KPMG

In Silico Regulatory Evidence Utilisation within the Life Science Sector

July 2024

Foreword

In an era defined by rapid technological advancements, digital innovation, and the transformative rise of artificial intelligence, the integration of Computational Modelling and Simulation (CM&S) technology and Model-Informed Evidence(MIE) / In Silico Evidence (ISE) stands poised to revolutionize the future of healthcare. These cutting-edge methods offer a thrilling opportunity to expedite Research and Development (R&D), spark unprecedented innovation, and usher life-changing pharmaceutical and medical device products to market with remarkable speed and enhanced safety. Imagine a world where research sample sizes are minimized, and the reliance on animal testing in pre-clinical trials is significantly reduced. In silico clinical trials (IST) can democratize access to medical breakthroughs by employing virtual patient cohorts that mirror diverse populations, ensuring new treatments are effective across various demographic groups, including those previously marginalized by traditional evidence approaches.

This report delves into the benefits of CM&S and challenges faced by manufacturers as they navigate this pivotal technology, exploring the promising future that lies ahead. Through the reflections of key stakeholders, we uncover the essential steps required to advance CM&S and ISE implementation safely, effectively, and robustly. We will examine how ISE can streamline the development of new pharmaceutical and medical device products, reducing R&D timelines, costs, and risks along the value chain, thus promoting the availability of innovative treatments to address unmet medical needs.

Consider the staggering costs associated with bringing a new pharmaceutical to market, estimated at approximately $2.6 billion.[1] A pivotal phase III clinical trial alone has a median cost of $48 million.[2] By leveraging ISTs and ISE to predict a product's safety and efficacy profile before initiating research, the likelihood of trial termination or futility can be significantly reduced, leading to substantial cost savings. Evidence suggests that ISTs can accelerate market entry by up to two years and reduce the number of patients required for clinical studies, potentially saving up to $10 million. Moreover, using ISE for product repurposing offers significant efficiency, time savings, and ethical advantages from a pre-clinical perspective.[3]

To fully harness the transformative potential of CM&S, MIE and ISE, manufacturers must navigate the complex landscape of global regulatory acceptance criteria. This involves developing robust methodologies, validating models, and providing compelling evidence that these models address specific research questions. Establishing National Centres of Excellence on MIE and ISE, which unite industry, academia, and regulators in a collaborative effort, will provide economies with a competitive edge on the global stage. These centres will foster R&D investment, cultivate a highly skilled workforce, and leverage extensive digital data repositories to design the next generation of ethical and inclusive medical products. There is a pressing need for a cross-sector effort to develop clearer regulatory guidelines, international standards, and best practices. Such initiatives will pave the way for the global harmonization of in silico technologies, if not their regulation by worldwide regulatory agencies.

Foreword

Despite the undeniable promise of this technology, the sector faces challenges, including a skills gap and the perception that adopting new technology offers a poor return on investment. Contrary to this belief, evidence shows that relevant skills can be sourced from other sectors transformed by the digital revolution, such as aerospace and automotive. Additionally, the healthcare industry can recoup its investment in *in silico* technologies multiple times during the R&D phase of the product life cycle. This misconception largely stems from regulatory uncertainty and a lack of incentives for adopting these technologies. Despite the unsustainability of the current status quo in life sciences and health technology R&D, the familiar often feels safer than the uncharted. However, those who dare to embrace innovation are poised to set new standards and lead the industry forward.

It is essential to recognize that there is no "one-size-fits-all" approach to CM&S, MIE and ISE generation, validation, credibility, or acceptance. Acknowledging this diversity when developing guidance and regulation will ensure that the benefits of this crucial technology are realized with appropriate safeguards, promoting a robust risk-benefit profile for patients. Let us embark on this journey together, embracing the potential of CM&S, MIE and ISE to transform healthcare and improve patient outcomes.

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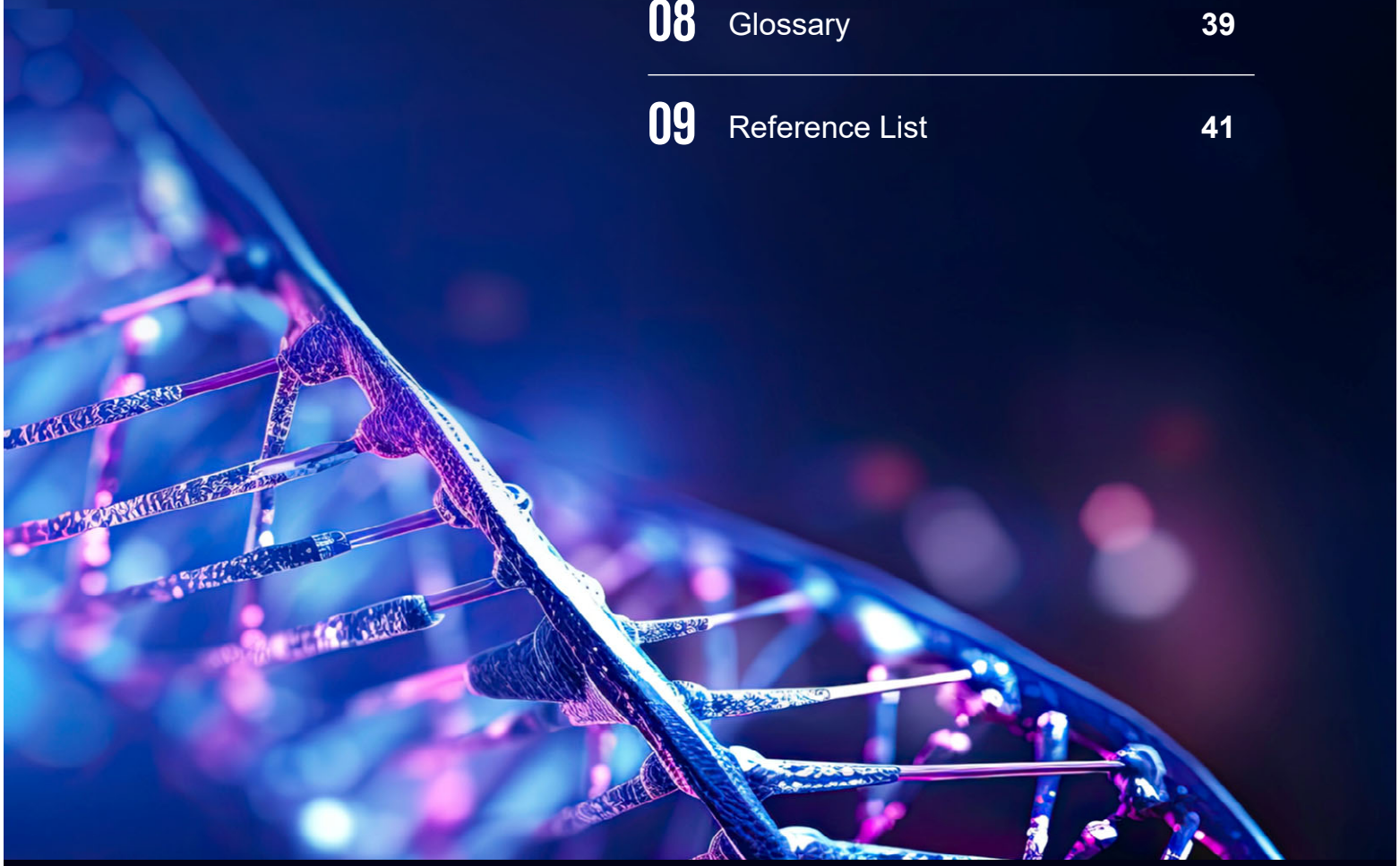
Table of Contents



Executive Summary

Aims of this report

- To evaluate the potential for MIE and ISE to support the authorisation of new drugs and devices, and ascertain global stakeholder perspectives on the current and future potential for this technology within the life science sector.
- To review the use of *in silico* regulatory evidence as a tool to enhance global regulatory frameworks and drive innovation and growth in the life science sector.
- To discuss the key attributes of *in silico* technology, and how the utilisation of this technology should be considered alongside existing clinical trial evidence.
- Key findings will be presented on how *in silico* regulatory evidence can support the body of data for life science product submissions and the current challenges with widescale adoption of the technology.
- Additionally, survey results from stakeholder interviews will be presented.[(a)]

Current use

In silico evidence (ISE) is already being used to varying degrees in medical device and pharmaceutical development and registration. Computational modelling and simulation (CM&S) is more established and has been more commonly used in the medical device sector than in pharmaceutical development. Whilst the use of ISE is growing in both sectors, the use of MIE and ISE for medical devices is considered more pivotal to development, due to greater historical use. Many regulators accept applications that have generated data using CM&S, MIE and ISE methodologies when applicants demonstrate scientific validity.

Benefits

The benefits of more widespread regulatory acceptance of ISE include greater research and investment for *in silico* technology, the potential for reduced timelines for new products to reach the market, increased evidence generation on risk, and reduced costs in the R&D value chain. Additional benefits could include the enhanced refinement of devices and techniques; greater availability of new, more advanced treatments; greater representation of under-represented patient populations in regulatory evidence; and critical data generation for areas of unmet medical need.

Challenges

A current barrier to the widespread use of MIE *and* ISE technology is divergent global regulatory acceptance criteria for MIE and ISE in some jurisdictions. Other challenges include difficulty demonstrating validation of *in silico* models and data; a lack of understanding and public trust in MIE and ISE; a skills gap within the sector; divergent quality of input data; potential bias with data sets; and the perception of a poor return on investment for organisations seeking to adopt the technology.

Validation

Validation is an issue affecting global regulatory acceptance criteria for ISE. A robust methodology, demonstrating validation of a model and verification that the model answers the research question, are key to *in silico* methods being developed. Whilst validation frameworks exist and can involve comparison with a 'gold standard', the challenge is understanding what the appropriate gold standard should be in any given context. Globally accepted validation standards would help to build cross-stakeholder trust in MIE and ISE.

Note: (a) Interviews were conducted with interviewees from key stakeholder organisations and an electronic survey was created. The aim of the interviews and survey was to gather stakeholder perspectives on current and future considerations in the field of ISE. Interviewees were selected according to their knowledge and involvement in the field of *in silico* regulatory evidence.

Executive Summary (cont.)

Economic considerations

Economic benefits associated with the use of MIE and ISE include the reduction of costs associated with R&D and increased opportunity for health equity by decreasing the time to market for important products. By using *in silico* technology to repurpose molecules, or improve process development, there are opportunities for significant efficiency gains. In addition, *in silico* technology offers promising returns on investment. See section below for further information

Regulations and guidance

The use of ISE to supplement clinical evidence is becoming more widespread. This follows considerable stakeholder collaboration across the life science sector to advance and develop understanding of ISE and its role in the regulatory approval of new drugs and devices. The US FDA has made progress in generation of guidance relating to the assessment of MIE and ISE methods.

In Europe, the EMA has published guidance for the sector. In the UK, formal guidelines related to *in silico* methodologies are yet to be produced, however it is accepted that *in silico* modelling plays a role in forming the evidence base for medicine and medical device approvals. The pharmaceutical and medical device sectors are currently experiencing growth in the development of MIE and ISE methods, encouraged by the development of regulatory guidance and direction, as well as industry technical standards and best practice.

Looking to the future

To promote more widespread adoption and regulatory acceptance of *in silico* methodologies and evidence, there is a need for greater sectoral harmonisation and education with regards to the potential of the technology.

Building trust, promoting communication across international stakeholder groups, and raising awareness of MIE and ISE are important factors. There is a need for a collaborative approach towards the development of guidance, which should be informed by cross sector experts and patient groups across therapeutic areas, working together with a shared common objective.

There isn't a unified approach to MIE and ISE generation, validation, or acceptance, this should be kept in mind when developing guidance and regulation to help ensure that the benefits of the technology can be realised with appropriate safeguards in place to promote a robust risk: benefit profile for patients.

Acknowledgement

This report was compiled on behalf of the University of Manchester, Christabel Pankhurst Institute by the KPMG Life Science Regulatory Solutions Team, based on a detailed literature review, surveys and structured interviews with stakeholders within the life science sector. We would like to thank all the stakeholders who have contributed towards this report.

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01 Introduction

For decades, randomised clinical trials (RCTs) and clinical investigations have been the gold standard to assess the quality, safety and efficacy of medicines and medical devices. The existing research methods are expensive, time and resource intensive and do not represent real-world effectiveness of products. Additionally, traditional research is often scrutinised for underrepresenting women, and different groups (ethnically diverse groups; people with different gender identities; people with different sexual orientation; people with disabilities)[1]. *In silico* clinical trials (ISTs) may utilise real-world datasets to enable a varying number of trial protocols to be created from a range of data sources, including: electronic health records; DNA sequencing (omics); and real-world datasets. ISTs are often designed to complement traditional research protocols and also provide an opportunity to investigate a product after registrational research has concluded. This allows for larger and more diverse sample sizes to be studied, or for adjustment of patient inclusion criteria to test new hypothesis.

What is ISE?

In silico Evidence (ISE) is a term synonymous with Model Informed Evidence (MIE). Both integrate empirical data to calibrate, validate and refine models, ensuring they reflect real-world scenarios more accurately, we refer to ISE in this report which includes MIE concepts. Data derived from computer simulations and computational models which is curated to support evidence required for regulatory product submissions are *In silico* Evidence.

Computational modelling and simulation is a powerful tool used as standard practice is numerous industries. Regulators do accept data generated *in silico* as part of the regulatory data evidence package.

In vitro and *in vivo* studies are essential components of experimental evidence generation for risk: benefit analysis (safety and efficacy) of medicinal products and medical devices (Figure 1).

In the last few years there has been a paradigm shift in approach to data generation, as regulatory authorities are now accepting evidence generated using computational modelling and simulation (CM&S), also known as MIE or ISE. This approach complements traditional *in vitro* and *in vivo* studies, offering advantages and contributing to a more comprehensive evaluation of products.

Regulatory acceptance of *in silico* data is now underpinned by agencies like FDA and EMA, who have developed guidelines and frameworks for the use of *in silico* data in product development. These include guidance on validation and qualification of computational models. Qualification programs such as FDA's Model-Informed Drug Development (MIDD) initiative and the EMA qualification of novel methodologies, encourage the integration of *in silico* models in regulatory evidence packages.

Finite-Element Analysis, a computational modelling tool has provided an extra edge to medical device design where model performance can be assessed on different patient-specific cases. The finite element method (FEM)(See Fig.1) is a numerical method used to solve boundary value problems. This method adopts an approach of computing reactions over a discrete number of points across a domain of interest.

For medical design, this typically translates towards verifying device performance in a virtual domain that is representative of a planned real-life application. A user may leverage results from such an analysis to interpret device performance and make educated recommendations for improvement and optimisation. Predictions of initial and long-term device performance *in vivo* may also be derived from FEM results through a multi-scaled and iterative analyses which may subsequently lead to better prepared *in vivo* studies.

Figure 1: *in silico*, *in vitro* and *in vivo* assay processes to identify new products based on biological targets

Using computational modelling and simulation (CM&S), powerful tools have been widely used across various sectors including the aerospace, automotive and construction industry. These tools help in designing, testing, and optimising products and processes, leading to improved performance, safety, and cost-efficiency with the goal of de-risking product design. With technological advancement shaping diagnosis and treatment in healthcare, CM&S is an important tool. Being able to understand and predict disease genesis, pathophysiology and response to treatment is invaluable in the support of regulatory, clinical and policy decisions[2]. This article seeks to discuss how augmenting experimental and clinical research with, *in silico* methodologies can be used to expand, bridge, and integrate *in vitro*, *in vivo* and *ex vivo* experimental and clinical research data, providing a clearer and more systematic development of medical therapies[3].

Table 1: Cross-Sector Computational Modelling and Simulation Tools

Industry	Example
Aerospace	Computational Fluid Dynamics: used to simulate airflow over aircraft surfaces, optimising the aerodynamics design to reduce drag and improve fuel efficiency
Automotive	Internal Combustion engines: Simulations of combustion processes help optimise engine performance, fuel efficiency and emissions
Construction	Building Information Modelling (BIM): used to integrate 3D modelling with project management tools, allowing for detailed planning, design, and management of construction projects

History of ISE

Biological systems are inherently complex and modelling them accurately remains a challenge. The history of computational technology in modelling how medicines work in the body, known as pharmacokinetics and pharmacodynamics (PK/PD), spans several decades and is marked by significant milestones.

as early as the 1960's. Initial efforts in modelling drug behaviour in the body used compartmental models. These simplified the body into compartments (e.g., blood, organs) and described drug distribution using differential equations. Computers were employed to allow for more complex calculations, but there were limitations due to the immaturity of computational power[4]. The next 10-15 years saw the establishment and use of these models, as PK as a formal discipline began to take shape, with models describing drug absorption, distribution, metabolism, and excretion (ADME). At this time the models comprised simple data regressions, where the body was treated as a 'black box', meaning the complex system and internal workings were not really understood, but equations were chosen as they appeared to fit the experimental observations. Advances in computational technology in the 1980's allowed for early PK/PD simulation software, such as NONMEM (Nonlinear Mixed-Effects Modeling), enabling the analysis of population Pharmacokinetics (PopPK) - providing unique insights in the variation of drug behaviours from person to person[5,6]. Physiology Based Pharmacokinetics (PBPK) models emerged in the 1990's, incorporating physiological and biochemical parameters to predict drug behaviours in different body tissues. Enhanced computational tools and software (e.g., WinNonlin) allowed for sophisticated modeling and simulation, including Bayesian approaches.

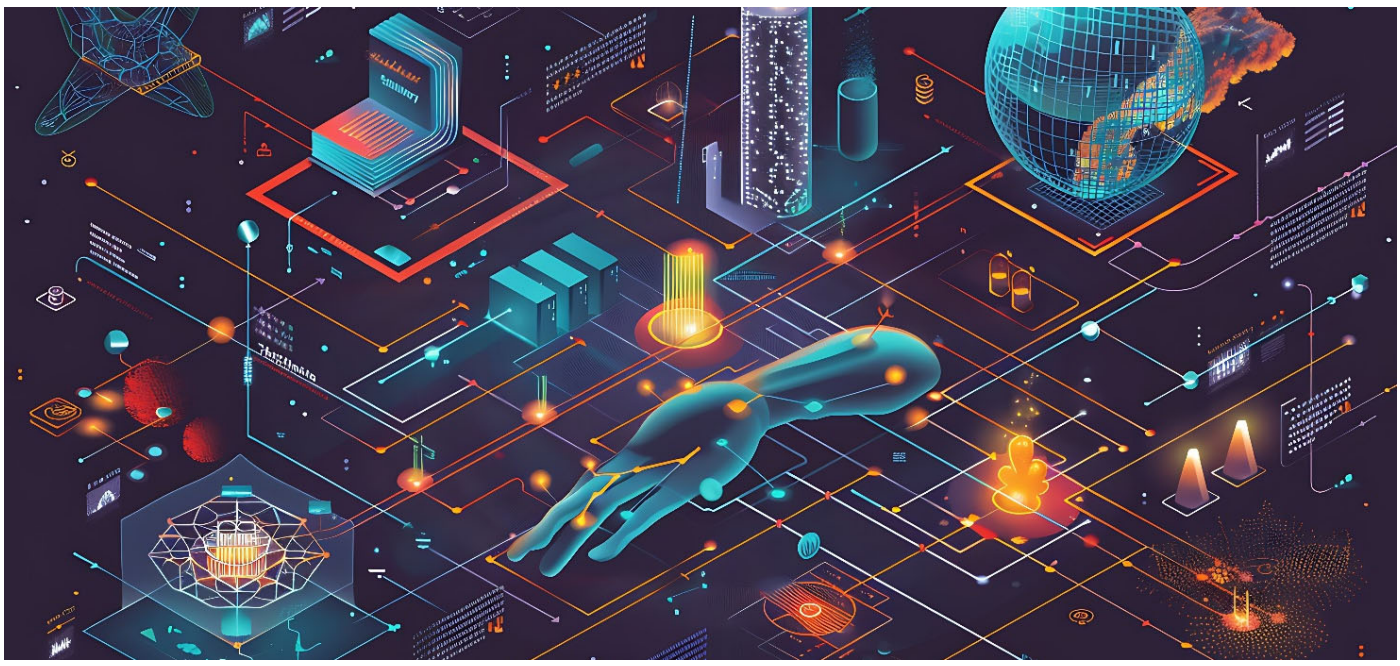
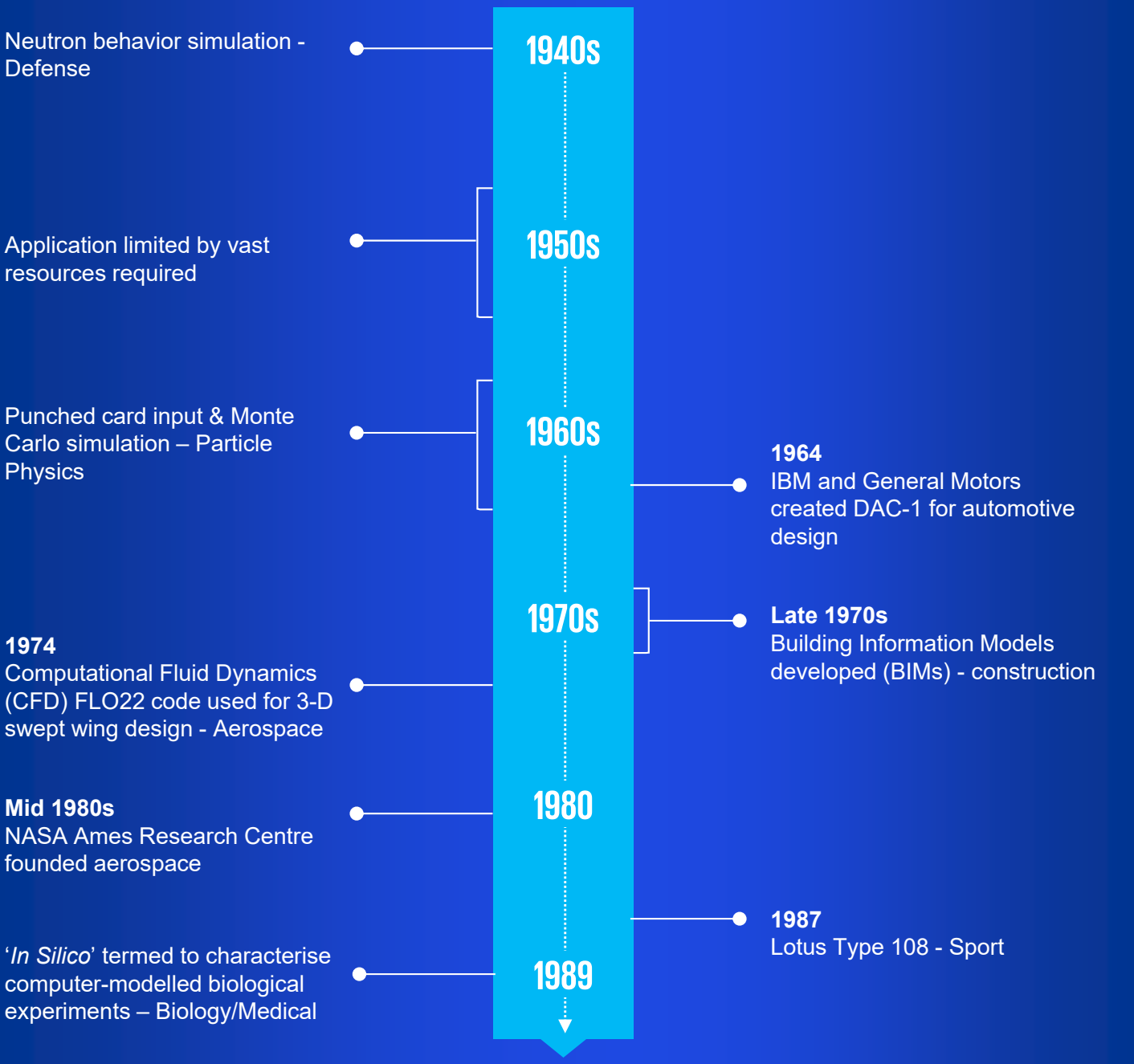


Figure 2: Evolution of Computer Simulation and Modelling



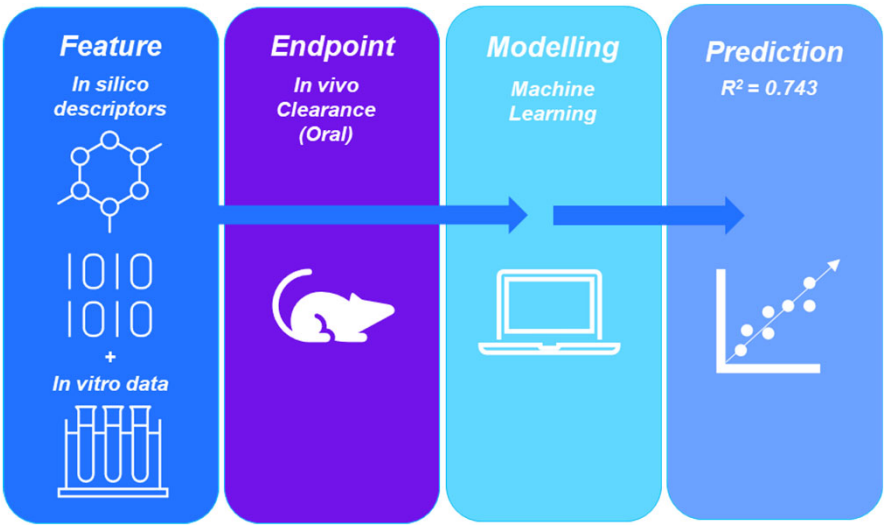
Early stages

In the early 2000s, the rise of high-performance computing enabled the simulation of more complex and large-scale models, including whole-body PBPK models. The use of *in silico* models was largely confined to the research setting. However, there is now a wealth of published research, advancements in technology and better understanding of their potential. *In silico* trials now utilise a range of data sets including digital medical imaging, pre-clinical (e.g., pharmaco-toxicology) and clinical PK/PD, to generate complex computational modelling of the mechanisms underpinning the physics, physiology and anatomy of a patient, which are foundational to understanding how medicines work in the body. **Figure 3** illustrates how the oral PK profile of structurally diverse compounds was modelled using a combination of *in silico* descriptors and *in vitro* PK properties, where a R2 (coefficient of determination) value closer to 1 equals a more accurate prediction[7].

Table 2: *In silico* Initiatives

Scheme	Background
FDA Critical Path Initiative	In 2004, the U.S. FDA launched the Critical Path Initiative as a response to the growing concern about the slowdown in development and approval of new medicinal products. The initiative aimed to modernise the scientific process through which a potential drug, biologic, or medical device is developed from an early phase asset to a commercial product with FDA approval. The initiative included the use of *in silico* models, with a focus on toxicity prediction prior to human clinical trials[8].
European Avicenna Alliance	Established in 2015 to advance *in silico* methods in drug development and lobby for its acceptance in policy and regulations. This alliance was inspired by the Avicenna Project, an EU-funded initiative aimed at creating a roadmap for *in silico* clinical trials. The alliance also aims to foster collaboration between stakeholders; promote education and training; and develop standards and guidelines for regulatory acceptance[9].
FDA Medical Device Innovation Consortium (MDIC),	FDA MDIC is a public-private partnership established in 2013 to advance regulatory science for medical devices. Bringing together various stakeholders, including industry, government, non-profits, and academia to enhance the efficiency and effectiveness of the medical device development process, lowering costs, and reducing timelines, whilst maintaining a patient-centric approach. This includes development of new tools and methods to assess safety, efficacy and quality of devices e.g., *in silico* (CM&S) models: develop best practices, standards, and validation methods[10].

Figure 3: The modelling of oral PK using a combination of *in silico* descriptors and *in vitro* absorption, distribution, metabolism, and excretion properties.

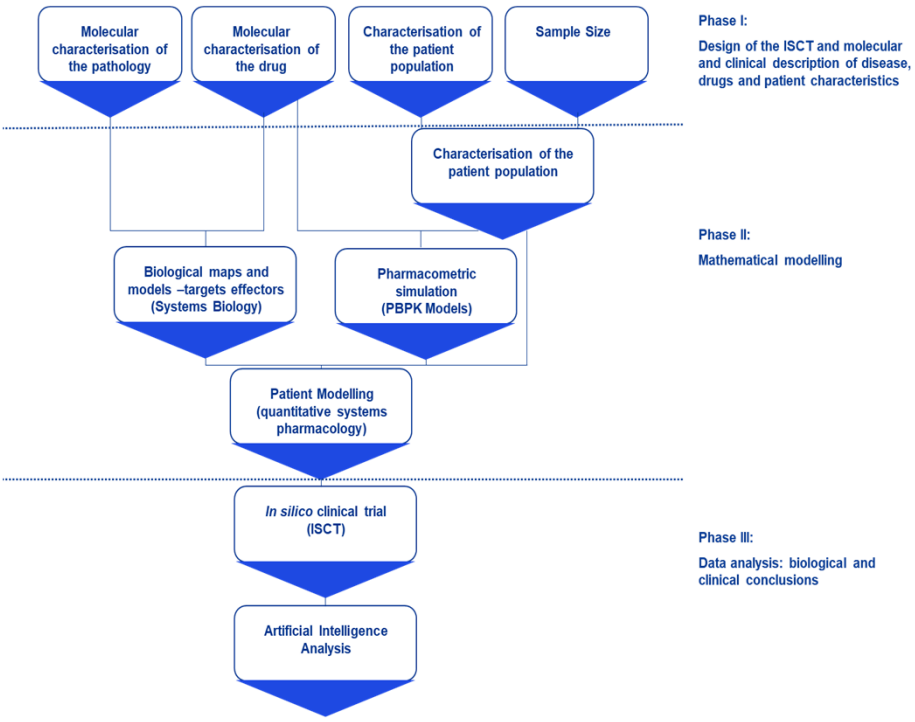


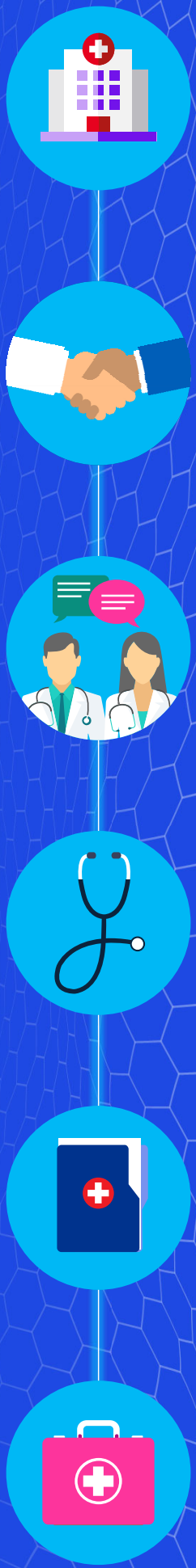
Where are we now?

CM&S techniques have evolved from being descriptive or auxiliary evidence in some cases to constituting a key source of evidence in drug and medical device development programmes and their associated regulatory submission[11]. **Figure 4** provides an example of an *in silico* trial review protocol, showing the data sets used and the modelling approach taken to inform the *in silico* clinical trial (IST).

Figure 4: *In silico* evidence protocol overview[12]

While there has been significant progress, the use of *in silico* data as regulatory evidence is still evolving. There are ongoing discussions about the standards and validation processes for these models, and how to ensure they are used appropriately and effectively[13].





Computational modelling can be used to simulate and better understand medical devices in several ways, as depicted in Figure 5. Computational modelling is a robust and efficient method for manufacturers to simulate a device under a variety of conditions including evaluation of its performance to mimic clinical or use environment. It is important to note that a 'virtual patient' is not necessarily a digitised patient; it is an approach that allows previously collected evidence (such as digital or other historical clinical evidence typically referred to as 'external evidence') to inform the collection of new data from a clinical trial using Bayesian methodology. It can offer an opportunity to address questions that cannot be explored clinically due to financial or ethical considerations, and investigate aspects of device performance in more clinically-relevant cases.

Figure 5: Simulation opportunities for medical devices

02 Current Use of ISE & Case Studies

Utilisation of *in silico* in medical devices regulatory decision making

Scientific evidence for the medical device regulatory approval process is generally sourced from four different types of model as depicted in the image below. Although each model has its strengths and weaknesses, one of the most striking features of CM&S methodology for data gathering is the promise of predictive and investigative capabilities.

CM&S models have the ability to demonstrate device performance under scenarios broader than those cleared or approved in the instructions for use (IFU) of the device. This is typically not possible for a clinical investigation because the inclusion and exclusion criteria pre-defined. The attribute 'represent disease states' indicates that the model has the ability to simulate the behaviour of a disease; this is typically achieved best with clinical evaluation[14].

Figure 6: Regulatory evidence are typically gathered from four models[15]

Clinical pathology, gross pathology and histopathology assessments

Allows for examination of the biological response to the implant at cellular level

Evaluate device performance in a controlled setting.

Allows for assessment of certain features of an entire device under simulation conditions

Controlled studies with specific inclusion/exclusion criteria for subjects, with specific treatment protocols, and has clear objectives, in general, to assess safety and effectiveness

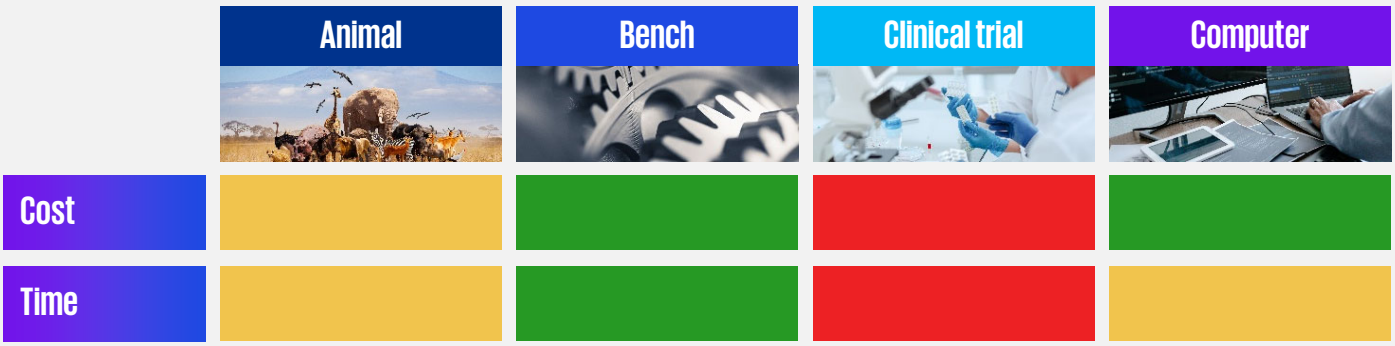
Different aspects of computational modeling of a medical device where you may simulate device interaction with anatomy, chemical toxicology, manufacturing process etc. across numerous scenarios

When the four models are evaluated sided by side, although not including device safety and performance, the cost and time attributes are important factors to consider when selecting a model to produce evidence for the evaluation of a medical device. See Figure 7. While the upfront investment of computer models may be high, especially to perform adequate verification and validation (V&V), the cost remains much less compared to traditional clinical evaluation formats. By augmenting clinical trials and investigations, the *in silico* data gathering approach may reduce clinical sample size and lower associated costs. By detecting potential incidents in advance of clinical use, it may also reduce the costs of remediating defective products. By providing compelling scientific data, *In Silico* trials may improve product performance.

These financial benefits are offset by the costs to develop and execute *In Silico* clinical studies (which include specialised personnel, software licenses, data storage, and acquisition of clinical data for validation).

The most significant benefit to a manufacturer is the potential to launch innovative products more quickly, by reducing the time of clinical research without compromising on the credibility of clinical evidence. As an example, early migration evaluated via Roentgen Stereo grammetric Analysis (RSA) two years after surgery is able to identify implants at risk of revision before actual failure, thus shortening the window of clinical observation from 10 years to 2 years. As depicted in the Figure 8 below, CM&S has minimal impact on the cost and time to bring product to the market.

Figure 7: Cost and time impact on four models

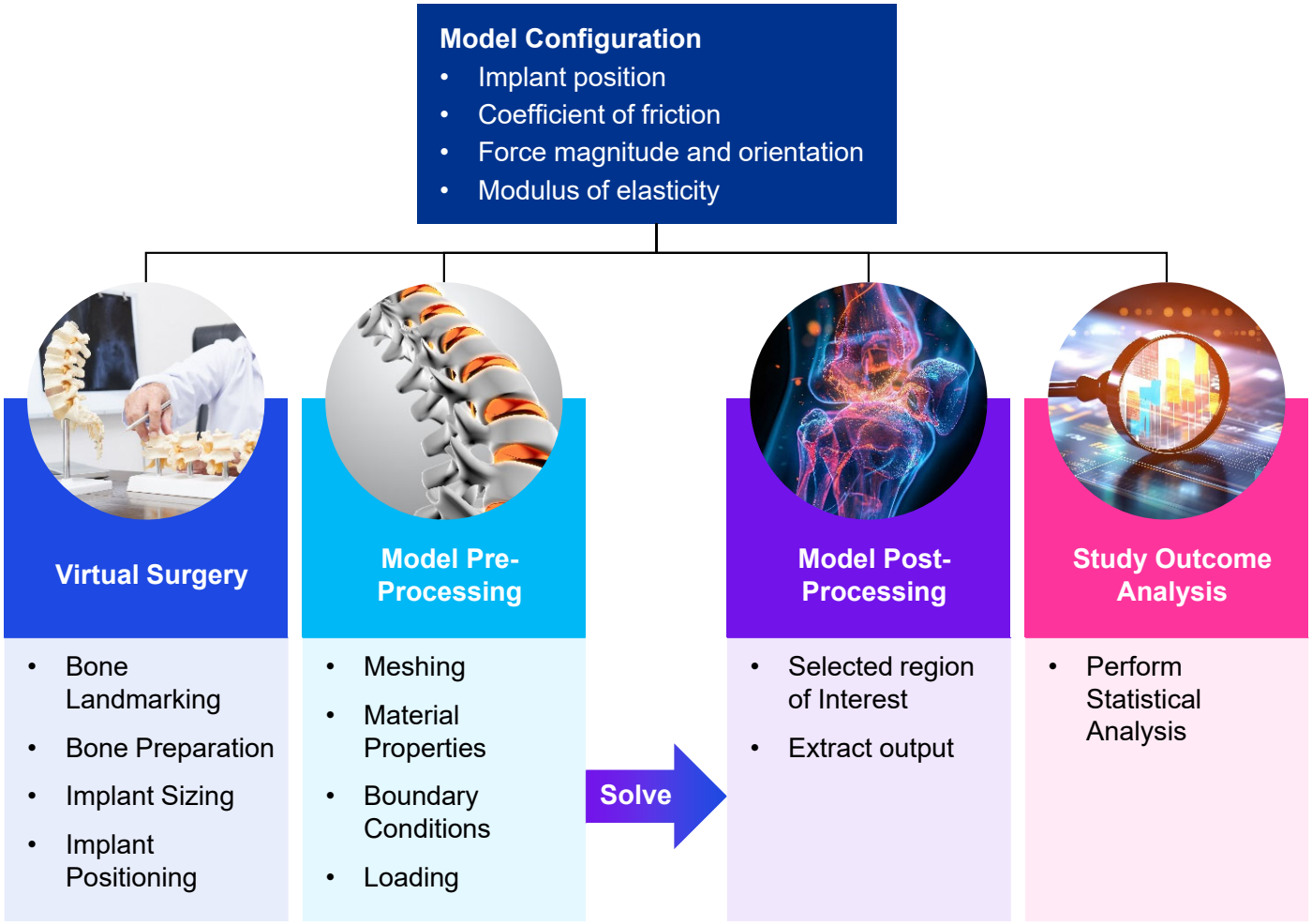


Examples of current utilisation of in silico methods

Medical devices

Medical device manufacturers are increasingly integrating *in silico* methods into their R&D programmes to accelerate the design process and shorten time-to-market. Utilisation of *in silico* methods help manufacturers to conduct early feasibility studies on devices without manufacturing and testing hardware prototypes[16]. In addition, *in silico* models can be tailored towards certain patient populations or groups to test the safety and efficacy of proposed device design with different patient cohorts and larger patient populations.

Figure 8: How model configuration takes place in orthopaedic simulation development (Figure adapted from[17])



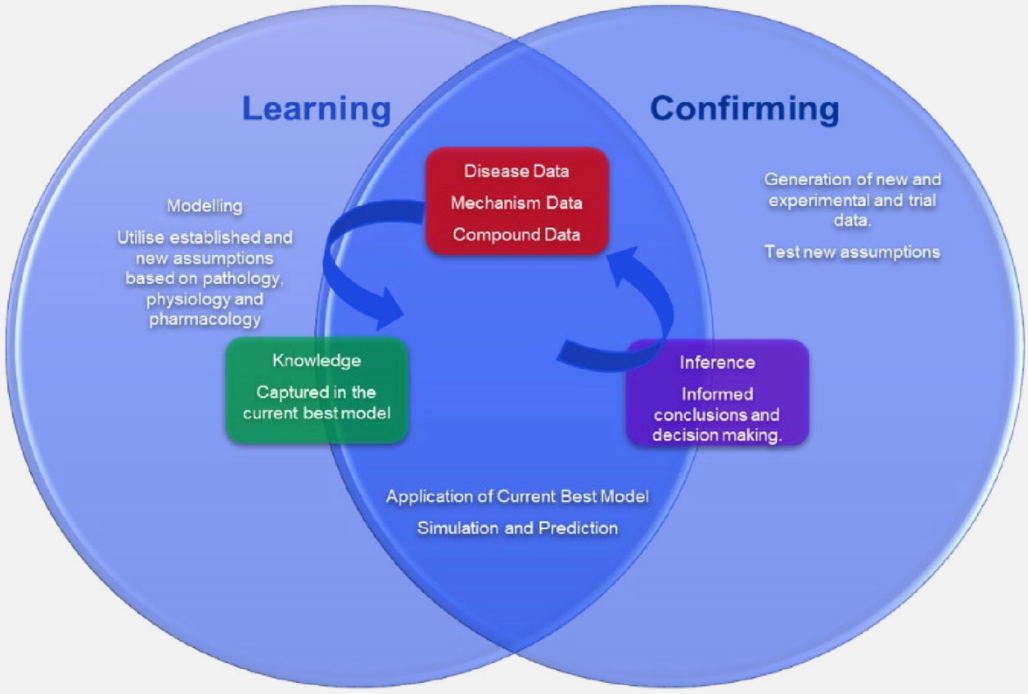
Beyond just complementing traditional clinical research, *in silico* clinical trials has the potential to positively impact design and safety of products due to increased pre-clinical evidence generation. *In silico* clinical trials offer an additional level of evidence data points that can impact patient care and could help to ensure patients receive the best possible treatment. Additionally, simulations can cut down the time taken for pre-clinical tests such as a 'physical fatigue test' which can typically take weeks or months, to a few days, depending on the number of test samples, test cycles and frequency, and number of available load frames. This will have a direct impact on the costs and market entry speed for a product. See **Figure 8**, which demonstrates model configuration in an orthopaedic *in silico* simulation, with the aim of improving patient response to a potential high risk Class III implant[17].

The adoption of *in silico* methods by manufacturers during medical device development is expected to increase as one of the main perceived barriers to acceptance, clarity of *in silico* data requirements by regulators, is changing as demonstrated by the increased FDA guidance in this area, for example in the FDA Pharmaceuticals sector, ISE is now included in many regulatory submissions, often as a supplementary and descriptive data set[18]. In many cases however, *in silico* models form a key source of evidence in drug development programmes and associated regulatory submissions. Examples include the extension of indications to paediatric patients based on *in silico* models.

Pharmaceuticals

Figure 9 illustrates the 'learn and confirm cycle' in model informed drug development (MIDD), an approach that involves developing and applying exposure-based biological and statistical models derived from preclinical and clinical data sources to inform drug development or regulatory decision making[19]. As success has been demonstrated by MIDD, its use has begun to be supported by global regulators. For example, the U.S. FDA has specific provisions under the Prescription Drug user Fee Act, including the opportunity to meet with the FDA as part of the MIDD Paired Meeting Pilot Program and receive input on their proposed application[20]. In the EU and Japan, there have also been several applications utilising MIDD accepted.[21]

Figure 9: The learn and confirm cycle.



In silico clinical trials

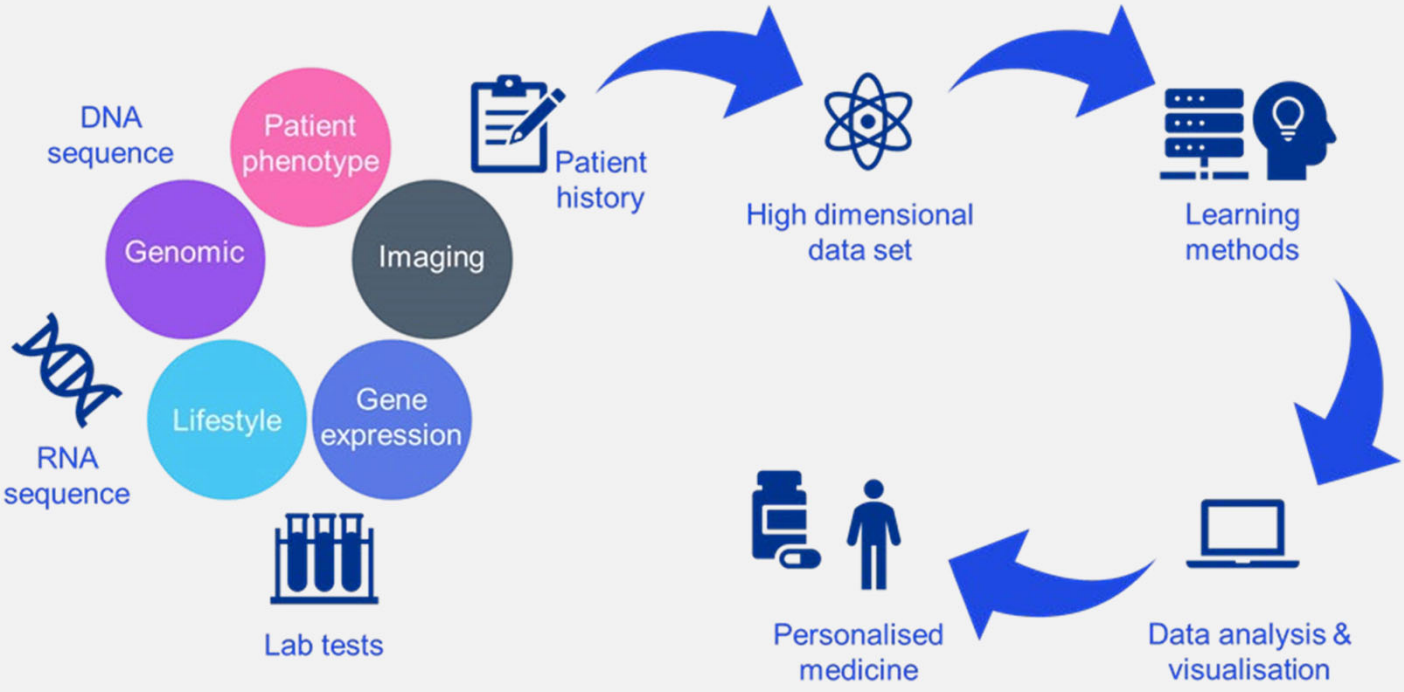
Under the same umbrella of MIDD, regulators and drug developers are beginning to embrace *in silico* clinical trials as a potential tool to refine, reduce, and support clinical trials. *in silico* clinical trials are gaining momentum due to their efficiency in evaluating the safety and efficacy of medicinal products through virtual patient cohorts.

Improved adverse event prediction with ISTs

In an example of a recent *in silico* clinical trial, using the OneFlorida medical records database Chen et al set out to recreate the safety profile of the drug Donepezil at 10mg, using a simulated clinical trial[22]. By using the de-identified patient records of patients prescribed Donepezil, where simulations were run on two distinct demographic groups, they concluded that the demographic make-up of the patient population can influence the safety profile of the drug. This approach is complimentary to the usage of Real-World Evidence (RWE) such as e.g., electronic health records, patient registries, insurance claims and billing data, provide insights from diverse patient populations and clinical settings that could not be captured in traditional randomised controlled trials (RCTs). This longitudinal data can be used to study long term outcomes and rare events that are difficult to capture in RCT's due to their limited duration and sample size.

The FDA and EMA are developing frameworks and initiatives to incorporate RWE into regulatory decision-making processes. Companies can now look to leverage *in silico* clinical trials with RWE to provide a comprehensive understanding of medical interventions. For example, RWE provides real-world insights that reflect clinical practice, which can be used to validate and refine computational models used in *in silico* clinical trials. Whilst *in silico* clinical trials can predict outcomes and identify potential risks, which can then be monitored and confirmed using RWE from real-world settings. **Figure 10** shows how *in silico* clinical trials draw on numerous data sets to improve outcomes related to patient safety and treatment efficacy.

Figure 10: How varied datasets are informing *in silico* predictive tools leading to better patient outcomes.



Further examples of ISTs

System biology-based models to evaluate the pharmacokinetic properties of new drugs[23]

- In a study utilising a systems-based model, researchers performed a mechanistic head-to-head IST
- between two treatments for attention deficit/hyperactivity disorder.
- The sensitivity analysis of systems biology mechanism of action models provided a list of common proteins that might affect both drugs' efficacy.

In silico Imaging Clinical Trials for Regulatory Evaluation (VICTRE)[24]

- VICTRE (Virtual Imaging Clinical Trial for Regulatory Evaluation) was an *in silico* clinical imaging trial evaluating digital breast tomosynthesis as a replacement for digital mammography.
- The results of the simulated trial were compared to those of a previously conducted human clinical trial that double-exposed more than 400 women to both modalities and had images interpreted by radiologists. The results indicated favourable results for the *in silico* trials compared to trials performed by humans

In silico clinical trial platform to evaluate drug-eluting bioresorbable vascular scaffolds (BVS)[25]

- This project has developed an IST platform to assist researchers, cardiologists, and biomedical industry experts in the design, development, and evaluation of drug-eluting BVS.
- The technology developed integrates the latest *in silico* computational models and enables the prediction of the optimal performance of drug eluting coronary stents in the treatment of coronary artery disease interventions

Stakeholder insights

To analyse current stakeholder thoughts on ISE and its utilisation in the life science sector we conducted surveys and structured interviews and the results are described below. Representatives from key stakeholder groups were interviewed and the conclusions from these discussions regarding their use of ISE are summarised in **Table 1**.

Summary

ISE is used variably between medical device and pharmaceutical development and registration. In the medical device sector, CM&S has been utilised for longer and is more embedded in medical device development than in the pharmaceutical sector. Representatives from both sectors confirmed that the use and interest in ISE is increasing. The regulator's perspective highlighted that ISE is routinely accepted, with CM&S used regularly to inform clinical trial protocols.

Summary of research from stakeholders on how ISE is viewed by different sectors

Medical device industry

- CM&S has been present in device development for over fifteen years.
- There has been an increased prevalence of its use in R&D to predict behaviours before being used in the finalisation of shapes and features of medical technologies.
- ISE regulatory acceptance and recognition has come with the refinement of methodologies and increased proficiency from industry and regulators, as well as the development of guidance and technical standards.
- ISE is often used in worst case scenario determination to feed into physical testing e.g. within the orthopaedic community, it has been used for a long time with very few issues. ISE has been utilised to greater and lesser degrees. When ISE, adequately validated, then regulatory agencies around the world are accepting it.

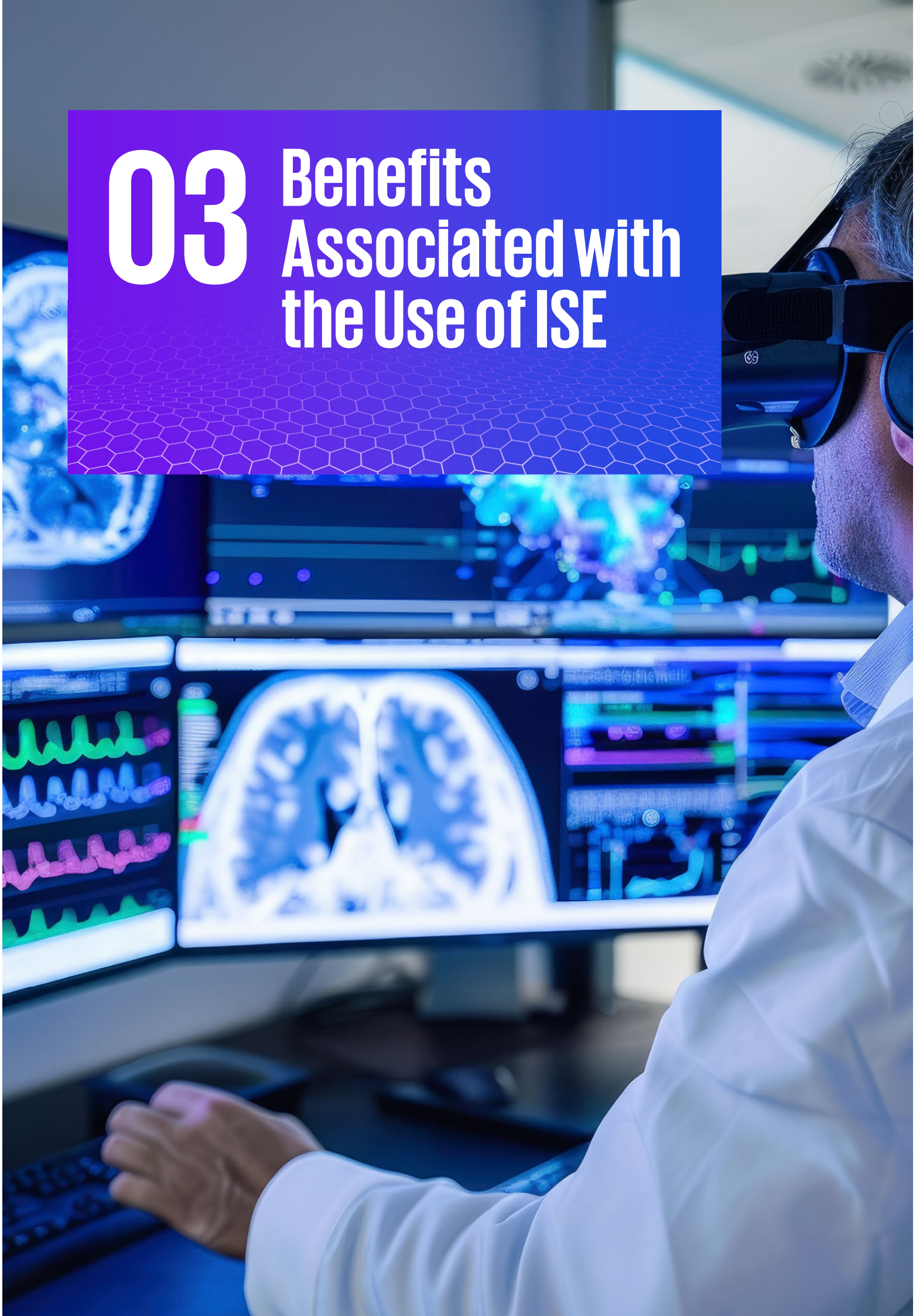
Pharmaceutical industry

- The focus of ISE generation in drug discovery is within predictive models.
- Machine learning and physics-based models are used to understand protein function and interactions to understand potential toxicity and target binding.
- In the pharmaceutical sector the use of ISE is limited, primarily being used to speed up pharmaceutical regulatory submissions.

Regulators

- Regulators described that they have seen some protocols which include ISE, this is welcome and accepted
- Even before applications reach the regulator, there is a lot of CM&S that is used to inform clinical trial protocols (e.g., PK, paediatric dosing).

KPMG



03 Benefits Associated with the Use of ISE

One of the key benefits of ISE is the potential for reducing time associated with product development. All interviewees and most survey participants strongly agreed that CM&S methodology has the potential to reduce timelines for R&D and could help speed up the regulatory approval process. Whilst *in silico* methodology will not replace human clinical trials, use of ISE to support early screening and identification of product risks and to inform decision-making processes could optimise design and development and develop products more efficiently. This could significantly accelerate studies leading to validation with in-human trials. By complementing clinical evidence with ISE, the amount of clinical research and number of trials required for market entry could be reduced. In addition, by defining the target product profile and target populations prior to conducting a pivotal study a trial size that is representative and precise could be established, leading to considerable benefit including reduction in the cost and resources required to conduct traditional clinical trials.

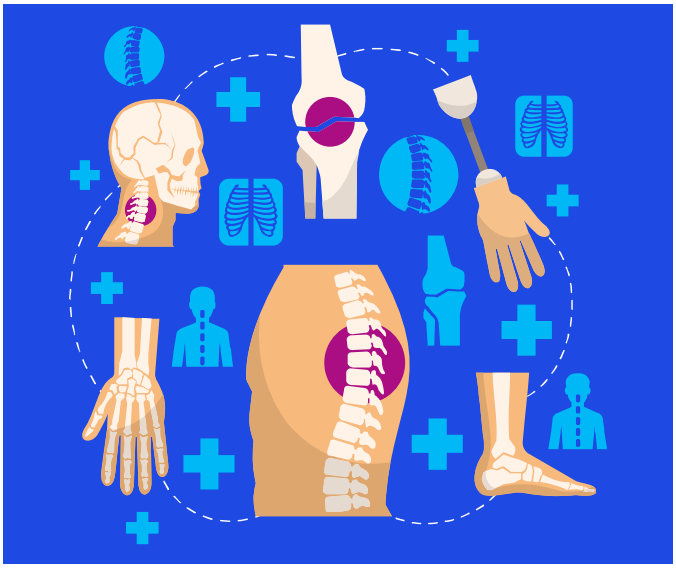
In silico models are now refined to the point where they can facilitate the exploration of deploying a medical device in populations that cannot easily be investigated clinically, e.g., patients with rare diseases, with high vulnerability e.g. in utero, neo-natal, and paediatric patients, without harm. In addition, minority groups who may not necessarily be captured by traditional trials could be better represented with *in silico* methods as ISE can power clinical trials in cases where recruitment is difficult. Most survey participants agree that in areas of unmet medical need the use of *in silico* trials would be beneficial.

The short-term benefit of clearly defined global regulatory acceptance criteria for ISE would be increased investment in *in silico* technologies promoting the refinement of devices, surgical techniques, and manufacturing conditions (see **Table 3**). This could support more agile development of products laying the foundation for longer term, patient-centric benefits such as the availability of new, more advanced, and more innovative treatments.

As ISE advances, so will the understanding of how to potentially correlate biomarkers or radiological indications with pain or other potential patient-related outcomes. This is a benefit of ISE which is not possible with clinical studies. ISE could also be beneficial in the context of accelerating development of high-risk orthopaedic medical devices where safety and performance concerns may exist.

Table 3: Short- and long-term benefits of clearly defined global regulatory acceptance criteria of ISE:

Short-term benefits	Long-term benefits
Promote investment in ISE by manufacturers	Promote refinement of devices and techniques
Reduce time to market for products	Enhanced availability of new, more advanced treatments
De-risk the R&D value chain	Greater representation of minority & vulnerable groups
Reduce R&D costs by reducing number of required trials	Advancement in areas of currently unmet medical need



Animal Testing

The 3Rs – Reduce, Refine and Replace

The 3R's principle refers to the ethical framework for conducting scientific research involving animals, aiming to minimise animal use and suffering.

These principles guide researchers in designing and conducting experiments in a more humane and ethical manner. *In silico* trial methodologies offer an opportunity to reduce, refine, and replace experimental studies, employing computer simulations, bioinformatics, and artificial intelligence to predict biological responses and drug interactions.

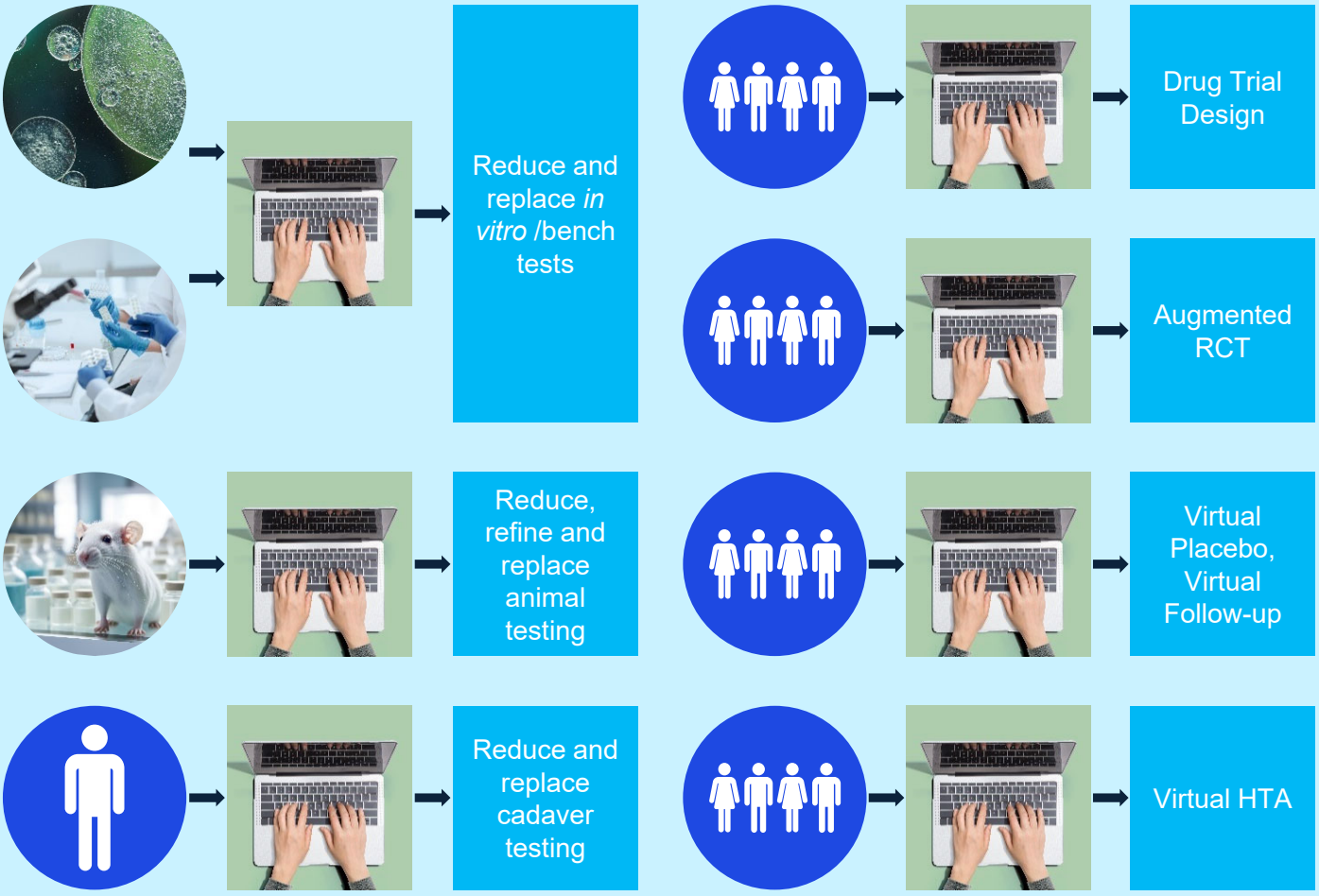
Any method that reduces the number of animals required in a study, or shortens the duration of the study, will drastically reduce the cost and is ethically superior, as it reduces animal harm and loss of life.

For example:

1) computational techniques like molecular docking and virtual screening can predict the interactions between drug candidates and biological targets without using animals. This approach can identify promising compounds early in the drug discovery process

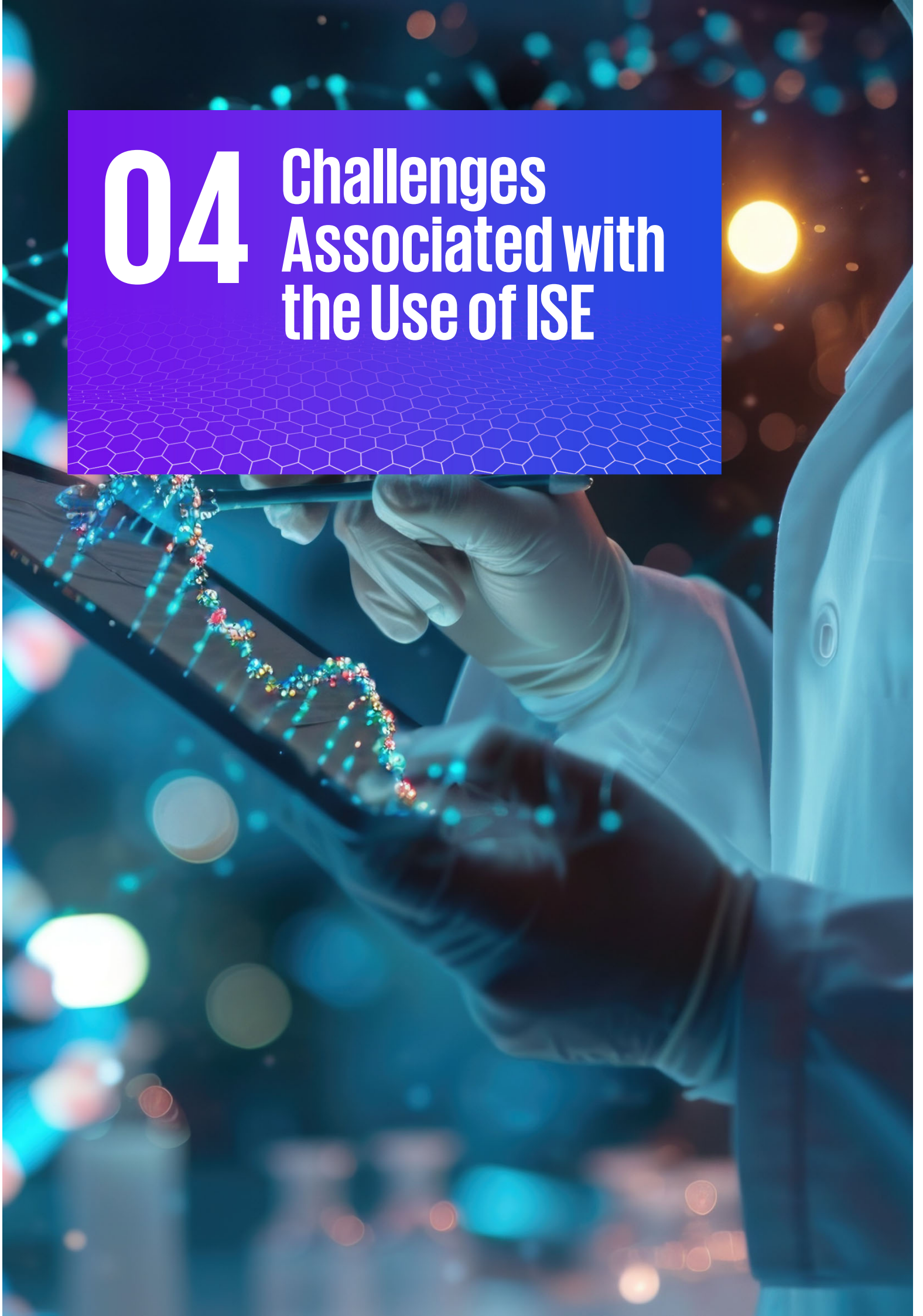
2) *In silico* models can predict toxicity of compounds using quantitative structure-activity relationships (QSAR) models and other algorithms. Under the European REACH regulation, use of QSAR models is encouraged to predict toxicity of chemicals. By using QSAR models, thousands of animal tests can be avoided as the guidance allows for use of QSAR predictions in pace of certain *in vivo* studies, provided models are validated (reproducible) and applicable - If a traditional toxicity test requires 100 animals, the equivalent QSAR approach might only need 10 for initial model training and validation, with the remaining predictions made computationally.

Figure 11: The proposed general framing of *In Silico* Trial Solutions in the CE marking of new medical devices[26]



The scientific and ethical advantages of a paradigm shift to human-based methods are well documented in several roadmaps devised by global regulatory agencies and stakeholder organisations over recent years. In the chemical safety testing, for instance, limitations of animal models are widely known, and they are no longer considered by many to be the gold standard. In drug discovery, significant progress has been made in the research and development of New Approach Methodologies (NAMs) to improve safety and efficacy assessment. Regulatory recognition of these methods is still lacking, but piecemeal progress is being made in some areas. For example, in 2017 the use of *in silico* screening tools was officially recognised in the European Medicines Agency (EMA) ICH M7 guideline for 'Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk' which permits a dual combination of QSARs if a prediction is negative and potentially avoid further *in vitro* and *in vivo* tests.

In silico modelling also has great potential in new drug discovery and repurposing of existing drugs and improved mitigation of idiosyncratic adverse drug reactions where major cost, time and resource savings can be made. A significant example of Horizon 2020 (H2020) program funded projects is EU-ToxRisk, which explored how the latest advances in human relevant, nonanimal approaches could be best used to support regulatory decision making in two key areas addressing complex endpoints; *i) repeat dose systemic toxicity,* and *ii) developmental and reproductive toxicity.*



04 Challenges Associated with the Use of ISE

Challenges to widespread adoption of ISE are described in this section, and reasons for limited global clarity on the regulatory acceptance criteria for ISE are outlined in the next section (Section 5).

Lack of clarity in global regulatory acceptance criteria is perceived as one of the biggest barriers to the use of ISE. The regulatory acceptance of ISE and non-traditional applications of CM&S is limited in some jurisdictions, and requirements vary globally. The U.S. system, for example, allows for authorisation of medical devices based on equivalence and predication, such as *de novo* or 510(k) routes. 80% of medical devices in U.S. are Class I or Class II and therefore either go through the 510(k)-clearance process (most Class II devices), or have minimal clearance requirements (most Class I devices- self certification, 510k exempt). As a result, manufacturers are not usually required to provide safety, performance and equivalence evidence derived from direct clinical investigation and instead leverage evidence from a predicate device (from another manufacturer) thereby saving time and research costs. Hence, it is unlikely that manufacturers of most Class I and a proportion of Class II devices (510(k) exempt) would use ISE.

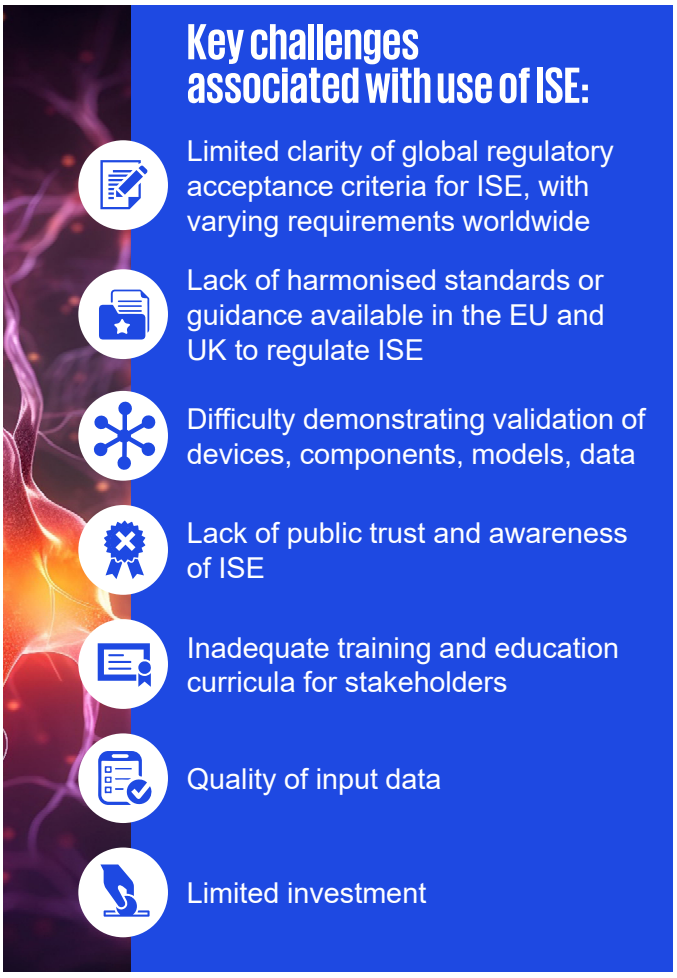
While the UK currently remains under a Medical Device Directive like framework (UK MDR 2002), within the EU, the recent transition of device frameworks from Directives to Regulations has led to the requirement for more safety, performance and clinical data, where 'sufficient clinical evidence' must be provided by a manufacturer. Both the UK and EU marking is based primarily on safety and performance rather than on equivalence and predication routes. This difference is seen as a significant regional variation in the generation of and potential regulatory acceptance of ISE.

With Class III products in the U.S. seeking FDA approval (PMA) or clearance in the EU, ISE can currently be used to augment additional evidence however part of the challenge is to focus on and select appropriate use cases and products. The risk surrounding acceptance of ISE limits funding in some situations. Additionally, lack of relevant standards or guidelines required to gauge the acceptance of data generated from *in silico* testing or trials has challenged manufacturers adoption of ISE as part of their data generation process for regulatory submission.

A lack of public trust and understanding of, *in silico* data is a barrier to the use of ISE. There is a sense of nervousness around the concept of trusting a product that has been developed using CM&S only, and which has never been subjected to *in vivo research*. Awareness and understanding of ISE is also perceived to be relatively low amongst the public and across the sector and regulatory authorities. Most survey participants agreed that the lack of awareness and expertise around CM&S within regulators was an important area to address to increase acceptance of *in silico* data as a source of evidence for product approval.

Inadequate training, education, and issues with input data (quality, availability, and cost of accessing technology) were highlighted as additional challenges associated with the use of ISE.

It is important to note that while barriers exist, the specific challenges experienced will vary on a case by-case basis. Issues are context-dependent and will differ according to key factors such as; the aim of a model; the type of model used; the assumptions made; the quality of the input data; and the type of validation performed.



Validation of ISE

In addition to the challenges described above which limit the use of ISE (Section 4), a further barrier to the use of ISE is validation of data, models and device components. Validation is perceived by stakeholders to be a core issue that impacts the development of global regulatory acceptance criteria for ISE. This section outlines the key considerations, difficulties and opportunities associated with demonstrating validation of models for ISE.

In our research interviewees agreed that having a robust methodology, demonstrating validation of a model and verification that the model answers the research question are paramount to any *in silico* method being developed, particularly when being used as part of a regulatory submission. Many regulators welcome applications that have generated data using CM&S and *in silico* methodologies if applicants can demonstrate their scientific validity.

From a regulatory perspective, ISE must be justified, monitored, and very carefully validated and verified. Validation frameworks already exist and can involve comparison with a 'gold standard' model. However, the challenge is understanding what the appropriate gold standard comparison should be.

Survey respondents suggested that computational model standards, such as ASME V&V40 C models and MID3, could be effective in supporting regulatory approvals for *in silico* trials.

In addition to validating a model, companies should also demonstrate verification of tools, to indicate that the code or programme is operating as it was intended to. There are different validation and verification techniques for software linked to manufacture of products, and there is a need to bridge the gap between empirical (clinical performance) data and software validation.

Whilst *in silico* models are advancing, they don't necessarily capture the three-dimensional, multi-faceted complexity of a real body with tissues, an immune system, and human anatomical complexity. Models are beginning to be used to try and answer complicated questions without the use of human studies. However, it is currently very challenging to provide sufficient validation of models without human trials. In addition, whilst many medical device manufacturers already know how to conduct CM&S and validate models, there is a need for further investment to support effective implementation.

Validation is a useful tool to demonstrate the importance of evidence generated via *in silico* methods and support how it may be applied to inform regulatory decisions. However, the importance of validation extends further. By producing an audit trail which allows for traceability, auditability and interpretability of an *in silico* model, companies can help to build stakeholder confidence as well as public and clinical trust in ISE.

Below is an example of how IST models could be effectively validated.

Sample subject:

In silico modelling of cancer nanomedicine, across scales and transport barriers [xxviii]

Model:

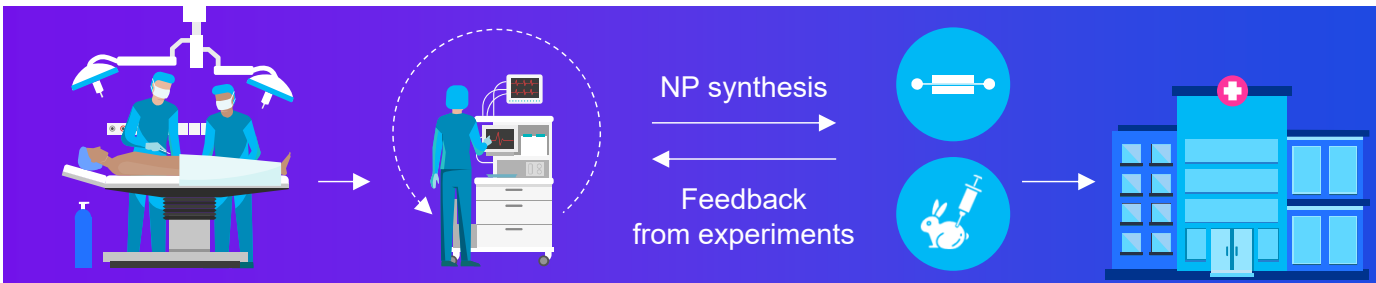
CHASTE (cancer, heart, and soft-tissue environment) was designed with the specific goal of being a multi-purpose library for computational simulations of biological problems.

Uptake:

Molecular dynamics (MD) simulations allow for *in silico* modelling of cellular uptake and intracellular trafficking of nanoparticles.

Validation model:

In silico models validated and optimised by in vivo and/or in vitro models to achieve better explanatory and predictive power.



Clinical challenge (e.g. optimal NP distribution in a specific tumour)

Multi-scale in silico models powered by parallel computing

In vitro & in Vivo validation

Translational medicine

Integrated pipeline for optimised anti-cancer nanoparticle design. A clinical challenge is identified, *in silico* models are used to
design NPs for overcoming this challenge, and iterative synthesis and testing of NPs leads to the development of effective translation medicine.

Regulation and Guidance

The use of ISE to supplement clinical evidence is becoming more acceptable. This follows stakeholder collaboration across the life science sector to advance understanding of ISE and its potential role in the regulatory approval of new drugs and devices.

The U.S. FDA has made progress in generating guidance relating to the assessment of *in silico* methods.

In November 2023, the FDA released the final guidance for *'Assessing the Credibility of Computational Modelling and Simulation in Medical Devices Submissions'*. This is in addition to the VV-40 Technical Standard, published by the American Society of Mechanical Engineering (ASME) in 2018, which provides a risk-based framework for establishing the credibility requirements of a computational model used in medical device development[28].

The FDA has also produced guidance for physiologically based pharmacokinetics, an area that draws on CM&S, and tends to be focused on the use *in silico* models to predict the fate of pharmaceuticals in the body[29].

In Europe, the EMA has its own guidance for PBPK, the *'Guideline on the reporting of PBPK modelling and simulation'* which provides a step-by-step overview of the assessment required to demonstrate credibility of predictive models[30]. Some have commented that the EMA PBPK guideline, whilst providing recommendations for PK model characterisation, utilises quality assessment methods for these mechanism-based models that have several points in common with the ASME VV-40 Standard[31].

In the UK, whilst formal guidelines related to ISE are yet to be produced, it is indicated from published literature that ISE plays a role in forming the evidence base for medicine and medical device approvals[31].

Based on the feedback we have received from stakeholders there was a clear indication that whilst frameworks for ISE are being developed, the key point when submitting ISE as part of a conformity assessment application is there must be a clear description of how a manufacturer developed their *in silico* model.

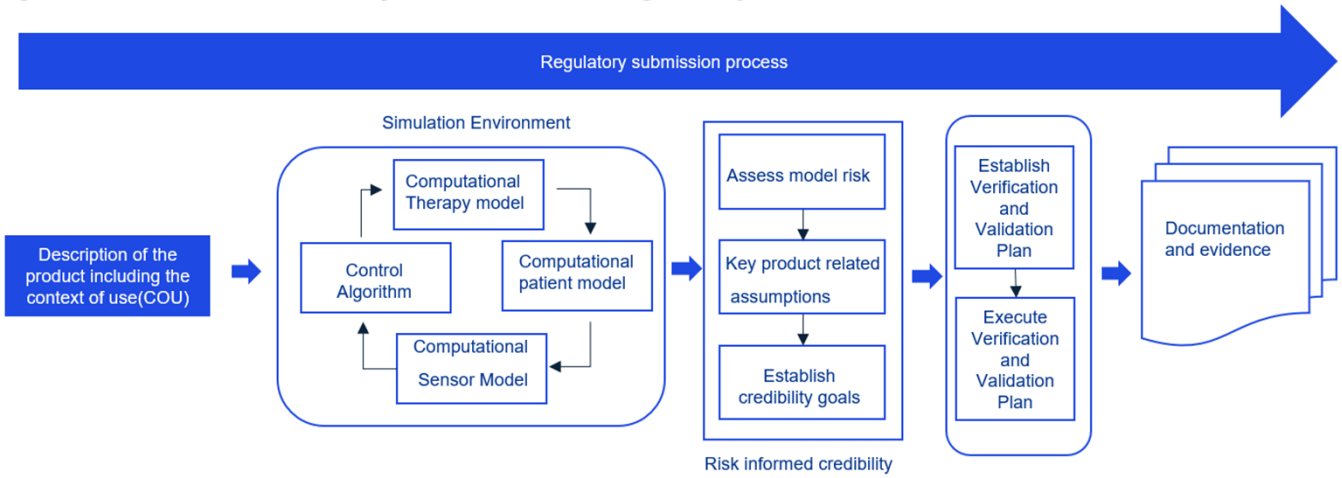
If the model is statistical, there should be a description of the data source and the key assumptions.

If mechanistic, there should be description of the evidence used. There needs to be acknowledgement of what the risks are if these assumptions aren't met.

The extent and success of validation needs to be explained, for example by comparing with a gold standard or with real patient data counterparts or comparative performance versus model training on real data. An indication of how the code and or algorithm was verified should also be included.

See the **Figure 12** below.

Figure 12: *In silico* evidence process flow for regulatory submission



Credit: **Credibility Evidence for Computational Patient Models Used in the Development of Physiological closed-Loop Controlled Devices for Critical Care Medicine- Bahram Parvinian"**

Currently, the life science sector is seeing growth in the development of IST models and methods, partly encouraged by the development of regulatory guidance and acceptance criteria, as well as the development of industry technical standards and best practice[32].

05 Economic Considerations

Cost benefits of ISE

The cost of bringing a new pharmaceutical to market has been estimated at roughly $2.6 billion dollars (~£2 Billion)[33].The average pivotal phase III clinical trial has been estimated as having a median cost of $48 million (£38 million), with an interquartile range of $20 million to $102 million (£15 million - £80 million)[34]. ISTs and the utilisation of ISE to predict a new molecule or device's safety and efficacy profile, prior to initiating clinical trials can reduce the chance of trial futility or ultimately reduce costs associated with running trials and product development (see **Table 3**).

Another positive economic impact of ISE can be demonstrated with the use of Artificial Intelligence in the repurposing of existing drugs. A systematic review found that de novo drug discovery and development can be a 10 to 17-year process, compared to repurposed drugs which take between 3 and12 years at about 50% of the cost[35]. Repurposing can provide significant savings, given the potential to save years spent on early-stage research, with a reduction in the number of animals required. However, in the later stage of clinical research, the repurposed compounds can still have the same failure rate as any other, if not higher after failing in a primary indication, which is a factor to consider[36].

Cost of setting up *in silico* trials

A paper from 2021 examined the principal advantages of using an *in silico* imaging clinical trial compared to a traditional clinical trial programme which was used for regulatory evaluation, this was known as the VICTRE study[37]. A key finding was the substantial cost savings, which varied depending on the device being modelled and the imaging system characteristics. The authors indicated that the *in silico* trial required a third of the resources required to design and complete a comparative trial, the *in silico* trial took under 2 years to complete compared to 4 years for the comparator.

Return on Investment

Considerations around return on investment (ROI) depend on the area that *in silico* tools are being used. For example, as outlined the use of CM&S in drug discovery can reduce costs, increase the probability of technical success, and decrease the time to market. Outside of repurposing an existing drug, a range of opportunities have already been identified starting with AI's contribution to discovery in areas where return on investment might not support profitability (rare diseases, targeted therapies)[38].

In addition *in silico* process development is an important area for consideration. This is, pharmaceutical manufacturing process development utilising mathematical models with a minimum, confirmatory set of experiments. An example of this is show in **Figure 13**. A recently simulated *in silico* process development, based on End-2-End digital twins, found total product cycle-times comparable, but net savings of 40 to 140 million dollars. However, a key focus is with reduction in development timelines and associated time to market, examples from industry indicate, reduction process development timelines have ranged from 50 to nearly 75%[39].

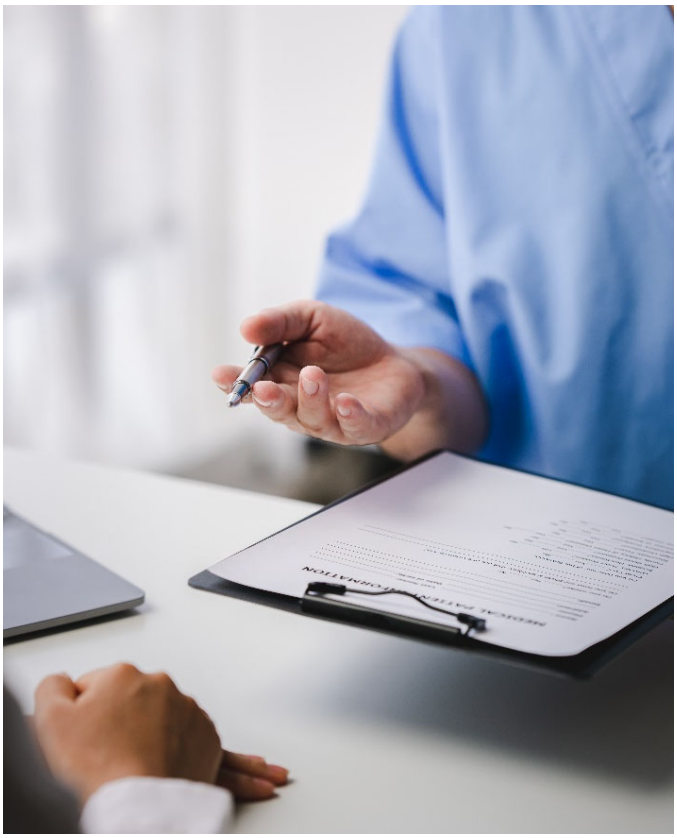
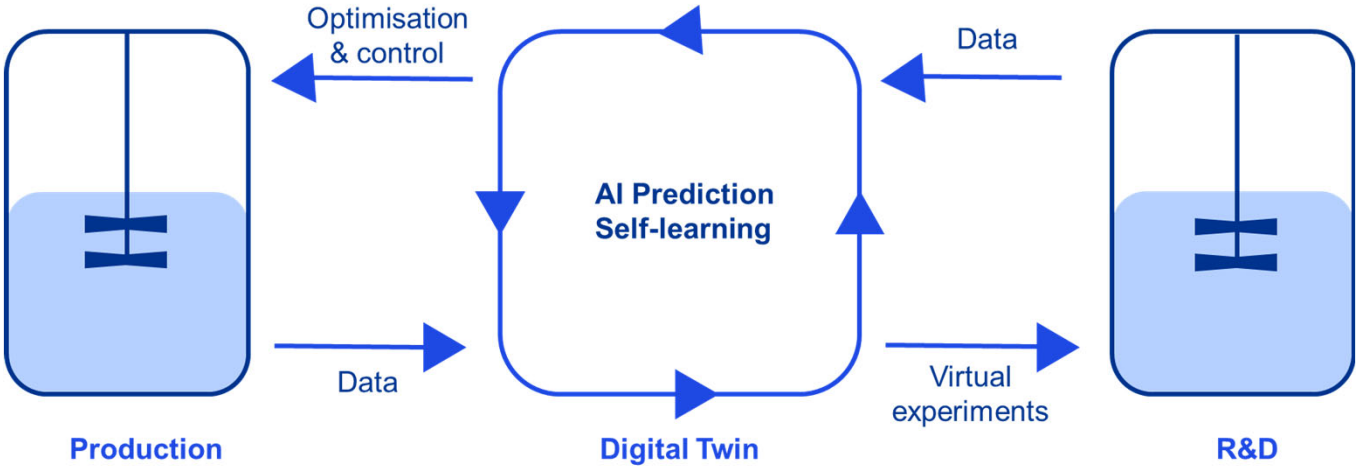


Figure 13: The use of an *in silico* digital twin in pharmaceutical process development. A digital twin is a virtual digital equivalent of a process, product, or service. It consists of the physical part, the virtual part and the connections between them.



If we look at ROI for medical device companies, the same concepts also apply where the use of *in silico* methodologies such as the implementation of digital twins can lead to quicker time to market and reduced development costs. An example of this is the development of an implantable device from **Medtronic**, which saved two years and €10 million by utilising digital twins instead of traditional clinical trials to answer question from the FDA[40].

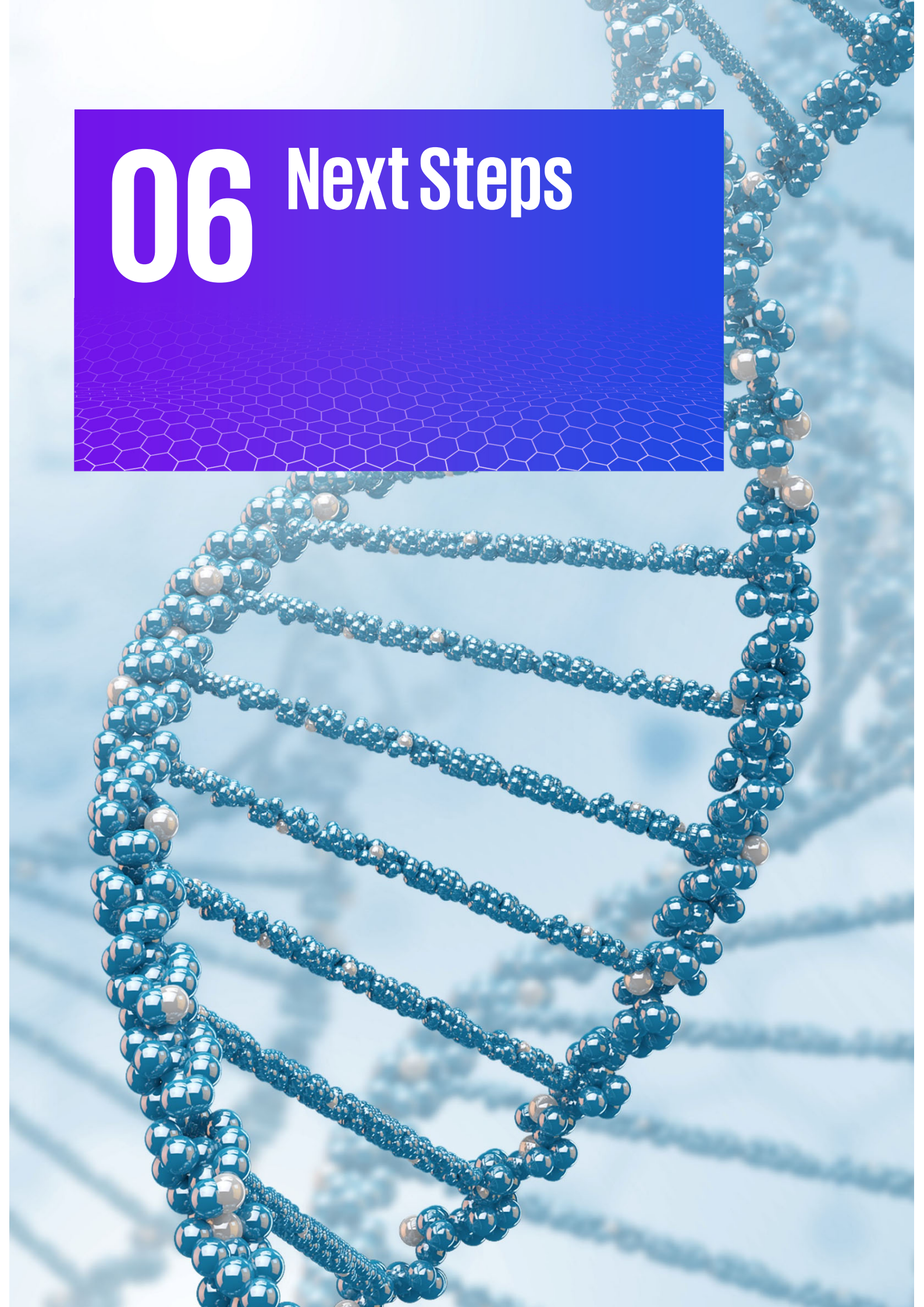
Would companies need to invest in CM&S in-house or could they outsource this (test house model)?

Many companies have developed in-house expertise in CM&S. However, others rely on partnerships with CM&S experts or utilise outsourced resources. Some organisations have concluded that owing to the nature of data ecosystems and the need for compilation of data originating from multiple corporations and external sources, it is unlikely that one company will have a sufficiently diverse data portfolio to proceed independently[41]. Some companies provide a Test House model of outsourced CM&S, offering tailored and regulatory compliant CM&S for pharmaceutical and medical device companies.

Table 4: Economic benefits and challenges of ISE:

Benefits	Challenges
Reduction of costs associated with clinical trials, and ISTs; may offer decreased set up costs	It is difficult for companies to justify investing heavily in IST.
Reduction of costs associated with clinical trials, and ISTs; may offer decreased set up costs	The work required to generate high quality ISE is expensive and can involve years of sustained effort
Can decrease the time to market, increasing the opportunity for profit	Companies will either need to develop in house *in silico* expertise or rely on test houses.
IST can be used to repurpose molecules or improve process development which can provide significant savings ($ millions) and boost profits	A lack of clarity on global regulatory acceptance criteria regarding the acceptability of ISE may lead to confusion increase burden for industry
IST can be used across a range of areas to improve efficiency and decrease costs	A lack of clarity on global regulatory acceptance criteria regarding the acceptability of ISE may lead to confusion increase burden for industry
IST offers a promising ROI	A lack of clarity on global regulatory acceptance criteria regarding the acceptability of ISE may lead to confusion increase burden for industry

06 Next Steps



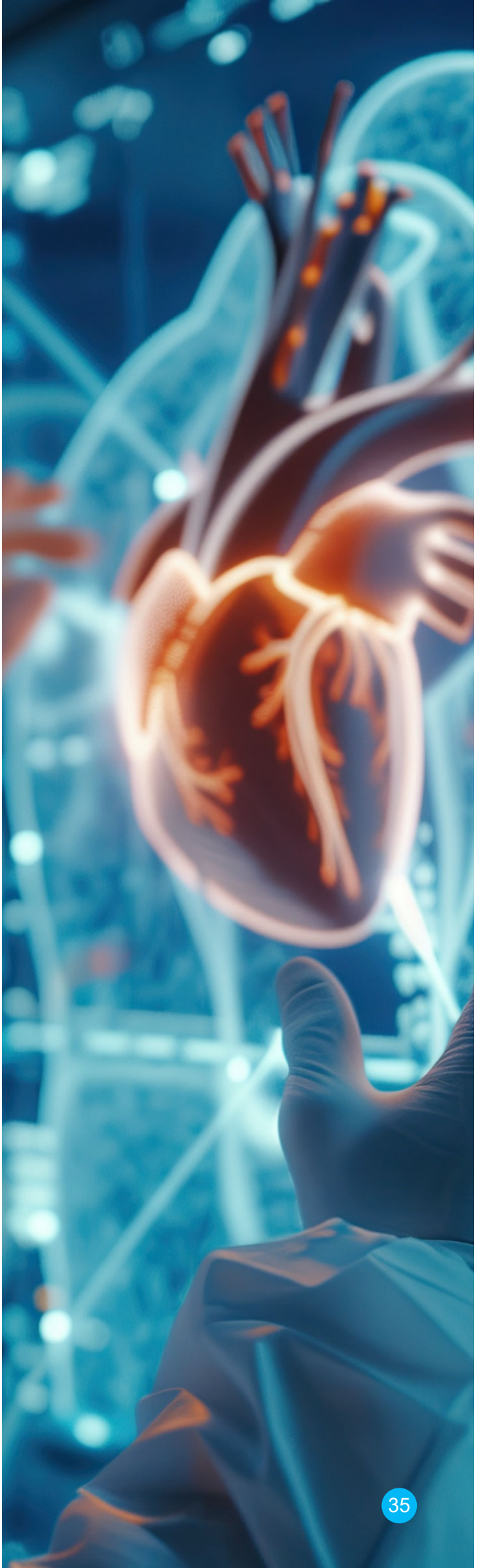
The use of ISE in life sciences is not new, however, to promote more widespread adoption and global regulatory acceptance of *in silico* methodologies and evidence, there is a need for greater stakeholder collaboration and the development of clear validation and assurance standards. Building trust, promoting communication across international stakeholder groups and raising public awareness of ISE are also important factors to consider.

Communication will play a significant role in terms of raising public confidence in ISE and CM&S as a technology. To promote understanding, trust, and confidence in ISE, it is vital that models are transparent and explainable and easy for non-experts to understand and use, despite their complexity. It will be beneficial to publicise case studies where ISE has been successfully utilised as part of a product approval as this would help to contextualise the utilisation ISE. Increased communication will also help to advance global regulatory acceptance criteria for ISE (Medtronic's)[41].

The Innovate UK Initiative and Regulatory Science and Innovation networks are important examples of partnerships between industry, regulators, and academia which have been established to help facilitate collaboration and advance important regulatory stakeholder discussion. The aim of this initiative is to support organisations with the potential to advance regulatory science as a tool that helps policymakers understand, identify and assess different approaches to regulating new technologies, leading to the development of policies that promote innovation[42].

In *silico* clinical trials can be used to evaluate medicinal products when clinical trials would be unethical (e.g., using the Virtual Family to assess thermal safety of implanted devices during MRI) to augment and potentially reduce the size of clinical trials. It could be used as an adjunct tool to evaluate safety and performance of a device prior to conducting traditional clinical trials and animal testing thus reducing the pressure on sampling size requirements during such studies. It will further emphasise the ethical aspirations of manufacturers through a reduction in subjects and animals in research.

There is a need for a collaborative approach towards the development of guidance, which should be informed by cross-sector experts and patients working together with a shared common objective.



By involving technical experts and patients, and by using simple, easy-to-understand terminology, we can help to bolster public understanding and confidence in the uptake of *in silico* technology. In the context of developing guidance, it will be useful to draw on and apply lessons learnt from real world evidence, real world data and good machine learning principles. Development of cross-industry and mutually recognised good simulation practice, on a par with good clinical practice, is a key next step to securing public trust.

The UK Medicines and Healthcare products Regulatory Agency (MHRA) are working with UK approved bodies and the NHS and have set up an AI Airlock regulatory sandbox aimed at addressing novel challenges and accelerating solutions for AIaMD (AI as a Medical Device) in the UK. It is open to any AI manufacturer where relevant stakeholders and product providers will be able to use AI Airlock product reports to share knowledge and findings to assist with further funding or assessment activities. Examples of regulatory challenges could include, understanding the safety, validation and design implications of:

- Detecting and reporting product performance errors (including drift) and failure modes in post market surveillance data.
- Increased automation and decision-making responsibilities within clinical workflow and producing pre-market evidence of safety.
- Breaking down the complexities of generative AI based medical devices.

Post-market surveillance procedures are one of the key aspects of medical device regulatory processes. The goal of proactive (e.g., clinical trials) and reactive (e.g., complaints) post-market surveillance is to monitor the safety of a medical device by detecting the incidents generated by its use, whether they are device-related, instrument-related, or procedure-related. *In silico* clinical trials could detect potential incidents in virtual populations, thus triggering solutions in advance of clinical use. *In silico* clinical trials could thus indirectly reduce healthcare costs due to hospitalisation of patients that suffer from complications, if factors contributing to such complications could be identified and corrected pre-clinically[43].

By supporting more widespread validation, building trust, and enhancing global clarity of regulatory acceptance criteria of ISE, there would be more investment and innovation in *in silico* methodologies and delivery of its potential benefits. It is important to note, that there isn't a one-size-fits-all approach to ISE, MIE generation, validation, or acceptance. This should be kept in mind when developing guidance to help ensure that associated requirements will appropriately safeguard patients. Considerations will vary on a case-by-case basis, and the next step in supporting widespread adoption and global clarity for regulatory acceptance criteria for *in silico* methodologies and evidence should reflect this.

07 Conclusion

In medical device and pharmaceutical development, MIE and ISE have been utilised for several years. There is an increase in the use of ISE in line with an increased clarity of global regulatory acceptance criteria over the decade. MIE and ISE present opportunities to reduce time for product development and reduce risk. Longer term benefits include enhancing the safety and efficacy data package for existing treatments, and development of more advanced treatments with more diverse and representative patient's groups, addressing areas of unmet medical need (e.g., orphan disease, paediatric groups).

The challenges associated with wider utilisation of MIE, ISE are the lack of clarity in global regulatory acceptance criteria and varying regional requirements, which many consider a barrier to fully adopting MIE, ISE methodologies. Other challenges include; difficulty in validation of models; establishment of best practice for validation; a lack of trust from patients and other stakeholder groups; the need for improved training and education related to MIE, ISE; lack of high-quality input data; potential data bias; and limited investment within the sector.

From an economic perspective the technology offers the chance for cost savings and R&D efficiency via the repurposing of molecules, improvements in process development and reduction in animal testing. However, there are financial risks including; the need to develop costly in-house expertise, or rely on test houses; and concern that current lack of clarity amongst global regulators will mean that investment in this technology presents a financial risk.

A key area of focus for the sector is to promote greater adoption and regulatory acceptance of MIE and ISE, and to ensure greater cross-sectoral harmonisation. Building trust, promoting communication, and raising awareness across international stakeholder groups is critical for the future. By supporting more widespread MIE, ISE technology validation, increasing trust and developing global regulatory acceptance criteria, stakeholders have the opportunity to encourage greater investment and adoption of MIE and ISE methodologies and realise the potential short- and longer-term benefits outlined in this report.

Utilising robust post-market surveillance and vigilance should be a priority for manufacturers and regulators to ensure the understanding of the short and long-term effects of treatments developed with MIE and ISE technology. The ability of ISE to generate longitudinal data would be helpful for regulators, especially for products where a high level of public scrutiny exists. This may support adoption and trust in ISE tools, whilst improving clinical outcomes.

From a sustainability perspective, it is important to consider the increasing consumption of energy to drive MIE, ISE tools and the associated environmental impact. It is important for the sector to monitor and consider the environmental affect of the use of MIE and ISE.

The potential benefits for patients and global healthcare systems with the utilisation of MIE, ISE technology is enormous and transformative and is an area to watch closely in the next few decades.

08 Glossary

Definitions

In silico Technology

The use of Computational Modelling and Simulation (CM&S) in pharmaceutical and medical device (see definitions below) research and development and regulatory evidence is known as '*in silico*', and the use of such methods and the data it generates are known as *in silico* technology and evidence, respectively.

The term '*in silico* clinical trials' (IST) refers to developing patient-specific computational models to form virtual patient cohorts upon which to test the safety and/or performance of new drugs and new medical devices[44].

Predictive CM&S approaches vary, ranging from pure data-driven, phenomenological modelling (seeking to explain the nature of things through the way they are experienced) to knowledge-driven, mechanistic simulations. CM&S and *in silico* methods and evidence, as with any technology, come in many forms, with different inputs, processes, and outputs, depending on the needs of the user. *In silico* evidence is not yet widely accepted within medicinal product regulatory pathways, but its use and recognition in the process are growing.

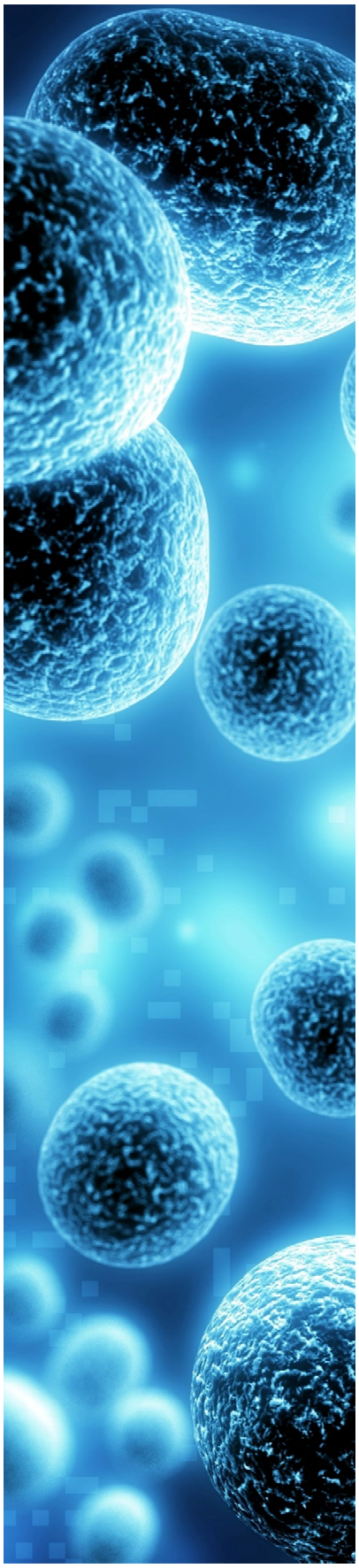
Pharmaceuticals

Using the WHO definition of a pharmaceutical: 'any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings'[45]. The terms drug, medicine and pharmaceutical are used often used interchangeably.

Medical Devices

Medical devices refer to the definition by WHO: a 'A medical device can be any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination for a medical purpose'[46].

Glossary



AI	Artificial intelligence
ASME	American Society of Mechanical Engineering
BVS	Bioresorbable vascular scaffolds
CM&S	Computational Modelling and Simulation
CDMO	Clinical development and manufacturing organisation
CRO	Clinical research organisation
EMA	European Medicines Agency
FDA	Food and Drug Administration
ISE	*In silico* evidence
IST	*In silico* clinical trial
MDIC	Medical Device Innovation Consortium
MIDD	Model-informed drug development
NAM	New Approach Methodologies
PBPK/ PK/PD/PV	Physiologically based pharmacokinetic/ pharmacokinetic/pharmacodynamic/ pharmacovigilance
QSP	Quantitative systems biology
R&D	Research and development
RCT	Randomised clinical trial
ROI	Return on investment
SAE	Serious adverse event
UK MHRA	United Kingdom Medicines Healthcare Regulatory Authority
VICTRE	Virtual Imaging Clinical Trial for Regulatory Evaluation
WHO	World Health Organisation

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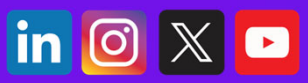

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