Avicenna

A strategy for *in silico* Clinical Trials

Background and Context
Aims and Achievements

The Consortium

Marco Viceconti

Insigneo Institute, The University of Sheffield, UK

Marco Viceconti is Professor of Biomechanics in the Department of Mechanical Engineering at the University of Sheffield and Professor Associate at the Department of Human Metabolism. He is the Scientific Director of Sheffield University's Insigneo Institute for *in silico* Medicine, a joint initiative between the University of Sheffield and the Sheffield Teaching Hospital NHS Foundation Trust.

Adriano Henney

OBSIDIAN Biomedical Consulting Ltd, UK

Adriano Henney, Director of Obsidian Biomedical Consulting Ltd (OBC), worked for 13 years in a top 5 multinational pharmaceutical company, before becoming the Programme Director of the German Virtual Liver Network, the largest VPH project currently running in Europe. Since 2010 Dr Henney, has directed this major German research programme focusing on modelling human liver physiology.

Edwin Morley-Fletcher

LYNKEUS srl, Italy

Edwin Morley-Fletcher is President of Lynkeus srl and has over 25 years experience in ebusiness. In the last 10 years he progressively focused on ICT for health, managing some of the largest VPH projects, including MD-Paedigree, one of the three IPs funded in call 9.

Martina Contin

VPH Institute, Belgium

Martina Contin worked as communication manager in various VPH initiatives, before taking the helm of the not-for-profit organisation that coordinates all VPH research worldwide. The organisation aims to ensure the VPH is fully realised, universally adopted and effectively used.

Karen El-Arifi

Sheffield University, UK

Karen El-Arifi is the Project Manager of the Avicenna project. She has a scientific background in Genetics and Epidemiology and works in the Project Management Office (PMO) of the Insigneo Institute for *in silico* Medicine at the University of Sheffield.

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 611819

Welcome

Avicenna: A strategy for *in silico* Clinical Trials, is a roadmap initiative funded by the European Commission (EC) which began in October 2013 and runs till September 2015. The project is co-ordinated by the University of Sheffield and the consortium includes three partners – the VPH Institute, Lynkeus srl and Obsidian Biomedical Consulting Ltd.

This consortium is proud to have been selected as facilitators for the challenging process of drafting the roadmap for the introduction of *in silico* Clinical Trials. Around a shared vision, the Avicenna project will develop and promote this roadmap, and work to overcome the legal, financial, organisational and technical barriers that could slow the adoption of computer simulation in this domain.

The Avicenna Consortium
February 2015

Avicenna

Avicenna was a Persian physician and philosopher (980-1037) who first gave a formal structure to the process of evaluating the effect of a treatment on a disease in his most famous work, the Canon of Medicine, by introducing systematic experimentation and quantification of the study of physiology and the introduction of experimental medicine, clinical trials, randomised controlled trials and efficacy tests. The fundamental nature of clinical trials remains essentially unchanged.

The birth of *in silico* medicine at the beginning of the 21st century, showed the possibility of a completely new way to investigate living organisms: using computer simulations to diagnose, treat, or prevent disease through the modelling, simulation and visualisation of biological and medical processes. It is based on the use of Virtual Physiological Human (VPH) models, which aim to integrate physiological processes across different scales (multi-scale modelling) to provide improved predictive and individualised healthcare.

in silico medicine will reduce the cost and risk (both clinical & financial) involved in clinical trials

What are clinical trials?

Currently, new medical treatments, drugs and devices to be distributed commercially undergo a development and assessment process. Initially, these tests take place *in vitro* – in a test system, and/or *in vivo* – trials in living organisms and on animal models, but the only way to ensure the safety and efficacy of a biomedical product conclusively is to test it in humans.

Clinical trials usually follow three phases: phase I, where the product is tested on a small group of patients or healthy volunteers under very controlled conditions, in order to ensure that the product can be used safely without any unexpected side effects; phase II, where the product is tested on a larger group of patients, in order to verify if the product is effective, i.e. it produces in those patients the beneficial effect that is expected; and phase III, where the product is distributed to a much larger group of patients, in multiple hospitals and possibly in multiple countries, to evaluate the product in a much larger patient community, reflecting the population at large, to see whether any less frequent, unexpected safety or efficacy problems emerge.

Due to the huge complexity of human pathophysiology and other variations, it is not unusual to find a product that performs exceptionally well in tightly controlled laboratory tests that shows some serious problems during clinical trials. When a product fails late in the process, for example at the end of a phase II or even phase III clinical trial, the financial loss for the company is huge.

What are *in silico* Clinical Trials and what are their benefits?

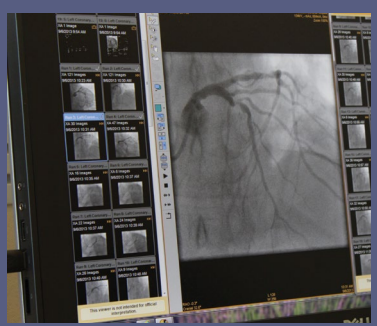
In silico Clinical Trials (ISCT) are computer modelling and simulation procedures, where the computer model of a treatment is applied to a collection of computer models, each simulating the pathophysiology of individual patients to predict the response of that patient to that treatment, in terms of efficacy and safety.

Computer Modelling and Simulation (CM&S) is often used in other industries during development and assessment. It is likely that CM&S could be used for biomedical products.

In addition to *in vitro* and *in vivo* studies, biomedical products could be tested by *in silico* methods, through computer simulation.

CM&S is already being used in the development of biomedical products. Pharmaceutical companies use computer models to estimate the pharmacokinetics (the fate of substances administered externally to a living organism) and the pharmacodynamics (biochemical and physiological effects of drugs on the body) of a new compound; medical device companies use computational fluid dynamics to predict how blood or other bodily fluids move inside and around the new device being tested, or structural finite element analysis to make sure that the forces exchanged between the body and the device will not damage one another.

While these CM&S technologies are essential, current *in silico* technologies struggle to help address a number of very difficult questions in the development of a biomedical product, such as: why do only some patients react adversely to the drug, while others are fine? Why is it that blood clots form around the



device in only a few patients, while in others it does not? What is missing is the ability to assess the individual determinants of this variability, for example by:

Using a computer model of the patient to take account of his/her particular physiology, the individual manifestation of the disease being treated, his/her life style, the presence of co-morbidities, etc.;

Using a computer model of the treatment, which accounts for the compliance, or lack thereof, in

taking the drug at the times and dose prescribed; or in the case of a surgically implanted device, to account for the variability between surgeons implanting a device because of surgical experience, technique, the particular anatomy of the patient, etc.

If we could develop accurate computer models of the treatment and its deployment, together with accurate computer models reflecting different patients, *in silico* clinical trials could be used to simulate a number of elements affected by the administration of the biomedical product. Models of many individual patients are treated with the model of the treatment, allowing us to observe through a computer simulation how the product performs and whether it produces the intended effect, without inducing adverse effects that might be potentially dangerous for the patient. We believe that *in silico* clinical trials could help to reduce, refine, and partially replace real clinical trials:

ISCT could reduce the size and duration of clinical trials by identifying characteristics to distinguish patients who might be at greater risk of complications and designing the trial to avoid this, or providing ways to confirm earlier that the product is working as expected, reducing the duration of the trial.

ISCT could refine clinical trials by improving the design through a much clearer knowledge framework and providing greater explanatory power to interpret any adverse observations that might emerge during the trial. ISCT can also be used to improve understanding of how the product interacts with individual patient anatomy, predicting long term or rare effects that clinical trials are unlikely to reveal.

ISCT could partially replace clinical trials in those situations where the clinical trial is not an absolute regulatory necessity, but only a legal requirement. We already have examples where regulators have accepted the replacement of animal models with *in silico* models under appropriate conditions. While real clinical trials will remain essential in most cases, there are specific situations where it is conceivable that a reliable predictive model can replace a routine clinical assessment.

The process would involve the generation of computer models for each patient enrolled in a trial that simulate patient pathophysiology, the treatment under test, and that predict the outcome, possibly undertaken alongside, or as part of an existing clinical trial. The predictive accuracy of these models can then be tested against the observations produced by the parallel clinical trial. Once this process is repeated for a

sufficiently large number of patients, we will have a library of virtual patients, which can be used to test another treatment *in silico*, whether for a different product or a refinement of an existing one. These simulations can first be used to develop the new product, and then to complement and refine the real clinical trial for a new product.

The addition of *in silico* trials could bring many benefits. ISCT will be faster, cheaper and safer than traditional clinical trials: by simulating the effects of biomedical products on large numbers of virtual patients, trials will not only be improved, but the door will be opened to *in silico* drug and device development; the key step identified by the EC as being required to support increased competitiveness for European industry.

Avicenna's Ambition

The project will define the grand challenges to make *in silico* Clinical Trials a reality. It will:

Community of Practice

Create a Community of Practice (CoP) between biomedical industries and European research organisations, with the purpose of developing the technology, methods, protocols and standards required in order to make possible the use of computer simulations before real clinical trials. Avicenna will foster collaboration between pharmaceutical, biotechnology, medical device, technology, clinical, academic and regulatory organisations, and lead to pre-competitive collaboration to jump-start drug discovery and development.

Roadmap

Build consensus among the CoP to create a Roadmap for how we can begin to systematically explore the manner in which computer simulations can be used to improve clinical trials of drugs, devices and biotechnology products using *in silico* medicine. Applying such a Roadmap can reduce costs and risks and ultimately increase the rate of innovation in healthcare.

Consensus

Build consensus on the conditions that are needed to allow this CoP to continue after the end of Avicenna.

Community of Practice

Avicenna aims to establish a partnership between biomedical industries and European research organisations to develop the technology, methods, protocols and standards required to enable the use of computer simulations within the clinical trials process. By defining a common approach to high quality, cutting-edge collaborative research in computer-based biomedical product development, Avicenna will foster collaboration between pharmaceutical, biotechnology, medical device, technology, clinical, academic and regulatory organisations and promote the formation of pre-competitive alliances to jump-start drug discovery and development.

The fact that biomedical products are heavily regulated reinforces a conservative attitude in the industrial sector. As a result, the cost of developing and assessing new products has been steadily increasing, and the rate of effective innovation has been decreasing. In other industrial sectors, where similar trends were observed, the optimum approach to keeping the cost and complexity of safe product development at bay has been computer simulation or Virtual Product Development (VPD). The adoption of VPD in the development of biomedical products has, so far, been frustratingly slow. Recent results from the use of Virtual Physiological Human (VPH) models, the progressive expansion of *in silico* methods in the design phase, and the extension of the VPH approach to animal models suggests a new approach to biomedical product development that we refer to as *in silico* clinical trials.

Avicenna aims to engage key stakeholders in a consensus process that will identify the primary scientific, technological, and methodological barriers that hinder the widespread adoption of *in silico* clinical trials, and promote a pre-competitive alliance amongst them to overcome such obstacles.

Development of the Alliance

What has emerged from the work done by Avicenna during this first year of activities is that there is already a significant amount of industrial interest in this concept and a huge potential for innovation and economic growth, which strongly justifies the activities towards the development of a precompetitive alliance.

Preparatory phase

A number of existing pre-competitive alliances in the pharma/biomedical field have been identified and analysed to create a repository of case studies. These case studies were used to investigate their: legal status and possible legal issues, internal structures, level of outreach and membership types, possible outputs and duration. Among the different structures, the Public Private Partnerships (PPP) was identified as a possible vehicle for the Avicenna goal: A consortium of industries select the research topics of greatest interest and award grants to consortia between companies and research organisations. The funding for each company is mostly provided internally, and for research organisations is provided by the EC.

First steps

After meetings with the EC, the Avicenna consortium adopted the following strategy:

Value Proposition: The consortium drafted a document: "Value proposition for the formation of a Public Private Partnership (PPP) on Patient-Specific Modelling (PSM) for the development and assessment of biomedical products".

Letters of Support: A cohort of companies was selected and requested to express their interest, formalised into a Letter of Support.

Working Group: The results of this preliminary investigation were recently presented to the EC, which if accepted will form the basis of a working group.

Developing the Research Roadmap

The ultimate aim of Avicenna is to create a Roadmap for *in silico* Clinical Trials. Over the 18-month period to mid 2015 a series of events will be organised to develop the Avicenna roadmap using a consensus building process called Alignment Optimisation. Experts will be invited from various relevant domains to help us by participating in discussion. The Roadmap will summarise all the discussions and the views gathered during the different events. It will ultimately be used by the EC as a guide for future investments.

Avicenna provides a chance for experts to broaden their horizons, and develop a collegial vision driven by the real needs of the industry - and of society at large - strong enough to impose a research funding allocation that is truly innovative, and that will lead to a significantly positive socio-economic impact. The roadmap will describe the route by which *in silico* techniques of computer simulation will be introduced into clinical trials, the studies that are routinely conducted to establish the safety and efficacy of new medical interventions. Over the length of the project till mid-2015 we are inviting experts and stakeholders from various relevant domains to help us by participating in discussions at a series of events. The Avicenna project will act as facilitator for the challenging process of drafting the roadmap for the introduction of *in silico* clinical trials. Around a shared vision, Avicenna will develop and promote this roadmap, and work to overcome the legal, financial, organisational and technical barriers that could slow the adoption of computer simulation in this domain.

Industrial Engagement, embracing those commercial interests, both large and small, that have a part to play in the clinical trials process is an essential part on the route towards the Roadmap. Key topics and areas that have emerged from our earliest discussions with industrial stakeholders have been identified, and this material was fed into the first Avicenna Event. Since then, there has been an expansion and refinement of our understanding of the industrial stakeholder landscape. This has also sought to engage the well-informed participants for each of the participating sectors beyond “industry”, to include academia, and regulatory authorities as an example. Our approach, Alignment Optimisation (AO) involves the acquisition of information and

opinions through a three-stage process, involving on-line opinion surveys, followed by analysis and alignment of the opinions generated.

AO has recently emerged as a prevalent concept, describing a crowd-sourcing knowledge discovery process and the quest for a convergence of viewpoints. Optimisation is brought about through the repeated operation of Future Mapping and Alignment Cycles, in which an identified process is rigorously executed in order to maximise the input from participants. This approach involves systems thinking - the recognition that many factors may combine in complex ways to create sometimes surprising futures (due to non-linear feedback loops), allowing the inclusion of factors that are difficult to formalise, such as novel insights about the future, deep shifts in technology, unprecedented regulations or inventions. Avicenna has used experts from SchellingPoint LLC1 (http://www.schellingpoint.com) to conduct Alignment Cycles before each event and achieve consensus among participants. These sessions were used to extract knowledge and points of view from the users that was then analysed and fed into the agendas for the physical events. There is direct continuity of the information generated, with the output from each Event being carried forward to inform the discussion of the subsequent event.

Who are the authors and editors or the Roadmap?

Avicenna's ambition is to bring around the table a broad range of stakeholders or representatives from the biomedical industries, researchers, developers of computational technologies and regulatory agencies, in order to cultivate consensus and develop and agree a research and technological development strategy and a pre-competitive reflection of what in silico methods can offer. It will also define where there are scientific, technological, or regulatory barriers that, if overcome would make the development of innovative biomedical products easier, faster and cheaper. As the initiative's organisers, we are inviting participation from all with an interest in this goal, in order to assemble the best possible far-sighted and comprehensive roadmap.

Different levels of participation are foreseen:

Author collaborator

Willing to help write/rewrite sections of the Roadmap – they will be acknowledged as a co-author of the Roadmap

Editor collaborator

Willing to help edit sections of the Roadmap – they will be acknowledged as a co-editor of the Roadmap

Reviewer collaborator

Willing to review and comment on the Roadmap – they will be acknowledged as a co-reviewer of the Roadmap

Avicenna Events

Event 1 - Trajectory, staging and goals

21st March 2014, Rome, Italy

Event 1 was designed to set out the skeleton roadmap and identify the range of topics that should be considered in later events. It started with a presentation on the background to Avicenna and ISCTs from Avicenna Coordinator, Marco Viceconti and was followed by an explanation from the SchellingPoint experts on the AO process.

The output from Event 1 contributed to establishing clarity over semantics and definitions associated with the term "*in silico* Clinical Trials" (ISCT), helping us to compile a lexicon of terminology that would underpin the design of the roadmap. The discussion also helped us to understand the current state of the art in clinical trials, where *in silico* technologies are being used, and which industrial sectors or stakeholders may have been omitted from our initial mapping exercises.

Following the initial "seeding" phase in Event 1 that began the first cycle of discussions, the process followed thereafter is an iterative one, using the AO techniques before and after each event to feed information into the discussion and to refine the output from it. This approach offers a process of continuity carrying information from one discussion event to the next, at each point building on and refining what was learnt from the previous one.

Event 2 - Conceptual completeness

Held on 6th June, 2014 in Rome, Event 2 brought together 50 participants to discuss conceptual completeness and identify missing expertise. The sessions started with a presentation of the current practice of ISCT from Steve Chang from Immunometrics, Piet van der Graaf from the Academic Center for Drug Research (LACDR) - Leiden University, Jim Bosley from Clermont Bosley LLC and Dawn Bardot from The Medical Device Innovation Consortium. Following the discussion and analyses of Events 1 & 2, the sector map and contact list were updated, as well as a more complete view of the position of *in silico* approaches across the full R&D value chain, as opposed to just the clinical trials element.

Event 3 – Integration

The third Avicenna Event on 31st October, 2014 in Lyon, France established the interactions required for success. The group of 50 stakeholder experts discussed the research challenges of modelling and simulation technologies, in the development of pharmaceutical products and medical devices. The day began with presentations on the research challenges related to *in silico* clinical trials in pharma and devices. Each presentation was followed by a lively question and answer session. A series of brainstorming sessions followed, in which attendees were asked to identify the research priorities related to their specific areas of expertise. Their conclusions will be used to form recommendations to the EC and other funding agencies.

Event 4 - Component development

Event 4 takes place on 19th and 20th February 2015 in Brussels, Belgium. It deconstructs the Avicenna Strategy into its components and develops the draft Roadmap. A selected group of authors and editors will come together to work on different sections of the Roadmap.

Event 5 - Strategy for continuation

The fifth event takes place in summer 2015. This event will highlight the major outcomes of all previous sessions, identify remaining areas of work to be progressed and agree a strategy for the continuation of Avicenna's work, after the end of the project in September 2014.

Who are the Stakeholders?

The different stakeholders have diverse viewpoints and motivations, but they all have crucial contributions to make to the Avicenna roadmap:

Biomedical Sector

Biomedical Industries

- Biopharmaceutical industries
- Medical devices industries
- Health technology industry
- Diagnostics industry

Biomedical Research Organisations
Research Hospitals
Contract Research Organisation
Regulatory Affairs Organisations
Patients Organisations
Healthcare Provision Organisations

Virtual Product Development

Hardware Manufacturers
Software Manufacturers
Consulting Firms
Computational Science & Engineering
Research Organisations

in silico Clinical Trials

Tools and services for in silico clinical trials
Data providers
in silico medicine research community
Bioinformatics
Systems Biology
Computational Physiology
Health informatics
Personal Health Systems
Computer Aided Medicine
Virtual Physiological Human

How will this help you?

Biomedical industry experts: Improve the rate of innovation, the time and cost to market and influence the research agenda at European level.
Biomedical researchers: Complement your wet-bench methods; manage the complexity; reduce and refine animal experimentation.
Clinical trials experts: Obtain better estimates of safety and efficacy; obtain outcome indicators earlier and more cheaply; reduce risk for patients.
Regulatory experts: Better rate of innovation with lower risk; ensure regulatory aspects are central in the development of *in silico* clinical trials.
Patient representatives: Better & faster innovation, more personalised products, better treatments for rare diseases, lower risk in clinical trials.
Healthcare providers: Develop more products, better products and cheaper products with better evidence of efficacy and safety.

Conclusion

The objectives of the Avicenna project are to:

- Develop a community of practice, across the EU, of individuals and organisations who are interested in expanding the use of *in silico* medicine approaches in the development and assessment of biomedical products - *in silico* Clinical Trials.
- Write a roadmap that is informed by industry and other stakeholders that defines the research work that needs to be done for ISCT to become widespread.
- Create a pre-competitive alliance that will pursue the implementation of the roadmap beyond the end of Avicenna, possibly in the form of an institutional Private and Public Partnership (PPP) to drive ISCTs.

Computerisation contributes to many aspects of the drug and device discovery and development process, especially by identifying promising compounds for further exploration. For many device designers their working methods already involve the use of computer-aided techniques and, increasingly, anatomically-informed individualisation has contributed to the understanding and refinement of the product development process. *in silico* Clinical Trials (ISCTs) can play an important role in almost every step of pre-clinical assessment, both for moderately or radically innovative products. Where innovation is moderate, ISCT can reduce the number of trial-and-error cycles required to optimise the product or its deployment. For radically innovative products it could drastically reduce the return on the investment threshold, below which the development of the product would not be cost-effective. By reducing the cost, the time to market, and the associated risks, ISCT can dramatically reduce the barriers to innovation, especially for SMEs.

www.avicenna-isct.org

For information about the alliance contact:

Martina Contin
Virtual Physiological Human Institute
for Integrative Biomedical Research
manager@vph-institute.org