Predictive or *in silico* medicine is the use of individualised computer simulations in all aspects of the prevention, diagnosis and prognostic assessment of disease and development of treatments.

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About Avicenna Alliance

The Avicenna Alliance is an association of industry and research organisations who have a commercial or research interest in the development of in silico medicine.

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The Alliance, established in 2016, has its origins in the Virtual Physiological Human Initiative, a European Commission endorsed research area on computer modelling and simulation. Tasked by the European Commission with developing a “Roadmap for in silico medicine”, the Alliance now seeks to put this roadmap into policy and ensure the development of a well-functioning framework for the in silico medicine ecosystem.

This Alliance bridges the gap between the scientific community, industry and policymakers by advocating for policy changes that take scientific and market developments into account.
Foreword

Forword by Thierry Marchal, Secretary General of the Avicenna Alliance

Today in healthcare we are held back by the comfort of “familiar uncertainty”. We know that our current models of healthcare do not do enough to guarantee patient safety. We know they do not go far enough to ensure we only fund the most effective treatments. Yet we have become familiar with these models and so have done little to challenge them.

Rising co-morbidities, global health epidemics and the challenges of an ageing population are forcing us out of our comfort zone and so once again, necessity is the mother of all invention. Complexity is the one trait that all of the healthcare challenges we face have in common and what we need is a means of understanding it. Computer modelling and simulation (CM&S) is the means by which we can turn vast quantities of data into actionable information we can use.

What can CM&S accomplish? Nothing short of redefining terms like ‘patient safety’, ‘efficacy’ and ‘cost effectiveness’ by forever raising the quality of data needed to meet high standards.

To do this we need to demonstrate what can be already done to give an idea of what we could do in future with the right regulator support and uptake across the healthcare sector.

The case studies in this document give but a glimpse of the potential that has yet to be unleashed by modelling and simulation.

I would like to thank our members for contributing these examples so that others may now ask the all important question – “how could computer modelling and simulation help my work?”

Thierry Marchal

Secretary General Avicenna Alliance
Using Modeling and Simulation to Establish Safety of the Metallic Passive Implants in MRI Scanners

The MRI scanner environment (Fig. 1) may pose risks to patients implanted with certain devices due to Radio-frequency (RF) induced heating. To mitigate this risk, the FDA requires the device makers to provide safety labeling for their devices. The RF heating safety labeling parameters are primary identified by performing ASTM F2182 test standard. For Multi-configuration devices, such as spinal implants, billions of configurations (Figure 2) are possible and identifying the worst-case through testing is impractical. Since 2012, FDA has recommended the device makers to use computational modeling to simulate RF heating in a digital ASTM F2182 and identify the worst performing (highest heat). In 2014, DePuy Synthes Spine of Johnson & Johnson began developing a computational model replica of ASTM F2182 (Figure 3) to determine the RF induced temperature rise in an ASTM F2182 Phantom. We followed the guidance documents developed by the FDA for, identifying the worst-case device in a multconfiguration system and the reporting of modeling and simulation and by implementing the ASME V&V40 standard (Figure 4) to show our model’s credibility. DePuy Synthes Spine received MR conditional labeling 510(k) clearance using these documents. Modeling and simulation was the primary source of data generation in these submission. Additionally, we used Ansys Virtual Human Model (Figure 5) with bioheat activation to provide more clinically relevant prediction about the device heating risk (Figures 6, 7), in our subsequent submissions. Those submissions were also accepted by the FDA. Currently, DePuy Synthes Spine can save significant amount of time and cost by providing digital evidence for regulatory submissions. An RF heating in an ASTM F2182 simulation could be completed in a few hours, whereas a test could take between 2 to 4 weeks. The cost of each test is also significantly higher than the cost of simulation.
Figure 2. Possible Number of Configurations

<table>
<thead>
<tr>
<th>Component</th>
<th>Parameter</th>
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<tbody>
<tr>
<td>Plate</td>
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$209 \times 10^{21}$ Configurations

Figure 3. ASTM F2182 Simulation Exemplar

Figure 4. Standards Guiding the Simulation Workflow and Documentation

- *Assessment of Radiofrequency-Induced Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices*
- *Guidance for Industry and Food and Drug Administration Staff*

- *Reporting of Computational Modeling Studies in Medical Device Submissions*
- *Guidance for Industry and Food and Drug Administration Staff*

- *Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices*

- *ASME V\&V 40-2018*
Figure 5. Virtual Human Model

Figure 6. Virtual Human Model in RF Coil

Figure 7. Virtual Human Model in RF Coil
Enabling early approval through a smarter approach to generating robust clinical evidence

KerusCloud is a ground-breaking new clinical study design and analytics software platform which delivers more intelligent real-time studies for today’s clinical research challenges.

The Challenge

1. C. difficile (CDI) is the most common single organism causing associated healthcare infections. In vulnerable patients, CDI infections have high mortality rates, ~30% for severe CDI and ~40% in elderly patients, yet there is currently no available approved treatment.

2. A new antibacterial treatment for CDI was developed by a small company with limited resources which was seeking early access for patients via the Breakthrough Therapy process in the US and the Medicines Adaptive Pathways for Patients (MAPPs) in the EU.

3. A previous study assessment indicated that the development programme for this new antibacterial agent would need ~1000 patients. This development plan was impractical and could not be executed.

4. How could evidence be generated to support rapid marketing authorisation?

The Approach

KerusCloud used information from published scientific literature and experts to simulate hundreds of studies to determine the best strategy for generating an evidence package for rapid approval.

This approach included collecting data on multiple correlated measurements comprising clinical and pharmacodynamic endpoints as well as baseline risk factors.

The impact of study design parameters on trial outcomes (cost, duration and probability of success) was then assessed rapidly in silico, allowing the company to select a feasible design with high chance of success.

Design options and simulated evidence were presented to the FDA and EMEA as part of a scientific advice procedure.
The Impact

KerusCloud helped to progress a new antibacterial treatment option to patients that will hopefully go on to save lives.

KerusCloud helped:

- Identifying the best design and endpoints for the study.
- Showing that an initial evidence package could be generated using 180 patients rather than 1000.
- Potentially saving the sponsor £18M and reducing the time to market by 3-5 years.
- Providing evidence that Regulators agreed would likely be sufficient for approval.
The Challenge

1. EU and US regulators are interested in enabling early access to novel treatments for patients with severe unmet need. In the EU, the Medicines Adaptive Pathways for Patients (MAPPS) is an initiative looking at ways to enable early access, such as:

- Flexible development and access pathways within the current regulatory framework that balance early patient access, public health and societal benefits.
- Early authorisation of a product-focused on a well-defined and targeted population with a clear safety and efficacy profile focused on a well-defined and targeted population.

2. In collaboration with NICE, MIT and NEWDIGS, Exploristics examined how the MAPPS could be applied in development, evaluating the benefits and risks of a treatment, and the commercial impact of this on the treatment.

The Approach

Information on a marketed treatment for relapsing Multiple Sclerosis (MS) was used to provide realistic data for a case study on MAPPS.

KerusCloud is a ground-breaking new clinical study design and analytics software platform which delivers smarter real-time studies for today’s clinical research challenges.
Exploristics designed an alternative MAPP development plan from the perspective of the forward-looking team to:

- Identify a higher benefit sub-population for early authorisation and real-world evidence collection comprised of moderate & severe (M&S) patients.
- Continue to develop the All-comers indication with no launch delay.

KerusCloud simulated drug development scenarios using information and assumptions from the approved drug. This approach used therapeutic and study conduct information derived from public sources, additional information from the MS literature.

Quantified sample-sizes and probability of success values from KerusCloud enabled economic modelling of the impact of MAPPs for Patients, Payers and Sponsors.

**The Impact**

The case study broadly supported the MAPPs approach with KerusCloud demonstrating that:

- The MAPPs design would provide sufficient evidence for approval in a larger Phase II trial.
- The Phase II trial would need to randomise 450 patients rather than 240 in the original design.

- Initial approval would be in five rather than eight years.
- Providing access for patients up to three years earlier.
- MAPPs was beneficial for developer and payer economics, with an increased expected Net Present Value (eNPV) of $600M rather than $460M for the sponsor.
Enabling early approval through a smarter approach to generating robust clinical evidence

Modeling and Simulation Platform Mimesis

The costs of research and development of new drugs are growing exponentially. According to a study by Tufts Center today it takes between ten and twelve years and 2.5 billion dollars to develop and take to the market a new drug. Companies must therefore find ways to reduce drug development costs by maintaining and improving their safety, and in silico methods represent one of the best opportunities.

MIMESIS provides to the biomedical industry the first generation of in silico solutions for the evaluation of safety and efficacy of medicinal products. Mimesis applies the power of computerized simulations to the pharmaceutical sector, allowing its customers to carry out “in silico” tests i.e., to reproduce structural-chemical-biological phenomena through a computer-based mathematical simulation.

MIMESIS revolves around a technological core of personalized (patient-specific) simulation of the human immune system, providing the Universal Immune System Simulator for Tuberculosis (UISS-TB) able to produce in silico predictions of the dose-response curve from new therapies for active tuberculosis in a reference population of adults affected by the Mycobacterium tuberculosis (MTB).

UISS-TB provides a reduction on the size and the duration of the human TB clinical trials. UISS-TB can be used as a conclusive evidence and as a partial replacement of the phase III clinical trial, including a mean to increase the confidence in investing in a phase III trial to demonstrate the efficacy in term of reduced recurrence. Moreover, UISS-TB optimize human clinical trials design, through the adjustment of the dosage and the timing of the treatments to maximize the chances of success.

We expect to have the EMA qualification for the pharmacodynamics of tuberculosis therapies in 2020.

Social innovation of MIMESIS consists in the demonstration that “in silico trials” are useful not only to identify new drugs, but most importantly they become essential to predict clinically-relevant adverse reactions of new developed drugs. According to this scenario, MIMESIS gives a relevant contribute to healthcare systems by offering a new path to protect public health and alleviate the disease burden and costs for society that can derive from unexpected adverse reactions of new drugs.
To date, there is still no curative treatment for chronic hepatitis B. The last few years have seen an increased interest for the combination of antiviral therapies with the common objective of increasing the rate of HBV eradication.

We used computational modeling to improve the design, dosage, timing, and patient selection for combination therapies based on EYP001 treatment. An in silico disease model of chronic HBV patients has been built based on public and expert knowledge, non-clinical, and clinical data.

The computational model is a system of differential equations that integrates 300+ biological variables and 800+ parameters. With 8 mechanistic submodels (Figure 1), the model has been used to predict quantitative efficacy of treatments on disease-related endpoints (e.g., plasma HBV DNA and HBsAg concentrations) in a virtual population, in order to explore the effects of multiple combinations of EYP001 (“EYP”) with Entecavir (“ETV”) and/or Pegylated interferon alfa-2a (“IFN”) therapies.

The virtual population and exploration tools were used to calibrate the model: 1,000 virtual patients were generated by randomly sampling from a set distribution for each patient descriptors and were selected on the basis of the score translating physiological and biological constraints that the model should comply with, as well as data from Phase I studies.
Figure 2: HBV DNA levels in plasma (log10 (copies/mL)) after 24 weeks of treatment and 24 weeks of follow-up. Comparison of control (EYP001 QD 400mg) with ETV + EYP and IFN + EYP bitherapies and EYP + IFN + ETV tritherapy.

Figure 3: HBsAg levels in plasma (log10 (copies/mL)) after 24 weeks of treatment and 24 weeks of follow-up. Comparison of control (EYP001 QD 400mg) with ETV + EYP and IFN + EYP bitherapies and EYP + IFN + ETV tritherapy.

- In silico Phase II trial simulations allowed us to identify the 24-week bi-therapy of EYP001 and PEG-IFNα2a as the best combination in reducing plasma HBV DNA and HBsAg levels, and in minimizing relapse after a 24 weeks follow-up period (Figures 2 and 3). The percentage of relapsing patients 2 months after the end of 24 weeks treatment was 26.5% for the bitherapy with EYP001 QD 400mg and PEG-IFNα2a, whereas it was of 94.2% for patients taking PEG-IFNα2a only, and 100% for the no treatment group.
- These simulated results will be quantitatively validated with data from upcoming Phase II studies.
- Results have been presented at the AASLD Liver meeting in Boston in November 2019.
CT-based patient-specific model to predict the risk of hip fracture

The use of state-of-the-art Biomechanics CT analysis (BCT) based on patient-specific computer models can reduce of 50% and more the number of patients to be enrolled in clinical trials of new drugs to reduce the risk of hip fracture in osteoporotic patients.

Result of 15 years of collaborative development between the Rizzoli Orthopaedic Institute, the Insigneo Institute for in silico Medicine, and the University of Bologna, the CT2S technology makes possible to predict with excellent accuracy the risk of hip fracture in an osteoporotic patient, starting from a Computed Tomography of the hip region. The CT-based model can predict the bone deformation under a given load with an accuracy of 96%, and the force required to fracture a human femur with an accuracy of 85%. When used in the clinical practice, the model is run dozens of times, each simulating a possible fall pattern, depending on the patient’s height and weight. This allow to evaluate the minimum femoral strength under realistic fall conditions, which is used as predictor of the risk of hip fracture.

When used to separate fractured and non-fractured patients in a clinical cohort of age, height, and weight matched osteoporotic women, the stratification accuracy is 83%. Compared to the clinical standard (bone densitometry) this is an improvement between 8 and 16% in accuracy. An improvement of 8% is enough to reduce the cohort size of bone drug clinical trials of more than 50%.

As the Secretariat of the Avicenna Alliance, RPP Group brings expert policy guidance to this revolutionary new field.

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