WHITE PAPER

InSilicoTrials

Advancing Women's Health with *In Silico* Design and Evaluation of Clinical Studies

Executive Summary

While women's health research has advanced, significant gaps remain in addressing their unique needs. Women often experience different drug responses and adverse effects compared to men, due to physiological differences. Besides, gender biases in healthcare research and a lack of funding have led to substantial knowledge gaps in the efficacy and safety of medications for female patients. Efforts to improve women's health are increasingly gaining attention, with regulatory agencies like the FDA, EMA and ICH emphasizing the importance of incorporating modeling and simulation approaches to enhance drug development and evaluation for women.

In silico methodologies, such as population pharmacokinetic and pharmacodynamic (PK/PD) modeling, physiologically-based pharmacokinetic (PBPK) modeling and quantitative systems pharmacology (QSP) modeling, offer valuable support for drug development. These approaches facilitate simulations of how treatments interact with women's unique physiological features, including pregnant and lactating women, providing insights into potential treatments in a risk-free and cost-effective manner. They are particularly useful for addressing sex-specific differences in drug efficacy and safety, and for optimizing treatment protocols for conditions like hormonal cycle-related disorders.

InSilicoTrials is pioneering the field of healthcare modeling and simulation by offering a comprehensive platform for *in silico* analyses. By leveraging advanced modeling techniques, InSilicoTrials facilitates the optimization of therapeutic strategies for female-specific conditions and the inclusion of women in *in silico* trials. These approaches enable the simulation of virtual patients cohorts, integrating gender-specific data and ensuring that the physiological differences of women are considered.

Incorporating *in silico* technologies into women's health research is essential for bridging knowledge gaps and advancing the development of women-specific medical therapies. Through innovative modeling and simulation, researchers can improve the safety and efficacy of treatments for women, ultimately leading to better health outcomes and a more equitable healthcare landscape.

Introduction

Advancements in women's health research and drug development have been significant, yet the journey toward fully addressing the unique needs of women in clinical settings still faces many challenges. A historical pattern of underrepresentation of women in clinical trials and underfunding of research on diseases mainly affecting women have often left women's specific health needs inadequately explored.
Historically, women were often excluded from clinical research due to concerns about reproductive health impact and the variability of hormonal cycles. This exclusion has led to a significant knowledge gap, with many medications reaching the market without adequate data on their effects in female patients. Today, there remains large differences in the efficacy and safety of marketed drugs between the sexes. A recent review by McKinsey (*Ellingrud et al., 2024*) found that for a large proportion of common interventions, women can be shown to benefit less because of lower efficacy, more limited access, or both. In fact, 64 % of the common interventions for which this was quantifiable were reported to disadvantage women (in comparison to only 10% for men).

At the same time, adverse events are reported in women 52% more often than in men, and products are 3.5 times more likely to be withdrawn for safety concerns in women than for men. The underlying reasons for these seemingly large disparities in drug safety and efficacy may be complex and include gender disparities in the likelihood of taking medication and of reporting adverse events in addition to physiological differences in e.g. fat mass, overall size and weight, rate of digestion and enzyme expression (*Rushovich et al., 2023; Soldin & Mattison, 2009*). While sex differences in drug response are important in development, recent studies proposes that social factors tied to gender, not biology alone, may explain why women report more adverse effects. (*Lee, Katharine M N, et al.*)

Nevertheless, it is clear that sex-based differences in both efficacy and safety remain a key point of attention in drug development.

Furthermore, pregnant and breast-feeding women are still often excluded from clinical drug development and research studies, these exclusions being motivated by ethical concerns stemming from the hesitancy to expose pregnant women and the developing fetus and breast-feeding women and the infant, to potential risks associated with experimental drugs (*McKiever et al., 2020*). Although non-clinical reproductive toxicology studies are mandatory before testing the new drug in humans to ensure the safety of medications for women of childbearing age, women continue to be underrepresented in Phase 1 clinical trial. This often leads to insufficient and inadequate safety information for women, and especially pregnant and breast-feeding ones.

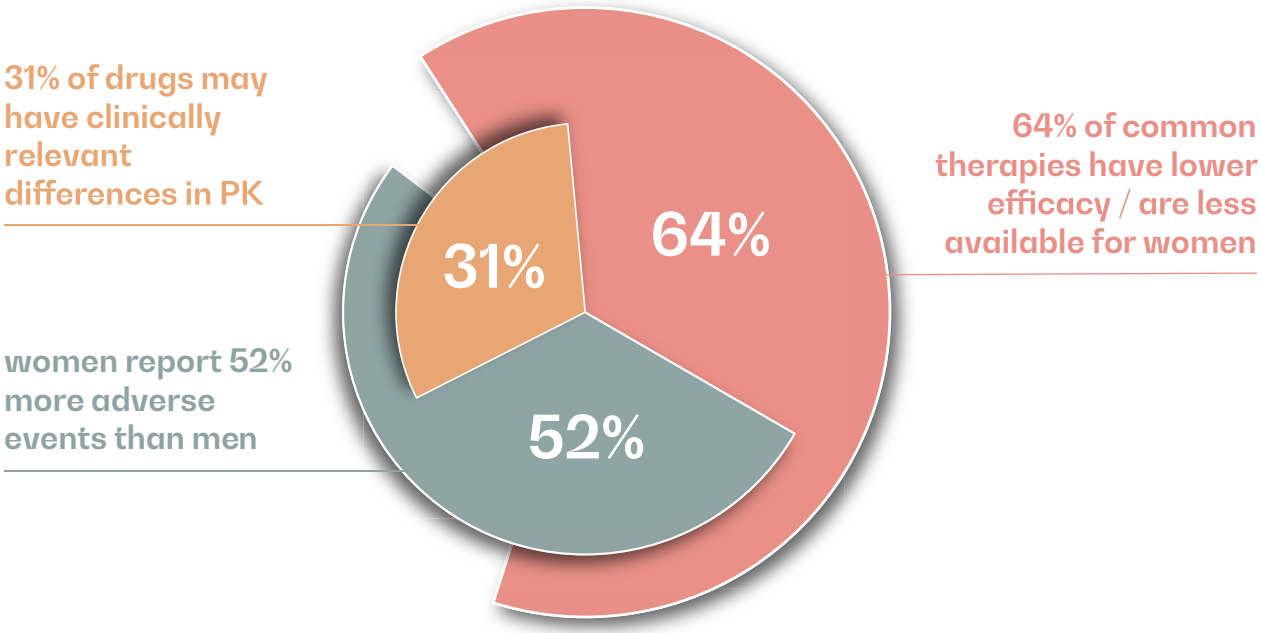
In addition to the underrepresentation of women in health studies, gender bias in healthcare is evident in the distribution of research funding across disease. A 2021 study (*Mirin, 2021*) revealed that the allocation of research funding for diseases predominantly affecting women does not align with their respective disease burdens, which measures the extent of death and disability caused by the disease. These findings emerged from an analysis of funding from the US National Institutes of Health (NIH), focusing on 74 diseases for

which both disease burden and funding levels were available. The study highlights the disparity in funding allocation, with 14 diseases primarily impacting women identified as underfunded, compared to just one disease primarily affecting men. Examples of such underfunded diseases include migraine, endometriosis, and uterine cancer. Moreover, an examination of cancer types reveals a similar trend, with gynecological cancers receiving less support relative to their mortality rates compared to other cancer types.

Efforts to improve women's health are increasingly gaining attention, with significant strides being made to address longstanding issues. The establishment of centers of excellence in women's health research and proactive involvement by regulatory bodies like the FDA are positive developments. Notably, the FDA's Women's Health Research Roadmap highlights the importance of evaluating and adopting novel modeling and simulation approaches to improve the regulatory evaluation of products for women, ensuring these interventions are both safe and effective (*US Food and Drug Administration, 2015*). Additionally, large-scale clinical trials, such as the Women's Health Initiative, are beginning to fill these gaps, offering more specific data to enhance treatment options and health outcomes for women (*Kim & Jarugula, 2020*).

This white paper will further explore these issues, underscoring the necessity of incorporating modelling and simulation into women's health research to bridge critical knowledge gaps. By deploying *in silico* technologies, researchers can simulate how treatments interact with women's unique (pato-)physiological features. These models allow for effective "what if" scenarios that provide insights into potential treatments in a risk-free, low-budget manner, significantly advancing our understanding and development of women-specific medical therapies (*Cassidy et al., 2019*).

Based on a review of drugs approved between 1994-2000



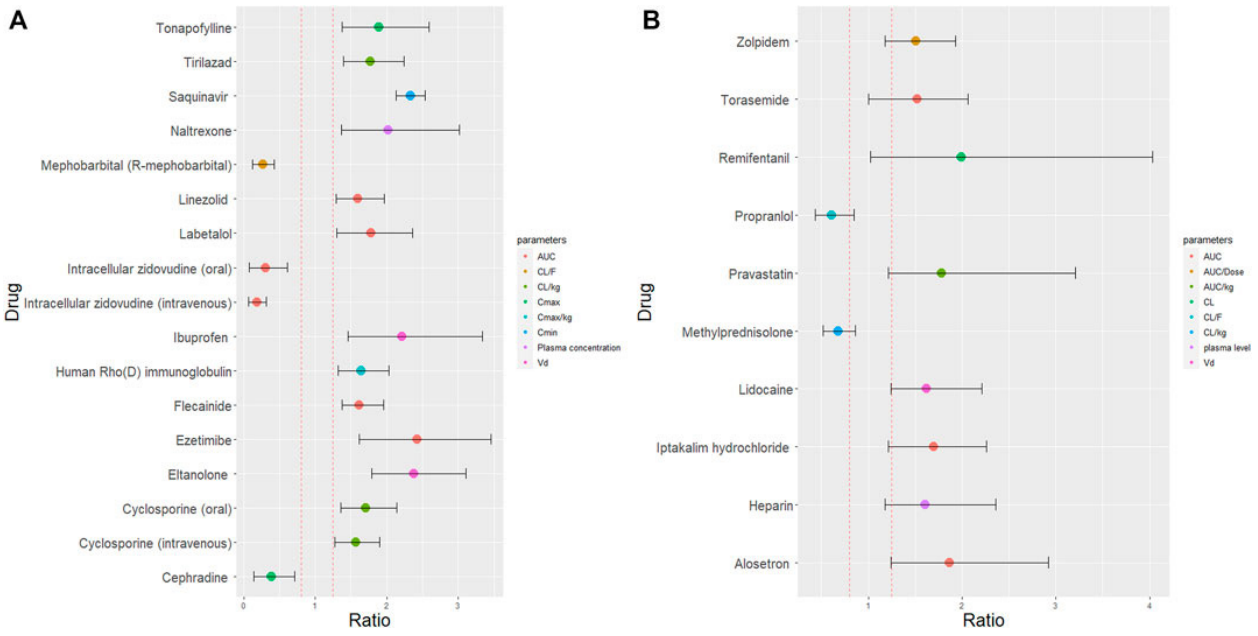
Disparities between men and women in drug PK, efficacy and safety.
(1) Based on a review of drugs approved by the FDA between 1994-2000, in 31% of cases one or more PK parameters is found to have a more than 20% sex difference [10]. (2) For a large proportion of common interventions, women benefit less than men – for 64% of the common interventions for which this was quantifiable women were disadvantaged [1]. (3) Women have been found to report adverse events 52% more often in women than men [1].

Sex differences in drug efficacy and safety

The need to understand how the efficacy and safety of new therapies is affected by sex differences in biology, pathophysiology and pharmacology has been recognized by regulators such as the FDA, EMA and global ICH guidelines for decades (*European Medicines Agency, 2005; Fadiran & Zhang, 2015*). As a result, the pharmaceutical community has acquired a large knowledge based on how sex underlies different dosing requirements.

Modeling and simulations can be a powerful tool to address sex-related differences in efficacy and safety. Specifically, population pharmacokinetic and pharmacodynamic (PK/PD) modeling is a powerful tool for the characterization of sex-related differences in drug exposure and effects. Modeling pharmacokinetic, biomarker, efficacy and safety data with this well-established methodology allows us to distinguish between the different factors that contribute to the patterns in the observed data, including a quantification of any sex-related differences in either pharmacokinetics or drug effects. Once the models have been developed, they also allow exploration of sex-specific dosing schedules and can provide evidence to set safe and effective labelling information.

However, evaluating sex-related differences in safety with the help of modeling and simulation can already take place in the non-clinical stage. For example, women



Sex-specific differences in PK parameters for a selection of drugs. Figure reproduced from [24], © 2022 Oi Yan Chan, Moullet, Williamson, Arends and Pilla Reddy

have a much higher risk of QT prolongation related Torsade des Pointes arrhythmias than men, because of higher drug concentrations, hormone-related differences in baseline heart rhythm and enzyme expression differences (*Vicente et al., 2020*). Such Torsade des Pointes arrhythmias are a common safety concern for new drugs that require thorough testing throughout non-clinical and clinical development. Torsade des Pointes is a potentially fatal arrhythmias that can be caused by small molecule drugs blocking ion channels of the cardiomyocytes. As the condition can result in sudden cardiac arrest, concerns over this type of cardiotoxicity have resulted in the removal from the market of over a dozen drugs. Currently, pharmaceutical companies are required to test thoroughly for risks, which include in vitro studies of ion channel blockage and clinical thorough QT studies to identify any potential elongation of the QT period observed in an electro cardiogram (ECG) (e), as this is a key clinical risk factor for TdP.

Modeling and simulation approaches can support testing for (sex-specific) Torsade des Pointes risk throughout the non-clinical and clinical studies.

Following a clinical thorough QT (TQT) study, Population PK/PD can support the analysis and derive dosing recommendations. Alternatively, modeling approaches such as exposure-response modeling can facilitate the replacing of the TQT by an extension of the Phase 1 ascending dose study by aiding in the design of the PK sampling and ECG schedule, as well as the analysis of the results (*US Food and Drug Administration, 2019*).

As the Phase 1 studies can focus on male subjects pending clearance of the investigational drug in women of reproductive age, *in silico* methodologies can also be leveraged to extrapolate the Phase 1 results to the female population. However, a critical phase for TdP risk evaluation is early development, as the development of promising compounds risks being terminated after in vitro testing if any signs of TdP risk is established. Here, the *in silico* approach can be instrumental in demonstrating a compound is safe, and can continue through development without cardiotoxicity risks.

Mechanism-based electrophysiology models have therefore been developed that can make a first prediction of sex-specific TdP risk from the earliest in vitro data (*Llopis-Lorente et al., 2023*). By combining pharmacokinetic models with these mechanistic models of the action potential in the heart itself, it is possible to account for not only sex-related differences in pharmacokinetics, but also in biology, to come to a prediction of sex-specific TdP risk.

Drug safety and efficacy in pregnant and lactating women

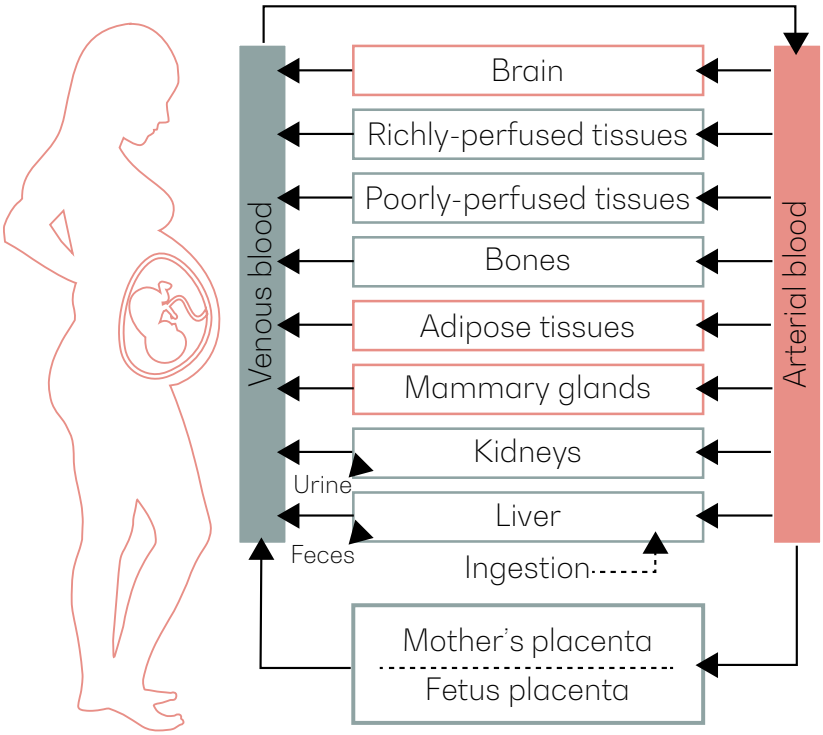
Women during pregnancy and breast-feeding may require medications for various reasons, such as pregnancy-related complications, but also chronic conditions like asthma, depression, diabetes, epilepsy, HIV/AIDS, or hypertension. However, data regarding safety, efficacy and, eventually the need for dose adjustment of these medications during pregnancy and breast feeding may not always be available. Instead, reliance is often placed on efficacy and safety data from research studies conducted in men and non-pregnant women, with the assumption that results can be generalized to pregnant women.

To help addressing these challenges, regulatory agencies advocate the use of innovative methods to enhance the assessment of any potential risk that a medicine may have to a pregnant woman and the unborn baby (*European Medicines Agency, 2020*), as well as to a breastfed infant through his/her mother's milk.

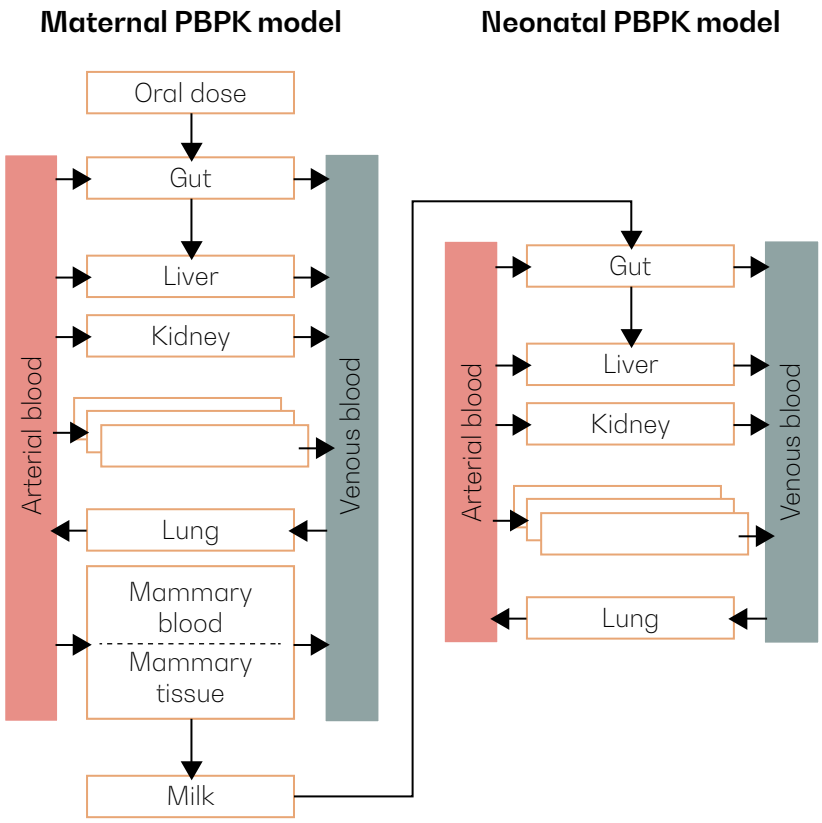
Quantitative mathematical approaches such as physiologically-based pharmacokinetic (PBPK) modeling have emerged as established and widely used methodologies for providing *in silico* support to drug development programs and regulatory submissions

(*European Medicines Agency, 2019; Shepard et al., 2015*). PBPK modeling is a mathematical framework that allows simulation of the drug concentration in tissues and blood over time, accounting for physiological, physicochemical, and biochemical characteristics. Besides being used for drug-drug interactions (DDIs) prediction and dose selection for pediatric and first-in-human trials (*European Medicines Agency, 2019; Shepard et al., 2015*), PBPK modeling approaches are also of interest to describe how anatomical and physiological changes during pregnancy may affect a drug's PK (*Coppola et al., 2021*). PBPK modeling can help to characterize drug exposure in the pregnant population and optimize the design of PK clinical trials for the investigation of drugs in this population, often necessitating a spare sampling approach to minimize participant burden (*Coppola et al., 2021*).

PBPK modeling may provide insights into drug transplacental passage and aids in predicting fetal drug exposure throughout pregnancy.



PBPK modeling integrates pregnancy-related changes into a mechanistic model. Allowing for simulation of drug concentrations in tissues and blood over time, as well as drug transplacental passage, this framework can be used to optimize clinical trial design and inform dose adjustments in pregnant women.



By coupling a maternal and a neonatal PBPK model, drug concentration in breast milk can be estimated, allowing determination of the total daily intake by the infant.

Moreover, PBPK can be employed to estimate drug concentration in breast milk, allowing determination of the total daily intake by the infant (*Coppola et al., 2021*).

Hormonal cycles and reproductive health

The female hormonal cycle is an intricately regulated interplay of hormones, with ultimate goals of successful ovulation, pregnancy and birth. As the system is so complex, dysregulation is not uncommon – conditions such as endometriosis, poly-cystic ovary syndrome and female infertility each affect up to 10-15% of the fertile-aged female population. Treating these conditions is especially challenging not only to the system's complexity, but also due to large variability between women. Treatment of e.g. infertility often requires a patient-centric approach with adjustments made regularly to treatment plan and dosing schedule, and assessing the efficacy of drugs can be complicated by the complexity of the treatment plans and the trials.

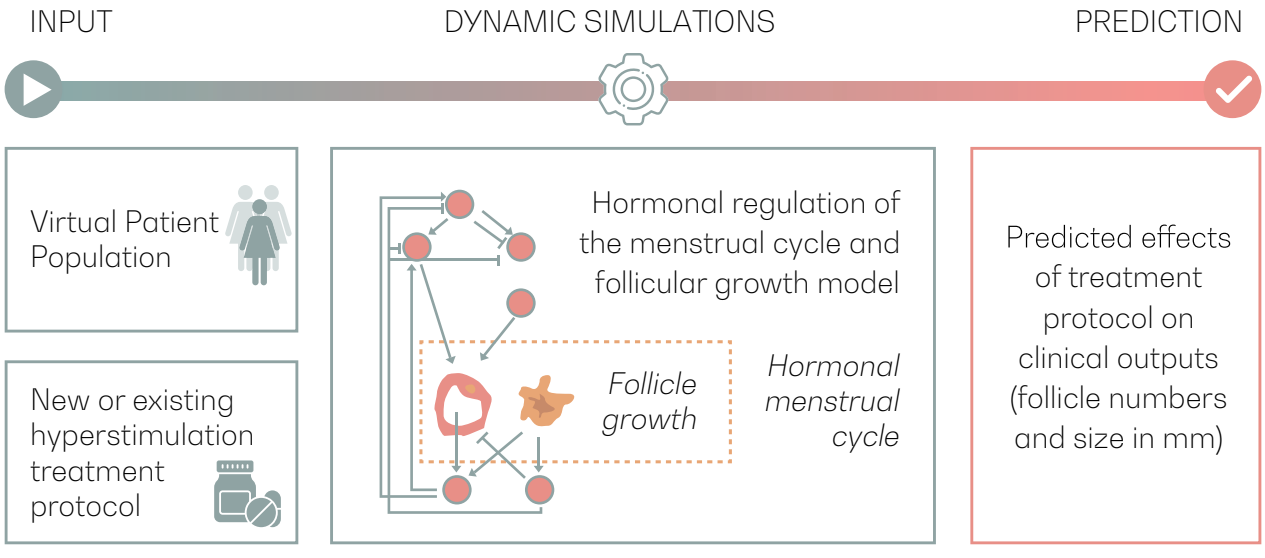
Population pharmacokinetic and pharmacodynamic (PK/PD) approaches can be used to analyze complex longitudinal data, whereas mechanistic models may

Modeling and simulation can accelerate development of novel therapeutics on this area by mitigating the complexity of both the system and the clinical trial data.

be valuable to understand and predict how treatment protocols will affect the cycle and follicle growth of patients during infertility treatment follicle stimulation by incorporating the biological complexity and heterogeneity in the methodology.

For example, *in silico* models of the menstrual cycle in health and infertility can be leveraged (*Fischer et al., 2021; Fischer-Holzhausen & Röblitz, 2022*) to help guide novel drug development, treatment protocol refinement and precision medicine. These models capture the complex dynamics of the hormonal cycle and its relation to follicle growth and ovulation, and have been developed to describe a heterogenous population of women. As such, they can be a valuable tool to support the development of ovarian stimulation protocols. These mechanistic models are inherently suitable to answer questions such as:

- *What biomarker response would correspond with the treatment effect we expect to see?*
- *How would this drug (synergistically) work with another in a combination therapy scenario?*
- *Based on non-clinical results and MoA, how would this novel drug that has not been tested in humans perform in this scenario?*

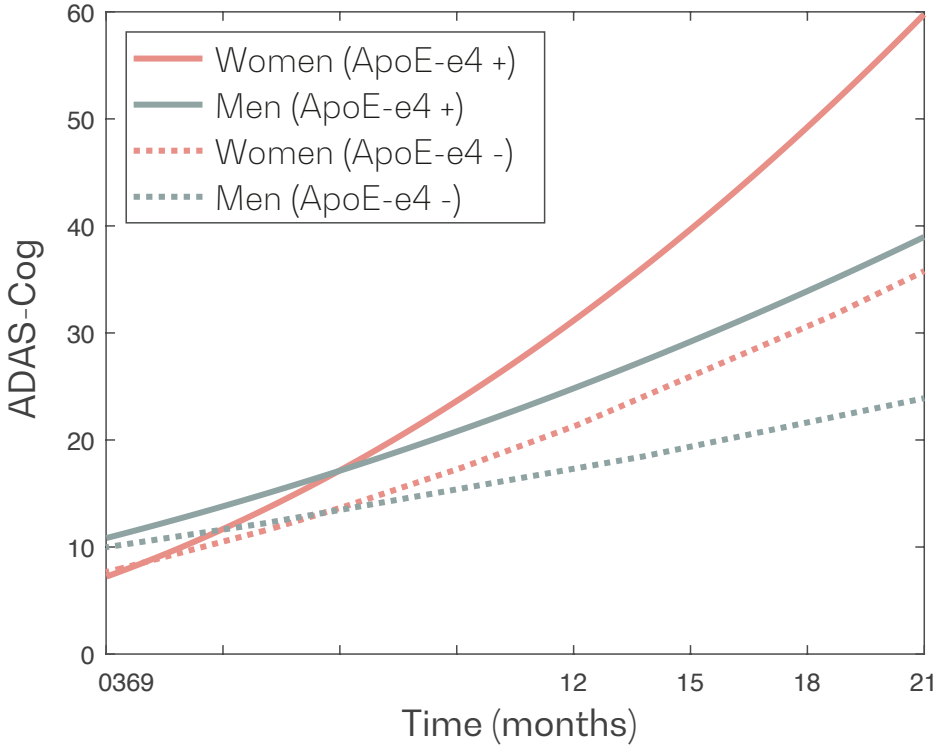


Mechanistic models of the female menstrual cycle capture the interplay between hormonal regulation and follicle growth [18], [19]

Diseases predominantly or differentially affecting women

In silico methodologies offer valuable support for drug development and allow to test more new treatment dosing or combinations compared to clinical trials and should therefore be increasingly utilized. In women's health conditions – those diseases affecting only or primarily women, which often lack sufficient funding, these approaches can facilitate a successful and efficient clinical program with limited funds. Additionally, *in silico* methodologies can be particularly useful in testing a variety of scenarios in conditions in which typical progression is known to differ between the sexes.

In fact, the list of diseases that affect primarily women, or affect women in a substantially different manner than men, is long. In addition to ovarian, cervical and breast cancers, polycystic ovary syndrome and endometriosis, a range of conditions affects women more often than men – including migraines, anemia, fibromyalgia, urinary tract disorders, thyroid disorders, depression and anxiety disorders, and auto-immune diseases. It should not come as a surprise that the overall disease burden and the number of medications taken by women is larger than men – further increasing chances of adverse events through drug-drug interactions.



Difference in disease progression in Alzheimer's Disease as quantified by the ADAS-Cog scale in women and men. Model from (Cho et al., 2021)

Furthermore, in many diseases there is a marked difference in the course of the disease between men and women. For example, sex-specific immune characteristics drive more optimistic prognoses and gentler disease courses for women in auto-immune diseases such as Multiple Sclerosis and Systemic Lupus Erythematosus – even if the prevalence in women is higher. In Alzheimer's disease, sex is a major determinant of disease outcome, and a negative prognostic factor (*Cho et al., 2021*).

Due to the results of menopause-driven hormonal changes, ischemic heart disease appears in women on average a decade in life later than in men (*Keteepe-Arachi & Sharma, 2017*).

In female-specific diseases with limited treatment options, such as triple-negative breast cancer (TNBC), leveraging *in silico* methodologies may help in identifying predictive biomarkers of treatment efficacy (*Arulraj et al., 2023*). Modeling and simulations framework can be used to address this challenge, by integrating detailed biological mechanisms underlying the disease, while also simulating the effects of novel therapies. Predictive biomarkers are then selected to identify responders to these treatments, improving health care in such diseases. A recent study (*Jörg et al., 2022*) reports the use of a

Mathematical models can be leveraged to describe disease mechanisms including factors related to women physiology.

mathematical modeling framework to quantitatively analyze and predict the progression of osteoporosis in postmenopausal women, the most widespread type of osteoporosis. This model incorporates various factors, including the influence of estrogen, a sex hormone crucial for maintaining a healthy balance between bone-forming and bone-resorbing cells, this balance being disrupted after a rapid decline in estrogen levels. Furthermore, this modeling framework was used to simulate the efficacy of existing treatments and to optimize potential drug dosing regimens through their combination. The results suggest novel treatment combinations that could then be tested during clinical trials to reduce the risk of bone fracture.

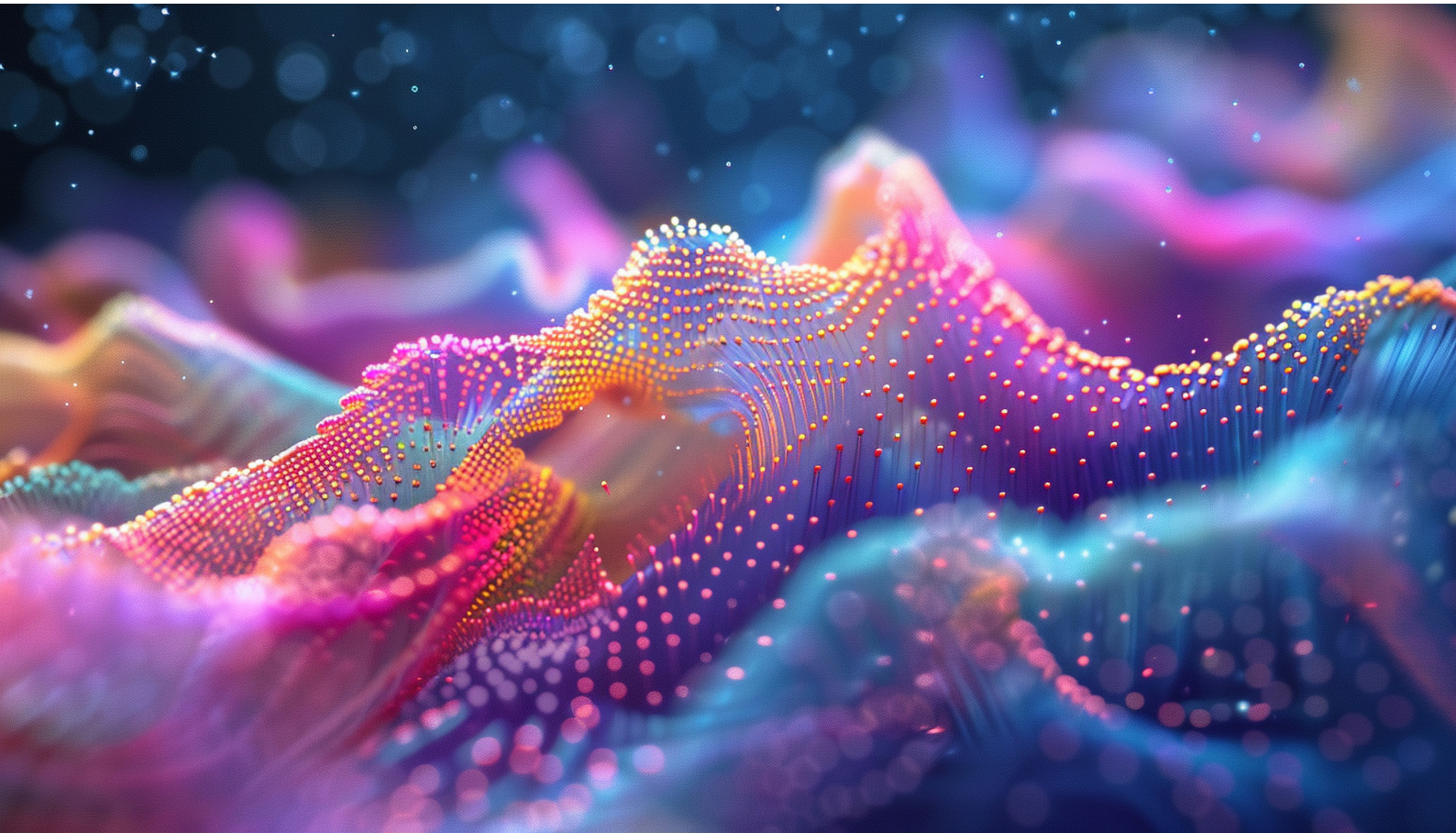
InSilicoTrials' Role

The critical role of data in robust, evidence-based analysis and decision-making cannot be overstated. Many epidemiological and clinical data sets currently in use fail to provide a complete picture of women's health, as they often undercount and undervalue the health burden faced by women.

When women's health is overlooked, it results in missed chances to enhance the well-being of those particularly in vulnerable populations.

A lack of comprehensive data leads to the potential underestimation of disease severity and health burden, influencing both the care that women receive and the level of innovation and investment in women's health. For instance, an emerging body of evidence indicates potential gender bias in the measurement of pain, where women's pain is routinely under-investigated and undertreated, with significant implications for clinical and psychological outcomes. Collectively, these incomplete data sets can influence decision-making and have the potential to exacerbate the women's health gap (*Ellingrud et al., 2024*).

InSilicoTrials, similar to how Spotify revolutionized music streaming, is pioneering the field of healthcare modeling and simulation. By offering a vast and diverse library of



advanced simulation tools on a cloud-based platform, InSilicoTrials enables pharmaceutical companies to accelerate their research and development processes.

This platform hosts a plethora of computational models developed by internationally recognized universities and research centers, allowing users to perform comprehensive *in silico* analyses, from preclinical assessments to clinical trial simulations. It integrates diverse modeling techniques, such as population pharmacokinetic/pharmacodynamic (PK/PD) models, physiologically-based pharmacokinetic (PBPK) models, mechanistic quantitative systems pharmacology (QSP) models, and agent-based models. By leveraging these advanced tools, InSilicoTrials facilitates the optimization of therapeutic strategies, particularly for female-specific conditions, and enhances the inclusion of women in clinical studies.

Integration and Analysis of Gender-Specific Data

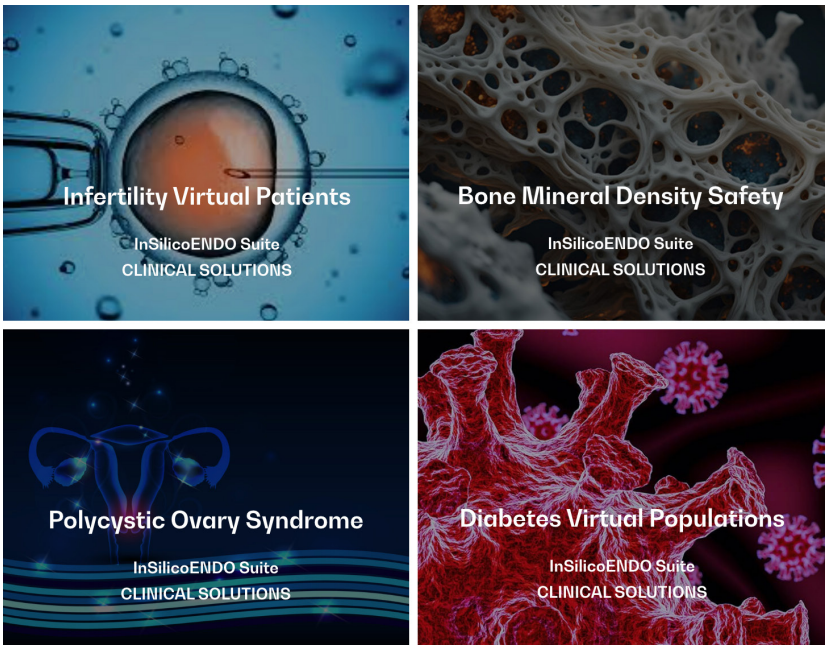
InSilicoTrials integrates gender-specific pharmacokinetic (PK) and pharmacodynamic (PD) data, allowing researchers to understand how drugs interact differently in female bodies. For example, physiologically based pharmacokinetic (PBPK) modeling integrates pregnancy-related anatomical and physiological changes to optimize clinical trial design and inform dose adjustments during pregnancy. This capability is critical for predicting fetal drug concentrations and maternal drug exposure during lactation. Furthermore, the use of QSP models describing the main mechanisms involved in a disease enables to include the specific physiology of women and leads to a better understanding of clinical outcomes. These types of models serve as tools to simulate and predict drug efficacy and toxicity in specific patient subpopulations, including women.

Improve Trial Design with Virtual Populations

One of the significant advantages of InSilicoTrials' platform is its ability to simulate virtual patient cohorts. These virtual patients are computational models representing diverse anatomical and physiological characteristics, allowing researchers to test hypotheses and refine trial designs before actual implementation. By simulating the inclusion of more women in clinical trials, the platform addresses the gender gap and ensures that the physiological differences of women are considered. This is crucial for conditions that affect women exclusively or differently than men, such as polycystic ovary syndrome (PCOS), breast cancer, and pregnancy-related health issues.

Optimization of Clinical Trials through Simulation

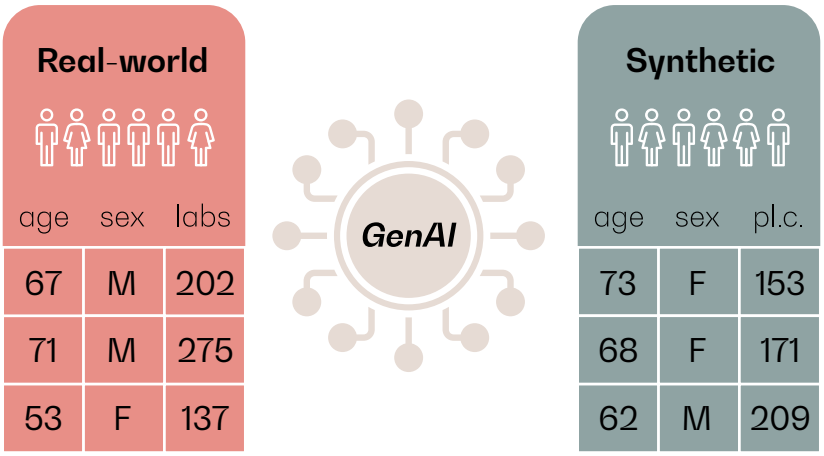
The platform's simulation tools optimize trial parameters such as dosage and treatment schedules tailored to female physiology. For instance, the InSilicoENDO suite includes models that simulate the female hormonal cycle and follicle growth, enabling the development of personalized fertility treatments. By incorporating these gender-specific parameters, InSilicoTrials can improve the efficiency and outcomes of clinical trials, ensuring that treatments are safe and effective for women.



Example of clinical solutions within the InSilicoENDO Suite available on InSilicoTrials' platform

Bridging the Gap in Data (through Synthetic Control Arms)

One of the innovative features of InSilicoTrials is the use of synthetic control arms to address the lack of female participants in clinical studies. By leveraging advanced modeling techniques and artificial intelligence (AI) methodologies, the platform can incorporate historical data and generative AI of placebo or standard-of-care to virtually augment the sample of women included in the control group of a clinical trial. This approach can support evidence of clinical effectiveness while reducing the size of the control group and therefore speeding up the enrollment, while providing relevant evidence on women's clinical response.



GenAI can be trained to encode the distribution of real-world data, without memorizing it exactly. Subsequently, samples can be drawn from the encoded distribution, effectively generating new, so-called synthetic data. In the context of healthcare, synthetic patients can allow to perform crucial data analysis while respecting real patients' privacy.

Supporting Regulatory Submission and Compliance

InSilicoTrials assists in preparing data and simulations for regulatory review, focusing on gender differences and modeling framework incorporating women's specificity. This support is crucial for the FDA, EMA and other regulatory body approvals, ensuring that treatments are validated for safety and efficacy in women. The platform's compliance with rigorous security standards ensures the integrity and confidentiality of the data used in these submissions.

InSilicoTrials is making significant strides in advancing women's health by leveraging virtual patient populations, optimizing clinical trials, integrating gender-specific data, supporting regulatory submissions, and bridging data gaps with synthetic control arms. These efforts ensure that women receive treatments that are safe, effective, and tailored to their unique physiological needs, ultimately leading to better health outcomes for women worldwide.

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