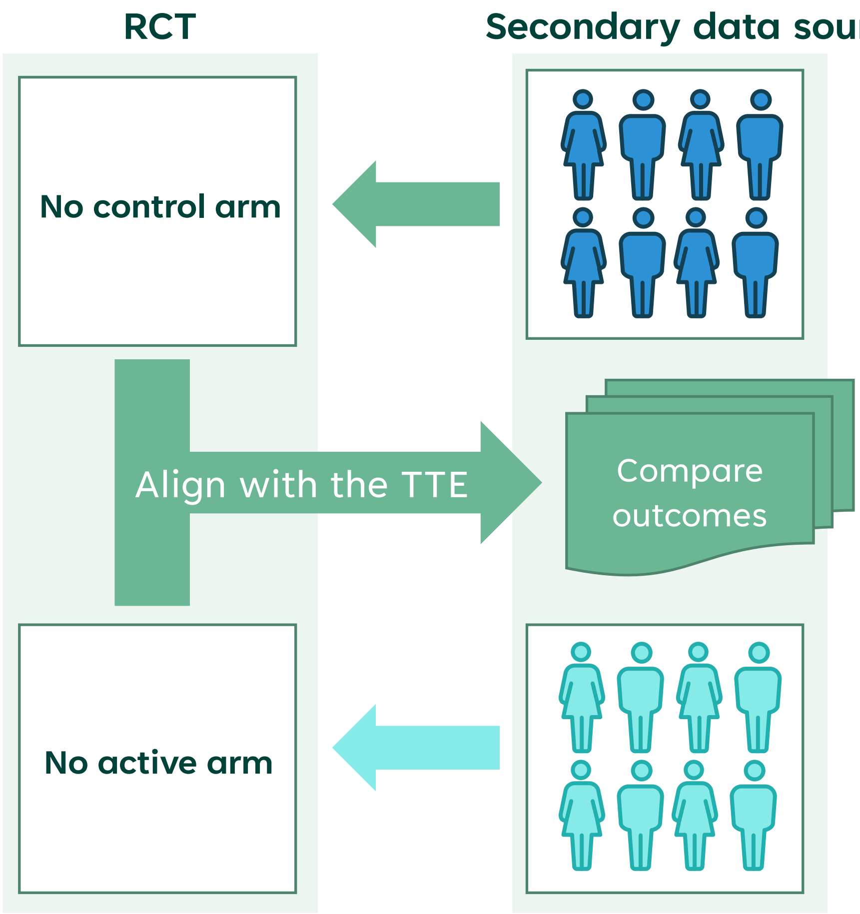
Previous clinical trials

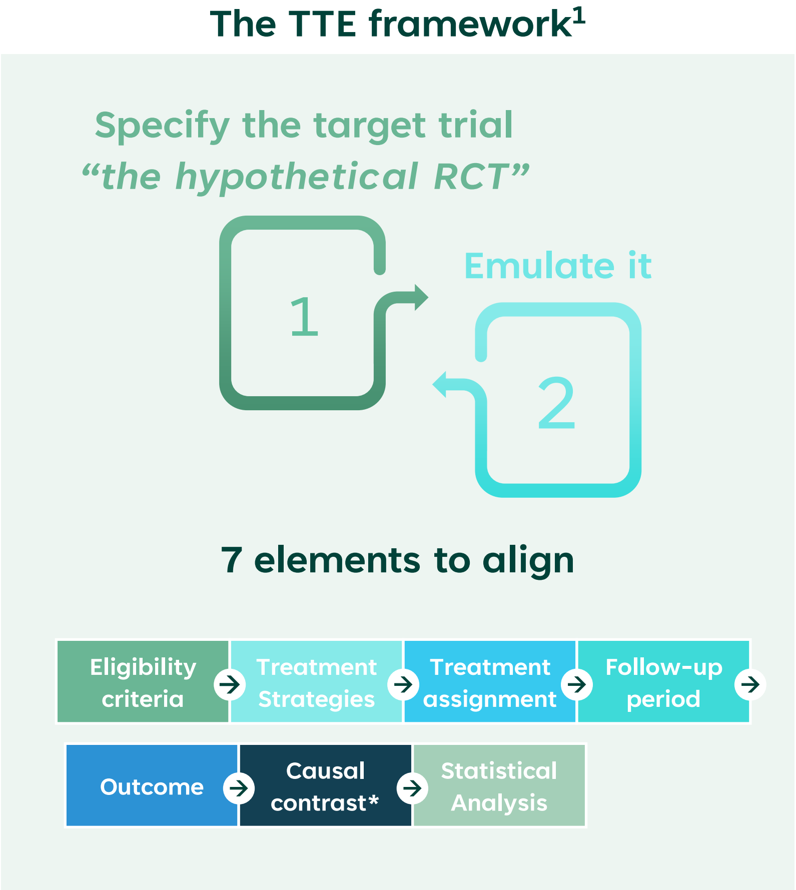
1. Framework for FDA’s Real-World Evidence Program

1. U.S. Food and Drug Administration. Framework for FDA’s Real-World Evidence Program [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2018 Dec [cited 2026 Apr 3]. Available from: https://www.fda.gov/

What is an Emulated Trial?

- Mimic a trial using secondary data to answer a **causal question**, ideally following the Target Trial Emulation (TTE) framework develop by Hernan et al.[1] that is strongly recommended in regulatory guidances[2,3]





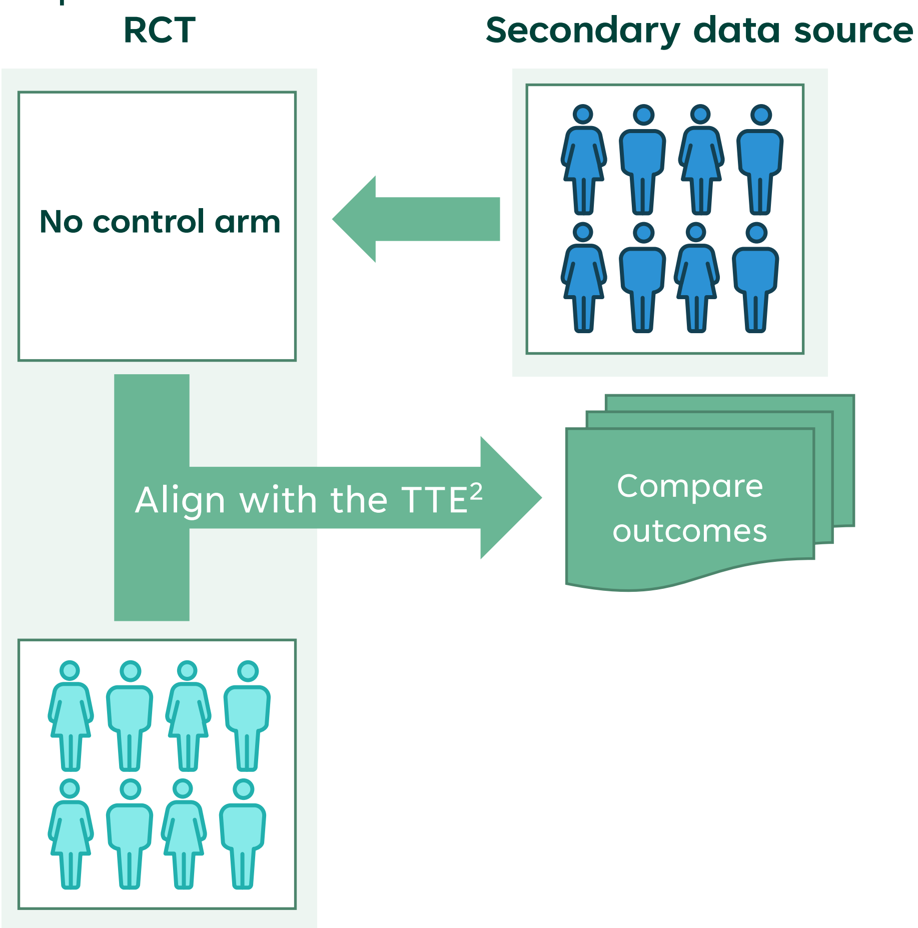
* *Following the ICH E9 (R1) addendum on estimands*

1. Hernán, Miguel A., and James M. Robins. "Using big data to emulate a target trial when a randomized trial is not available." American journal of epidemiology 183, no. 8 (2016): 758-764
2. Food, Drug Administration, et al. "Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products". In: (2024)
3. European Medicines Agency. "Reflection Paper on Use of Real-World Data in Non-Interventional Studies to Generate Real-World Evidence". In: (2024)

What is an External Control Trial?

Emulating half the Target Trial

- Defined as “one in which the control group consists of patients who are not of part of the randomized study as the group receiving the investigational agent i.e., there is no concurrently randomized control group”[1]



When to pivot an ECT?

- **Disease context**
  Rare disease and/or oncology (i.e., dramatic treatment effect & course of the disease highly predictable, unmet medical needs)
- **Randomization infeasible**
  Strong ethical justification
- **Estimand**
  Requires formal comparison, otherwise prioritize Single-Arm Trial
- **Prospectively planning**
  External comparator defined a priori (i.e., avoid converting a SAT to an ECT)
- **Fit-for-purpose data**
  High-quality external data source
- **Robust statistical analyses**
  Focus on alignment (TTE remains recommended)

1. ICH Harmonised Tripartite Guideline. “Choice of control group and related issues in clinical trials” E10
2. External controls and emulation of a target trial [Internet]. [cited 2026 Apr 3]. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-external-controls-emulation-half-target-trial-m-hernan_en.pdf

ECT: Primarily supportive today, with potential for pivotal role through robust studies

Scoping Review: Identification of eligible EMA applications

Identification

Oncology and rare disease drug submissions to the EMA from the 31st of October 2015 to 31st of October 2025 (n=501)

Records excluded before screening (n=101)

- Generic or hybrid (n=76)
- Biologics (n=25)

Screening

Records assessed for eligibility by automatic keywords search

(n=400)

Records excluded before manual full-text review due to absence of historical or external control-related keywords (n=281)

Records assessed for eligibility by manual full-text review (n=119)

Records excluded before final analysis (n=68)

- Not mentioned in the efficacy section (n=45)
- Limited information (n=9)
- Mentioned as recommendation by the EMA (n=5)
- Other reasons (n=9)

Included

Studies included in the final analysis (n=51):

- **Oncology (n=13)**
- **Rare Disease (n=22)**
- **Oncology and rare disease (n=16)**

Key Takeaways

- 501 applications reviewed
- 51 (10%) used external information to demonstrate efficacy
- Overall, 63 pivotal trials: 36 (57%) were SATs, 19 (30%) were RCTs, and 8 (13%) were ECTs

Medicine Name	Indication	Type of external arm	Comments
Zolgensma	Muscular Atrophy, Spinal	Retrospectively Collected Natural History	Pediatric Neuromuscular Clinical Research database
Amvuttra	Amyloid Neuropathies, Familial	Previous Clinical Study	APOLLO (NCT01960348)
Libmeldy	Leukodystrophy, Metachromatic	Retrospectively Collected Natural History	Telethon Institute for Gene Therapy Natural History Study
Zokinvy	Progeria;Laminopathies	Retrospectively Collected Natural History	Progeria Research Foundation International Registry
Nulibry	Metal Metabolism, Inborn Errors	Retrospectively Collected Natural History	Natural History of Molybdenum Cofactor and Isolated Sulfite Oxidase Deficiencies (NCT01735188)
Strensiq	Hypophosphatasia	Retrospectively Collected Natural History	Historical controls from the same centre under similar clinical management protocol
Qarziba	Neuroblastoma	Retrospectively Collected Natural History/Previous Clinical Study	Italian Neuroblastoma Registry/SIOPEN high risk neuroblastoma study (NCT01704716)

Example of pivotal study (HELIOS-A)

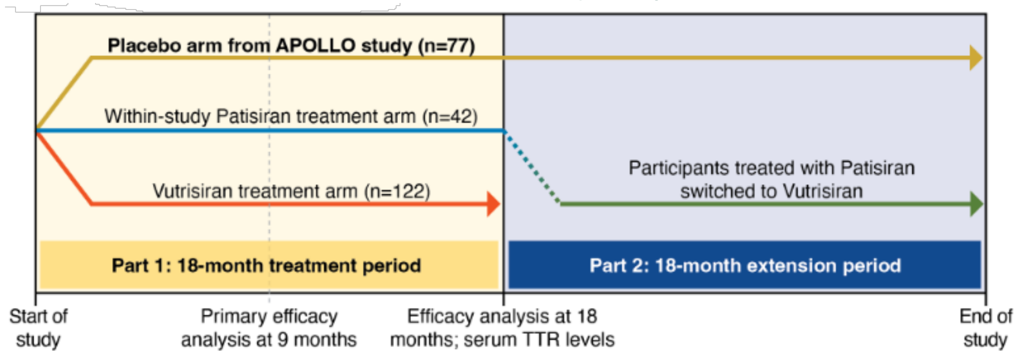
Amvuttra (vutrisiran)

- **Condition:** Rare genetic disease (~1 per 1M), affects nerves, heart, sometimes kidneys, eyes, tendons/ligaments

- **Trial design:** Phase 3, randomized, open-label

- **Study participants:**
  - 122 received vutrisiran
  - 42 received patisiran
  - 77 placebo participants from previous APOLLO study (external control arm)

The HELIOS-A study design



What points did the regulators highlight?

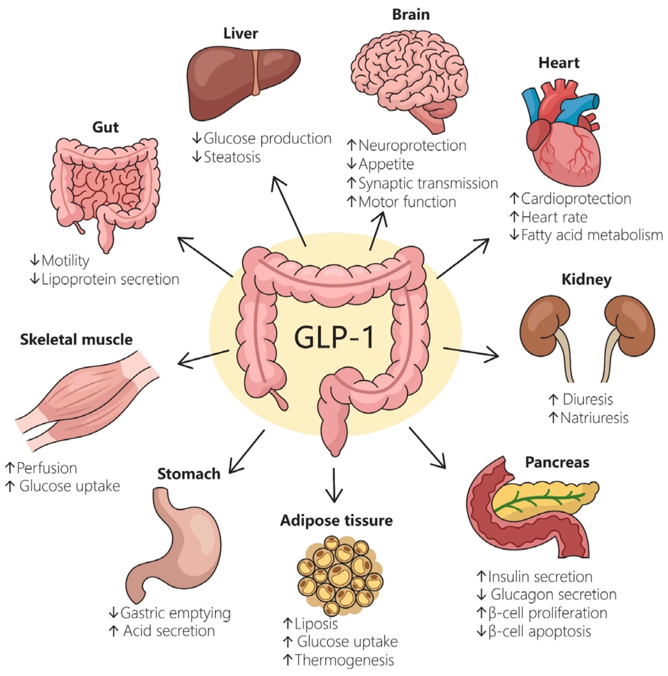
1. Early Engagement with regulators
2. Appropriate disease context
3. Prospective plan of the external control arm
4. Fit for purpose data
5. Good aligment to mitigate bais

Explore New Indication

Early Efficacy Assessment in Multi-Organ Targeted Therapies To De-risk Future Clinical Trial

- Example with Glucagon-like peptide-1 receptor agonists (GLP-1) indicated for Type 2 Diabetes and obesity

GLP-1 actions and target organs



Source: News-medical.net

Emulated Trial in Many Target Organs

Therapeutic Area	First Author	DOI
Alzheimer Disease	Tang H et.al., 2025	10.1001/jamaneurol.2025.0353
Pancreatic cancer	Wang L, 2025	10.1093/jnci/djae260
Type 1 Diabetes	Xu Y, 2026	10.1038/s41591-026-04274-0
Pulmonary Disease	Avik Ray, 2025	10.1001/jamainternmed.2024.7811.
Osteoarthritis	Jeon M,2026	10.1016/j.diabres.2026.113091

1. Extracted from PubMed using ("target trial emulation" OR "target trial emulated" OR "trial emulation") AND ("GLP-1" OR "GLP1" OR "glucagon-like peptide-1" OR "GLP-1 receptor agonist*")

Design Optimization

Which Patients Are Eligible?

Article | Published: 07 April 2021

Evaluating eligibility criteria of oncology trials using real-world data and AI

Ruishan Liu, Shemra Rizzo, Samuel Whipple, Navdeep Pal, Arturo Lopez Pineda, Michael Lu, Brandon Arnieri, Ying Lu, William Capra, Ryan Copping & James Zou

Nature 592, 629–633 (2021) | Cite this article

Stanford University

Roche Genentech A Member of the Roche Group

In oncology, using the Flatiron database:

- Apply eligibility criteria sequentially
- Define treatment groups
- Adjust for confounding with IPTW
- Estimate weighted Hazard Ratio

1. Liu R, Rizzo S, Whipple S, Pal N, Pineda AL, Lu M, et al. Evaluating eligibility criteria of oncology trials using real-world data and AI. Nature. 2021 Apr;592(7855):629–33

When Initiating Treatment?

ESSAY

Emulation of a target trial with sustained treatment strategies: an application to prostate cancer using both inverse probability weighting and the g-formula

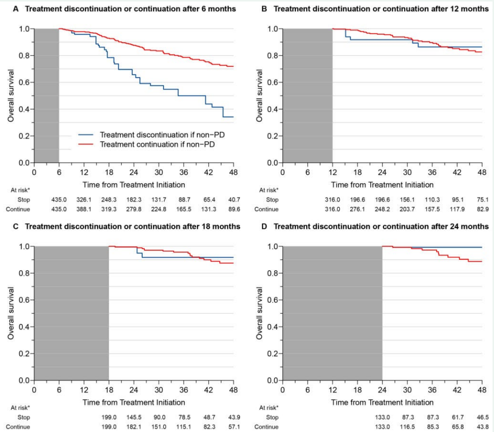
Louisa H. Smith[1,2] · Xabier García-Albéniz[1,3] · June M. Chan[4,5] · Shoujun Zhao[5] · Janet E. Cowan[5] · Jeanette M. Broering[5,6] · Matthew R. Cooperberg[4,5] · Peter R. Carroll[5] · Miguel A. Hernán[1,7,8]

Received: 29 March 2022 / Accepted: 3 October 2022

Abstract
As with many chronic illnesses, recurrent prostate cancer generally requires sustained treatment to prolong survival. However, initiating treatment immediately after recurrence may negatively impact quality of life without any survival gains. Therefore, we consider sustained strategies for initiating treatment based on specific characteristics of prostate-specific antigen (PSA), which can indicate disease progression. We define the protocol for a target trial comparing treatment strategies based on PSA doubling time, in which androgen deprivation therapy is initiated only after doubling time decreases below a certain threshold. Such a treatment strategy means the timing of treatment initiation (if ever) is not known at baseline, and the target trial protocol must explicitly specify the frequency of PSA monitoring until the threshold is met, as well as the duration of treatment. We describe these and other components of a target trial that need to be specified in order for such a trial to be emulated in observational data. We then use the parametric g-formula and inverse-probability weighted dynamic marginal structural models to emulate our target trial in a cohort of prostate cancer patients from clinics across the United States.

1. Smith LH, García-Albéniz X, Chan JM, Zhao S, Cowan JE, Broering JM, Cooperberg MR, Carroll PR, Hernán MA. Emulation of a target trial with sustained treatment strategies: an application to prostate cancer using both inverse probability weighting and the g-formula. European Journal of Epidemiology. 2022 Dec;37(12):1205-13

How Long Should Patients Be Followed?



In oncology, using the MelBase cohort, the optimal duration of anti-PD-1 therapy was unclear. Amiot et al. found that 1 year is sufficient, longer treatment shows no extra OS benefit.

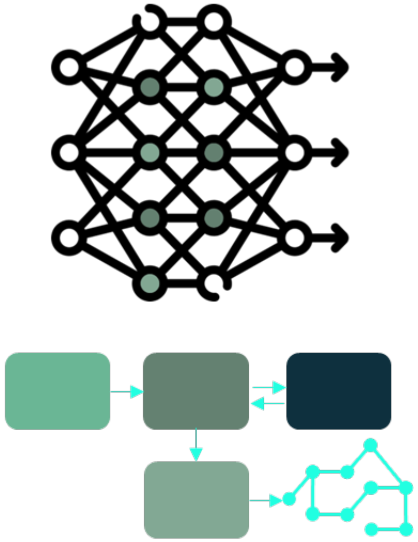
1. Amiot, Mathilde, Laurent Mortier, Stéphane Dalle, Olivier Dereure, Sophie Dalac, Caroline Dutriaux, Marie-Thérèse Leccia et al. "When to stop immunotherapy for advanced melanoma: the emulated target trials." EClinicalMedicine 78 (2024)

Two ways to create a synthetic cohort: EMULATION & SIMULATION

Statistics *versus In silico*

Emulation of a cohort using **Advanced Statistics**

OR



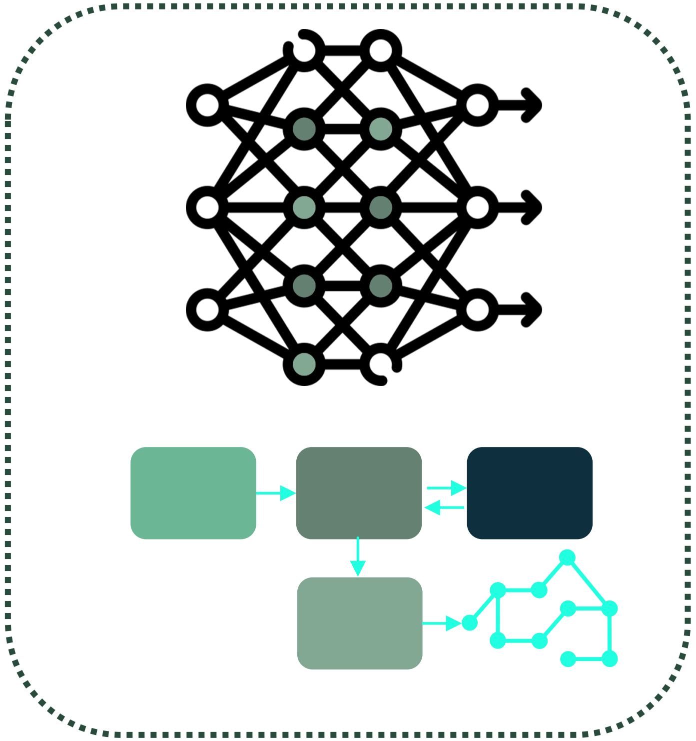
Simulation of a cohort using **Machine Learning** or **Mechanistic Modeling** (PKPD, QSP)

synthetic cohort

Simulated trials

Let’s create virtual patients using SIMULATION

Each patient is generated through computer (*in silico*) simulation



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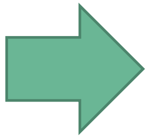

Synthetic cohort

Simulated trial
Definition

Essai clinique simulé, également appelé *in silico* : essai clinique effectué **à l'aide de simulations numériques** pour tester un médicament, un dispositif médical ou une intervention, dans des conditions bien définies, **à l'aide de modèles vérifiés et validés selon des protocoles bien définis**.

Le *In silico* désigne une expérimentation ou intervention par simulations numériques (dans l'ordinateur), par opposition à *in vivo* (chez l'organisme vivant, animal ou humain) ou *in vitro* (en laboratoire). L'expression s'applique aussi bien à l'échelle d'une expérience ou intervention prête à confusion biologique simple qu'à celle d'un patient, d'une étude clinique complète ou d'une cohorte de patients


RÉPUBLIQUE FRANÇAISE

État d'avancement des évolutions méthodologiques en recherche clinique

De la recherche expérimentale au suivi d'évaluation en phase d'usage courant

GT AIS/F-CRIN « *L'évolution des méthodologies d'essais cliniques : nouveaux outils, nouveaux usages et conditions de recours* »

Annexes
Mai 2025

AGENCE DE L'INNOVATION EN SANTÉ

F-CRIN

https://www.fcrin.org/sites/default/files/brique/fichier/05-2025/Rapport%20AIS%20GT%20F-CRIN-AIS_Annexes_20250515_vf_1.pdf

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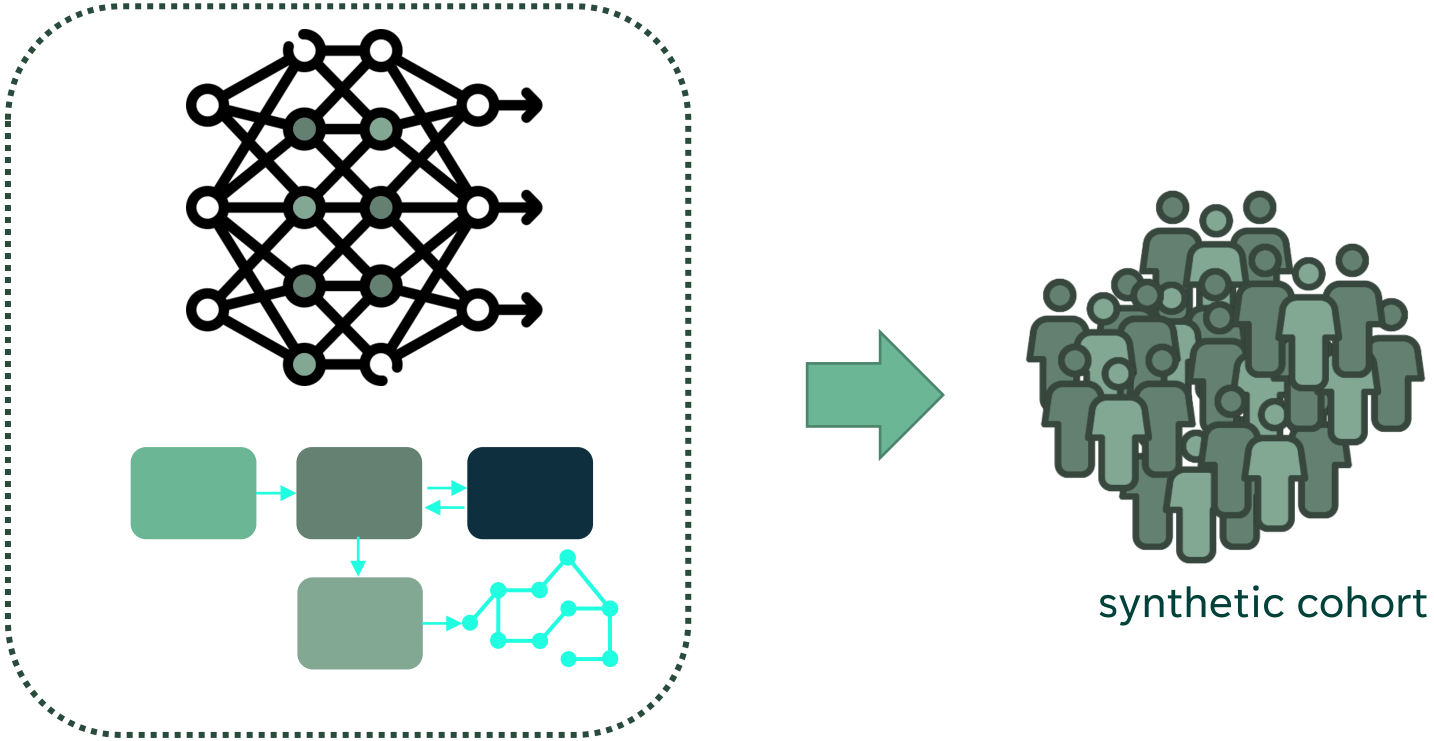

In Silico study

Let’s create virtual patients using SIMULATION

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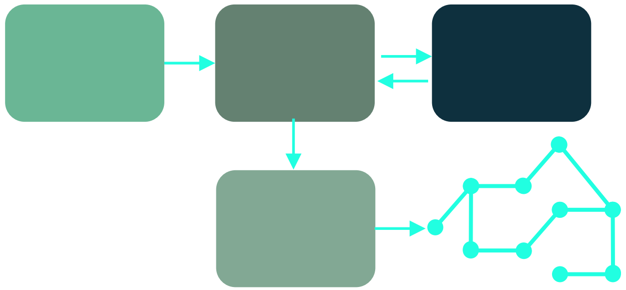
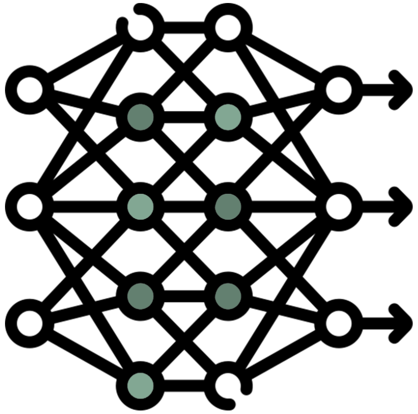
In Silico study

Mechanistic



Non Mechanistic



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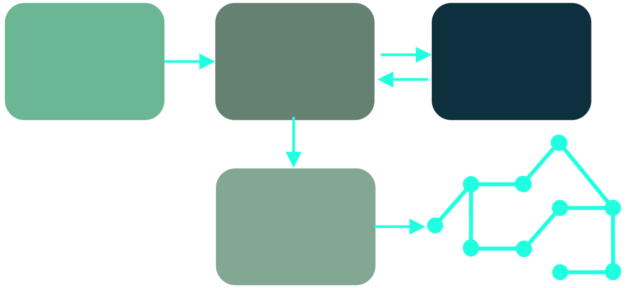
***In Silico* study**

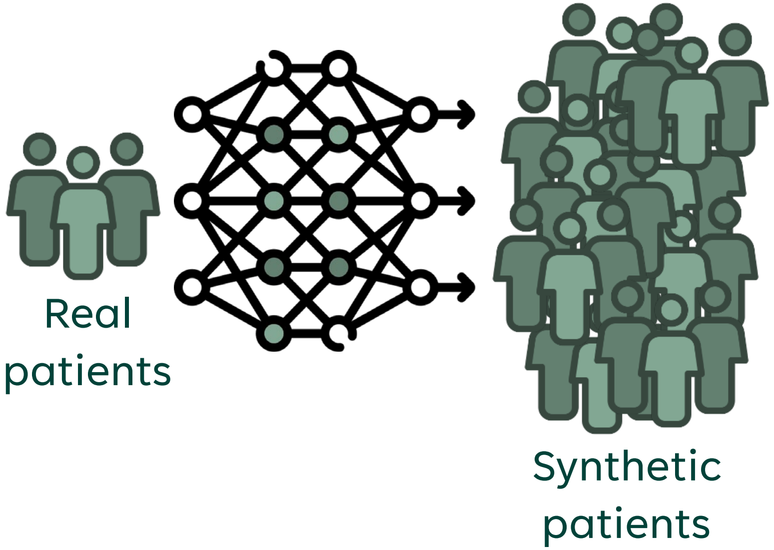
Mechanistic

Biological and pharmaceutical phenomena are described according to a comprehensible model. For instance a PK model, a PD model, a PKPD model.



Non Mechanistic

Biological and pharmaceutical phenomena are described according to a statistical / AI model reproducing patterns of real populations (EHR, images...)



Regulatory vision of simulated trial

FDA and EMA perspectives

U.S. FOOD & DRUG ADMINISTRATION

EMA EUROPEAN MEDICINES AGENCY

Guiding Principles of Good AI Practice in Drug Development
January 2026

Artificial Intelligence (AI) has the potential to transform the way drugs (medicines)[1] are developed and evaluated, ultimately improving health care. In this context, AI refers to system-level technologies used to generate or analyze evidence across the drug product life cycle, including nonclinical, clinical, post-marketing, and manufacturing phases.

Drugs are authorized based on demonstrated quality, efficacy and safety, and when their benefits outweigh their risks. As new technologies emerge, including AI, it is essential that their use reinforces these requirements for the benefit and safety of patients.

The use of AI throughout the drug product life cycle has increased significantly in recent years. The complex and dynamic processes involved in developing, deploying, using, and maintaining AI technologies benefit from careful management throughout the drug product life cycle to ensure outputs are accurate and reliable. Among other innovations, AI technologies are anticipated to support a multi-faceted approach that promotes innovation, reduces time-to-market, strengthens regulatory excellence and pharmacovigilance, and decreases reliance on animal testing by improving the prediction of toxicity and efficacy in humans. This document outlines a common set of principles to inform, enhance, and promote the use of AI for generating evidence across all phases of the drug product life cycle.

These 10 guiding principles are intended to lay the foundation for developing good practice that addresses the unique nature of these technologies. They will also help cultivate future growth in this rapidly progressing field.

The 10 guiding principles identify areas where the international regulators, international standards organizations, and other collaborative bodies could work to advance good practice in drug development. Areas of collaboration include research, creating educational tools and resources, international harmonization, and consensus standards, which may help inform regulatory policies and regulatory guidelines in different jurisdictions, in line with applicable legal and regulatory frameworks.

As the use of AI in drug development evolves, so too must good practice and consensus standards. Strong partnerships with international public health partners will be crucial to empower stakeholders to advance responsible innovations in this area. Thus, this initial collaborative work can inform our broader international engagements.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 September 2024
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023
Final version agreed by MWP	6 September 2024
Final version adopted by CHMP	9 September 2024
Final version adopted by CVMP	11 September 2024

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 February 2026
EMA/CHMP/ICH/496426/2024
Committee for Human Medicinal Products

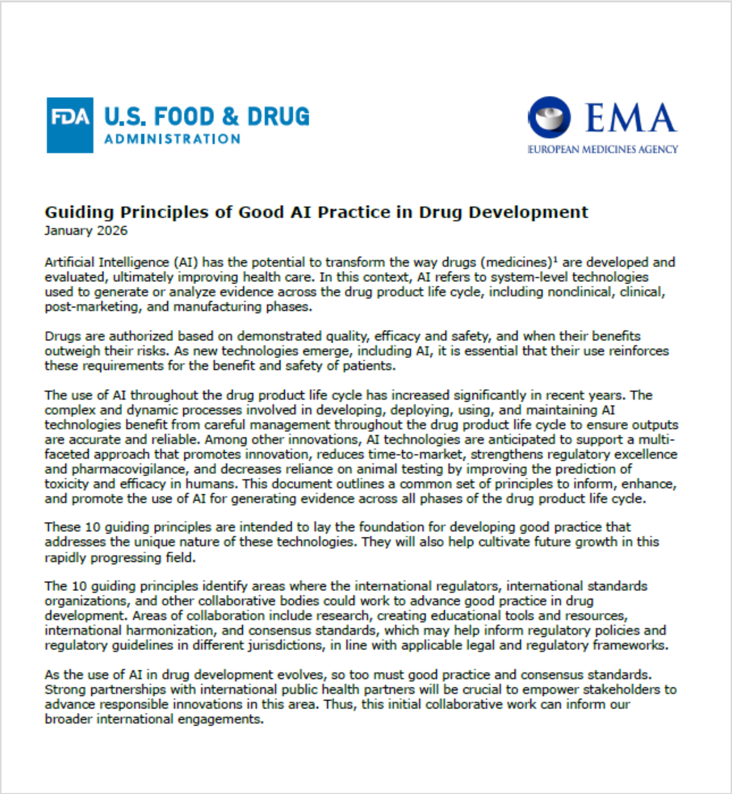
ICH M15 Guideline on general principles for model-informed drug development

Step 5

Transmission to CHMP	24 October 2024
Adoption by CHMP	14 November 2024
Release for public consultation	29 November 2024
Deadline for comments	28 February 2025
Final adoption by CHMP	23 January 2026
Date for coming into effect	23 July 2026

Regulatory vision of simulated trial

FDA and EMA perspectives



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As the use of AI in drug development evolves, so too must good practice and consensus standards. Strong partnerships with international public health partners will be crucial to empower stakeholders to advance responsible innovations in this area. Thus, this initial collaborative work can inform our broader international engagements.

1. Human-centric by design
The development and use of AI technologies align with ethical and human-centric values.

2. Risk-based approach
The development and use of AI technologies follow a risk-based approach with proportionate validation, risk mitigation, and oversight based on the context of use and determined model risk.

3. Adherence to standards
AI technologies adhere to relevant legal, ethical, technical, scientific, cybersecurity, and regulatory standards, including Good Practices (GxP).

4. Clear context of use
AI technologies have a well-defined context of use (role and scope for why it is being used).

5. Multidisciplinary expertise
Multidisciplinary expertise covering both the AI technology and its context of use are integrated throughout the technology's life cycle.

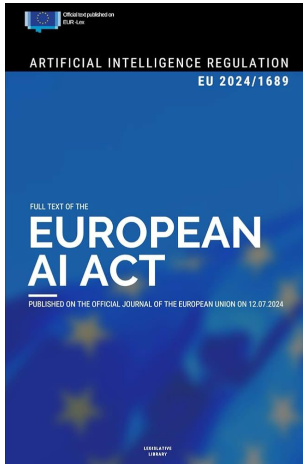
6. Data governance and documentation
Data source provenance, processing steps, and analytical decisions are documented in a detailed, traceable, and verifiable manner, in line with GxP requirements. Appropriate governance, including privacy and protection for sensitive data, is maintained throughout the technology's life cycle.

7. Model design and development practices
The development of AI technologies follows best practices in model and system design and software engineering and leverages data that is fit-for-use, considering interpretability, explainability, and predictive performance. Good model and system development promotes transparency, reliability, generalizability, and robustness for AI technologies contributing to patient safety.

8. Risk-based performance assessment
Risk-based performance assessments evaluate the complete system including human-AI interactions, using fit-for-use data and metrics appropriate for the intended context of use, supported by validation of predictive performance through appropriately designed testing and evaluation methods.

9. Life cycle management
Risk-based quality management systems are implemented throughout the AI technologies' life cycles, including to support capturing, assessing, and addressing issues. The AI technologies undergo scheduled monitoring and periodic re-evaluation to ensure adequate performance (e.g., to address data drift).

10. Clear, essential information
Plain language is used to present clear, accessible, and contextually relevant information to the intended audience, including users and patients, regarding the AI technology's context of use, performance, limitations, underlying data, updates, and interpretability or explainability.



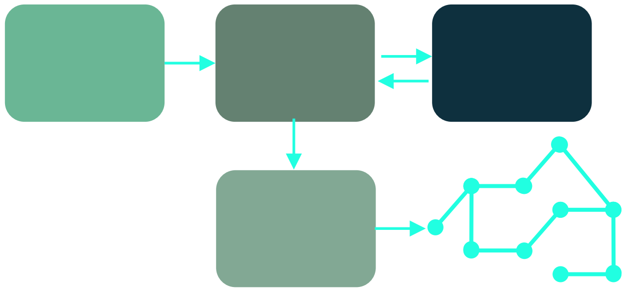
Let's create virtual patients using SIMULATION

Each patient is generated through computer (*in silico*) simulation

***In Silico* study**

Mechanistic

Biological and pharmaceutical phenomena are described according to a comprehensible model. For instance a PK model, a PD model, a PKPD model.



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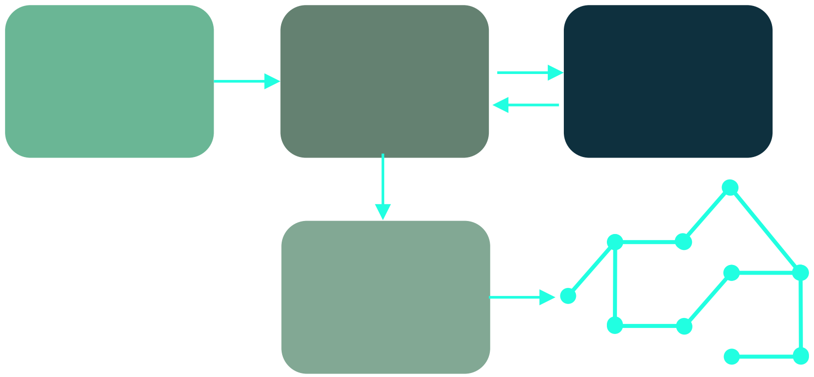
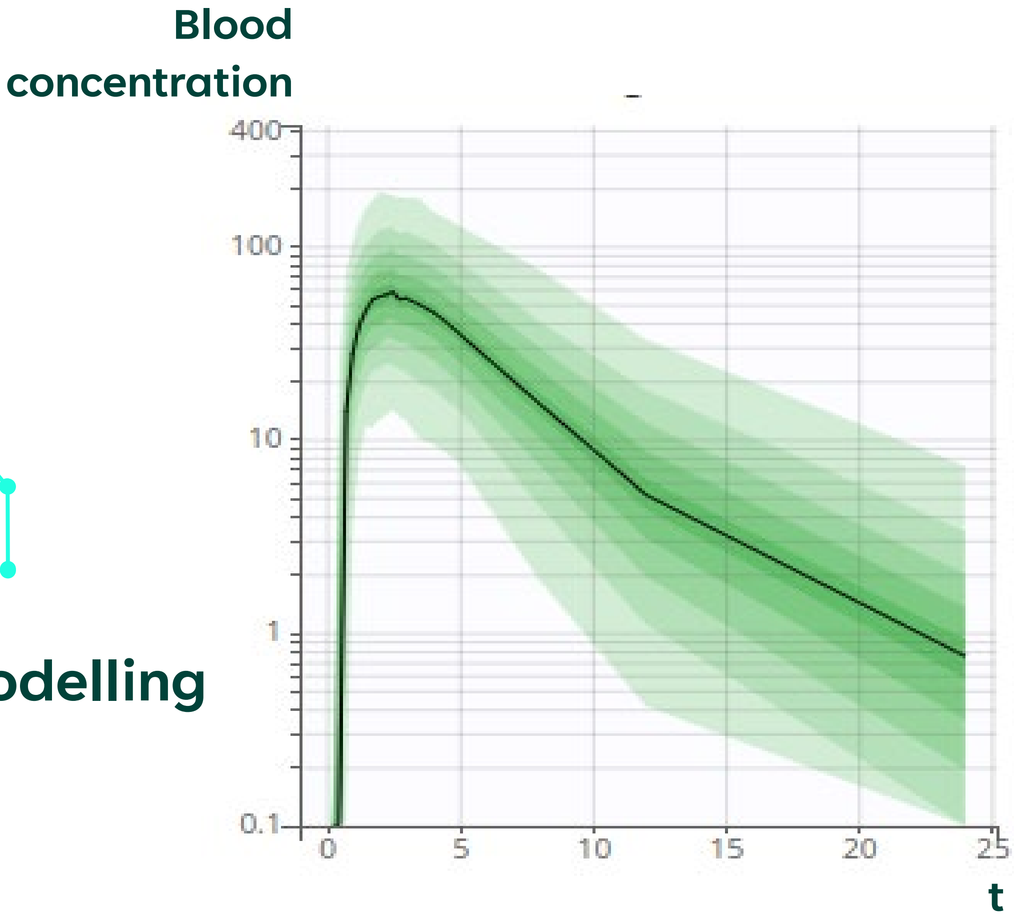
Biological and pharmaceutical phenomena are described according to a statistical / AI model reproducing patterns of real populations (EHR, images...)

Case study with simulated trial: mechanistic modeling

Mechanistic modeling 1 (Tofacitinib): meta-modeling in PKPD for a repositioning in Sjören Syndrome





Pop PK: Nonlinear Mixed Effects Modelling

Mechanistic + Patient variability

Case study with simulated trial: mechanistic modeling

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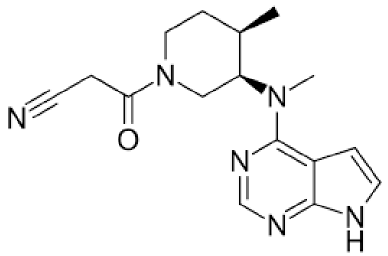
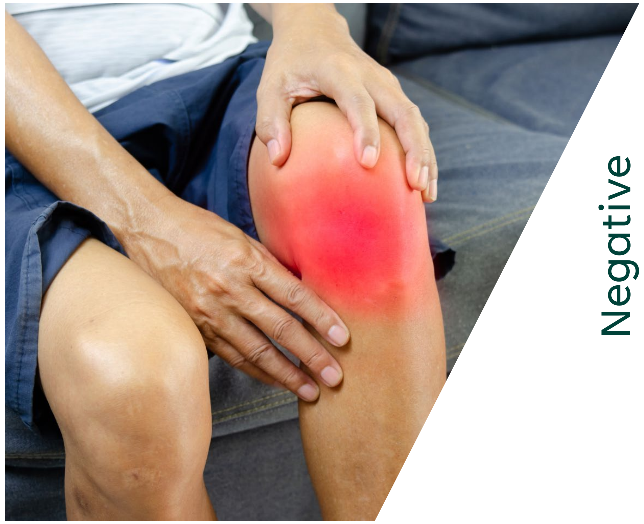


Pharmacokinetics

Blood concentration

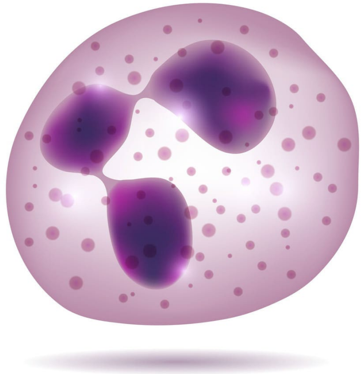
Pharmacokinetics/Pharmacodynamics

Positive Effect



Anti-inflammatory

Negative Effect

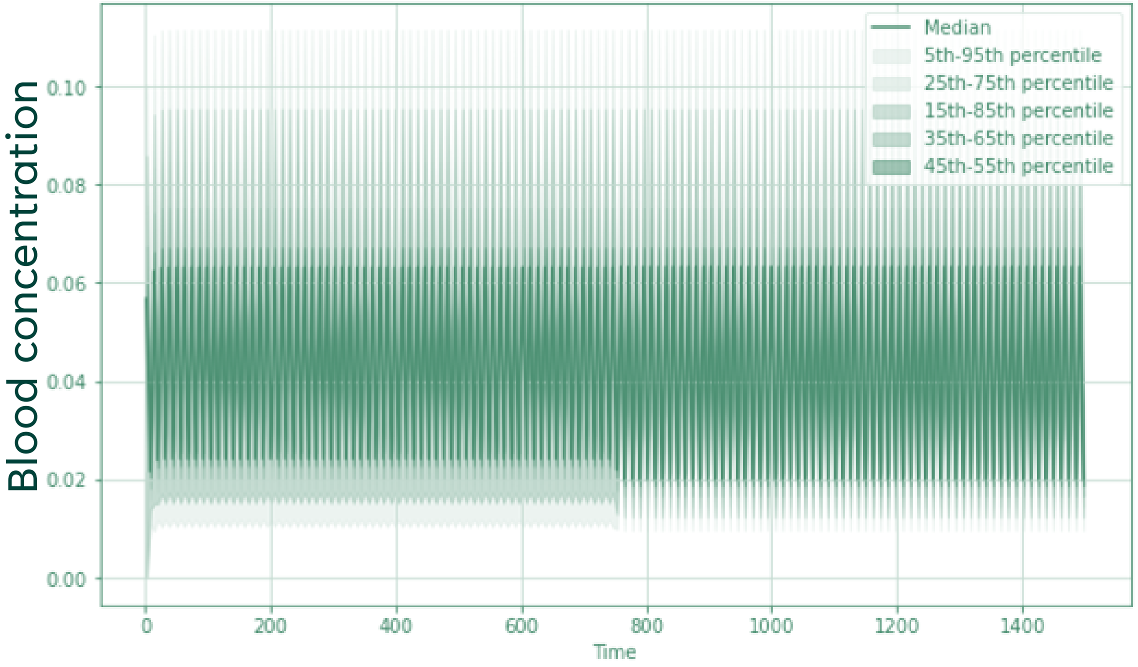


Neutropenia (tox)

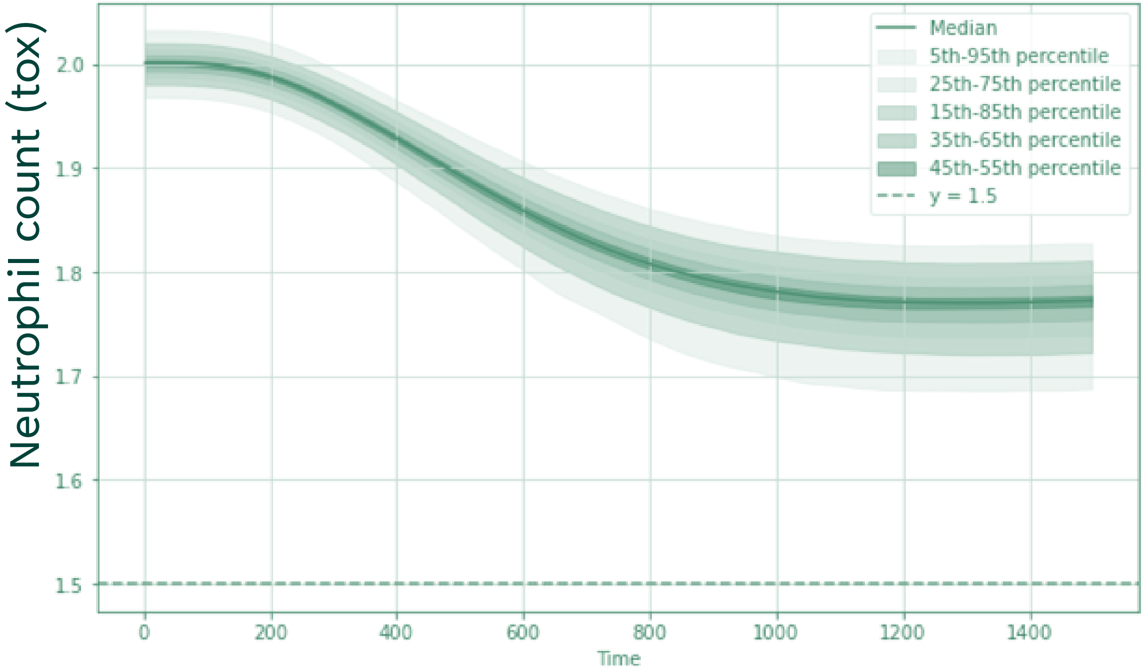
Case study with simulated trial: mechanistic modeling

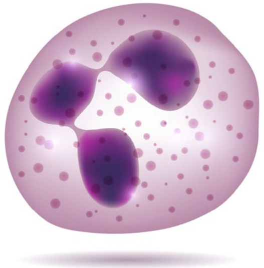
Mechanistic modeling 1 (Tofacitinib): meta-modeling in PKPD

Pharmacokinetics



Pharmacokinetics/Pharmacodynamics

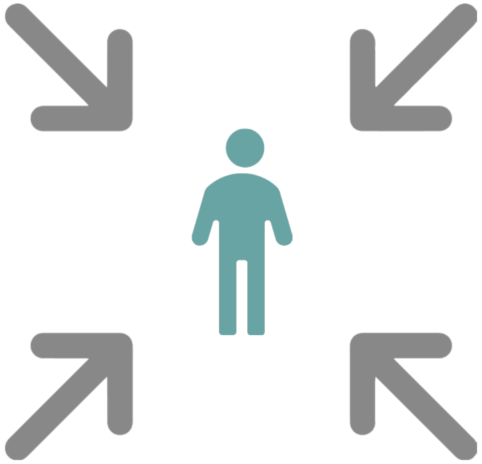




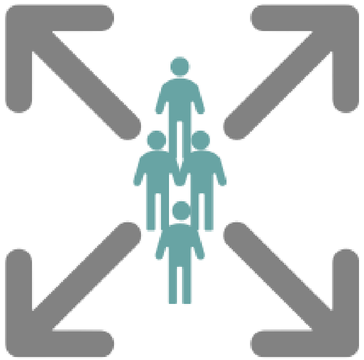
Case study with simulated trial: mechanistic modeling

Mechanistic modeling 1 (Tofacitinib): meta-modeling in PKPD for a repositioning in Sjören Syndrome

- A concrete **use case of Design Optimization** using a Mechanistic Approach**: Model based meta-analysis.**
  → A research area and legacy expertise of Biotrial Data Science



Reduce the targeted population
by excluding risky patients



Increase the targeted population
by including non-risky patients

Case study with simulated trial: mechanistic modeling

Mechanistic modeling 1 (Tofacitinib): meta-modeling in PKPD for a repositioning in Sjören Syndrome

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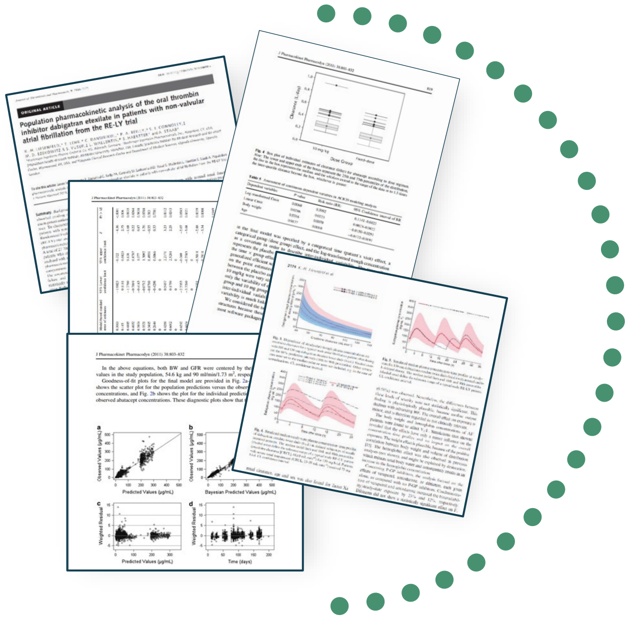
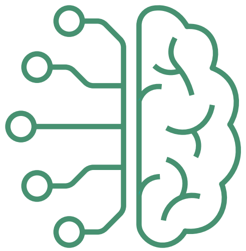
  → A research area and legacy expertise of Biotrial Data Science

1

Proprietary NLP to mine heterogeneous sources (literature++)





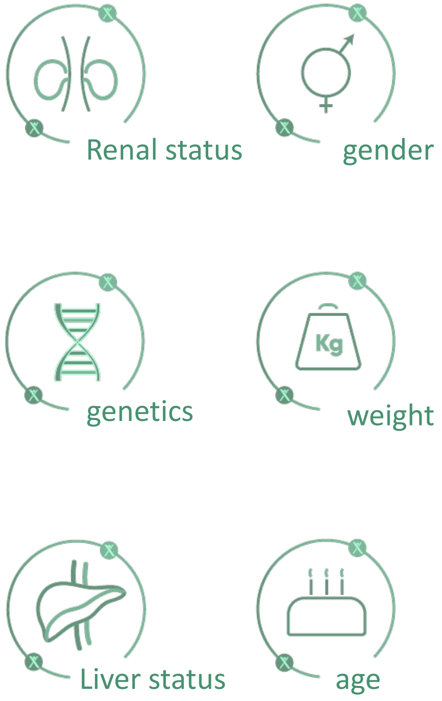
NLP

\+ Human expert qualification

2

Mathematically aggregate selected models

Meta-Model by Biotrial Data Science



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Original Paper

Towards precision dosing in psychiatry: Population pharmacokinetics meta-modelling of clozapine and lithium

Journal of Psychopharmacology
1–9

DOI: 10.1177/02698811241275630
journals.sagepub.com/home/jop
Sage

Aurélie Lereclus[1,2], Julien Welzel[2], Raoul Belzeaux[3], Théo Korchia[4], Frédéric Dayan[2], Olivier Blin[1,5], Sylvain Benito[2] and Romain Guilhaumou[1,5]

Abstract

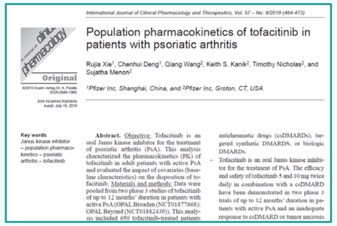
Background: Treatment optimization is mandatory in psychiatric diseases and the use of population pharmacokinetics (popPK) models through model informed precision dosing (MIPD) has the potential to improve patient medical care. In this perspective, meta-modelling methods could provide popPK models with improved predictive performances and most of covariates of interest. The aims of this study were to develop meta-models of clozapine and lithium, assess their predictability and propose optimized dosing regimens for both drugs.
Methods: Two popPK models for each drug were retained to develop the meta-models. For clozapine, the model with the best predictive performances and gender as a covariate and one with smoking status were retained. For lithium, the model with the best predictive performances and fat-free mass as covariate and one with glomerular filtration rate were retained.
Results: Both meta-models showed improved predictability compared to the original models. Clozapine meta-model simulations allowed us to propose dosing regimen according to gender and smoking status. Steady-state doses ranged from 375 to 725 mg/day for clozapine once daily, and from 350 to 650 mg/day for clozapine twice daily. Lithium meta-model simulations allowed us to propose dosing regimen according to weight, body mass index, gender and GFR. Our steady-state dose propositions ranged from 625 to 1125 mg/day for males, and from 375 to 750 mg/day for females.
Conclusion: Both meta-models met the acceptability criteria for use in clinical practice on all subpopulations of interest. Those models could be used in the perspective of MIPD for clozapine and lithium.

Keywords
Precision dosing, psychiatry, meta-modelling, population pharmacokinetics, lithium, clozapine

Case study with simulated trial: mechanistic modeling

Mechanistic modeling 1 (Tofacitinib): meta-modeling in PKPD for a repositioning in Sjören Syndrome

Original basis PK model

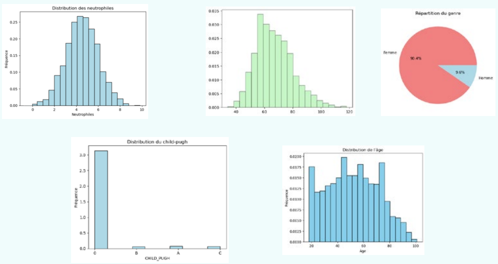

International Journal of Clinical Pharmacology and Therapeutics, Vol. 57 – No. 9/2019 (464-473)

Population pharmacokinetics of tofacitinib in patients with psoriatic arthritis

Rujia Xie, Chenhui Deng, Qiang Wang, Keith S. Kanik, Timothy Nicholas, and Sujatha Menon

Xie *et al.* 2019

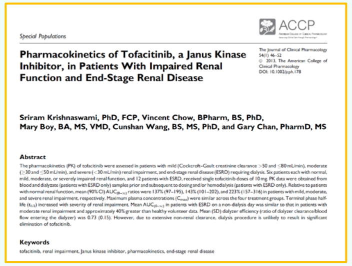
Age, Weight, Sex



ExactCure generates virtual populations with characteristics of Sjögren Syndrome

"Phase II Data"

ExactCure Meta Model augmented by

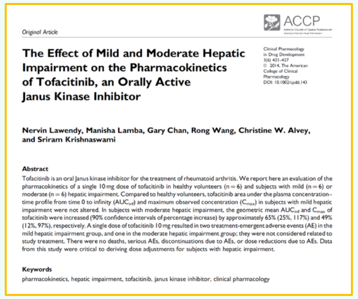

Special Populations

Pharmacokinetics of Tofacitinib, a Janus Kinase Inhibitor, in Patients With Impaired Renal Function and End-Stage Renal Disease

Sriram Krishnaswami, PhD, FCP, Vincent Chow, BPharm, BS, PhD, Mary Boy, BA, MS, VMD, Cunshan Wang, BS, MS, PhD, and Gary Chan, PharmD, MS

Krishna-swami *et al.* 2014

\+ Renal Function (GFR)


Original Article

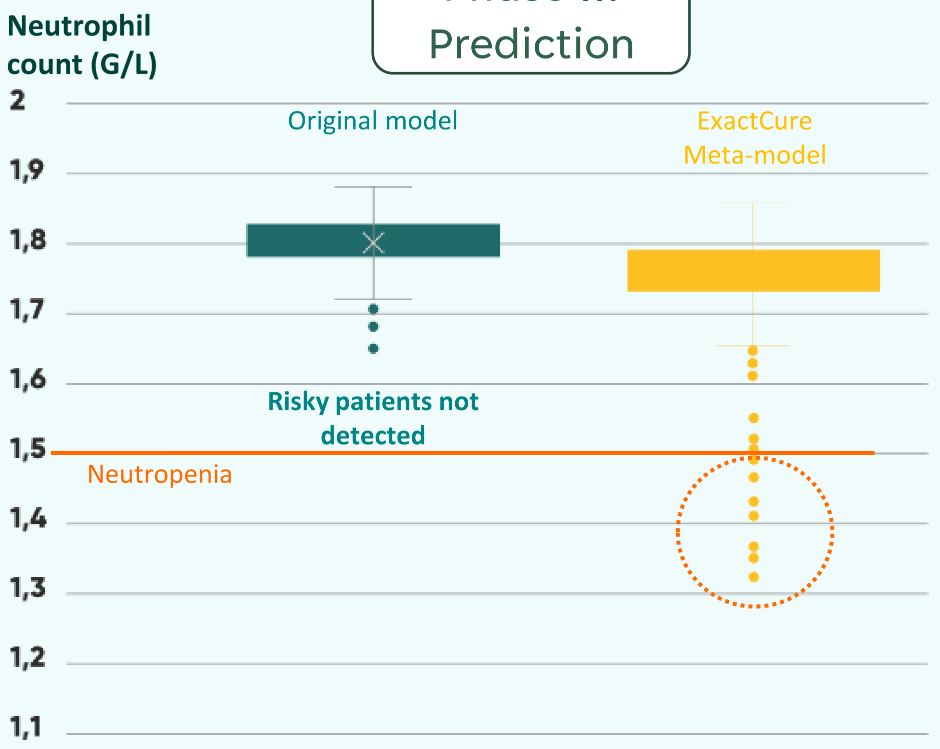
The Effect of Mild and Moderate Hepatic Impairment on the Pharmacokinetics of Tofacitinib, an Orally Active Janus Kinase Inhibitor

Nervin Lawendy, Manisha Lamba, Gary Chan, Rong Wang, Christine W. Alvey, and Sriram Krishnaswami

Lawendy *et al.* 2014

\+ Liver Function

Phase III Prediction



22 patients at risk of neutropenia are detected

Trial I/E criteria can be refined and adapted in line with these findings

Let’s create virtual patients using SIMULATION

Each patient is generated through computer (*in silico*) simulation

***In Silico* study**

Mechanistic

Biological and pharmaceutical phenomena are described according to a comprehensible model. For instance a PK model, a PD model, a PKPD model.

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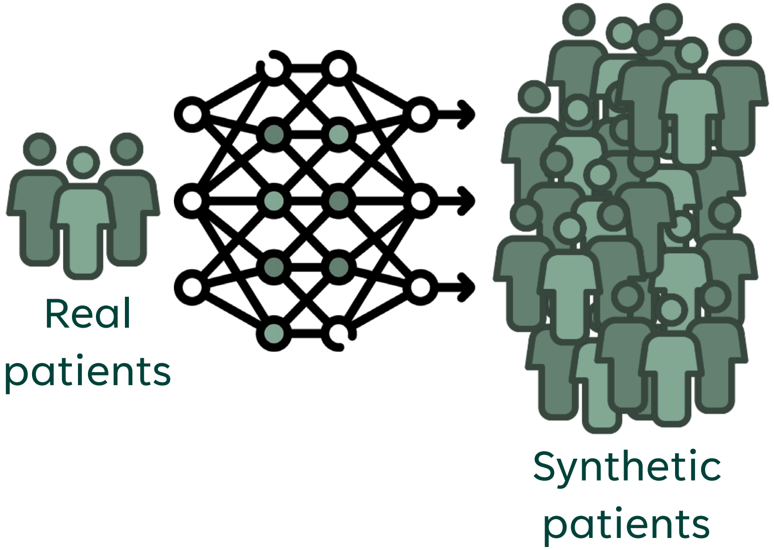
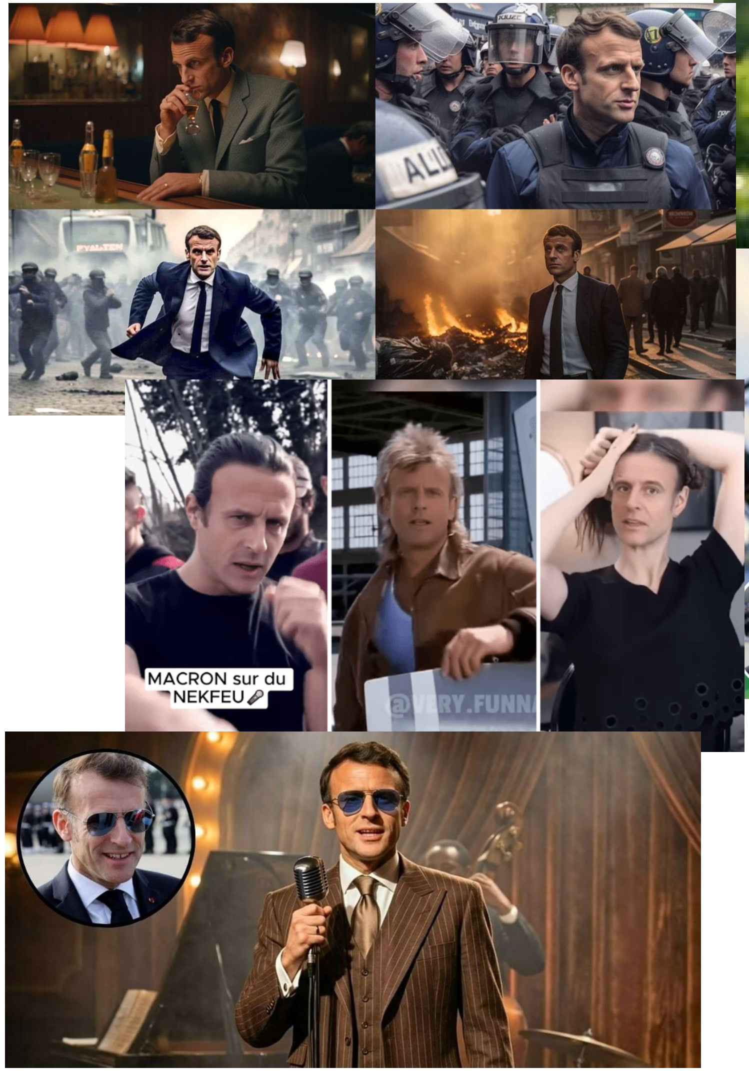
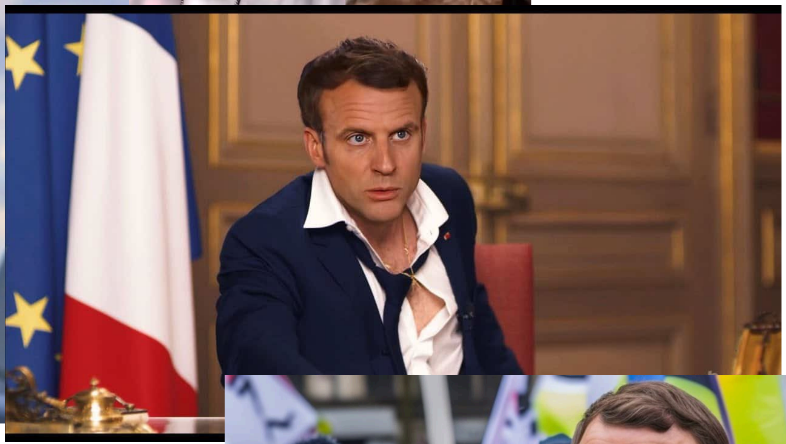


Let’s create virtual patients using SIMULATION

Non-Mechanistic principles





We all know the **power of AI**

Let’s create virtual patients using SIMULATION

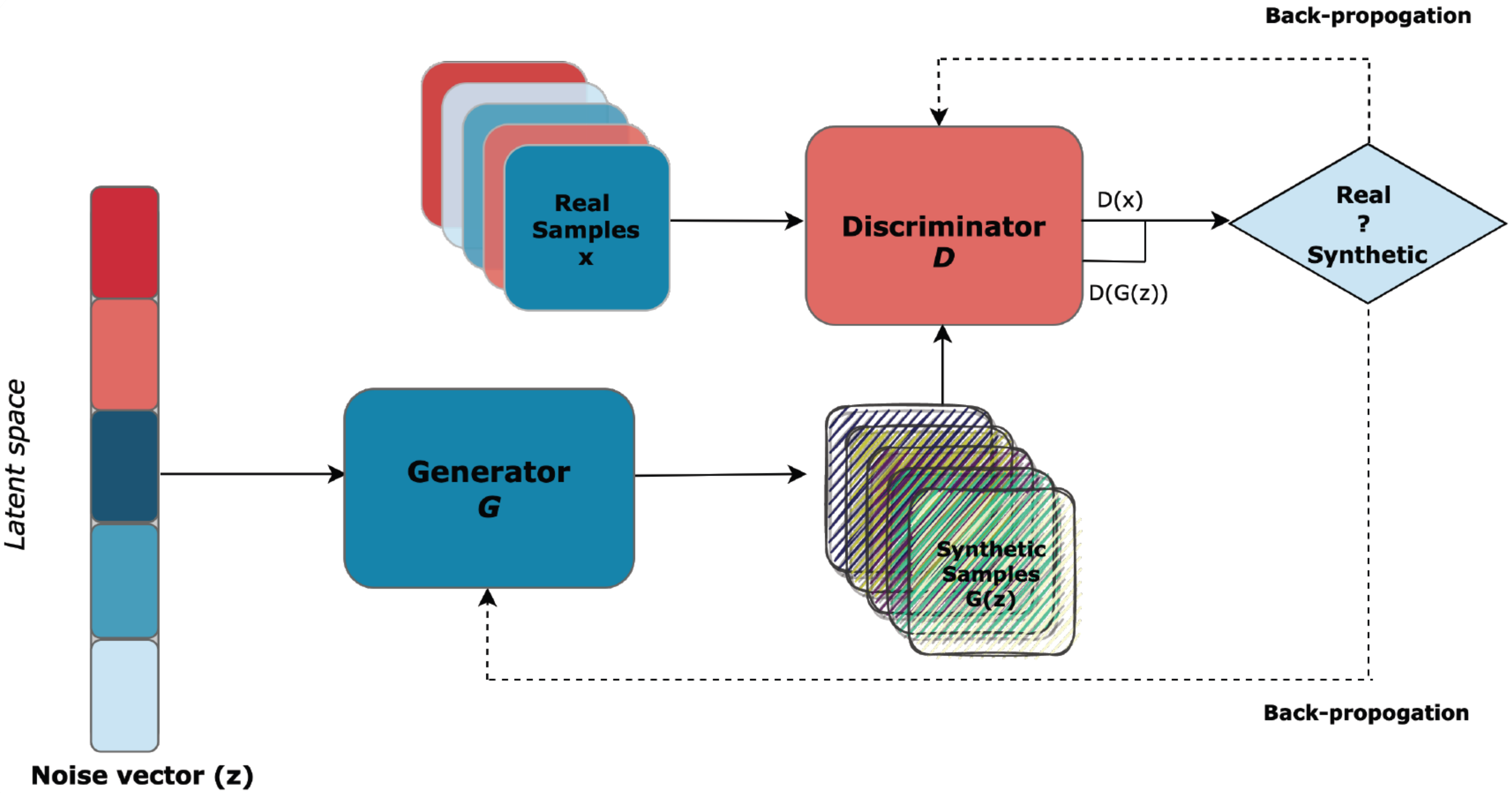
Non-Mechanistic principles

What if…
We used the **power of AI** to support clinical trials?

Let’s create virtual patients using SIMULATION

Non-Mechanistic principles

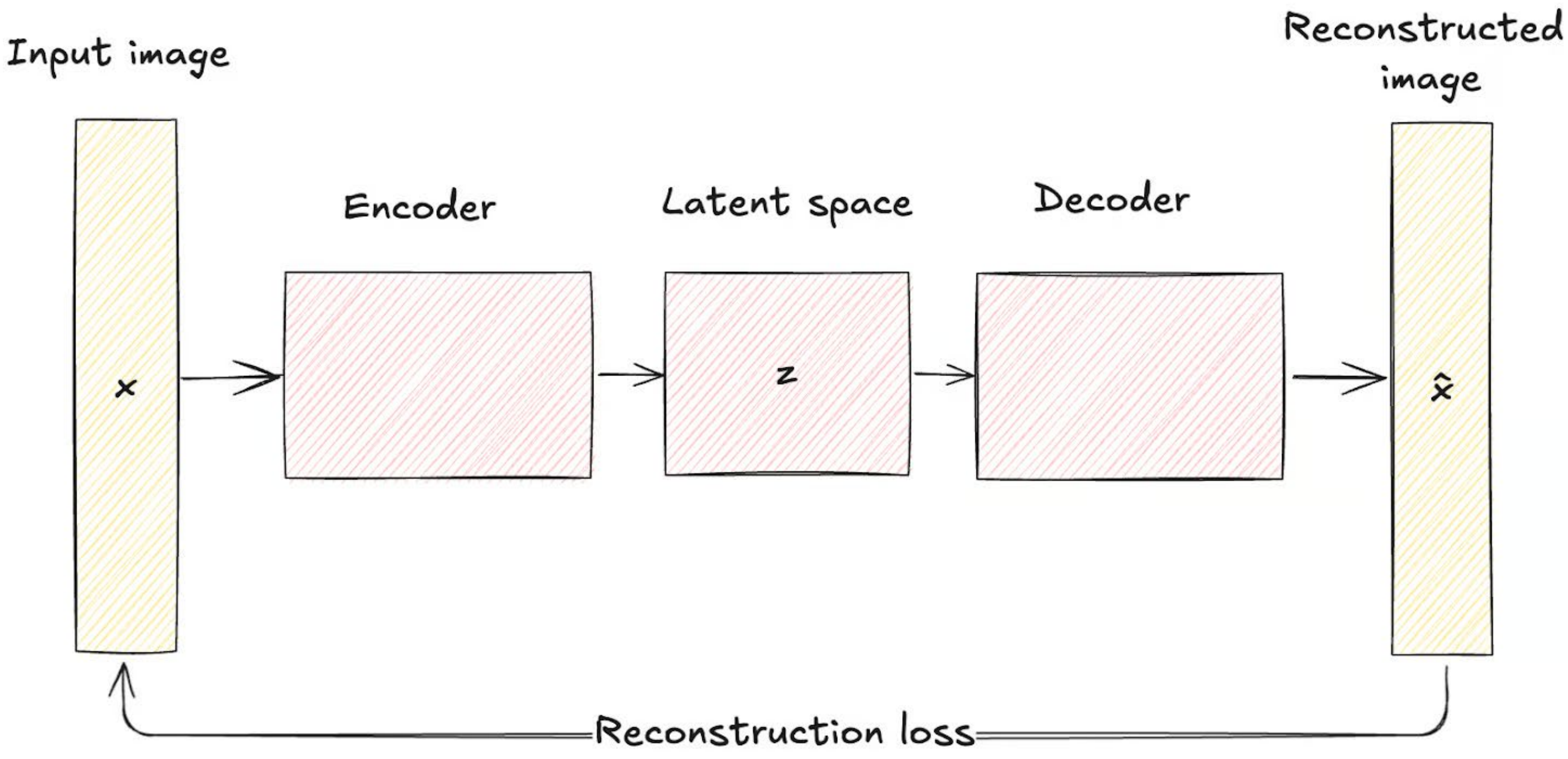
Generative
Adversarial
Networks
(GAN)



Let’s create virtual patients using SIMULATION

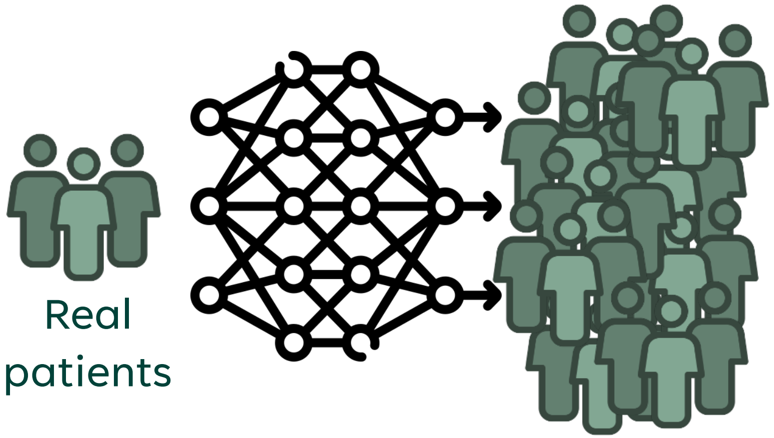
Non-Mechanistic principles

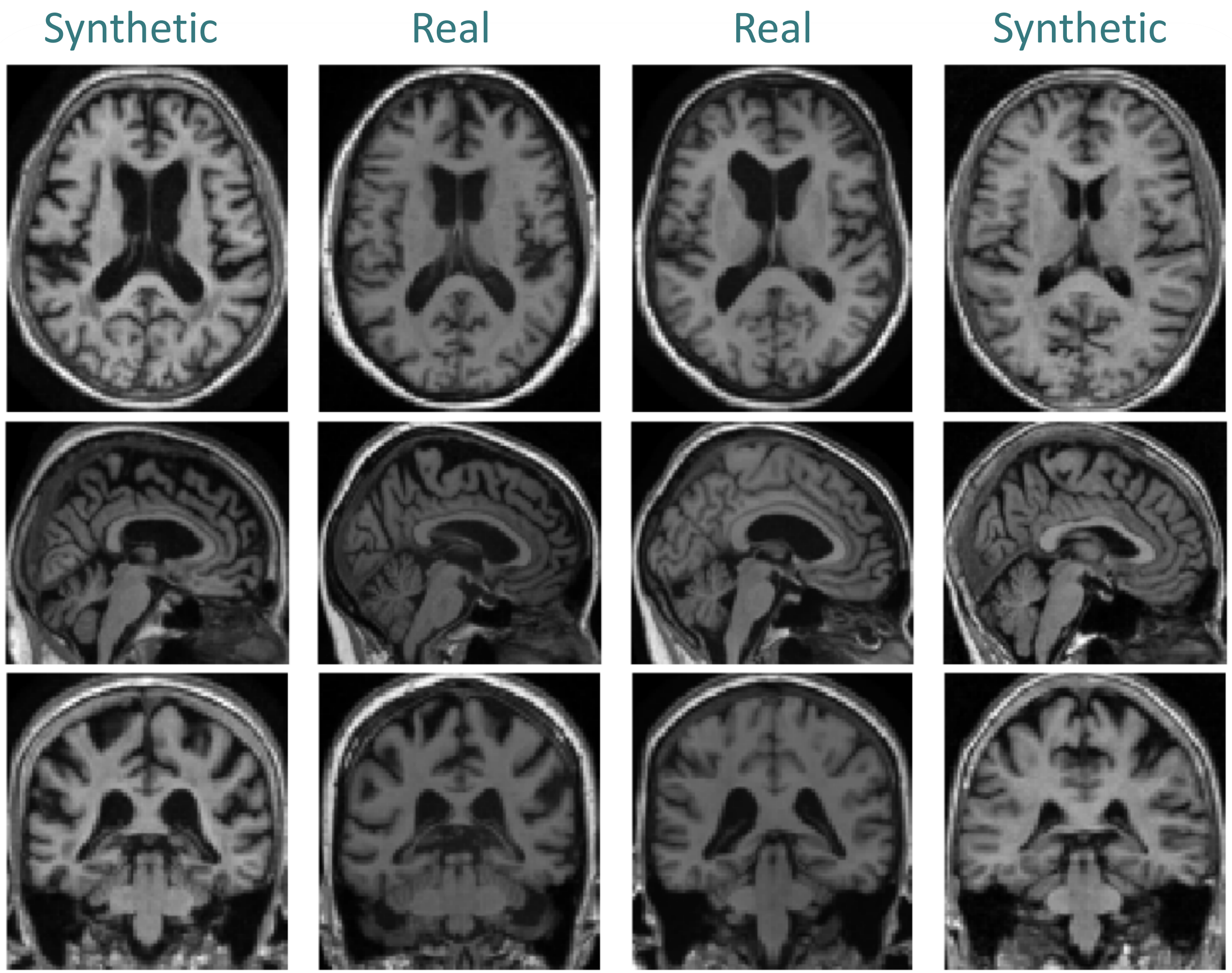
Variational
Auto
Encoder
(VAE)



Case study with simulated trial: non-mechanistic modeling

Non-mechanistic use case 1: control patients in Alzheimer disease imaging (VAE)



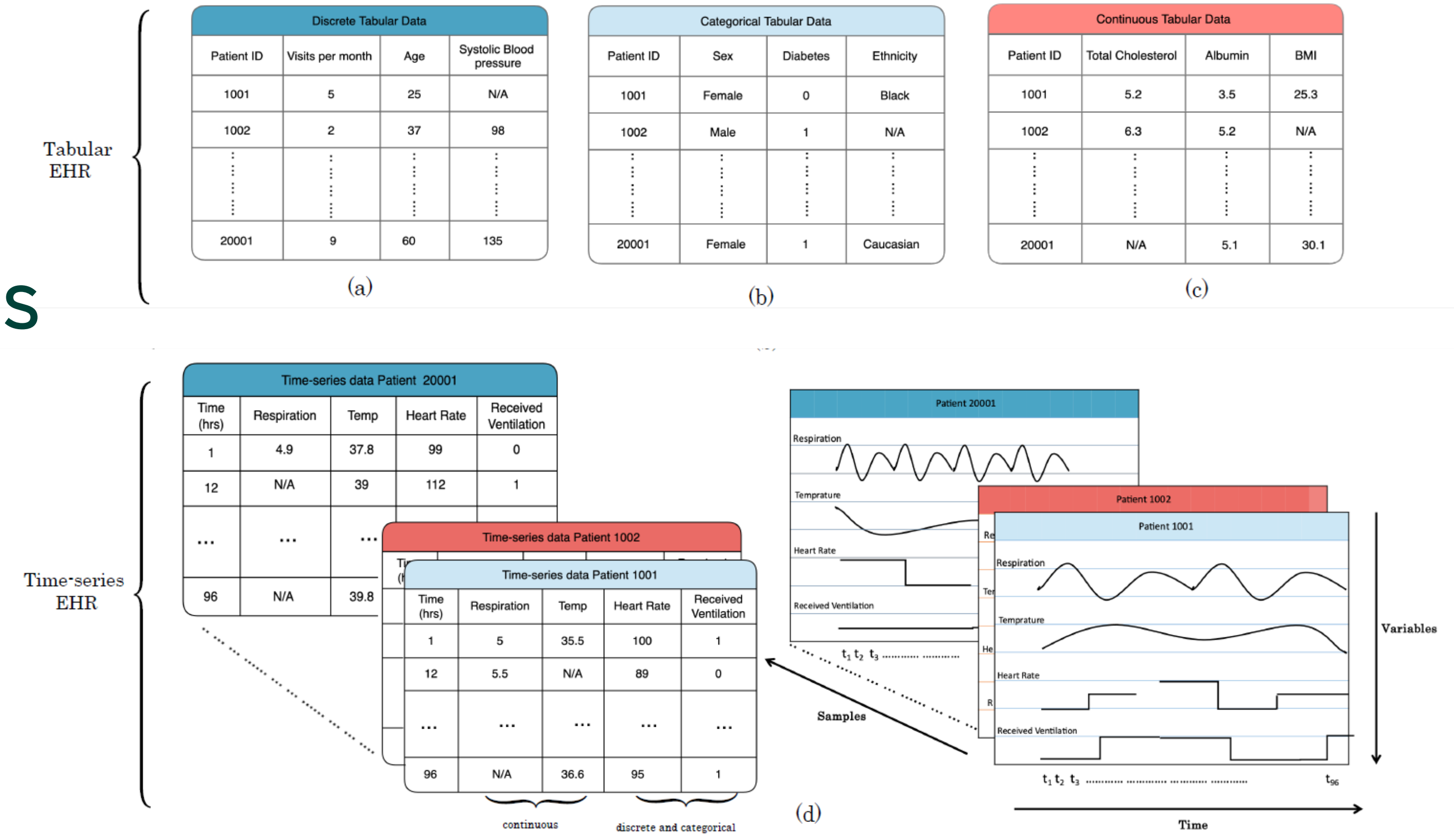


Synthetic MRI of Alzheimer patients based on 210 training images

Case study with simulated trial: non-mechanistic modeling

What is a patient in a clinical study?

In most study reports, patients are mainly figures in tables...



AI has proved its power in imaging, but can be applied to many other fields

Case study with simulated trial: non-mechanistic modeling

Non-mechanistic use case 2: Amplification of RCT in oncology

JOURNAL OF MEDICAL INTERNET RESEARCH El Kababji et al

Original Paper

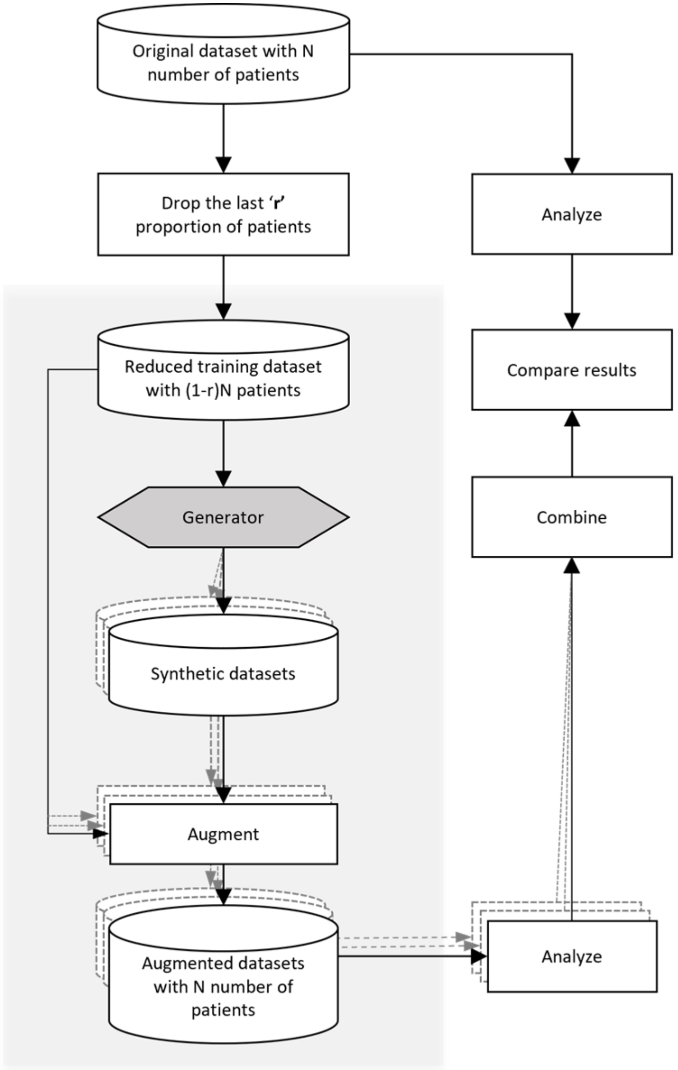
Augmenting Insufficiently Accruing Oncology Clinical Trials Using Generative Models: Validation Study

Samer El Kababji[1,2], PhD; Nicholas Mitsakakis[2], MSc, PhD; Elizabeth Jonker[2], BA; Ana-Alicia Beltran-Bless[3], MD; Gregory Pond[4], PhD; Lisa Vandermeer[3], MSc; Dhenuka Radhakrishnan[2], MD; Lucy Mosquera[5], MSc; Alexander Paterson[6], MD; Lois Shepherd[7], MDCM, FRCP; Bingshu Chen[7], PhD; William Barlow[8], PhD; Julie Gralow[9], MD; Marie-France Savard[3], MD; Christian Fesl[10], PhD; Dominik Hlauschek[10], MSc; Marija Balic[11], MD, PhD; Gabriel Rinnerthaler[11], MD; Richard Greil[12], MD; Michael Gnant[13], MD; Mark Clemons[3], MD; Khaled El Emam[1,2], BEng, PhD

"We performed a retrospective analysis **using 10 datasets** from 9 fully accrued, completed, and published cancer trials. For each trial, we r**emoved the latest recruited patients (from 10% to 50%)**, trained a generative model on the remaining patients, and simulated additional patients to replace the removed ones using the generative model to augment the available data."

"**Four different generative models** were evaluated: sequential synthesis with decision trees, Bayesian network, generative adversarial network, and a variational autoencoder."

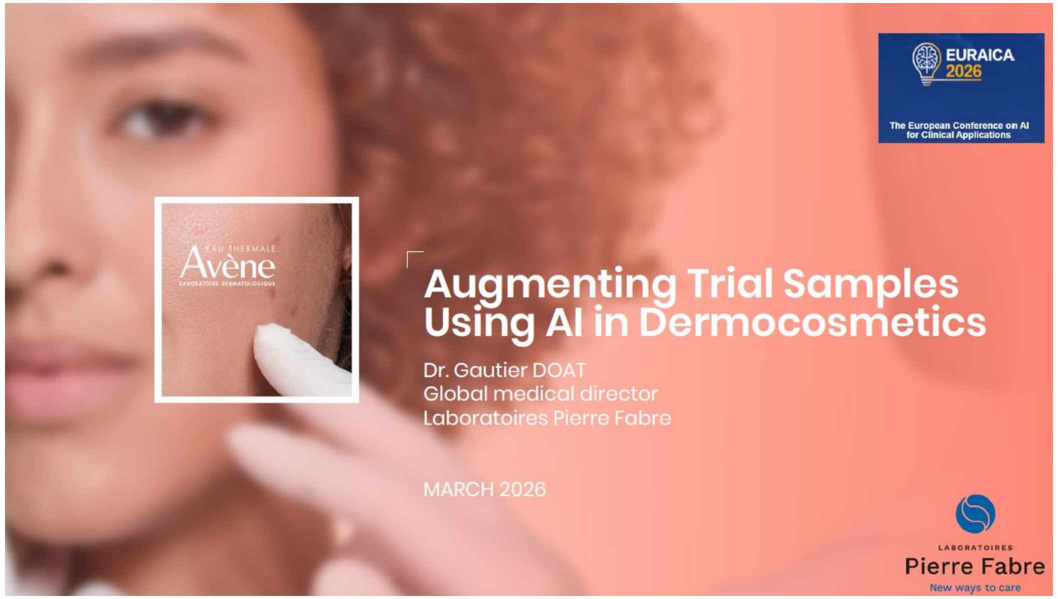
"For an oncology study with insufficient accrual with **as few as 60% of target recruitment**, sequential synthesis can enable the simulation of the full dataset had the study continued accruing patients and can be an alternative to drawing conclusions from an underpowered study."

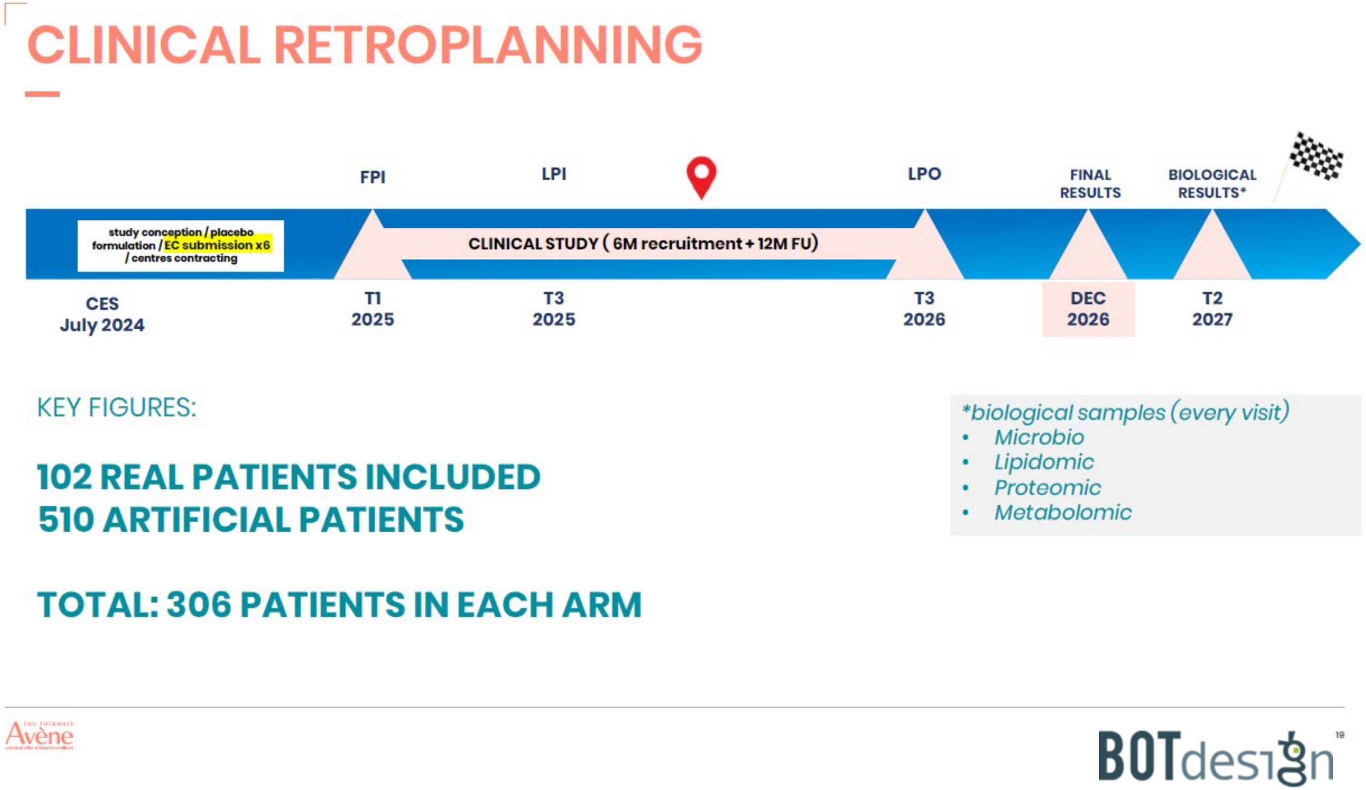


El Kababji S *et al*. 2025. Augmenting Insufficiently Accruing Oncology Clinical Trials Using Generative Models: Validation Study. J Med Internet Res 2025;27:e66821

Case study with simulated trial: non-mechanistic modeling

Non-mechanistic use case 3: Amplification of RCT in dermocosmetics (VAE)





Case study with simulated trial: non-mechanistic modeling

Non-mechanistic use case 4: Bioptimus (Foundation multimodal model)

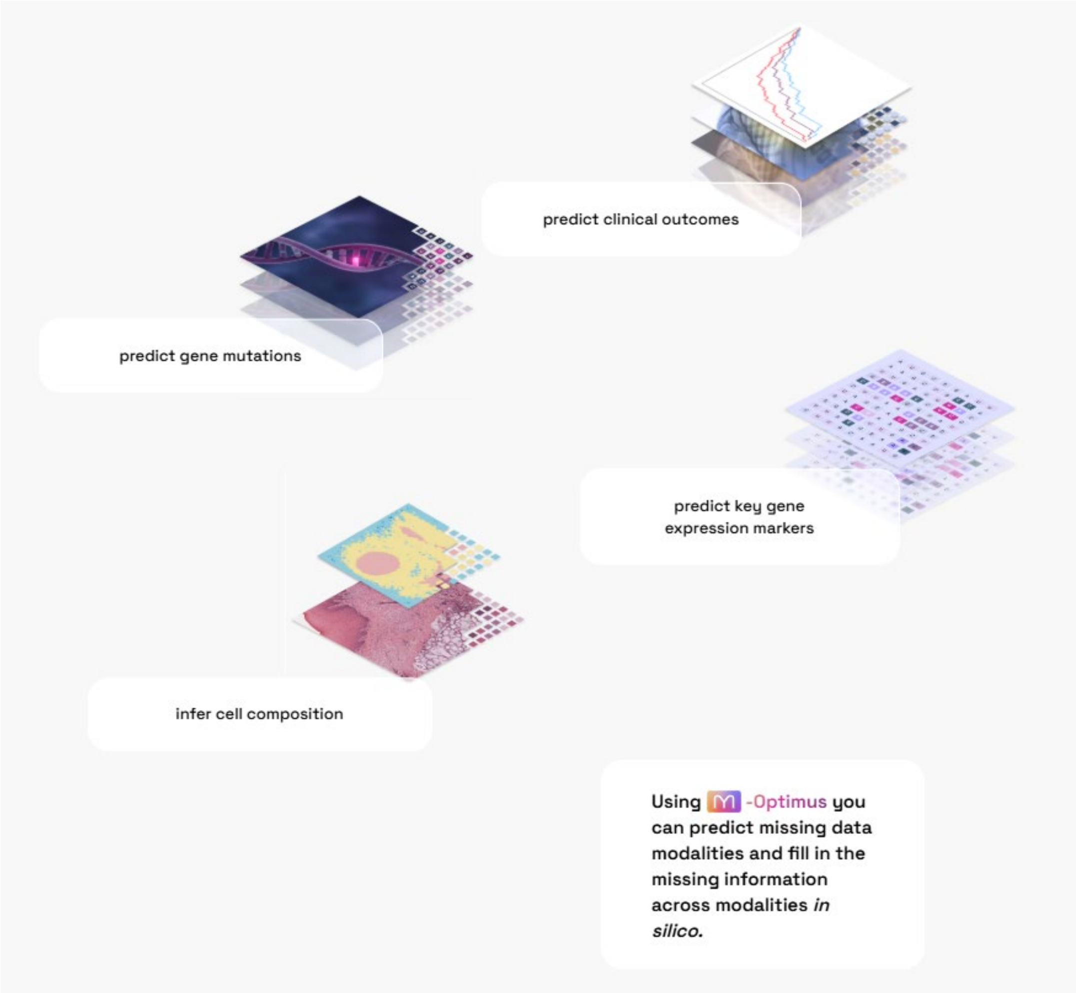
BIOPTIMUS

LAUNCH Q1/2026

Introducing

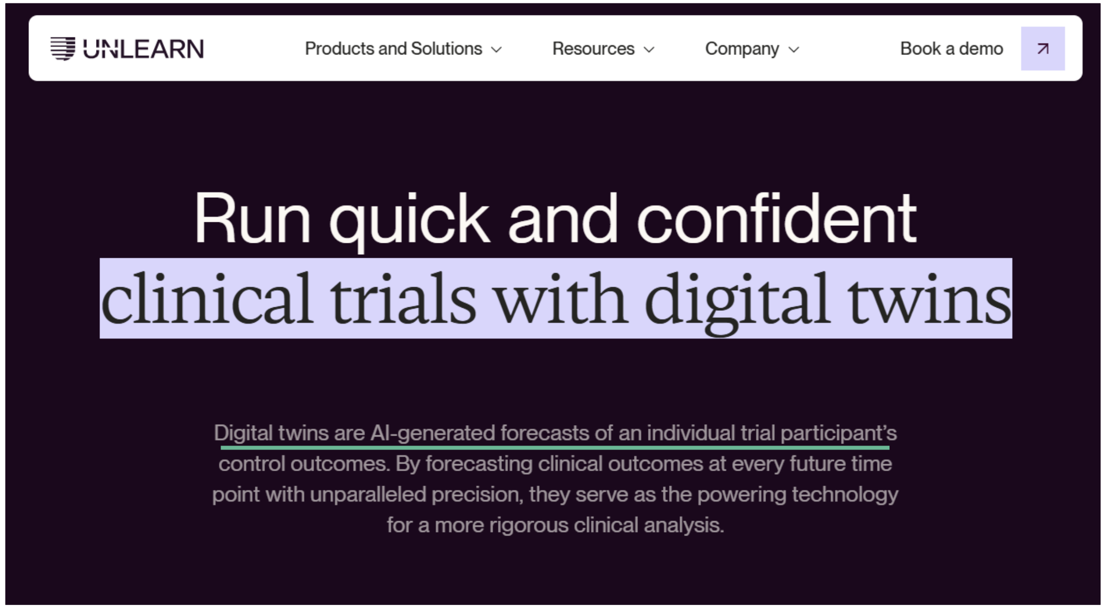
We believe the solutions to the world's toughest diseases exist — hidden in plain sight, but obscured by noise and locked in siloed biological data.

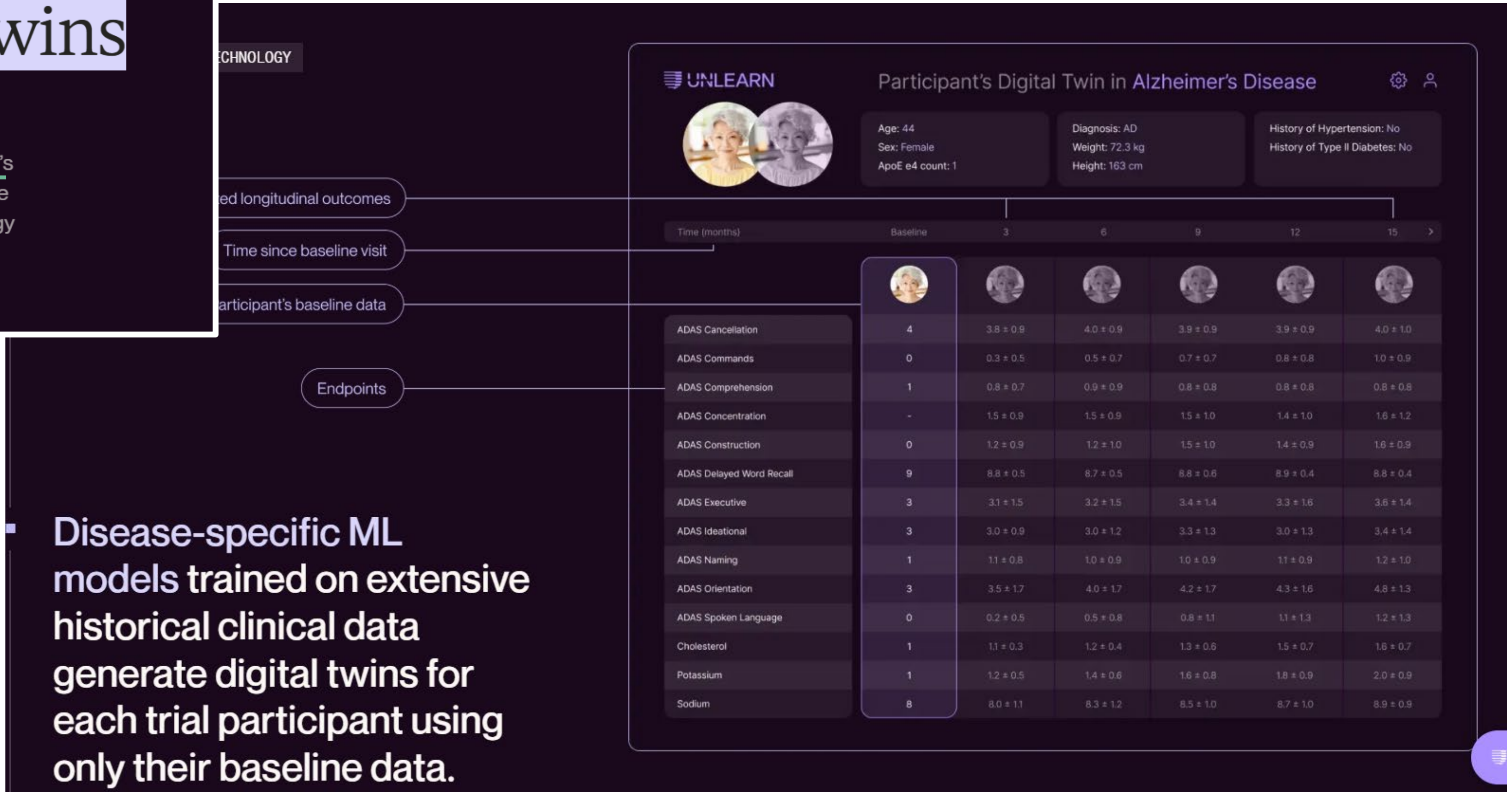
Operating on this simple belief, Bioptimus built the world's most powerful Foundation Model of Biology:



Case study with simulated trial: non-mechanistic modeling

Non-mechanistic use case 5: PROCOVA, an AI-based Digital Twin for covariate adjustment





Case study with simulated trial: non-mechanistic modeling

Non-mechanistic use case 5: PROCOVA, an AI-based Digital Twin for covariate adjustment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2022
EMADOC-1700519818-907465
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion for Prognostic Covariate Adjustment (PROCOVA™)

Draft agreed by Scientific Advice Working Party (SAWP)	10 February 2022
Adopted by CHMP for release for consultation	24 February 2022[1]
Start of public consultation	22 March 2022 [2]
End of consultation (deadline for comments)	03 May 2022[3]
Adopted by CHMP	15 September 2022

Keywords	Qualification of Novel Methodology, Statistical methodology, Prognostic Covariate Adjustment, Sample size estimation

Typically, trials that use ANCOVA adjust for simple baseline covariates such as each participant's age. In **PROCOVA**, by contrast, a **pre-specified model based on artificial intelligence** trained on historical patient data is used to construct a **prognostic score** for each participant collected at their first visit in a trial. This way, historical patient data is used to learn to construct an approximation to the optimal covariate that maximizes power in a future study, thereby leveraging rapidly improving machine learning technologies and increasingly vast quantities of individual participant data to improve clinical trials.

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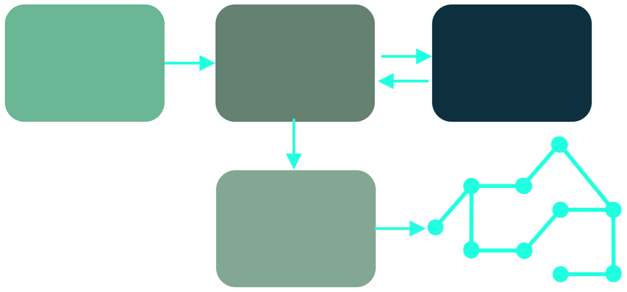

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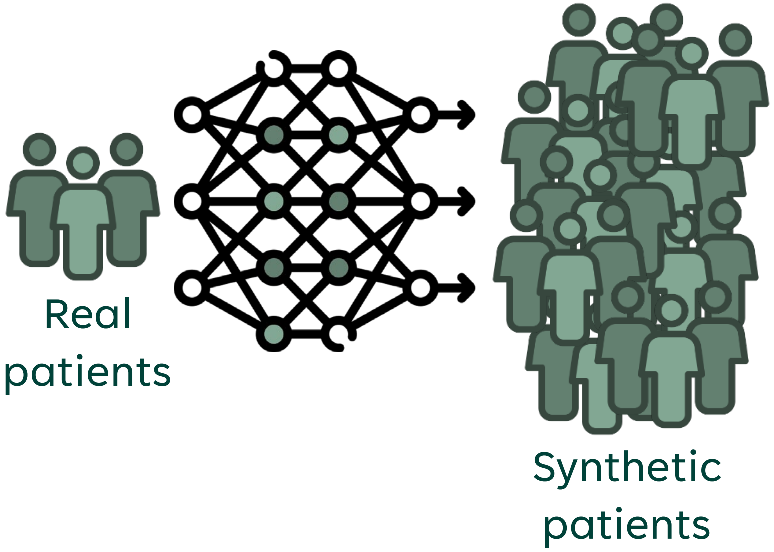
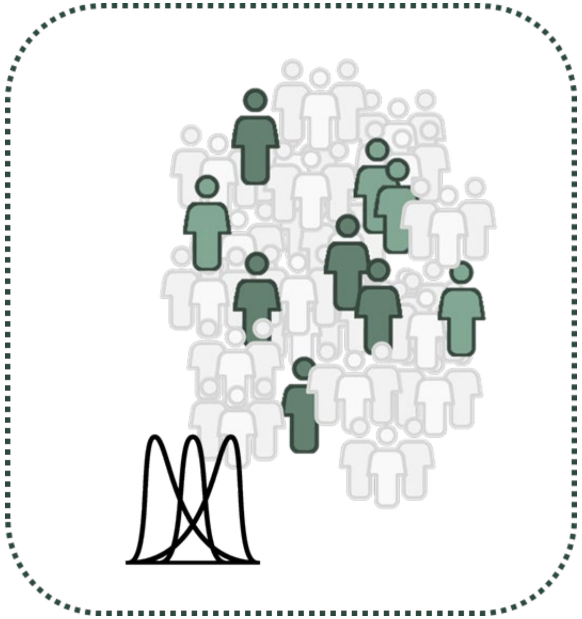


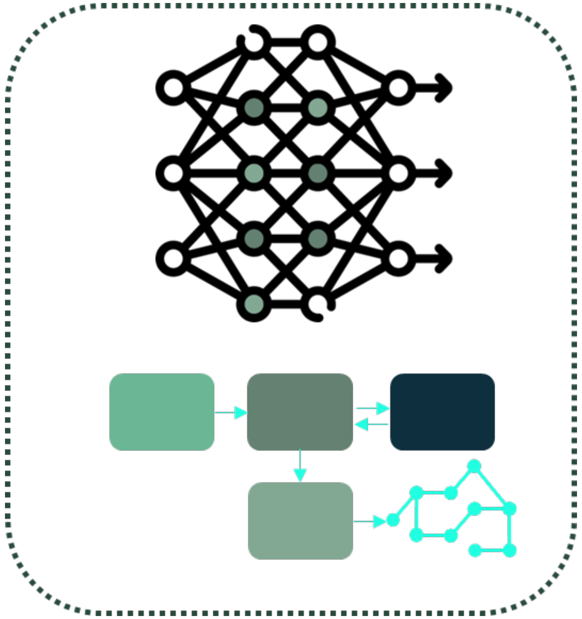
Two ways to create a synthetic cohort: EMULATION & SIMULATION

Statistics *versus* *In silico*

Emulation of a cohort using **Advanced Statistics**



OR



Simulation of a cohort using **Machine Learning** or **Mechanistic Modeling** (PKPD, QSP)

synthetic cohort


The future of
clinical research
has already been
written in the sky.