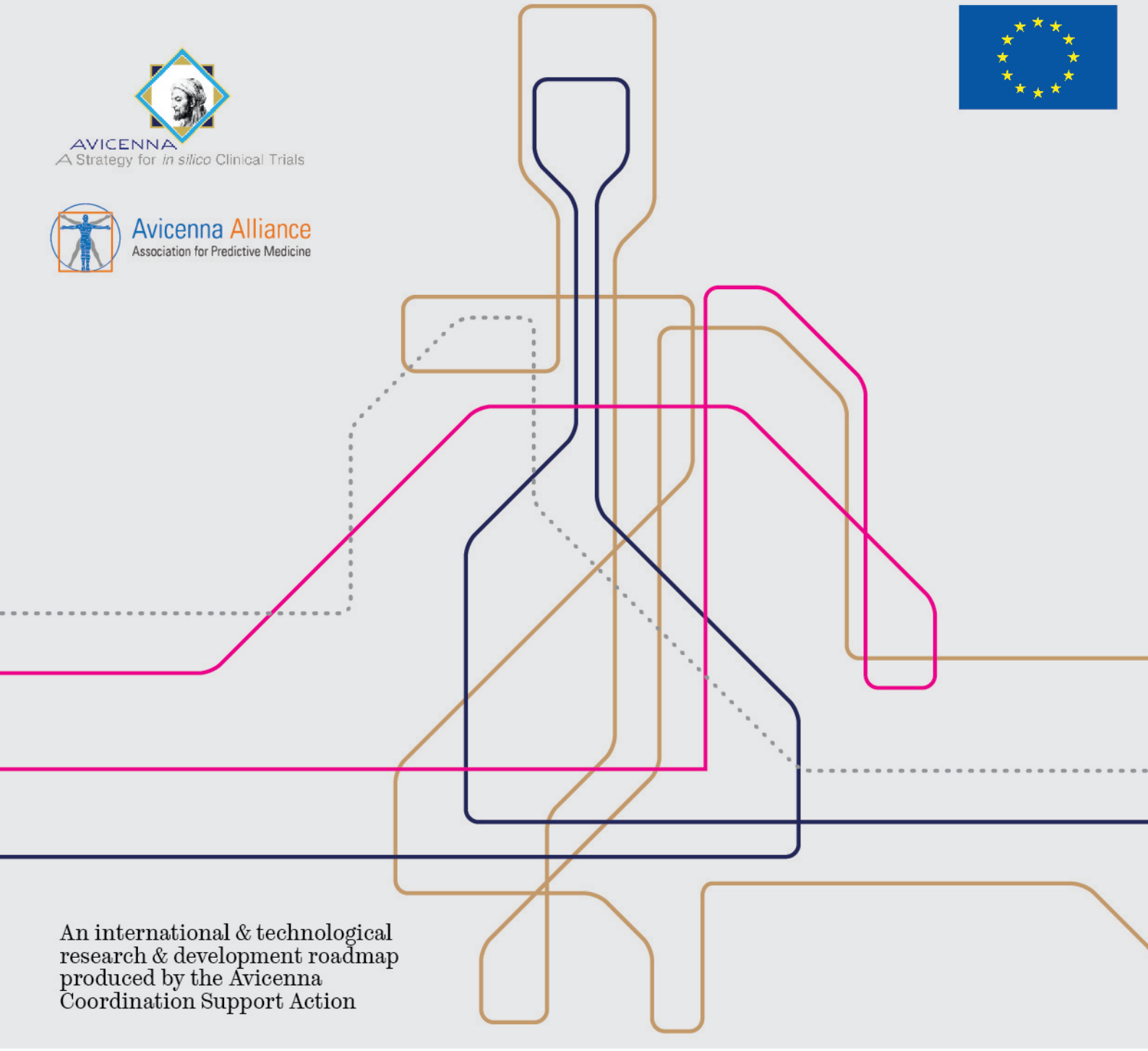

AVICENNA
A Strategy for *in silico* Clinical Trials

Avicenna Alliance
Association for Predictive Medicine

An international & technological research & development roadmap produced by the Avicenna Coordination Support Action

in silico Clinical Trials:

How Computer Simulations will Transform the Biomedical Industry

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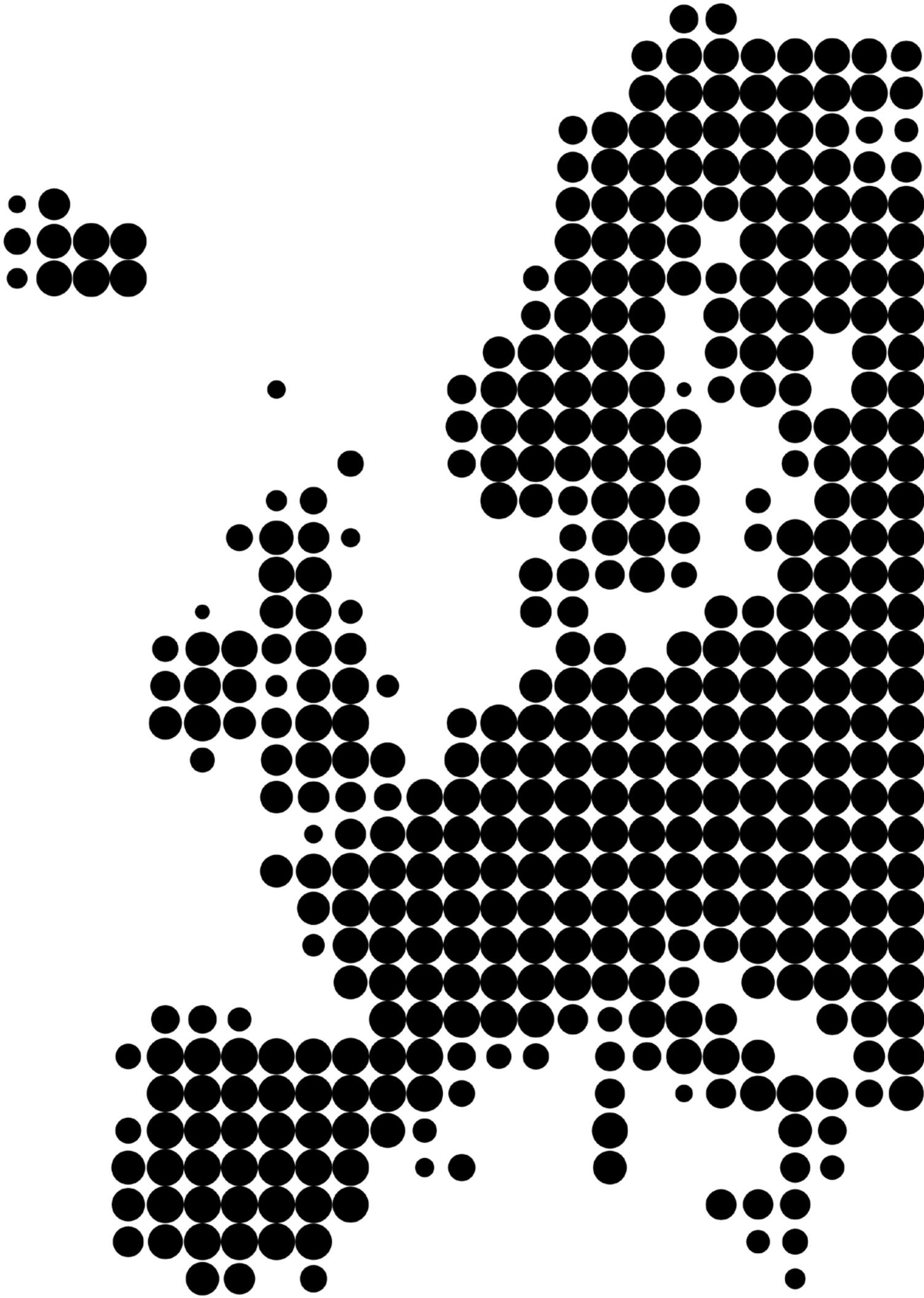

Layout: T. Robjohns (University of Sheffield)
Printed by: Print & Design Solutions, University of Sheffield

in silico Clinical Trials:

How Computer Simulation will Transform the Biomedical Industry

General Index

Reading Guide

As it evolved, the Avicenna Research and Technological Development Roadmap became a very large document, which was intended to serve multiple purposes, and inform multiple categories of stakeholders. To facilitate the reading, it was decided to divide it into 11 independent chapters, each a stand-alone document, but at the same time part of multiple reading trajectories:

EC reviewers, other organisations interested in similar roadmapping exercises: **I-XI**

Policy makers, research funding agencies, charities: **I, II, VII-X**

Industry executives: **Executive Summary, I, IV, X**

Pharma producers, research hospitals, CROs, consultants, regulators: **I, VI, IX, X**

Device producers, research hospitals, CROs, consultants, regulators: **I, V, VIII, X**

Patients' organisations: **I, II, IV, X**

Providers: **I, V-X**

Executive Summary

The term '*in silico* clinical trials' refers to: "The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention."

While computer simulation is widely used for the development and de-risking of a number of 'mission-critical' products such as civil aircraft, nuclear power plants, etc., biomedical product development and assessment is still predominantly founded on experimental rather than computer-simulated approaches. The need for long and complex experiments *in vitro*, on animals, and then on patients during clinical trials pushes development costs to unsustainable levels, stifling innovation, and driving the cost of healthcare provision to unprecedented levels.

The Avicenna Action, funded by the European Commission, has engaged 525 experts from 35 countries, including 22 of the 28 members of the European Union, in an 18-month consensus process, to produce this research and technological development roadmap.

This document provides an overview of how biomedical products are developed today, where *in silico* clinical trials technologies are already used, and where else they could be used. From the identification of the barriers that prevent wider adoption, we derived a detailed list of research and technological challenges that require pre-competitive funding to be overcome.

We recommend that the European Commission, and all other international and national research funding agencies, include these research targets among their priorities, allocating significant resources to support approaches that could result in huge socioeconomic benefit.

We also recommend industrial and academic stakeholders explore the formation of a pre-competitive alliance to coordinate and implement public and privately funded research on this topic.

Last, but not least, we recommend that regulatory bodies across the world embrace innovation and, in collaboration with academic and industrial experts, develop the framework of standards, protocols, and shared resources required to evaluate the safety and the efficacy of biomedical products using *in silico* clinical trials technologies.

Chapter I

In silico clinical trials: A layperson's introduction

Authors

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Summary

Chapter I provides an introductory description of *in silico* clinical trial technologies and the problems that they are expected to solve.

Any biomedical product[1] to be distributed commercially must undergo a development and assessment process before being placed on the market. The appropriate level of scrutiny and rigorous testing before commercialisation is of paramount importance, due to the risk of potential harm. In most cases, especially for products that fall into the higher risk classes, the producing company must demonstrate the efficacy of the product in healing or alleviating the effects of a disease or disability, as well as an acceptable safety profile, before any widespread use.

The only conclusive way to ensure the safety and efficacy of a biomedical product is to test it on humans. This is done through clinical assessment, which is usually carried out in three phases prior to the product reaching the market as well as during post-marketing surveillance:

- **Phase I.** The product is tested on a small group of patients or healthy volunteers under strictly controlled conditions, in order to ensure that it can be used safely.
- **Phase II.** The product is tested on a larger group of patients, in order to verify whether it is effective, and produces the expected effects (through direct indicators of efficacy, or simple proxy measures) in those patients.
- **Phase III.** The product is administered to a much larger group of patients, in multiple hospitals and possibly in multiple countries, to evaluate its efficacy on clinical outcomes in a much larger community, ideally reflecting the wider population, to further characterise its safety and efficacy profiles.
- **Post-marketing studies.** Following the successful completion of development studies and the approval of a new medicine, post-marketing studies are undertaken to continue to monitor the effectiveness and cost-efficiency of the drug in 'the real world'. That is necessary because typically phase II and III study populations are selected to optimise for demonstrating improvement over comparator treatments. These patient populations are very different from what is encountered in general practice in the wider treatment population, which is far more diverse in terms of, for example, disease severity, co-morbidities, multiple medications, and ethnicity. For this reason, post-marketing studies are undertaken to evaluate the efficacy and effectiveness of the medicine in the normal population and how it compares with other similar treatments already in use, in terms of population level benefit. These are important factors in assessing the cost/benefit of new treatments that require additional studies once the drug is on the market to address periodic re-assessment of efficacy and effectiveness often requested by regulators and payers.

By the time a clinical trial for a new product starts, the company will have already completed extensive testing using a series of laboratory experiments in what is called the pre-clinical evaluation period. Depending on the type of product, these tests can be done on a laboratory bench or in a mechanical testing frame, *in vitro* (literally meaning inside the glass), which may include looking at how a small culture of cells responds to the product; *ex vivo* (meaning out of the living organism, and used to indicate studies done on tissues or organs extracted from a body), for example inserting a medical device into a cadaver to verify that it can be safely implanted; or *in vivo* (meaning in the living) using animal models designed to mimic the human condition that the product is intended to treat.

The preclinical testing process represents an essential step in the development of any potential biomedical product. It is the means by which the fundamental basis for why a product might work is evaluated, and, hopefully confirmed. However, due to the hugely complex nature of human diseases, the significant differences between individuals, and the inevitable variability in how a treatment is administered, it is not unusual for a product to perform exceptionally well in tightly controlled laboratory tests, but show some serious problems during clinical trials. According to the Tufts Center for the Study of Drug Development[2], the development of a new pharmaceutical product, and its introduction into the market, is estimated to exceed US$2.5 billion, nearly 75% of which is spent in the various phases of clinical development. Every time a product fails late in the process, for example at the end of phase II or even phase III, the company suffers a huge loss.

Whilst clinical trials may tell us that a product is unsafe or ineffective, they rarely tell us why, or suggest how to improve it. As such, a product that fails during clinical trials may simply be abandoned, even if a small modification would solve the problem. This results in an 'all-or-nothing' mind-set in the biomedical industry, where the scope of the research and development investment virtually requires that a biomedical company focuses on reducing the risk of a potential product. This paradigm stifles innovation, decreasing the number of truly original biomedical products presented to the market every year, and at the same time increases the cost of development (which, paradoxically, further increases the risk). As a result, it is also becoming increasingly difficult for companies to undertake projects on rare diseases, since the associated costs cannot be justified against the limited return on investment, or the resulting sale prices are so high as to pose a challenge for universal healthcare systems.

> "Computer modelling and simulation is already being used in the development of biomedical products."

The biomedical industry is not the only technology sector that deals with highly complex and potentially critical

1 Hereinafter we will use the term biomedical product to indicate any product intended to prevent, alleviate, or cure any human disease. This includes pharmaceutical and biological products, as well as medical devices.

2 http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

systems. In other sectors, such as aerospace, computer/chip design, and nuclear industries, computer modelling and simulation is used extensively during both product development and assessment to overcome similar problems with mission-critical products. Can the same approach be used for biomedical products? In addition to traditional *in vitro* and *in vivo* studies, might we adopt a third way for developing and testing biomedical products by making use of this '*in silico*' technology? *In silico* is an allusion to the Latin phrases *in vitro* or *in situ*, and stands for computations carried out on a silicon computer chip.

Computer modelling and simulation is already being used in the development of biomedical products. Pharmaceutical companies use computer models to estimate the pharmacokinetics (the movement of a drug into, through, and out of the body) and the pharmacodynamics (the biochemical and physiological effects of the drug 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 device being tested, or structural finite element analysis to make sure that the forces exchanged between the body and the device will not cause any harm.

> "We believe that such ISCT could help to reduce, refine, and partially replace real clinical trials."

While these technologies are of great value, current *in silico* technologies struggle to help address a number of very difficult questions, including: Why do some patients react adversely to a drug, while others are fine? For instance: Why in a few patients, blood clots form around the device, while in most they do not? In short, what is missing is the ability to assess how potential biomedical products affect individual patients, who may have multiple variable factors that lead to the questions posed above. Some examples of how computer modelling and simulation can help to address this individual variability include:

- Using a computer model of the patient to take into account factors such as his/her particular physiology, the individual manifestation of the disease being treated, lifestyle, and the presence of other unrelated diseases.
- Using a computer model of the treatment to take into account the consequences of compliance, or lack thereof, on expected outcomes in taking the drug at the times and dose prescribed. Or, in the case of a surgically implanted device, to account for the variability in surgeons' experience and technique, as well as the particular anatomy and activity level of the patient.

If we could develop reliable computer models of the treatment (effect of the drug or device on the organism) and its deployment (administration of the drug or surgical procedure), together with reliable computer models of the patient's characteristics, we could perform exploratory trials within the computer: *in silico* clinical trials (ISCT). This would enable the simulation of a number of elements affected by the administration of the candidate biomedical product. In such a scenario, 'virtual' patients would be given a 'virtual' treatment, enabling 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 such ISCT could help to reduce, refine, and partially replace real clinical trials by:

- Reducing the size and the duration of clinical trials through better design, for example, by identifying characteristics to determine which patients might be at greater risk of complications or providing earlier confirmation that the product is working as expected. ISCTs might also be used to 'leverage' a smaller clinical trial population, by adding simulated patients that might fill gaps in the individual variability seen in 'real' patients. ISCT might also be able to determine those patients that will not respond to the candidate biomedical product. The removal of predicted non-responding patients would potentially improve the outcomes of the clinical trials.
- Refining clinical trials through clearer, more detailed information on potential outcomes and greater explanatory power in interpreting any adverse effects that might emerge, as well as better understanding how the tested product interacts with the individual patient anatomy and physiology, and predicting long-term or rare effects that clinical trials are unlikely to reveal.
- Partially replacing clinical trials in those situations where ISCT can generate scientifically robust evidence. We already have examples where the 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 a reliable predictive model could conceivably replace a routine clinical assessment.
- Complementing clinical trials by offering the ability to test experimental scenarios, which would normally be less probable in real patient cohorts. For example: What if the patient has the disease under investigation, but also diabetes and a heart rhythm disorder?

ISCT will involve the generation of computer models that will be applied to each patient enrolled in a trial simulating his/her disease and the treatment being tested. These models will predict the outcome and will be used alongside, or as part of, an existing clinical trial. The predictive accuracy of the models can be tested against the observations produced by the parallel clinical trial. Once this process is repeated for a sufficiently large number of patients, these data can be used with other available information (for example, the distribution of genotypes that are known to be relevant to the course of the disease for product mode of action but which are not regularly recorded in clinical trials) to design 'virtual populations'. Altogether, this will produce a virtual library of data that can be used to test

other *in silico* treatments, either for a different product or a refinement of the existing one. These simulations can first be used to develop a new product, and then to complement and refine the real clinical trial.

On this basis, we have defined ISCT as:

"The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention. It is a subdomain of '*in silico* medicine', the discipline that encompasses the use of individualised computer simulations in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of disease."

Ultimately, ISCT can be used to obtain a quick and informed answer to questions such as: What if the effect is 20% less than expected?; What if the body weight is twice the one observed in our population?; What if the patient has a 10% increase in creatinine clearance? This opens the door to a whole new concept of medicine, based on the ability to predict reliably. The rest of this report will investigate in detail the issues with the current methods, and the factors that still prevent a wider adoption of ISCT technologies. From these reflections we set out the roadmap for research and technological development in the area of ISCT.

Chapter II

Avicenna roadmap: Motivation and process

Authors

Marco Viceconti, Anders Karlström, Martina Contin, Jean-Pierre Boissel

Summary

Chapter II provides a general motivation for the roadmap and a description of the consensus process.

II.1. Engineering a new industry

In 1955, Solomon and Gold published a three compartments model of potassium transport in human erythrocytes (Solomon and Gold, 1955). This appears to be the first paper indexed by Index Medicus (now PubMed) with the keywords 'physiology' and 'computer'. From that first study until the late 1980s, most computer models aimed to capture the basic mechanisms underlying physiological or pathological processes in mathematical form, without intending to make quantitatively accurate predictions.

In the 1990s, the development of stochastic modelling and increased computational powers enabled the development of population-specific models that aimed to predict the average value of specific quantities over a population (Eberl *et al.*, 1997; Chabaud *et al.*, 2002; Duval *et al.*, 2002; Clermont *et al.*, 2004; Kansal and Trimmer, 2005; Bouxsein *et al.*, 2006; Ribba *et al.*, 2006; Vande Geest *et al.*, 2006; Rostami-Hodjegan and Tucker, 2007).

In the early 2000s, the computational ecology community started to debate the virtues of individual-based models for population ecology (Lomnicki, 2001). Soon after *in silico* medicine research also began to use the first patient-specific models (Chabanas *et al.*, 2003; Viceconti *et al.*, 2004; Fernandez and Hunter, 2005; Wolters *et al.*, 2005; Li *et al.*, 2008; O'Rourke and McCullough, 2008). Some analysts started to suggest that such approaches could be useful in the development of new medical products (PriceWaterhouseCoopers, 2008).

In 2007, a group of experts published *Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human*[3]. They presented a scenario where imaging and sensing technologies were used to generate quantitative information about the biology, physiology, and pathology of a patient at different scales of space and time. This information would then be used as the input for multiscale computer models encapsulating all the knowledge available for a given disease process, in order to produce patient-specific predictions for diagnosis, prognosis, and treatment planning.

Since then, dozens of single groups and consortia around the world have developed a whole set of new technologies and methods, initiated with a similar perspective to that original research roadmap. While the vision of the Virtual Physiological Human (VPH) is not yet entirely realised, VPH technologies are being assessed clinically in a number of practical applications, and preliminary results suggest important improvements over current standards of care. In some of these projects it has been necessary to simulate the treatment in addition to the pathophysiology in order to predict how a patient would respond to a particular treatment option.

In the RT3S project[4], the deployment and the fatigue cycling of peripheral vascular stenting was modelled. The VPHOP project[5] included a model of the effect of bisphosphonates on the metabolism of bone tissue. Some other projects have gone even further, for example, the PreDICT study[6] which used VPH models to assess the cardio-toxicity of new drugs. Another project used an *in silico* acute stroke model to explore why hundreds of compounds that have been shown efficacious in rodent models failed in phase II or III clinical trials. The ratio of astrocytes over neurons, which is quite different in human brains and in rodents, was suggested as the cause (Dronne *et al.*, 2007). One of the essential traits of the VPH approach is the recognition that there is no preferential scale, and each problem should be tackled starting from the space-time scale where the process is observed (middle-out approach).

Of course this is not the only approach that was pursued. Many research teams worldwide adopted a bottom-up process, in an attempt to translate the systems biology approach into clinical practice (Bousquet *et al.*, 2014; Wolkenhauer *et al.*, 2014; Wang *et al.*, 2015). Some envisaged a future model of Predictive, Preventive, Personalized and Participatory medicine (P4) based on the translation of systems biology, or as it was later referred to, systems medicine (Hood *et al.*, 2012). While this approach holds the potential for huge impact, especially in relation to the discovery of new pharmaceutical compounds, in many cases there are knowledge gaps that make the clinical application difficult (Noble, 2003). One particularly important limitation is the ability to model the cell-tissue interaction, as was stressed in the 2009 workshop jointly organised by the United States Environmental Protection Agency and the European Commission[7]. Some authors have tried to bridge this with phenomenological models, such as the Effect Model Law (Boissel *et al.*, 2013; J-P Boissel, 2015).

All these research activities embraced a scenario in which VPH models could be used not to enhance the clinical management of patients affected by particularly difficult pathologies, but rather to design and assess biomedical products. In 2011, the VPH Institute introduced the term *in silico* clinical trials (ISCT) to describe this type of activity.

In this document we define ISCT as the use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention.

The term individualised probably needs some further clarification. In most if not all ISCT applications the goal is to predict how a product will perform across a population, so why insist on the need for individualised models?

Most of the time a model captures one mechanistic theory, and in this sense is generic; however, it is parameterised to mimic each individual patient. In this sense it would be more correct to say that the model is generic and the parameters are patient-specific. But occasionally, a complex model can be fully identified with direct measurements taken from individuals; in most cases some parameters are subject-

3 http://www.vph-institute.org/upload/step-vph-roadmap-printed-3_5192459539f3c.pdf
4 http://www.rt3s.eu
5 http://www.vphop.eu
6 http://www.vph-predict.eu
7 http://www.vph-institute.org/upload/v-tissue-position-paper-2009_555460b051aaa.pdf

specific while others are population-specific. In this roadmap, we will refer to individualised or patient-specific models not in relation to how they are parameterised, but in relation to their predictive intent, ie., how they are validated. There are three possible expectations for such a model:

1. Over a cohort of N patients, for whom one can measure the quantity to be predicted, we consider a model validated if it returns a prediction within the distribution of measured values; in other words the model captures one generic behaviour considered representative of a member of that population.
2. Over the same cohort, the model predicts a central value of the distribution of measurements, typically an average value over the population.
3. The model is parameterised for each patient in the cohort, and its predictions are compared to the measurements for that individual.

Most predictive models available today are somewhere in between 1 and 3. So what really defines the Avicenna Community of Practice is the tendency toward 3; the recognition that when possible, a fully mechanistic, quantitative model capable of an accurate prediction for each individual member of the population would be superior to any other type of model. What we are proposing is an ideal to which we should aim as a community; of course case by case there will be variation in how close we get to this ideal for a number of practical reasons, including lack of measurements, lack of knowledge, computational complexity, etc.

This document aims to define the research and technological development roadmap needed to make this vision a tangible reality, much as the 2007 document did for VPH research. But it also aims to support the case for the creation of a novel industrial sector capable of providing technologies, consulting, and services for ISCT to the biomedical industry.

This new sector will emerge from two existing areas. The first is the clinical trials industry composed of Contract Research Organisations (CROs), research hospitals, and regulatory experts, which serves the biomedical industry in the design, execution, interpretation, and regulation of clinical trials. The second is the virtual prototyping industry, which provides *in silico* design and assessment for a variety of products in other industrial sectors such as aerospace and nuclear energy. We propose a new industrial sector that is built on expertise from these existing areas of industry with additional capabilities that are specific to the ISCT domain.

The birth of a service industry to support ISCT is vital for the rapid and widespread adoption of this novel approach. This roadmap will chart the ISCT territory not from a purely cultural point of view, but with guidance from a variety of industry experts, by assessing the barriers and challenges that we need to overcome for this industrial

Fig II-1. The new community of practice

sector to thrive (see figure II-1).

II.2. The Avicenna consensus process

II.2.a. Overview

The process the Avicenna consortium used to develop this roadmap can be summarised in four steps.

1. Form a community of practice.
2. Capture the consensus of the experts within this community by repeating the following steps four times:
    a. Poll the community using a formal process known as Alignment Optimisation;
    b. Capture the consensus in draft versions of the roadmap;
    c. Organise small-group meetings to validate the draft, and brainstorm the next step.
3. Consolidate all the inputs in a final draft version of the roadmap.
4. Publicly validate the roadmap with all stakeholders, and present it for discussion at Event Five.

II.2.b. The formation of the community of practice

II.2.b.i. The process

In the development of a research roadmap, the first challenging task the consortium had to face was the identification of the correct panel of experts to involve in the process. This panel needed to balance a number of criteria including level of expertise and seniority, field of interest, country of origin, etc. Since the first initial landscape investigations, it emerged that due to the novelty of the ISCT concept and its strong level of interdisciplinary working, there was no pre-existing community of practice the project could have easily opened a dialogue with. So the consortium had to invest a significant amount of effort in supporting the creation of such a community to be able to reach its objectives.

To overcome this initial barrier, an *ad hoc* engagement process was put in place and followed till the late stages of the project. The process was developed around these main milestones (see also figure II-2).

- Mapping of the territory: understanding the composition of the industrial sector.
- Stakeholder identification: identification of the different types of stakeholders involved, their viewpoints, and motivations for contributing to the development of the roadmap.
- Contact establishment: identification of the single companies to engage and the right experts within those companies, beginning with personal contacts from within the consortium then broadening to include others through thorough trawling of the Internet and engagement via professional social media, such as LinkedIn.
- Building awareness: development of a public identity for the project through the release of the Avicenna website, the creation of marketing material, and the dissemination of project information via a variety of channels.
- Definition of a contribution mechanism: offering different contribution methods and level of engagement (participation at events, subscription to forums, contribution to online surveys) to create opportunities to exchange views and help develop a sense of community.

Thanks to this systematic approach, over the course of the project the consortium was able to engage over 500 experts, which formed our experts' database. Each one of these experts was initially contacted and invited to participate in the project, with an 'opt out' choice, that allowed us to remove the people who were not keen to collaborate with us.

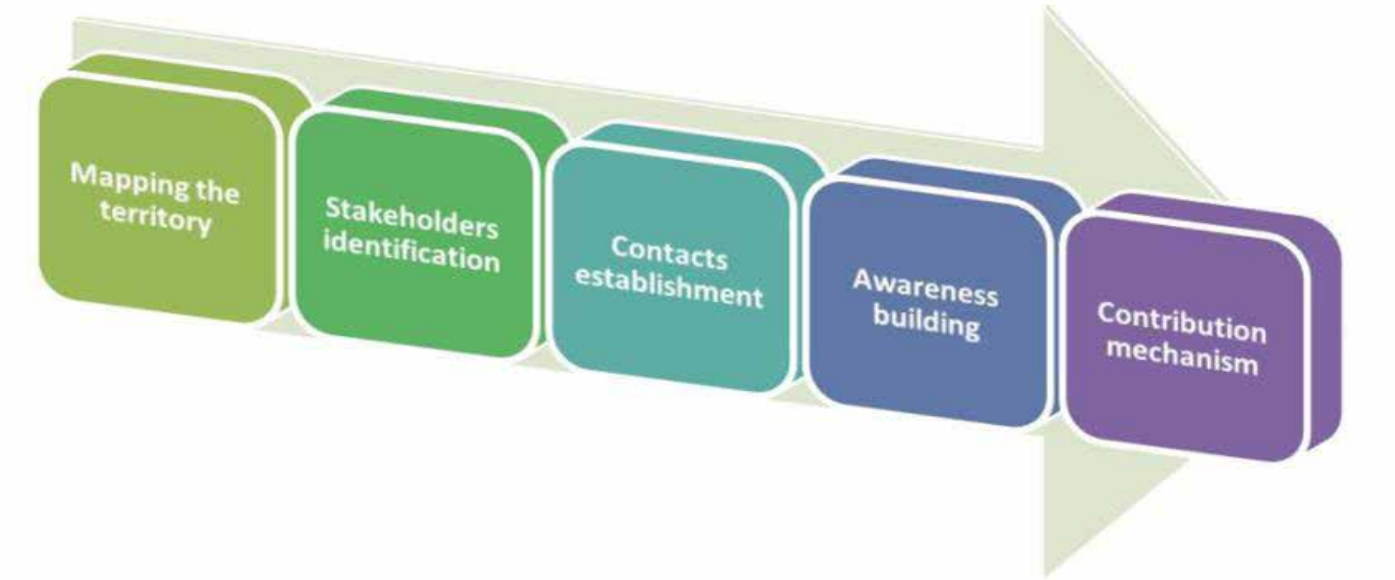


Figure II-2. The engagement process

II.2.b.ii. Mapping the stakeholders

An important step in the consolidation of the community of practice was the recognition that all key stakeholders were well represented, which in turn implied the definition of who the key stakeholders are (see table II-1).

In this roadmap, we will use the term 'biomedical product' generically to indicate a product that is intended for the improvement of human health, while recognising that this covers an extremely varied and complex list of components. Within this, a crude taxonomy is needed. There are medicinal drugs, which achieve their purpose through chemical reactions and processes, and medical devices that fulfil their objective through any other physical means. Importantly, there is a deep industrial divide between the two; they are regulated differently, manufactured differently, and marketed differently. Of course, there is a small group of disparate products that combines both chemical and physical means, which we will refer to as hybrid products.

A second taxonomy relates to the business model adopted by the producers. Large companies operate in mature and stable market segments, and because of the relatively high access barriers, they tend to function as an oligopoly – that is a small number of sellers dominate. Small companies usually operate in niche markets and/or develop innovative products. These are generally more flexible and are able to adapt to changes in the market more quickly. This would include working with radical innovations such as ISCT. In spite of their differences, all companies are driven by profit. However, there is an emerging third sector where the development and assessment of a biomedical product is primarily driven by not-for-profit entities such as charities or patients' organisations.

Another group is that of the providers, which includes those traditionally involved in product development and assessment services (CROs, consultants, and research hospitals), as well as ISCT providers (hardware, software, data banks, ISCT services).

There are then the payers, which depending on the national model can be insurance companies, or health providers. In many countries an essential role is played by assessment agencies, such as the National Institute for Health and Care Excellence (NICE) in the UK, that advise the payers on the cost-benefit ratio for new products.

Next are the regulators, which include the Food and Drug Administration (FDA) in the USA, the European Medicines Agency (EMA) in Europe, but also national agencies such as the UK's Medicines and Healthcare products Regulatory Agency (MHRA), bodies such as the International Organization for Standardization (ISO), and of course the research ethical committees that monitor clinical trials. Last but not least are the consumers, represented by patients' organisations and by charities.

In all these stakeholder groups we have separated representative experts into 'technical' and 'executive' functions, or both. Technical stakeholders are the people in that organisation who would be the end users or providers of ISCT, and can inform this roadmap from the technical point of view. Executive stakeholders are those who can take strategic decisions such as joining an alliance, investing in research and development, and so on. The technical experts know the internal key performance indicators that are important in their respective organisations and will be key for developing bespoke 'value propositions' to be targeted at those with executive power. Stakeholders who fall into both categories are typically those in small organisations where the same person covers both roles. In this case the technical discussion and the value proposition can take place simultaneously.

II.2.b.iii. The experts list

The complete list of all the experts who were engaged in the Avicenna consensus process are listed in Annex 1. This includes 525 experts, from 35 countries, including 22 of the 28 members of the European Union. The largest representation is from the USA, followed by the UK, and then Italy, France, Germany, Belgium, Spain, The Netherlands, and Switzerland.

II.2.c. The Alignment Optimisation process

In 2005, Thomas Schelling received the Nobel Prize in Economics for "having enhanced our understanding of conflict and cooperation through game-theory analysis". In particular, he developed the concept of a 'focal point' (known as a Schelling point), which is the solution to an opportunity most people will select when sub-optimal communication hinders consensus building. From this, and two related behavioural sciences, 'Alignment Optimisation' (AO) has emerged as a management science, providing a crowd-sourcing knowledge discovery process that

Providers	Producers	Payers	Regulators	Consumers
CRO	Large Biopharma	Health Providers	Supranational	Patients' Orgs
Hospitals	Small Biopharma	Insurers	National	Charities
Consultants	Medical Devices	Assessors	Standardisation	
Hardware	Health Technologies		Ethics	
Software	Hybrid Products			
Data Banks	Third sector producers			
ISCT services				

Table II-1. Clusters and subcategories of the Avicenna database

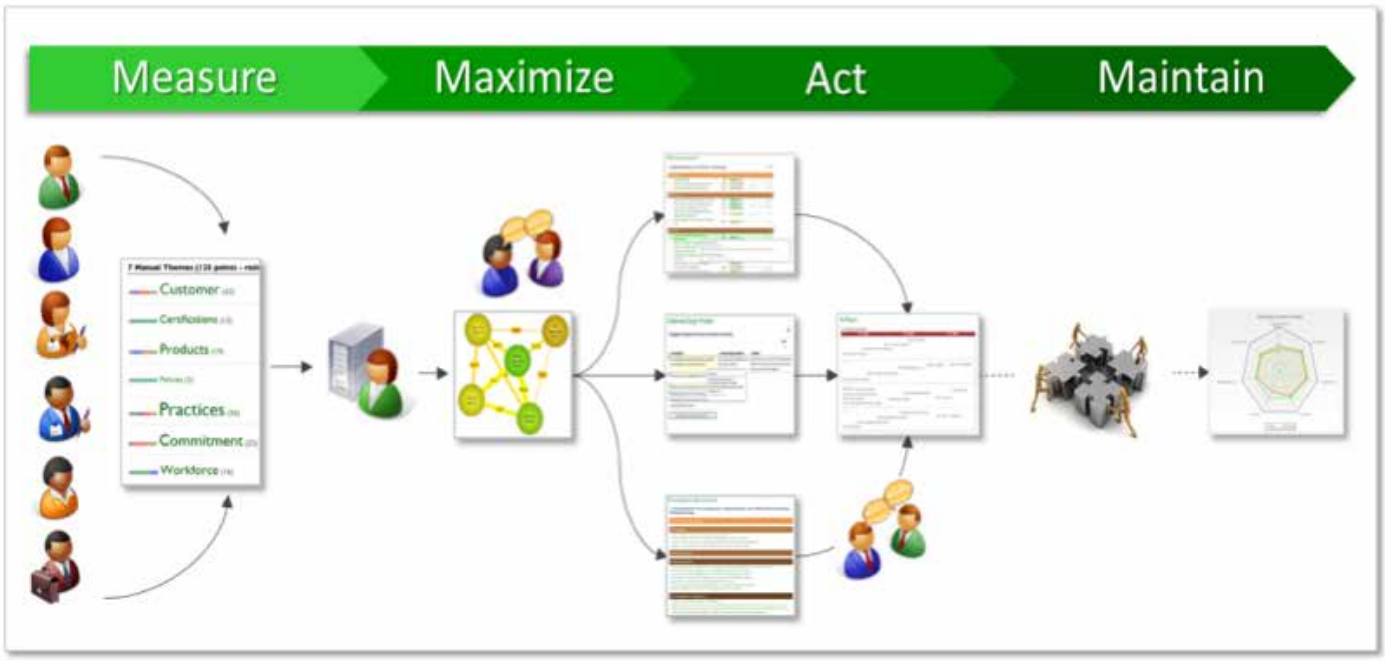


Figure II-3. Alignment Cycles

efficiently yields endorsed, coordinated actions for a group with a shared purpose.

AO is brought about through Future Mapping via an Alignment Cycle (AC) – an explicit process that is rigorously executed in order to maximise the input from participants to yield the most valuable, viable, and endorsed plans.

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. This method starts by dividing the participants' knowledge into two broad domains: first, things they believe they know something about and second, elements they consider uncertain or unknowable. Its focus is on blending the known and the unknown into a limited number of internally consistent views of the future spanning a wide range of possibilities (see figure II-3).

The AO process gathers information on the four categories of thought driving a person's action and inaction on a subject. These are 'Goals', 'Unintended consequences', 'Barriers', and 'Assumptions' (GUBA). This process helps to transform the group from "We each think" into "We are here to", "We should go there" and, perhaps most importantly, "This is how we agree to get there".

The result is the creation of the four pre-requisites for coordinated action embodied in four documents:

- The Foundation Document describing the current state, case of action, assets, and core values to guide action design (from the Assumptions).
- The Rich Scorecard outlining the desired future state (from the Goals).
- The Collaborative Design documents identifying how barriers to success were validated and their mitigating solutions (from the Barriers and Unintendeds).
- The Roadmap, which is the endpoint of the workflow listing tangible activities that have emerged from the previous three analyses, all placed in a time-sequence designed to deliver the previously defined Future State.

These outputs are produced through a defined, transparent workflow, which:

- Invites participation from appropriate stakeholders to offer their opinions, learn about the opinions of others, respond to those opinions, provide reasoning and switch opinions (all under a personal non-disclosure commitment).
- Provides alignment visualisations that enable the organiser to pinpoint and triage the necessary conversations.
- Translate aligned opinions into agreements and endorsed actions.
- Reconcile misalignments through understanding which of the three reasons for misalignment is present.

The AO opinion-gathering steps were conducted remotely using the 'virtual conversation' technique, with pinpointed opinions validated or modified during live discussions at the Avicenna one-day events.

AO was selected as the primary method for crowd-sourcing knowledge from participants in the Avicenna process, based on previous experience of one of the partners using the technology in a similar context relating to the application of systems biology to drug discovery and development (Henney and Superti-Furga, 2008). The information we gathered into the aforementioned four documents has been incorporated into this Avicenna roadmap. Note that the alignment visualisations enabled a close examination of

the degree of alignment that exists within and between the different stakeholder communities involved in the virtual conversations (depicted in figure II-4).

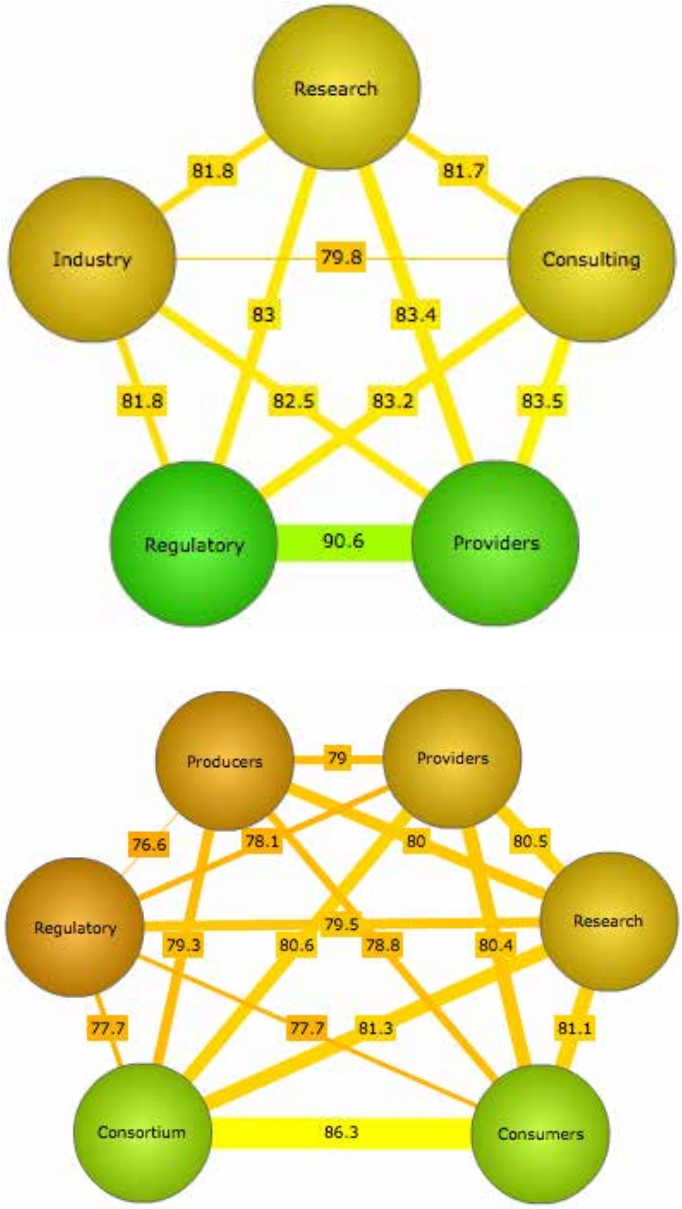


Figure II-4. The Stakeholder Class Analysis AC1 and AC2

AO is based on the notion that alignment is not a binary yes/no, or we are/we aren't, but that every group has a degree of alignment at any time. On a 100-point index, where 0 is complete misalignment and 100 represents complete alignment, every group measured has been between 44 and 83. The colour of the node indicates the strength of alignment within that community, on a red (low) to green (high) scale. The colour and thickness of the line shows the degree of alignment between two communities.

Alignment assessments are done around an explicit topic, and all topics comprise several themes. For example, designing the advancement of ISCT encapsulates opinions related to diseases, devices, modelling, validation, collaboration, communication, and so on. These are examples of the themes of the topic. Each statement on the opinion survey can be assigned a theme for grouping with other similar statements to gauge like-mindedness and divergence at a theme level.

II.2.c.i. The first virtual conversation

Step one: Gather opinions. One-hour telephone 'seed' interviews were conducted with 19 carefully selected experts representing the six different classes of affiliation to solicit their opinions in response to a series of 43 questions, which were a consensus set defined and agreed by the Avicenna leadership team. This seeding interview process is based on identifying reactions to questions spanning the GUBA four key elements (see figure II-5).

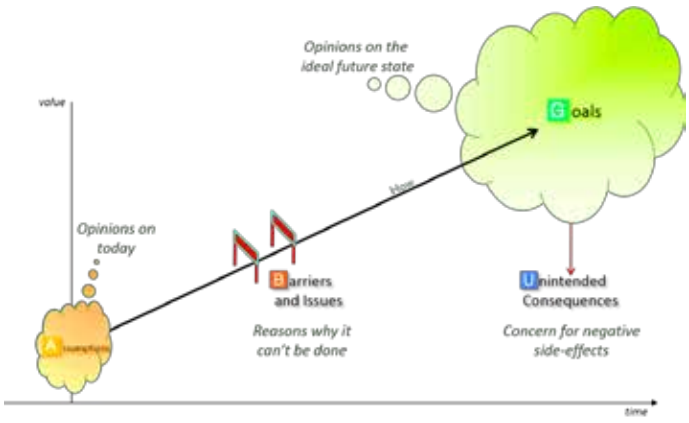


Figure II-5. GUBA

Step two: Share opinions. A total of 755 opinions emerged from the 19 telephone interviews. After removal of duplications, and removal of others that were not considered relevant to the core objectives of the first event, a total of 179 unique opinions were used in an online opinion survey. It is worth noting at this point that, on average, groups have 167 unique opinions about their shared topic. Overall, 56 participants representing the six different classes of affiliation: industry, academic research, regulatory agencies, consultants, providers, and patient organisations, were invited to learn and respond to the opinions via the opinion survey, rating each one from strong agreement to strong disagreement. In total, 44 (80%) of the participants shared their views this way.

Step three: Gather reasoning and switching. Upon completion of step two, the alignment indices are generated. One dimension of this is the ability to see how each person responded compared with the bias of the group. This insight is used to present a personalised online form to each participant, displaying the subset of opinions where they are not like-minded to the consensus of the group. Avoiding peer pressure or group think, participants can elect to switch their original response or provide reasoning to support their agreement/disagreement with the opinion.

II.2.c.ii. Pinpoint necessary conversations

The overall alignment amongst the respondents, as well as the degree of alignment in the separate core GUBA categories is displayed in a 'standard dashboard' (see figure II-6).

The dashboard shows that the overall Alignment Index (AI) figure was high at 81. Looking in greater detail at the separate categories, and explaining the components of the dashboard, we can see that for 'Goals', the total number of opinions expressed was 99, of which 14 were

Figure II-6. Standard Dashboard AC1

'Schelling points' (six of which were added after step three described above). A Schelling point, where all participants support the goal without talking, represents "that focal point which gives a group of like-minded individuals their common purpose. Groups with strong Schelling points can coordinate their actions with minimal communications".

Convergent views, where most agree, but there is some slight disagreement, were registered for 10 opinions (which became six after step three), moderate convergence of opinion was seen for another 56 points, and 19 opinions were divergent, where the degree of alignment across the experts was low.

The breakdown for 'Unintendeds' is an overall, low AI of 65 and no Schelling points. For 'Barriers' the AI was a reasonable 77, with two Schelling points. In the category of underlying 'Assumptions' the AI was a strong 81, with five Schelling points.

These insights were used to pinpoint the opinions to be presented to the expert groups for discussion and resolution during the in-person meeting.

II.2.c.iii. The second virtual conversation

New opinions generated during the live discussions at Event One and Two were used in another alignment cycle to validate their relevance in the establishment of an ISCT platform.

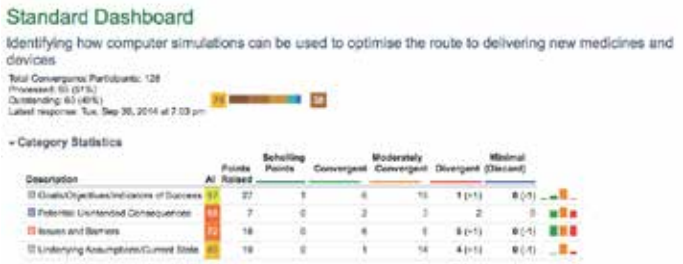


Figure II-7. Standard Dashboard AC2

Step one: Gather opinions. A total of 71 new opinions raised during Event One were selected as those warranting further investigation.

Step two: Share opinions. These 71 opinions were presented to a broader group of 355 participants via the step-two opinion survey method, representing the same six different classes of affiliation as in the first conversation. The participants were invited to indicate their level of agreement with these 71 opinions. In all, 128 (36%) of the participants engaged in step two (see figure II-7).

Step three: Gather reasoning and switching. This time, 65 (51%) of the experts were involved in the analysis of the spread of these opinions, seeking to identify the reasons for the differences of opinion between them. The dashboard shows that the overall AI figure was quite high at 79 with a very strong AI of 87 for the 'Goals' alone. For the 'Unintendeds' the AI was 68, for 'Barriers' the AI was 72, and in the category of underlying 'Assumptions' the AI was 80.

The theme-based dashboard shows the overall alignment in the different themes. Around 30 themes were identified and the strongest alignment existed around the need for validation (AI, 91), model interoperability (AI, 91), and good communication with both specialist and non-specialist stakeholders (AI, 92). Weakest alignment was around the barriers to model creation (AI, 56) (see, figure II-8).

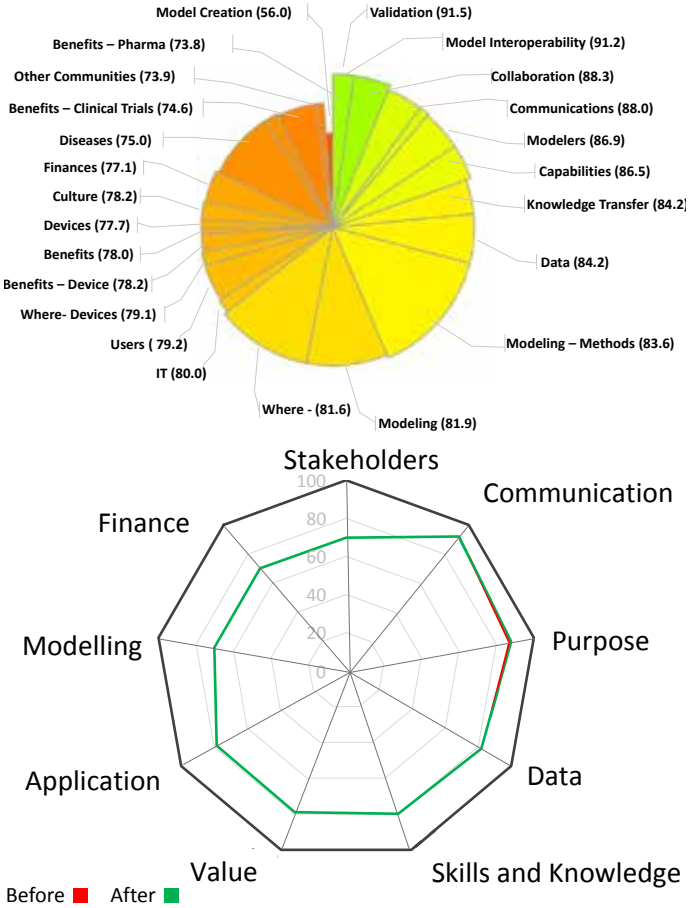


Figure II-8. Theme-based dashboard AC1 and AC2.

All the data were captured in detail and the information retained for future more detailed analysis as part of the foundation for projects that will emerge from the Avicenna Alliance.

Alignment Cycles were conducted before Events One, Three and Five. The result being:

- The virtual conversations put in place a process to acquire relevant opinions from experts and ISCT stakeholders.
- The virtual conversations enabled us to learn the expert's alignment around key opinions without the dynamics that normally compromise in-person meetings and workshops.
- The alignment visualisations meant we could pinpoint the valuable conversations in which to engage the meeting attendees to stimulate further discussion,

bring up required actions, and resolve differences of opinion.

- The online, cloud-based nature of the Schelling point software allowed us to collaborate with participants who were not able to attend the Avicenna events, to add their voice and expertise to the process.
- Overall 376 people were invited to participate in the AO process and 159 individuals contributed via the process to support generation of the content included in the roadmap.

II.2.d. The Avicenna small group meetings

Another essential tool in developing consensus among our experts was the four smaller group meetings held in Rome, Lyon, and Brussels. Attended by 30-50 handpicked experts, they provided essential elements of reflection and drove the development of the roadmap very effectively. Figure II-9 shows the timeline:

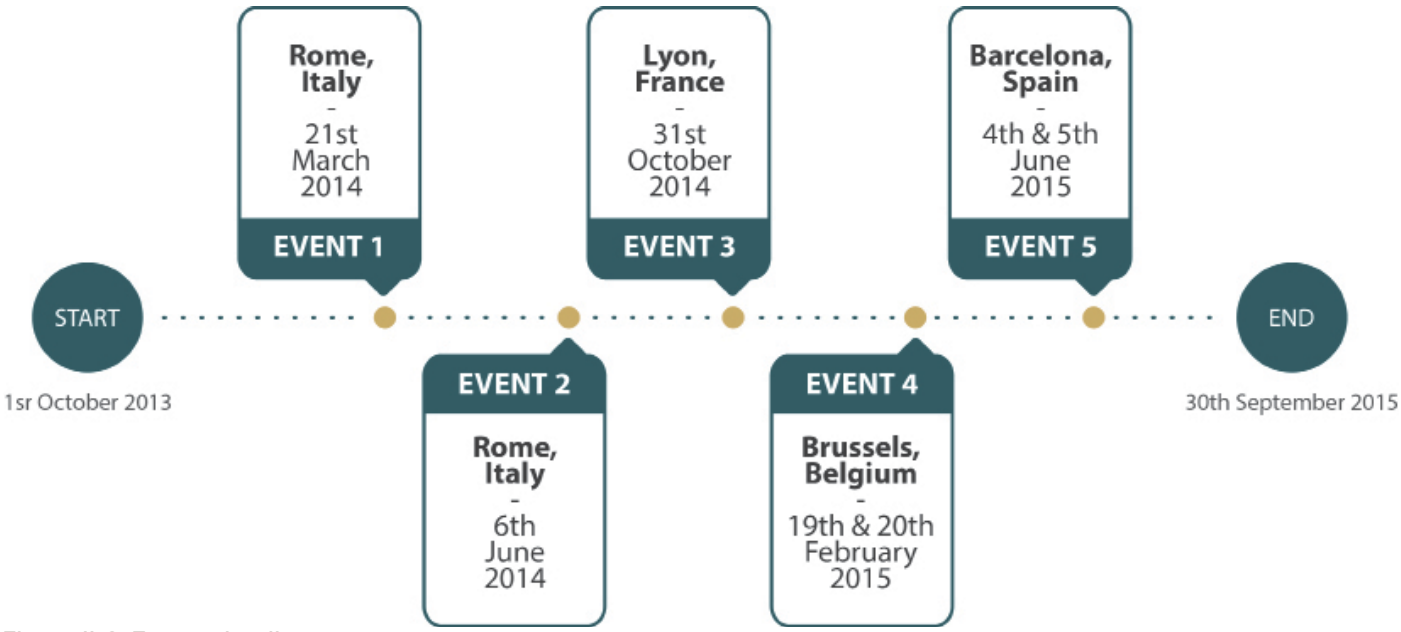


Figure II-9. Events timeline

Each event was designed in terms of preparatory materials and activity, event facilitation, and post-event debriefings to reflect the needs of the consensus process at that point.

Event One was designed as a private gathering of 35 'deep thinkers' with the headline aims of establishing a common vocabulary to be used for ISCT, setting out the skeleton roadmap, and identifying the range of topics that should be considered in the remaining meetings scheduled to take place over the course of the project.

The participants at the second event, held in Rome, were drawn predominantly from practitioners in areas relevant to the application of ISCT, many from industry, and the vast majority having no previous exposure to the processes being used by Avicenna. Three experts in pharma applications (Chang, van der Graaf, and Bosley) and one in devices (Bardot) gave perspective talks that defined the territory. Then a session was dedicated to the closure of the first and most complex Alignment Cycle. From that we moved to an exercise designed to elaborate a set of potential Goals and Assumptions for the whole process, and another to identify Barriers and Unintended consequences.

Event Three, held in Lyon, was attended mostly by industry representatives – either providers of tools and services for ISCT or producers of biomedical products. We asked seven experts to provide early examples of ISCT, and then we drove a discussion around a single question: "What is missing before you could apply something similar to your products?" We divided the experts in six breakout groups defined by product type (device, pharma, or combined). Each group was expected to identify some challenges in research, technological development, and prototyping/ demonstration, which were fed to the consensus process afterward.

Event Four, held in Brussels, was entirely focused on the research and technological challenges. Intense pre-meeting work drove the distillation of a limited number of examples of the use of ISCT, and from them during the event, derived a list of specific research and technological challenges, that provided the core for the final part of this roadmap.

Event Five held in Barcelona, was unlike the previous small meetings, designed as a widely open and public event, aimed to showcase the final draft of this roadmap, the formation of the Avicenna Alliance, and a number of other associated themes, such as the reflection on the socioeconomic aspects.

II.2.e. The editorial process

Initially the roadmap was intended to be a single booklet to be read in its entirety by all stakeholders. Thus, we organised a first tentative index for such a document, and started to populate it with the inputs generated by the AO process. At each cycle a stand-alone document or 'position paper' was derived from the current draft, and circulated to all experts in advance of the meeting. Written comments, as well as all the inputs collected during the meeting were combined with the outputs of the following AO cycle to compose the next draft.

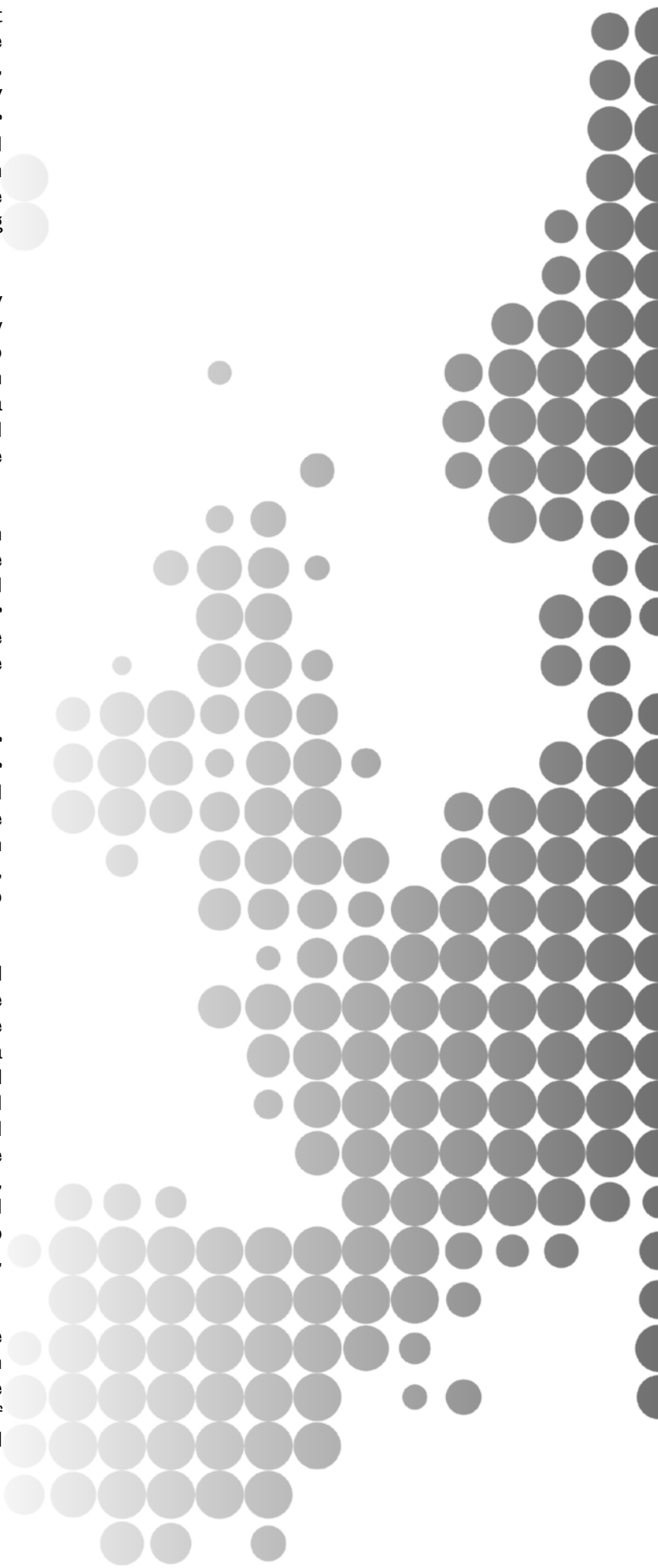
After the third event in October 2014, the complexity of the roadmap started to increase exponentially. New sections were added, some of which were relevant only to some stakeholders. During the first review meeting with the Commission, the reviewers identified the need for a structured approach, a sort of reading guide that would point each category of stakeholder to read only those chapters that were relevant to them.

As a result of these reflections and after the fourth event, the roadmap was completely re-organised. The document was divided into 11 chapters, each one designed to be readable either as a stand-alone document, or together with the others. We developed a reading guide for different categories of readers to ensure an effective comprehension of the roadmap.

After this re-organisation, a draft version of each chapter was posted as an unformatted Google Doc open for editing to anyone with the link. The links were sent to all 500 plus members of our community, giving everyone the opportunity to edit the content of the entire roadmap. In parallel, a Mendeley bibliographic database, also public, was made available for everyone to add relevant papers to be cited in the roadmap.

After this revision round, the text was collected, and formatted into Microsoft Word documents, with the inclusion of figures and bibliographic references. These were sent for revision by our scientific writer, Emma Wilkinson, to ensure homogeneity of the language used and to present the information in a clear, concise, and readable format. The resulting documents were posted on the public Avicenna website and all the available communications channels were used to invite our experts, but also any other interested parties to revise and comment on these documents. The final draft roadmap was circulated in advance of the final Avicenna meeting, where it was discussed extensively.

All comments collected online or during Event Five were consolidated into the final version of the roadmap, which was finalised at the end of August, to allow sufficient time for copyediting, composition, and printing. The list of experts involved in the consensus process can be found in Annex 1.



Chapter III

The industrial need for *in silico* clinical trials

Authors

Marco Viceconti, Anders Karlström, Giuseppe Assogna, Markus Reiterer, Sebastian Polak, Robert Hester, William Pruett, Lars Mulder, Jean-Pierre Boissel, Egils Stalidzans, Martina Contin, Adriano Henney

Summary

Chapter III analyses the current processes used to develop and assess new products in the biomedical industry, and reports the issues identified by the experts who participated in the Avicenna consensus process.

III.1. Pharma and devices: Development pipelines

The industry research and development pipelines for medical devices and pharmaceuticals, including the regulatory processes that oversee them, present considerable differences depending on the type of product being developed, but have the same essential components:

1. Identification of a clinical need.
2. Design of a product to meet that need.
3. Assessment of the risk associated with the product.
4. Identification of the efficacy of that product in answering the need.
5. Clinical assessment of the product in the medical marketplace.

In the pharmaceutical industry, the design phase is known as discovery (see figure III-1a, blue), the assessments of risk, efficacy, and clinical utility are called development (green), and the launch and post-market analysis are referred to as business development (red).

Figure III-1a. Development schemes of pharmaceuticals

In the device industry (see figure III-1b), the phases are design (blue), pre-clinical (risk) assessment (orange), clinical assessment for efficacy (green), and post-market analysis, also called business development (red). Besides differences in the naming conventions, medical devices also undergo specific pre-clinical risk assessments of the possible modes of failure of the device.

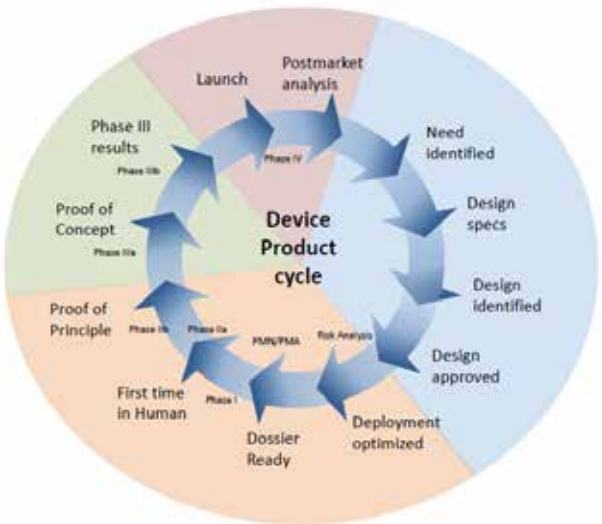


Figure III-1b. Development schemes of medical devices

The main difference between pharmaceuticals and medical devices is how they are tested clinically. Drugs are tested through a well-established and codified process called a clinical trial. In order to produce an unbiased and transposable estimate of efficacy, this should ideally be a randomised controlled clinical trial, which is double blind, and placebo or best-comparator controlled. For devices we usually talk of clinical assessment. The main difference is that a device must be deployed, in many cases with a surgical procedure. Therefore, the outcome is not only due to the device-patient interaction but also to the way it was deployed. Also, deployment prevents any blind design (although the assessment might be done by a blinded third party). The concept of placebo is rarely applicable to devices (Kaptchuk *et al.*, 2000; Fregni *et al.*, 2010; Redberg, 2014).

While in the past the technologies used in pharma and device products were entirely separate, today the boundary is becoming blurred, and hybrid products such as the now fairly widely used drug-eluting stents (McGinty, 2014), and drug-eluting contact lenses (Ciolino *et al.*, 2009), as well as antibiotic-loaded bone cements (Passuti and Gouin, 2003) are becoming increasingly common. Implantable drug delivery devices (Blackshear *et al.*, 1979) are also contributing to weaken this separation.

So while in further chapters of the roadmap, when the discussion became specialised, we separated pharmaceuticals from medical devices, in the first phase, we engaged experts from both industrial sectors. We asked them to jointly elaborate on the main issues with the current development process that require and justify a much broader and pervasive adoption of *in silico* clinical trials (ISCT), as well as the main barriers that have prevented, until now, a wider adoption.

III.2. Modelling and simulation in the current industrial practice

The first reaction of many experts when contacted to contribute to the Avicenna consensus process was "but modelling and simulations are already widely used in my company". For instance, several examples from the same company, covering diverse issues, were recently reported (Milligan *et al.*, 2013). This drove us to explore in depth the current practices around modelling and simulation in both the medical devices and pharmaceutical industries. The results of this exploration are detailed in chapters V and VI. Here we summarise the key elements that emerged in this investigation as common to all biomedical industrial sectors.

The first common pattern is the failure to adopt the use of ISCT consistently throughout the product life cycle. In the pharma industry, systems biology modelling is used (moderately) in the discovery phase; some specialised molecular dynamics (protein docking, protein folding) is used in the chemistry departments; and pharmacokinetics-

pharmacodynamics (PKPD) modelling is used during the pre-clinical phase mostly for dose selection. In the medical device industry, computer-aided engineering technologies are used in the design phase, and more refined biomechanical simulations are sometimes used in pre-clinical assessment, or in post-market failure studies. Nowhere did we find a case where ISCT was used over the entire product development and assessment process. A recent survey of members of the Medical Devices Innovation Consortium reached the same conclusion[8].

The second aspect that emerged in the examples of the use of modelling and simulation we identified, is that it is rare that physiology or individual patient variability is taken into account. Although it was apparent that in some cases, both are taken into account through the variability which is inherently present due to physiological, phenotypic, genetic, and, in particular for medical devices, anatomical differences, surgical deployment, or disease status (Maltais *et al*., 1999; Ferrarin *et al*., 2001; Chabaud *et al*., 2002; Pancanti *et al*., 2003; Imennov and Rubinstein, 2009; Kovatchev *et al*., 2009; Longest *et al*., 2012; Martelli *et al*., 2012; Britton *et al*., 2013; Cárdenes *et al*., 2013; Bischoff *et al*., 2014; Polak *et al*., 2014). Molecular dynamics and computer-aided engineering are modelling tools developed in chemical and structural engineering, not specifically to tackle biomedical problems. Most PKPD models used in industry are exclusively statistical, and consider the patient as an average black box. In a few cases we found instances of physiology-based pharmacokinetics, but almost always used to predict average properties for populations, rather than used to create models capable of making predictions accurate for individual patients.

ISCT technologies should try to capture as much biological and physiological knowledge as possible, first to improve their accuracy, and second to provide an explanatory power that a statistical model by definition cannot provide. Statistical models might predict accurately (though only within the domain captured by the data they are based on), but they will never tell you why something is happening. The other problem with these methods is that they are entirely based on induction, so they are only as good as our observations. For example, they cannot be used to explore infrequent tails of statistical distributions, because if these are infrequent they are not observed. Similarly, they cannot be used to explore a scenario even slightly different from the one they are collected on; if the data were collected on naïve patients (patients who did not receive any pharmaceutical treatment yet), they cannot be used on a cohort that assumes another drug for a co-morbidity, because we have no way to even speculate how the two things would interact in a statistical model. While statistical PKPD models are an important tool, the ISCT of tomorrow, to really transform the biomedical industry, must include all available physiological and biological knowledge and capture the feature of individual patients, introducing the concept of the patient-specific model.

We must move towards relative ISCT, when the intervention is simulated for a cohort of computer models, each simulating one particular patient. Genome-scale human metabolism reconstruction is already available in model form, enabling some mechanistic investigations of genotype-phenotype relationship (Thiele *et al*., 2013). But again, this is mostly limited to molecular phenotype traits and the association with cells, tissue, organ, or even organism phenotype traits (somehow easier to relate to symptoms and other clinical signs) still mostly remains an open challenge.

III.3. Identifying the 'issues'

Why should we spend time and money to develop new ISCT technologies? Is there a true need for radical innovation in the way we develop and assess biomedical products?

The literature is quite clear about the crisis that pharma industry is facing (Pammolli *et al*., 2011). Attrition rates (the proportion of compounds that fail to become products) are increasing brutal. The attrition rate for phase III trials (the most expensive) increased from 20% to nearly 50% between 1990 and 2004 (Pammolli *et al*., 2011). Overall, less than 10% of new compounds that enter clinical trials ultimately arrive to market (Manolis *et al*., 2013). Most of the failures we now see are due to efficacy; in 2011-2012, 56% of the failures were due to lack of efficacy (Arrowsmith and Miller, 2013).

In 2004, the US Food and Drug Administration report *Challenge and Opportunity on the Critical Path to New Medical Products* said: "As biomedical knowledge increases and bioinformatics capability likewise grows, there is hope that greater predictive power may be obtained from *in silico* (computer modelling) analyses such as predictive toxicology. Some believe that extensive use of *in silico* technologies could reduce the overall cost of drug development by as much as 50%."

During our first alignment optimisation cycle, the panel of experts we interviewed made a number of statements that were categorised as underlying assumptions about the current state of the product development and assessment process in their industries, and the part they thought ISCT could play to transform it. These statements were collected and submitted to the experts using the Schelling point web-based technology (see chapter II for details). The vast majority of our experts agreed on a number of them (for each statement the level of alignment among experts is provided).

III.3.a. Issues with current clinical trials

- Device clinical trial failures occur frequently in the last 10% of the pipeline where 90% of the activity needed to get the device out to market takes place (alignment 98%).
- Many device clinical trials involve a low number of patients, leading to low quality without a broad benefit to the device industry (alignment 93%).
- Microfluidics and nanotechnology are hugely

8 http://mdic.org/wp-content/uploads/2014/06/Computer-Modeling-Simulation-CMS-Project-update.pdf

disruptive and will result in consequences for existing clinical trial businesses (alignment 93%).
- With more and more electronic health records in use, the innovation will become accessing health outcomes digital data (alignment 100%).
- Pharma cannot afford the increasing cost of failure and must advance ISCT (alignment 97%).

III.3.b. Current adoption and expected benefits for ISCT

- There are examples of successful ISCT (alignment 88%).
- The application of ISCT is minimal within the pharma industry (alignment 93%).
- There are ISCT used in pharmacokinetics/pharmacodynamics (PKPD), paediatrics, and for multi-trials in the elderly, that show model-specific aspects of the trial (alignment 100%).
- Attempts are being made to replace some organ functions *in silico* using biomimetics, for, example, the artificial pancreas (alignment 95%).
- Combinatorial chemistry of *in silico*-designed molecules has enhanced discovery (alignment 100%).
- Computer-based models are being used to study the influence of pharmacogenomics (alignment 100%).
- Good examples of the potential of ISCT have been prototyped by Entelos (Mamchak *et al*., 2012; Schmidt *et al*., 2013), but not successfully implemented from a commercial point of view (alignment 89%).
- Pharmacology models do exist for understanding chemical interaction modelling; quantitative systems pharmacology is an area that has enjoyed some adoption (alignment 100%).
- There are few examples of models that can predict drug absorption, distribution, metabolism, excretion, and toxicology (alignment 96%).
- We can begin to advance ISCT with the science and modelling capabilities we have now – modelling capabilities are not what is holding up progress (alignment 92%).
- We have not yet exploited the models and simulations that already exist (alignment 97%).
- Over-sophistication of models is not the reason why today's ISCT methods suffer low adoption (alignment 86%).
- There is great interest in ISCT in pharma (alignment 81%).
- ISCT will help us understand host-device response up to 80% (alignment 84%).
- There will be greater openness to ISCT methods in areas with high research activity (alignment 100%).

III.3.c. Limits and challenges for ISCT

- ISCT will never entirely replace clinical trials, but only reduce and refine them (alignment 100%).
- A poor example of using ISCT is where groups are focused on specific areas but do not include that in the clinical trial workflow (alignment 96%).
- An excellent example of ISCT is what is being done in the Virtual Physiological Human/Physiome (VPH), but there is still a lot to do before it gets close to what's going on in the body (alignment 96%).
- For ISCT to ultimately work, we will need to create a systems dynamics model of the human body (alignment 90%).
- Modelling animal to human – there have been whole companies established to do this – but with no concrete results (alignment 91%).
- Problems that have been encountered in mapping reality with modelling outcomes in process design can be useful in developing ISCT (alignment 100%).
- The validation of models is far from sufficient now (alignment 100%).
- A culture of trust and openness is required to make ISCT successful (alignment 100%).
- ISCT is hugely multidisciplinary and cannot be delivered by small groups working in a lab (alignment 95%).
- Resistance to ISCT will exist from basic research and development to regulators until we can show that it has a remote chance of succeeding (alignment 94%).

III.4 Drivers and barriers for ISCT

So from these statements agreed by most of the experts we consulted with, and from the opinions that emerged during the various Avicenna events, we formulated a list of drivers and barriers for the adoption of ISCT.

III.4.a. Drivers

D1. There is a general perception that in drug development the current clinical trials model is not sustainable and needs to be revised to make it more effective in detecting potential issues early in the process, reducing costs, and making innovation more affordable.

D2. The vast adoption of electronic health records and the emergence of new technologies such as microfluidics and nanotechnology are disruptive to the current way we run clinical trials, and drive the adoption of new approaches such as ISCT.

D3. There is a need to avoid expensive clinical trials when the assessment has already been done, but often repetition is required (for example because of a new indication) despite the need being questionable.

D4. The need to reduce the cost of assessment for problems such as re-labelling (for example for paediatric use) and to help reduce the number of orphan diseases where an intervention exists but cannot be prescribed for that use because it was considered anti-economic to test for it.

D5. Early examples of ISCT use are promising. These include application in: trials for special groups (such as paediatrics and the elderly); in PKPD and in the prediction of drug absorption, distribution, metabolism, excretion, and toxicology using physiology-based approaches; in the development of artificial pancreas

technologies; determining the optimal mode of action once a target has been identified; the work of Entelos on diabetes and rheumatoid arthritis; and quantitative systems pharmacology.

D6. The growing public pressure against animal experimentation in most developed countries is leading to the development of alternative methods for pre-clinical assessment, where ISCT can play a key role.

D7. We need techniques that reinforce the pre-clinical assessment of efficacy to avoid drugs that fail in phase II.

D8. ISCT can supplement phase II drug trials to explore the safety and efficacy in the more infrequent phenotypes that usually appear only in phase III, and to predict the dose-effect relationship.

D9. For some classes of medical devices the current clinical assessment procedures are not entirely effective, so when failures are intercepted by post-marketing surveillance, the company must withdraw the product and face significant litigation costs.

D10. Better reinforcement of the design of trials for medical devices is needed to account for patient and surgeon variability, effects of lifestyle differences, and co-morbidities, to help avoid post-marketing recalls.

D11. There is a need to better understand the host-device response earlier in the assessment process.

D12. We need to reinforce the regulatory pathways for products classed as both drugs and devices (hybrid or combination products) that are extremely difficult to regulate.

III.4.b Barriers

B1. ISCT is being developed mostly through accidental findings during research projects not targeting ISCT. The lack of coordinated research and a technological development roadmap prevents the consolidation of the sector and encourages fragmentation.

B2. The adoption of ISCT requires the active participation of a number of different stakeholders from industry, regulatory agencies, patients' organisations, etc. This requires a balanced, pre-competitive setting where these discussions can be conducted without the risk of any unwanted bias.

B3. To be effective in a number of diseases ISCT must better predict the systemic responses; but more research is necessary to unravel systemic processes using VPH strategies, systems dynamics models, and the lessons learnt from process design.

B4. The use of *in silico* methods to translate from animal models to humans is promising in principle, but requires a lot more research and technological development before it can be used effectively.

B5. The adoption of ISCT requires a significant investment in validation studies to identify those approaches that work reliably, but when conducted publicly and openly, will help to establish some trust among stakeholders.

B6. The development of ISCT is a grand science. Because of its extreme interdisciplinarity that can be tackled only in very large research institutes, we need to support their formation, but also explore virtual organisation approaches where small groups can join forces and work together to tackle complex problems.

III.5. A special barrier: The biological empiricism

The community of practice engaged with ISCT is broad and heterogeneous. If we try a crude categorisation based on the academic background, the main groups represented are biologists and pharmacologists, biochemists and chemical engineers, bioengineers, biophysicists and physiologists, and medics. While being aware of the risks that all generalisations pose, if we analyse how the different epistemologies relate to the concepts proposed in this roadmap, some interesting elements emerge.

Biochemists, biophysicists, and physiologists, all share a similar epistemology where the reality is investigated by formulating mechanistic theories, and experiments done to attempt their falsification. These stakeholders are perfectly comfortable with the idea of a predictive model, which is seen as a container/concretisation of the mechanistic theory.

Engineering and medicine have quite different epistemologies, but they share a strong pragmatism, summarised in the motto "whatever works". To them it is not important what the models are or how we build them, but only how accurate they are in predicting the reality. If their predictive accuracy is high enough to make predictions practically useful, they are happy to adopt them.

Most biologists do use models (for example model organisms, such as zebra fishes or fruit flies), but in many cases the way they use them is completely different from what is advocated in this roadmap. Every model described in this roadmap is expected to be interpreted as an *analogy* of the reality (Keller, 2003). The model is not the reality, it might even not resemble it visually, but through an analogical process we can use model simulations to predict the reality. However, for a biologist who investigates the methylation of RNA in chicken embryo fibroblasts, the cell culture they work with represents a *homology* of the same methylation process in human fibroblasts. In this approach, it is assumed that with respect to the process under investigation, the experimental model 'is the same' as the reality, ie., it behaves in the same way.

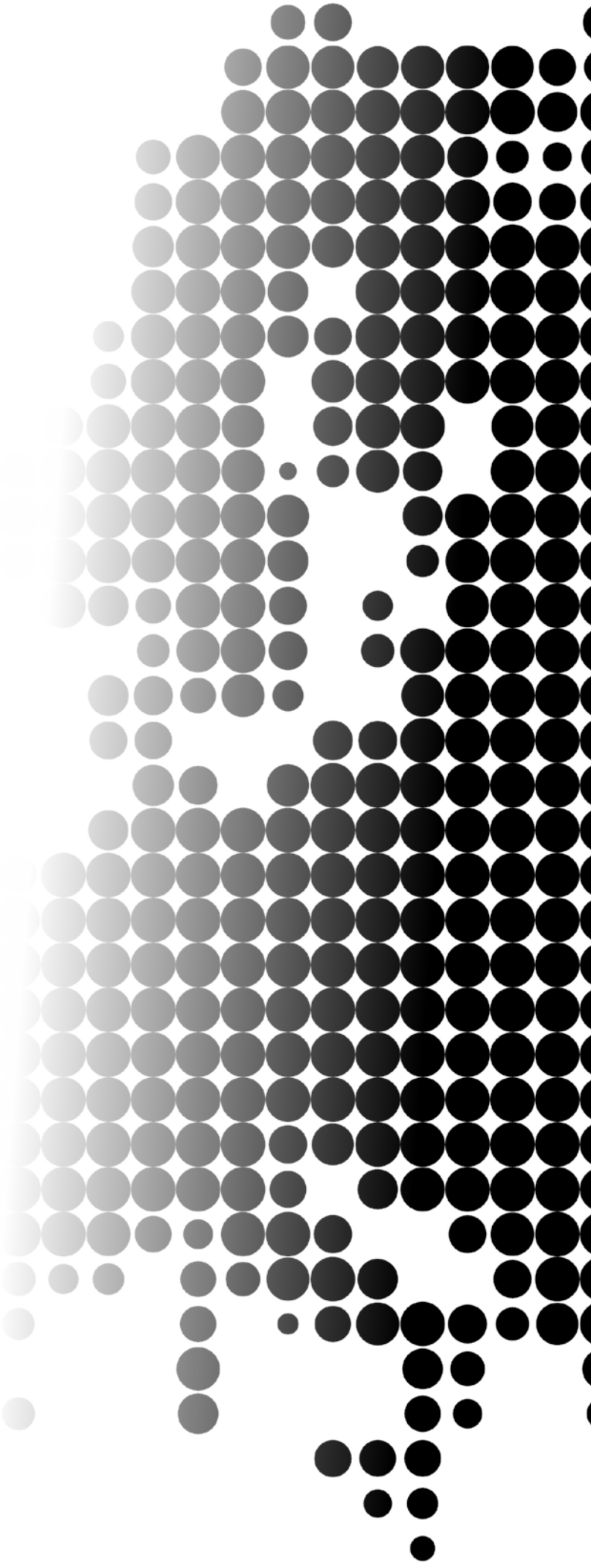
For many researchers in biological sciences, nature is understood by accumulating observations and then building narratives that explain *ex-post* as many observations as possible. But these explanatory theories have a much lower status than theories in physics, and their lifespan tends to be much shorter; a typical example is the so-called central dogma of molecular biology, summarised in the sentence "DNA makes RNA and RNA makes protein" first proposed by Francis Crick in 1956 (Crick, 1958), but that became popular only after his 1970 paper (Crick, 1970), and is now being called into question (Noble, 2012).

While computer modelling unquestionably has an

important role in modern biological research, it is mostly used, and more importantly represented, as a tool to process, compose, and organise observational data. Even molecular systems biology, which aims to build mechanistic models, is more frequently presented as a tool to assemble a large volume of observational data than a container of a mechanistic theory.

One of the greatest challenges that interdisciplinary research poses is how to bridge these epistemological differences. If we want the concept of ISCT to be widely adopted in the biological community, we need to develop a narrative that uses the language and the underlying epistemology this community uses. While this is an aspect on which the Avicenna Alliance (see chapter X) will have to work on, some preliminary indications are possible:

1. In physics, the theory that informs the model holds the greatest value and the parameters that feed into the model matter much less; in biology the discourse must start from the data collected from individual patients, and the mechanistic theory underpinning the model is downplayed.
2. The ambition of developing a theory that explains any observations is perceived as unrealistic and arrogant. We need to describe the models as procedural implementation of a possible explanation, which composes all available observational data into a quantitative prediction consistent with many other observations.
3. We should not speak of validation, predictive accuracy, etc., but rather claim that accurate models produce predictions that are consistent with the experimental observations under a wide range of conditions. Because the truth is built by induction, it is necessary to produce a very large number of very diverse pieces of evidence, to build confidence.



Chapter IV

The socioeconomic need for *in silico* clinical trials

Authors

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Summary

Chapter IV analyses the need for *in silico* clinical trials technologies and the resistances toward a wider adoption from a socioeconomic, ethical, and cultural perspective.

IV.1 The cultural resistances

During the Avicenna process we repeatedly polled our experts about the non-technical factors that have slowed down the penetration of *in silico* clinical trials (ISCT) in the biomedical industry. We received very different and articulated opinions, some reflecting very local or specific situations. But a general pattern emerged around two themes. The first is the difficulty for some industrial sub-sectors to embrace a technology for which most of the experts have never been trained, and even more importantly has roots in cultural domains quite far from where most of such experts were originally educated. We call this effect *uptake of 'alien' technology*. The second has more to do with the cultural resistance to the whole concept of simulation; that because of complex reasons tends to carry the stigma of fake or unreal and thus not trustworthy or reliable. We refer to this as *acceptance of simulation* (Carusi, 2011; Carusi, 2014).

IV.1.a. Uptake of 'alien' technology

From the views collected during our opinion surveys and the syndicate discussions at the events, there is agreement over the value of ISCT, either for devices or medicines. It is regarded as a disruptive technology that will improve the research and development (R&D) process for both, and ultimately improve the current healthcare information marketplace. Following from this, perhaps logically, it is considered that life science companies first adopting ISCT approaches could make the greatest progress in the marketplace, and also open up new markets based on ISCT. In this context, it is believed that those laboratories that have a multidisciplinary ethic and practice will most likely gain from the introduction of ISCT compared with those that do not have such an approach. Educational institutions that do not include training in this area as part of the curriculum might lose some of their competitiveness in the future.

Some specific points were identified in the surveys that relate to the introduction of an alien or new technology, and that will need to be taken into account for successful exploitation of research and technological development in this area:

- The advancement of ISCT will require new levels of close collaboration between scientific disciplines.
- ISCT is hugely multidisciplinary and cannot be delivered by small groups working in a lab. There is a need for large highly multidisciplinary institutes, and/or for large pre-competitive consortia.
- A recognisable and respected group of people from academia and industry should be visibly dedicated to ISCT predictive science.
- IT companies need to be fully engaged in ISCT to deliver the advanced technologies that are needed.
- Regulators should have a group focusing on *in silico* approaches. (Post-survey note: The Avicenna consortium made visible in the process that both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) do have such working groups, but the fact that many of our experts raised this as an issue suggest that such groups and their work is not effectively disseminated).
- Organisations need to be satisfied that ISCT is not being used for purposes that could be deemed unethical.
- Academia/ industry partnerships need to be enhanced.
- European co-operation schemes should promote the sharing of assessment results, from proof of concept, to efficacy results, alongside toxicity.
- We will need to gain access to electronic medical records and prescribing practice.
- ISCT needs an interactive modelling database operating between academia and profit organisations to be used for prospective and retrospective studies.
- Big data issues will need to be addressed in a similar way to that proposed in the *Digital Patient Roadmap* elaborated by the Discipulus action[9].
- We need to identify how to share ISCT data fluently.
- Proprietary data needs to be shared appropriately.
- There should be ISCT 'Cloud' resources that facilitate data sharing across R&D silos.
- ISCT should allow sharing of public databases over country borders.
- We need to build research data repositories that can be easily shared and accessed.
- Resistance to ISCT will exist from basic R&D through to regulators until we can show that it has a remote chance of succeeding.

Finally, training was identified as a key element for successful implementation. This was seen as important not only for understanding modelling and simulation in biomedical disciplines, which are typically unaccustomed to these concepts, but also in the need to effectively validate and interpret emerging results and understand how to apply ISCT approaches to support risk assessment. The possible need to provide appropriate training packages for clinicians was also emphasised.

A similar problem was reported in relation to regulators. In absence of a clear framework to assess the reliability of *in silico* analyses, regulators are frequently concerned that such evidence might be manipulated.

What did not emerge explicitly from our surveys, but became evident as the consensus process developed is that the medical device industry is adopting ISCT more rapidly than the pharma industry perhaps due to important differences in the average size of the industries in the two sectors, in the severity of the regulatory process between the two type of products, and the fact that macro-scale behaviour used in medical devices is better understood and more easily measured in models than the micro-scale pathways of pharmaceutical products. Medical device companies also recruit many more engineers than life scientists. While engineers accept the logic behind ISCT, and question its predictive accuracy and the degree by which it can be approximated to an acceptable level (show me it works and I will use it), life scientists are much more sceptical that ISCT is even possible. We also must report that these conversations tend to be biased. In some conversations, rather than an epistemological distance, we

9 http://www.vph-institute.org/upload/discipulus-digital-patient-research-roadmap_5270f44c03856.pdf

perceived the worry of being made professionally obsolete, if technologies based on computer science, mathematics, physics, and physiology, rather than on chemistry and biology, develop.

IV.1.b.Acceptance of simulation

ISCT rely on computational modelling methods for the simulation of biological, physiological, and physical processes in the human body. From the surveys conducted among our experts, certain aspects were identified as essential to building trust in ISCT:

- The development of standardised processes for code verification – are the equations being solved correctly? – to demonstrate that the implementation of the computational modelling and simulation methods, including the analysis and post-processing tools, is correct. Code verification must critically assess the suitability (accuracy and validity) of the code with regard to all features of relevance within the context of use, including, for example, the modelling of material interfaces or boundary conditions. Validation is based on a comparison between computed results and known solutions.
- The development of standardised processes for model validation – are the correct equations being solved? – to ascertain whether the model reliably reproduces the crucial behaviour and quantities of interest within the intended context of use. Model validation is based on a comparison between simulation results and experimental data capturing critical behaviour with high fidelity. Model validation is only possible within a portion of the reality for which experimental or observational data can be gathered. When the model is used to make predictions beyond these limits, extrapolation is necessary.
- The generation of reference approaches for experimental and computational uncertainty quantification, which is necessary for evaluating the quality of the validation and ascertaining that the validated range adequately covers the context of use.
- The adoption of a standardised documentation and reviewing procedure for verification and validation documents and for uncertainty quantifications.
- The adoption by the R&D community, including executives of biomedical industries, product developers, and clinical research organisations, of official verification and validation standards that have been reviewed and accepted by the regulators and the health care providers.
- The availability of realistic and illustrative verification benchmark examples that medical professionals and patients can understand.
- The availability of verified simulation platforms that are designed for life science applications and have been validated for specific applications as ISCT demonstration tools. However, some experts fear that such a platform could introduce a bureaucratic flavour in a process, which should remain flexible, and allow trained persons to explore the models' capabilities and limitations. They advocate instead the establishment of standards to assess the models' credibility.

A key concept, that emerged in the work done by the FDA, the MDIC Consortium, and the ASME V&V-40 standardisation committee for medical devices, and that we believe has some general validity, is that of model credibility (Popelar, 2013). The idea, presented in Chapter X in greater detail, is that to decide if the predictive accuracy of a model is good enough, it will depend on the question we are trying to answer. If the goal is to show that a product's property is one order of magnitude lower than what would be considered a concern, then a model with a predictive accuracy (as measured against experimental data) of only 70% is good enough. This raises a general research theme on the assessment of predictive models in mission-critical high-uncertainty applications, which needs to be further explored in biomedical research.

IV.2. Socioeconomic issues

IV.2.a. A broken model?

Though scientific breakthroughs in the biomedical sector are clearing the way for revolutionary applications, the image that some observers project regarding the health of the pharmaceutical industry is highly critical.

Eric Topol is one such critic (Topol, 2012, pp 196-198): "Sure" – he says – "the pharmaceutical sector is the biggest component of the life science industry, which includes biotechnology, medical devices, and diagnostics. Still, if there was ever an industry in peril, this is it. It faces a triple whammy – R&D costs have increased from $15 billion in 1995 to $85 billion in 2010; the number of new prescription medications (known as new molecular entities) approved per year by the FDA has fallen from fifty-six in 1996 to about twenty in each of the past few years (including twenty-one in 2010); and the 'patent cliff' of lost revenue as a result of branded drugs going generic is $267 billion through 2016, with $52 billion in 2011 alone. [...]

"The pharmaceutical industry, once considered the ultimate blue chip and extraordinarily profitable, has gone from a blockbuster to a busted model. [...] In the fifteen-year period from 1995 to 2010, the approximate expenditure for a newly approved drug for the overall industry went from $250 million to over $4 billion, a sixteen-fold increase. [...] Rather than innovate, at least in the short term, the industry has been going into consolidation [...]. Furthermore the big pharmaceutical companies have been buying up large biotechnology companies [...]. These companies have also been buying up generic manufacturers, once their dreaded competitors [...]. Where is the innovation to develop exciting new drugs and confront the real challenges of public health?"

If we turn to the *Official Sector Inquiry*[10], published in 2009 by the European Commission (EC), the pharmaceutical

10 A sector inquiry, as per Article 17 of Regulation 1/2003 on the application of the EC Treaty competition rules (Articles 81 and 82), is the tool the European Commission makes use of when there is ground for suspecting a potential systemic problem in a specific industry. Such inquiries are the regular "upstream" approach in any specific case where an antitrust proceeding may or may not follow.

sector was shown to be vital to the health of Europe's citizens with medicines a major expense, nearing 2% of the EU GDP, and around €500 per year for every man, woman, and child. These figures make no mention of Europe's ageing population, with its likely subsequent increase in pharmaceutical costs due to an increased chronic disease burden. The same could be said of the medical devices sector, where the European medical technology industry generates annual sales of roughly €100 billion, invests some €4 billion per year in R&D and employs around 575,000 highly skilled workers.

Both sectors therefore occupy important positions in the EU economy: pharma on its own accounts for 600,000 jobs and for some 4% of total manufacturing in terms of value added. This share is much higher in some member states, such as Belgium, Denmark, Sweden, and Slovenia, reaching between 8.5% and 10% of manufacturing, again in terms of value added. Together, the pharmaceutical and the medical devices sectors account for some 4% of total manufacturing employment in the EU.

The *Sector Inquiry* aimed "to examine the reasons for observed delays in the entry of generic medicines to the market and the apparent decline in innovation as measured by the number of new medicines coming to the market". A natural complement to this was a subsequent study on the EU market and industry for pharmaceuticals, which set out to provide "a comprehensive, comparative, and macro-level analysis of the relationships between the economic performance of the pharmaceutical industry in Europe ie., its potential for investment, economic growth, development, and employment on the one side and external factors, in particular externalities induced by European public/governmental bodies which affect this industry on the other side".

IV.2.b. Pharmaceutical equilibrium within healthcare equilibrium

Analysing *per se* the pharmaceutical and biomedical market can be misleading. Pharmaceuticals and biomedical devices are prescribed as part of a wider medical treatment yet the financial restrictions affected by the biomedical industry are a close reflection of the shrinking paying capacity of national health systems.

Public healthcare budgets appear to be increasingly less capable of keeping up with the pace of healthcare expenditure. The *OECD Dataset*[11] provides an overall picture of the astonishing growth of healthcare expenditure in industrialised countries since World War II. It shows how healthcare expenditure relative to GDP in all such countries has doubled, or even tripled, in half a century. This happened regardless of whether they were Bismarck-driven or Beveridge-driven welfare systems, notwithstanding the relative prevalence of the public or the private financing pillar in any of the systems. In all cases, the growth of pharmaceutical expenditure was part of the picture. This deserves to be highlighted because of its significance in clarifying the dynamics at play and, conversely, in showing the way for possible policy solutions.

There are, as yet, no concrete signs of saturation of healthcare needs and, after a short fall/stabilisation due the crisis, expenditure is continuing on the same long-term trend, which is traceable back to 1960. The same can be said for pharmaceuticals (see figures IV-1, 2, 3, 4).

Figure IV-1. Total current health care expenditure, % GDP (Source: Lynkeus on OECD).

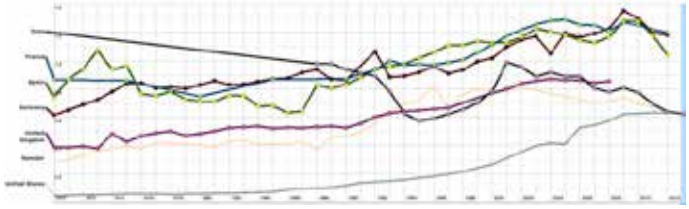


Figure IV-2. Public expenditure for medicines and non-durable medical devices, % GDP (Source: Lynkeus on OECD).

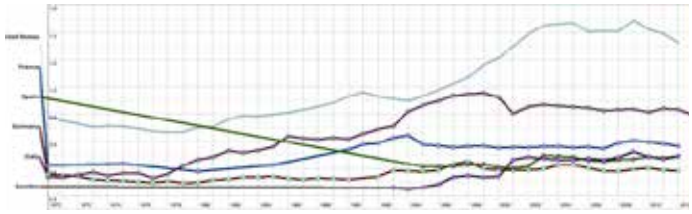


Figure IV-3. Private expenditure for medicines and non-durable medical devices, % GDP (Source: Lynkeus on OECD).

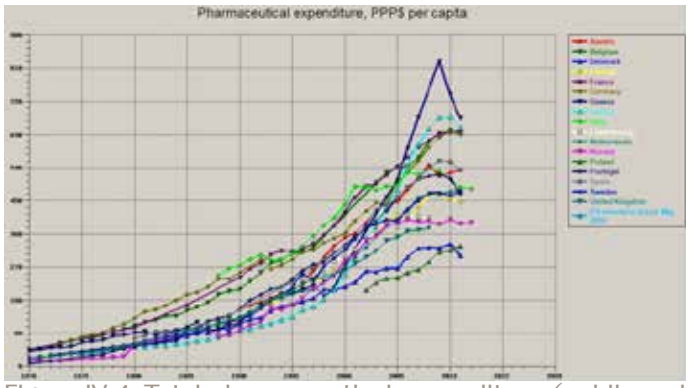


Figure IV-4. Total pharmaceutical expenditure (public and private), per-capita values US$ PPP (Source: Lynkeus on European Health for All database (HFA-DB)).

What can we expect for the future? Of course, the answer is not trivial; a number of efforts to produce projections scenarios are underway, driven partly by the US aiming to improve the governance of its healthcare system. In

11 Data accessible online at: http://www.oecd.org/health/.

summarising the main evidence available at this point, the following issues are worth mentioning.

The first efforts to project healthcare expenditure (in academia and in governmental institutions) were made in the late 1980s (Sonnefeld *et al*., 1991; Burner *et al*., 1992). The longest horizon of projections was ten years, although longer horizons were sometimes considered. What can we see if we compare the real evolution of the total healthcare expenditure against GDP with the forecasted values? The predictive capacity was good in periods when the recent trends of expenditure had been sufficiently stable and, on average, more or less aligned to what would be the future long-term trend (of course analysts did not know, at the time, what future trends would be). Conversely, it proved to be bad in periods of evident acceleration or slowing down of the rate of growth of expenditure.

The previous point can probably be explained on the basis of the structure of old projections models/tools. Only recently (in the past 15 years) have they been improved with the introduction of profiles of per-capita expenditure by sex and age brackets, and with the development of multiple scenarios supported by a wide range of sensitivity analysis. In the 1980s and 1990s, projections were based mainly on extrapolations of recent historical trends and on demographic change. This probably made projections too sensitive to recent trends and for this very reason also to conjuncture and short-term policy interventions. Nevertheless, the way projections worked when aligned to the long-term, and did not when they incorporated accelerations or decelerations of the rate of growth, could bring some information about the strength of the drivers leading the long-term trend of total healthcare expenditure that persist over decades. In other words, when analysts came from periods of rates of growth in line with what we now can call the trend of the last 50 years, they performed well on ten-year projections. However they performed badly when analysts had to consider, in the extrapolation exercise, periods of rates of growth falling significantly outside what would be the long-term trend (either over or under).

Since then, projection methodologies have been much improved. Today three institutional sources periodically perform mid-long term projections: the IMF[12], the OECD[13] and the Ageing Working Group of Ecofin[14]. Their projections are based on a much more refined methodology. Though different in several aspects (scenarios, sensitivity analysis, techniques, etc.), their general outcome is common and can be summarised in the crucial value of the so called 'excess of growth', that is the spread between the rate of growth of per-capita GDP and the rate of growth of per-capita healthcare expenditure. Historically, this spread counted for 1-1.5 percentage points per year over the past half a century, despite the fact that on several occasions governments have intervened to stabilise or even reduce health expenditure. It is not a trivial task to disentangle which components the spread is made of, but the excess of growth can be seen as incorporating both the effect of ageing as well as the effect of technical progress (where pharmaceutical R&D is included).

This parameter is crucial because if projections assume it is positive (ie., that the rate of growth of expenditure is higher than the rate of GDP), in the mid-long term we are bound to see more or less what we have seen since World War II: a continuous rise in GDP with ever more problems for financing healthcare. On the one hand, we do not have any evidence, today, that this parameter could be declining with respect to historical data. On the other hand, even if we focus on projections that use mainly demographic drivers (ignoring or reducing the effect of technological progress), results show that in the mid-to-long run, the burden on active citizens and on workers, to finance healthcare via pay-as-you-go systems, could reach critical ceilings, with possible negative spill-overs on labour, productivity, and investments[15].

In the future it will become increasingly urgent to develop tools and 'philosophies' of governance capable of simultaneously pursuing two potentially conflicting goals: financial sustainability and adequacy of care. Adequacy has a twofold dimension: the equity of access for all citizens, and the quality of provision. The first dimension implies the process of reforming universal systems toward schemes of selectivity[16]; the second dimension implies avoiding the financial goal becoming detrimental to the re-distributional purposes at the basis of health (and welfare) systems, and thus slowing down or damaging the process of R&D and innovation.

This sustainability-adequacy puzzle affects healthcare as a whole, as well as specific areas of expenditure such as pharmaceuticals. The more an expenditure item is exposed to innovation and potential vehicles of innovation, the more this trade-off is expected to be tough to balance. As the EMA[17] has been suggesting as primary policy guideline for quite some time, it will be essential to provide an in-depth evaluation of the impact of innovative medicines and innovative biomedical devices. This should be done taking into account both direct and indirect costs, as well as the expected benefits, and extending to the mid-long term the assessment horizon, aligning it to forecast expenditure. As *in silico* techniques are at the crossroads of pharmaceuticals and medical devices, this policy guideline is valid for all varieties of *in silico* projects.

The policy indication is not to take the 'excess of cost' as predetermined or influenced by basic natural drivers

12 C. Cottarelli and A. Schaechter, *Long-Term Trends in Public Finances in the G-7 Economies*, IMF SPN/10/13, September 1, 2010. See also O. Blanchard and C. Cottarelli, *Ten Commandments for Fiscal Adjustment in Advanced Economies*, IMF Staff Note, June 24, 2010. For the US another source can be the CBO; see for example: P.R. Orszag, *The Long-Term Outlook for Health Care Spending*, CBO, November 2007.

13 "*What Future for Health Spending?*", OECD Economics Department Policy Notes, No. 19 June 2013. See also "*Public spending on health and long-term care: a new set of projections*", OECD Economic Policy Papers, n. 6-2013.

14 "*The 2012 Ageing Report Economic and budgetary projections for the 27 EU Member States (2010-2060)*", European Economy n. 2-2012.

15 For example, see computations on Stability Program reported in "*Sustainability of Pensions and Health Care*", available on www.reforming.it/articoli/paygo-sustainability-brief-investigation-on-mid-long-term-projections.

16 See the recent prolusion of Anne Mills "Universal Health Coverage: The Holy Grail?", available on https://www.ohe.org/publications. Similar computations for the US are described in: L. Kotlikoff, *The Health Care Fix. Universal Coverage for all Americans*, MIT Press, Cambridge 2007.

17 http://www.ema.europa.eu/ema/

outside policy control, but to look at it as an endogenous variable that can be challenged and changed by sectorial policies and regulatory frameworks. Of course, not in the trivial sense of cutting expenditure or truncating demand or renouncing technological improvements, but reorienting healthcare systems towards selecting high-value-for-money R&D projects.

The *in silico* approach is still in its starting phase. Moreover, it embraces a wide variety of applications, from the setting up of big comprehensive datasets, to neural networks simulating the functioning of vital organs or the whole body, to bio-engineering and bio-robotics reproducing a full-scale human body with the possibility of adapting it to individual characteristics (ie., not a general average avatar of the human body but a patient-specific one). As yet there is little in the way of scientific literature on the effects we may expect on the quality and the costs of treatments. In particular, impact evaluations of the most extreme applications (robotics and personalised avatars) are rare, while more references are available for advantages of big data for clinical trials and pre-clinical trials. Bringing all such information into a single structured repository would be highly expedient in terms of robustness of the analysis and the time needed to produce reliable evidence (that is evidence that can be generalised and not dependent on specific artificial laboratory conditions).
An important addition to/completion of this roadmap is a systematic review of the most important literature available. While the territory is so vast that exhaustiveness would be practically impossible, our experts collected and shared with each other, during the Avicenna action, over 230 publications, a good number of which are cited throughout the roadmap.

IV.2.c. Assessing competition

In this context, competition in the pharmaceutical sector has been analysed on two different grounds. On one hand, there is dynamic or non-price competition among so-called originators, competing in the R&D of new drugs. On the other hand, static or price competition between originators and generic companies, which, as soon as the originator product encounters loss of exclusivity, enter the market with a medicine that is equivalent – in terms of efficacy, safety, and quality – to the original, and sell their product at a much lower price than the original, enhancing access to affordable treatments. Normally, in economic jargon, competitors à la Bertrand[18] are called generics, though this name should not be misunderstood, because the only real and relevant characteristic should be the will to compete on prices in order to align them to efficient manufacturing costs. Also a brand company could start playing as a competitor on prices as soon as a patent (even its own patent) has expired.

Originator companies carry out research into new pharmaceuticals, develop them from the laboratory to marketing authorisation and sell them on the market. These companies can range from very large multinationals to small and medium sized enterprises concentrating on certain niche products (see table IV-1). Their products are largely patent-protected.

Generic companies active on the European market tend to be significantly smaller than originator companies (see table IV-2). The use of generic medicines has been increasing worldwide and is being promoted through government policies. Generic penetration is more successful in countries that permit (relatively) free pricing of medicines (for example, Germany, the Netherlands, and the UK) than in countries that have stricter pricing regulation (such as, Austria, Belgium, France, Italy, Portugal, and Spain). This is because in these countries, medicine prices are generally higher, providing greater incentive to generic medicines companies to enter these markets as competitors à la Bertrand. In regulated markets, by contrast, price regulation lowers the originator price over the life cycle of medicines, lowering the potential profit margin for a generic medicine company, discouraging their market entry.

> “The *in silico* approach is still in its starting phase.”

According to the European Generic Medicines Association, generic products sell at a 20-90% price differential to the off-patent brand product, generating €25 billion in drug cost savings each year for European healthcare systems.
So far, even in countries where pricing has been historically less regulated than elsewhere, the two sectors of branded and unbranded, or generic, medicines have been seen – and often treated by legislators – as adversaries and not easily compatible with each other. Brand diversification, commercial licensing before patent expiration, and other commercial agreements have been largely documented as strategies to slow down the entry of low price equivalent products and maintain market power. In the light of future budget constraints a pervasive reversal of paradigm is necessary. Full price competition in the sector of off-patent medicines is a key factor in saving resources to finance R&D and pay for new in-patent medicines/techniques. This is a virtuous circle that should be supported by all industrialised countries, also thanks to a better coordination of their regulatory frameworks, at least within the single European market but also within transatlantic relationships.

The structure and functioning of distributional channels (gross and retail) should not be undervalued in the promotion of fully separated market equilibrium (innovative products on one side, off-patent products on the other). The level of competition in the distribution sector can affect competition in the production sector. Moreover, distributional channels that are closed or resilient to competition absorb more resources to the detriment of other healthcare or pharmaceutical provisions. Promoting competition among pharmacies is one of the steps the

18 Bertrand competition is an economic competition model named after Joseph Louis François Bertrand (1822–1900), which describes interactions taking place among sellers, who set prices, and their buyers, who choose quantities at the prices set.

EC suggests to reinforce the financial sustainability of pharmaceutical systems[19].

IV.2.d. European pharmaceutical exports

The EC 2009 sector inquiry found that in Europe there was a comparatively low level of innovation by originators and a slowing down of the entry of generic drugs. However, it was remarked that although the US is a major producer of pharmaceutical products, its exports are relatively limited compared with the EU, which is clearly the largest exporter. This fact is due also to the re-import of products manufactured abroad by delocalised branches of US multinationals.

Within the EU, Germany, Belgium, the UK, and France are the largest exporters and overall Germany, Belgium, and Switzerland each export more pharmaceuticals than the US. The market shares in world trade confirm the important role of the EU in pharmaceutical trade, accounting for about 70% of world exports and almost 60% of world imports in 2007.

Strikingly, the pharmaceutical sector is the EU high-tech sector which has experienced by far the highest increase of real business R&D expenditure over the past decade. The sector also shows the second highest increase in real value added among all sectors considered. Furthermore, since the business expenditure on R&D increase was twice as high as the increase in value added, the pharmaceutical sector is the high-tech sector in the EU which recorded the fastest growing research and development intensity.

There were four EU-based pharmaceutical companies in the world's top 50 R&D companies based on their total R&D investment: Sanofi Aventis (France, place 12), GlaxoSmithKline (UK, place 20), AstraZeneca (UK, place 23), and Boehringer Ingelheim (Germany, place 49), and two Swiss companies, Roche (Switzerland, place four) and Novartis (Switzerland, place ten). However, most of the largest R&D pharmaceutical companies had their headquarters in the US.

Although a kind of repartition of roles in not so clear-cut, looking at macro data it is possible to argue that free pricing for pharmaceuticals, together with the particular interaction binding industries and universities, has led the US to specialise in pharmaceutical R&D and to be the first market for launching new entities. On the other side of the Atlantic, Europe is lagging behind in R&D efforts with the higher average level of market regulation (compared with the US) slowing down price dynamics and the launch of new entities. A stronger role for Europe is necessary for a global rebalancing. The US cannot afford such high pharmaceutical prices for much longer, and the re-import of pharmaceuticals (that so far has helped to benefit from low manufacturing costs abroad) is creating problems for the external equilibrium (US balance of payments). Europe should try to become a bigger player in R&D than it has been so far.

IV.2.e. Pharmaceutical innovation – less for more

Despite the increase in R&D intensity in the EU, the success rate of innovation seemed recently to have declined. The rising R&D costs, partially explaining the increased R&D intensity, resulted from the fact that many of the 'easy' inventions had already been made, making current clinical development more complex; and also that regulatory requirements (for example on clinical trials) had become stricter and may differ by country, making testing more expensive. Regarding the decreasing success rate of innovation, the pharmaceutical industry was investing twice as much as a decade ago but achieving only some 40% of the previous number of new medicines launches[20].

R&D outputs had lowered in recent years *inter alia* due to launch delays and non-approvals. With regard to the low level of innovation, the EC inquiry had ascertained an extensive recourse to defensive patent strategies, which interfered with the development of competing medicines precisely by focusing on patents, which were aimed at excluding competitors without really pursuing innovative efforts.

The sector inquiry also found that originator companies used a variety of strategies and instruments to maintain revenue streams from their medicines, in particular blockbusters, for as long as possible. These practices delay generic entry and lead to healthcare systems and consumers paying more than they would otherwise have done for medicines. Also some patent settlements in the pharmaceutical sector may prove to be problematic from a competition law perspective, such as settlements that lead to a delay of generic entry in return for a value transfer by the originator company to the generic company.

One increasingly common practice has become the introduction of a generic version of the original drug prior to the loss of exclusivity – expiry of patent or supplementary protection certificate – either through a subsidiary or a licensee/supply partner (early entry).

In order to identify which settlements delay generic market entry to the detriment of the European consumer possibly in violation of European competition law, four rounds of monitoring, conducted annually from 2010 to 2013, have followed-up to the initial inquiry.

The blockbuster-model appeared to be under pressure. Despite the huge amount spent on R&D, the big pharmaceutical companies appear to be failing to develop new blockbusters. Leading pharmaceutical companies have increasingly been making biotech acquisitions in order to refill their product pipelines. Acquisitions are often the result of earlier alliances or joint ventures between big pharmaceutical companies and smaller companies. For

19 "Report on Competition in Professional Services", European Commission, 2004, COM(2004)_83.

20 "*Medical research: how long does it take?*", Stephen R. Hanney *et al*, 2014, http://www.health-policy-systems.com/content/13/1/1.

Company	EU Turnover	US Turnover	Global Turnover	% EU/Global
Sanofi-Aventis (FR)	11.06	9.47	28.05	39%
GlaxoSmithKline (UK)	8.19	13.51	28.03	29%
Pfizer (US)	8.00	15.59	32.43	25%
Hoffman LaRoche (CH)	6.98	9.01	22.39	31%
Astra-Zeneca (UK)	6.26	8.40	19.82	31%
Novartis (CH)	5.46	6.47	17.53	31%
Wyeth (US)	3.33	6.16	11.59	29%
Johnson & Johnson (US)	3.31	11.39	18.03	18%
Eli Lily (US)	3.20	7.02	12.87	25%
Abbott (US)	2.84	5.70	10.88	26%
Total	58.65	92.72	201.70	29%

Table IV-1. Originator companies active in the EU (2007 turnover in billion euro: prescription medicines)

Company	EU Turnover	US Turnover	Global Turnover	% EU/Global
Teva (IL)	3388	1450	5763	58.8%
Sandoz (DE)1	2041[2]	1319[2]	5407	37.7%
Ratiopharm (DE)	1021	n/a	1384	73.8%
Stada (DE)	950	7	1570	57-64%
Mylan (US)	850[3]	1259	1436^4	56-63%
Actavis (IS)	497	340	1544	32.0%
Zentiva (CZ)	341	0	512	66.6%
Gedeon Richter (HU)	315	15	607	51.9%
Pliva (HR)	282	105	565	49.9%
Ranbaxy (IN)	237	287	1182	20.0%
Total	9940	4780	19969	49.8%

Table IV-2. Largest generic companies active in the EU (2007 turnover in million euro: medicines in general)

a lot of smaller companies, acquisition is the only way to bring their product to the market, because they lack funds and market expertise. Selling the company (or product) appeared also as a way to realise previous investments and efforts as cash. For smaller pharmaceutical firms licensing and cross-marketing alliances with 'big pharma' represent their most probable exit strategy for their initial investment.

Integrated big pharma companies remain at the top of this chain because of their unchallenged superiority in running clinical trials and dealing with regulation issues. However, these firms are increasingly acting as receivers, rather than originators, of new drug candidates. Potential new drug candidates (especially those with early-stage clinical data) come from a variety of sources, but increasingly this niche is being satisfied by 'small pharma', corporate organisations that employ between 25 and 500 employees. A role for 'micro pharma' has also been observed, mainly in combining the academic knowledge with a more business oriented approach.

In conclusion, the European pharmaceutical market can be considered to be characterised by the dominance of a relatively small group of big pharmaceutical companies, which represent a significant part of the annual European turnover[21].

Past experience shows, furthermore, that mergers and acquisitions have rarely produced significant advances in innovation or research productivity[22]. The relevant question is therefore whether such a relatively concentrated European biopharmaceutical industry will be open to the potentially disruptive competition which could ensue from the wider adoption of *in silico* drug development and ISCT.

Within this general context, new signals, however, could start to be recorded.

Contrary to earlier assessments – according to which pharmaceutical R&D expenditure had expanded at a Compound Annual Growth Rate (CAGR) of 6% from 2000 to 2011, whereas the number of new molecular entities approved during this same period had dropped on average, decreasing at a CAGR of 1%.[23] – the most recent

21 From 1999 to 2008 the market share in turnover of the bigger pharmaceutical firms (> 250 employees) had increased from 78% to 82%, while the other categories had seen a decrease: ECORYS, Competitiveness of the EU Market and Industry for Pharmaceuticals, Final report, Vol. 1, Rotterdam, December 2009, p. 29.

22 C. Ornaghi, "Mergers and innovation in big pharma. International", Journal of Industrial Organization, 27 (1), pp. 70-79, 2009.

23 GBI, *Accelerating Drugs to Market - Despite Challenges, Adaptive Clinical Trials Reduce Drug Development Costs and Time to Market*, 2012.

EvaluatePharma forecast states that "the Industry has clearly turned a corner and is set to enjoy a sustained period of growth (CAGR 2013 to 2020: 5.1%), supported by the cushion of soft biological patent expiries. The dramatically improved R&D productivity, two years of excellent new drug approvals, and a replenished industry R&D pipeline, set against a back drop of R&D cost containment, all suggest the fundamentals have changed"[24]. Furthermore, "one industry dynamic that appears to have changed is the speed at which new technology waves are moving through the pipeline and hitting the market"[25].

The elements highlight another strong reason for the filtering of projects through detailed impact assessment valuations. If, on one hand, the easy inventions were made in the past, and if inventions dedicated to widespread needs that are common to the entire population have largely been already developed, on the other hand, the current challenge seems to focus R&D efforts on specific diseases as they arise and progress on specific groups of patients or even on stratifications of very few patients (Koelsch *et al*., 2013). Incorporating this personalised dimension comes with a huge potential[26], but initially it can be extremely costly, besides taking time before attaining safe and effective treatments.

Take as an example the recent approval by the FDA of the new Gilead Sciences drug for hepatitis C, *Sovaldi*: in 2014 it reached, just in the US, $8 billion of sales, at a price of $1,000 per pill, with an overall cost of $84,000 for a 12-week treatment per patient which can be compared with an estimated cost of $500,000 for a liver transplant. Or take into account – as an even more extreme case – the new immuno-oncological drugs approved by the FDA at the beginning of 2015, like *Yervoy*, *Keytruda*, or *Opdivo*, which all show a remarkable effectiveness in keeping alive patients who would otherwise be in their terminal phase, but at a cost of over $300,000 per year per individual therapeutic cycle.

The central issue becomes therefore: can ISCT bring advantages in challenging this new and very promising season of R&D in pharmaceuticals?

IV.2.f. ISCT – a new context

A majority of the stakeholders involved in the first three Avicenna events posited that ISCT would lead mainly to contextual changes, determining the entrance of a number of new entities in the market, like more specialised contract research organisations, new diagnostic modelling research centres, new apps for personalised medicine, rather than to changes in business models. In this sense they have deemed that at least in the short to medium term, ISCT is going to be a sustaining component of the pharmaceutical and biomedical industry, rather than a disruptive one.

This assumption needs to be carefully framed within the new vibrant development phase in pharmaceuticals.

Healthcare should by definition be a non-cyclical area of economic activity, and the increasing need for better treatment should in principle also translate into a steadily growing demand for constantly improved drugs and medical devices.

Before the post-2008 wave of austerity measures, drug companies faced relatively low resistance from European governments when they were setting prices and introducing products. However, the ongoing EU pressure for budget cuts is affecting healthcare, showing an increasing willingness of many European governments to exert as much as possible their monopsony[27] buying power in order to reduce the required expenditure for pharmaceuticals and medical devices.

Spending on healthcare in Europe has in fact constantly grown more rapidly than the economy, even before the post-2008 downturn. Difficult as it may be to assess directly the impact of technological change on healthcare spending, the promise of personalised medicine is to "reverse the ever escalating costs of healthcare – introducing diagnosis to stratify patients and disease, less expensive approaches to drug discovery, preventive medicine and wellness, and exponentially cost-decreasing measurement technologies" (Hood and Friend, 2011).

The EC had rightly assumed that new technologies would have "the potential to revolutionise healthcare and health systems and to contribute to their future sustainability"[28], even though this assumption contrasted with a generalised belief that healthcare expenditure was necessarily increasing faster than incomes and that new technologies were a cost driver[29].

ISCT can represent a fundamental element in making this forecast prove true. It may even be said that the necessary conjunction of sustainable healthcare expenditure and universal affordable care provision will only be ensured if *in silico* medicine can become the trigger for the transformation of the entire healthcare system and biomedical industry as an overarching aim of the EU. This is set out in Hunter *et al*'s 2010 vision for the Virtual Physiological Human: "The sustainability of healthcare systems is becoming the number one issue in a number of member states… [where] some common requirements are emerging, [ie.] to maximise the yield of biomedical research expenditure; to achieve personalised healthcare for individuals and groups (women, children, etc.); to improve the reliability, repeatability, and the timeliness of medical decisions; to integrate digital health information

24 EvaluatePharma, *World Preview 2014, Outlook to 2020*, June 2014.

25 Ibid.

26 "Personalised Medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention […] The future vision is to move towards prevention and prediction" (PerMed, *Shaping Europe's Vision for Personalised Medicine*, Strategic Research and Innovation Agenda funded by the European Commission, May 2015, http://www.permed2020.eu).

27 A monopsony is a monopoly operating from the side of demand.

28 EC, Together for Health: A Strategic Approach for the EU 2008-2013, White Paper, Brussels 2007.

29 CBO, Technological Change and the Growth of Health Care Spending, January 31, 2008.

on a global scale" [Hunter, 2010].

As Eurozone countries lower the prices they pay for traditional drugs, the European market is also feeling the effects of cross-referencing by governments, looking to drug prices in other countries to help determine what they accept to pay.

While general financial conditions are highlighting and accelerating the need to demonstrate value for medicines, and to growingly correlate their price to specific levels of added value and of performance (Henshall and Schuller, 2013; Raftery, 2013; Leopold *et al.*, 2014; Dranitsaris *et al.*, 2015), generalised policies of pharma price reductions in Europe can have a ripple effect, since profits from sales in emerging markets may also fall, because governments in emerging markets refer to the prices set in Europe to determine their own.

Notwithstanding all this, one may question what impact ISCT will exert in a context where, as we have seen, the pharmaceutical industry is currently characterised by substantial problems related to a failure of competition, which is linked to the existence of barriers to entry. Let us examine this issue with respect to the following points: barriers to entry (economic and legal), double pricing, blockbuster vs. orphan drugs, circulation, and transparency of information.

IV.2.g. Barriers to entry

We know that, like in many other industries, any new entrant into the pharmaceutical sector is faced with various hurdles that have been previously erected by already established businesses and by national and European standards and regulations. These include, but are not limited to:

- Economies of scale – manufacturing, R&D, marketing, sales.
- Distribution product differentiation – established products, brands, and relationships.
- Capital requirements and financial resources.
- Access to distribution channels – preferred arrangements.
- Regulatory policy – patents, regulatory standards.
- Switching costs – employee retraining, new equipment, technical assistance.

Barriers to entry are particularly high in the pharmaceutical industry. Of course, many of the top firms have manufacturing capabilities that are hard (and extremely costly) to replicate. Also, they have extensive patents that guarantee the protection of their products while they defend their brands with large marketing budgets. New medicines are often very expensive, and we have seen that this tends to be ever more so, with the newest and most effective drugs. This, of course, may cause market access problems as long as these drugs are not inserted in the welfare or insurance reimbursement lists.

In order to cope with this, innovative approaches have been introduced based on performance-based agreements and payback schemes. Beyond the role of economies of scale and scope, as well as of sunk costs of investments and reputation effects, incumbent producers usually tend to create artificial barriers to entry by having recourse to brand loyalty, market segmentation, cross-subsidisation, and vertical foreclosure conditional schemes, not to mention strategic uses of advertising and marketing.

"We know that, like in many other industries, any new entrant into the pharmaceutical sector is faced with various hurdles that have been previously erected by already established businesses and by national and European standards and regulations"

Will ISCT be at risk of exacerbating these characteristics of pharmaceutical markets or, on the contrary, provide solutions for them? This is not a trivial question, because it will depend on several regulatory aspects and of the forms that *in silico* technologies and methodologies take:

- Will big data be public domain or private property of market players?
- Will neural networks for testing medicines be available to all market participants, or private assets that may be used for creating monopolistic or oligopolistic influences?
- Will there be any international legislative framework for regulating the use of *in silico* technologies and methodologies?
- If *in silico* proves to be a way to accelerate testing (using big data) and perform a wide range of sensitivity analyses (using neural networks fed by big data, or even robots reproducing vital parts of the body), will it be treated with guarantees comparable to those of natural monopolies?

Taken *per se*, *in silico* is bound neither to aggravate entry barriers nor eliminate them; *ex-ante* it is difficult to solve doubts only on a theoretical basis. The end result crucially

depends on how this technology is developed and regulated at the international level. The issue – the consequences of *in silico* on structural properties of pharmaceutical markets – is vast and huge and surely deserves a European multidisciplinary task force to work on it. It can be seen as part of those detailed impact assessment evaluations that, as already argued, will stay at the core of R&D strategies for future decades.

IV.2.h. Legal barriers and the patent-based intellectual property rights system

On top of these elements, there are also the legal barriers: patents and market authorisation, and related to that, the approval costs.

Traditionally, it was taken for granted that the present intellectual property rights system is the only mechanism that can ensure the continuity of the flow of biomedical innovation in the future. Recent economic literature has however shown growing criticism of patents in general, and of pharmaceutical patents in particular[30]. Even globalised media like *The Economist* now point out "today's patent regime operates in the name of progress. Instead, it sets innovation back. Time to fix it"[31]. With regard to medicines, the world-renowned magazine adds: "even pharmaceutical firms could live with shorter patents if the regulatory regime allowed them to bring treatments to market sooner and for less upfront cost"[32]; this is exactly the case of ISCT, as discussed in this roadmap.

The Strategic Research and Innovation Agenda, titled *Shaping Europe's Vision for Personalised Medicine*, drafted by the PerMed consortium for the EC (May 2015), has posited that "new models for pricing and reimbursement have to be discussed. [...] Reimbursement has to ensure fair rewards for the research investment and risks taken by the producer, but also affordability for the entire health system as well as equity for each patient"[33].

Maintaining an incentives system that encourages innovation by granting a monopoly and by allowing the owner to set prices for the resulting product, may appear a much too rudimentary tool in the new scientific-productive context. The expectation – as with other sectors of rapid innovation – to couple the hugely increased knowledge discovery potential with continuous cost reductions clashes sharply with the paradox that, within the current incentives system, the only way by which R&D, including clinical testing costs, can be covered is apparently through making it easier for the producer to establish high prices for the resulting drugs.

When R&D costs are small, there is no serious problem. But when R&D costs are very large relative to production costs, as is precisely the case for life-saving pharmaceuticals, using price for drugs as the only mechanism for rewarding the product developer drives prices upward, and far higher than can be believed to be economically efficient.

Among the growing criticism now surrounding the patents system, a recurrent theme is the acknowledgement that, as it usually happens in all government-granted monopolies, the same inefficiencies and rent-seeking behaviours apply to this sector as to any other such market distortion[34]. As stated by *The Economist*, if "patents are supposed to spread knowledge [...] they often fail [...]. Instead, the system has created a parasitic ecology of trolls and defensive patent-holders, who aim to block innovation, or at least to stand in its way unless they can grab a share of the spoils"[35].

On top of this comes the *evergreening* practice: as revealed by the National Institute of Health Care Management, "over the period 1989-2000, 54% of FDA-approved drug applications involved drugs that contained active ingredients already in the market. Hence, the novelty was in dosage form, route of administration, or combination with other ingredients [...] Only 238 out of 1035 drugs approved by the FDA contained new active ingredients and were given priority ratings on the base of their clinical performances. In other words, about 77% percent of what the FDA approves is 'redundant' from the strictly medical point of view"[36].

If *in silico* technologies can trigger faster clinical trials at much lower costs than today[37], than it would perhaps deserve being incentivised also by prompting a re-definition of what patents are to be in an *in silico* biomedical sector. This way *in silico* could bring about some parallel innovation in the intellectual property rights conceptual framework, making it much more manageable, and no more a long-lasting exclusive right to recover huge investments.

We have already seen that the *in silico* and personalised medicine need to be fuelled by systems approaches to disease, emerging technologies and analytical tools, within a vision which relies, in fact, on some crucial assumptions allowing to revert the continuous growth of healthcare costs:

30 M. Boldrin and D. K. Levine, "The Case against Patents." Journal of Economic Perspectives, 27(1): 3-22, 2013; E. Budish, B.N. Roin, H. Williams, "Do fixed patent terms distort innovation? Evidence from cancer clinical trials", NBER, September 5, 2013.

31 Ibid.

32 Ibid.

33 PerMed, *Shaping Europe's Vision for Personalised Medicine*, Strategic Research and Innovation Agenda funded by the European Commission, May 2015, http://www.permed2020.eu.

34 J.E. Stiglitz: *Give prizes not patents,* NewScientist, 16 September 2006; *Innovation: A better way than patents*, New Scientist, 17 September 2006; Economic Foundations of Intellectual Property Rights, Duke Law Journal, 57, 2008; *Medicine for tomorrow: Some alternative proposals to promote socially beneficial research and development in pharmaceuticals*, Journal of Generic Medicines, 7(3), 2010; *Shift from patents regime to prize-based system will revolutionize research and healthcare*, The Economic Times: Comments and Analysis. May 21, 2012; *A Global Health Care Remedy – Why We Must Fix High Drug Prices*, Economy Watch, May 22, 2012; *The Price of Inequality*, Norton & Co., New York 2012; *How intellectual Property Reinforces Inequality*, The New York Times, 14 July 2013; *Don't trade away our health*, The New York Times, 30 January 2015.

35 The Economist, *Time to fix patents. Ideas fuel the economy. Today's patent systems are a rotten way of rewarding them*, August 8th, 2015.

36 M. Boldrin and D.K. Levine, Against Intellectual Monopoly, Cambridge University Press, New York 2008, Chapter 9.

37 Thanks, for example, to the possibility of repeating tests at a close to zero marginal costs, or to performing computations over a sample population of dimension never available before, having recourse to virtual patients.

1. A less costly drug discovery and development process.
2. An even faster continuous reduction of measurement technologies.
3. A growing capacity for making use of big data analytics for outcome analysis, making it possible to diagnose ever more subtly stratified cohorts of patients, correlated to ever more precise and personalised disease signatures.

The disruptive coming into play of post-scarcity elements (big data analytics, computational medicine, and *in silico* drug development are all proof of the possibility of dealing with abundance in biomedical research)[38] raise the issue of rethinking the traditional framework of intellectual property rights, checking whether something better cannot be found, rather than simply relying on provisional monopoly protection for innovation.

IV.2.i. Patents and induced scarcity

The link between property rights and scarcity had already been highlighted in the 1930s, in a well-known essay by Arnold Plant, then Ernst Cassel Professor at London University, who had remarked that "it is a peculiarity of property rights in patents (and copyrights) that they do not arise out of the scarcity of the objects which become appropriated. They are not a consequence of scarcity"[39]. Rather, "they make possible the creation of a scarcity [...] which could not otherwise be maintained"[40] and, whereas it would be expected that "public action concerning private property would normally be directed at the prevention of the raising of prices, in these cases the object of the legislation is to confer the power of raising prices by enabling the creation of scarcity"[41].

Furthermore, Plant had also remarked that "monopoly conditions tend to promote the diversion of the scarce means of production from a more to a less generally preferred utilisation"[42], diverting "inventive activity into those fields in which the monopoly grant will be expected to prove most remunerative"[43].

Some 30 years later, an American economist who was to become a Nobel laureate in 1972, Kenneth Arrow, argued that, in a capitalist economy, "inventive activity is supported by using the invention to create property rights"[44], and consequently, "precisely to the extent that it is successful, there is an underutilization of the information"[45].

More recently, along analogous lines, two Yale Law School scholars have highlighted how "patents link the expected private returns not to social value simpliciter, but rather to the portion of social value that can be effectively (or cheaply) extracted through the exercise of exclusionary rights"[46]. There is, however, no reason "to think that variations in the ease or costs of exclusion are correlated with the underlying social value of different information goods"[47]. Reasoning in ideal terms – they say – "patents will drive innovative effort and investments away from an optimally efficient allocation providing the greatest net social value and instead toward information goods that may provide lower net social value but higher private value owing to lower costs or barriers to effective excludability"[48]. In such cases, "shifting some resources from the patent system to alternatives will provide a greater welfare 'bang for our buck'"[49].

The fact that patents may therefore undersupply some very valuable innovations whenever these happen to be "highly non-excludable" provides "a new justification for a significant role in our innovation system for institutional approaches, such as direct public funding, prize schemes, and commons-based approaches that do not rely on exclusionary mechanisms to enable the generation of expensive information goods"[50].

A proper appreciation of the *continuum of excludability* – conclude the Yale Law School scholars – has significant implications for innovation theory and policy: "patents, as property rights, do not act simply as transparent conduits for market signals, but rather may introduce their own allocative distortions"[51].

IV.2.j. The double pricing hypothesis

Trying to summarise a great amount of academic discussion, one can say that most of the arguments have focussed on the potential advantages correlated with finally introducing a double pricing mechanism, by which biomedical R&D investments would be repayable separately from the resulting products.

Contrary to the current approach, by which, through the patents system, industry determines a price for the material production of pharmaceuticals without distinguishing this latter phase from R&D, the fact of introducing two prices would allow for an initial predefined amount for enabling a wide access to the drug's production, and then a further

38 The issue of the impact of post-scarcity in economics is a huge theoretical challenge for a science based on a generalised assumption of scarcity. See, as initial references: P.F. Drucker, *Post-Capitalist Society*, Butterworth Heinemann, Oxford 1993; K. Kelly, *New Rules for the New Economy*, Viking, New York 1998; Y. Moulier Boutang, *Le capitalisme cognitif: La nouvelle grande transformation*, Editions Amsterdam, 2007; E. Morley-Fletcher, *Innovation and Big Data*, pp. 243-279, in: B. Bressan (ed.), *From Physics to Daily Life: Applications in Biology, Medicine, and Healthcare*, CERN 60th Anniversary Book, Wiley-Blackwell, 2014; C. Hidalgo, *Why information Grows: The Evolution of Order, from Atoms to Economies*, Basic Books, New York 2015; P. Mason, *Postcapitalism: A Guide to Our Future*, Allen Lane, Milton Keynes 2015.

39 A. Plant, *The Economic Theory Concerning Patents for Inventions*, Economica, 1(1), Feb. 134, pp. 30-51. Plant was explicitly referring here to the famous statement by David Hume, in his *Enquiry Concerning the Principles of Morals* (1777), that property has no purpose where there is abundance.

40 A. Plant, cit. p. 31.

41 Ibid.

42 Ibid.

43 A. Plant, cit., p. 38.

44 K. Arrow, *Economic Welfare and the Allocation of Resources for Invention*, in: Id., *The Rate and Direction of Inventive Activity: Economic and Social Factors*, NBER, 1962, p. 617.

45 Ibid.

46 A. Kapczynski and T. Syed, *The Continuum of Excludability and the Limits of Patents*, Yale law School, Faculty Scholarship Series, Paper 4695, 2013, p. 1942.

47 Ibid.

48 Ibid.

49 A. Kapczynski and T. Syed, cit. p. 1944.

50 A. Kapczynski and T. Syed, cit. p. 1951.

51 A. Kapczynski and T. Syed, cit. p. 1962.

level of remuneration, linked to the effective use of the product.

The goal would be to allow the treatment of innovation (and especially of *in silico* innovation) as a public good deserving appropriate regulation[52], instead of leading to the establishment of temporary legal monopolies.

On another note, the main purpose of patents should be to smooth over long periods the repayment of R&D, in order to make them affordable for the final payers and also to call different generations to contribute to scientific enhancements that will continue bringing direct and indirect benefits in the future. As far as an *in silico* approach succeeds in abating the scale of R&D clinical costs, the purpose of de-linking R&D and final production is to make it possible to consider wider and more flexible schemes to treat the remuneration of innovation. Among these schemes would be a wider involvement of the public through universities and network of research centres, in the R&D process.
The proposed plan would have two components.

First, it would imply having the possibility of massive awards being made to the developers of safe and effective new patented pharmaceuticals. In effect, appropriate public authorities would purchase *in silico* patents. Would the EMA, adequately expanding its functions, be the body best positioned to become such a European public authority, moving beyond current national prerogatives? This would mean paving the way for a new and extremely significant European role on *in silico* development, comparable to what has happened with research through the various Framework Programmes and now Horizon 2020. Whatever the eventual answer to the question about which public authority it should be, developers of successful new drugs would be rewarded by it for successful R&D, partly immediately, partly as royalty on future sales by competing producers.

Second, use of the patents would be freely offered to any firm wishing to produce the drugs. The aim would be that of ensuring maximum competition among generic producers and low prices, as competition would force prices down toward their lowest marginal production cost.

The two elements of the process, *in silico* innovation and drugs production, would be separated so that "consumers would get low prices, and innovators would get financial awards"[53]. The time-smoothing role currently entrusted to private monopolies would be transferred to the public sphere and R&D would open up to all the actors now impeded by the huge time scale required for recuperating its costs.

The advantage of the double pricing would mainly be in promoting the highest level of competition and efficiency in the manufacturing of medicines and devices, in order to maximise, under budget constraints, the resources available to incentivise and remunerate R&D. Of course, this perfect discrimination (manufacturing on one side, R&D on the other) can only be set up and work properly as long as there are sufficient resources to remunerate *in silico* innovation activities and clinical trials at the beginning of the life-cycle of the medicine/device. A virtuous circle that would reinforce the dynamic properties of the other virtuous circle already mentioned – the one between full competition within off-patent products and reinvestment of saved resources onto the launch of innovative entities. Full competition on the manufacturing side could also be beneficial in developing a pan-European manufacturing pharmaceutical industry, now impeded by the fragmentation of pricing rules and the overlap with R&D remuneration.

IV.2.k. Requiring a high degree of centralised information and decision making?

A current objection to such innovative intellectual property rights proposals is that they would present both theoretical and practical problems, depending on their design and on whether they would be mandatory alternatives or voluntary supplements to the existing patents system.

As to the theoretical issue, Jean Tirole has bluntly summarised it into the following quip: "the patent system, for all its flaws, has the major benefit that its market-based reward approach is not subject to the two rocks that bureaucratic procedures usually strike: capture and overpayment, and opportunistic expropriation and underpayment"[54].

As to the practical issue, the usual argument is that either through government contracts or through a prize system for specified *in silico* drug innovations, public expenditures would be necessarily funded by additional taxation, even though this should be theoretically offset, at least in part, by lower prices from the immediate 'genericisation' of all the drugs covered by such programmes at launch. However – it is said – "as mandatory alternatives, they would introduce more immediate generic price competition but also risks of reduced innovation incentives, R&D delays, and therefore fewer new therapies being developed and coming to market. As supplements, depending on their design, they might address important unmet needs and gaps"[55].
Whatever the chosen approach, an objection facing both of those analysed here is that any direct government purchase through grants and contracts which would operate as widespread replacement for private-sector later-stage R&D investment, would "generally require a degree of centralised information and decision making that would introduce uncertainties and delays into biotechnology's

52 Even though also the public good definition is subject to several qualifications. See: J.F. Duffy, *Intellectual Property as Natural Monopoly: Toward a General Theory of Partial Property Rights*, utexas.edu, 2005.
53 B. Weisbrod,cit.
54 Jean Tirole, Intellectual Property and Health in Developing Countries, in A.V. Banerjee, R. Bénabou, and D. Mookherjee (eds.), Understanding Poverty, Oxford University Press, Oxford 2006, p. 313.
55 H.G. Grabowski, J.A. Di Masi and G. Long, *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, "Health Affairs", 34, 2, 2015, pp. 308. See also: M. Kremer, H. Williams, *Incentivizing innovation: adding to the tool kit*, in: J. Lerner, S. Stern (eds.), *Innovation policy and the economy*, Vol. 10, University of Chicago Press, Chicago 2010, pp. 1–17.

scientific and business environment"[56]. Programme administrators – it is said – would face "challenges in 'picking winners' among constantly changing scientific opportunities and competing organizations"[57], while, in comparison, "[US National Institutes of Health] NIH grants have focused on basic research and technology transfer, instead of on late-stage drug development, and the grants amount to a fraction of private-sector investment"[58].

Mariana Mazzucato, author of *The Entrepreneurial State*, has countered this argument by stating that "rather than worrying too much about the State's in/ability to 'pick winners', more thought should be dedicated to how to reward the wins when they happen so that the returns can cover the losses from the inevitable failures, as well as funding future wins. [...] Where an applied technological breakthrough is directly financed by the government, the government should in return be able to extract a royalty from its application. Returns from the royalties, earned across sectors and technologies, should be paid into a national [or European, in this case] 'innovation fund' which the government can use to fund future innovations"[59].

In fact, the US example shows that there has been a massive amount of NIH spending. From 1978 to 2004, its spending on life sciences research totalled $365 billion, and every year from 1970 to 2009, with the exception of a small decline in 2006, NIH funding increased in nominal terms, in contrast to the widely fluctuating funds from venture capital and stock market investments[60]. Total NIH spending between 1936 and 2011 (in 2011 dollars) was $792 billion. All NIH budgets from 2009 to 2014 have stably exceeded $30 billion each year, but for 2013, when it was $29.1 billion[61]. Lazonick and Tulum argue that the US government, through the NIH, "has long been the nation's (and the world's) most important investor in knowledge creation in the medical fields"[62]. Mazzucato adds "three quarters of the new molecular biopharmaceutical entities owe their creation to publicly funded laboratories. Yet in the past ten years the top ten companies in this industry have made more profits than the rest of Fortune 500 companies combined"[63].

Analysing comparative European data, it is sufficient to remember how the EC has evolved, from handling little less than an amount corresponding to €3 billion in its first Framework Programme in 1984-1987, to €70 billion in its *Horizon* 2020 Eighth Framework Programme.

IV.2.I. Tending towards a paradigm shift?

At the final Avicenna Event (Barcelona, 4th-5th June, 2015), Alistair McGuire, Professor at the London School of Economics and Politics[64], analytically articulated the double-pricing issue, distinguishing several ways in which de-linking the reward for innovation from product price can be envisaged, such as: patenting the new chemical entity rather than the product, introducing forms of public-private partnerships, or International Finance Initiatives (especially for developing countries), Advanced Purchase Agreements, R&D tax credits, and more generally experimenting different ways by which the remuneration or prize mechanism could be applied to distinct parts of the R&D process (basic research, early phase drug discovery, pre-clinical, value-based purchasing, cost-effectiveness studies).

This comes as a confirmation of the complexity of an approach such as double-pricing, while providing a further academic endorsement to the validity of the question which is thereby raised, ie., of whether uncoupling *in silico* R&D and manufacturing of biomedical products could be a way for triggering a 'compound accumulation' process for knowledge. Could such an alternative incentive approach be an avenue for a faster introduction of ISCT? Were Europe to experiment paying separately for *in silico* R&D, would this innovative incentives scheme prompt a new wave of enhanced applied technological knowledge supporting European leadership in personalised medicine?

After many years of uncontested primacy of the Property Rights school (where the definition of clear property rights was considered as the necessary precondition for reducing transaction costs), the debate on patents has now gone beyond the famous balancing statement by Fritz Machlup, in his report 1958 to the US Congress, that "if we did not have a patent system, it would be irresponsible, on the basis of our present knowledge of its economic consequences, to recommend instituting one. But since we have had a patent system for a long time, it would be irresponsible, on the basis of our present knowledge, to recommend abolishing it"[65].
Rather, a tendency towards some sort of paradigm shift with regard to patents is taking shape[66], and new paradoxes appear, like the fact that patents, if applied within universal coverage healthcare systems, cannot act as effective demand indicators. The artificial scarcity which they generate cannot be used to reveal the consumers'

56 H.G. Grabowski, J.A. Di Masi and G. Long, cit.
57 Ibid.
58 Ibid.
59 M. Mazzucato, The Entrepreneurial State: Debunking Public vs. Private Sector Myth, Anthem, London 2013, pp. 187-189.
60 W. Lazonick and O. Tulum, US Biopharmaceutical Finance and the Sustainability of the Biotech Business Model, "Research Policy", 40, 9, 2011, pp. 1170-1187.
61 National Institutes of Health, Actual Total Obligations by Budget Mechanism, FY 2000 - FY 2014.
62 W. Lazonick and O. Tulum, cit.
63 M. Mazzucato, p. 188.
64 A. McGuire, *Rewarding innovation: The role of patents and research and development incentives in biopharmaceutical innovation*, keynote lecture at Avicenna Event 5, Agència de Qualitat i Avaluació Sanitàries de Catalunya, Barcelona, 4th June, 2015. Prof McGuire is also advisor to a number of governments and governmental bodies, including the UK government, the UK National Institute for Clinical Excellence (NICE), the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), as well as for a number of international bodies, including the World Bank, the World Health Organisation (WHO), and pharmaceutical companies.
65 *An Economic Review of the Patent System*, Study of the Subcommittee on Patents, Trademarks, and Copyrights of the Committee on the Judiciary United States Senate 85th Congress, 2nd Session, Pursuant to S. Res. 236, Study No. 15, p. 80.p. 80. See also: F. Machlup and E. Penrose, *The Patent Controversy in the Nineteenth Century*, The Journal of Economic History, 10, 01, May 1950, pp. 1-29.
66 As indirectly highlighted, for instance, in: D.J. Hemel and L. Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, Texas Law Review, 92, 2013, pp. 304-382; or in: B.N. Roin, *Intellectual Property versus Prizes: Reframing the Debate*, The University of Chicago Law Review, 81(3), Summer 2014, pp. 999-1078.

willingness to pay because it is pre-empted in as much as pharmaceutical prices ultimately reflect a negotiation system conditioned by the public monopsonist[67].

Beyond patents, a crucial factor will be the degree of efficiency and innovativeness of the retail distribution. Indeed, the importance of ISCT for the production side has a direct correspondence on the distribution side. *In silico* projects targeted on the needs of individual patients (the final goal of *in silico*) could largely benefit from pharmacies/ pharmacists ready to craft personalised medicines in terms of number of capsules or doses, dimension of packaging, content of active principles or excipients, and timing of release.

For sure this would imply a profound renovation of the profession of pharmacist, but also a rediscovering of its ancient medical value as experts in galenic formulation. Of course, with respect to ancient times, pharmacists would have the entire modern support of medical devices and information technology. For example, 3D printers can, properly fed with software planning and outcomes controls, be the tools to adapt gross pharmaceutical products into retail *ad personam* medical treatments.

A lot of positive side effects can also be imagined, including avoiding the waste of medicines (often a consequence of the fact that only few packaging formats are distributed), or avoiding cases of over-treatment or under-treatment when patients try to manually adapt dimensions of pills or dosage. It would be advantageous for treatment compliance. From this point of view, the *in silico* project embraces all the pharmaceutical chain, from production to distribution, and can strongly underpin a crucial move towards personalised medicine.

IV.2.m. Transparency of information

Another interesting element of analysis is determined by the drive to improve the transparency of information on efficacy and safety of medicines, allowing regulators and users to assess the existence and magnitude of the therapeutic added value of a new product.

In the past it has been customary that companies would not report all the clinical trials of a given drug, but predominantly only those that would give favourable results for the new product[68].
Now, the biopharmaceutical industry is officially committed to sharing with qualified medical and scientific researchers patient-level data, study-level data, and clinical study designs and protocols[69].

Given the concern that the data requestor could intend to use the company's patient-level data or other information to help gain approval of a potentially competing medicine, the European Federation of Pharmaceutical Industries and Associations has stated that "while companies may enter into agreements to co-develop medical products, these data sharing principles are not intended to allow free-riding or degradation of incentives for companies to invest in biomedical research"[70].

Their chosen approach has been therefore that "in order to maintain incentives for future investment in biomedical research, individual companies may choose at their discretion to withhold from public access to clinical study reports, various business and analytical methods; manufacturing and pre-clinical information or other confidential commercial information; any information not directly related to the conduct of the study or that could jeopardise intellectual property rights; or information that the company has no legal right to share (eg., due to an existing co-development agreement)"[71].

Of course, ISCT can potentially have a huge impact on transparency issues, given their very nature of wholly digitised process.

IV.2.n. The long tail

In silico technology can also be used to understand more about the study population; particularly to distinguish between potential responders and non-responders to a drug implementing the approach of personalised medicine at clinical trial level. This information can then be used to reassess the study inclusion and exclusion criteria, identifying, through appropriate simulations, which patients may experience adverse events.
With drugs being targeted to specific populations, one can imagine the importance of *in silico* modelling increasing and becoming more widely accepted. In fact, the main concern surrounding targeted medicine in the past has been the cost. How can an appropriate return on investment be made when the market is limited?

As the virtual patient model becomes increasingly validated for specific disease areas, can it increasingly replace biomarker-based stratification, tremendously simplifying the approval of drugs for molecularly defined patient subgroups?

The 80/20 mathematical formula, introduced in 1906 by the Italian economist Vilfredo Pareto to describe the unequal distribution of wealth, has long been a recurrent mantra in organisation studies. The so-called Pareto's Principle, or 80/20 Rule, states that 20% of something would normally be responsible for 80% of the results.

A few years ago, an economics paper[72] started to revert the traditional 80/20 approach, following the innovative insight of Chris Anderson's The Long Tail, and the concept that, when transaction costs are greatly lowered, "the

67 L. Garattini, D. Cornago, and P. De Compadri, *Pricing and reimbursement of in-patent drugs in seven European countries: a comparative analysis*, Health Policy, 82(3), 2007, pp. 30-39; B.N. Roin, cit., p. 1040-1041.
68 B. Goldacre, *Bad Pharma: How Medicine Is Broken, and How We Can Fix It*, Harper Collins, London 2012; Institute of Medicine, *Sharing Clinical Research Data*, Workshop Summary 10, 2013.
69 EPFIA, *Principles for Responsible Clinical Trial data Sharing*, July 18, 2013.
70 Ibid.
71 Ibid.
72 Brynjolfsson, Erik and Hu, Yu Jeffrey and Simester, Duncan, Goodbye Pareto Principle, Hello Long Tail: The Effect of Search Costs on the Concentration of Product Sales (January 1, 2011). Management Science, Forthcoming. Available at SSRN: http://ssrn.com/abstract=953587.

biggest money is in the smallest sales"[73], whereby a series of small niches cumulatively achieve a much larger amount than the traditional focus on selling the preferred 20% of the items.

The Internet has dramatically changed business, because it has infinite shelf space. The long tail has been extremely lengthened, and consumer can really find and choose what they want. Within the music industry, for instance, about 40% of the market was not seen.

Blockbusters are now 'niche busters'. One size does not fit all, and while niches had not been economic in the past, they can now better fulfil the market.

IV.2.o. Is the era of the 'blockbuster' now past?

Can the long tail insight also be applied to the area of pharma business, and specifically to drug discovery, if the implied transaction and processing costs are considered, and if clinical trials can be focused on specific cohorts of virtual patients for personalised drugs?

We are seeing signs of life on the long tail in some ways, with futuristic predictions of people receiving drugs specifically targeted to their own DNA (pharmacogenetics). Tailoring content (drugs) to everyone's individual needs (DNA) is precisely what the long tail is all about. Additionally, the long tail applies to all those diseases and ailments suffered from a relatively small number of people or by a large number of people who are being under-serviced.

Without a regulatory update, personalised stem cell therapies, gene therapies, and customised drugs are at risk of being commercial failures, crushed by the huge costs of antiquated regulatory systems.

ISCT can bring about long-tail medicine, delivering drugs with enhanced personalised information content, based on customised algorithms tackling the individual disease conditions which can best cured only by personalised treatment.

IV.2.p. Orphan drugs

Traditional orphan diseases affect no fewer than 200,000 people in the EU each year. Because of their low prevalence, little direct investment has been made in research to understand them or to develop new treatments for them.

Such developments, however, would reduce risks for patients participating in clinical trials, reduce the likelihood of detrimental effects on specific sub-populations of patients, and reduce the number of clinical trial participants to achieve statistical significance, markedly reducing time and cost of drug development.

The biopharmaceutical industry has long focused on the one size fits all approach, but one-size medicines do not fit all patients, and the same is true of the R&D process. The limitations of this approach - on which the industry has relied for many years - have become increasingly clear.

Data sets from a sub-population or from longitudinal clinical data have the potential to expedite the development of targeted therapies in terms of both patient population and disease.

So far, blockbuster drugs have been a strong point of pharmaceutical markets dynamic (big volumes of selling to recover clinical costs), while orphan drugs have been a weak point (insufficient volumes to make R&D efforts profitable). The 'orphan drugs syndrome' is normally referred to developing countries, where in theory there would be a high demand for volumes but very low capacity to pay for them. The correspondent syndrome in developed countries is the niche one. The economic roots are the same. Niche medicines or treatments bring limited volumes with possible difficulties in recovering R&D costs, despite the fact that a single European citizen would have a strong will to pay. *In silico* technologies, if and when capable of abating R&D and clinical trial costs, will also help by freeing pharmaceutical firms from this double tie: the necessity to look for blockbusters and, conversely, the incapacity to respond to needs that do not represent sufficient shares of the potential market.

It would also be a real revolution for the pharmaceutical industry from another socio-political point of view, in that an industry usually seen as strongly oriented towards volume of sales and capturing large numbers of patients would have reworked its financial basis to develop drugs for developing countries and drugs targeted to the single citizens.

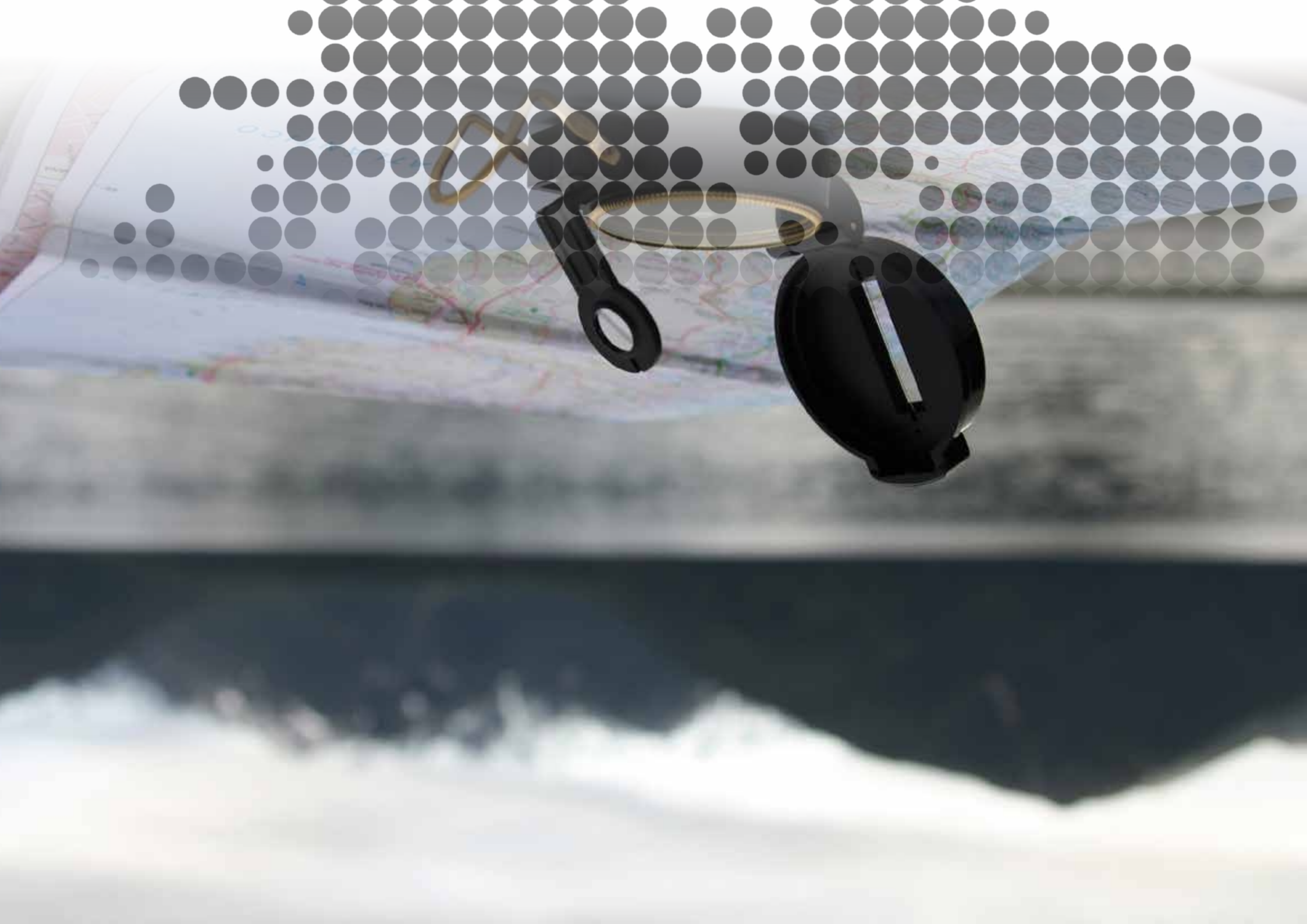
IV.3. Ethical issues

A project, like ISCT, so revolutionary in its approach, raises several ethical issues such as privacy, secure storage and management of big data, the need to protect individual citizens from harmful usage of their personal data (social stigma, screening in insurance contracts, discrimination on the labour market, etc.), and the need for a regulatory framework to prevent eugenic radical manipulations, and finally the risk that these new frontiers could remain available only to a limited portion of the population thus creating possible continuous states of conflicts (a sort of post modern social struggle for health or for the life).

Nevertheless, from another point of view, ISCT could offer important tools to avoid or challenge these ethical risks. If, as expenditure projections show, in the future the balancing between financial sustainability and universal access to care will become more and more difficult, we have to invest now in technologies and methodologies that can help to develop cost-saving innovation. Above all, we have to invest now in technologies and methodologies that can make niche therapies and *ad personam* therapies available for all, despite differences in income, social status, living country, race, and cultural origins. Before the huge rise of

73 C. Anderson, *The Long Tail*, 2006.

expenditure described at the beginning of this chapter, a major ethical issue is surely the production of life-saving new therapies that only address fortunate groups or are even ordered by some powerful groups. ISCT is at the crossroad between cost-saving R&D and *ad personam* therapies, and the *in silico* progress can really be expected to bring about interesting and fruitful enhancements.



Chapter V

In silico clinical trials: Use cases for medical devices

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Summary

Chapter V analyses how a medical device is developed and assessed, where *in silico* clinical trials are already used, success stories and cases in which *in silico* clinical trials could help.

V.1. Modernising the development of high-risk medical devices

The term 'use case' is hereinafter used to indicate a possible usage for *in silico* clinical trials (ISCT) technologies; in this sense, a use case is a short narrative describing how ISCT can be used to solve a particular problem, or to refine one particular step in the development and/or assessment process.

In chapter IV we reported the industrial needs that drive the development of ISCT technologies, according to the experts we surveyed during the Avicenna consensus process. Such needs were general in nature, and applied to all kinds of biomedical products. Here we want to look more closely at the issues specific to the medical devices industry.

The complexity of the regulatory process for high-risk medical devices is in part due to a significant fragmentation within the global market. Essentially, each country has its own set of rules and procedures. For example, while the USA and Europe agree in dividing risk in three classes (with two sub-classes for class II), many Asian countries use four. A full review is beyond the scope of this roadmap, but regional differences have been explained elsewhere for Europe, (Thompson, 2012) the USA, (Thompson, 2012), and the rest of the world (Thompson, 2012).

By contrast, the internal development process of a new high-risk medical device is quite similar across companies and families of products, and can be roughly divided into three stages:

- Design.
- Pre-clinical assessment.
- Clinical assessment.

It is useful to discuss the modernisation of the relevant processes separately for these three stages.

V.1.a. Design

When the development of a medical device starts from a clearly identified clinical need, in most cases this need is formulated as a change or improvement over an existing device, and the innovation is only incremental. Less frequently the device is designed from scratch to meet a previously unmet clinical need.

In the first case, the manufacturer will claim some similarity with existing, clinically tested devices, and will pursue a pre-marketing notification[74] (PMN) process. For the second scenario – an entirely novel product – the manufacturer must obtain a pre-marketing authorisation (PMA) (van Drongelen *et al.*, 2015). The differences between PMN and PMA, and the criteria when one or the other must be used, vary considerably between countries. But the general principle is that if the new design is similar enough to one already widely used in clinics, a fairly simple notification (PMN) is required prior to the first in-man procedure. Otherwise, before the device can be tested in humans, a full set of pre-clinical studies must be conducted to ensure that it is safe, at least with respect to the known failure modes for that type of device (PMA). Which one of these two scenarios applies makes a considerable difference in terms of the bottlenecks that occur in the current design process.

Design changes driven by commercial needs tend to be very conservative and minimally innovative. The two most common scenarios are product diversification, such as adding something that makes the product 'special', or patent circumvention. In both these cases, the primary problem is regulatory. From the producer point of view, the similarity principle applies and no additional controls are needed because a similar product is already on the market without any adverse reports. But the regulators are concerned about situations where apparently minor changes in the design trigger entirely new failure modes, ultimately resulting in serious clinical complications.

When improvements to existing designs emerge from clinical needs, they are usually triggered by reported usability issues, such as surgeons reporting issues with implantable devices, or by complications that can be highlighted by clinical case reports. This causes two major difficulties. Firstly the confirmation of anecdotal reports, which would then need to be translated into a specific functional requirement that can be addressed with a design change. Secondly, the confidence that the solution of a minor problem does not trigger unpredicted failure modes, creating a much bigger problem. In addition, tension with the regulator around the applicability of the similarity principle is always present.

Regardless of the motivation, when designs emerge as a minor modification of an existing one, and the manufacturer is planning to pursue a PMN, the major challenge is to ensure that the changes introduced to the pre-existing design do not considerably change its risk profile, without having to repeat the whole pre-clinical experimental evaluation.

Using ISCT it would be possible to compare the old and new design with respect to all failure modes relevant for that family of devices, revise the design if major risks appear, pursue the PMN when the differences are minimal, and conduct some experimental tests only when the ISCT evaluation indicates small but not negligible differences. Of course such processes must be designed in close collaboration with the regulators, so that when properly applied they would most likely produce the PMN.

The metrics of success for ISCT in such cases would be:

1. Proportion of cases where the manufacturer requests a PMN, and the regulator agrees.
2. Proportion of cases where further design revision is not required later on in the development process, for example, in response to complications made evident in

74 This terminology is the one commonly used by the US FDA. In the EC system the two cases are not treated with a separate pathway, but the regulatory bodies handle the dossier differently, so for all practical purposes, the distinction made here also applies.

early clinical trials

The most complex scenario, however, is when a device is designed from scratch. The first challenge is the capture of the clinical need, in a reproducible and quantifiable form. Once it is clear what problem needs to be solved, the design cycle can start. Traditionally, engineering design is divided into design for assembly, for function, for manufacturing, and for cost.

- Assembly: for a medical device this means deployability/ implantability and anatomical compatibility.
- Function: how the device physically interacts with the host organism, both with respect to the intended function (for example an artificial heart valve) and with respect to the secondary unavoidable interactions (such as movement of the valve during a cardiac cycle).
- Manufacturing: for a medical device, choice of the materials is the most important aspect with biostability, biocompatibility, and bioactivity being of primary concern. But materials must be manufacturable, and how physical and chemical properties relate to, are affected by, or impact on the manufacturing process must be considered.
- Cost: most high-risk medical devices are high unit value products, so the issue of cost is less pressing than in other engineering sectors. However, in some areas, where innovation stagnates, buyers tend to buy on price rather than on features, and producers end up competing on the selling price (and thus on the production costs). There are also indirect costs, for example, some design choices might make sterilisation or packaging much more expensive. Similarly, some designs require that a set of specialised instruments is made available in every hospital where the device will be implanted.

The most challenging aspects of this design process are those involving the proper representation of the patient anatomy, physiology, and biology, as well as deployment (the surgical procedure). For example, if we refer to devices that are expected to fit the patient anatomy quite closely, such as a hip replacement or a cardiac valve, too frequently the device is designed to target one generic anatomy. Such designs are frequently found to be inadequate at the pre-clinical assessment stage, requiring multiple design revisions. ISCT would enable the designer to perform 'virtual deployment' of the new design rapidly into hundreds of simulated patients' anatomies, immediately highlighting whether some features of the device need revision.

If the ISCT-supported design of conceptually new devices is properly codified and regulated, the evidence it produces should be usable as part of PMA, thus drastically simplifying the authorisation process. In this case, the metrics of success are quite similar to those described previously:

1. Percentage reduction of the time/costs to receive the necessary PMA, when compared to average time for devices of the same classes without using ISCT.
2. Percentage of cases where an additional design revision is not required later on in the development process (say to overcome complications made evident in early clinical trials).

V.I.b. Pre-clinical assessment

The term pre-clinical assessment indicates every activity aimed at assessing the safety and the expected effects on physiology and anatomy of medical devices that do not involve human clinical trials. Depending on the type of device and on the failure mode under investigation, pre-clinical assessment might be a device-only experimental test, an *ex vivo* test where the device interacts with some animal or human cadaveric tissues, an *in vitro* test where the device or part of it interact with cells and tissues cultures, or an *in vivo* test, where an adapted version of the device is implanted in an experimental animal.

Once the candidate design is finalised and internally approved, the pre-clinical assessment process starts. One effective approach to pre-clinical assessment is to use the risk analysis as a guidance (Viceconti *et al*., 2009). Most regulatory processes require a full risk analysis, based on methods such as Failure Mode and Effects Analysis (FMEA). The essential concepts discussed here would change very little if other risk management methods, such as Failure Mode or Effects and Criticality Analysis were used instead.

FMEA requires the manufacturer to list all known failure modes for that class of device, and for each of them provide an estimate of probability that such failure will occur in the device under examination with regards to the intended use, and of the severity of the effects in case such failure occurs. This produces the following two extreme scenarios:

1. Best case – known clinical failure modes: the clinical failure mode is associated with engineering failure modes.
    a. A technical standard is available to test the risk for such failure.
    b. The severity of the effects of the failure is known.
2. Worst case – unknown clinical failure modes: the clinical failure mode when observed cannot be accounted for by known engineering failure modes.
    a. No technical standard exists to test such risk.
    b. No clinical experience is available to estimate the severity of the effects if such failure occurs.

Every real-world case falls in between these two extremes.

When the device under examination involves mostly risk of failure modes close to the best-case scenario, the current methods are usually adequate. In these cases the use of ISCT is rarely necessary. However, even when most elements of the risk analysis are well known, if the pre-clinical assessment highlights an unacceptable risk, and a design revision becomes necessary, some experts report benefits of using ISCT to shorten the trial-and-error cycle by revising the design, making a prototype, and repeating the experimental testing on the new prototype.

When there is only limited prior knowledge available, ISCT could show the biggest benefits. But first, a word of caution – computer modelling and simulation help to organise all the knowledge available, even when it is fragmentary and incomplete. However, they cannot help when there is no prior knowledge. The interpretation and evaluation of the clinical failure modes that may be produced by devices depends on the extent and type of prior observations. At an extreme limit, even if the device were to produce a clinical failure mode that is unprecedented and never observed before, this could only be assessed in conjunction with clinical trials.

> "While the idea of ICST is radically innovative, there are examples of its early adoption, some of which can be considrered success stories"

Most realistically, ISCT could play an important role in refining, streamlining, and reducing the cost of the pre-clinical assessment in the following scenarios:

- The design is at risk for a clinical failure that can be produced by multiple engineering failure modes.
- The risk for an engineering failure mode to occur does not depend only on the design, but also on the patient, their lifestyle, and the way the device has been deployed.
- The severity of the effects that such failure could produce is hard to estimate.

Once the design is approved, its deployment needs to be optimised. This activity varies considerably depending on the type of device. For implantable devices this involves the definition of the surgical procedure, and the related instrumentation.

Usually, optimisation of the deployment requires imposing some changes to the design of the device itself. For example, cement-less orthopaedic implants are frequently deployed by anchoring them into a surgically prepared cavity inside a bone using an instrument called impactor. The re-design of an impactor may require that the features on the cement-less joint replacement that connect to such impactor may also have to be re-designed. Again, the manufacturer usually assumes that these changes are negligible with respect to the safety and performance of the device, and thus no additional laboratory testing is required. But in practice this separation is a thin line, and on rare occasions the regulator accepts laboratory tests done on a design even if only marginally different from the final one.

Deployment optimisation frequently involves a lot of cadaver testing. A specific aspect of the deployment might be explored on dissected organs in the company laboratories, but full surgical procedures are usually tested on an intact cadaver at morgues specifically selected to conduct experimental surgical studies. The costs and the logistical complications involved in these experimental surgery sessions are considerable, calling on the availability of a highly specialised surgeon, the whole development team, possibly a radiographer if imaging is required to check the surgical result, and a full set of prototype devices and instrumentation, all of which are located at the experimental surgery facility with the cadavers. The optimisation process is largely trial and error. It is not unusual that one such experimental surgery session is interrupted after five minutes because a major problem with the device or the instrumentation emerges. The session is then stopped, a design revision is done, new prototypes have to be manufactured, and a new session must be organised.

In such cases, when the development plan is already delayed and marketing is pressing the technical team, it is easy to end up cutting corners and not to fully optimise the deployment. However, this would most likely result in the need for modifications to be made to the devices and/or the instrumentation at a later stage when the first human studies are running, with all the complexity and costs that this involves from a practical and regulatory point of view.

In conclusion, ISCT can play an important role in almost every step of the 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 investment threshold below which the development of the product would not be cost-effective, reducing the cost, the time to market, and the associated risks. In this way ISCT can dramatically reduce the barriers to innovation, especially for small and medium sized enterprises.

The metrics of success for ISCT in the pre-clinical assessment of medical devices would be:

1. Percentage reduction of the time/costs to receive the necessary PMA, when compared with average time for devices of the same classes not using ISCT.
2. Percentage of cases where an additional design revision is not required later in the development process, such as when complications become evident in early clinical trials.

V.1.c. Clinical assessment

In the previous section it was made clear that in no case could ISCT completely replace the clinical assessment, when the product requires it. Thus, the question here is rather to explore how ISCT can be used to supplement and

support the clinical assessment.
However, this is a very complex territory, primarily because the clinical assessment of medical devices is a highly heterogeneous and non-organised activity. This is due to historical, but also operational reasons. In general, well-controlled clinical trials are difficult to design for medical devices because:

- Device performance is not independent from the patient or the surgeon. Frequently the clinical outcome of a medical device is dominated by the conditions of the patient, his/her lifestyle, and the quality of surgical procedure used to deploy the device.
- Comparative trial design is limited. In some cases there are no other similar devices on the market, so the design would be required to compare patient with the intervention to those without it. Also the performance of most devices is not independent from the deployment (surgical technique) and the surgical teams have significant experience with the old device, but not with the new one. All these problems exist also with pharma products, but they are certainly more common for medical devices.
- Single or double blind studies are impossible. In most of cases, the surgeon cannot be blinded to the type of device implanted, and no placebo exists (sham operations are almost never ethical). It is not unusual that the consultant who contributed to its design accomplishes the first clinical trial for a device, so the level of investigator bias is much higher than usual. One exception is those devices that can be switched on and off remotely.

To use a parallel with animal experimentation, ISCT could be used in relation to the clinical trials of new medical devices to reduce, refine, and partially replace them.

In many device clinical trials the endpoint that can confirm the quality of the outcome of the device is difficult to measure, it is affected by a large variability, or it requires an observational study to run for a long time. In all these cases, the use of patient-specific models as part of the clinical trials could allow a reduction of the cohort size and/or the duration of the trial in several ways. These include replacing the outcome with a surrogate outcome that requires easier measures in combination with some modelling; a drastic reduction of the inter-subject variability and/or of the reproducibility of the outcome measurement; and the provision of a model-based surrogate outcome that is evident much earlier than the standard one, thus reducing the duration of the clinical trial. In all these ways, Patient Specific Modelling (PSM) can help to reduce clinical trials in size and duration.

PSM can also drastically improve our ability to quantify the most complex outcomes (ie., functional outcomes, which typically are poorly captured by unreliable questionnaires), and also capture side effects with a much broader observational angle than normal trials can provide. Thus, the use of ISCT could refine clinical trials of medical devices, making them more effective, and reducing the risk of complications emerging only after full marketing.

Finally, while ISCT will never fully replace clinical trials, there are special cases, typically where replications are necessary for regulatory purposes but the outcome is quite obvious from previous data, where a clever combination of ISCT and conventional clinical experimentation could partially remove the need for such clinical trials. Of course this would have to happen within a very robust regulatory framework, such as the one that Medical Device Innovation Consortium (MDIC), and the US Food and Drug Administration (FDA) are developing, through the American Society of Mechanical Engineers (ASME) Verification & Validation V&V-40 standardisation sub-committee.

V.2. *In silico* clinical trials: Current practice

The outcome of the various opinion surveys and syndicate discussions as part of the Avicenna consensus process have identified some core statements describing the current state of the use of ISCT in the medical device industry:

- Modelling and simulation are used extensively in the early design phase, but primarily using computer-aided design and engineering software for the device design and for some very basic functional assessment related to mechanical strength, pressure drops, etc.
- In a few cases, modelling and simulation are also used in the pre-clinical phase, in combination with *in vitro* or *ex vivo* experiments, when the failure modes being investigated are too complex to be analysed purely on an experimental basis.
- Modelling and simulation are also used in some limited cases in the post-marketing surveillance, and analysis of retrieved specimens, to explain the observed failures.
- Only in a few examples that emerged in our surveys are models used to represent individual patients, or the inter-subject variability in anatomy, physiology, life style, and severity of the pathology. Even more rarely are models used to account for the effect of variability in deploying the device, whether in placement, surgical, or anatomical alignment, etc.
- We are not aware of any case where patient-specific modelling was used as part of the clinical trial of a new medical device.
- From a regulatory point of view, modelling and simulation are accepted to support risk analysis in the formation of a medical device dossier, or in some special cases, where experimental results alone would not be sufficient to assess the risk associated with a complex failure mode. But, as far as we know, European notified bodies currently do not accept model-based prediction as a hard fact, comparable to an experimental result. In the USA the situation is different: the FDA accept RF simulations as main evidence for MRI compatibility of medical devices; recently a minor modification on a high-risk device was approved based primarily on simulation evidences.
- No technical standards exist in relation to the specific use of modelling and simulation in the regulatory process (de-risking) for medical devices; generic standards on the application of risk management such

as ISO 14971 have to be referred instead. However, the ASME Verification and Validation 40 sub-committee is currently drafting a standard aimed to assess the credibility of a predictive model with respect to a specific application.

V.3. *In silico* clinical trials: Best practice

While the idea of ISCT is radically innovative, there are examples of its early adoption, some of which can be considered success stories; these represent the best practice so far in this domain. Below, we list a few of them, which emerged during the Avicenna consensus process. Without claiming to be exhaustive, we believe these examples can give a tangible representation of what ISCT can mean:

V.4. Use of *in silico* clinical trials for medical devices

In preparation for Event Four, a group of medical device specialists, both from industry and academia, developed the following list of examples of the use of ISCT in the medical devices industry. While surely not exhaustive, this list provides an overview of how and where ISCT could be used in the development and assessment (both pre-clinical and clinical) of medical devices. These cases were the basis for the identification of research and technological challenges reported in chapter X. As before, we separate the use of ISCT in design, pre-clinical assessment, and clinical assessment and business development.

V.4.a. Design use cases

UC1. When new designs emerge as a minor modification of an existing one (which has been thoroughly validated with clinical results), the major challenge is to ensure that the changes introduced to the pre-existing design do not considerably change its risk profile, without repeating the whole pre-clinical experimental evaluation. Would it be possible to use ISCT to compare the old and new design with respect to all failure modes relevant for that family of devices, revise the design if major risks appear, and conduct some experimental tests only when the ISCT evaluation indicates small but not negligible differences?

UC2. If we refer to devices that are expected to fit the patient anatomy quite closely (ie., a hip replacement, or a cardiac valve), too frequently the design is made targeting one generic anatomy but later on during the pre-clinical assessment such design may turn out to be inadequate, and multiple design revisions are required. Could ISCT enable the designer to rapidly perform the virtual deployment of the new design into hundreds of simulated patients' anatomies, immediately highlighting whether some design features are in need of revision?

Marco Viceconti

Stryker Corp: In silico pre-clinical assessment of proximal epiphyseal hip replacement – Marco Viceconti, University of Sheffield

Stryker Corp designed an innovative mini-invasive total hip replacement called Proximal Epiphyseal Replacement (PER). The geometry of the femoral component was designed to reduce the risk of bone avascular necrosis in the residual epiphyseal portion. The conceptual design was a modular head and a short curved stem. However, experimental tests on cadaver bones highlighted a weakening of the host bone implanted with the initial conceptual design of the PER, considerably increasing the chances of a post-operative femoral bone fracture (Cristofolini *et al.*, 2011) even more significantly to that observed for current mini-invasive hip devices. An *in silico* model of the implant-bone interaction was developed, and used to revise the prototype design by optimising the bone-implant load transfer mechanism while keeping the risk of implant loosening and prosthesis fracture low. Extreme anatomies and surgical misplacements were studied. The revised design strengthened the femoral neck of the implanted femur by an average 10% over the intact contralateral femur while reducing the relative risk associated with loosening from 45% to 60% (Martelli *et al.*, 2011). The model was then used to generate a virtual population where the patients' anatomy, their bone quality, and surgical procedure were varied using a stochastic scheme, and the risk associated with each failure mode was obtained (Martelli *et al.*, 2012). This confirmed over a whole population the good performance of the new design that was further corroborated by experimental tests using the newly developed prototypes.

INSIGNEO
Institute for *in silico* Medicine

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

The University Of Sheffield.

V.4.b. Pre-clinical assessment use cases

UC3. If the ISCT-supported design of conceptually new devices is properly codified and regulated, could the evidence it produces be usable as part of the PMA process, thus drastically simplifying authorisation?

UC4. When most elements of the risk analysis are well known, if the pre-clinical assessment highlights an unacceptable risk, and a design revision becomes necessary, can the use of ISCT shorten the trial-and-error cycle (revise design, make prototype, repeat experimental testing on new prototype)?

UC5. Could ISCT help to refine, streamline, and reduce the cost of pre-clinical assessment when:

- The link between clinical failure and engineering failure modes is unknown.
- The risk of failure depends also on the patient, his/her lifestyle, or the way the device was deployed.
- The severity of the effects if such failure mode occurs are hard to estimate.

V.4.c. Clinical assessment use cases

UC6. Can ISCT be used to **reduce** the size of the cohort required to ensure statistical power, by using patient-specific models to reduce the inter-subject variability and/or the reproducibility of the outcome measurement?

UC7. Can ISCT be used to **reduce** the duration of a clinical trial by replacing the outcome metrics with surrogate metrics provided by patient-specific models that can be observed earlier in time?

UC8. Can ISCT be used to **reduce** the size of the cohort required to ensure statistical power, by using patient-specific models based on real subjects enrolled in previous studies, in other words mixing real and virtual patients?

UC9. Can ISCT be used to **reduce** the duration of a clinical trial by validating the ability to predict the temporal evolution on a small cohort with long-term follow-up, and then use patient-specific models to extrapolate how all the other patients, with only short term follow-up would respond?

UC10. Can ISCT be used to **refine** clinical trials, by replacing a difficult-to-observe outcome metrics with a surrogate outcome based on patient-specific modelling, which can be observed more easily (less invasively, with lower risk or discomfort for the patient, at lower cost)?

UC11. Can ISCT be used to **refine** clinical trials, by using PSM to improve our ability to quantify the most complex outcomes (ie., functional outcomes, which typically are poorly captured by unreliable questionnaires), and also capture side effects with a much broader observational angle that normal trials can provide?

UC12. ISCT will never fully **replace** clinical trials. However, when trials must be replicated only for regulatory purposes but the outcome is quite obvious from previous data, could a clever combination of ISCT and conventional clinical experimentation partially remove the need for such clinical trials?

Claudio Cobelli

UVA/Padova Diabetes Simulator: A proof of concept for in silico pre-clinical trials

In 2008, the FDA accepted the type 1 diabetes computer simulator developed by Kovatchev and Cobelli as a substitute to animal trials for the preclinical testing of certain insulin treatments including in artificial pancreas studies (Kovatchev *et al.*, 2009). A new version has been recently released (Dalla Man *et al.*, 2014). The simulator has enabled an acceleration of human studies in the hospital with considerable savings in money and time. The simulator has been used by 15 groups in academia, four pharma companies (Becton, Dickinson & Co, Hospira Inc, Merck, Roche Diagnostics Operations Inc) and four tech companies (Tegra Medical, Tandem Diabetes, Epsilon Group, Dexcom). The simulator is also the core of the model predictive control algorithm used in the EU-funded AP@home project. Inpatient studies have resulted in a number of artificial pancreas studies (Bruttomesso *et al.*, 2009; Clarke *et al.*, 2009; Kovatchev *et al.*, 2010; Breton *et al.*, 2012; Luijf *et al.*, 2013). In 2011, the FDA approved the DiAs (Diabetes Assistant), which has allowed artificial pancreas studies to move to the outpatient (Cobelli *et al.*, 2012; Kovatchev *et al.*, 2013; Del Favero *et al.*, 2014; Kovatchev *et al.*, 2014). Some useful review papers are also listed (Cobelli *et al.*, 2011; Renard *et al.*, 2013; Renard *et al.*, 2013; Cobelli *et al.*, 2014; Cobelli *et al.*, 2014; Peyser *et al.*, 2014).

DEPARTMENT OF INFORMATION ENGINEERING
UNIVERSITY OF PADOVA

Charles Taylor

HeartFlow: Non-invasive assessment of coronary disease – Charles Taylor, HeartFlow Inc.

A recent meta-analysis of nearly 50,000 patients has confirmed that the best way to stratify patients for percutaneous coronary intervention is an invasive measurement called Fractional Flow Reserve (FFR) (Zhang *et al*., 2015). Unfortunately, FFR measurement is a complex, somewhat risky, and expensive procedure, and thus its adoption is moderate in spite of strong evidence of its effectiveness. Taylor and his team developed an image-based patient-specific modelling protocol called FFR-CT that can provide an accurate estimate of the FFR non-invasively from a coronary computed tomography angiography. A recent clinical trial concluded: "FFR-CT provides high diagnostic accuracy and discrimination for the diagnosis of haemodynamically significant CAD with invasive FFR as the reference standard" (Nørgaard *et al*., 2014). In November 2014, the FDA authorised the marketing of the HeartFlow FFR-CT software.

HeartFlow™

Chapter VI

In silico clinical trials: Use cases for pharmaceuticals

Authors

Adriano Henney, Anders Karlström, Marco Viceconti, Ben G. Small, Sebastian Polak, Giuseppe Assogna

Summary

Chapter VI analyses how a pharmaceutical product is developed and assessed, where *in silico* clinical triasl are already used, success stories and cases where *in silico* clinical trials could help.

VI.1. Modernising the development of pharmaceuticals

Pharmaceutical research and development (R&D) is built upon the concept that diseases and disorders can be broken into underlying biological processes that can be defined in terms of their constituent elements or targets. By developing therapies that interact with these target elements, pharma selects interventions to alter the biological process in question, assuming this will intervene in the disease process with the ultimate aim of delivering therapeutic benefit to the patient.

The industry has largely been built on an approach composed of a variety of *in vitro* and *in vivo* screens, studying the interaction of therapeutic targets with medicinal or biological therapeutic entities. With the development of highly detailed molecular and cellular technologies, especially post-genome, the approaches have adopted an increasingly reductionist focus. The pharma R&D pipeline is typically broken down into three broad phases: Discovery (decision points 1-5), translational studies and pre-clinical assessment (decision points 5-6), and clinical development (decision points 6-11).

VI.1.a. The status quo

Discovery scientists typically begin target identification in areas of high unmet medical need by using information on disease epidemiology, pathways, mechanisms, and potential targets culled from the literature in the public domain. These data are used to frame hypotheses about how intervention with a drug might alter the course of disease and, importantly, to build the case why these are starting points for the development of a successful and commercially viable product. This case can be built from experimental studies in a variety of cellular and, possibly, animal models designed to confirm, or partially validate the connection between the target and the biological process, sufficient to build confidence in the rationale.

Prioritised molecular targets are subjected to the first of a number of screening strategies to identify potential therapeutic entities. For small molecules, this involves the use of high-throughput screening of a library of compounds, often numbered in the millions, to identify active compounds that have an element of selectivity for the target and are potentially 'druggable'. That is structures that, from a medicinal chemistry perspective, have properties that would be required for a successful drug, and are readily modifiable. The process is different in the case of biological therapeutics (eg., antibodies). In recent years, the ability to screen virtual chemical structures in computers has enabled the expansion of the "chemical space" (Paolini *et al*., 2006) that is otherwise available only through the use of physical compound libraries, increasing the potential for novel starting points for chemical synthesis. This process culminates in hit identification; that is, a series of many structures that represent potential chemical starting points for more detailed study alongside the biology being investigated.

The lead identification phase turns these initial structural 'hits' into potential 'leads'. *In vitro* cellular assays are used to assess how structural changes to the chemical starting points influence the target. An iterative make-test cycle creates a much smaller number of compounds, typically represented by a range of different chemical series, that the assays have shown interact with the target in such a way as to demonstrate the potential to become an effective treatment.

Chemical leads then undergo a major focus on further refinement. Lead optimisation focuses on the prioritised compounds to optimise them in terms of absorption, duration of action, and delivery to the target *in vivo*. As before, these studies involve similar make-test cycles between chemical modifications and biological assays, this time including studies in animal models designed to investigate the physical and toxicological properties of the molecules. This is with a view to building confidence that the compounds have the potential eventually to undergo principle and concept testing in humans. Usually this will result in no more than two or three compounds emerging as potential drug candidates.

These detailed investigations become even more focused on these two or three compounds during the pre-nomination phase, to scrutinise them in terms of safety, the method/route of administration, and bioavailability *in vivo*. Another important consideration at this point, is the ease with which synthesis of the compound can be scaled up for routine manufacture, as well as the cost of goods associated with that, either or both of which could be hurdles to further progression of promising molecules. At the end of this phase, a dossier supporting the profile of a single compound as a candidate drug is submitted for transition into the development process. One or two back-up molecules that are similar to the preferred candidate, but for whatever reason are ranked below it, normally support a candidate drug nomination, ready to be called upon in the event that it fails.

The handover between discovery and development typically takes place during a pre-clinical development phase. Here, pivotal toxicity studies are undertaken, alongside safety pharmacological, and other investigations to compile the necessary regulatory dossier for submission to the relevant authorities to allow the first administration of the compound in human subjects (first in man) as an investigational new drug, in preparation for principle testing.

Phase I clinical studies are conducted in healthy volunteers, or patients, and are usually non-therapeutic, intended to study the safety and tolerability of the candidate drug in humans as opposed to animal models, as well as its pharmacodynamic and pharmacokinetic properties, using single and multiple ascending doses. Phase II studies follow on from these, and are designed to test proof of principle in a limited number of patients. This provides evidence that an intended pharmacological effect results in an expected change in a biomarker in a dose range, without

any unwanted effects. Studies are also designed to test dose-response relationships and efficacy to help select suitable doses for subsequent phase III studies.

Concept testing is the phase during which demonstrable evidence of clinical efficacy and safety emerges in studies conducted on the target patient group – ie., proof of concept. This provides the clinical confirmation that an investigational product has the desired effect in patients with the disease of interest through placebo-controlled studies. This phase and the subsequent clinical development for launch is where various phase IIIa and IIIb studies are carried out to add further evidence confirming safety and efficacy, dosage, formulation, and all other studies conducted in targeted patient populations to complete the dossier required for regulatory approval. Following the successful launch of the new drug, additional post authorisation studies will be done as part of the approach to support product maintenance and life-cycle management, including long-term effects and health economic aspects.

A representation of the typical duration for each phase in the pipeline is shown in figure VI-1.

which is the need to finance many failures to have a chance of delivering a successful outcome. If failure comes early, the cost is relatively low, but once in development, the cost of project failure escalates the later it happens.

A comprehensive review of the AstraZeneca small molecule pipeline over the five years from 2005 to 2010 was done to identify the most important technical determinants of project success – the five 'R's': right target, right patient, right tissue, right safety, and right commercial potential (Cook *et al*., 2014). All of these could be said to be obvious, but they are more credible than more emotive assumptions as they are supported by a thorough and rigorous retrospective analysis over years that, interestingly, also identified a sixth 'R', the need for establishing the right culture for effective decision making based on these factors. In their conclusions, the authors have stated that there have been encouraging signs of improved success since implementing this process as part of their core project framework. This may be a sign of changing culture within, at least one, pharmaceutical company, showing the potential to embrace modelling and simulation platforms as an alternative approach to improve the odds of success of hits on target by refining our ability to predict outcomes at each point in the value chain.

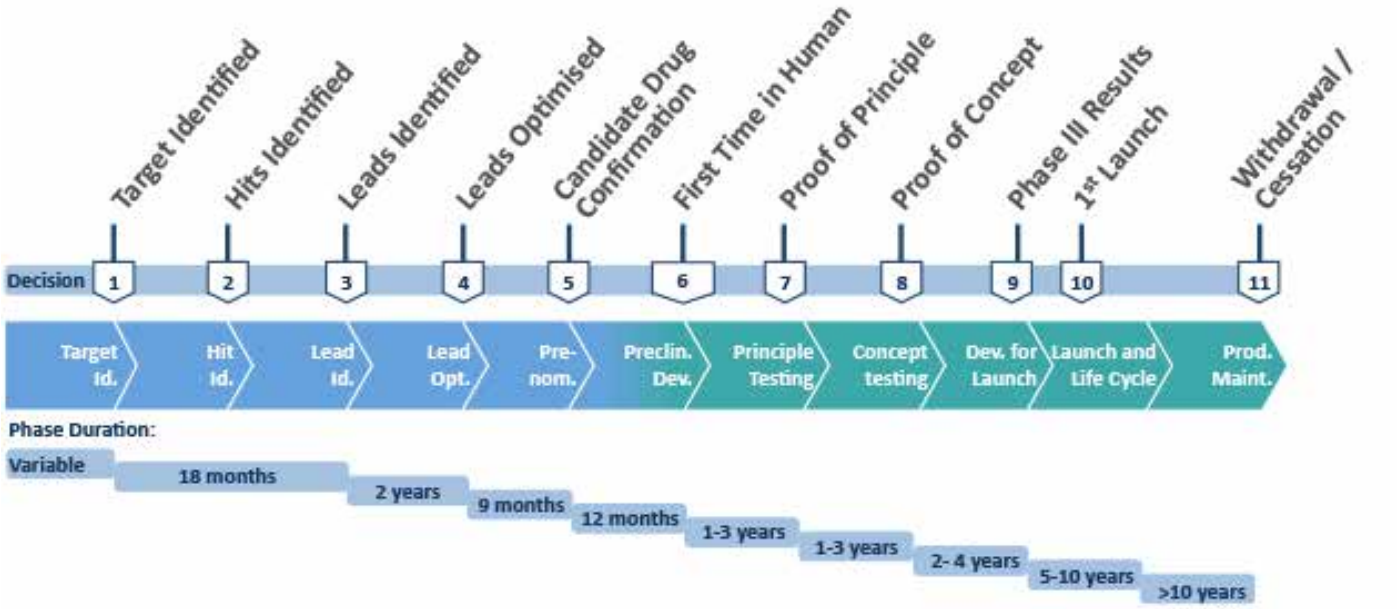

Figure VI-1 Duration of phases in the pharmaceutical R&D pipeline.

The latest estimates of the cost to bring a successful new medicine from project start to the market provided by the Tufts Center for the Study of Drug Development is close to $2.5bn, with less than one in every ten projects entering into development succeeding, with the failure of many hundreds of projects at the discovery phase (Paul *et al*., 2010). As has been written at length in various articles, the majority of late stage failures tend to be in phase II and phase III, the most costly phases of the pipeline accounting for nearly 50% of the R&D costs[75], and are due to failure of efficacy and clinical safety (Arrowsmith and Miller, 2013). The approach to dealing with this historically has been to adopt an increased number of "*shots on goal*" as a route to cope with the attrition in the pipeline, the consequence of

VI.1.b. Applications of *in silico* clinical trials in discovery

Discovery is the engine that drives pharmaceutical R&D and to this end activities that are undertaken in this phase broadly span the target identification and pre-nomination stages of compound development (see section VI.1.a). Pharmaceutical companies invest much time and money in developing, maintaining, and parsing their compound libraries to locate appropriate chemical starting points (lead identification) for their intended targets. A large compound library may be composed of around 4-5 million chemical structures. Efforts to structure

75 Source: "The Pharmaceutical Industry in Figures. Key Data 2014" European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels. www.efpia.eu

physicochemical and Structure-Activity Relationship (SAR) data and transform them into knowledge have been undertaken (Paolini *et al*., 2006). Similarly, application of appropriate visual and statistical analysis to chemo-informatics databases has enabled more informed judgements to be taken in the choice of lead compound classes for starting high-throughput screening campaigns (Akella and DeCaprio, 2010). Often initial hypotheses indicating a drug target in a disease are predicated on the idea that stimulating or inhibiting the target will result in a return of the system (eg., whether it be a cell type, organ, or tissue) to a 'normal' homeostatic equilibrium. Nevertheless, owing to the complexity of biology and its myriad, multiscale positive and negative feedback loops (Henney *et al*., 2015), this simplistic ideal is rarely realised without either significantly locating less efficacious ligands than desired against candidate selection criteria or producing unwanted or 'off-target' effects or at worse both. Addressing this challenge can in part be accomplished via application of 'dry' computational methods to guide the next experiment to data derived from 'wet' experimental high-throughput screening methods in successive iterative cycles.

> "The industry has largely been built on an approach composed of a variety of *in vitro* and *in vivo* screens, studying the interaction of therapeutic targets with medicinal or biological therapeutic entities."

The use of multi-objective evolutionary algorithms (EA) to drive the search for efficacious drug combinations as either anti-tumoural agents (Zinner *et al*., 2009; Zhao *et al*., 2015), or as inhibitors of an inflammatory protein, such as IL-1ß commonly elevated in inflammatory disease (eg., cancer, heart disease, arthritis) (Small *et al*., 2011) has been demonstrated. The multi-objective nature of EA ensures that assay data measuring both desired and undesired effects can be incorporated and parsed to nominate the next generation of combinations to be tested, until such a time that there is no change in the objective function criteria (eg., inhibition of protein synthesis coupled with either no or little cell death – as this latter criterion would necessarily reduce the first but not in the desired manner). Applications of machine learning to gain knowledge on (patho)-physiology and confirm drug efficacy and safety are likely to see future growth as more objective measures for candidate drug nomination (see section VI.1.a)

VI.1.b.i. Applications of *in silico* clinical trials in pre-clinical testing

Genesis of the mathematical modelling of the cardiac action potential began with Dennis Noble and was predicated on the seminal work of Hodgkin and Huxley (Hodgkin and Huxley, 1952; Noble *et al*., 2012). Although these models were of academic interest, their importance in drug development was not recognised until it was realised that the human ether-a-go-go (hERG) ion channel (Kv 11.1) encoded the pore forming subunit of the 'rapid' delayed rectifier current (IKr) and is principally responsible for repolarisation of the cardiac action potential (AP). Blockade of this channel by the once popularly prescribed antihistamine terfenadine as a result of its raised concentration via metabolic inhibition of CYP3A4 by co-administered conazole class anti-fungal drugs (Gras and Llenas, 1999) resulted in AP and consequent Q-T interval prolongation (Pohjola-Sintonen *et al*., 1993) and its subsequent withdrawal from the market.

These events stimulated formation of regulatory documents advising the routine non-clinical evaluation of a new drug entities' likely pro-arrhythmic risk (Anonymous, 2015). It quickly became apparent that early screening of hERG liability during the hit identification stage was important for removing this unintended activity. This catalysed the generation of medium-throughput electrophysiological assays to quantify a new drug entities' hERG activity and therefore potential risk moving forward (Bridgland-Taylor *et al*., 2006). However, the multiple ion channel basis of cardiac AP propagation indicated that measurement of IKr inhibition alone was insufficient to explain all instances of aberrant cardiac repolarisation principally directed via ion channel blockade. Integrating all the data from the molecularisation (ie., measurements of drug-induced blockade of sodium, calcium, and voltage-dependent potassium currents) of the cardiac action potential presented a significant challenge. Formal models of cardiac cell AP conduction have been established (Bottino *et al*., 2006; Davies *et al*., 2012) that facilitated integration of this data and transformation into knowledge about whether a molecule was likely to adversely affect cardiac conduction. The predictivity of these simulations when integrating appropriate assay data has shown promise (Glinka and Polak, 2014; Mirams *et al*., 2014).

VI.1.b.ii. Applications of *in silico* clinical trials in development

A crucial tenet when translating pre-clinical findings into human subjects is that the molecule or device under test should do no harm. The advantage that modelling and simulation of the cardiac electrophysiological response offers to studying a new drug entity in a virtual population is of obvious utility. *In vitro–in vivo* extrapolation (IVIVE) defines a method of scaling *in vitro* data to define an observed *in vivo* phenomenon and has been used in the scaling of metabolic clearances in physiologically-based pharmacokinetic (PBPK) modelling (Rostami-Hodjegan, 2012). The recent leveraging of this technique in

combination with single cell (see section 1.a.ii) and cellular string models has enabled the simulation of action potential duration (APD) and Q-TcF parameters respectively (Polak *et al*., 2014). For example, population models of human atrial electrophysiology calibrated against human electrophysiological data mimic AP variability in 'normal' and altered (atrial fibrillation) sinus rhythm (Sánchez *et al*., 2014). The use of IVIVE approaches has recently been illustrated by the gender-specific prediction of changes in Q-TcF as a consequence of co-administration of domperidone and a CYP3A4 inhibitor, ketoconazole, in virtual human subjects that was reflective of the observed clinical data (Mishra *et al*., 2014). The evolution of cardiac AP/Q-T modelling and simulation approaches to predict these observed clinical endpoints are timely given that terfenadine blockade of IKr was only realised via a drug-drug interaction (see section V1.1.b.i).

VI.2. *In silico* clinical trials: Current practice

The various opinion surveys and syndicate discussions undertaken as part of this research programme led to the identification of some core statements describing the 'current state':

- The ability of pre-clinical testing to predict efficacy and safety in the clinical phase is insufficient.
- All drug projects include modelling as part of PKPD studies.
- Laboratories that are multidisciplinary will gain from the introduction of *in silico* clinical trials (ISCT) compared with laboratories that are not.
- An excellent example of ISCT is what is being done in the Virtual Physiome, but there is still a lot to do before it gets close to what is going on in the body.
- Good examples of the potential of ISCT have been prototyped by the US company Entelos, but not successfully implemented.
- A number of companies have been established to do animal to human modelling, but with no material results.
- There are examples of models that can predict absorption, distribution, metabolism, elimination, and toxicity (ADMET) (eg., Simcyp, Gastro-Plus, PK-Sim).
- We can begin to advance ISCT with the science and modelling capabilities we have now – modelling capabilities are not what is holding up progress.
- We have not yet exploited the models and simulations that already exist.
- The validation of models is far from sufficient currently.
- Modelling and simulation approaches are clearly being used within biomedical research so demonstrating their scientific feasibility. However, a lack of convincing evidence exists regarding where they can be optimally used.

VI.3. *In silico* clinical trials: Best practice

While the idea of ISCT is radically innovative, there are examples of its early adoption, some of which can be considered success stories; these cases represent the best practice so far in this domain. Below, we list a few of them, which emerged during the Avicenna consensus process. Without claiming to be exhaustive, we believe these examples can give a tangible representation of what ISCT can mean:

Entelos' in silico model predicted 2010 revision of UK guidelines – a success story for in silico drug trials.

In 2007, *in silico* studies done by Entelos, a leader in predictive biosimulation for pharmaceutical and consumer product R&D, predicted that rituximab would be superior to anti-TNF in preventing bone erosion in patients with severe (but not moderate) disease. This recommendation was later confirmed by clinical research. This modelling insight predated a revision to the UK National Institute for Health and Care Excellence (NICE) guidelines for the use of rituximab by several years. In 2010, NICE issued guidelines recommending that rituximab, adalimumab, etanercept, infliximab, and (in certain circumstances) abatacept, be used as possible treatments for rheumatoid arthritis after treatment with a tumour necrosis factor (TNF) inhibitor has failed (Malottki *et al*., 2011). Further, rituximab (MabThera) in combination with methotrexate, was recommended as an option for the treatment of adults with severe active rheumatoid arthritis that have responded inadequately to other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one TNF inhibitor, or who are intolerant of other DMARDs. These guidelines are aligned with and were supported by insights derived from predictions from the Entelos model made in 2007. The Entelos biosimulations showed that rituximab induces sustained benefits in joint structure; a decrease in the rate of cartilage degradation and bone erosion persists for months after cessation of treatment, even after joint inflammation returns. The success of Entelos' *in silico* predictions suggests broad application in more efficient drug development and wide implications for the future of clinical trials. (http://www.entelos.com/).

ENTELOS®

John Graf

GE Global Research: Pharmacokinetic modelling in the development of contrast agents

In 2013, GE Healthcare announced the US Food and Drug Administration (FDA) approval of Vizamyl™, a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging (Lerman and Gibson, 2013). The cost of developing biomedical imaging agents can be very high. The process includes identifying a biomarker target that is specific to a disease and that is expressed at levels sufficient for detection. A molecule must then be developed with specific binding affinity to the biomarker target. This molecule must also exhibit good delivery and clearance pharmacokinetics over the imaging time frame. Furthermore, the binding molecule must include a detectable marker that provides a measurable signal well above the noise level of the imaging modality and at a dose that can be safely administered in humans. John Graf and his colleagues at GE Global Research have used physiological-based pharmacokinetic modelling (PBPK) in combination with physics-based image simulators to assess feasibility of molecular imaging using PET in oncology, neurology, and cardiology (Simmons *et al.*, 2005; Zavodszky *et al.*, 2011; Graf *et al.*, 2012). The *in silico* models and calculations they have generated have been used to assess the feasibility of imaging during the early research and preclinical stages. "We have learned that this model-driven approach focuses the project team on the clinical problem from a system perspective. *In silico* calculations can promote asking the right questions and making early decisions based on quantitative calculations rather than on speculative, and sometimes wishful thinking." But the early detection of potential issues with a product is not always necessarily good news. Dr Graf comments: "Unfortunately, many of proposed imaging targets and agents have flaws. It is not always easy for the computational biologist to be the bearer of bad news or to stop a project with strong support or too much momentum and investment. I wonder: does a company need to have a computational mindset in its leadership for an *in silico* paradigm shift to really take hold?"

Steve Chang

Immunetrics: An ISCT company

Immunetrics[1] is an *in silico* modelling company that builds predictive computer models based on the biological response to disease and intervention. With the expertise of biologists, mathematicians, and software engineers, Immunetrics employs their own powerful suite of modelling tools to predict clinical outcomes of therapeutic interventions in acute and chronic inflammatory diseases and autoimmunity at both individual patient and trial population scales. For over a decade, Immunetrics has been engaged in the endeavour of more than 20 *in silico* trial applications for large pharmaceutical companies across several different disease states. More specifically, they have been working continuously with select large pharma companies for the past eight years using bio-simulation to assist in actual trial designs that have been implemented. One of their most recent successes involved the FDA waiving the requirement for a second trial for one of their clients based on the simulation outcome in combination with statistical results. Building on years of experience, Immunetrics has worked out example solutions to a large number of technological and scientific barriers, including how to employ phase II trial results within simulation models to predict whether the efficacy observed would translate successfully into phase III trials, how best to power phase III trials for a greater likelihood of success, and predict pre-trial novel entities which are not likely to meet that threshold. While many challenges still remain, their perspective is that the most difficult challenges to widespread adoption of *in silico* trial applications are rooted in the cultural state of the industry.

1 http://www.immunetrics.com

Alfonso Bueno-Oravio

Virtual Assay: In silico pre-clinical trials to enhance drug safety and efficacy assessment

No two individuals respond to a drug in exactly the same way, and what works for one person may not work for another, even before accounting for any additional complicating factors. This is one of the most significant challenges faced by the pharmaceutical industry; clearly it is neither practical nor desirable to test a new drug on the entire population to ensure it is both safe and effective. To overcome this, *in silico* modelling is becoming increasingly important in drug testing (Sager *et al.*, 2014). However, traditional modelling approaches tend to ignore the variability between individuals. A new modelling perspective, naturally incorporating this variability, has been recently developed at the University of Oxford in collaboration with Janssen Pharmaceuticals (Britton *et al.*, 2013). The methodology has further been developed into a user-friendly package called Virtual Assay, to facilitate industry uptake (Anonymous, 2015). Virtual Assay starts with well-understood models of cellular biology and modulates their variables to generate a population of models in agreement with experimental observations. These populations can then be used to conduct ISCT to analyse the effects of pharmaceutical agents at the population level. The methodology has been demonstrated to quantitatively predict the range of cellular responses observed in drug safety studies in different species and cell types, specifically human. This new approach has the potential to contribute to a faster and cheaper drug development process, to overcome difficulties inherent in the design of clinical trials (such as underrepresented high-risk subgroups within the recruited cohorts of patients), and to minimise animal experimentation in drug testing, as recognised with the 3Rs Prize for the Replacement, Refinement and Reduction of animals in research (NC3R, 2015).

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Simcyp: Physiologically-based pharmacokinetic modelling enables understanding, predicts pharmacodynamic effect and can guide statistical powering of clinical studies.

A bridge between classical, top-down PKPD modelling approaches and incorporation of genotype-phenotype, bottom-up data can be realised using mechanism-based physiologically-based pharmacokinetic PBPK modelling. A PBPK-pharmacodynamic (PD) model considered the impact of genotypic variation in the cellular transporter OATP1B1 on the efficacy of the cholesterol lowering drug rosuvastatin. The studies used melavonate concentration as a marker of PD effect, comparing different input sites that drove the PD effect (Rose *et al*., 2014). Further, PK differences in OATP1B1 genotypes were propagated to the PD response from the plasma but to a much lesser extent from the liver intracellular water compartments respectively, demonstrating the importance of modelling the relevant biological effect compartment to assess accurately the impact on pharmacodynamics of the compound (Aoyama *et al*., 2010; Rose *et al*., 2014). Similarly, PBPK models were used to study the prospective powering of clinical studies, specifically looking at detecting a difference in Area Under the Curve between 0 and 24 h (AUCt) for the first dose of midazolam in different populations (Barter *et al*., 2013). These examples showed that the standard approach to assess statistical power required to detect a difference in the AUCt for the first dose of midazolam between North-European Caucasian and Chinese subjects would require recruitment of over 338 individuals from both populations in order to power the study theoretically to 100%. However, using modelling, it was shown that the recruitment of as few as 54 and 80 individuals from both populations could deliver 80 and 90% power to detect a difference respectively. The conclusion from these studies is that appropriate prospective powering of clinical studies based on representative virtual populations can guide subject recruitment (see figure VI-2).

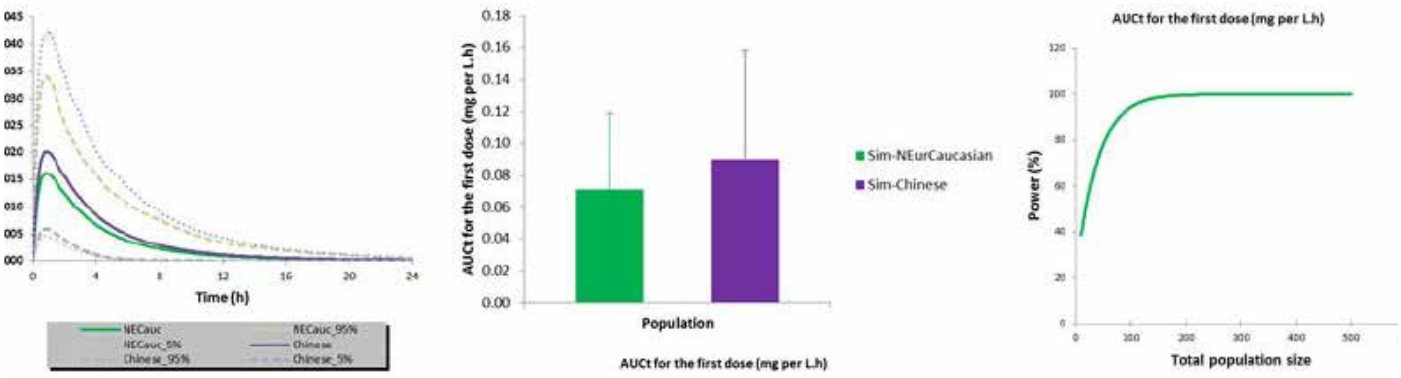

Figure VI-2 Simulations of single-dose oral administration of Sim-Midazolam (0.5 mg = 24h) in a North-European Caucasian (Sim-NEurCauc: N=500; Males=256, Females=244; 20-50 y,) and Chinese (Sim-Chinese: N=500; Male=257, Females=243; 20-50 y) population. Plasma concentration–time profiles reveal differences in Cmax, AUCt for the first dose and CL between North-European Caucasian (Cmax: 0.0162 mg/L (upper plot); AUCt: 0.071 mg per L/h (middle plot); and CL 126.7 L/h (not shown)) and Chinese (Cmax: 0.0202 mg/L (upper plot); AUCt: 0.090 mg per L/h (middle plot); and CL 99.2 L/h (not shown)) respectively. All parameters were significantly different as assessed by ANOVA at the 95% confidence level. Assessment of statistical power required to detect a difference in AUCt for the first dose between North-European Caucasian and Chinese subjects respectively (lower plot) reveals that over 338 individuals would need to be recruited from both populations in order to have certainty (P=1, power=100%) in detecting a difference in these pharmacokinetic parameters. However, 80 and 90% power to detect a difference in AUCt could be achieved through recruitment of as few as 54 and 80 individuals respectively.

Chapter VII

In silico clinical trials: Horizontal challenges and emerging technologies

Authors

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Summary

Chapter VII reports the research and technological development challenges that are horizontal in nature and analyses how *in silico* clinical trials relate to other emerging technologies.

VII.1. Scope: Horizontal research challenges

One of the primary motivations of this roadmap is to identify, through a consensus process among all the various stakeholders, the research and technological development (RTD) challenges that need to be overcome to ensure a broader and more effective adoption of *in silico* clinical trials (ISCT), defined as "the use of individualised computer simulation in the development or regulatory evaluation of a medical intervention".

In order to focus the discussion, a large part of the consensus process relative to the identification of the specific RTD challenges has been driven separately for pharmaceutical, and for medical devices. A third group of experts worked on the so-called horizontal challenges, those related to aspects such as infrastructures, policies, regulations, and in general looking at socio-economic aspects.

In this chapter we focus on horizontal challenges, those that apply to all types of biomedical products. The starting point is a list of 12 RTD horizontal challenges (referred to as HC#) that were identified during Avicenna Event Four and are listed in Annex VII-1.

The RTD challenges relative to medical devices are discussed in chapter VIII. Those specific to pharmaceutical products are presented in chapter IX. All the socioeconomic aspects were discussed in chapter IV.

Here we focus on the remaining challenges, which have mostly to do with infrastructural aspects.

VII.1.a. A validation and certification framework for in silico models

While it was recognised that the validation and certification of *in silico* models is a problem for all types of biomedical product, the experts agreed that specific discussion on the models' validation cannot be conducted in general terms for both devices and pharmaceuticals. The topic is thus covered in those respective chapters.

A related argument, which is horizontal in nature, is the need for shared and widely accepted benchmarks problems, against which to verify the predictive accuracy of the models in use. While extensive technical standards exist for this purpose for other mission-critical products, such as nuclear power plants[76], ISCT, and *in silico* medicine in general are far from that level of maturity. An interesting approach is provided by the so-called modelling challenges. One quite popular promoted by BJ Fregly and colleagues, funded by the National Institutes of Health (NIH) and hosted by the USA SimTK consortium, aimed to challenge all modellers in the world to predict accurately the forces transmitted through the knee joint in a given individual[77]. Every year the organisers publish a set of subject-specific measurements relative to a patient who received a special total knee replacement fitted with an embedded force sensor that transmits in telemetry the actual force during a certain movement. All musculoskeletal modelling specialists in the world are then invited to predict the telemetry force measurements, using patient-specific models. The competition has now run for five years, and the results have improved each time (Kinney *et al.*, 2013). Another example is the PhysioNet Computers in Cardiology Challenge[78]. We recommend that the research funding agencies consider sustaining the development of many more similar experimental benchmarks for ISCT technologies. These could then be used to accredit specific modelling technologies in term of predictive accuracy against publicly available benchmarks.

An '*in silico* service' would also need to be regulated as a medical device in its own right (ie., software as a medical device) and would likely be class III. Many of the software codes that are suitable for use in the medical arena are not certified to be used in this way.

VII.1.b. Policy and governance frameworks for sharing

The public release of validated gold standard patient specific models for other users to use, assess applicability to different problems, test limitations, and improve upon could in principle further contribute to building trust in ISCT.

A number of initiatives and funding projects have in the last few years tried to establish sharing mechanisms for data and models for *in silico* medicine. The advantage of having such shared repositories is self-evident, and the technologies to make this possible are already largely available[79,80]. The real problem is the lack of appropriate polices and governance frameworks to operate such repositories. There are essentially two issues:

1. The legislation on the secondary use for research purposes of patients' data, even in fully anonymised form, is unclear, confusing, and differs from country to country. This potentially exposes the hosting organisations to risks of legal liability, and in the case of misuse, to public deprecation in the media, something most academic organisations fear immensely.
2. The competition between academic groups for research funding, and that between companies for market share, creates major barriers to the widespread adoption of policy sharing.

In both cases, the issue is not scientific or technological, but related to policies and governance frameworks. It is essential to promote the systematic exploration of different governance models, toward the establishment of best practices that the community could use to drive all sharing initiatives.

76 http://tinyurl.com/WNA-report
77 https://simtk.org/home/kneeloads
78 http://www.physionet.org/challenge/
79 http://www.vph-share.eu
80 http://p-medicine.eu

VII.1.c. Computational infrastructures for ISCT

The agencies in charge of supporting the European e-infrastructures have not invested so far in any initiative dedicated to the deployment and support of pre-competitive high-performance grid/cloud computing infrastructures for data storage, modelling, and simulation required by ISCT or more in general by *in silico* medicine. This is in spite of the clear case for making *in silico* 'a service' available to all, both in academia and industry.

The VPH-Share project4 has developed most of the software technology that would be required to operate such facilities, which could be configured to consume computational resources (whether high-performance computing or cloud computing) from the user accounts, thus separating the cost of running and supporting the infrastructure from the cost of using it.

But here, like in other similar cases, there seems to be a difficulty with the current funding opportunities supporting an infrastructure that cannot be mapped to a fundamental research community (such as high-energy physics, molecular biology, computational chemistry), but is not developed enough yet to be commercially self-sustainable.

VII.1.d. Training and re-training

Another horizontal issue is the educational activities required to prepare industry for a wide-scale adoption of ISCT. We distinguish here between training (targeted to those who have not entered the work market yet) and re-training (targeted to those who are already employed).

In terms of training, we recommend the establishment of graduate study programs (masters and PhDs) on patient-specific modelling, predictive medicine, and ISCT.

Curricula that focus on the technical and technological aspects would be opened to students with a first degree in engineering, computer science, mathematics, physics, chemistry, or similar disciplines, who would be trained to transform imaging, sensing, laboratory, and clinical data into quantitative predictive models to be used in all applications of *in silico* medicine, including ISCT. These specialists would typically join companies that develop services for ISCT, or the product development and assessment teams in biomedical industries as specialists of *in silico* medicine technologies.

A second type of curriculum could be opened to students with a first degree in biomedical disciplines (biology, medicine, pharmacology, etc.), and would aim to train them to use the available ISCT technologies effectively, critically revise the results they provide, and integrate them into drug discovery, device design, pre-clinical assessment, and clinical assessment activities. These specialists would join research and development (R&D) departments or contract research organisations (CROs) as specialists in ISCT and related technologies.

A second training strategy is to inject into the more traditional degrees in medicine, biology, bioengineering, clinical research, drug discovery, etc., one or more courses on *in silico* medicine. This in the long run would provide to all those involved with the biomedical industry, a better understanding of the possibilities (and the limitations) of ISCT technologies.

Similar educational content can be used in some re-training programs. Targeted re-training opportunities, from industry workforce training seminars to part-time masters degrees, and online training offers, would help professionals working in research hospitals, CRO, pharma and device companies, regulatory agencies, and so on, to become familiar with the concept of *in silico* medicine technologies, and their applications to ISCT. Again, the primary purpose would be to promote a critical thinking around ISCT, so that these technologies become not only widely adopted, but also used properly and effectively.

Yet another dimension is that of documentation. Standard ways of documenting use and development of methodologies could allow for easier handover between experienced and inexperienced users, promoting easier uptake from new users.

VII.2. The bigger picture: Horizontal challenges

The focus of the Avicenna roadmap is the use of *in silico* medicine technologies in the development and assessment of traditional biomedical products, such as pharmaceuticals and medical devices. But how do ISCT technologies relate to the other ideas that represent the future of healthcare?

VII.2.a. From in silico clinical trials to in silico medicine

As we started to poll our industrial experts, it became evident that the narrow scope that we gave to this exercise does not reflect the perception of many industrial players. While there is a considerable interest in exploring how *in silico* technologies can improve the development process of biomedical products, there is an equally significant interest in understanding how *in silico* technologies can themselves become radically innovative products, alone or in combination with other technologies. Some examples that emerged during our consensus process were: patient-specific, simulation-assisted surgical planning (Audigier *et al.*, 2013; Grbic *et al.*, 2013; Ceresa *et al.*, 2014; Swee and Grbic, 2014; Bouzid *et al.*, 2015); imaging plus modelling systems for diagnosis-prognosis (Morris *et al.*, 2013; Zarins *et al.*, 2013; Falcinelli *et al.*, 2014; Lungu *et al.*, 2014; Roldán-Alzate *et al.*, 2015); patient-specific models to tune complex medical devices such as ventricular assistive devices (Brown *et al.*, 2012; Tzallas *et al.*, 2014); and devices with embedded *in silico* technologies, such as implantable drug delivery systems for artificial pancreas applications

(Zavitsanou, *et al.*, 2015). So while ISCT is a good starting point, the emerging pre-competitive alliance (see chapter X) should target *in silico* medicine in a broader sense.

VII.2.b. 3D organ printing and synthetic biology

A number of synthesis technologies, which allow the fabrication of complex systems with very high level of control, are being explored in the context of biomedical applications (Ozbolat and Yu, 2013; Zhang and Zhang, 2015). ISCT is the backbone of these futuristic ideas: if 3D printing can print a heart, *in silico* medicine technologies are necessary to design it (McCune *et al.*, 2014; Sun *et al.*, 2014; Kucukgul *et al.*, 2015).

> "The focus of the Avicenna roadmap is the use of *in silico* medicine technologies in the development and assessment of traditional biomedical products, such as pharmaceuticals and medical devices."

VII.2.c. Organ-on-chip

A number of tissue-engineering technologies are now being exploited not with a regenerative medicine perspective, but in order to realise *in vitro* systems that combine the level of control of an *in vitro* experiment with a much higher level of realism, in relation to the interaction between fluids, cells, and tissues (Huh *et al.*, 2013; Wikswo *et al.*, 2013; Ahmad *et al.*, 2014; Ebrahimkhani *et al.*, 2014; Luni *et al.*, 2014; Tourovskaia *et al.*, 2014; Esch *et al.*, 2015). These complex biological devices are being used, for example, to screen large numbers of candidate compounds in contexts where the mechanisms emerge from the systemic interaction of different cell types, tissues, and transport mechanisms. ISCT models can be validated using organ-on-chip set-ups, as the very high controllability of these experiments ensure a solid validation framework. Organ-on-chip results can then be generalised using ISCT models, where the generalisation to a whole organ, and to its interaction with other organs or the whole organisms would become prohibitively complex to model physically.

VII.2.d. The digital mouse

ISCT entertain a similar relationship with animal models, and their digital counterparts. Animal models can be used to validate ISCT models (Mardel *et al.*, 1995; Arakelyan *et al.*, 2005; de Jong *et al.*, 2007; Trachet *et al.*, 2011; Trachet *et al.*, 2015); ISCT models can help to reduce, refine, and partially replace animal models (Beattie *et al.*, 2013; Brinkmann *et al.*, 2014; Törnqvist *et al.*, 2014). In addition, ISCT can be used to better translate observations from the animal model to the human target (Beard *et al.*, 2012).

VII.2.e. Big data analytics in healthcare

Healthcare is a major target for big data analytics (see for example the NIH Big Data To Knowledge initiative[81]). A recent paper (Viceconti *et al.*, 2015) has identified an interesting potential relationship between big data analytics and *in silico* medicine models, even though there may also be a tendency to see them as somehow opposite in their intent (the first focused on predicting from the data, the other to use knowledge). The main specific requirements that *in silico* medicine imposes to big data technologies are:

- Those related to the sensitive, confidential nature of the data.
- The need for algorithms to process efficiently data that are more complex (typical big data problems deal with billions of records each with less than 10 fields but *in silico* medicine typically deals with millions of records with 10,000 fields or more).
- The complex linking of genomics and rich phenomics data, at the organism, organ, and tissue scales.
- The need for a continuum range of options from purely phenomenological to purely mechanistic models.
- The need to account for the 'physiological envelope'.
- The problem of computational vicinity for the data to special computational resources (typically high performance computing clusters).

VII.2.f. Systems biology

'Systems biology' as we know it today emerged as a term in the latter part of the 20th and early part of the 21st century (J-P Boissel, 2015) and was arguably the re-invigoration of physiology. How systems biology differed from the dominant molecular, univariate focus of the preceding decades was that it sought to measure multivariate (multiple DNA, RNA, protein) species in parallel using newly developed 'omics technologies (Ideker *et al.*, 2001). The next significant challenge was to integrate this multivariate molecular information to provide context (perturbation)-dependent and predictive outputs. Application of statistical (eg., regression) and mechanistic

81 https://datascience.nih.gov/bd2k

(eg., continuous ODE, discrete Boolean) computational modelling approaches allowed dynamic 'top-down' (eg., secretion of a hormone in response to perturbation) and 'bottom-up' (eg., determining the molecular entities responsible for hormone secretion) modelling to take place respectively.

The use of 'middle-out' (Noble, 2001) approaches are likely to hold a significant advantage, where a variable such as 'tumour growth' in an animal model can be measured in response to a perturbation (eg., a cytotoxic drug). This could enable comparison and correlation either 'upwards' to an observable clinical response for a patient receiving the same or a similar dosing regimen or 'downwards' towards the molecular entities underlying the inhibitory drug effect on tumour growth. This convenient, multi-scale (molecule–cell–tissue–animal/human–population) paradigm is ripe for translation. Systems biology is closing the loop by allowing correlations between dynamic changes in molecular entities and corresponding changes in physiology and clinical response and *vice versa* (Holzhutter *et al*., 2012; Kuepfer *et al*., 2014; D'Alessandro *et al*., 2015).

Is systems biology part of *in silico* medicine? It depends. Research focusing on single cells, including chemistry, and molecular systems biology describing very complex pathways with limited or no notion of time and/or space plays probably a limited role in *in silico* medicine. The other mode of systems biology, which is still described more frequently in vision papers (Dada and Mendes, 2011; Schadt *et al*., 2014; Wolkenhauer *et al*., 2014; Bunyavanich and Schadt, 2015) than in research papers (Krauss *et al*., 2012; AlQuraishi *et al*., 2014; Sneyd *et al*., 2014; Makadia *et al*., 2015), which attempts to provide largely mechanistic quantitative models for complex biochemical and biophysical processes, described over space, time, and from the molecular scale to the whole organism scale, is another name for *in silico* medicine. Another potentially relevant dimension is that described in the 2011 NIH White Paper on Quantitative and Systems Pharmacology[82].

It also must be recognised that the scientific discourse is constantly biased by other agendas. Recently a position paper stated: "Large, long-term research initiatives, like the Virtual Physiological Human, [...], are aiming to develop comprehensive, computational representations of organs and organ systems. Here, we focus on opportunities for comparatively small interdisciplinary collaborations between clinicians and modellers who are targeting specific questions of clinical relevance" (Wolkenhauer *et al*., 2014). Anyone vaguely familiar with the VPH initiative knows that the totality of the models developed as part of it, target a specific clinical task (diagnosis, prognosis, treatment) of a specific disease, contrary to what this paper erroneously states. And it could not be more different: a predictive model cannot be used to answer *every* question about the system it represents; each model is purposeful, in the sense that it is designed and tests in relation to a specific set of questions (Viceconti, 2011). Different questions require different models.

VII.2.g. Mobile health and personal health forecasting

Another technology that is growing rapidly is mobile health, ie., the use of smart phones and mobile technologies in general to monitor the health status of individuals, their lifestyle, the compliance with medical recommendations, and to provide support for self-management of chronic conditions such as diabetes. There are two dimensions that are worth analysing.

The first is what the VPH Institute calls "Personal Health Forecasting" (Hunter *et al*., 2013); a support action similar to Avicenna, PHS Foresight, is dedicated to roadmapping this area[83]. Patient-specific predictive models can be parameterised on detailed information collected continuously by implanted or wearable sensors, by the sensors within the smart phone, or provided directly by the user, and update patient-specific prediction, which can be used to support the self-management process, providing an element of prediction, for example for what-if scenarios such as "if you keep doing this in three weeks this will happen".

More relevant for our purposes is the second, that is, the relationship that the mobile technology could have with the medical product. We have already mentioned that implanted sensors could send data to our smart phones, but in principle we could also imagine the opposite, when active implanted medical devices are involved. The implanted artificial pancreas could update its insulin model on the basis of the physical activity recorded by the mobile phone accelerometer. Similarly, technologies such as the Helios ingestible sensor developed by Proteus Digital Healthmor[84], could inform our smart phone when we took a certain medication, warn the patient if they are not compliant with the medication protocol, and calculate the right time to take another medication that could interfere with the first. In these cases the device or the pill and the mobile technology become an integral health technology that provides therapy and monitoring in a coordinated fashion. The recent announcement from Apple Inc. of a new software development kit, called ResearchKit[85], entirely dedicated to the development of health research apps, suggests that large consumer IT companies are developing business plans around consumer health technologies of this kind.

82 http://www.nigms.nih.gov/training/documents/systemspharmawpsorger2011.pdf

83 http://www.phsforesight.eu
84 http://www.proteus.com
85 http://github.com/ResearchKit

VII.3. Annex VII-1: RTD challenges from Event Four

During Avicenna Event Four, a group of specialists from academic, industrial, and regulatory organisations were presented with examples, that described some typical scenarios where ISCT could be used during the development or the assessment of a new biomedical product. We then asked them to identify for each case the barriers and the challenges to be met for that to become a widespread reality.

ID	RTD Challenge
HC1	The definition of a validation and certification framework for *in silico* models and providers is a pre-competitive requirement.
HC2	Research into study of intellectual property rights legislative framework on the nature of modelling and biomedical research industries.
HC3	Call for study on regulatory issues, which could prompt a transformation/regeneration of the biomedical industries to implement/promote *in silico*, eg., by making *in silico* models acceptable in place of animal models.
HC4	Policy and governance framework for access to the data, storage, processing, and infrastructure needed for *in silico* modelling and simulation.
HC5	What are the societal consequences of a patient using an *in silico* simulation to make informed decisions about their treatment and lifestyle?
HC6	Can *in silico* be a significant opportunity for CRO 2.0s?
HC7	And could such contract research organisations be a driver for changing the biomedical sector?
HC8	European pre-competitive high performance and grid/cloud computing infrastructure for data storage, modelling, and simulation for *in silico* – making "*in silico* as a service" open to all.
HC9	Patent durations could be shortened to act as a driver to use cheaper clinical trial systems (leading to greater use of *in silico* simulation).
HC10	In what measure can *in silico* derived stratification of patients reduce short-term and long-term as well as direct and indirect welfare costs?
HC11	What is the economic potential of sharing *in silico* knowledge for defining different healthcare systems?
HC12	How can we make the type of testing used in development and testing of a biomedical product transparent? '*In silico* as a socially responsible brand'.

Chapter VIII

In silico clinical trials: Research challenges related to medical devices and combined products

Authors

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Summary

Chapter VIII reports the research and technological development challenges that are relevant for medical devices, regenerative medicine, and similar products.

VIII.1. Scope: Device challenges

One of the primary motivations of this roadmap is to identify, through a consensus process among all various stakeholders, the research and technological development (RTD) challenges that need to be overcome to ensure a broader and more effective adoption of *in silico* clinical trials (ISCT), defined as "the use of individualised computer simulation in the development or regulatory evaluation of a medical intervention".

In order to focus the discussion, a large part of the consensus process relative to the identification of the specific RTD challenges has been driven separately for pharmaceutical products, and for medical devices. A third group of experts worked on the so-called horizontal challenges, those related to aspects such as infrastructures, policies, regulations, etc.

The RTD challenges relative to these horizontal aspects are discussed in chapter VII. Those specific to pharmaceutical products are presented in chapter IX.

In this chapter we focus on medical devices, and all other biomedical products that require an intervention for their deployment, such as products for regenerative medicine. The focus is primarily on implantable high-risk devices (class IIb and III according to the EC system); while there is probably a potential for *in silico* technologies also for lower risk devices, its discussion falls beyond the scope of this roadmap. The starting point is a list of 18 RTD device challenges (referred to as DC#) identified during Avicenna Event Four and listed in Annex VIII-1.

VIII.2. Beyond validation: Model credibility

The validation of ISCT models poses relevant theoretical problems. However, these have been recently framed into specialised publications (see chapter 12, Coveney *et al.*, 2014) and a standardisation committee (ASME V&V-40 verification and validation in computational modelling of medical devices), is currently working on some codified guidelines (Popelar, 2013).

A key aspect, which was promoted within the Medical Device Innovation Consortium (MDIC) (Kampfrath and Cotten, 2013), but that emerged again and again during the Avicenna consensus process, is that of model credibility. The Interagency Modeling and Analysis Group (IMAG) coordinated by Grace Peng has created an *ad hoc* committee on this topic[86]. The process to ensure that a predictive model is indeed accurate in its predictions is somehow at the centre of a paradox. Models are usually developed to predict things that cannot be easily measured, so how do we know how accurate these predictions are?

A predictive model is designed within certain limits of validity, which must at least partially overlap with the portion of interest of the physical reality. This overlap is the predictive domain, where the model is expected to predict the physical reality. Similarly, we can measure the quantities of interest only over another limited portion of the physical reality, and only a portion of this also overlaps with the limits of validity of the predictive model. The space where validation studies occur is the narrow space between what we can measure, what the model can predict, and what is physically relevant (see figure VIII-1). Then we must assume that the predictive accuracy of the model will be maintained over that portion of physical reality that we cannot measure. Validation studies require that we make clear how those assumptions are made and supported.

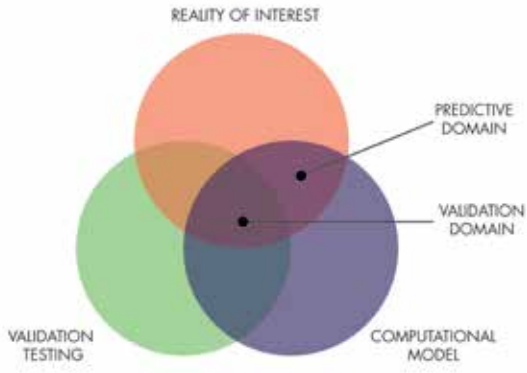

Figure VIII-1. Model validation paradox

So there is an element of uncertainty inherent in the fundamental concept of validation. We can assess the predictive accuracy of a model within a certain range of conditions, and then we use the model to make predictions beyond this range of conditions. But how credible must the model be to be able to reliably extrapolate its use beyond the region of validation? The 'distance' between the predictive accuracy within the validated range, and the whole range over which we use the model, defines the risk of the prediction being incorrect beyond an acceptable margin of error. But this cannot be isolated from the effect that such an erroneous prediction would have. The concept of model credibility, is presented in a recent MDIC document essentially as a risk analysis process:

- Define model context of use.
- Assess model risk – RAM.
- Establish credibility requirements – CAM.
- Develop and execute verification and validation (V&V) plan.
- Determine model credibility levels.

Here is the first challenge: we need to develop for each family of devices, and for each type of simulation, a set of good practices, widely tested and accepted, that provide guidance on the delicate question of the level of V&V evidence that a given model requires to achieve the credibility necessary for that intended use. While this is not strictly speaking an RTD challenge, we recognise the need to sustain a specific type of RTD that:

1. Conducts systematic reviews to define for a family of

86 Committee on Credible Practice of Modeling & Simulation in Healthcare. http://www.imagwiki.nibib.nih.gov/content/committee-credible-practice-modeling-simulation-healthcare-description.

models the contexts of use, the risks associated with the use of the model (RAM), and provides fully justified requirements for model credibility (CAM).
2. Provides ground truth measurements for very challenging quantities (sensors embedded in implantable devices, intra-operative measurements, post-mortem measurements, etc.) and more generally, data that can be used to validate families of predictive models.
3. Conducts extensive V&V studies to establish best practices across the medical devices modelling community.
4. Make models interoperable, so they can test each other's use. Independently designed models confirming each other may significantly increase trust and decrease risk.

For a broader discussion see also the IMAG CCPMSH Committee "Ten Simple Rules of Credible Practice"[87].

In the Avicenna consensus process, the issue of model credibility emerged with considerable overlaps with the reflections cited above. Still, some original elements emerged that are worth mentioning.

The concept of individualised computer simulation in the Avicenna definition of ISCT, should be formulated not in terms of how the model is identified (ie., how many of its input values are directly measured on the individual) but rather in relation to the expectations we have for that model, ie., how we define its predictive accuracy:

1. 'Low' expectation models aim to provide a predicted value for a given quantity that is simply within the range of all the values observed in reality for that quantity in the reference population; in this case the predictive accuracy is measured as the difference between the predicted value and the upper or lower boundary (whichever is closer) of the observed values.
2. 'Medium' expectation models aim to provide a prediction of a parameter of the statistical distribution of values observed in reality; in this case the predictive accuracy is measured as the difference between the predicted value and the parameter of choice (ie., the average).
3. 'High' expectation models aim to provide a prediction for each individual member of a population; in this case the predictive accuracy is measured by comparing the value observed for each individual member of the population with the prediction the models provide for that member, and then aggregating with some error metrics (such as the area under the ROC curve, the coefficient of linear correlation between measured and predicted values, or the average RMS or peak errors).

Another key element that emerged in the discussion is that of reproducibility. Whereas the reproducibility is the desired feature, a measure of it is probably the robustness of the predictor (ie., the ability of tolerating perturbations in the input values without drastic degradation of the predictive accuracy), which can be explored with sensitivity analysis. But the concept also relates to the more literal issue for a third party to materially reproduce the prediction reported; this aspect is linked to a third concept that emerged during the discussion – transparency.
To establish the credibility of a predictive model to replace experimental (clinical or pre-clinical) observations, we need of course to complete the entire verification, validation, and uncertainty quantification process. Sensitivity analysis can also be used to test the robustness of the predictor, for example to human errors. But until a model is a black box that only its author can operate, establishing credibility will always be a difficult process. We should then consider alternative business models, where the predictive models in themselves are developed and validated as pre-competitive activities and then made potentially accessible to anyone, so to make them transparent, before they can be used in de-risking activities.

In this discussion so far we always implicitly assumed that the quantity we want to predict could be observed experimentally in a population, with an excellent observational accuracy, ie., significantly better that the predictive accuracy we expect from our model (predictor). Under these conditions, one can assume the experimental measurement as true value (comparator), and consider the difference between prediction and observation entirely due to the predictor. However, in many cases this assumption is not simply not true, and the experimental observations we obtain, even under the best and most controlled conditions, are affected by errors comparable, or in some cases even higher than those affecting the predictor. This raises a specific research challenge from a methodological point of view: what is the correct framework to estimate the accuracy of the predictor in such circumstances?

VIII.3. *In silico* design and pre-clinical assessment of wearable or implantable devices

Wearable and implantable biomedical products, hereinafter simply referred to as medical devices, have a complex design and pre-clinical assessment process that is described in detail in chapter V of this roadmap. It can be, with some simplifications, represented as an extended risk analysis process (Viceconti *et al*., 2009):

1. Identification of all clinical failure scenarios reported in the literature in association with that family of products, usually referred to as undesired effects in risk analysis jargon.
2. Translation of clinical failure scenarios in specific failure modes for that family of products sometimes referred to as engineering failure modes.
3. Incidence of such failure modes in clinical practice, in association with specific design features used in clinically tested products.
4. Estimation of the severity these undesired effects have when they occur (for example are lethal for the patient, produce permanent impairment, etc.).

87 http://wiki.simtk.org/cpms/Ten_Simple_Rules_of_Credible_Practice

Once this general analysis is completed, the designer starts to define the new product, beginning from the specifications that he/she receives from the design group (reflecting marketing and clinical needs). They will need to keep in mind all failure modes reported for such devices, and consider how the probability that such failures may occur are affected by the interaction between the design, the variability of the deployment (ie., surgical variability), and variability of the patient's characteristics and lifestyle. Not surprisingly, it is almost impossible to account for all this during the design phase, resulting in multiple designs, expensive prototypes, and pre-clinical experiments to estimate the actual risk of such failure modes. When this risk is found to be too high, the design has to be revised and the whole cycle repeated.

Because this process is very expensive and time-consuming, every design team tries to cut corners by assuming that a certain design revision will not affect the risk associated with a given failure mode, that was found low in the previous design version. Sometimes, these assumptions are not valid, for complex unexpected reasons, and this is usually discovered only during the clinical trial or even worse when the device has to be recalled.

Another issue is that we necessarily have to assume that design features and failure modes do not interfere with each other, or the complexity would be become unmanageable. But such an assumption is not always verified, and again this becomes evident only much later in the life of the product.

So there is a complexity issue, which the use of modelling and simulation is known to mitigate, as demonstrated conclusively in the design of many other types of complex, mission-critical products such as airplanes and nuclear reactors.

Indeed, according to a recent questionnaire the MDIC submitted to many product developers working for their 46 member companies, design is the product development and assessment phase where simulation is most commonly used. But if we analyse the practice, we see that such use is very limited in scope, and rarely goes beyond the very basic mechanical engineering needs for design for resistance and design for manufacturing. According to the experts who participated in the Avicenna consensus process, this is due to some specific challenges.

> "Reduce, Refine, Replace"

The first is to develop for each family of devices, and for each failure mode, a reliable computational predictor of the probability that such a failure mode will manifest in a specific design. This implies the development of modelling techniques for all clinically reported failure modes (DC1), but also the retrospective application of these modelling techniques to designs already widely tested in the clinics, both successful and unsuccessful, in order to build confidence in the proposed modelling techniques (DC2). Of course this means the ability to run such simulations over very large retrospective cohorts of patients (DC6). Last, it is necessary (again to increase confidence) to run in parallel double blind *in silico* and experimental evaluations of new designs (DC7). For some families of devices, the real problem is that the association between the adverse effects observed clinically, and the underlying failure mechanisms of the device is not clear. In these cases, the challenge is to use ISCT to test mechanistic theories, simulating if the described failure of the device could actually produce the effects observed clinically (DC11).

It should be kept in mind that the world of medical devices is wide and complex. While what we state here is intended for the largest possible level of generality, we acknowledge that there might be additional elements, or different definitions, when we consider for example active devices, which involve power sources, and more and more frequently on-board software. Also while we refer to medical devices, we intend also to include some complex medical instrumentation (surgical or otherwise) that pose the same problems of design and assessment as with a medical device.

VIII.4. Automate ISCT for medical devices

During the design-testing cycle it is frequently necessary to explore a large number of variations, in terms of design options, but more frequently to capture patient and surgical variability. In the past few years, specialised software tools were developed to simplify the process of transforming medical imaging data into models, but very little has been done to automate the simulation process.

The first barrier is the need for large, validated, and widely available statistical atlases of specific anatomical or anatomo-physical models, which can be used to describe the anatomical variability over given populations (DC5). These atlases should be treated as models on their own, and should undergo a thorough validation to build confidence they can represent actual patients.

When available, large databases of patients' anatomies, whether obtained by analysis of available images, or synthetically generated using statistical atlases, are initially used to simulate the deployment of a device under testing. Once this simulation is completed, a series of controls can be performed, ranging from the simpler geometrical ones during the early stages of design to test anatomical compatibility, to those aimed at testing if a series of sizes of a device should be made available, and finally to more detailed functional assessments, typically associated with the analysis of specific failure modes. In order to be effective, this process should be performed on hundreds and sometimes thousands of anatomies, which implies a need for automation. We need to develop 'anatomical fitting' tools, fully integrated in the design suites, which automate the process of fitting a new design into hundreds or thousands of digital anatomies, and automatically analyse

the anatomical fitting, highlighting cases where the design poses some anatomical fitting issues (DC4). These tools, as well as the analysis tools used to conduct the various simulations, should also support 'replay' technologies that allow to the designer to fully automatically re-run whole *in silico* assessment workflows once minor modifications are made to the device design (DC8).

VIII.5. Visual analytics to explore high-throughput simulation results

In the scenarios described above, an ISCT-assisted design cycle could end up with thousands of distinct simulation results, relative to a number of design variations, virtual patients, or associated with the variability of the deployment. In some cases, the questions the ISCT models have to address accept simpler answers. But in other cases, there are many conflicting factors that need to be taken into consideration before we can choose which is the best design, or the most critical situation (under which it might be worth running the experimental tests), or simply to identify the limits of use for this device, so as to restrict its indications.

Two barriers were identified in this context. The first is the need for information and scientific visualisation technologies that allow rapid comparison of multiple simulation cases in meaningful ways (DC9). We imagine information visualisation technologies that allow drilling down in the multidimensional data space, automatically identifying salient cases that are more likely to be worthy of inspection. Then scientific visualisation technologies can be used to interactively explore data-rich visualisations specifically designed to simplify the comparative exploration.

The second barrier to overcome is the need for specialised interactive visualisation technologies that facilitate communication with non-technical members of the design team, such as clinical specialists, or regulators (DC10).

VIII.6. The physiological envelope, the deployment envelope

Anyone who has designed or tested a medical device is always obsessed with a fundamental question: How will the patient who receives this device cope with it? Which stresses, which traumas will he/she experience, and how will this device behave under expected and unexpected conditions? Any designer knows that you cannot design a device to withstand every possible condition, but on the other hand we cannot design devices under the assumption that they will always work even under the most ideal conditions. Where do we draw the line?

The real challenge is being able to quantify for selected populations the range of lifestyle and environmental conditions relevant for a class of medical devices, under which such medical devices must operate when implanted. The entire range of possible values a physiological parameter can assume in a given subject is referred to as the 'physiological envelope' (Viceconti *et al.*, 2015). It is clear that in order to account accurately for the actual operational conditions under which the new device will operate, we need to have reliable estimations of the physiological envelope for relevant populations. In some cases such physiological parameters can be measured directly and non-invasively, but in many other cases we can only collect proxy measures – other quantities that when provided as inputs to a physiology-based predictive model return an estimate of the physiological parameter of interest.

Two challenges were identified in this regard. The first is the collection of sufficient data and the elaboration of the necessary models to reliably estimate the physiological envelope for a number of physiological parameters relevant to the design of specific families of medical devices (DC12).

The second is the quantification of the reproducibility of the deployment/implantation of specific classes of medical devices (DC13). How accurate is the clinical specialist in positioning an electrode, in performing a certain surgical gesture, in aligning the segments in a bone fracture? Given that most of these procedures cannot be repeated many times on the same patient, we need to develop deployment simulators (which are another kind of ISCT model) that we can use to estimate the reproducibility of specific procedures across multiple specialists, at different levels of training and experience. And of course we need to conduct comparative studies with real deployment procedures to establish sufficient confidence in these simulators.

VIII.7. Reducing, refining, and partially replacing clinical trials

The last, and most important group of RTD challenges is related to clinical trials. Here we used a terminology (reduce, refine, replace, the so-called 3Rs) normally adopted with reference to animal experimentation. But the concept is the same: we want to reduce the number of patients who need to be involved in clinical trials; we want to refine the clinical trials so that the patients involved are exposed to less suffering and discomfort; and to lower risks of adverse effects.

Recently, the MDIC surveyed 35 medical device companies on where in the development cycle of a new product modelling and simulation is currently used. While 82% confirmed they use it during invention and prototyping, and 48% in regulatory submission, only 18% use it in pre-clinical assessment, and no company reported using it as part of the clinical assessment. But in spite of this, across the Avicenna consensus process many industrial experts stressed the potential importance that ISCT could have to "augment" clinical trials of medical devices.
A few challenges were identified in this area. The first is to use ISCT models where no clinical trial can reasonably

go: predicting very long-term outcomes, and over selected (unusual) populations (DC14). In too many cases, an efficiently working medical device has had to be withdrawn from the market because it produced very severe adverse effects in a very small number of patients who had a very unlikely, but still possible, combination of characteristics. The same applies to time: clinical trials typically observe a finite period of time, between six months and two years. If the adverse effects appear only in certain patients and after a much longer time, it is very unlikely that any clinical trial will be able to observe them. But with ISCT we can intentionally skew the parameters of our virtual patients toward rare but not impossible patient phenotypes, and explore the accumulation of certain effects observed during the clinical trial over a much longer period of time.
The second challenge is to develop and to validate with sufficient confidence patient-specific models to be used to refine the clinical outcome quantification (DC15). This should be aiming to estimate quantitative endpoints for the clinical trial that are impossible, dangerous, or simply too expensive to measure directly. But also done to provide quantifications of quantitative end points with a much higher reproducibility than those normally used, allowing the design of trials with much smaller cohorts to achieve the same level of significance. A variation of this scenario is when the model provides reliable surrogate metrics for endpoints that could be directly observed only much later, thus allowing considerable shortening of the clinical trial (DC16). Of course in both cases model credibility must be addressed with targeted research projects. In some cases, we will replicate running clinical trials *in silico*, so as to demonstrate they reach the same conclusions (DC17). In others, we will have to predict the surrogate outcome, and then follow-up until the real outcome can be measured, to test how reliable the model surrogate prediction is (DC18).

A related topic that emerged in the discussion among our experts, especially when the regulatory process of medical devices is compared to that of pharmaceutical products, is the balance between safety and efficacy. The argument is complex, as it intertwines with the differences between the regulatory processes in USA and Europe, and the role that the organisations responsible for deciding which products can be reimbursed by the healthcare service (ie., the National Institute for Health and Care Excellence in the UK) have in this process. Still, various experts voiced the need to include in the regulatory process, even for medical devices, a serious and systematic evaluation of efficacy, in addition to the aspects of safety. Another point that was raised is the tension there is between the desire of the policy makers to avoid at all costs the public image and legal costs around the safety issues of some medical products, and the need for the patients to properly balance the risks with the benefits.

VIII.8. Annex VIII-1: Device RTD challenges from Event Four

During Avicenna Event Four, a group of specialists from academic, industrial, and regulatory organisations were confronted with 12 examples, which describe some typical scenarios where ISCT could be used during the development or the assessment of a new medical device. We then asked them to identify for each case the barriers and the challenges to be met for it to become a widespread reality. Nine of these examples inspired one or more challenges, for a total of 18 RTD challenges, which are detailed below.

For each challenge we indicate the example that inspired it, the progressive number within that case, a general ID that will be used throughout the text, specific for device challenges (DC), as opposed to pharmaceutical challenges (PC), and horizontal challenges (HC). Each expert involved agreed to be champion for one or more of the challenges. Challenge DC3 was considered part of the horizontal challenges, and is discussed in chapter VII.

Use Case	Prog.	ID	Description
UC1	RC1	DC1	Develop, as part of pre-competitive industrial collaborations, an *in silico* assessment framework for each family of devices, which investigates all relevant failure modes for that device. Allow for research groups to extend the framework with refined/alternative predictors for the various failure modes.
UC1	RC2	DC2	Retrospective assessment: to build confidence in the methods, a well-defined *in silico* assessment framework for each family of devices, which investigates all relevant failure modes for that device, should be tested retrospectively on a number of designs for which the clinical outcome is well known. These should include both successful and unsuccessful devices; no design-specific tuning should be allowed.
UC2	RC1	DC3	Create digital marketplaces for the accumulation and usage of large-scale repositories for anatomical and/or organ and tissue physical property information relevant to the design of selected medical devices. Focus on the exploration of business models that favour the participation and the long-term sustainability after the termination of public funding.
UC2	RC2	DC4	Develop anatomical fitting tools fully integrated with widely used industrial design tools (such as 3D CAD software) that automate the process of fitting a new design into hundreds or thousands of digital anatomies, and automatically analyse the anatomical fitting, highlighting cases where the design poses some anatomical fitting issues.
UC2	RC3	DC5	Statistical atlases can be used to generate artificial digital patients, when data relative to real patients are not available for whatever reason. It is necessary to demonstrate for selected anatomies, and for specific features relevant for classes of devices, if and when such artificial digital patients can be used as replacement of real digital patients, generated from the data of an existing individual.
UC2	RC4	DC6	Develop *in silico* analysis frameworks that model a new medical device and its deployment and simulate the implantation over large collections of digital patients, and provide an *in silico* risk assessment for various failure modes relevant for that device.
UC3	RC1	DC7	Develop an audit trail process where for a set of new devices submitted for PMA, both the *in silico* and the experimental evaluation are conducted in parallel, so as to confirm (using double blind design) that the conclusions based on *in silico* predictions are the same as those based on experimental data.
UC4	RC1	DC8	Develop replay technologies that allow the designer to fully automatically re-run whole *in silico* assessment workflows once minor modifications are made to the device design.
UC4	RC2	DC9	Provide information visualisation technologies that allow a rapid comparison of the expected clinical performance for each design variation, and support decision-making and reporting. Use additional information available that only *in silico* models can provide to refine your design decision.
UC4	RC3	DC10	Develop specific interactive visualisation technologies that facilitate communication with non-technical members of the design team, such as clinical specialists, or regulators.
UC5	RC1	DC11	Develop *in silico* models to falsify mechanistic theories that would explain clinically observed failure modes, with the underlying engineering failure modes.

Use Case	Prog.	ID	Description
UC5	RC2	DC12	Collect data and develop *in silico* models to account for the physiological envelope – the range of lifestyle and environmental conditions relevant for a class of medical devices, under which such medical devices must operate when implanted in a given population.
UC5	RC3	DC13	Design validation studies to confirm that the procedural variability observed using surgical simulators is comparable, for the same device type, to that achieved in reality by comparably trained surgeons.
UC5	RC4	DC14	Develop *in silico* outcome models capable of predicting the long-term outcomes that a device-related adverse effect may cause over selected populations.
UC6	RC1	DC15	Development and validation of *in silico* models to improve outcomes reproducibility in clinical trials, or simplify the trials by surrogate outcomes which are less challenging to obtain.
UC7	RC1	DC16	Development and validation of *in silico* models to provide patient-specific surrogate metrics for late outcomes, so as to reduce the duration of clinical trials. This should include investigating the implication in terms of statistical power of adverse rare clinical events and of relevant inclusion/exclusion criteria.
UC8	RC1	DC17	Replication of clinical trials of new medical devices with ISCT, so as to demonstrate that each patient, and the *in silico* digital version individualised on the data of that patient, present comparable outcomes/complications.
UC11	RC1	DC18	ISCT of new medical devices capable of predicting functional or other complex outcomes from proxy measurements on the patient.

Chapter IX

In silico clinical trials: Research challenges related to pharmaceuticals and biotech products

Authors

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Summary

Chapter IX reports the research and technological development challenges specific to pharmaceuticals and other similar biomedical products.

IX.1. Scope: Pharmaceutical challenges

One of the primary motivations of this roadmap is to identify, through a process of stakeholder engagement, the research and technological development (RTD) challenges that need to be addressed to ensure a broader and more effective adoption of *in silico* clinical trials (ISCT), defined as "the use of individualised computer simulation in the development or regulatory evaluation of a medical intervention".

In order to focus the discussion, a large part of the consensus process relative to the identification of the specific RTD challenges has been driven separately for the pharmaceutical and medical device industrial sectors. A third group of experts worked on horizontal challenges, that is those related to aspects that fall outside this very defined area, but which are nevertheless highly relevant to the RTD challenges, for example infrastructures, policies and regulations, as well as more general socio-economic questions. The RTD challenges relative to these horizontal aspects are discussed in chapter VII, whilst those specific to medical devices are discussed in chapter VIII.

In this chapter we focus on pharmaceutical products. The list of ten pharmaceutical challenges (reffered to as PC#) presented in the table in Annex IX-1 was compiled during a breakout group discussion at Avicenna Event Four. The scope of this session was, within a restricted group of experts, to define a list of RTD challenges that, once met, would make the adoption of *in silico* technologies in the discovery and development of medicines much more widespread and effective than it is today. As a first step towards this goal we suggested starting by identifying a small number of examples, tasks, or applications, so called 'use cases', where modelling and simulation could be used to address known issues and bottlenecks in the drug discovery and development pipeline.

Pharmaceutical research and development (R&D) is built upon the concept that diseases and disorders can be broken into underlying biological processes that can be defined in terms of their constituent elements or targets. By developing therapies that interact with these target elements, pharma target their interventions to alter the biological process in question, assuming this will intervene in the disease process with the ultimate aim of delivering therapeutic benefit to the patient.

IX.2. Clinical trials fail

Although clinical trial methodology and practice have improved tremendously over the last half-century, the approach has left many key issues unmet.

The pharmaceutical industry has largely been built on an approach composed of a variety of *in vitro* and *in vivo* screens, studying the interaction of therapeutic targets with medicinal or biological therapeutic entities. With the development of highly detailed molecular and cellular technologies, especially post-genome, the approaches have adopted an increasingly reductionist focus. Once in the clinic, the compound can fail due to a wrong choice of the dose to be administered to patients. In addition, the compound can fail because of failure of the mechanism, ie., the mechanism targeted by the drug lacks sufficient relevance in the physiological or pathophysiological (cascade of) mechanism(s), which determine downstream the overall clinical efficacy. Finally, a compound can fail because of its own intrinsic pharmacokinetics (absorption, residence time, terminal half-live, inhibition and/or induction of specific metabolising enzymes) and pharmacodynamics (lack of efficacy, QT prolongation, liver- and/or nephrotoxicity, etc.) profile.

Exploration of these aspects is undertaken using pharmacokinetics and pharmacodynamics (PKPD) modelling, an established approach in the industry. However, the exploration of failure, ie., efficacy and the reasons for lack of it, involves more complex mechanistic modelling of biological pathways and network interactions at the cell, tissue, organ, and integrated physiological level. Such mechanistic models are not routinely used in industry pipelines, although examples of their use do exist. A number of points have emerged from the various surveys and discussions undertaken as part of the Avicenna project, where modelling and simulation could be considered to improve the status quo. Not surprisingly these points have focused on the non-PKPD modelling topics, ie., those models that are concerned with efficacy.

The following were the examples chosen for this discussion, distributed by phase in the typical pharma R&D pipeline: discovery, pre-clinical, and clinical development. All focus on aspects of efficacy, as well as the refinement of study processes and the trials themselves.

IX.2.a. Discovery

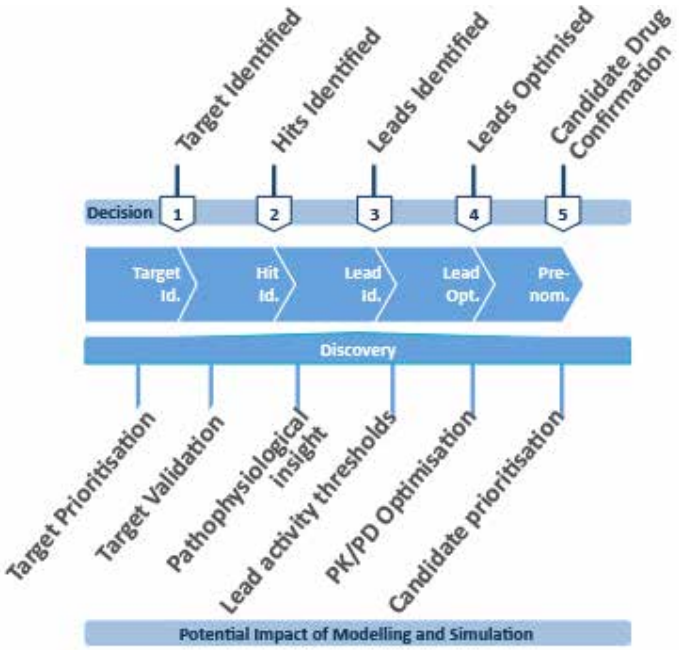


Figure IX-1. Potential impact of modelling and simulation – discovery

UC1. Target identification: How could modelling and simulation combined with complex data analysis be used

to explore novel biological insights, currently constrained by our understanding of biology and physiology?

UC2. Target prioritisation: Given a complex signalling network involved in a disease endpoint, how could modelling and simulation help to identify which member of the network would be the optimal target for pharmacological or biopharmaceutical therapy?

UC3. Similar to the above, but this time considering approaches to combination therapy, how could modelling and simulation help to explore and prioritise various multiple hit combinations in a given biological network?

UC4. Opportunities for reprofiling/repurposing: How could modelling and simulation help to explore options for small molecules or biopharmaceuticals, developed for one particular therapeutic area or disease endpoint, to be exploited in a different context?

UC5. Optimisation of *in vivo* experimentation during lead optimisation: How can modelling and simulation be used to refine, reduce, and replace animal/human experimentation?

IX.2.b. Translational studies and pre-clinical assessment

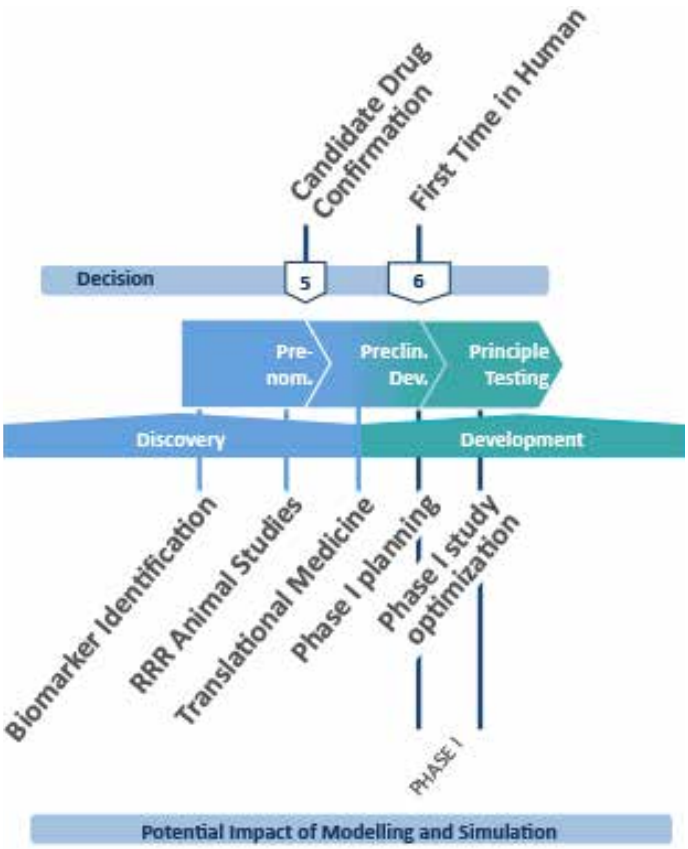


Figure IX-2. Potential impact of modelling and simulation – translation

UC6. How can modelling and simulation be used to aid the identification of candidate biomarkers for patient stratification?

UC7. How can modelling and simulation be used to offer insight in the translation of *in vivo* animal experimentation data to a human context to add confidence in its relevance and as an aid to decision making (species extrapolation)?

UC8. Phase I trial planning: How could modelling and simulation be used to optimise trial design to reduce size, duration, and cost?

IX.2.c. Clinical development and life-cycle management

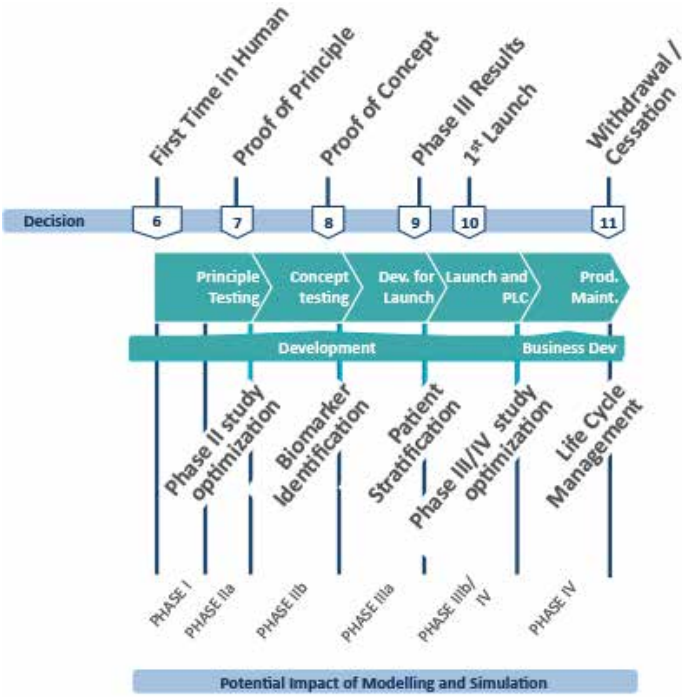


Figure IX-3. Potential impact of modelling and simulation – development

UC9. How can ISCT be used to reduce the size of the cohort required in a trial to ensure statistical power, by using patient-specific models to reduce the inter-subject variability and/or the reproducibility of the outcome measurement, or to design eligibility criteria from the profiles of *in silico* individuals who respond during *in silico* experiment?

UC10. How can ISCT be used to reduce the duration of a clinical trial by replacing the outcome metrics with surrogate metrics provided by patient-specific models that can be observed earlier in time?

UC11. How can ISCT be used to optimise the duration of a clinical trial in chronic diseases by identifying the duration that maximises the chances to achieve the expected size of effect for a given cost?

UC12. How can ISCT be used to refine clinical trials, by replacing difficult-to-observe outcome metrics with a surrogate outcome based on patient-specific modelling, which can be observed more easily (less invasively, with lower risk or discomfort for the patient, at lower cost)?

UC13. How can ISCT be used to refine clinical trials, by using patient-specific modelling to improve our ability

to quantify the most complex outcomes (ie., functional outcomes, which typically are poorly captured by unreliable questionnaires), and also capture side effects with a much broader observational angle than normal trials can provide?

UC14. ISCT will never fully replace clinical trials. However, when trials must be replicated only for regulatory purposes but the outcome is quite evident from previous data, could a smart combination of ISCT and conventional clinical experimentation partially remove the need for such clinical trials and if so how?

The discussion at the breakout was guided by three presentations of examples where modelling and simulation has been used in areas relevant to the above use cases. Although not in every case did the studies address the specific points listed above, for example UC3, UC4, and UC6 were not covered by this discussion, although they will undoubtedly represent opportunities for investigation in subsequent analyses. The first of these focused on examples that created a bridge between the classical PKPD approaches and more mechanistic modelling, using physiology-based pharmacokinetic (PBPK) tools. In one case, a PBPK-pharmacodynamic (PD) model was used to consider the impact of genotypic variation in the cellular transporter OATP1B1 on the efficacy of the cholesterol-lowering drug rosuvastatin. Addressing UC10, UC11, and UC13 above, the studies used melavonate concentration as a marker of PD effect, comparing different input sites that drove the PD effect (Rose *et al*., 2014). Further, PK differences in OATP1B1 genotypes were propagated to the PD response from the plasma but to a much lesser extent from the liver intracellular water compartments respectively, demonstrating the importance of modelling the relevant biological effect compartment to assess accurately the impact on pharmacodynamics of the compound (Aoyama *et al*., 2010; Rose *et al*., 2014). Similarly, PBPK models were used to study the prospective powering of clinical studies, specifically looking at detecting a difference in AUCt for the first dose of midazolam in different populations (Barter *et al*., 2013). These examples, which addressed UC8, UC9, and UC12, showed that the standard approach to assess statistical power required to detect a difference in the AUCt for the first dose of midazolam between North-European Caucasian and Chinese subjects would require recruitment of over 338 individuals from both populations in order to power the study theoretically to 100%. However, using modelling, it was shown that the recruitment of as few as 54 and 80 individuals from both populations could deliver 80% and 90% power to detect a difference respectively. The conclusion from these studies is that appropriate prospective powering of clinical studies based on representative virtual populations can guide subject recruitment. Discussion around these examples contributed to the definition of PC3 and PC6.

It is interesting to notice how the use of individual-based population models is already accepted as the state-of-the-art in other life science research communities, such as ecology. In 2001, Adam Lomnicki wrote: "The individual-based approach is a concept of population ecology that rests on the premise that population properties should be derived from properties of individuals. It was developed due to conceptual advances in evolutionary biology in the second half of the twentieth century and as a consequence of access to computers. The advances in biology have allowed the rejection of the notion of adaptations of units of natural selection other than individuals whereas the computers made possible the simulations of very complex phenomena in many fields of science, engineering and economy. Investigations of individual variation have shown its origin and its impact on population dynamics. Computer simulations of particular ecological systems, especially those of economic and conservation importance have proven to be very useful and able to discover relations that cannot be found out by analytical inquiries. It seems that in the future the individual-based approach will be fully integrated into theoretical and applied ecology" (Lomnicki, 2001). The distinction between conventional statistical models and individual-based population models is foundational: in the first case we assume there is an 'average' behaviour for the population, and that the deviation from this average is due to uncertainty and measurement noise. In the second we acknowledge that each individual is different, and define population patterns as summation of individual behaviours.

The following example addresses UC5 and UC7. The US Food and Drug Administration (FDA) has accepted a mathematical model of type 1 diabetes as a possible replacement for animal testing for the certification of some insulin treatments (Kovatchev *et al*., 2010). This model is based on the physiological interactions between the major organs in the human body, relying on the strength of the data, where the fluxes of glucose and insulin have been experimentally measured in more than 200 healthy subjects (Dalla Man *et al*., 2007). The FDA certification of this model means that a step that used to take four to six years, cost ~€100 million, and involved thousands of test animals (primarily dogs), now takes a few months, costs less than €100,000 (ie., a reduction in cost with three orders of magnitude), and involves no animal testing prior to the human trials. This certification by the FDA has led to corresponding acceptance by certification agencies in other countries (eg., Italy and the Netherlands), and has stimulated the design and testing of many new devices for insulin dosage, a number of which are in various phases of human clinical trials (see chapter V.3., UVA/Padova Diabetes Simulator). The successful implementation of this model, and the availability of high-quality quantitative data have also influenced similar developments in modelling for drug development in relation to type 2 diabetes.

Recently a report has shown how to use existing data to build a computer model of cardiac electrophysiology that incorporates variations in 'normal' heart properties that occur between individuals of the same species (Britton *et al*., 2013). This differs from usual approaches where modelling tends to ignore this and uses averaged data instead. The system that has been developed has the potential to refine computer models so that they can identify compounds at risk of cardiac toxicity more accurately and far earlier, enabling them to be discarded before they reach the stage where regulatory animal studies are required. This has a direct impact on UC5, and it is possible that as proof of the model accuracy in substituting for animal studies grows and builds confidence, it may fully replace some *in vivo* studies.

An important factor in its ultimate success is the delivery of a software package that is user-friendly, removing the need for expert training and leading to the potential for broader adoption in industry. This technology platform recently won the National Centre for the Replacement, Refinement and Reduction of Animals in Research 2014 3Rs Prize, recognising its potential to reduce the number of animals used in research, particularly in the safety assessment of new drugs[88].

UC1 and UC2 were in part addressed by the following example. Type 2 diabetes is more complex than type 1 disease, in that it is caused not only by the lack of insulin, but also by insulin resistance, the malfunction in a complicated network of proteins inside insulin-responding cells. Experimental studies on these networks have been fragmented, and have not led to a consensus on the origin of the underlying malfunction, as almost all aspects of the network are altered in the disease. Thus, the origin of the dysfunction remains an open question. Recently, an integrated modelling/experimental approach (Brännmark *et al*., 2013) has gathered internally consistent, time-resolved, quantitative data for all the main players in the network, both in normal and type 2 diabetes conditions. The internal consistency of these data has enabled a single model to test some of the most well-supported mechanistic hypotheses regarding type 2 diabetes, and has provided a mathematical multi-level model that explains how insulin resistance could start in one particular feedback loop and then spread from there both to the rest of the intracellular network and to the whole-body level. Several drug-development companies (eg., AstraZeneca, Sanofi) are using this multi-level model to support development and early testing of new diabetes drug candidates. Taken together, these diabetes studies informed the challenges PC4 and PC5.

The two previous examples show how *in silico* disease models combined with a drug model (PKPD) can be validated (Chabaud *et al*., 2002). Additional issues pertained to companion biomarkers (UC6), and optimal clinical trial planning (UC9) in the case of a phase II dose-effect-relation study where the *a priori* sources of variation are doses and regimens, with an almost infinite number of possible combinations. *In silico* exploration of this latter issue enabled the design of a three-dose, two-regimen clinical trial for a new anti-angina pectoris drug. The clinical trial findings validated the *in silico* prediction *ex post*. With the same model, and a virtual population, it was possible to predict the number of angina attacks that various daily doses could prevent over 24 hours in normally living patients. Extension of the disease model by adding a coronary atherosclerotic plaque sub-model and blood model across the resulting stenosis enabled the exploration of the number of plaque ruptures prevented according to the duration of the treatment and various patient characteristics (biomarkers).

It demonstrated, for example, that with moderate coronary stenosis the number of prevented plaque ruptures plateaued after two to three years of treatment whereas with severe stenosis, after a peak at one year it dropped down to zero. This ISCT also showed that weight was a major marker of efficacy. These findings were obtained by applying the Effect Model Law (J-P Boissel, 2015) which enables the transposition of simulation outputs in predictions of individual and group (population) clinical benefit. This law states that for each subject, group or population, a quantitative relationship exists between the rate of event with and without the treatment (Boissel *et al*., 2008). Thus, with appropriate instruments (ie., disease and drug models, virtual populations) it is possible to predict the number of prevented events in the population of interest with a single additional piece of information: the target the drug alters. These examples cover UC13, UC14, and UC15.

A significant portion of the discussion focused on what are seen to be significant barriers to generating sufficient credible, validated examples of modelling and simulation applications to the pharma R&D process for mechanistic modelling to become accepted in the way PKPD modelling has. This led to the definition of challenges PC1, PC2, and PC7. These challenges relate to recognition of the need to capture 'knowledge', not just information and data, as the fundamental fuel for building models that can address any of the use cases above. The primacy of knowledge over data as a modelling material stems from the latter's intrinsic limitations. First, data is heavily time and context dependent. Knowledge, which emerges from data after the aggregation of multiple analyses over time – until it becomes a scientific fact, is far more reliable. Second, knowledge-based models are mechanistic in nature, whereas data-driven models risk mistaking correlation for causation. Making sense of *in silico* simulation outputs, ie., deriving a causal explanation of an *in silico* observation, is only possible with a mechanistic representation of the pathophysiological processes at play. Knowledge-based disease model design is a rigorous process, which needs to be supported by carefully crafted standardised methodologies and procedures. The process starts with an extensive review of the scientific literature to identify relevant pieces of knowledge describing the various mechanisms thought to play a part in the pathophysiology (eg., inflammation, cell adhesion, apoptosis, etc). Each piece of knowledge needs to be thoroughly curated by applying a strength of evidence (SoE) score, which will eventually form part of the simulation output uncertainty measurement. The SoE is derived from the critical analysis of the findings documented in the scientific article from which the piece of knowledge is extracted. It is driven by the quality of the experimental design, the fitness of the experimental design to the study objective(s) and the quality of execution.

The output of this first step is a current up-to-date review of the pathophysiology. Such a substantial effort in structuring and evaluating knowledge makes the remainder of the typical modelling process (mathematical formalisation and conversion into computer code) much more efficient and reliable. Part of this was seen to include an essential building of integrated networks of the key stakeholders that hold the information, data, and knowledge needed not just to develop the models, but who may already have potentially informative case studies. This also recognised the need to ensure that other relevant consortia, networks, and projects studying aspects of modelling and simulation

88 http://www.cs.ox.ac.uk/news/893-full.html

in medicine are engaged in a comprehensive approach.

Finally, the discussion focused on what could be done to generate additional compelling evidence of the power and potential of modelling and simulation that could be the basis for a call. Two approaches were considered attractive and feasible. The first (PC8) considered that running parallel prospective studies or clinical trials, comparing the current best practice with a modified approach that included modelling and simulation. Such studies would best focus on a priority area of therapeutic interest such as paediatric and/or rare diseases, rather than much larger studies associated with core therapeutic area R&D pipelines. The second is the reverse, where a retrospective study (PC9) of a completed trial is this time run but using a modelling and simulation toolbox. This is open to the challenge that it could not be genuinely 'pure' in the sense that information, data, and knowledge unavailable in the original study would be accessible to the retrospective study, and would therefore need to be carefully controlled. The process of transforming PKPD into mechanistic modelling that has begun with the development of PBPK models needs to be extended to a complete and comprehensive 'systems pharmacology' platform, where mechanistic models are used and where mechanistic knowledge is available. This needs to recognise that there are three discrete, but complementary domains that contribute to this development:

1. Physics-based, physiology-based, heavily mechanistic models to describe organisms, organ, and tissue behaviour.
2. Biology-based, chemistry-based heavily phenomenological models to describe single cells or intracellular processes.
3. Physics-chemistry based, heavily mechanistic models to describe molecular processes such as docking, protein folding, etc.

Because these domains also imply a significant cultural and epistemological gap among experts, models that bridge the cell-tissue gap and the molecule-pathway gaps are the most difficult to address. Dedicated funding should target the development of such models by heavily interdisciplinary consortia leading to definition of PC10.

A possible trajectory might involve quantitative system biology (QSB) and quantitative system pharmacology (QSP), as necessary following step of modelling and simulation towards handling complexity, ie., a full *in silico* representation of human physiology. Because different in nature by technique and scientific approach, population PKPD modelling and QSB/QSP should complement each other whenever possible because they share the same scope: to understand how we can bring more effectively, and at sustainable costs, better drugs to patients.

IX.3. Annex IX-1: Pharma RTD challenges from Event Four

During Avicenna Event Four, a group of specialists from academic, industrial, and regulatory organisations were presented with use cases that described some typical scenarios where ISCT could be used during the development or the assessment of a new biomedical product. We then asked them to identify the barriers and the challenges to be met for it to become a widespread reality.

For each of the challenges below, the use case that inspired it was identified in the text above and it was assigned a general ID that will be used throughout the text, specific for pharmaceutical challenges (PC), as opposed to device challenges (DC), and horizontal challenges (HC).

ID	Description
PC1	What makes *in silico* simulation findings trustworthy and their consequence/interpretation capable for helping a new medicine to be put on the market? Define and agree a minimum set of standards and criteria to build confidence in models reliability and work more closely with FDA.
PC2	Create a framework to share knowledge, collection, curation, assessment of strength of evidence, and library of models.
PC3	Define models that scale and extrapolate *in vitro* and *in vivo* data to predict clinical observation.
PC4	Based on the successful showcase of type 1 diabetes model, generalise the model to type 2 diabetes or other multi-factorial diseases. This requires: • Multi-level and multi-organ mechanistic models (we have some but we need more). • Multi-scale in terms of time (ie., for diabetes: both response to a meal and disease progression). • Prediction of clinical outcome.
PC5	Develop multi-level models to merge image-based data with intracellular data, blood samples, and other biomarkers that are used in the clinic for individualised therapy
PC6	Using the model to inform decision making in the value chain (conceptual/experimental /mathematical)
PC7	Identify the stakeholders (actors, regulators, patients) we wish to involve and how to cross-fertilise between different industries and sectors for having the most comprehensive case studies.
PC8	Modelling and simulation driven/directed R&D compared with standard approach/paediatric-rare disease-focus
PC9	Confirmation of clinical outcome from retrospective studies using modelling and simulation. Could modelling and simulation have given you the answer?
PC10	How to create an entity that can represent the community (CASyM, Avicenna, System Pharmacology)?

Chapter X

The Avicenna Alliance

Authors

James Kennedy, Adriano Henney, Martina Contin

Summary

Chapter X describes the Avicenna Alliance.

X.1 Establishing a pre-competitive alliance

The type of research and technological development that this roadmap describes cannot be achieved effectively within a single type of setting. The more fundamental methodological and scientific challenges must be tackled primarily in academic settings, or in private research laboratories. The technological aspects, such as standardisation or interoperability are typically best tackled at the industrial level as, while *de facto* standards might emerge, the definition and the adoption of such standards is much quicker and effective when industry can formulate pre-competitive agreements. There is a third zone, in between research and technological development, that involves delicate issues such as evaluation of reliability, limits of validity, and best practices, which will require academics, industrial and clinical researchers, standardisation and regulatory experts, developers of *in silico* clinical trial (ISCT) solutions and services, contract research organisations, and research hospitals to work together to define a set of reliable, effective, and sustainable practices for the use, assessment, and interpretation of ISCT. The Avicenna Alliance - Association for Predictive Medicine will focus on bringing these various stakeholders together in a precompetitive structure to address these issues by exploring, evaluating, and implementing the recommendations emerging from this roadmap.

While the advent of the digital age brought with it a range of regulatory and policy changes, high-throughput processing of data on a scale unthinkable a mere decade ago is putting increasing pressure on regulatory systems that are still relatively new.

That *in silico* medicine will be regulated and that policy makers will need expert guidance in this endeavour is inevitable.

The prelude to the creation of new policies is always marked by confusion and open-ended questions. The regulation of *in silico* medicine is a crucial requirement for a much-needed new model of healthcare, which will be the answer to the many open-ended questions currently being posed by policy makers on existing EU policies.

The 2012 EU Data Protection Regulation raised questions on the very nature of data and how we use it. Should a risk-based approach be taken? Should the purpose for which the data is being processed or the sensitive nature of the data itself be the deciding factor in restrictions on data processing?

The revision of the clinical trials regulation raised no less complex issues about access to data, high-throughput data, and the use data for health research purposes.

Even now, questions still abound in the medical devices regulation on what constitutes software, at what point does a phone app for medical purposes become medical software and subject to regulation?

These questions will require answers from a coalition of experts and industry working in tandem to improve the uptake of *in silico* solutions both in healthcare research and healthcare delivery.

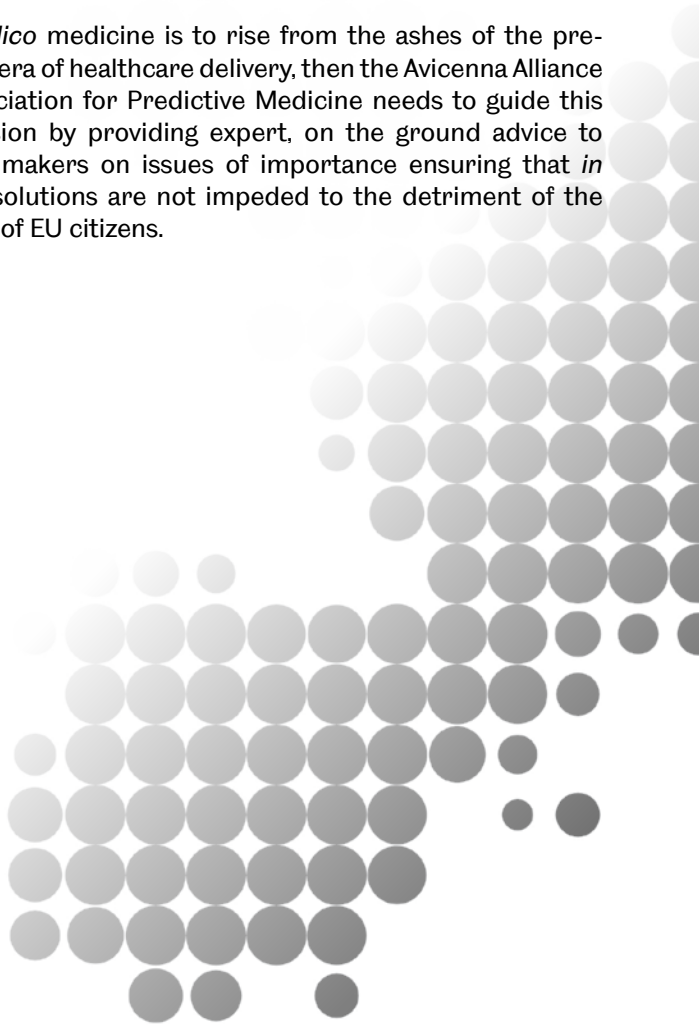
The best medium for discussion, advocacy, and ensuring that all parties having an interest in *in silico* medicine are represented, is through the creation of a pre-competitive alliance. The Avicenna Alliance - Association for Predictive Medicine will operate as both a trade association tackling key regulatory and market barriers to *in silico* solutions, and as a forum for experts to discuss EU policy, its effect on the interests of members, and to respond to these developments accordingly.

This association will act as the interlocutor, between industry, the scientific community, and policy makers in the European Medicines Agency, European Commission, European Council, and the European Parliament.

The association will have an on the ground presence in Brussels, capable of responding in real time to political and regulatory issues that represent opportunities or threats to the ability of members to conduct their research or to place their products on the market.

Having a market-focused association with a heavy industry representation provides the opportunity to quickly identify issues that hinder the entry of *in silico* solutions onto the market place, and to bridge the gap between the scientific community and their industry affiliates through focused collaborations.

If *in silico* medicine is to rise from the ashes of the pre-digital era of healthcare delivery, then the Avicenna Alliance - Association for Predictive Medicine needs to guide this ascension by providing expert, on the ground advice to policy makers on issues of importance ensuring that *in silico* solutions are not impeded to the detriment of the health of EU citizens.



Chapter XI

Conclusions and recommendations

Authors

Marco Viceconti

In 2005, a group of researchers proposed the term 'Virtual Physiological Human' (VPH) to define "a framework of methods and technologies that once established will enable the collaborative investigation of the human body as a single complex system". Soon after a white paper was produced out of this meeting[89]. It was immediately clear that this idea included a hugely vast territory of knowledge, methods, and technologies; also, as for any new paradigm in research, there was a continuous pressure to reduce it to one of the previous paradigms. To address these issues, the European Commission (EC) decided to support the elaboration of a research and technological development roadmap through a consensus process across the community[90].

Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human, published in 2007, turned out to be an extremely useful document. It provided this new research paradigm with a collective identity that would manifest as the VPH Network of Excellence. It also charted the knowledge territory, providing the necessary structure to pursue the vision through thematic funding, which the EC did in the Seventh Framework Program, through the VPH priority.

While this process happened mostly in Europe, from the outset it was driven by experts from all over the world; the advisory board of the original EuroPhysiome action included Peter Hunter of New Zealand, Yoshihisa Kurachi of Japan, and Jim Bassingthwaighte from the USA, just to name a few. But in spite of this, the perception was that this was a European idea. The ARGOS Transatlantic Observatory[91] was established to explore, in this case between the EU and USA, possible collaborative approaches to the development of the VPH vision.

The VPH Network of Excellence periodically updated the 2007 roadmap. In 2009, in one such update[92], the community indicated the need to consider additional steps: the creation of a not-for-profit organisation, called the VPH Institute, to represent the emerging community of practice; and the need for an ulterior roadmapping exercise, in the specific area of future and emerging technologies, which was published in 2011[93].

In 2011 the VPH Institute was established, and one of its first steps was the publication of a position paper on the then forthcoming Horizon 2020[94]. This document identified three further directions of development for the VPH, beyond patient-specific diagnosis, prognosis, and treatment planning:

1. Digital Patient – VPH-based decision-support systems for personalised medicine to the medical professional.
2. Personal Health Forecasting – where patient-specific models are constantly updated by personal health systems, and provide decision-support systems for self-management to the patients/citizens.
3. *In silico* Clinical Trials (ISCT) – where patient-specific models are used to generate simulated populations on which new biomedical products can be safely tested.

The Discipulus action, coordinated by Vanessa Diaz, produced a research roadmap for the Digital Patient concept[95]. The PHS Foresight consortium[96] produced a number of reports that partially address the Personal Health Forecasting concept. This roadmap completes the trilogy, providing a detailed chart of the new knowledge territory that the use of VPH models in developing new biomedical products implies.

It took ten years, but today the VPH paradigm is a reality; far from being fully accomplished or even fully accepted, but a reality nevertheless.

In 2013 Marco Viceconti (VPH Institute), Vanessa Diaz (Discipulus Support Action), Ferran Sanz (INBIOMEDvision Support Action), Laura Pombo-Juárez (PHS Foresight action), David Harrison (CaSyM support action), Edwin Morley-Fletcher (Avicenna support action), Charles Auffray and Ian Dix (IMI-eTRIKS Consortium) published a *Joint statement on in silico medicine research in Europe*[97]. It is important here to re-state the four key concepts that document proposed:

1. Integrative means across scales, across organ systems, and across disciplines.
2. There is no preferential scale, preferential clinical target, or preferential approach.
3. Funders should support *in silico* medicine research across the whole value chain:
    a. Generation of information (sequencing, imaging, sensing, etc.).
    b. Management of information (bioinformatics, health informatics, etc.).
    c. Processing of information (turnaround time, data mining, image processing, etc.).
    d. Explorative modelling (Bayesian modelling, machine learning, etc.).
    e. Mechanistic modelling (systems biology, VPH, physiological modelling.).
    f. Complete clinical systems (decision support systems, computer aided medicine).
    g. Validation and assessment (pre-clinical and clinical).
4. Funders should support *in silico* medicine at all maturity levels:
    a. Initial – fundamental methodological research, visionary research.
    b. Repeatable – pre-clinical exemplification and validation (*in vitro*, *in vivo*, *ex vivo*).
    c. Defined – pre-clinical and early clinical validation of complete pathways.

89 http://www.vph-institute.org/upload/file517569145f61b.pdf
90 http://www.vph-institute.org/upload/step-vph-roadmap-printed-3_5192459539f3c.pdf
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96 http://www.phsforesight.eu
97 http://www.vph-institute.org/upload/joint-statement-on-in-silico-medicine-research-in-europe-v6_52a5cb630f98b.pdf

d. Managed – clinical accuracy, mono-centric efficacy studies.
e. Optimising – multi-centric efficacy studies, cost-benefit studies.

The same concepts are of course valid also for ISCT. The research vision must be driven by an ambitious agenda, where all physiological and pathological processes can be modelled across scales, from the molecule to the organism, and from the microsecond to the lifetime. While we may not have a complete mechanistic explanation for each step, we acknowledge that when a validated mechanistic theory is available the resulting predictive models are infinitely more accurate, robust, and reliable than any phenomenological alternative. And predictive models must be assessed in the frame of pure physics epistemology, where models make quantitative predictions about one patient, and their predictive accuracy is measured against measurements made on that patient.

> “The time is now, the challenge is huge; only if we all work together will we be able to address and overcome that challenge.”

The Avicenna Research and Technological Roadmap ideally completes and concludes this decade of pioneering work. This document shows, in our opinion unequivocally, that the use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention, what we refer to as *in silico* clinical trials, is at the same time already a tangible reality in industrial practice to some limited degree. Furthermore, it is one of the most important strategic priorities in biomedical and technological research, if we want to make the development and the safety assessment of new biomedical products simpler, cheaper, faster, and safer, while at the same time minimising those activities such as animal or human experimentation that pose ethical concerns.

We collectively recommend to all public and private research funding agencies across the world to:

1. Acknowledge the extreme socioeconomic relevance that research and technological development, assessment, and adoption of ISCT technologies poses; in a word the future of universal healthcare provision in developed countries pass by our ability to innovate more quickly and efficiently and ISCT are the best possible answer to this need.
2. Progressively increase the expenditure in this area in the next five years, so that by 2020 at least 1% of the total public and private expenditure in biomedical R&D worldwide (estimated to be US$268 billion in 2012 (Chakma *et al*., 2014)) is dedicated to the development and adoption of ISCT technologies used to translate more quickly, safely, and efficiently the discoveries of biomedical research into new products and services. This should be initiated with a dedicated programme in the 2016-2017 work programme of H2020, with a budget of at least €50 million per year.
3. Ensure that such public and private research and technological development funding is dedicated in equal parts to the core scientific and technological development of ISCT predictive models, to their pre-clinical and clinical validation including the necessary regulatory science aspects, and to support their early adoption in the industrial and regulatory practice.

As the Avicenna consensus process demonstrated in a globalised economy the discourse on ISCT must develop worldwide; thus, we recommend all agencies remove as many barriers as possible, and actively support pre-competitive research and technological development across countries and world regions.

The time is now, the challenge is huge; only if we all work together will we be able to address and overcome that challenge.

Brussels, September 30th, 2015

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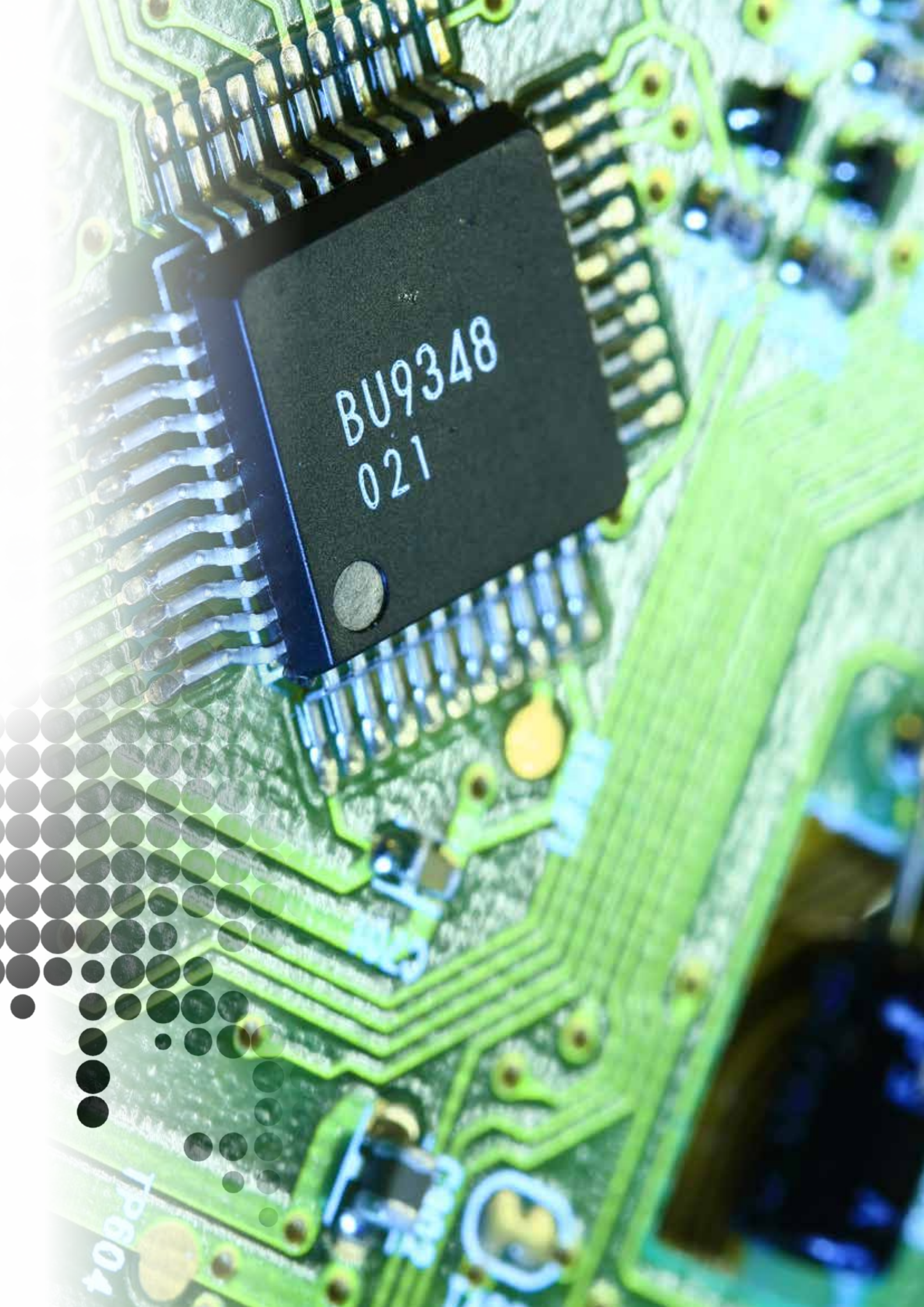
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References - A Roadmap Bibliography

Ahmad, A. A., Wang, Y., Gracz, A. D., Sims, C. E., Magness, S. T., Allbritton, N. L., 2014. Optimization of 3-D organotypic primary colonic cultures for organ-on-chip applications. Journal of Biological Engineering 8, 9.

Akella, L. B., DeCaprio, D., 2010. Cheminformatics approaches to analyze diversity in compound screening libraries. Current Opinion in Medical Biology 14(3), 325-30.

AlQuraishi, M., Koytiger, G., Jenney, A., MacBeath, G., Sorger, P. K., 2014. A multiscale statistical mechanical framework integrates biophysical and genomic data to assemble cancer networks. Nature Genetics 46, 1363-71.

Anonymous, 2015. Virtual Assay: Drug safety and efficacy prediction software.

Aoyama, T., Omori, T., Watabe, S., Shioya, A., Ueno, T., Fukuda, N., Matsumoto, Y., 2010. Pharmacokinetic/pharmacodynamic modeling and simulation of rosuvastatin using an extension of the indirect response model by incorporating a circadian rhythm. Biological and Pharmaceutical Bulletin 33, 1082-7.

Arakelyan, L., Merbl, Y., Agur, Z., 2005. Vessel maturation effects on tumour growth: validation of a computer model in implanted human ovarian carcinoma spheroids. European Journal of Cancer 41(1), 159-67.

Arrowsmith, J., Miller, P., 2013. Trial watch: phase II and phase III attrition rates 2011-2012. Nature Reviews Drug Discovery 12, 569.

Audigier, C., Mansi, T., Delingette, H., Rapaka, S., Mihalef, V., Sharma, P., Carnegie, D., Boctor, E., Choti, M., Kamen, A., Comaniciu, D., Ayache, N., 2013. Lattice Boltzmann method for fast patient-specific simulation of liver tumor ablation from CT images. Medical Image Computing and Computer-Assisted Intervention: MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention 16(Pt 3), 323-30.

Barter, Z. E., Tucker, G. T., Rowland-Yeo, K., 2013. Differences in cytochrome p450-mediated pharmacokinetics between chinese and caucasian populations predicted by mechanistic physiologically based pharmacokinetic modelling. Clinical Pharmacokinetics 52, 1085-100.

Beard, D. A., Neal, M. L., Tabesh-Saleki, N., Thompson, C. T., Bassingthwaighte, J. B., Shimoyama, M., Carlson, B. E., 2012. Multiscale modeling and data integration in the virtual physiological rat project. Annals of Biomedical Engineering 40, 2365-78.

Beattie, K. A., Luscombe, C., Williams, G., Munoz-Muriedas, J., Gavaghan, D. J., Cui, Y., Mirams, G. R., 2013. Evaluation of an in silico cardiac safety assay: using ion channel screening data to predict QT interval changes in the rabbit ventricular wedge. Journal of Pharmacological and Toxicological Methods 68(1), 88-96.

Bischoff, J. E., Dai, Y., Goodlett, C., Davis, B., Bandi, M., 2014. Incorporating population-level variability in orthopedic biomechanical analysis: a review. Journal of Biomechanical Engineering 136, 021004.

Blackshear, P. J., Rohde, T. D., Prosl, F., Buchwald, H., 1979. The implantable infusion pump: a new concept in drug delivery. Medical Progress Through Technology 6, 149-61.

Boissel, J.-P., Cucherat, M., Nony, P., Chabaud, S., Gueyffier, F., Wright, J. M., Lièvre, M., Leizorovicz, A., 2008. New insights on the relation between untreated and treated outcomes for a given therapy effect model is not necessarily linear. Journal of Clinical Epidemiology 61, 301-7.

Boissel, J.-P., Kahoul, R., Marin, D., Boissel, F.-H., 2013. Effect model law: an approach for the implementation of personalized medicine. Journal of Personalized Medicine 3, 177-90.

Boissel, J.-P., Auffray, C., Noble, D., Hood, L., Boissel, F.-H., 2015. Bridging systems medicine and patient needs. CPT: Pharmacometrics & Systems Pharmacology 4(3), e00026

Bottino, D., Penland, R. C., Stamps, A., Traebert, M., Dumotier, B., Georgiva, A., Helmlinger, G., Lett, G. S., 2006. Preclinical cardiac safety assessment of pharmaceutical compounds using an integrated systems-based computer model of the heart. Progress in Biophysics and Molecular Biology 90(1-3), 414-43.

Bousquet, J., Jorgensen, C., Dauzat, M., Cesario, A., Camuzat, T., Bourret, R., Best, N., Anto, J. M., Abecassis, F., Aubas, P., Avignon, A., Badin, M., Bedbrook, A., Blain, H., Bourdin, A., Bringer, J., Camu, W., Cayla, G., Costa, D. J., Courtet, P., Cristol, J.-P., Demoly, P., de la Coussaye, J.-E., Fesler, P., Gouzi, F., Gris, J.-C., Guillot, B., Hayot, M., Jeandel, C., Jonquet, O., Journot, L., Lehmann, S., Mathieu, G., Morel, J., Ninot, G., Pelissier, J., Picot, M.-C., Radier-Pontal, F., Robine, J.-M., Rodier, M., Roubille, F., Sultan, A., Wojtusciszyn, A., Auffray, C., Balling, R., Barbara, C., Cambon-Thomsen, A., Chavannes, N. H., Chuchalin, A., Crooks, G., Dedeu, A., Fabbri, L. M., Garcia-Aymerich, J., Hajjam, J., Melo Gomes, E., Palkonen, S., Piette, F., Pison, C., Price, D., Samolinski, B., Schunemann, H. J., Sterk, P. J., Yiallouros, P., Roca, J., Van de Perre, P., Mercier, J., 2014. Systems medicine approaches for the definition of complex phenotypes in chronic diseases and ageing. From concept to implementation and policies. Current Pharmaceutical Design 20, 5928-44.

Bouxsein, M. L., Melton, L. J., Riggs, B. L., Muller, J., Atkinson, E. J., Oberg, A. L., Robb, R. A., Camp, J. J., Rouleau, P. A., McCollough, C. H., Khosla, S., 2006. Age- and sex-specific differences in the factor of risk for vertebral fracture: a population-based study using QCT. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research 21, 1475-82.

Bouzid, D., Bert, J., Dupre, P.-F., Benhalouche, S., Pradier, O., Boussion, N., Visvikis, D., 2015. Monte-Carlo dosimetry for intraoperative radiotherapy using a low energy x-ray source. Acta Oncologica (Stockholm, Sweden), 1-8.

Brännmark, C., Nyman, E., Fagerholm, S., Bergenholm, L., Ekstrand, E.-M., Cedersund, G., Strålfors, P., 2013. Insulin signaling in type 2 diabetes: experimental and modeling analyses reveal mechanisms of insulin resistance in human adipocytes. The Journal of Biological Chemistry 288, 9867-80.

Breton, M., Farret, A., Bruttomesso, D., Anderson, S., Magni, L., Patek, S., Dalla Man, C., Place, J., Demartini, S., Del Favero, S., Toffanin, C., Hughes-Karvetski, C., Dassau, E., Zisser, H., Doyle, F. J., De Nicolao, G., Avogaro, A., Cobelli, C., Renard, E., Kovatchev, B., 2012. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. Diabetes 61, 2230-7.

Bridgland-Taylor, M. H., Hargreaves, A. C., Easter, A., Orme, A., Henthorn, D. C., Ding, M., Davis, A. M., Small, B. G., Heapy, C. G., Abi-Gerges, N., Persson, F., Jacobson, I., Sullivan, M., Albertson, N., Hammond, T. G., Sullivan, E., Valentin, J. P., Pollard, C. E., 2006. Optimisation and validation of a medium-throughput electrophysiology-based hERG assay using IonWorks HT. Journal of Pharmacological and Toxicological Methods 54(2), 189-99.

Brinkmann, M., Eichbaum, K., Buchinger, S., Reifferscheid, G., Bui, T., Schäffer, A., Hollert, H., Preuss, T. G., 2014. Understanding receptor-mediated effects in rainbow trout: in vitro-in vivo extrapolation using physiologically based toxicokinetic models. Environmental Science & Technology 48, 3303-9.

Britton, O. J., Bueno-Orovio, A., Van Ammel, K., Lu, H. R., Towart, R., Gallacher, D. J., Rodriguez, B., 2013. Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology. Proceedings of the National Academy of Sciences of the United States of America 110, E2098-105.

Brown, A. G., Shi, Y., Arndt, A., Müller, J., Lawford, P., Hose, D. R., 2012. Importance of realistic LVAD profiles for assisted aortic simulations: evaluation of optimal outflow anastomosis locations. Computer Methods in Biomechanics and Biomedical Engineering 15, 669-80.

Bruttomesso, D., Farret, A., Costa, S., Marescotti, M. C., Vettore, M., Avogaro, A., Tiengo, A., Dalla Man, C., Place, J., Facchinetti, A., Guerra, S., Magni, L., De Nicolao, G., Cobelli, C., Renard, E., Maran, A., 2009. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: preliminary studies in Padova and Montpellier. Journal of Diabetes Science and Technology 3, 1014-21.

Bunyavanich, S., Schadt, E. E., 2015. Systems biology of asthma and allergic diseases: a multiscale approach. Journal of Allergy and Clinical Immunology 135(1), 31-42.

Burghaus, R., Coboeken, K., Gaub, T., Kuepfer, L., Sensse, A., Siegmund, H. U., Weiss, W., Mueck, W., Lippert, J., 2011. Evaluation of the efficacy and safety of rivaroxaban using a computer model for blood coagulation. PLoS One 6(4), e17626.

Burghaus, R., Coboeken, K., Gaub, T., Niederalt, C., Sensse, A., Siegmund, H. U., Weiss, W., Mueck, W., Tanigawa, T., Lippert, J., 2014. Computational investigation of potential dosing schedules for a switch of medication from warfarin to rivaroxaban-an oral, direct Factor Xa inhibitor. Frontiers in Physiology 5, 417.

Burner, S. T., Waldo, D. R., McKusick, D. R., 1992. National health expenditures projections through 2030. Health Care Financing Review 14(1), 1-29.

Cárdenes, R., Larrabide, I., Román, L. S., Frangi, A. F., 2013. Performance assessment of isolation methods for geometrical cerebral aneurysm analysis. Medical and Biological Engineering and Computing 51, 343-52.

Carusi, A., 2011. Computational Biology and the Limits of Shared Vision. Perspectives on Science 19, 300-336.

Carusi, A., 2014. Validation and variability: dual challenges on the path from systems biology to systems medicine. Studies In History And Philosophy Of Biological And Biomedical Sciences 48 Pt A, 28-37.

Ceresa, M., Lopez, N. M., Velardo, H. D., Herrezuelo, N. C., Mistrik, P., Kjer, H. M., Vera, S., Paulsen, R. R., González Ballester, M. A., 2014. Patient-specific simulation of implant placement and function for cochlear implantation surgery planning. Medical Image Computing and Computer-Assisted Intervention: MICCAI... International Conference on Medical Image Computing and Computer-Assisted Intervention 17, 49-56.

Chabanas, M., Luboz, V., Payan, Y., 2003. Patient specific finite element model of the face soft tissues for computer-assisted maxillofacial surgery. Medical Image Analysis 7, 131-51.

Chabaud, S., Girard, P., Nony, P., Boissel, J.-P., 2002. Clinical trial simulation using therapeutic effect modeling: application to ivabradine efficacy in patients with angina pectoris. Journal Of Pharmacokinetics And Pharmacodynamics 29, 339-63.

Chakma, J., Sun, G. H., Steinberg, J. D., Sammut, S. M., Jagsi, R., 2014. Asia's ascent--global trends in biomedical R&D expenditures. The New England Journal of Medicine 370(1), 3-6.

Chaudhury, S., Abdulhameed, M. D. M., Singh, N., Tawa, G. J., D'haeseleer, P. M., Zemla, A. T., Navid, A., Zhou, C. E., Franklin,

M. C., Cheung, J., Rudolph, M. J., Love, J., Graf, J. F., Rozak, D. A., Dankmeyer, J. L., Amemiya, K., Daefler, S., Wallqvist, A., 2013. Rapid Countermeasure Discovery against Francisella tularensis Based on a Metabolic Network Reconstruction. PLoS ONE 8.

Ciolino, J. B., Hoare, T. R., Iwata, N. G., Behlau, I., Dohlman, C. H., Langer, R., Kohane, D. S., 2009. A drug-eluting contact lens. Investigative Ophthalmology & Visual Science 50, 3346-52.

Clarke, W. L., Anderson, S., Breton, M., Patek, S., Kashmer, L., Kovatchev, B., 2009. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. Journal Of Diabetes Science and Technology 3, 1031-8.

Clermont, G., Bartels, J., Kumar, R., Constantine, G., Vodovotz, Y., Chow, C., 2004. In silico design of clinical trials: a method coming of age. Critical Care Medicine 32, 2061-70.

Cobelli, C., Man, C. D., Pedersen, M. G., Bertoldo, A., Toffolo, G., 2014. Advancing our understanding of the glucose system via modeling: a perspective. IEEE Transactions on Bio-medical Engineering 61, 1577-92.

Cobelli, C., Renard, E., Kovatchev, B., 2011. Artificial pancreas: past, present, future. Diabetes 60, 2672-82.

Cobelli, C., Renard, E., Kovatchev, B., 2014. The artificial pancreas: a digital-age treatment for diabetes. The Lancet Diabetes and Endocrinology 2, 679-81.

Cobelli, C., Renard, E., Kovatchev, B. P., Keith-Hynes, P., Ben Brahim, N., Place, J., Del Favero, S., Breton, M., Farret, A., Bruttomesso, D., Dassau, E., Zisser, H., Doyle, F. J., Patek, S. D., Avogaro, A., 2012. Pilot studies of wearable outpatient artificial pancreas in type 1 diabetes. Diabetes Care 35, e65-7.

Cook, D., Brown, D., Alexander, R., March, R., Morgan, P., Satterthwaite, G., Pangalos, M. N., 2014. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nature Reviews Drug Discovery 13(6), 419-31.

Coveney, P., Diaz, V., Hunter, P., Viceconti, M., Eds., 2014. Computational Biomedicine. Oxford, Oxford University Press.

Crick, F., 1970. Central dogma of molecular biology. Nature 227(5258), 561-3.

Crick, F. H., 1958. On protein synthesis. Symposia for the Society for Experimental Biology 12, 138-63.

Cristofolini, L., Juszczyk, M., Taddei, F., Field, R. E., Rushton, N., Viceconti, M., 2011. Assessment of femoral neck fracture risk for a novel proximal epiphyseal hip prosthesis. Clinical Biomechanics 26, 585-591.

D'Alessandro, L. A., Hoehme, S., Henney, A., Drasdo, D., Klingmuller, U., 2015. Unraveling liver complexity from molecular to organ level: challenges and perspectives. Progress in Biophysics and Molecular Biology 117(1), 78-86.

Dada, J. O., Mendes, P., 2011. Multi-scale modelling and simulation in systems biology. Integrative Biology: Quantitative Biosciences from Nano to Macro 3, 86-96.

Dalla Man, C., Micheletto, F., Lv, D., Breton, M., Kovatchev, B., Cobelli, C., 2014. The UVA/PADOVA Type 1 Diabetes Simulator: New Features. Journal of Diabetes Science and Technology 8, 26-34.

Dalla Man, C., Rizza, R. A., Cobelli, C., 2007. Meal simulation model of the glucose-insulin system. IEEE Transactions on Bio-medical Engineering 54, 1740-9.

Davies, M. R., Mistry, H. B., Hussein, L., Pollard, C. E., Valentin, J. P., Swinton, J., Abi-Gerges, N., 2012. An in silico canine cardiac midmyocardial action potential duration model as a tool for early drug safety assessment. American journal of physiology. Heart and circulatory physiology 302(7), H1466-80.

de Jong, P., Vissers, M. M. M., van der Meer, R., Bovee-Oudenhoven, I. M. J., 2007. In silico model as a tool for interpretation of intestinal infection studies. Applied and Environmental Microbiology 73, 508-15.

Del Favero, S., Bruttomesso, D., Di Palma, F., Lanzola, G., Visentin, R., Filippi, A., Scotton, R., Toffanin, C., Messori, M., Scarpellini, S., Keith-Hynes, P., Kovatchev, B. P., Devries, J. H., Renard, E., Magni, L., Avogaro, A., Cobelli, C., 2014. First use of model predictive control in outpatient wearable artificial pancreas. Diabetes Care 37, 1212-5.

Dranitsaris, G., Dorward, K., Owens, R. C., Schipper, H., 2015. What is a new drug worth? An innovative model for performance-based pricing. Eur Journal of Cancer Care (Engl) 24(3), 313-20.

Dronne, M.-A., Grenier, E., Dumont, T., Hommel, M., Boissel, J.-P., 2007. Role of astrocytes in grey matter during stroke: a modelling approach. Brain Research 1138, 231-42.

Duval, V., Chabaud, S., Girard, P., Cucherat, M., Hommel, M., Boissel, J. P., 2002. Physiologically based model of acute ischemic stroke. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism 22, 1010-8.

Eberl, S., Anayat, A. R., Fulton, R. R., Hooper, P. K., Fulham, M. J., 1997. Evaluation of two population-based input functions for quantitative neurological FDG PET studies. European Journal Of Nuclear Medicine 24, 299-304.

Ebrahimkhani, M. R., Neiman, J. A., Raredon, M. S., Hughes, D. J., Griffith, L. G., 2014. Bioreactor technologies to support liver function in vitro. Advanced Drug Delivery Reviews 69-70, 132-57.

Esch, E. W., Bahinski, A., Huh, D., 2015. Organs-on-chips at the frontiers of drug discovery. Nature Reviews Drug Discovery 14(4), 248-60.

Falcinelli, C., Schileo, E., Balistreri, L., Baruffaldi, F., Bordini, B., Viceconti, M., Albisinni, U., Ceccarelli, F., Milandri, L., Toni, A., Taddei, F., 2014. Multiple loading conditions analysis can improve the association between finite element bone strength estimates and proximal femur fractures: A preliminary study in elderly women. Bone 67, 71-80.

Fernandez, J. W., Hunter, P. J., 2005. An anatomically based patient-specific finite element model of patella articulation: towards a diagnostic tool. Biomechanics and Modeling In Mechanobiology 4, 20-38.

Ferrarin, M., Palazzo, F., Riener, R., Quintern, J., 2001. Model-based control of FES-induced single joint movements. IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society 9, 245-57.

Fregni, F., Imamura, M., Chien, H. F., Lew, H. L., Boggio, P., Kaptchuk, T. J., Riberto, M., Hsing, W. T., Battistella, L. R., Furlan, A., 2010. Challenges and recommendations for placebo controls in randomized trials in physical and rehabilitation medicine: a report of the international placebo symposium working group. American Journal of Physical Medicine & Rehabilitation 89, 160-72.

Glinka, A., Polak, S., 2014. The effects of six antipsychotic agents on QTc--an attempt to mimic clinical trial through simulation including variability in the population. Computers in Biology and Medicine 47, 20-6.

Graf, J. F., Scholz, B. J., Zavodszky, M. I., 2012. BioDMET: A physiologically based pharmacokinetic simulation tool for assessing proposed solutions to complex biological problems. Journal of Pharmacokinetics and Pharmacodynamics 39, 37-54.

Gras, J., Llenas, J., 1999. Effects of H1 antihistamines on animal models of QTc prolongation. Drug safety 21 Suppl 1, 39-44; discussion 81-7.

Grbic, S., Mansi, T., Ionasec, R., Voigt, I., Houle, H., John, M., Schoebinger, M., Navab, N., Comaniciu, D., 2013. Image-based computational models for TAVI planning: from CT images to implant deployment. Medical Image Computing and Computer Assisted Intervention 16(Pt 2), 395-402.

Hendriks, B. S., Griffiths, G. J., Benson, R., Kenyon, D., Lazzara, M., Swinton, J., Beck, S., Hickinson, M., Beusmans, J. M., Lauffenburger, D., de Graaf, D., 2006. Decreased internalisation of erbB1 mutants in lung cancer is linked with a mechanism conferring sensitivity to gefitinib. Systems Biology 153, 457-66.

Henney, A., Hunter, P., McCulloch, A., Noble, D., 2015. Multi-bio and multi-scale systems biology. Progress in Biophysics and Molecular Biology 117(1), 1-3.

Henney, A., Superti-Furga, G., 2008. A network solution. Nature 455(7214), 730-1.

Henshall, C., Schuller, T., 2013. Health technology assessment, value-based decision making, and innovation. International Journal of Technology Assessment in Health Care 29(4), 353-9.

Hodgkin, A. L., Huxley, A. F., 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. The Journal of Physiology 117, 500-44.

Holzhutter, H. G., Drasdo, D., Preusser, T., Lippert, J., Henney, A. M., 2012. The virtual liver: a multidisciplinary, multilevel challenge for systems biology. Wiley Interdisciplinary Reviews: Systems Biology and Medicine 4(3), 221-35.

Hood, L., Balling, R., Auffray, C., 2012. Revolutionizing medicine in the 21st century through systems approaches. Biotechnology Journal 7, 992-1001.

Hood, L., Friend, S. H., 2011. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nature Reviews Clinical Oncology 8(3), 184-7.

Huh, D., Kim, H. J., Fraser, J. P., Shea, D. E., Khan, M., Bahinski, A., Hamilton, G. A., Ingber, D. E., 2013. Microfabrication of human organs-on-chips. Nature Protocols 8, 2135-57.

Hunter, P., Coveney, P.V., de Bono, B., Diaz, V., Fenner, J., Frangi, A.F., Harris, P., Hose, R., Kohl, P., Lawford, P., McCormack, K., Mendes, M., Omholt, S., Quarteroni, A., Skår, J., Tegner, J., Randall Thomas, S., Tollis, I., Tsamardinos, I., van Beek, J.H., Viceconti, M. 2010. A vision and strategy for the virtual physiological human in 2010 and beyond. Philosophical transactions. Series A, Mathematical, physical, and engineering sciences 368(1920), 2595-614.

Hunter, P., Chapman, T., Coveney, P. V., de Bono, B., Diaz, V., Fenner, J., Frangi, A. F., Harris, P., Hose, R., Kohl, P., Lawford, P., McCormack, K., Mendes, M., Omholt, S., Quarteroni, A., Shublaq, N., Skår, J., Stroetmann, K., Tegner, J., Thomas, S. R., Tollis, I., Tsamardinos, I., van Beek, J. H. G. M., Viceconti, M., 2013. A vision and strategy for the virtual physiological human: 2012 update. Interface Focus 3, 20130004.

Ideker, T., Galitski, T., Hood, L., 2001. A new approach to decoding life: systems biology. Annual Review of Genomics and Human Genetics 2, 343-72.

Imennov, N. S., Rubinstein, J. T., 2009. Stochastic population model for electrical stimulation of the auditory nerve. IEEE Transactions on Bio-medical Engineering 56, 2493-501.

Kampfrath, T., Cotten, S. W., 2013. The new collaborative path in medical device development: The medical device innovation consortium. Clinical Biochemistry 46, 1320-1322.

Kansal, A. R., Trimmer, J., 2005. Application of predictive biosimulation within pharmaceutical clinical development: examples of significance for translational medicine and clinical trial design. Systems Biology 152, 214-220.

Kaptchuk, T. J., Goldman, P., Stone, D. A., Stason, W. B., 2000. Do medical devices have enhanced placebo effects? Journal of Clinical Epidemiology 53, 786-92.

Keller, E. F., 2003. Making Sense of Life. Harvard University Press, Cambridge, MA.

Kinney, A. L., Besier, T. F., D'Lima, D. D., Fregly, B. J., 2013. Update on grand challenge competition to predict in vivo knee loads. Journal of Biomechanical Engineering 135, 021012.

Koelsch, C., Przewrocka, J., Keeling, P., 2013. Towards a balanced value business model for personalized medicine: an outlook. Pharmacogenomics 14(1), 89-102.

Kovatchev, B., Cobelli, C., Renard, E., Anderson, S., Breton, M., Patek, S., Clarke, W., Bruttomesso, D., Maran, A., Costa, S., Avogaro, A., Dalla Man, C., Facchinetti, A., Magni, L., De Nicolao, G., Place, J., Farret, A., 2010. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. Journal of Diabetes Science and Technology 4, 1374-81.

Kovatchev, B. P., Breton, M., Man, C. D., Cobelli, C., 2009. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. Journal of Diabetes Science and Technology 3, 44-55.

Kovatchev, B. P., Renard, E., Cobelli, C., Zisser, H. C., Keith-Hynes, P., Anderson, S. M., Brown, S. A., Chernavvsky, D. R., Breton, M. D., Farret, A., Pelletier, M.-J., Place, J., Bruttomesso, D., Del Favero, S., Visentin, R., Filippi, A., Scotton, R., Avogaro, A., Doyle, F. J., 2013. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 36, 1851-8.

Kovatchev, B. P., Renard, E., Cobelli, C., Zisser, H. C., Keith-Hynes, P., Anderson, S. M., Brown, S. A., Chernavvsky, D. R., Breton, M. D., Mize, L. B., Farret, A., Place, J., Bruttomesso, D., Del Favero, S., Boscari, F., Galasso, S., Avogaro, A., Magni, L., Di Palma, F., Toffanin, C., Messori, M., Dassau, E., Doyle, F. J., 2014. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 37, 1789-96.

Krauss, M., Schaller, S., Borchers, S., Findeisen, R., Lippert, J., Kuepfer, L., 2012. Integrating cellular metabolism into a multiscale whole-body model. PLoS Computational Biology 8, e1002750.

Kucukgul, C., Ozler, S. B., Inci, I., Karakas, E., Irmak, S., Gozuacik, D., Taralp, A., Koc, B., 2015. 3D bioprinting of biomimetic aortic vascular constructs with self-supporting cells. Biotechnology and Bioengineering 112, 811-21.

Kuepfer, L., Kerb, R., Henney, A. M., 2014. Clinical translation in the virtual liver network. CPT: Pharmacometrics and Systems Pharmacology 3, e127.

Leopold, C., Mantel-Teeuwisse, A. K., Vogler, S., Valkova, S., de Joncheere, K., Leufkens, H. G., Wagner, A. K., Ross-Degnan, D., Laing, R., 2014. Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries. Bulletin of the World Health Organization 92(9), 630-640d.

Lerman, S., Gibson, A., 2013. GE Healthcare Announces FDA Approval of Vizamyl™ (Flutemetamol F18 Injection) for Detection of Beta Amyloid. Business Wire.

Li, N. Y. K., Verdolini, K., Clermont, G., Mi, Q., Rubinstein, E. N., Hebda, P. A., Vodovotz, Y., 2008. A patient-specific in silico model of inflammation and healing tested in acute vocal fold injury. PloS One 3, e2789.

Lomnicki, A., 2001. Individual-based Models in Population Ecology. eLS. John Wiley & Sons, Ltd.

Longest, P. W., Tian, G., Walenga, R. L., Hindle, M., 2012. Comparing MDI and DPI aerosol deposition using in vitro experiments and a new stochastic individual path (SIP) model of the conducting airways. Pharmaceutical Research 29, 1670-88.

Luijf, Y. M., DeVries, J. H., Zwinderman, K., Leelarathna, L., Nodale, M., Caldwell, K., Kumareswaran, K., Elleri, D., Allen, J. M., Wilinska, M. E., Evans, M. L., Hovorka, R., Doll, W., Ellmerer, M., Mader, J. K., Renard, E., Place, J., Farret, A., Cobelli, C., Del Favero, S., Dalla Man, C., Avogaro, A., Bruttomesso, D., Filippi, A., Scotton, R., Magni, L., Lanzola, G., Di Palma, F., Soru, P., Toffanin, C., De Nicolao, G., Arnolds, S., Benesch, C., Heinemann, L., 2013. Day and night closed-loop control in adults with type 1 diabetes: a comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient self-management. Diabetes Care 36, 3882-7.

Lungu, A., Wild, J. M., Capener, D., Kiely, D. G., Swift, A. J., Hose, D. R., 2014. MRI model-based non-invasive differential diagnosis in pulmonary hypertension. Journal of Biomechanics 47, 2941-7.

Luni, C., Serena, E., Elvassore, N., 2014. Human-on-chip for therapy development and fundamental science. Current Opinion in Biotechnology 25, 45-50.

Makadia, H. K., Anderson, W. D., Fey, D., Sauter, T., Schwaber, J. S., Vadigepalli, R., 2015. Multiscale model of dynamic neuromodulation integrating neuropeptide-induced signaling pathway activity with membrane electrophysiology. Biophysical Journal 108, 211-23.

Malottki, K., Barton, P., Tsourapas, A., Uthman, A. O., Liu, Z., Routh, K., Connock, M., Jobanputra, P., Moore, D., Fry-Smith, A., Chen, Y.-F., 2011. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 15, 1-278.

Maltais, C., Dansereau, J., Aissaoui, R., Lacoste, M., 1999. Assessment of geometric and mechanical parameters in wheelchair seating: a variability study. IEEE Transactions on Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society 7, 91-8.

Mamchak, A. A., Manenkova, Y., Leconet, W., Zheng, Y., Chan, J. R., Stokes, C. L., Shoda, L. K. M., von Herrath, M., Bresson, D., 2012. Preexisting autoantibodies predict efficacy of oral insulin to cure autoimmune diabetes in combination with anti-CD3. Diabetes 61, 1490-9.

Manolis, E., Rohou, S., Hemmings, R., Salmonson, T., Karlsson, M., Milligan, P. a., 2013. The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output From the EFPIA/EMA Modeling and Simulation Workshop. CPT: Pharmacometrics and Systems Pharmacology 2, e31.

Mardel, S. N., Simpson, S. H., Kelly, S., Wytch, R., Beattie, T. F., Menezes, G., 1995. Validation of a computer model of haemorrhage and transcapillary refill. Medical Engineering and Physics 17, 215-8.

Martelli, S., Taddei, F., Cristofolini, L., Schileo, E., Rushton, N., Viceconti, M., 2011. A new hip epiphyseal prosthesis: Design revision driven by a validated numerical procedure. Medical Engineering and Physics 33, 1203-1211.

Martelli, S., Taddei, F., Schileo, E., Cristofolini, L., Rushton, N., Viceconti, M., 2012. Biomechanical robustness of a new proximal epiphyseal hip replacement to patient variability and surgical uncertainties: A FE study. Medical Engineering and Physics 34, 161-171.

McCune, M., Shafiee, A., Forgacs, G., Kosztin, I., 2014. Predictive modeling of post bioprinting structure formation. Soft Matter 10, 1790-800.

McGinty, S., 2014. A decade of modelling drug release from arterial stents. Mathematical Biosciences 257, 80-90.

Milligan, P. A., Brown, M. J., Marchant, B., Martin, S. W., van der Graaf, P. H., Benson, N., Nucci, G., Nichols, D. J., Boyd, R. a., Mandema, J. W., Krishnaswami, S., Zwillich, S., Gruben, D., Anziano, R. J., Stock, T. C., Lalonde, R. L., 2013. Model-based drug development: a rational approach to efficiently accelerate drug development. Clinical Pharmacology and Therapeutics 93, 502-14.

Mirams, G. R., Davies, M. R., Brough, S. J., Bridgland-Taylor, M. H., Cui, Y., Gavaghan, D. J., Abi-Gerges, N., 2014. Prediction of thorough QT study results using action potential simulations based on ion channel screens. Journal of Pharmacological and Toxicological Methods 70(3), 246-54.
Mishra, H., Polak, S., Jamei, M., Rostami-Hodjegan, A., 2014. Interaction between Domperidone and Ketoconazole: Toward prediction of consequent QTc prolongation using purely in vitro information. CPT: Pharmacometrics and Systems Pharmacology 3, e130.

Morris, P. D., Ryan, D., Morton, A. C., Lycett, R., Lawford, P. V., Hose, D. R., Gunn, J. P., 2013. Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary lesions: results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. JACC: Cardiovascular Interventions 6(2), 149-57.

NC3R, 2015. Improving computer modelling of cardiac properties by ditching the one-size-fits-all approach. http://www.nc3rs.org.uk//news/improving-computer-modelling-cardiac-properties-ditching-one-size-fits-all-approach [Accessed on 20/9/2015].

Noble, D., 2001. From genes to whole organs: connecting biochemistry to physiology. Novartis Foundation Symposia 239, 111-23; discussion 123-8, 150-9.

Noble, D., 2003. The future: putting Humpty-Dumpty together again. Biochemical Society Transactions 31(Pt 1), 156-8.

Noble, D., 2012. A theory of biological relativity: no privileged level of causation. Interface Focus 2(1), 55-64.

Noble, D., Garny, A., Noble, P. J., 2012. How the Hodgkin-Huxley equations inspired the Cardiac Physiome Project. The Journal of Physiology 590, 2613-28.

Nørgaard, B. L., Leipsic, J., Gaur, S., Seneviratne, S., Ko, B. S., Ito, H., Jensen, J. M., Mauri, L., De Bruyne, B., Bezerra, H., Osawa, K., Marwan, M., Naber, C., Erglis, A., Park, S.-J., Christiansen, E. H., Kaltoft, A., Lassen, J. F., Bøtker, H. E., Achenbach, S., 2014. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). Journal of the American College of Cardiology 63, 1145-55.

O'Rourke, M. J., McCullough, J. P., 2008. A comparison of the measured and predicted flowfield in a patient-specific model of an abdominal aortic aneurysm. Proceedings of the Institution of Mechanical Engineers. Part H, Journal of Engineering in Medicine 222, 737-50.

Ozbolat, I. T., Yu, Y., 2013. Bioprinting toward organ fabrication: challenges and future trends. IEEE Transactions on Bio-Medical Engineering 60, 691-9.

Pammolli, F., Magazzini, L., Riccaboni, M., 2011. The productivity crisis in pharmaceutical R&D. Nature Reviews Drug Discovery 10(6), 428-38.

Pancanti, A., Bernakiewicz, M., Viceconti, M., 2003. The primary stability of a cementless stem varies between subjects as much as between activities. Journal of Biomechanics 36, 777-85.

Paolini, G. V., Shapland, R. H., van Hoorn, W. P., Mason, J. S., Hopkins, A. L., 2006. Global mapping of pharmacological space. Nature Biotechnology 24(7), 805-15.

Passuti, N., Gouin, F., 2003. Antibiotic-loaded bone cement in orthopedic surgery. Joint Bone Spine 70(3), 169-74.

Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., Schacht, A. L., 2010. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug discovery 9, 203-14.

Peyser, T., Dassau, E., Breton, M., Skyler, J. S., 2014. The artificial pancreas: current status and future prospects in the management of diabetes. Annals of the New York Academy of Sciences 1311, 102-23.

Pohjola-Sintonen, S., Viitasalo, M., Toivonene, L., Neuvonen, P., 1993. Torsades de pointes after terfenadine-itraconazole interaction. British Medical Journal (Clinical research ed.)

306, 186.

Polak, S., Wišniowska, B., Fijorek, K., Glinka, A., Mendyk, A., 2014. In vitro-in vivo extrapolation of drug-induced proarrhythmia predictions at the population level. Drug Discovery Today 19, 275-81.

Popelar, C. F., 2013. Verification & Validation in Computational Modeling of Medical Devices (V&V-40): ASME subcommitee and guide. FDA/NIH/NSF Workshop on Computer Models and Validation for Medical Devices. Silver Spring, MD.

PriceWaterhouseCoopers, 2008. Pharma 2020: Virtual R&D which path will you take? http://www.vph-institute.org/upload/pwc-pharma2020-virtualrd-final_519245021a53a.pdf [Accessed on 18/9/2015].

Raftery, J., 2013. Value based pricing: can it work? British Medical Journal 347, f5941.

Redberg, R. F., 2014. Sham controls in medical device trials. The New England Journal of Medicine 371, 892-3.

Renard, E., Cobelli, C., Kovatchev, B. P., 2013. Closed loop developments to improve glucose control at home. Diabetes Research and Clinical Practice 102, 79-85.

Renard, E., Cobelli, C., Zisser, H. C., Kovatchev, B. P., 2013. Artificial pancreas goes outpatient: a new diabetes ecosystem. Journal of Diabetes Science and Technology 7, 1411-5.

Ribba, B., Saut, O., Colin, T., Bresch, D., Grenier, E., Boissel, J. P., 2006. A multiscale mathematical model of avascular tumor growth to investigate the therapeutic benefit of anti-invasive agents. Journal of Theoretical Biology 243, 532-41.

Roldán-Alzate, A., García-Rodríguez, S., Anagnostopoulos, P. V., Srinivasan, S., Wieben, O., François, C. J., 2015. Hemodynamic study of TCPC using in vivo and in vitro 4D Flow MRI and numerical simulation. Journal of Biomechanics 48, 1325-30.

Rose, R. H., Neuhoff, S., Abduljalil, K., Chetty, M., Rostami-Hodjegan, A., Jamei, M., 2014. Application of a physiologically based pharmacokinetic model to predict OATP1B1-related variability in pharmacodynamics of rosuvastatin. CPT: Pharmacometrics and Systems Pharmacology 3, e124.

Rostami-Hodjegan, A., 2012. Physiologically based pharmacokinetics joined with in vitro-in vivo extrapolation of ADME: a marriage under the arch of systems pharmacology. Clinical Pharmacology and Therapeutics 92(1), 50-61.

Rostami-Hodjegan, A., Tucker, G. T., 2007. Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. Nature Reviews Drug Discovery 6, 140-8.

Sager, P. T., Gintant, G., Turner, J. R., Pettit, S., Stockbridge, N., 2014. Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium. American Heart Journal 167, 292-300.

Sánchez, C., Bueno-Orovio, A., Wettwer, E., Loose, S., Simon, J., Ravens, U., Pueyo, E., Rodriguez, B., 2014. Inter-subject variability in human atrial action potential in sinus rhythm versus chronic atrial fibrillation. PloS One 9, e105897.

Schadt, E. E., Buchanan, S., Brennand, K. J., Merchant, K. M., 2014. Evolving toward a human-cell based and multiscale approach to drug discovery for CNS disorders. Frontiers in Pharmacology 5, 252.

Schmidt, B. J., Casey, F. P., Paterson, T., Chan, J. R., 2013. Alternate virtual populations elucidate the type I interferon signature predictive of the response to rituximab in rheumatoid arthritis. BMC Bioinformatics 14, 221.

Simmons, M. K., Manjeshwar, R., Agdeppa, E. D., Mattheyses, R. M., Kiehl, T. R., Montalto, M. C., 2005. A computational positron emission tomography simulation model for imaging Beta-amyloid in mice. Molecular Imaging and Biology, 7, 69-77.

Small, B. G., McColl, B. W., Allmendinger, R., Pahle, J., Lopez-Castejon, G., Rothwell, N. J., Knowles, J., Mendes, P., Brough, D., Kell, D. B., 2011. Efficient discovery of anti-inflammatory small-molecule combinations using evolutionary computing. Nature Chemical Biology 7(12), 902-8.

Sneyd, J., Crampin, E., Yule, D., 2014. Multiscale modelling of saliva secretion. Mathematical Biosciences 257, 69-79.

Solomon, A. K., Gold, G. L., 1955. Potassium transport in human erythrocytes: evidence for a three compartment system. The Journal of General Physiology 38, 371-88.

Sonnefeld, S. T., Waldo, D. R., Lemieux, J. A., McKusick, D. R., 1991. Projections of national health expenditures through the year 2000. Health Care Financing Review 13(1), 1-15.

Sun, Y., Yang, X., Wang, Q., 2014. In-silico analysis on biofabricating vascular networks using kinetic Monte Carlo simulations. Biofabrication 6, 015008.

Swee, J. K. Y., Grbic, S., 2014. Advanced transcatheter aortic valve implantation (TAVI) planning from CT with ShapeForest. Medical Image Computing and Computer-Assisted Intervention: MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention 17, 17-24.

Thiele, I., Swainston, N., Fleming, R. M. T., Hoppe, A., Sahoo, S., Aurich, M. K., Haraldsdottir, H., Mo, M. L., Rolfsson, O., Stobbe, M. D., Thorleifsson, S. G., Agren, R., Bölling, C., Bordel, S., Chavali, A. K., Dobson, P., Dunn, W. B., Endler, L., Hala, D., Hucka, M., Hull, D., Jameson, D., Jamshidi, N., Jonsson, J. J., Juty, N., Keating, S., Nookaew, I., Le Novère, N., Malys, N., Mazein, A., Papin, J. a., Price, N. D., Selkov, E., Sigurdsson, M. I., Simeonidis, E., Sonnenschein, N., Smallbone, K., Sorokin, A., van Beek, J. H. G. M., Weichart, D., Goryanin, I., Nielsen, J., Westerhoff, H. V., Kell, D. B., Mendes, P., Palsson, B. O., 2013. A community-driven global reconstruction of human metabolism. Nature Biotechnology.

Thompson, H., 2012. An engineer takes on CE marks and European commercialization. medical device and diagnostics industry (part I). Medical Device and Diagnostic Industry On-line Newsletter. http://www.mddionline.com/article/engineer-takes-medical-device-regulatory-process-part-I [Accessed on 18/9/2015].

Thompson, H., 2012. An engineer takes on FDA clearance and approval processes (part II). Medical Device and Diagnostic Industry Online Newsletter. http://www.mddionline.com/article/engineer-takes-medical-device-regulatory-process-part-ii [Accessed on 18/9/2015].

Thompson, H., 2012. An engineer takes on global regulatory processes: Asia, Latin America, and more (part III). Medical Device and Diagnostic Industry Online Newsletter. http://www.mddionline.com/article/engineer-takes-medical-device-regulatory-process-part-iii [Accessed on 18/9/2015].

Topol, E., 2012. The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care. New York: Basic Books.

Törnqvist, E., Annas, A., Granath, B., Jalkesten, E., Cotgreave, I., Öberg, M., 2014. Strategic Focus on 3R Principles Reveals Major Reductions in the Use of Animals in Pharmaceutical Toxicity Testing. PLoS One 9, e101638.

Tourovskaia, A., Fauver, M., Kramer, G., Simonson, S., Neumann, T., 2014. Tissue-engineered microenvironment systems for modeling human vasculature. Experimental Biology and Medicine (Maywood) 239(9), 1264-71.

Trachet, B., Bols, J., De Santis, G., Vandenberghe, S., Loeys, B., Segers, P., 2011. The impact of simplified boundary conditions and aortic arch inclusion on CFD simulations in the mouse aorta: a comparison with mouse-specific reference data. Journal of Biomechanical Engineering 133, 121006.

Trachet, B., Bols, J., Degroote, J., Verhegghe, B., Stergiopulos, N., Vierendeels, J., Segers, P., 2015. An animal-specific FSI model of the abdominal aorta in anesthetized mice. Annals of Biomedical Engineering 43(6), 1298-309.

Tzallas, A. T., Katertsidis, N. S., Karvounis, E. C., Tsipouras, M. G., Rigas, G., Goletsis, Y., Zielinski, K., Fresiello, L., Molfetta, A. D., Ferrari, G., Terrovitis, J. V., Trivella, M. G., Fotiadis, D. I., 2014. Modeling and simulation of speed selection on left ventricular assist devices. Computers in Biology and Medicine 51, 128-39.

van Drongelen, A., Hessels, J., Geertsma, R., 2015. Comparison of market authorization systems of medical devices in USA and Europe. Dutch National Institute for Public Health and the environment. RIVM Report 2015-0001. http://www.rivm.nl/dsresource?objectid=rivmp:271453&type=org&disposition=inline&ns_nc=1 [Accessed 18/9/2015].

Vande Geest, J. P., Di Martino, E. S., Bohra, A., Makaroun, M. S., Vorp, D. A., 2006. A biomechanics-based rupture potential index for abdominal aortic aneurysm risk assessment: demonstrative application. Annals of the New York Academy of Sciences 1085, 11-21.

Viceconti, M., 2011. A tentative taxonomy for predictive models in relation to their falsifiability. Philosophical transactions. Series A, Mathematical, Physical, and Engineering Sciences 369(1954), 4149-61.

Viceconti, M., Affatato, S., Baleani, M., Bordini, B., Cristofolini, L., Taddei, F., 2009. Pre-clinical validation of joint prostheses: A systematic approach. Journal of the Mechanical Behavior of Biomedical Materials 2, 120-127.
Viceconti, M., Hunter, P., Hose, D., 2015. Big data, big knowledge: big data for personalised healthcare. Biomedical and Health Informatics, IEEE Journal of, 19(4), 1209-15.

Viceconti, M., Pancanti, a., Dotti, M., Traina, F., Cristofolini, L., 2004. Effect of the initial implant fitting on the predicted secondary stability of a cementless stem. Medical and Biological Engineering and Computing 42, 222-9.

Wang, R. S., Maron, B. A., Loscalzo, J., 2015. Systems medicine: evolution of systems biology from bench to bedside. Wiley Interdisciplinary Reviews: Systems Biology and Medicine 7, 141-61.

Wikswo, J. P., Block, F. E., 3rd, Cliffel, D. E., Goodwin, C. R., Marasco, C. C., Markov, D. A., McLean, D. L., McLean, J. A., McKenzie, J. R., Reiserer, R. S., Samson, P. C., Schaffer, D. K., Seale, K. T., Sherrod, S. D., 2013. Engineering challenges for instrumenting and controlling integrated organ-on-chip systems. IEEE Transactions on Bio-medical Engineering 60(3), 682-90.

Wolkenhauer, O., Auffray, C., Brass, O., Clairambault, J., Deutsch, A., Drasdo, D., Gervasio, F., Preziosi, L., Maini, P., Marciniak-Czochra, A., Kossow, C., Kuepfer, L., Rateitschak, K., Ramis-Conde, I., Ribba, B., Schuppert, A., Smallwood, R., Stamatakos, G., Winter, F., Byrne, H., 2014. Enabling multiscale modeling in systems medicine. Genome Medicine 6, 21.

Wolters, B. J. B. M., Rutten, M. C. M., Schurink, G. W. H., Kose, U., de Hart, J., van de Vosse, F. N., 2005. A patient-specific computational model of fluid-structure interaction in abdominal aortic aneurysms. Medical Engineering and Physics 27, 871-83.

Zarins, C. K., Taylor, C. A., Min, J. K., 2013. Computed Fractional Flow Reserve (FFTCT) Derived from Coronary CT Angiography. Journal of Cardiovascular Translational Research 6, 708-14.

Zavitsanou, S., Mantalaris, A., Georgiadis, M., Pistikopoulos, E. In-silico closed loop control validation studies for optimal insulin delivery in type 1 diabetes. 2015. IEEE Transactions on Bio-medical Engineering, Apr 29 [Epub ahead of print].

Zavodszky, M. I., Graf, J. F., Tan Hehir, C. A., 2011. Feasibility of imaging myelin lesions in multiple sclerosis. International Journal of Biomedical Imaging 2011, 953806.

Zhang, D., Lv, S., Song, X., Yuan, F., Xu, F., Zhang, M., Yan, S., Cao, X., 2015. Fractional flow reserve versus angiography

for guiding percutaneous coronary intervention: a meta-analysis. Heart (British Cardiac Society) 101, 455-62.

Zhang, X., Zhang, Y., 2015. Tissue engineering applications of three-dimensional bioprinting. Cell Biochemistry and Biophysics 72(3), 777-82.

Zhao, D., Long, X. D., Lu, T. F., Wang, T., Zhang, W. W., Liu, Y. X., Cui, X. L., Dai, H. J., Xue, F., Xia, Q., 2015. Metformin decreases IL-22 secretion to suppress tumor growth in an orthotopic mouse model of hepatocellular carcinoma. International Journal of Cancer 136(11), 2556-65.

Zinner, R. G., Barrett, B. L., Popova, E., Damien, P., Volgin, A. Y., Gelovani, J. G., Lotan, R., Tran, H. T., Pisano, C., Mills, G. B., Mao, L., Hong, W. K., Lippman, S. M., Miller, J. H., 2009. Algorithmic guided screening of drug combinations of arbitrary size for activity against cancer cells. Molecular Cancer Therapeutics 8(3), 521-32.

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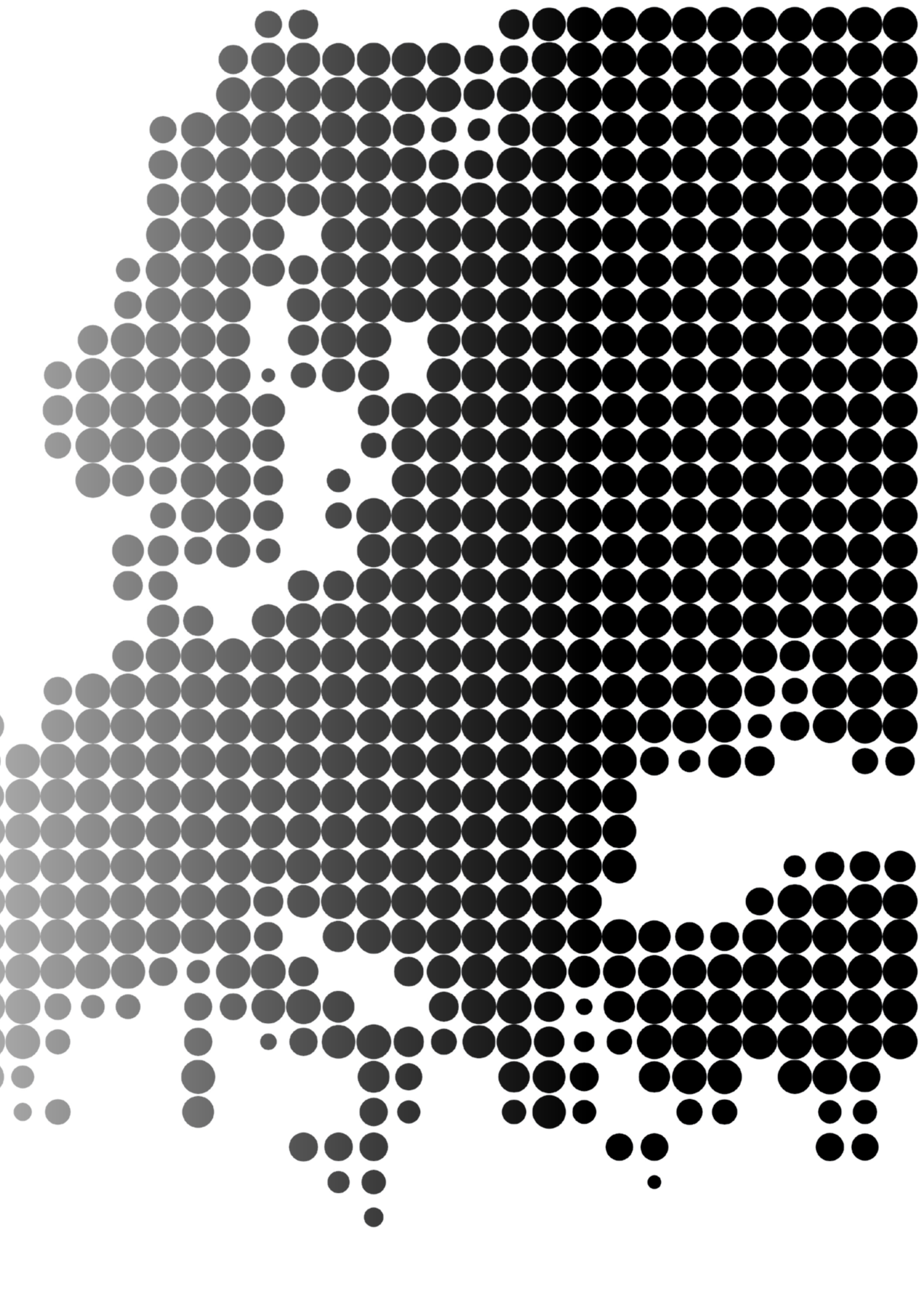

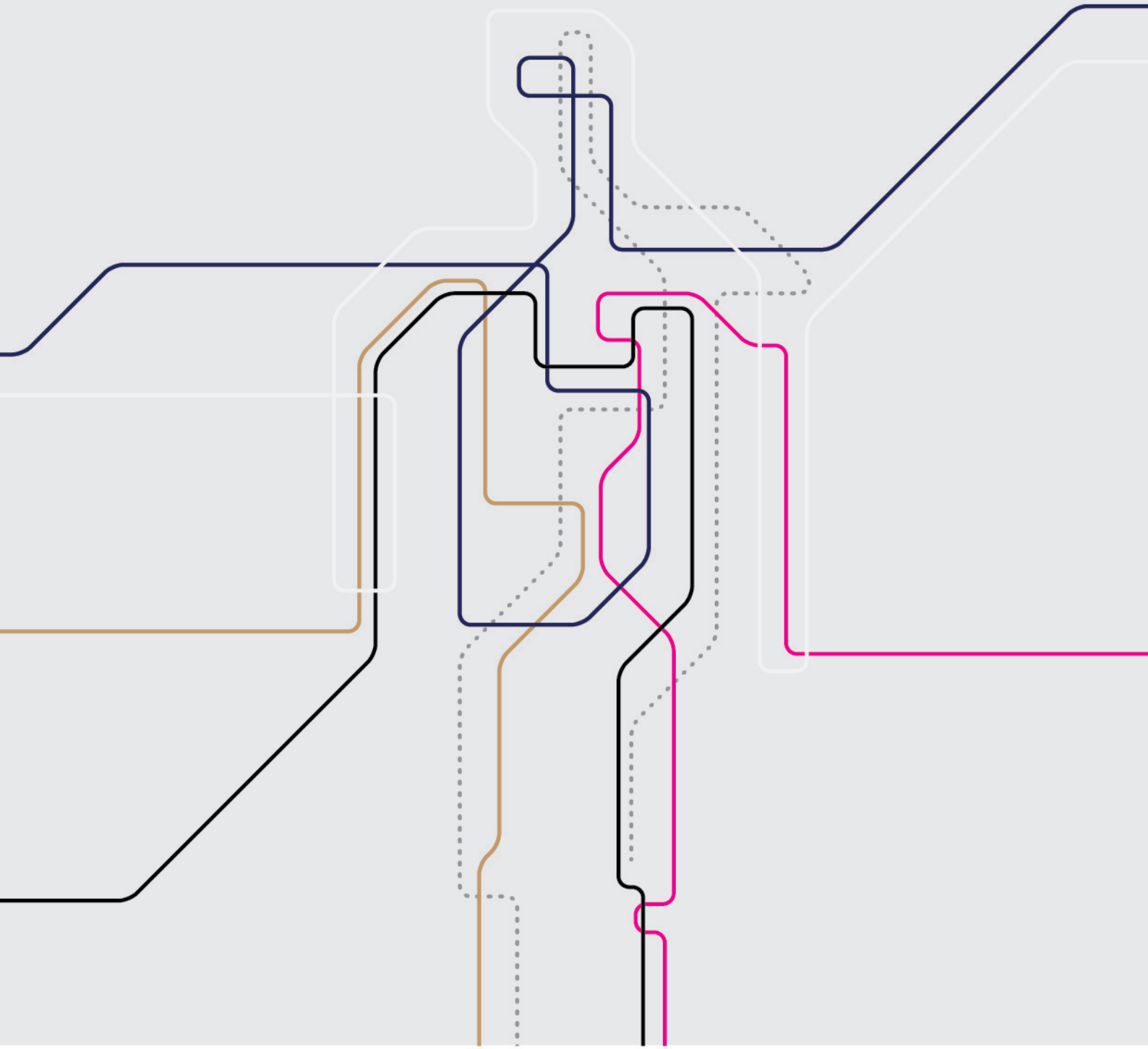

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"Avicenna – A Strategy for *in silico* Clinical Trials" is a Coordination and Support Action funded by the European Commission as part of the Seventh Framework Program for Research and Technological Development (FP7), under the Information Communication Technologies Programme (Contract Number 611819).