INSILICO UK

Unlocking the power

of computational modeling and simulation across the product lifecycle in life sciences.

Sounder, safer, faster and more sustainable innovation and regulatory evidence of medicines and healthcare products.

A UK Landscape Report - September 2023

A UK Landscape Report

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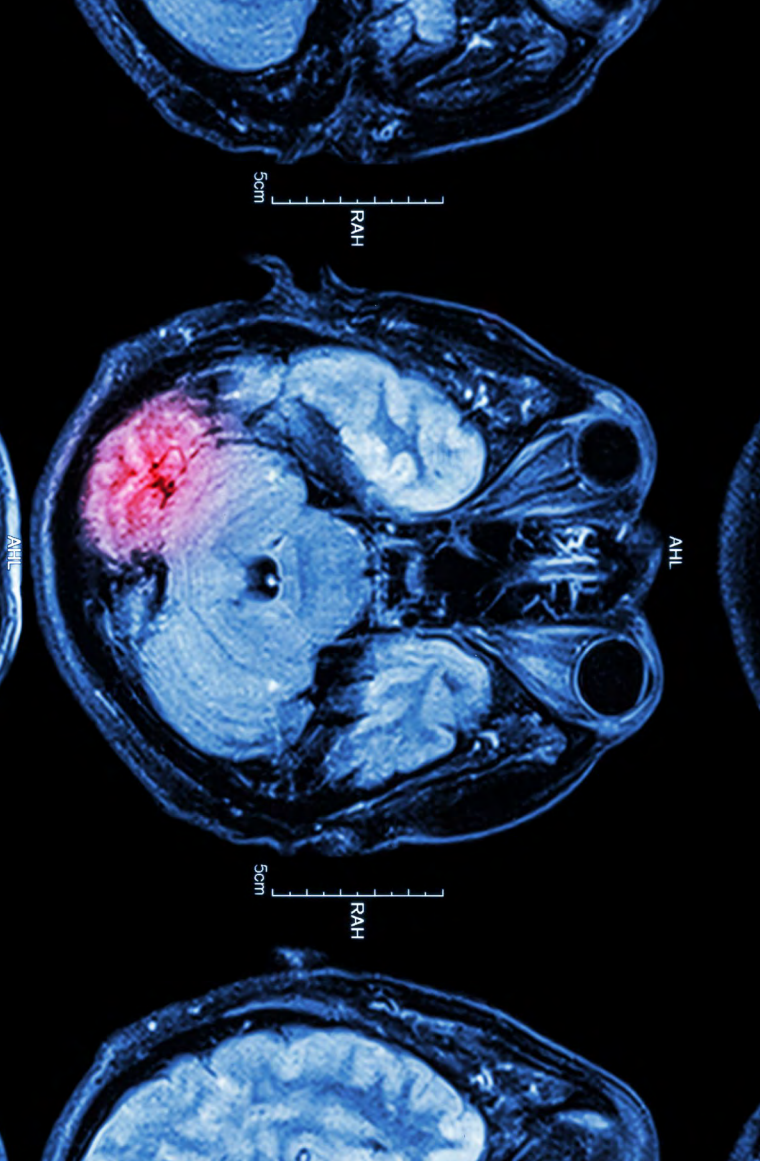
Foreword

Over the centuries, the United Kingdom pioneered life sciences and contributed to progress in medicine and healthcare. British scientists have been responsible for many Nobel Prizes in Physiology and Medicine: from breakthroughs in malaria, hepatitis C virus, embryonic stem cells, and neurosciences to making the discoveries of penicillin, insulin, and split genes, all the way through elucidating cell cycle regulation, pluripotent cell reprogramming and the structure of DNA and antibodies, or the invention of computed tomography and magnetic resonance imaging. It is important to note that the UK's contributions to the development of methods for testing for the safety and efficacy of medical and public health interventions have been equally transformational.

James Lind (1716-1794) is considered the first physician to have ever conducted a controlled clinical trial in modern times. Whilst working as a surgeon on a ship, he was appalled by the high mortality of scurvy amongst the sailors. His vivid description of the comparative trial on cures for scurvy covers the essential elements of a controlled trial. In May 1941, the Axis powers captured Archie Cochrane (1909-1988). Smart, inquisitive and bored, the young doctor passed the time in a prisoner-of-war camp in Salonika (Greece), treating his fellow inmates—and conducting trials on them. His experience in the camp led him to understand that much of medicine lacked sufficient evidence to justify its use. His post-war work laid down the foundations of randomised controlled trials which have become the gold standard source of scientific evidence in medicine and associated regulatory agencies.

Recent national and international reports have increasingly evidenced the problems and pressures of our regulatory systems. Even randomised controlled trials have challenges and limitations in their practical implementation or the inferences they enable. Other sources of scientific evidence, viz., bench and animal experiments, are equally limited. Ultimately, bench, animal, and human testing are controlled models to gain insights into the safety and performance of medical products in less controlled real-life conditions. Recent investigations into failures and recalls of medical therapies demonstrated that even regulated products (i.e., those that underwent best practices for their approval) have risks and limitations that the current regulatory process cannot detect or avoid. Despite an annual gross growth rate of 5-6% in demand for drugs and medical



devices, the number of new medicines and therapies with regulatory approval has remained stagnant for the past two decades. Whilst our age is the most scientifically advanced, translating these breakthroughs cost-effectively into sustainable patient benefits seems elusive. In addition, healthcare systems are under enormous pressure due to changing socio-demographics and care costs. The cost of medical technologies has grown due, in part, to the expensive and time-consuming nature of research, development and regulatory product lifecycles. Finally, combining AI, digital, pharma and devices technologies increasingly lead to more complex interventions and combination therapies for which conventional testing methods are suboptimal. In parallel, the eruption of Industry 4.0, fuelled by data-driven, digital, and virtual paradigms, is impacting complex sociotechnical systems and transforming highly regulated industry sectors. These developments present possibilities that neither Lind nor Cochrane could have imagined. Is this the moment to take stock of how these profound challenges call for equally profound transformations? We believe the moment is now, using the invitation by The Taskforce on Innovation, Growth and Regulatory Reform (TIGRR)[1] to identify and develop proposals across a range of areas to drive innovation, growth and competitiveness through regulatory reform.

InSilicoUK is a grassroots cross-sector effort articulating a vision in collaboration with many stakeholders since its kick-off in March 2022[2]. This is the third in a series of open reports[3] published over the past year, which successively build the case for adopting computational modelling and simulation as innovation-friendly sources for modern design and regulatory evidence.

1 Duncan-Smith I, Villiers T, Freeman G (2021) Taskforce on Innovation, Growth and Regulatory Reform independent report. www.gov.uk/government/publications/taskforce-on-innovation-growth-and-regulatory-reform-independent-report.

2 InSilicoUK Innovation Network, Virtual Launch Event, https://iuk.ktn-uk.org/events/insilicouk-network-launch/

3 InSilicoUK Publications are all available at https://zenodo.org/communities/insilicouk.

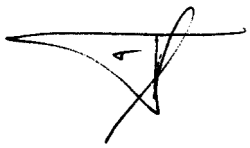
The first report focused on public and private investment[4] through innovative *in silico* spin-offs and start-ups. In contrast, the second report articulated the economic impact[5] of *in silico* approaches on the UK economy.

In this report, InSilicoUK proposes a paradigm shift that can reduce, refine, and sometimes replace conventional sources of safety and efficacy evidence. However, it does not suggest traditional methods should be abandoned, as bench, animal and human testing can be the best source of evidence in some circumstances. Ethically and economically, however, one should weigh every source of scientific evidence on its merit, i.e., on a risk-informed credibility assessment.

This report explores the challenges of human clinical trials and defines *in silico* clinical trials based on computational modelling and simulation technologies. The document then identifies several barriers to *in silico* trial adoption that emerged from broad community consultation. Finally, it analyses the market readiness for embracing *in silico* trials. A key part of this document is the set of nine recommendations that have emerged from this reflection and are offered for the consideration of the UK Government.

The InSilicoUK Innovation Network is a coalition of actors from academia, industry, standardisation, compliance testing, policy, and regulation. This community is comprised of awardees from the Royal Academy of Engineering and supported by the Royal Academy of Engineering and InnovateUK KTN. It aims to make the UK the best milieu for delivering medical innovations using *in silico* evidence and regulatory science. The UK also has a unique opportunity to combine a world-leading academic system, targeted public funding, and vibrant entrepreneurship. InSilicoUK thus builds upon the immense legacy of Lind and Cochrane while harnessing the power of approaches and technologies only available in the current digital era.

On behalf of the InSilcoUK Innovation Network



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4 Whorwood, H, Frangi, AF, & Wilkinson, K. (2023). *In Silico* Medicine: Investment in next-generation life sciences innovations empowered by computational modelling and simulations. Zenodo. https://doi.org/10.5281/zenodo.7725224

5 Frangi, AF, Denison, T, & Lincoln, J. (2023). The Economic Impact of In-silico Technology on the UK and its Lifesciences Sector. Zenodo. https://doi.org/10.5281/zenodo.7558649

Executive summary

This report:

- **Outlines the public health and economic benefits of using *in silico* trials (ISTs) to reduce, refine and eventually even partially replace the need for conventional human clinical trials and animal and physical testing in the development of new medical products**
- **Describes current barriers to the expanded use of ISTs**
- **Identifies opportunities for the UK to spearhead the global effort to develop ISTs, making the UK a leader in the field and, therefore, friendly to inward investors**
- **Details the significant commercial and economic benefits in the development of the UK life sciences sector and broader societal benefits to the NHS, the UK and the world**
- **Makes recommendations on how the UK Government can support this initiative.**

Human clinical trials are the most costly and time-consuming part of development and approval for drugs, *in vitro* diagnostics (IVDs) and medical devices. Clinical trials, by their nature, medical procedures whose safety profiles are not yet fully known, they pose potential risks of harm to subjects and must be limited in their scope. Whilst at the same time, delays in new therapies represent a huge cost to patients and their communities seeking treatment. Cost, time, patient safety, and ethical and practical considerations can all delay the introduction of beneficial new healthcare products. As the pace of new healthcare products coming to market is ever-increasing, particularly for new and niche conditions, clinical trial efficiency is more important than ever.

In silico trials (ISTs) – using computer-generated digital models of animals, humans, or organ systems – can enhance, refine and eventually even replace clinical studies. Doing so more rapidly, less expensively, all without putting patients at risk. ISTs also enable investigators to create virtual populations of

patients that can be arbitrarily large, studied for extended periods and include subjects who would be excluded for practical, ethical, or other reasons that prevent subjects from being eligible for human trials. Virtual patient populations also support evidence generation for healthcare products that only benefit certain subgroups or very few patients (e.g. those with rare or orphan diseases) by modelling outcomes where a traditional clinical trial cannot be performed due to the limited number of available trial participants, or to generate data in cases where clinical testing would be unethical, as in the assessment of paediatric dosing of new drugs. When subsequent confirmatory human trials are needed, ISTs also help refine study designs to be more efficient and more accurately focused on critical issues.

Computational modelling and simulation (CM&S) has been widely used in aerospace, automotive and other industries to prototype and test products, reducing and sometimes eliminating the need for physical prototyping. Though adoption in the biomedical field is more recent, rapid progress is being made. For example, CM&S is used in pharmaceutical lead compound discovery, pharmacokinetics and pharmacodynamics. Medical device companies use CM&S for medical device design conceptualisation and optimisation, prototyping, testing and root cause analysis in case of failures.

The US Food and Drug Administration (FDA)[6] and, to a lesser extent, the European Medicines Agency (EMA),[7] encourage credible IST methodologies. Specifically, a US standard[8] for verifying and validating modelling and simulation techniques and an FDA guidance document[9] on including digital evidence in regulatory submissions have helped drive the adoption of ISTs. They have recently been transformed into a Draft Guidance for Industry and Food and Drug Administration Staff that is under public consultation.[10] Medical product manufacturers are increasingly investing in digital technologies as a result. Highly respected organisations also advocate for their use, notably the Medical Device Innovation Consortium[11] and the Avicenna Alliance[12].

6 www.fda.gov

7 www.ema.europa.eu/en

8 Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices ASME V&V 40 Standard, Americal Society for Mechanical Engineering, 2018, www.asme.org/codes-standards/find-codes-standards/v-v-40-assessing-credibility-computational-modeling-verification-validation-application-medical-devices.

9 Reporting of Computational Modeling Studies in Medical Device Submissions, Guidance for Industry and Food and Drug Administration Staff, Center for Devices and Radiological Health, Food and Drug Administration, 2016, www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions.

10 Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions Draft Guidance for Industry and Food and Drug Administration Staff, Center for Devices and Radiological Health, Food and Drug Administration Staff, Dec 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

11 Medical Device Innovation Consortium, www.mdic.org

12 Avicenna Alliance, www.avicenna-alliance.com

There is, nonetheless, a deadlock in IST adoption. Regulators and conformity assessment bodies can only accept digital evidence once it is sufficiently credible. Their understanding of CM&S techniques is not good enough to establish equivalent confidence levels between ISTs and human trials. Meanwhile, medical product developers will only invest in credibility activities if they have confidence that regulators and conformity assessment bodies will accept this form of evidence. We must overcome several barriers to expand the use of digital evidence in the medical product regulatory process. For instance, there is a need for better anatomical and physiological models, data privacy and consent considerations, education of stakeholders on model credibility, a shortage of workers with skills at the intersection of biomedicine and data science and the need for 'safe harbours' or 'sandboxes' to foster industry collaborations without fear of jeopardising intellectual property rights.

Through collaborative efforts of regulators, conformity assessment bodies, industry, policymakers and others in the UK's biomedical ecosystem, all of these barriers can be overcome, unleashing a cascade of benefits.

The UK's new special interest group, InSilicoUK, proposes that the UK Government, through the Department for Business, Energy and Industrial Strategy (DSIT)[13], adopt the task of accelerating the development of ISTs as a priority tactic in its strategy for the life sciences industries. It proposes that the UK Government invests public money, contributing 20% of the overall cost to seed-fund technical solutions that establish IST's evidence credibility and regulatory acceptance.

13 UK's Department of Science, Innovation and Technology, www.gov.uk/government/organisations/department-for-science-innovation-and-technology.

In the healthcare sector, digitalisation and the genomics revolution are coming together to create the most profoundly disruptive but exciting opportunity to transform the way we develop medicines and diagnostics and therapeutics. We will take a ton of time and money and cost out of the system. We can reimburse properly and get people healthier. That's the dream. To do that we've got to both keep investing in deep science and in digital but, crucially, the UK has got to make a play to be the global regulatory testbed for digitalisation of healthcare.

About InSilicoUK

InSilicoUK is a community of healthcare and technology organisations promoting medical innovations using *in silico* evidence and regulatory science to improve patient safety and accelerate the development of beneficial medical products. Founded in March 2022 and now including more than 1,700 members, InSilicoUK agrees that CM&S techniques offer enormous benefits for industry and the public good. The UK is currently well-placed to lead their development and wider adoption.

Royal Academy of Engineering

INSILICO UK

UKRI Innovate UK KTN

Avicenna Alliance
Association for Predictive Medicine

ABHI HealthTech for Life

abpi Bringing medicines to life

techUK FOR WHAT COMES NEXT

Department for Business, Energy & Industrial Strategy

bsi.

MHRA

Vision, Mission & Rationale

Vision and Mission

Vision

Make the UK the best milieu for delivering medical innovations, supported by *in silico* evidence and regulatory science.

Mission

Through collaborative efforts of regulators, industry, policymakers, academics and others in the UK's life sciences ecosystem, barriers to adoption can be overcome, unleashing a cascade of benefits.

Rationale

The UK is especially well positioned to take a leading role in the implementation of *in silico* technologies in the medtech and pharmaceutical industries because:

- UK Government has consistently and recently reiterated its aim to be a global science super-power. Leadership in technology-enabled life science is an essential contributor to this.
- UK Government policy is already well aligned and has prioritised the data, engineering and life sciences as a leading economic driver in the UK.
- UK medical regulation is newly reformed and its now independent regulatory body has the opportunity to create a more agile and innovation-friendly regulatory system.
- The UK has a world-class science base in many fields, including biomedicine and data science, a thriving life sciences sector and a strong ecosystem of supporting research centres.
- The unique UK National Health Service potentially offers unparalleled access to data that can inform and support computational modelling and simulation in healthcare.
- The UK has a strong track record in ethical innovation.

Success in accelerating the development of ISTs would lead to:

- **Better patient outcomes** by enabling faster and safer development of better medicines and healthcare products,[14] including those for rare conditions and ethically challenging patient groups and for personalised medicine,[15] and through the ability to perform trials in more diverse populations.
- **Boosting the UK's life sciences sector and supply chain** because ISTs reduce the cost, duration, difficulty, ethical jeopardy and risks to patient safety of conventional clinical trials.
- **Less burden on the NHS** owing to early diagnosis and faster and better therapeutic outcomes potentially free NHS beds and reduce waiting lists.
- **More direct translation to human benefits reducing animal harm and compromised animal welfare.** Leveraging real-world human data and population cohorts for more direct translation to human benefits and reducing reliance on animal research where animal welfare is compromised.
- **Simpler trials process** because ISTs can reduce the pressure to recruit, supervise and administer research subjects during clinical trials without compromising outcomes.[16]
- **Increasing the UK's pharmaceutical and medical device market share,** becoming a world leader in novel medical products whose product lifecycle has been greatly accelerated or transformed thanks to *in silico* methods.
- **Increasing the UK's market share** in selling tools and services that support computational modelling and simulation (CM&S) and ISTs.
- **A raised profile for the UK's life science sector** because its expertise and global leadership in ISTs will open British companies to worldwide investment and international markets.
- **National economic growth** because global leadership attracts inward investment. The global pharmaceutical and medical device market, currently worth $1,685 billion[17] will seek engagement and access to the UK's clinical research enviroment[18] and CM&S expertise. This increased interest will also create new highly skilled jobs and revenues.

Recommendations

***In silico* evidence and trials are currently in a development phase but are poised to transform how health and life sciences R&D and the associated regulatory oversight are conducted in future.**

They can also reduce the need to trials in the first place when *in silico* approaches cast already serious concerns about the safety or efficacy of a new therapy. *In silico* trials will be essential in the refinement, reduction and partially replacement of conventional clinical trials in some circumstances. For instance, they will inform a clinical trial protocol design (e.g., optimising patient selection criteria or identifying failure scenarios). They will also replace clinical trials where there are currently evidence gaps due to practical or ethical issues with conventional trials. They can also reduce the need to trials in the first place when *in silico* approaches cast already serious concerns about the safety or efficacy of a new therapy.

The UK can take a leadership position in *in silico* trials which would cement its position as a global leader in health and life sciences, help drive the UK economy and provide UK citizens with early access to innovative health products.

The UK Government understands the importance of computational modelling and simulation to our future productivity and competitiveness for businesses of all sizes and across all sectors of the economy.[19] The InSilicoUK Innovation Network[20] recommends that the UK government acts decisively to position the UK as a global powerhouse in computational modelling and simulation for activities associated with the life sciences and identify ISTs as an important part of the UK Life Sciences Strategy.

1 **Create an impartial UK network of Centres of Excellence in Regulatory Science & Innovation (UK CERSI) to bring together the government, corporate sector, academia and the NHS.** It would consider how to govern and, where necessary, manage future regulatory science methods, tools and processes, including those related to the creation, acceptance and credibility of *in silico* evidence. The UK Life Sciences Advisory Group[21] recently recommended exploring the creation of UK CERSI. An independent UK CERSI could draw together both domestic and international partners to agree and carry out a coordinated plan with common goals to achieve these objectives, including representation from the UK Government, regulators (MHRA,[22] OPSS,[23] FSA,[24] HSE[25]), health technology assessment (NICE[26]), the UK's conformity assessment bodies (e.g. BSI,[27] DEKRA,[28] SGS[29]), standardisation bodies (e.g. BSI), industry associations (e.g. ABHI,[30] ABPI,[31] techUK,[32] etc.), academic and professional organisations (e.g. Royal Academy of Engineering, the Academy of Medical Sciences, etc.) and patient and clinical organisations.

2 **Create a Centre of Excellence in *In Silico* Regulatory Science & Innovation should be created as an independent public-private partnership or joint undertaking.**[33] Within the UK CERSI network, we recommend creating a CERSI node with a mission to drive global traction and scale up of next-generation *in silico* regulatory evidence and innovation across medicines and medical devices. This core mission will be guided by the North Star to contribute to ensuring patient safety and effective and quality care while accelerating patient access to the latest technologies. A key activity of this centre will be to provide a national technical capability to regulators like MHRA and HSE. Although independent, this will be similar to the role that the Office for Science and Engineering Laboratory (OSEL)[34] provides to the regulatory function within the US Food and Drug Administration. This national capability will also contribute, among other functions, to:

- De-risk early-phase discovery and innovation leading to a reduction in late failures across life sciences products
- Reduce current time/cost to generate *in silico* regulatory evidence by industry
- Make readily available curated and validated virtual populations and *in silico* models
- Co-create good simulation practices, standards and regulatory frameworks for *in silico* methods' adoption[35]
- Contribute to upskilling and reskilling of the future industry and regulatory workforce
- Provide UK presence and thought leadership on international regulatory science and innovation initiatives

3 **Provide CM&S resources and training to widen the capacity and capability within the Medicines & Healthcare Products Agency (MHRA).** MHRA is already under enormous strain due to its current workload, agency demands, and priorities. This situation hinders its ability to remain innovative and forward-looking. Regulatory science and innovation within MHRA must be prioritised and resourced with additional capacity, capability and skills. Short-term focus and skills gaps lead to further unpreparedness and inertia to change, creating conditions that put patients at risk and discourage regulatory innovation. This will enable the MHRA to respond to future regulatory needs, including evaluating how ISTs can be incorporated into accelerated regulatory pathways for pre-market clinical investigations, innovative medicines (ILAP) and medical devices (IDAP). THE MHRA will also need to support the changing requirements for post-market surveillance and vigilance activities. A well-designed regulation system provides certainty to reduce investment risk and the clarity needed to make markets function effectively. It can encourage innovation, create consumer confidence, steer the development of new products and enable the rapid but safe adoption of new and disruptive technologies. Finally, further investment is recommended in research, training and awareness around the legal and liability positioning and frameworks underpinning the regulatory adoption of CM&S *in silico* trials.

4 **Capitalise on the partnership with the NHS and the UK infrastructure to inform, develop and validate ISTs.** The globally respected NHS could provide real-world data to generate virtual populations with relevant UK demographics that could serve as a platform for validating ISTs. We recommend foresight in developing NHS infrastructures, viz. Secure Data Environments[36] (SDE), to accommodate IST use cases. In addition, the proposed UK CERSI node outputs will increase patient benefit through the timely adoption of innovative products and services and increase efficiency while reducing healthcare costs to the NHS associated with accelerated and efficient R&D lifecycles. We recommend that the proposed UK CERSI node engages with a range of NHS and National Institute for Health and Care Research (NIHR) infrastructure,[37] including Biomedical Research Centres, Clinical Research Networks and Applied Research Collaborations, BioResource, among others. The proposed UK CERSI node should closely partner with relevant data discovery and access infrastructures like Health Data Research UK.[38]

5 **The Department of Science, Innovation and Technology and UK Research and Innovation (UKRI) should fund fundamental regulatory science and innovation, encourage the pre-competitive piloting and implementation of ISTs and help de-risk regulatory adoption and reforms, uptake by the life sciences corporate and SMEs and make the UK attractive for driving inward investment on ISTs.**
This could be directed through UK CERSI or through dedicated grant funding programmes. Public funding should focus on transitioning to IST adoption by modernising regulatory processes and requirements supporting publicly funded regulatory agencies, i.e. MHRA, in their decision-making as well as national pre-competitive capabilities supporting the life science sector as a whole.

6 **Engage with stakeholders responsible for ISTs implementation, identify, define and position new roles and skill sets underpinning a proficient national ecosystem on CM&S.** Ensure the UK future-proofs its industry and regulatory workforce with competencies and thought leadership on computational modelling, complex simulations, virtual and non-animal testing, data science skills to become a world superpower and attract inward investment. This would include working with the Department for Science, Innovation and Technology (DSIT) alongside UKRI, businesses, universities, learned societies and research institutes.

7 **Promote international collaboration and cross-sectoral outreach to engage expertise and share findings and lessons learnt, recognising that success depends on concurrent global collaboration.** Ensure UK presence and IST advocates at key international organisations providing thought leadership or regulatory harmonisation in ISTs. For instance, Avicenna Alliance,[39] the Medical Device Innovation Consortium (MDIC), the International Medical Device Regulators Forum[40] (IMDRF), the International Consortium for Innovation and Quality in Pharmaceutical Development[41] (IQ Consortium®) and the International Pharmaceutical Regulators Programme[42] (IPRF), amongst others.

8 **Provide thought leadership ensuring regulatory preparedness and resilience to accommodate the emerging and ever-changing future of healthcare and medical product innovation.** Lead and contribute to generating sound scientific evidence informing future regulatory policy in collaboration, amongst others, with the Government Office for Science, the Office of Lifesciences, the Office of Artificial Intelligence, the Parliamentary Office of Science and Technology, the Royal Academy of Engineering, the Academy of Medical Sciences, the National Engineering Policy Centre and UK funders and charities engaged in policy, science and technology.

9 **Foster a long-term co-production culture and trustworthy communication strategy around CM&S.** This aim is to engage stakeholders across all sectors to co-create and share information and help build regulatory credibility, patient acceptance and public trust in CM&S and its use in ISTs and therefore encourage its mainstream adoption. The communication strategy will explain how these novel techniques and new regulatory strategies seek to put the patient and the public at their centre by adopting best practices, standards[43] and frameworks developed by regulators,[44] trade associations,[45] funders,[46] and charities.[47] Maximise using excellent and consolidated UK infrastructures[48] to reach out to patients and the public.

Establishing trusted *in silico* clinical trials sparks a cascade of positive benefits

Benefits Colour Key:

- **Medical / Healthcare**
- **Commercial**
- **Public Good**

Clinical trials are faster, less expensive, safer, less uncertain and easier to conduct.

The medical products industry (i.e. the manufacturers of pharmaceuticals, medical devices and hybrid products) are incentivised to invest in more trials, more willing to tackle rare or ethically challenging diseases and medical conditions and less likely to abandon hopeful medical products.

With more certainty, faster development times, easier R&D pathways and fewer costs, investment is more likely to yield a profitable return.

Clinicians and patients are more likely to have access to more and better treatments sooner and at less expense, including for rare and/or ethically challenging diseases and health conditions.

Trusted CM&S of biological systems and whole bodies will speed up the realisation of personalised medicine, with all the benefits of more effective treatments, faster recovery times, better prevention of ill-health for ordinary citizens.

With the populace healthier, national economies will benefit from better productivity and growing GDP.

With businesses more profitable and private equity more willing to invest, national economies will benefit from higher, sustainable tax revenues.

National economies will be more able to afford healthcare systems, freeing up resource to attend to, e.g. the crisis in social care.

Nationally funded healthcare systems will be more effective, less wasteful, less pressurised and thus more able to cope with existing needs, known trends (including an ageing and growing population) and global emergencies (such as the COVID pandemic).

Section References

14 In this report, 'medicines and healthcare products' means the broad range of medical solutions addressing human health. It includes drugs (e.g. molecules, biologics, compounds), medical devices (e.g. wearables, implants), software (e.g. as a medical device or used to operate medical devices) and hybrid products (i.e. that combine two or more of these categories).

15 Personalised medicine allows treatments and therapies tailored to the individual. Exploiting bioscientific knowledge, depends on a computational model where parameters can be adjusted to represent the individual. Running simulations of different treatment options on the personalised model allows clinicians to predict likely outcomes and thus tailor the treatment plan to the group or individual, thereby reducing adverse events, improving outcomes, avoiding waste and speeding up treatment durations.

16 As set out by the Department of Health and Social Care in Saving and Improving Lives: The Future of UK Clinical Research Delivery, the current policy is to embed streamlined, efficient and innovative clinical research enabled by data and digital tools at the heart of patient care across the NHS and ensuring that all health and care staff feel empowered to support research. A regulatory environment that accepts IST evidence reduces the overall number of real subjects needed, reducing the burden on staff.

17 Frangi AF, Denison T, & Lincoln J. (2023) [The Economic Impact of *in silico* Technology on the UK and its Lifesciences Sector. Zenodo. doi. org/10.5281/zenodo.7558649] estimated the value of pharmaceutical and medical devices industries in 2020 from various sources, which averaged out at $1,260 billion and $425 billion, respectively, or $1,685 billion in total.

18 Between 2016 and 2019, clinical research supported by the NIHR generated an estimated £8 billion of gross value added and supported over 47,000 full-time equivalent jobs across the UK. Every £1 the government spends on research and development via NIHR generates over £19 in total economic returns – the highest return on investment for any public service. Saving and Improving Lives: The Future of UK Clinical Research Delivery.

19 Government Office for Science (2018) Computational modelling: technological futures. www.gov.uk/government/publications/computational-modelling-blackett-review.

20 This report is intentionally ambiguous on the extent to which the UK will model its UK CERSI on the FDA model The US FDA has developed over the years a "CERSI Program", a "network of CERSIs" and individual CERSIs each within a university consortium (currently 4 CERSIs led by four universities). The exact format of the UK CERSI will emerge from co-creation with all stakeholders following an initial piloting stage, building on the successful practices of the US FDA CERSI ecosystem but also addressing some of its limitations, namely, a more vibrant industry engagement and pre-competitive coproduction.

21 Medicines and Healthcare products Regulatory Agency, Office for Life Sciences and Department of Health and Social Care (2023) Advisory Group Reform Proposals www.gov.uk/government/news/advisory-group-reform-proposals.

22 Medicines and Healthcare products Regulatory Agency (MHRA), www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.

23 Office for Product Safety and Standards (OPSS), www.gov.uk/government/organisations/office-for-product-safety-and-standards.

24 www.food.gov.uk

25 www.hse.gov.uk

26 The National Institute for Health & Care Excellence (NICE), www.nice.org.uk.

27 British Standards Institution, BSI Group, www.bsigroup.com

28 DEKRA, www.dekra-uk.co.uk

29 SGS, www.sgs.com

30 Association of British HealthTech Industries, www.abhi.org.uk

31 Association of the British Pharmaceutical Industry, www.abpi.org.uk

32 UK's technology trade association, www.techuk.org

33 Private Public Partnerships like UK Catapults www.catapult.org.uk or European Joint Undertakings eur-lex.europa.eu/EN/legal-content/glossary/joint-undertakings.html are well-tested models. The Medicines Discovery Catapult (md.catapult.org.uk) and the Innovative Health Initiative (www.ihi.europa.eu), respectively, are relevant exemplars.

34 Office of Science and Engineering Laboratories, Food and Drug Administration, www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories.

Section References

35 One model would be to build on the FDA partnership projects (e.g. the Living Heart Project) where an exemplar regulatory submission is used and developed as a driving template.

36 Secure data environment for NHS health and social care data - policy guidelines, Department of Health and Social Care, Policy Paper, www.gov.uk/government/publications/secure-data-environment-policy-guidelines/secure-data-environment-for-NHS-health-and-social-care-data-policy-guidelines, 2022.

37 National Institute of Health Research, Research Infrastructure, www.nihr.ac.uk/explore-nihr/support/research-infrastructure.htm and www.bioresource.nihr.ac.uk.

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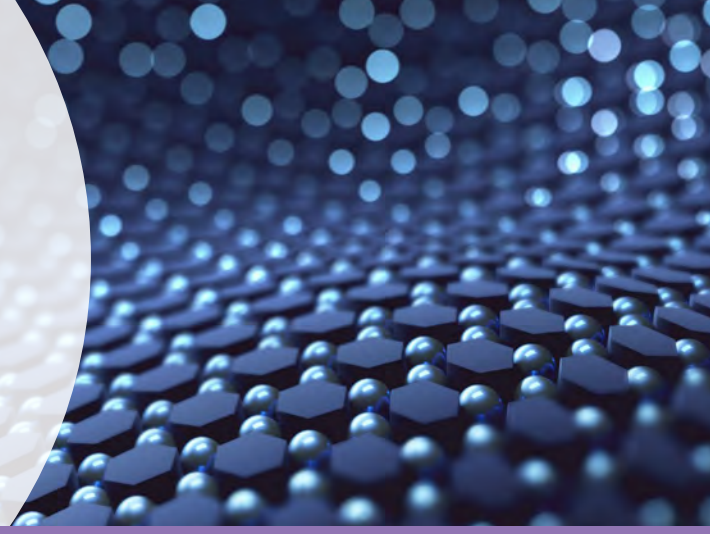
What Are *In Silico* Trials?



Computational modelling and simulation

CM&S use computers to study complex systems by using multiple variables that characterise a system, then adjusting the variables and observing the outcomes. CM&S enables scientists and engineers to rapidly conduct multiple simulated experiments or test physical systems without constructing prototypes.

CM&S is used extensively in product development and testing in industries such as automotive and aerospace and has also been employed in fields such as physics, chemistry, biology, climatology, economics and psychology. The use of this technology continues to grow and holds important benefits for the public good.[49]

Experience from other sectors

The trend to move away from physical testing in favour of virtual testing is already happening extensively in many sectors,[50] notably the regulated aerospace and automotive industries.[51] Physical testing techniques (e.g. wind tunnels and crash test dummies) are gradually being replaced by computational models representing physical systems, processes and objects, giving researchers greater predictive power and allowing developers and manufacturers to accelerate and de-risk R&D. Exploring options and optimising solutions on virtual models significantly reduces the cost, inefficiency and risks of physical prototyping. Once populated with sufficient data and validated, these models can yield safety and performance predictions that all stakeholders trust, including the regulators and end-users.

Digital Twins

Computational modelling is sometimes used to monitor the ongoing performance of existing physical objects, processes and systems. These 'digital twins' are used where vigilance lets pre-emptive action save money, improve performance and, potentially, save lives. One of the most prominent examples is weather forecasting. The Met Office[52] has invested in sophisticated digital twins that run on supercomputers, producing reliable predictions that help mitigate the weather's negative social, economic and environmental impacts, yielding enormous benefits.[53]

'*In silico* trials' in biomedical science refers to using CM&S to conduct virtual experiments (chips are largely silicon, hence the name). *In silico* differs from *in vivo* (meaning 'in life') and *in vitro* ('in glass'). *In vivo* studies are conducted on living organisms, while *in vitro* studies are performed in test tubes or other laboratory equipment outside living organisms.

In silico studies use computational modelling to simulate cellular,[54] molecular, or even subatomic interactions, such as DNA replication, protein folding and RNA splicing. More recently, methods underpinned by very similar fundamental approaches have been used to model tissues, organs, full organisms and entire populations in health and disease.

In drug development, *in silico* methods are commonly applied to compound discovery, molecular dynamics, computational chemistry, pharmacokinetics, pharmacodynamics and toxicology for new molecular entities.[55] In the development of medical devices, the use of computational fluid dynamics, stochastic engineering models, electrophysiology simulations and structural finite element analysis is common. [56]

These approaches are used routinely in the following ways:

- The visualisation, characterisation and functioning of human biochemistry, cells, anatomy and systems in relation to pathologies;
- The modelling of pharmacodynamics, pharmacokinetics and other physiological processes to, for example, investigate modes of action;
- The discovery, screening, selection and optimisation of candidate pharmaceutical molecules and compounds; and
- The ideation, design and optimisation of medical devices.

Physical prototyping and testing new medical devices can be time-consuming and costly, which limits the number of design iterations that can be studied. On the other hand, virtual models can be generated and modified quickly and tested against multiple conditions over extended periods, optimising designs more confidently before producing physical models for confirmatory studies.

A brief history of CM&S in biomedicine[68]

CM&S has been used in biomedicine since the 1940s. In the past few decades, its use has greatly accelerated in physiology, biochemistry and especially genetics, where there was a dramatic influx of data from human genome sequencing in the 1980s and 1990s. The rapid increase in computer processing power allowed modeling of increasingly complex systems.[57]

CM&S techniques gained momentum in the 1990s and 2000s. At first, the biomedical research community clustered around two distinct applications:

- Mechanistic modelling of human physiology. Based on the published body of biophysical, biochemical and biomedical imaging data, interest initially focused on physiology at the tissue-organ-organism scales. Efforts were coordinated under the Physiome Project,[58] officially launched in 1997 under the auspices of the International Union of Physiological Sciences (IUPS). Several similar projects have launched since, including the European Human Brain Project,[59] its US equivalent, the BRAIN Initiative,[60] and the Living Heart Project[61]
- A systems biology approach to modelling. Based on foundational science, initial interest concentrated on the molecular scale, investigating single cells as complex biochemical systems. This has practical applications in drug discovery.

In 2005, a white paper [62] introduced the Virtual Physiological Human (VPH) concept, bringing these two paradigms together. Inspired by the Physiome Project, it highlighted the critical importance of translating CM&S techniques to the clinical setting, especially for predictions of patient-specific models to support clinical decision-making. This led to the creation of the VPH Institute.[63]

In 2011, Sager et al. published a white paper promoting systems pharmacology, which integrates mechanistic physiology-based pharmacokinetics (PBPK) and pharmacodynamic (PD) modelling with systems biology.

In the same year, in a position paper[64] about the European Commission's proposed Horizon 2020 research framework, the VPH Institute introduced an alternative use for patient-specific models, which the authors referred to as *in silico* clinical trials.

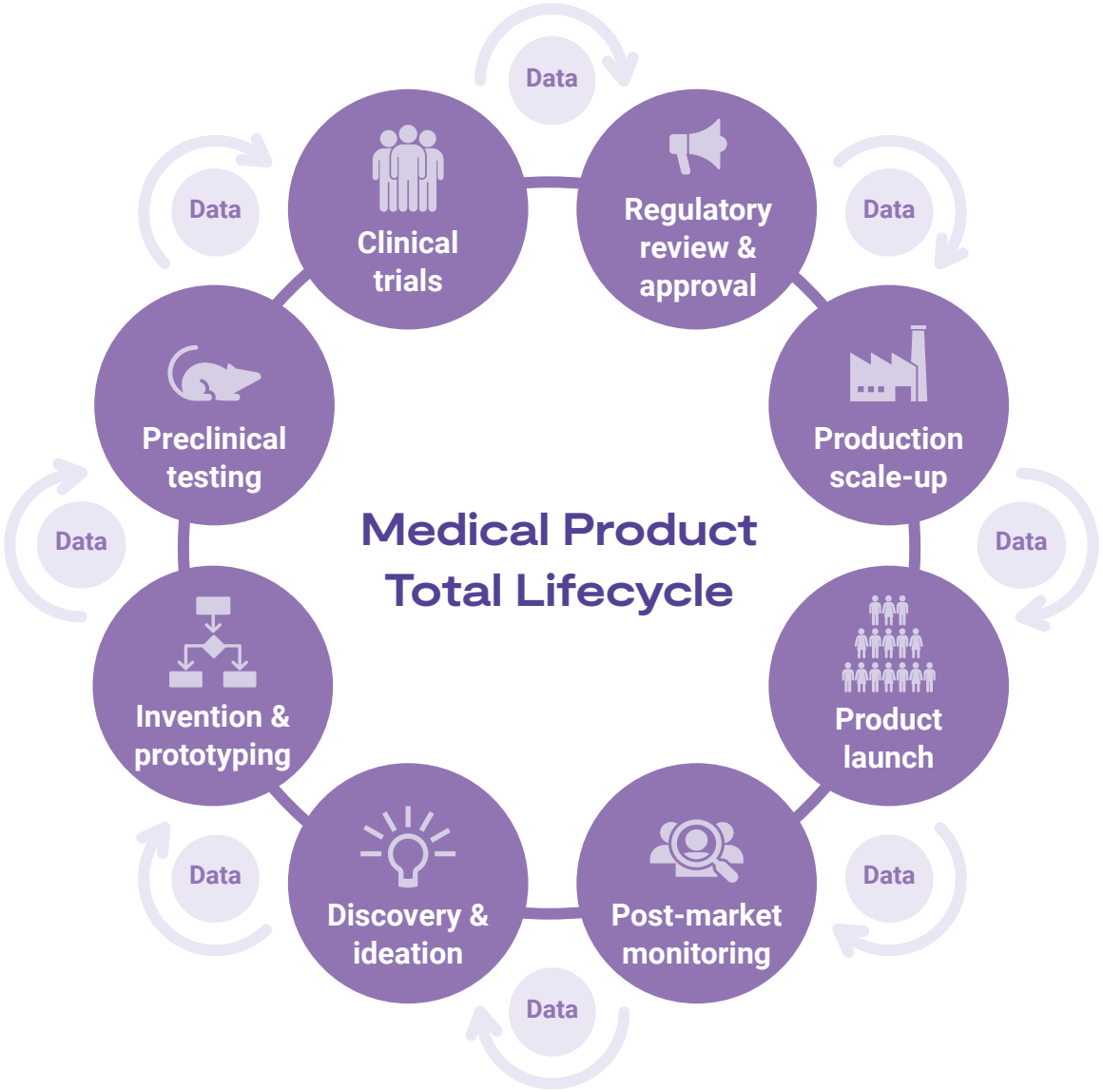
In 2013, academic, industrial and regulatory experts began working to build consensus about the scope of ISTs under the Avicenna[65] banner. The European Commission charged the group with producing a research roadmap[66] for establishing the implementation of ISTs, published in 2016.

Along with similar initiatives (such as those by the Medical Device Innovation Consortium[67] in the US), the Avicenna Alliance's work and roadmap precipitated policy shifts. Between 2015 and 2016, the US Congress and the European Parliament recommended that their respective regulatory agencies enable the inclusion of CM&S results as one of the primary evidence sources in the regulatory process for authorising biomedical products.

This report also deals with applying *in silico* studies to clinical trials as a special case of an IST. The term **'*In silico* clinical trial'** refers to using CM&S techniques to evaluate a medicine or healthcare product's safety, effectiveness and performance using a virtual population of simulated patients in a clinical trial, rather than conducting a trial with actual human subjects.[69] ISTs, as a complement to clinical trials, rely on three computational elements – the product, the targeted physiological system and, sometimes, patients – being simulated digitally and integrated to yield results replicating what might be found using real human subjects. This definition focuses on the techniques' ability to generate credible evidence to satisfy regulators instead of solely using CM&S in internal product development and testing.[70]

'Virtual cohorts' may comprise digital representations of real individuals (i.e. digital twins) or digital 'chimaeras' (i.e. groups of synthetic virtual individuals that together approximately represent variability in the target population).[71]

Altering parameters in the model allows it to be personalised to particular individuals.[72] As well as allowing proper representation of the target distribution, this opens up the long-cherished prospect of personalised (also known as precision or individualised) medicine, which promises to reduce the risk of adverse reactions and unforeseen or undesirable consequences in healthcare. Researchers can then identify and focus on single individuals or sub-populations that will benefit from their products, sparing the expense and side effects of experimenting on those who will not. The Avicenna Alliance[73] describes benefit from a therapy[74], 'The removal of predicted non-responding patients would potentially improve the outcomes of the clinical trials.'[75]


Medical Product
Total Lifecycle
Clinical trials
Regulatory review & approval
Production scale-up
Product launch
Post-market monitoring
Discovery & ideation
Invention & prototyping
Preclinical testing
Data
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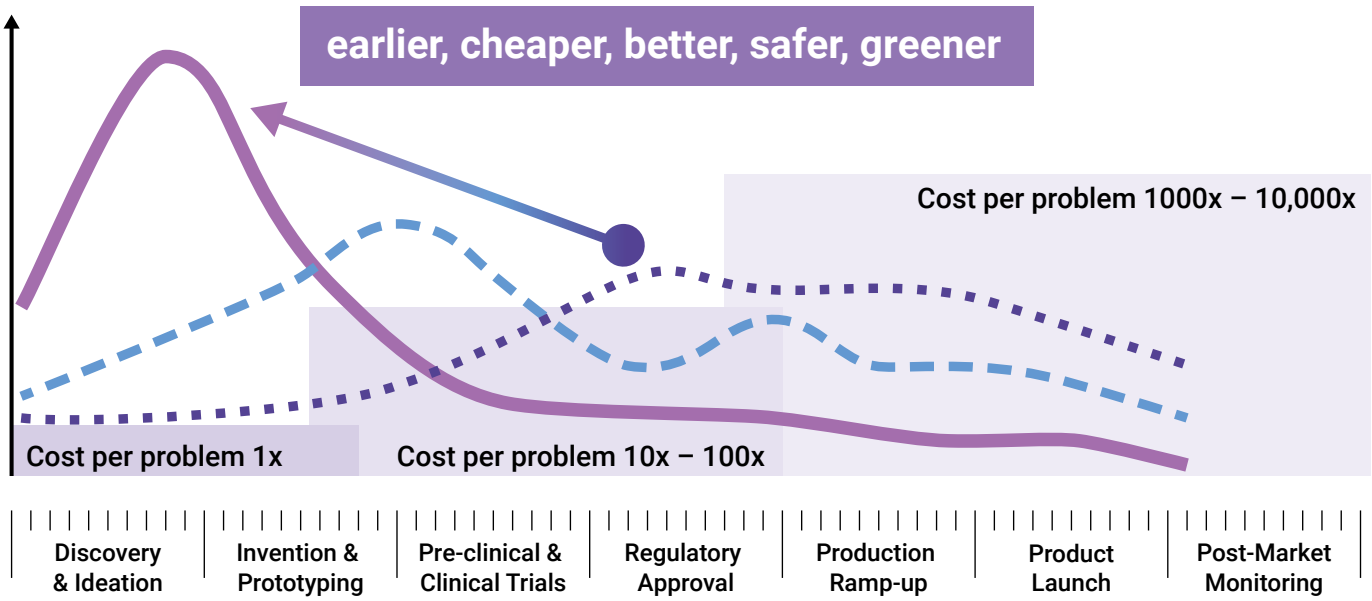
Paradigm Shift *in-silico* evidence for regulatory science & innovation

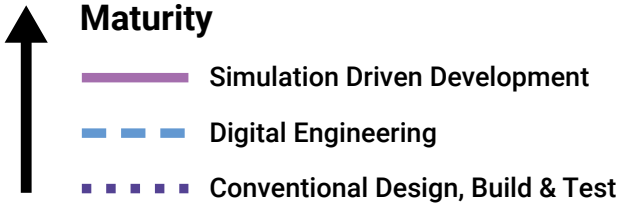
safer, earlier, more sustainable evidence maximising design freedom and robustness

Number of Problems Resolved



Source: Adapted from J Lemon, ITI Global

The use of *in silico* methods can yield better results more quickly and economically.



Computational modelling and simulation (CM&S) use computers to study complex systems by using multiple variables that characterise a system, then adjusting the variables alone or in combination and observing the outcomes.

***In silico* trials (ISTs)** in biomedical science refer to using CM&S to conduct virtual experiments used as surrogates to simulate and predict the outcomes of bench, animal, or human studies.

***In silico* clinical trials (ISCTs)** use CM&S to reduce, refine and partially or completely replace animal and human studies to demonstrate the safety and effectiveness of medical products to satisfy regulatory requirements.

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69 Pappalardo F, Russo G, Tshinanu FM, Viceconti M. *In silico* clinical trials: concepts and early adoptions. Brief Bioinform. 2019 Sep 27;20(5):1699-1708.

70 As a consequence, this report refers to ISTs more narrowly than the Avicenna Alliance Roadmap, which defines an ISTs as 'the use of individualised computer simulation in the development or [our emphasis] regulatory evaluation of a medical product, device, or intervention.' Avicenna Alliance: Avicenna Roadmap. The authors acknowledged the inconsistency but felt that, as the Avicenna Alliance definition is not universally adopted and because the concepts underpinning ISTs are still maturing, the need to focus on the strategic objective outweighed the need for consistency.

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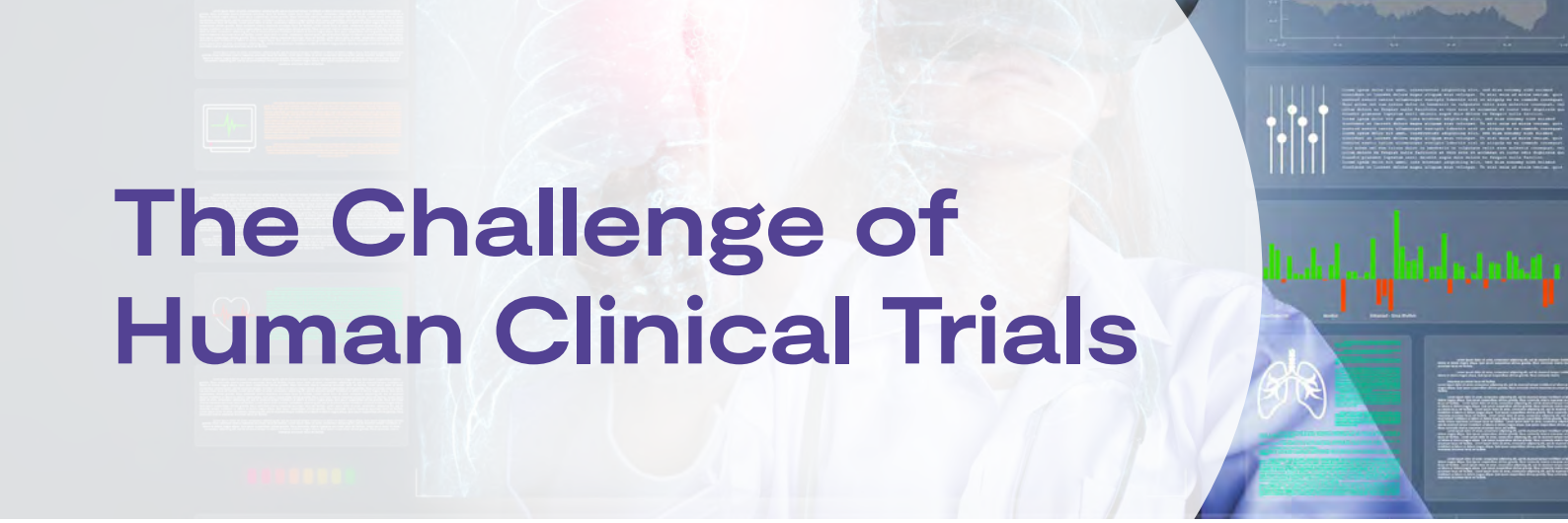


The Challenge of Human Clinical Trials

Many medical products must undergo lengthy and expensive clinical trials to demonstrate their safety and efficacy before gaining regulatory approval and release into medical practice. Clinical trials may recruit hundreds or thousands of subjects evaluated at multiple study sites for months or even years, at the cost of tens or hundreds of millions, even billions of pounds.[76] Failure rates are persistently high and can be extremely costly. Over 30% of drugs entering Phase II studies fail to progress and over 58% fail in Phase III.[77] Because of the limited time and money available to evaluate medical products, even the largest clinical studies do not always adequately predict performance in a large and diverse patient population in real-world conditions. And it is generally considered unethical to include vulnerable populations that will ultimately be exposed to the products in clinical trials, such as pregnant women and children. In some cases, such as with imaging machines or orthopaedic or cardiovascular implants, it is impossible to design the randomised, double-blinded, placebo-controlled studies considered the gold standard.

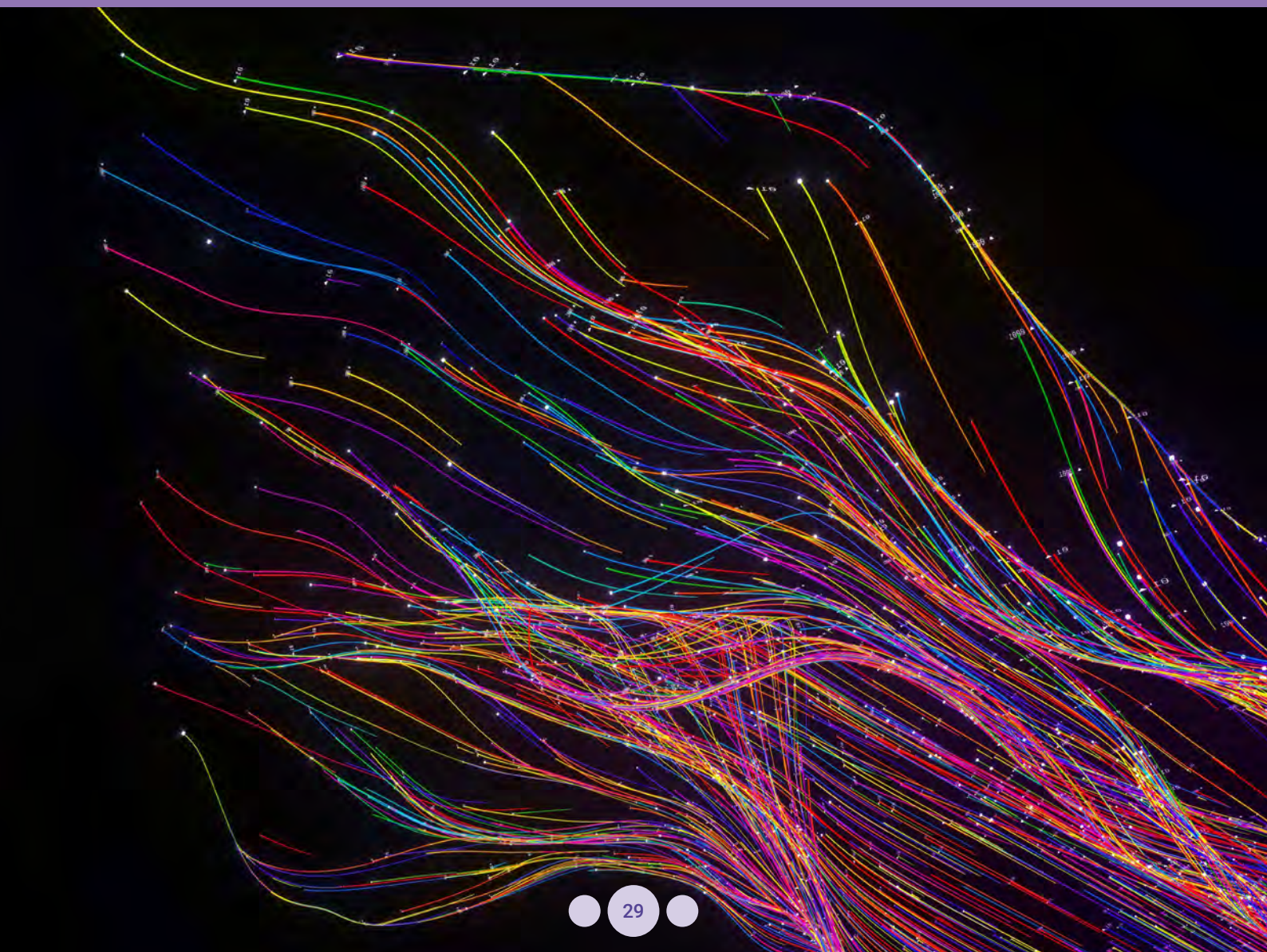
The high cost and risk of medical product development, largely due to the expense and risk of clinical trials, drive up product costs. Not only must products recoup their own development, trial and ongoing production costs, but they must also cover the cost of past failed products and the risk of future unsuccessful ones to yield a profit. One result is expensive medicines and healthcare products that exclude potential beneficiaries who cannot afford them. Moreover, sponsors often neglect rare diseases or short-duration health conditions because products that could address them have comparatively small markets and are not seen as a worthy investment, leaving patients suffering from these conditions without treatments that could be developed if costs were lower.

76 See, for example, (2022) *in silico* Drug Discovery Market: focus on product, workflow, technology and end user. Analysis and Forecast: 2021-2031 by BIS Research

77 Phase I drug clinical trials involve a small number of healthy subjects to test safety; Phase II involve a larger number of subjects with the target condition to test safety, effectiveness and to help determine proper dosage; Phase III are longer trials involving hundreds or thousands of subjects, often randomised against a placebo or currently available treatments.

Weaknesses of human clinical trials

- Very high costs
- Risk of significant harm to human subjects
- Long duration of trials
- Risk of failure (attrition)
- Difficulty of recruiting and retaining subjects and the risk of subjects being lost to follow-up
- Shortage of appropriately skilled researchers and investigators
- Extreme risk-aversion of sponsors
- Regulators' lack of resources and flexibility
- Complexity of the regulatory process
- Informed consent and data privacy concerns
- Risk of biases and lack of consistency in how they are run
- Difficulty of extrapolating meaning from results
- For medical devices, the difficulty of blinding or no placebo arm at all
- The possibility of patients with implanted devices being abandoned after trials

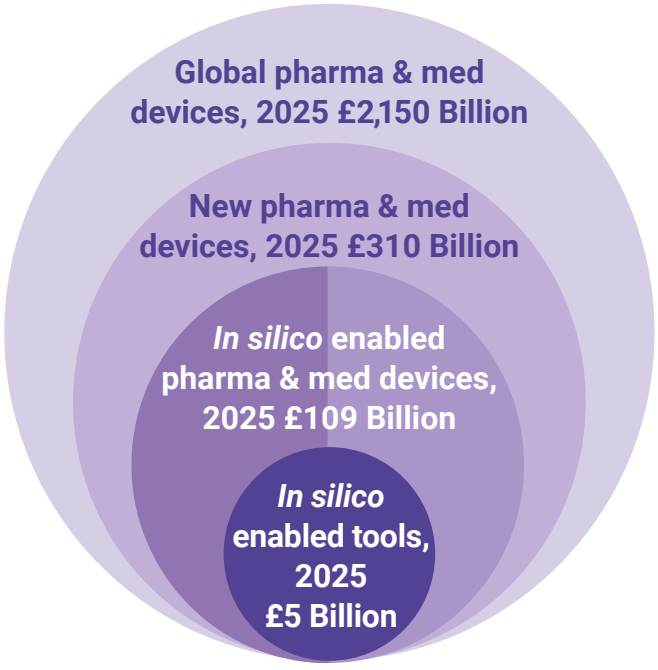


Benefits of *In Silico* Trials

In silico trials employ computational modelling to help evaluate the safety and effectiveness of drugs or medical devices. They can refine clinical trial design to more narrowly define the questions that need to be asked in animal or human clinical studies. They can consequently reduce the number of subjects exposed to the product under development, better targeting the right subjects for a trial and improving the accuracy and reliability of results. Increasingly, with sufficient data and appropriate study design, they can supplement or fully replace *in vivo* clinical studies. Because there are no actual risks to virtual 'patients' *in silico*, studies can include vulnerable populations not normally enrolled in clinical trials, such as children, pregnant women, or patients with comorbidities. They can examine arbitrarily large numbers of subjects over extended periods. *In silico* studies can be very rapid, saving time and money for manufacturers and delivering beneficial new products to patients sooner. They can serve as accelerators for gaining access to investigational medical products for compassionate use. *In silico* modelling can also be used in benefit-risk assessments once a product has come to market. In contrast, cost and bandwidth considerations limit the extent to which human studies are conducted for this purpose.

Obtainable market for the *in Silico* enabled pharmaceuticals and medical devices

- Total addressable market
- Serviceable addressable market
- Pharmaceuticals - Serviceable obtainable market
- Medical devices - Serviceable obtainable market



Source: Frangi, AF, Denison, T, & Lincoln, J. (2023). The Economic Impact of *in silico* Technology on the UK and its Lifesciences Sector. https://doi.org/10.5281/zenodo.7558649

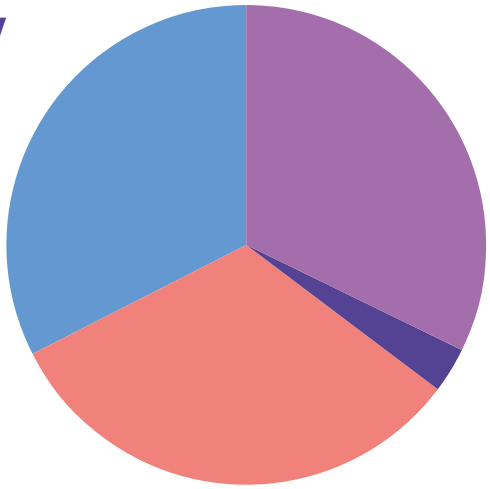
In silico methods (and the derived *in silico* scientific evidence) are predicted to have a major transformative role in increasing pharmaceutical and medical device development efficiencies.

Experts estimate that by 2025, at least 25% of all new pharmaceuticals and 50% of new medical devices will use *in silico* technology at some point in their ideation, design, development, production, regulatory approval or post-market surveillance.

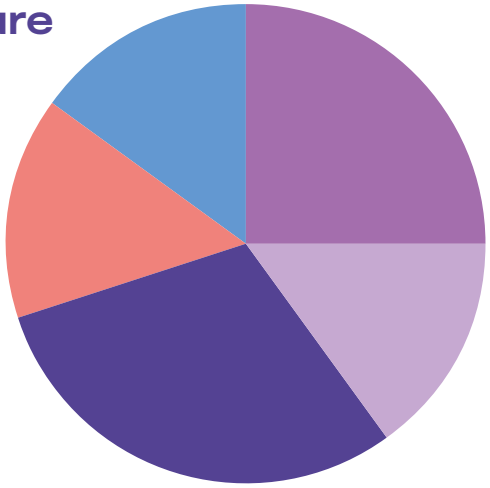
Because new healthcare products are coming to market at an ever-increasing pace, trial efficiency is more important than ever. Medtronic reported using *in silico* methods for the Micra leadless pacemaker exposed 256 fewer human subjects during clinical trials, saved the company $10 million and got the product to market two years earlier. During that time, the device was used to treat 10,000 patients.[78]

Leading global regulatory agencies have steadily, if cautiously, encouraged using *in silico* methods as part of medical product development. '*In silico* trials should be at the core of the EMA 2025 strategy,'[79] according to a presentation on EU regulatory science strategy. The US FDA has endorsed CM&S for over a decade and released guidance documents[80] on using *in silico* data in submissions.

Now



Future



Computational simulations have the potential to reduce reliance on clinical studies on animal and human testing.

- Human
- Animal
- Research
- Computer
- Virtual Patients

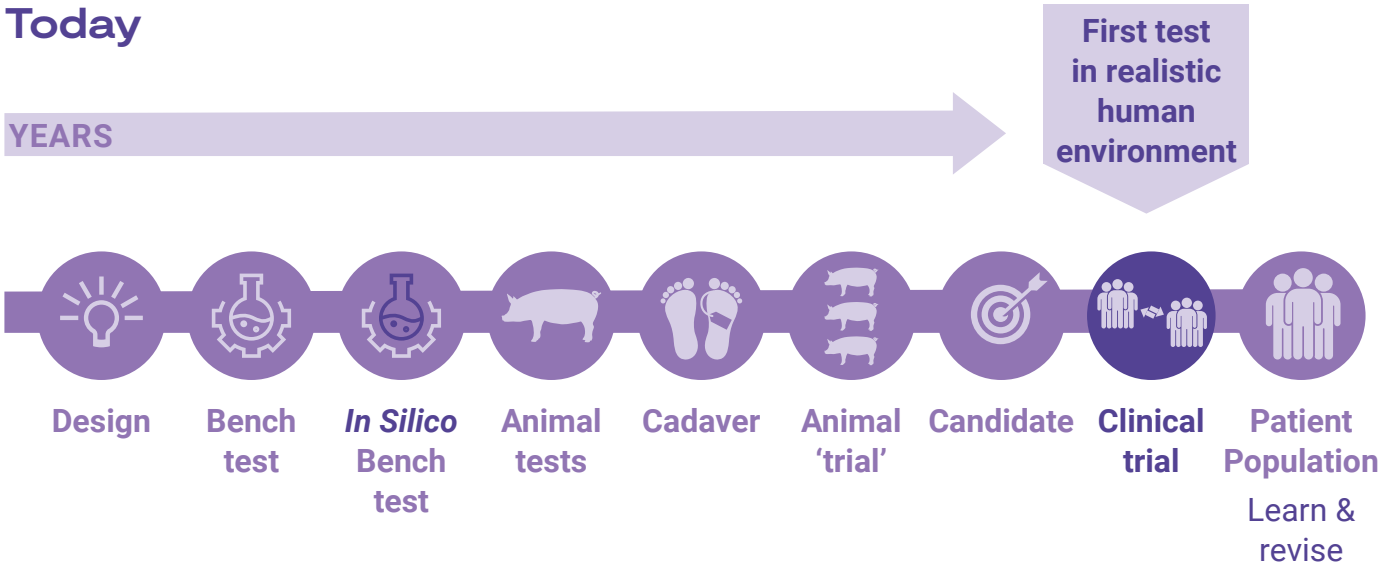
Future Evidence Blend ≈ *f* (Context of use, Model Maturity, Risk involved, Pre-existing evidence etc.)

Adapted from: Medical Device Innovation Consortium (MDIC)
www.mdic.org/event/computational-modeling-simulation

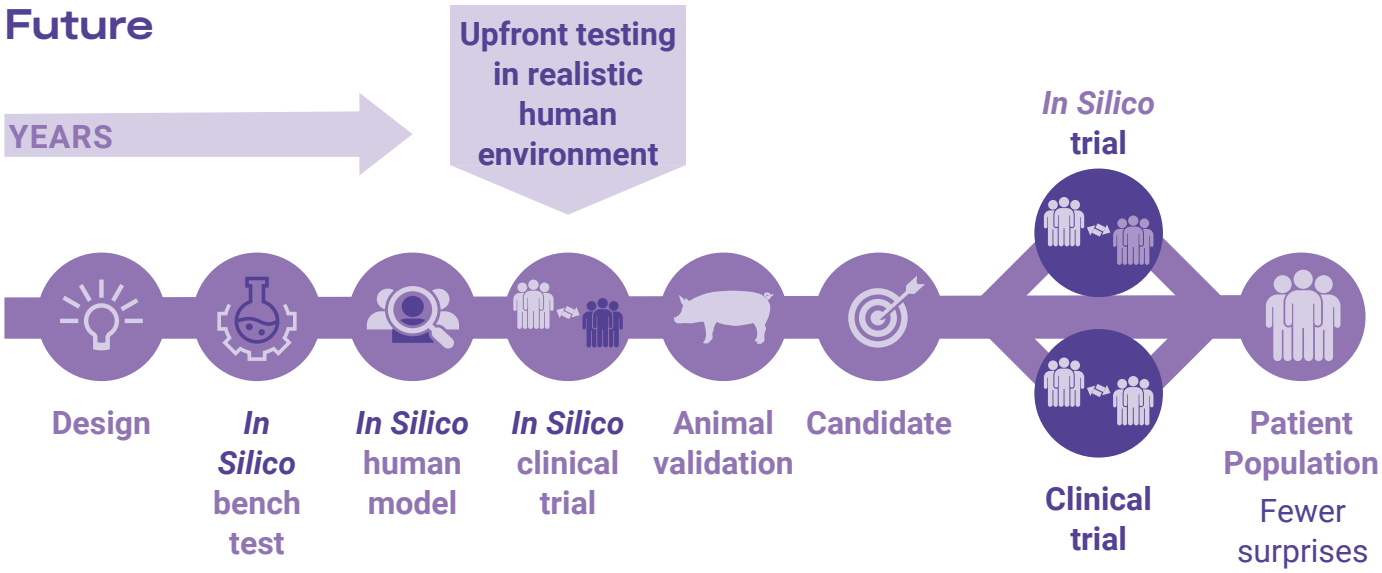
Value proposition for computational modelling & medical devices

Can we go from years to days?

Today



Future



- **Tested in 'human' environment from the start**
- **Digital continuity to speed feedback loop**

- **Less Risk to Patients**
- **Better Patient Outcomes**
- **Fewer Recalls**
- **Better Device Designs**
- **Reduced Time to Market**
- **Reduce R&D Costs**
- **Reduced Animal Harm**
- **Fail Faster and Earlier**

Adapted from a graphic by Dassault Systèmes

Benefits of Replacing Human Subjects with Virtual Subjects

- Reduces, refines and replaces the use of other kinds of experimentation, sparing humans from unnecessary and unethical risk and suffering
- Increases the ability to explain product interactions with anatomy and physiology and any adverse effects
- Enables testing of products that could not ethically be tested in human subjects (e.g. orthopaedic implants)
- Accelerates trials because processes that take a long time using conventional methods can be simulated more quickly
- Reduces the number of human patients, easing the logistical burden of running trials and the risk of patients dropping out
- Makes it possible and ethically safe to study rare and paediatric diseases, and to detect high-impact but low-likelihood adverse events

- Offers better early-stage risk assessment, especially from extreme but plausible (e.g. off-label use) scenarios
- Improves the ability to identify groups at greater risk of adverse events, filter them out early and more accurately target the product to patients with less risk of failure
- Fills in gaps in real trial cohorts to represent variations in the target group
- Facilitates personalised medicine
- Allows the repetition of many more trials than would otherwise be possible, thus improving safety and efficacy and amortising the cost of product development

CM&S techniques used in medical product R&D
Exemplars

Greater experimental flexibility

A trial[81] using 164 virtual patients with 82 distinct anatomies replicated results reported in three previous clinical trials regarding the performance of flow diverters used in treating intracranial aneurysms. The CM&S approach made it possible to investigate the factors affecting flow reduction in ways that are difficult or impossible to ascertain with conventional trials.

Better explanatory power

Experiments into designing a novel hip stem implant using conventional methods could not resolve the unacceptable risk of femoral fractures. The sponsor turned to CM&S techniques to resolve the problem in the design. Statistical shape modelling based on a library of femur CT scans revealed the shape variations present in the representative patient population, pinpointing the cause of the problem in the original implant design. The design was adjusted and the implant was successfully used in over 5,400 hip replacements.[82]

Regulatory-grade evidence

The ENRICHMENT heart simulator system[83] explored the merits of designing and virtually testing a medical device in its end-use environment before building and physically testing prototypes. It also investigated the possibility of using data generated in virtual patients as credible evidence in a regulatory device review. The system uses the device's physics-based computational models, implanted within a cohort of virtual beating heart models, to represent the disease state and other inclusion criteria in a virtual patient population. The system also incorporates clinical information from human subjects to create and confirm these virtual patient models. This CM&S technique was used to develop a device that treats functional mitral regurgitation, which has since been implanted in over 80,000 patients.

Significant cost and time savings

Researchers developed a CM&S technique[84] for simulating the safety and efficacy of devices designed to control Type 1 diabetes mellitus, providing realistic computer simulations of clinical trials based on a virtual population of 300 subjects. The method has been validated against actual clinical data and, in 2008, was accepted by the FDA as a substitute for pre-clinical animal trials in testing certain control strategies for Type 1 diabetes mellitus. This model saved years and millions of dollars in pre-clinical development and testing.

Potential to replace conventional clinical trials

The simulated Virtual Imaging Clinical Trial for Regulatory Evaluation (VICTRE) trial[85] was designed to replicate a clinical trial for breast cancer detection. Images obtained with *in silico* versions of digital mammography and digital breast tomosynthesis systems were interpreted by a computational reader trained to detect the presence of lesions. A total of

2,986 synthetic image-based virtual patients were generated using an analytic approach in which anatomical structures are randomly created within predefined parameters. A positive cohort had a digitally inserted microcalcification cluster or spiculated mass. Unusually, the simulation accounted for the variable diagnostic performance of human radiologists - a far from trivial factor.

The study found an improved lesion detection performance favouring tomosynthesis, replicating the findings of a comparative trial using human patients and radiologists. While further research is needed, these findings suggest that computational simulation tools can, in some cases, be considered viable sources of evidence for the regulatory evaluation of imaging devices in *in silico* imaging trials.

Ethical and cost-effective option to address orphan diseases

A study[86] showed the potential of CM&S technologies in tackling treatments for orphan diseases, which are often neglected because of the challenges associated with the small patient population. An IST was undertaken on patients with congenital pseudarthrosis of the tibia (CPT), a paediatric orphan disease. Investigators generated 200 virtual subjects from an established model of murine bone regeneration. Each virtual subject was simulated to receive both no treatment and bone morphogenetic protein (BMP) treatment. The study showed that the severity of CPT is significantly reduced with BMP treatment, although the effect is highly subject-specific. Using machine learning techniques, the investigators stratified the virtual subject population into four categories - adverse responders, non-responders, responders and asymptomatic – enabling them to distinguish between subjects who would benefit from treatment and those who would not.

Valid virtual populations for drug trials

This study[87] looked at generating virtual populations to investigate two drugs for treating attention-deficit/ hyperactivity disorder - lisdexamfetamine (LDX) and methylphenidate (MPH). It involved three phases:

1. The molecular characterisation of the drugs and pathologies
2. The generation of adult and paediatric virtual populations totalling 2,600 individuals and the creation of physiologically based pharmacokinetic (PBPK) and quantitative systems pharmacology (QSP) models
3. Data analysis with artificial intelligence methods

The features of the study's virtual populations closely agreed with real reference populations extracted from clinical trials. The PBPK models closely agreed with *in vivo* parameters. The mechanisms of action of LDX and MPH were obtained from QSP models combining PBPK modelling of dosing schemes and systems biology-based modelling technology, i.e. therapeutic performance mapping systems.

The authors concluded that the system would yield mechanistic conclusions that could be extrapolated and used for predictions to a certain extent at the clinical level that would help achieve personalised medicine.

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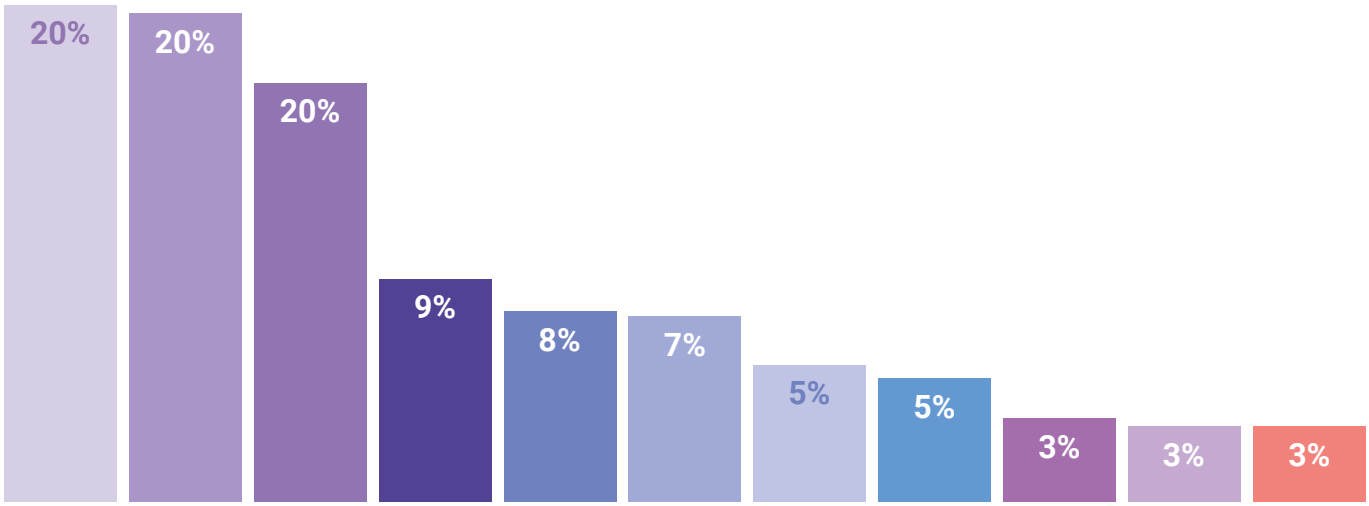
Barriers to Increased Adoption

The pan-sector coalition InSilicoUK surveyed over 200 participants across all sectors (academia, industry, clinicians and regulators) to determine the most significant obstacles to adopting ISTs.

'Regulatory acceptance uncertainty,' 'Scientific maturity and model credibility,' and 'Insufficient CM&S skills, expertise and awareness in regulators' were the top three barriers.

What do you perceive to be the top 5 barriers for *in silico* trial adoption as a source of regulatory evidence?



- CMS/IST Regulatory Acceptance Uncertainty
- CMS Scientific Maturity & Model Credibility
- Insufficient CMS Skills & Expertise/ Awareness in Regulators
- Insufficient CMS Skills & Expertise in Industry
- No relevant CMS & IST UK Standards or Guidelines
- Insufficient Data Availability (e.g. to build Virtual Populations in UK populations)
- Lack of UK Use Case Studies or ISTs Success Stories
- Lack of UK leadership on ISTs for Regulatory Science & Innovation
- ISTs Implementation Costs compared to Conventional Trials
- Return on Investment in Running a CMS Capability
- Insufficient funding for Industry - Academia-NHS collaboration

Adapted from a presentation by Prof AF Frangi at the InSilicoUK Innovation Network Launch Event,[88] InSilicoUK Community Survey #1: Enablers and Barriers.

Regulatory Acceptance

Although the use of CM&S is already widespread in pre-clinical R&D for many new medicines and healthcare products and despite their considerable promise of advantages in all areas of medicine and healthcare, progress is currently hindered by uncertainty about the reliability of digital evidence by regulators.

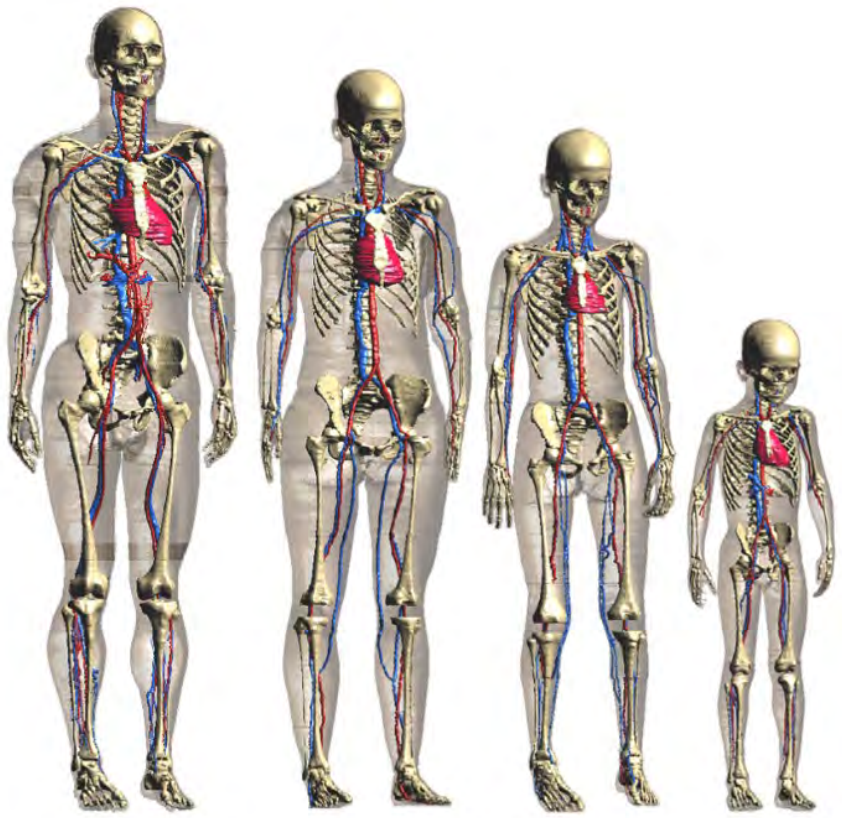
Regulators' reluctance to trust digital evidence is understandable. Estimating and incorporating human diversity is more difficult than in other engineering disciplines, where systems can often be accurately defined. No two humans are alike. Biomedical researchers are therefore tasked with reverse-engineering complex systems composed of disparate elements, with only a partial understanding of their properties or even their functions. This poses challenges in developing confidence in IST results.[89] As the UK Government Office for Science said in its report[90] on computational modelling, 'While models can be powerful assistants in decision-making, they can also be dangerous and misleading if misused and misapplied.' In their duty to protect the public, regulators must ensure that any source of regulatory evidence meets basic scientific requirements (i.e. is verifiable, validated, reliable, applied consistently and trusted by specialists), to the point that, given a choice, a well-informed patient would accept digital evidence on innovative medicines and healthcare products with the same confidence they would accept evidence derived from bench, animal and human trials.

In reality, animal and human study evidence are often as limited and problematic as digital evidence, but, as the saying goes, better the devil you know than the devil you don't know. The public has grown comfortable with conventional clinical studies. As long as regulators fail to hold digital and other sources of evidence to the same standards, developers are disincentivised from investing in the verification, validation, uncertainty quantification, applicability analysis and adequacy assessment needed to satisfy regulator concerns regarding ISTs.[91] With the uncertainty and additional costs involved, this lack of expertise and knowledge on how digital evidence can complement *in vivo* evidence conspires to impede progress.

Scientific Maturity and Model Credibility

An important consideration is the lack of adequate digital anatomical and physiological models for ISTs. Human anatomy, the multi-scale physiological systems that underpin it and the sheer number of variables and factors that influence its expression and affect its functioning (including comorbidities) are extremely complex and will not give up their secrets easily.

Fortunately, the extraordinary increase in computer processing capacity, combined with advances in biomedicine (e.g. in genomics and proteomics) and imaging technology, are rapidly expanding and improving the knowledge base. The aggregation of this data into curated libraries will help its integration with real-world evidence into virtual models on accessible digital platforms. The ultimate expression of this knowledge could be in whole-body models such as the European Commission-funded Virtual Physiological Human[92] (VPH), FDA-supported Virtual Family,[93] and ITIS Foundation Virtual Population.[94]



Source: Virtual Patient Family from Christ A, Kainz W, Hahn EG, Honegger K, Zefferer M, Neufeld E, Rascher W, Janka R, Bautz W, Chen J, Kiefer B, Schmitt P, Hollenbach HP, Shen J, Oberle M, Szczerba D, Kam A, Guag JW, Kuster N. The Virtual Family-development of surface-based anatomical models of two adults and two children for dosimetric simulations. Phys Med Biol. 2010 Jan 21;55(2):N23-38.

The VPH is a methodological and technological platform enabling the collaborative investigation of tissues, organs, subsystems or even the whole human body as a single complex system. The aim is to make it possible to share resources and observations formed by institutions and organisations, creating disparate but integrated computational models of the mechanical, physical and biochemical functions of a living human body.

The Virtual Family consists of four detailed, anatomically correct whole-body models of an adult male, an adult female and two children. They can be used as input to electromagnetic, thermal, acoustic and fluid dynamics simulations for various patient safety scenarios. For example, electromagnetic and thermal simulations have been used to assess the safety of active and passive medical implants in an MRI environment[95] and to evaluate the safety and efficacy of ablation devices.[96]

While it is certainly true that CM&S techniques are only as accurate as the data that underpin them, incomplete or imperfect ones can nonetheless be extremely useful for discrete areas of enquiry, provided the relevant critical variables are adequately simulated. Indeed, simulations are sometimes more easily interpreted and thus more useful if the model is simplified to eliminate irrelevant noise and/or to match the available computer processing power. Thus, while absolutely perfect digital representations of real systems, structures or whole bodies are mostly not yet possible, CM&S techniques are still powerful tools.

Skills Gap

ISTs require new skills at the intersection between biomedicine and data science. A recent Association of the British Pharmaceutical Industry (ABPI) report[97] shows that the perennial difficulty of recruiting people with the right skills in the UK's biopharmaceutical sector is somewhat easing.

Nonetheless, recruiting for disciplines identified as top priorities, many of which require data and digital skills, are of particular concern and require intervention. The skills gap in these areas has been acknowledged as a strategic priority in the UK for many years, a point highlighted in InSilicoUK's first survey of members. Additionally, a 2015 Nesta report[98] found that so-called 'datavores' – data-driven companies – were struggling to find suitable talent, stating that: 'While data may be part of the answer to the UK's productivity gap with other countries, it appears that barriers to accessing analytical talent are preventing businesses from fully harnessing its potential.'

A more recent policy paper[99] from the UK's Department for Digital, Culture, Media & Sport (DCMS) found that the data skills gap persisted. Just under half of businesses struggled to recruit for roles requiring data skills, with supply from the UK's higher education sector unlikely to meet future demand.

More directly related to CM&S skills, the 2018 report from the UK Government Office for Science recommended that the Department for Business, Energy and Industrial Strategy (DSIT), as part of the implementation of the Industrial Strategy, should 'work with UK Research and Innovation, businesses, universities, learned societies and research institutes to consider how to support the skills, research and innovation needed for the UK to remain in the forefront of advanced modelling technologies.'

The UK's National Data Strategy[100] highlights how the challenge is being addressed. For example, the long-term skills pipeline is boosted by a requirement that all post-16 T-Level[101] qualifications need digital skills. The Digital Production T-Level includes content on data, digital analysis and software development. Additionally, the DCMS and Office for Artificial Intelligence (AI) recently funded the Office for Students to support degree conversion courses in data science and AI, including scholarships. This initiative is expected to create 2,500 graduate places.[102]

As positive as these and other moves may be, they are unlikely to supply the skills needed for establishing ISTs in the regulatory process, especially since the competition for advanced computational modelling skills is fierce across many geographies and sectors. The goal of establishing CM&S techniques in biomedicine (and healthcare more generally) will need to pay close attention to this issue, carefully considering routes to up-skilling, the cost-benefit of training and the challenges of recruitment and retention.

Data Integrity

The data used in CM&S and ISTs must be handled carefully to remain complete, consistent and accurate. Data can easily lose their integrity without careful governance and monitoring throughout the R&D process, damaging the validity of the evidence.[103]

In addition to the data generated by CM&S techniques, there is an enormous and growing pool of input data from primary bioscience, biomedical libraries and real-world sources (e.g. electronic medical records, wearables, post-market surveillance studies and population-wide, social media digital signals). Not all of this is digitised or formatted consistently, which limits how easily it can inform ISTs. Though considerable progress is being made in establishing interoperable conventions,[104] e.g. through standards and protocols for marking up and structuring health data so they can be shared and readily used in new applications, the issue remains a significant challenge.

Use of Personal Data

Sharing personal data collected during healthcare or health research is a basic condition for the successful development of personalised medicine and the exploitation of CM&S more generally.

Much of this information sits idle and fragmented beyond reach[105] because of the familiar consent and privacy restrictions from, for example, UNESCO's Universal Declaration on Bioethics and Human Rights.[106] There is substantial literature[107] about the issues raised by biomedical research and how they can be resolved – much of it led by the UK. Consequently, developers must currently consider data protection legislation, which varies from country to country – even in the EU under the General Data Protection Regulation (GDPR).[108]

The considerable potential advantages to the public good from the use of aggregated and anonymised (or pseudonymised) data[109] in digital subjects/patients raises questions about the importance of individual's personal data rights, further muddying the already murky waters of consent, privacy, confidentiality and autonomy that currently constrain the wider use of personal data.[110]

The 2016 Council for International Organizations of Medical Sciences (CIOMS) guidelines[111] offer some clarification, suggesting that consent should anticipate foreseeable plans for future use of the

data in research. Similarly, the European Federation of Pharmaceutical Industries and Associations' forthcoming GDPR Code of Conduct on Clinical Trials and Pharmacovigilance is currently being scrutinised to align key data protection positions in the GDPR with the Clinical Trials Regulation, clarifying matters for the pharmaceutical sector.

One tactic for extending the use of personal data is to circumvent privacy concerns by creating realistic synthetic datasets that capture the statistical properties of the original data, including distributions, non-linear relationships and noise, without including any real patient data.[112] This approach would protect privacy by adding statistically similar information, rather than stripping away unique identifiers, allowing the effect of a medical intervention to be studied on a virtual patient population that closely and accurately reflects the population of interest.[113]

The outcomes of a recent EU-funded project, MyHealthMyData,[114] proposed solving the challenges of sharing big data about health by establishing a so-called 'visiting mode'. Rather than data being physically accessed by third parties, 'algorithms are brought to the data' and only the outcomes of secure computations are released.

Data Security

A corollary of privacy is data security, an issue that concerns all developers and sponsors, especially those developing medical devices that communicate data wirelessly, such as wearables or implants.

The UK enacted the Security of Network and Information Systems Regulations in 2018[115] to establish requirements for the security of essential services, including healthcare. Meanwhile, the industry is trying to manage the risks by developing best practices. The International Medical Device Regulators Forum (IMDRF), of which the UK's Medicines and Healthcare products Regulatory Agency (MHRA) is a member, is currently developing a Medical Device Cybersecurity Guide.[116]

Stakeholder Acceptance

The credibility of evidence produced by CM&S techniques is a central challenge to establishing ISTs. Credibility is the extent to which evidence is verified and validated and, beyond that, trusted to be reliable not only by regulators and sponsors/developers but also by clinicians, insurers, patients and the general public. Regulatory approval does not mean clinicians will begin using the product (even if they knew about it), nor will patients trust it.[117]

The FDA, in collaboration with the Medical Device Innovation Consortium (MDIC), has attempted to bridge the credibility gap using a variety of 'sandboxes' including mock submissions,[118] collaborative workshops to stress-test ideas with stakeholders and 'round-robin' modelling and benchmarking. Their work has been a successful means for gathering input from the industry and FDA about new and innovative approaches for medical device evaluation.

A 2021 report[119] from Axendia contains survey findings about perceived barriers in mainstreaming CM&S techniques in the US medical device sector. As well as reflecting the barriers laid out above, it highlighted the need to publish and disseminate CM&S success stories to familiarise the sector with the techniques' potential and thus accelerate their adoption.

Regulatory Inertia

Instituting the change needed to shift the needle on IST acceptance is likely too slow, with many wrong turns and false dawns. There is considerable inertia in the system blocking progress on ISTs despite their many commercial and public good benefits. Regulatory bodies are typically under-resourced and averse to change. Companies are risk-averse, their business model predicated on business-as-usual regulatory pathways and protecting intellectual property (IP). Both must invest in developing the bandwidth to explore and implement the evolutionary change demanded by establishing ISTs.[120]

Achieving the goal and reaping its rewards will require a determined and focused effort, coordinating activities with an overarching plan. It is particularly important to avoid duplicating and thus wasting efforts and to acknowledge and respectfully accommodate all stakeholders' sensitivities and particular concerns.

Regulators need assurance that evidence produced in novel ways is safe, reliable and robust, preferably codified in widely adopted standards. To help develop this assurance, commercial partners must share ideas confidentially – perhaps with the protection of 'safe harbours' and 'sandboxes' – without fear for their IP. Plans need to coordinate the work of researchers and investigators and involve the clinicians who will one day have to decide whether to trust medicines and healthcare products assessed in ISTs.

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Market Readiness

Despite the obstacles outlined above, pressure from global regulators, animal rights activists and industry and the growing economic burdens of healthcare all contribute to the need for IST. The research community has responded, supported by critical government funding that has led to credible solutions slowly being adopted by industry. During the COVID-19 pandemic, lockdown restrictions made it difficult or impossible to conduct human clinical trials. This encouraged regulators and industry sponsors to consider alternative approaches, including ISTs, for generating safety and effectiveness evidence to support market approval of new medical products.[121] Large pharmaceutical companies are reportedly increasingly adopting and promoting their use, adding pressure to formalise and standardise ISTs.[122] In December of 2022, the FDA Modernization Act 2.0[123] lifted the requirement for animal testing prior to human studies, opening the door to other forms of evidence supporting safety and efficacy in humans.

This has sparked industry growth, reflected in market predictions for products developed with CM&S techniques. According to InSilicoUK research that extrapolated data from several published forecasts[124] and combined with it InSilicoUK's survey results, the global market for medicines and healthcare products will grow at 16% per annum. New pharmaceutical drugs will make up 43% of this market and medical devices 57%.

CM&S techniques are already a key innovation enabler for the pharmaceutical and medical devices markets, sized at $1,260 billion and $425 billion, respectively, in 2020. This market is forecast to grow to $1,600 and $550 billion, respectively, by 2025, with, in addition, a similar growth trend in the in-house development of CM&S capability. Experts predict that by 2025, 25% of all new pharmaceuticals and 50% of all new medical devices will use CM&S techniques at some point in their development and approval. Specifically, InSilicoUK survey respondents predicted that CM&S techniques would enable the following:

- Average drug and medical device development costs are to be reduced by up to 40%, rising to 60% by 2030; and
- 30% more medicines and healthcare products to be brought to market annually by 2025 using CM&S techniques.

Meanwhile, rapid advances in raw computer processing power, graphics processing units and other aspects of digital technology have facilitated the building of higher fidelity models with greater complexity and improved robustness and enhanced visualisation. These models leverage advances in foundational areas of science, such as genomics, proteomics, medical imaging and diagnostics, which further contribute to the accuracy and completeness of models. Most importantly, however, have been the efforts of global regulatory agencies, standards bodies and other academic, industry and stakeholder organisations to encourage this progress.

The global market for tools and services enabling CM&S was $2.7 billion in 2020, forecast to rise to $5 billion by 2025 and $9.2 billion by 2030. The consensus value used here for the CM&S tools and services market supporting pharmaceutical and medical device development is within the optimistic scenario given by BIS Research for CM&S tools and services used in drug discovery alone. Assuming that CM&S tools and services will be applied 60:40 between drug discovery and medical devices, this implies a potential upside market for CM&S tools of up to $15 billion by 2030. (Note that this does not account for the value of CM&S tools and services developed internally (i.e. not marketed but used to develop new medicines and healthcare products in-house). For example, the UK's Exscientia[125] can develop 25 new drug candidates with a workforce of just 210 people.)

The research assumes that the financial benefit of CM&S is in making development much more efficient and with a higher chance of clinical success, which makes it possible to bring more products to market per year. In theory, the step-change in development productivity enables much greater security in the life science sector by spreading new product income among a greater variety of products, size of companies and total cost to develop. It should also broaden the scope of treatable conditions with a more diverse range of medications and medical devices, tailored to individual needs, yielding a significant positive dividend for society.

In Silico Testing and Trials Success Stories

1. **Cardiac arrythmia** risk estimation based on cell and animal experiments is limited to examining one ion channel at a time. Electrophysiology CM&S permits the integration of data from multiple ion channels to better estimate the chance of adverse side effects after treatment. This online simulator has been utilised by more than 140 companies to carry out drug safety testing.
   See Annex A: Case Study 1

2. The **Virtual Assay** Software builds on multiple electromechanical cellular models to evaluate arrhythmia risk. This population-level modelling approach accounts for the drug dose-dependent response of humans with different age, sex and genetic background. The European Medicines Agency and the FDA expressed their interest in this model which estimates arrhythmia risk more accurately than animal tests.
   See Annex A: Case Study 2

3. **Catheter ablation** therapy scars the heart tissue to treat atrial fibrillation. Here, a novel organ-scale computational and statistical modelling pipeline is presented describing ablation and estimating atrial fibrillation recurrence. This approach combines modelling with patient records including imaging to provide long-term treatment outcome estimation with superior accuracy compared to previous methods.
   See Annex A: Case Study 3

4. Researchers demonstrated that an organ-scale computational **electrophysiology** model is suitable to evaluate heart failure patients' responses to different cardiac resynchronisation therapies. Standard biventricular pacing and conduction system pacing are compared. The results provided a mechanistic explanation for optimal pacing delivery, laying the foundation for future *in silico* trials of pacemakers.
   See Annex A: Case Study 4

5. The FD-PASS trial simulated the treatment of **intracranial aneurysms** in 164 virtual patients accounting for stenting and thrombus formation. The results accurately replicated findings from previously published clinical trials and offered additional information about populations more likely to experience device failure that would not usually be available from clinical trials.
   See Annex A: Case Study 5

6. The INSIST *in silico* trial environment describes the key processes involved in **acute ischaemic stroke** treatments: thrombolysis and thrombectomy. Blood flow, tissue perfusion, infarct formation and treatment simulations are combined with a statistical model for patient outcome estimation. The results demonstrate that simulations can estimate the efficacy of stent retrievers and blood thinners.
   See Annex A: Case Study 6

7. OM Pharma, developing a prophylactic treatment for **respiratory tract infections**, used an *in silico* model delivered by Novadiscovery to calculate the most effective trial strategy to generate valid clinical evidence under the pandemic conditions. The corresponding model describes within-host disease mechanisms, between-host infections and treatments to mitigate clinical trial risks in populations suffering from COVID-19.
   See Annex A: Case Study 7

8. **Parastomal herniation** is a common source of postoperative morbidity after abdominal surgery. Developing effective prevention methods is hampered by a lack of knowledge about the mechanisms undermining tissue integrity. Biomechanical simulations of the abdominal wall suggest that incision shape and mesh design have a major impact on hernia formation and progression.
   See Annex A: Case Study 8

9. The friction and lubrication between **hip implant** parts and bones play an important role in the clinical failure of the employed devices. This study describes a model of a standardised experimental friction test required for efficacy estimation before clinical trials. Computational predictions agreed with experiments and thus it is anticipated that computational models will assist in future implant development.
   See Annex A: Case Study 9

10. **Knee osteoarthritis** impacts about 20% of the population and causes suffering due to the underlying bone-on-bone contact. The TOKA *in silico* trial evaluated personalised versus generic high tibial osteotomy stabilisation plates based on biomechanical simulations. The resulting simulations contributed to designing two clinical trials approved by the UK MHRA and an Italian regulator.
    See Annex A: Case Study 10

11. **Craniosynostosis** is a birth defect in which the bones in a baby's skull merge too early. Researchers employed a biomechanical computational framework validated based on animal data to quantify the interactions that directly shape human skull growth and bone formation after birth. The results highlight various treatment options to recover normal skull growth in craniosynostosis, a condition caused by early fusion of cranial joints causing unusual head shape.
    See Annex A: Case Study 11

12. Zimmer Biomet developed a **shoulder replacement** simulator to assess the risk of post-surgery notching based on measurable geometric features. *In silico* trials replicated former clinical findings. Furthermore, simulations enabled direct patient-specific assessment of the impact of implant position and bone resection on the range of motion, adding mechanistic insights to clinical observations.
    See Annex A: Case Study 12

Growing Regulatory Recognition

Efforts by biomedical research and industry communities to promote ISTs are being heard. The European Parliament and the United States Congress have recommended that their respective regulators allow wider use of modelling and simulation within the regulatory process.[126] The FDA and the European Medicines Agency (EMA) have prepared the ground with pilot programmes and guidance and contributed to standards development. However, the evolving situation is far from straightforward for medical product companies operating in global markets.

Regulatory pathways vary depending on the medical product and the geographic region. Medicines and healthcare products must meet different thresholds for regulatory approval – the precautionary principle for medicines and proportionality for devices. Companies are therefore faced with the challenge that what works in one jurisdiction may not work in another, which often encourages them to default to the most universally accepted approach: relying completely on human clinical trials.

As Europe gets used to the new Clinical Trials Regulation[127] and the UK confronts its future outside of that regime with the Medicines and Medical Devices Act 2021,[128] international agreement on how to settle these questions to enable the full potential of CM&S and ISTs techniques' potential – backed by workable and harmonised regulations – will be an important milestone.

United States

The US Food and Drug Administration (FDA) has taken the lead in adopting ISTs. Its mission is to keep people safe and advance public health by helping to speed up innovation. Part of their strategy for doing so is to break down operational silos and transform science into digestible outputs that can be used to support the regulatory process. They have developed tools and approaches to assess safety, performance, efficacy and quality. In the context of ISTs, they have been involved in developing the American Society of Mechanical Engineers (ASME) Verification and Validation (V&V) 40:2018 standard[129] and various FDA guidance documents.[130]

FDA strategic priorities are organised into what they call 'focus areas of regulatory science'.[131] Under five broad priority targets – paediatrics, women's health, minority health, diverse groups and rare diseases – they have established four cross-cutting initiatives:

1. Public health preparedness and response
2. Increasing choice and competition through innovation
3. Unleashing the power of data
4. Empowering patients and consumers

Initiatives 2 and 3 are most relevant to ISTs, with the following topics nested under them:

- Individualised therapeutics and precision medicine
- Complex, innovative trial design
- Product development tools (biomarkers, novel technologies to improve predictability of pre-clinical studies and replace, reduce and refine reliance on animal testing)
- Model-informed product development
- Artificial intelligence
- Digital health
- Use of real-world evidence to support medical product development and regulatory decision-making

A subdivision of the FDA, the Office of Regulatory Science and Innovation (ORSI),[132] was established in 2010 to foster the creation and use of innovative tools to support the scientific foundation for regulating products and emerging science and technologies. They deploy creative collaborations to harness the best science through twelve scientific working groups, a funding scheme with annual calls, an intramural grants programme and four Centres of Excellence in Regulatory Science and Innovation (CERSI),[133] funded on five-year grant cycles with selected academic institutions.

The FDA is proactively promoting CM&S techniques in medical product R&D by offering guidance on how evidence from these methods can be used in the regulatory process. In 2010 it published guidance for using Bayesian statistics in clinical studies for medical devices[134] and, in 2016, guidance on how to report computational modelling studies in medical device submissions. [135]

While this latter guide explains how to report evidence from CM&S techniques, it does not comment on the adequacy of such evidence. For that, the FDA supported the development of the American Society of Mechanical Engineers' (ASME) V&V40:2018 standard (see figure below for their evidentiary framework), which provides best practices in developing and evaluating *in silico* models for medical devices.

Model Credibility

The Validation & Verification[40] risk-informed credibility assessment framework

This generic structure that can be used in standardising other verification and validation procedures.

COU = Context of Use

V&V = Verification and Validation

Adapted from: Parvinian B, Pathmanathan P, Daluwatte C, Yaghouby F, Gray RA, Weininger S, Morrison TM, Scully CG. Credibility Evidence for Computational Patient Models Used in the Development of Physiological Closed-Loop Controlled Devices for Critical Care Medicine. Front Physiol. 2019 Mar 26;10:220.

In 2018 the FDA launched a Model-Informed Drug Development Pilot Program (MIDD)[136] to examine ways to verify and validate CM&S techniques in pharmaceutical development.[137] The Agency's Model-Informed Drug Development Paired Meeting Pilot Program[138] funds studies to determine whether *in silico* methods can reproduce traditional results. This approach is yielding encouraging results and giving hope that MIDD approaches in drug development could be adopted as routine.

Ultimately, the FDA hopes to establish an overarching framework to standardise regulatory evaluation across therapeutic medicines and healthcare products (i.e. drugs, medical devices and hybrids).[139] However, despite several FDA documents listing 'computational modelling' as one of four forms of accepted science-based regulatory evidence (the others being bench, *in vitro* and *in vivo*), formally approved guidance has not yet been adopted into the regulatory process.[140]

European Union

For many years, the European Medicines Agency (EMA) has been interested in CM&S applications in medical product R&D, including ISTs. In 2015 they produced guidelines for Model-Informed Drug Discovery and Development (MID3)[141] that describe the quantitative framework for predicting and extrapolating 'models' conclusions. It proposed that models can be categorised into different impact levels based on the relevance of the conclusions to guide industry decision-making and regulatory assessment:

- **Low impact,** when evidence cannot be directly used to make clinical or commercial decisions
- **Medium impact** for models that usefully inform future trial design (e.g. to determine optimal dosing, target population, sample size, design of future trials, or study of mechanisms of action)
- **High impact,** where conclusions support decision-making without additional experimental or trial studies (e.g. simulations replacing direct clinical trial data in children or oncologic patients that provide evidence on efficacy and safety to uphold regulatory submission and labelling)

The EMA's strategy for 2025 is to optimise capabilities in modelling, simulation and extrapolation and to exploit digital technology and AI in decision-making,[142] and have proposed an overarching risk-based framework for doing so.[143] EMA has responsibilities for certain categories of medical devices and in these instances, the EU regulation 2017/745 for medical devices could be applicable.

The EU Medical Device Regulations[144] (EU MDR) define clinical investigations as systematic investigations involving human subjects. Therefore, despite the plans and initiatives, data from CM&S techniques cannot currently be accepted as a substitute for *in vivo* clinical data. However, this data can be considered pre-clinical data or a model for comparison for long-term data collection, for example, when predicting the lifetime or outcome of a medical device. The regulation states that 'the results of biophysical or modelling research, the validity of which has been demonstrated beforehand[145] may be considered regarding device design and manufacturing requirements. This emphasises the importance of ensuring that models and simulation outputs are credible. This reasonable requirement is hindered by a lack of standardisation that would define what good CM&S techniques should look like. For example, there is little available information on what evidence has been accepted by the conformity assessment bodies (in Europe, the 'notified bodies') responsible for evaluating product safety and performance before marketing authorisation in Europe. Most existing European guidelines and recommendations focus on very specific products and modelling technologies rather than offering general direction, leaving industry and regulators with no agreed-upon set of rules for applying ISTs.

Rest of the World

Other countries are exploring the potential of ISTs. China's National Medical Product Agency (NMPA) established the Center for Drug Evaluation in 2016.[146] The NMPA has expressed interest in the potential role of *in silico* methods and has conducted training on the ASME V&V 40:2018 standard,[147] but it is difficult to find current regulatory documentation on the acceptability of digital evidence.

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) began to receive digital data in new drug applications in 2016.[148] The Ministry of Economy, Trade and Industry and the Japan Agency for Medical Research recently issued guidelines for developing *in silico* evaluations. Still, these methods are not yet utilised for new drug or device approvals.

South Korea's Ministry of Food and Drug Safety (MFDS) accepts digital evidence and supports model-informed drug development.[149]

Other countries worldwide are discussing *in silico* drug and medical device development methods. At this stage, they are watching the regulatory status in the US and EU before implementing their own changes. The Avicenna Alliance has begun advocacy efforts in Brazil, the Kingdom of Saudi Arabia and within the Global Harmonization Working Party (GHWP)

United Kingdom

Compared to the US and EU, the UK has until now been less directly focused on ISTs, though the methods are the subject of research effort. For example, the UK Government's second Life Sciences Sector Deal[150] announced in December 2018, recognised the value of CM&S techniques in biomedicine by supporting Roche's £30m collaboration with the Christie NHS Foundation Trust to use big data to accelerate trials for treating rare cancers.

Small manufacturers make up 90% of the UK HealthTech sector, who are often confounded by the EU and UK regulatory systems and seek a more favourable regulatory environment in the US. Brexit offers the opportunity to create a more agile and innovation-friendly regulatory system that will first encourage evidence development and product introduction in the UK. Because of the advantages of *in silico* methods, the InSilicoUK Innovation Network held a March 2022 kick-off event[151] to promote their adoption as a complementary route to provide regulatory evidence.

Standards Developing Organisations

It is possible to overcome this unevenness by producing robust international standards. Consensus standards are recommendations or best practices created by expert organisations that describe consensus best practices for bench testing, manufacturing and even CM&S. In the medical device sector, many standards are developed and published by organisations such as the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). Standards do not have legal or regulatory authority in themselves but are often recognised by regulatory agencies and then used by the industry to support claims of conformity to regulatory requirements. In the UK and Europe, over 250 standards provide a presumption of conformity to respective national and European regulations. The FDA recognises over 1,400 national and global medical device consensus standards[152] accepted in submissions following manufacturers' declarations of conformity.[153] The global standard for clinical investigation of medical devices, ISO 14155:2020,[154] addresses good practices for human subjects but does not currently allow for ISTs.

The variety of products, regions, approval thresholds and types of CM&S techniques make it unlikely that one standard can fit all use cases. Even so, it is helpful if standards have a 'family resemblance' underpinned by overarching principles and if stakeholders define best practices to help overcome the barriers to their use. The Committee on Credible Practice of Modelling and Simulation in Healthcare,[155] an interdisciplinary group seeded by a US governmental interagency initiative, has worked to codify best practices[156] by establishing ten generic rules for CM&S in healthcare:

1. Define the context clearly
2. Use contextually appropriate data
3. Evaluate within context
4. List limitations explicitly
5. Use version control
6. Document appropriately
7. Disseminate broadly
8. Get independent reviews
9. Test competing implementations
10. Conform to standards.

To date, the generic standard that offers the most hope is the American Society of Mechanical Engineers (ASME) Assessing Credibility of Computational Modeling through Verification & Validation: Application to medical devices (V&V 40 - 2018),[157] which 'provides procedures for assessing and quantifying the accuracy and credibility of computational modelling and simulation' for regulatory decision-making, overcoming the challenges of variety and complexity by prescribing governing principles rather than precise methods and recommending that researchers collaborate with regulatory bodies to agree on details at the earliest opportunity. Developed in collaboration with the FDA for application in the US, V&V 40 and other relevant standards are being scrutinised by the *In Silico* World Consortium[158] (which comprises experts from six European countries and the US) to assess the extent to which they are applicable in European regulatory jurisdictions and R&D context.[159]

Both of the documents mentioned above apply only to medical devices. The development of standards covering CM&S techniques for medicines and healthcare products, including drugs, is far less advanced.

Other Stakeholder Organisations and Initiatives

In addition to the efforts of regulators and standards organisations to establish regulatory frameworks and best practices, organisations such as the Medical Device Innovation Consortium (MDIC), the Avicenna Alliance and *In Silico* World are working towards improved anatomical and physiological models that can be used in product development, testing and *in silico* trials.

The MDIC, a US government-funded interface between the FDA and industry, is developing the virtual patient (VP) model.[160] Their framework creates the potential for smaller, shorter, more cost-efficient clinical trials of medical devices using Bayesian methods to incorporate prior knowledge into simulations to allow adaptive trials. Their working group has conducted retrospective clinical trial case studies leveraging the VP Model. This working group developed and launched several methods, tools and resources to facilitate VP Model implementation and has released the VP Model's code in R,[161] a free public repository for statistical code.

The use of Virtual Patients (VP) has the potential to revolutionise how medical device companies conduct clinical trials

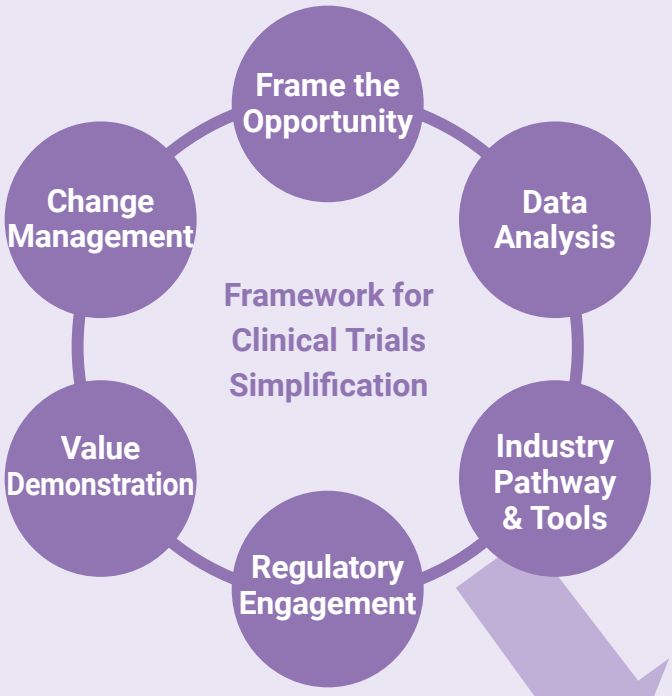
VP model opportunity

- Clinical trials have long struggled to enroll the needed number of patients in the right amount of time
- Apply virtual patients (VP)s to positively impact clinical trial costs, timelines and data quality
- Sponsors and regulators need scientific confidence in newer approaches for acceptance

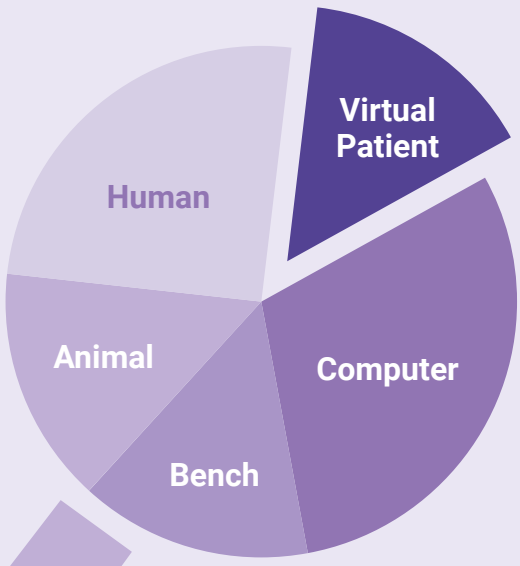
VP Project Approaches:

- Apply VP Retrospectively: Identify therapeutic areas and products conducive to the new approach
- Apply VP Prospectively: Sponsor submissions to FDA of clinical trial plans leveraging VP science

Clinical Trial Innovation & Reform (CTIR)



Computer Modelling & Simulation (CM&S)



Application of Clinical Trial Practises (ACTP)

- Pivotal trials
- Post-market data
- Reimbursement

Adapted from: Medical Device Innovation Consortium (MDIC) Virtual Patient (VP) Model

The Avicenna Alliance, a global non-profit organisation, is lobbying for the development of ISTs.[162] The Alliance was established after a two-year EU-funded project to produce a research and technological development roadmap[163] outlining a strategy for ISTs. It strives to make '*in silico* medicine standard practice in healthcare through a collaborative ecosystem of patients, clinicians, academics, industries, policymakers, regulators and payers.' Its goal is 'to significantly accelerate medical innovation and its practical implementation, to ensure safe, affordable and cost-effective healthcare through the large-scale adoption of *in silico* medicine.'

InSilicoWorld, funded through the European Commission's Horizon 2020 programme,[164] aims to accelerate the uptake of CM&S technologies used for the development and regulatory assessment of medicines and medical devices by lowering seven barriers: development, validation, accreditation, optimisation, exploitation, information and training. One of its key outputs will be a 'Good Simulation Practice' guide.[165]

The European Commission's upcoming ninth framework programme, Horizon Europe,[166] targets the health 'cluster', whose targets include 'digital solutions for health and care, including personalised medicine.' For the first time, it is organising moonshot 'missions', one of which addresses cancer. To get properly underway, the cancer mission implementation plan mentions opportunities in the fields of cloud computing and digital applications, including 'the integration of AI, machine learning and deep learning approaches to facilitate a better understanding of cancer, to improve prevention screening and early detection, diagnosis, clinical decision-making, administration of combinational therapies and clinical management of patients living with and after cancer.'[167] A fully functioning IST system would help such initiatives.

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The UK Landscape for Developing ISTs

With a confluence of global drivers pushing the adoption of ISTs to a tipping point, there is an opportunity to accelerate their development by breaking the remaining deadlock. Establishing internationally agreed protocols and standards for accepting ISTs can open the floodgates to faster, more efficient, safer and more affordable medicines and healthcare products and therapeutics and, indeed, improvements in the prevention, diagnosis and management of ill health.

The members of the InSilicoUK Innovation Network believe that the UK is well-positioned to seize this opportunity. The increased development and use of ISTs in the UK can benefit patients and the NHS and has the potential to boost the UK's economy with inward investment by building on the country's expertise in clinical trials, which can create new jobs and bolster valuable export sales for new IST tools and services.

The life sciences sector is valuable to the British economy. From 2016 to 2019, clinical research supported by the National Institute for Health Research (NIHR)[168] generated an estimated £8 billion of gross value added and supported over 47,000 full-time equivalent jobs across the UK. For every £1 the government spends on research and development via NIHR, the country generates over £19 in total economic returns – the highest return on investment for any public service.

By 2025, it is predicted that 100,000 people in the UK life sciences sector will be working with *in silico* technology daily. This is equivalent to 40% of all the people employed in the biopharma and med-tech sectors in the UK.[169]

Demand from medical device and pharma developers will grow the open market for *in silico* software tools and services to $5.0 billion globally by 2025 and $9.2 billion by 2030,[170, 171, 172, 173] with the UK share of this being at least 5%. This will form a key part of the global $110 billion market[174] for drug discovery technologies in 2025.

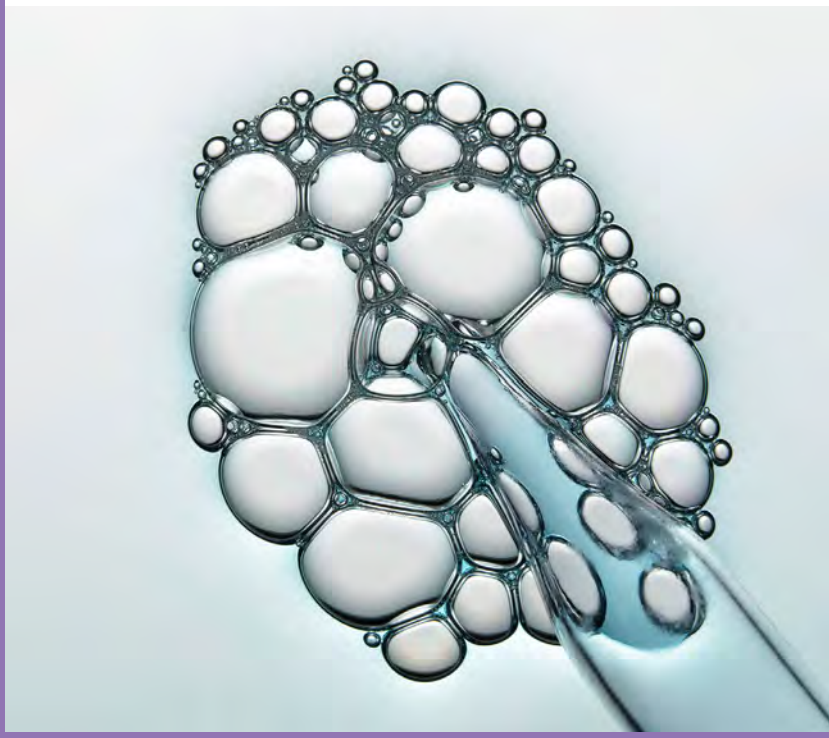
The economic impact of *in silico* methods is large and growing:

- **In 2025, there will be a $109 billion global market for medicines and medical devices developed with *in silico* methods, growing at 15% CAGR;**
- **By 2025, 25% of new pharmaceuticals and 50% of new medical devices will utilise *in silico* technology in their R&D life cycle;**
- **By 2025, *in silico* methods will enable 30% more new drugs and 30% more new medical devices to be brought to market annually;**
- **By 2030, *in silico* methods will enable 60% more new drugs and 30% more new medical devices to be brought to market annually;**
- **Demand from medical product developers will grow the market for *in silico* software tools and services to $5 billion globally by 2025 and $9.2 billion by 2030;**
- ***In silico* technologies will be critical to the future of the 111,200 directly employed by 2,010 UK drug and device companies;**
- **By 2025, at least £2.6 billion worth of drugs and medical devices developed with *in silico* methods will be made in the UK;**
- **By 2025, the UK will export at least £800 million worth of drugs developed using *in silico* methods annually.**

The UK Government's Innovation Strategy,[175] R&D Roadmap,[176] Taskforce on Innovation, Growth and Regulatory Reform Report (TIGRR),[177] and policy on clinical research[178] all target the UK's NHS and world-leading £ 88.9 billion life sciences sector as significant levers for building back better as we recover from the COVID-19 pandemic and realign the MHRA after departure from the EU.

The implementation plan[179] of the policy paper on the future of UK clinical research clearly states the objectives:

- Make the UK one of the best places in the world to conduct fast, efficient and cutting-edge clinical research;
- Ensure the UK has the world's most advanced and data-enabled clinical research environment.



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"We will use the provisions of the Medicines and Medical Devices Act 2021 to overhaul our clinical trial frameworks, giving a major boost to the UK's world-class R&D sector and get patients access to new lifesaving medicines more quickly."

Lord Frost, statement to the House of Lords on Brexit opportunities, Sep 16th 2021.

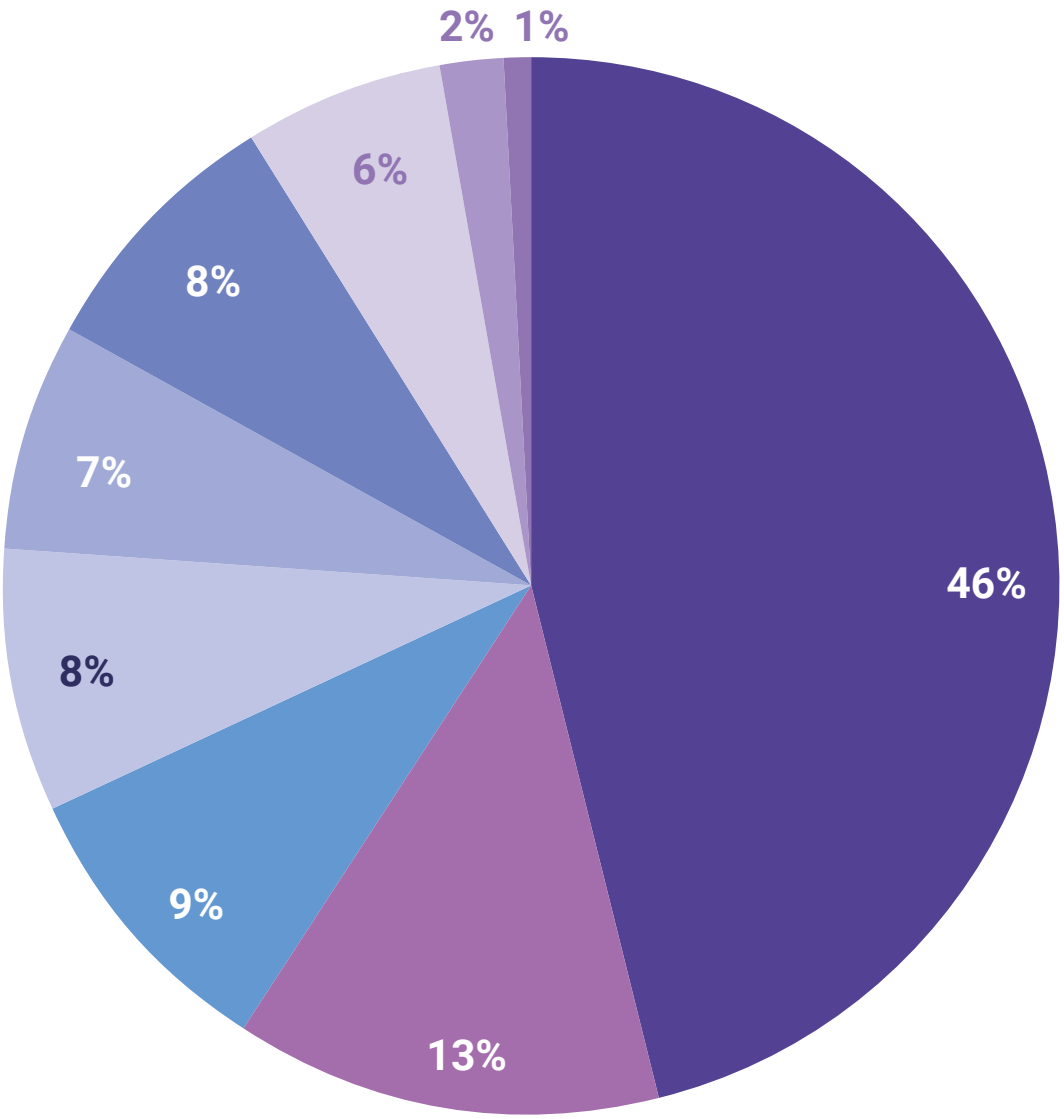
"We should replace the EU Clinical Trials Directive with a new UK clinical trials framework based on UK leadership in innovative trials design, patient recruitment, translational medicine protocols, streamlined processes and a unified health research data structure."

Report of the Taskforce on Innovation, Growth and Regulatory Reform

Obstacles to greater adoption of ISTs in the UK, as elsewhere, include a lack of familiarity with the technology, uncertainty about regulatory acceptance of *in silico* data, the need for more standards and validated models of biological systems and insufficient workers with the necessary skills and expertise. The solution to these challenges must be driven in a coordinated fashion from the top. A survey conducted by InSilicoUK in 2022 asked which stakeholders were most important to drive the adoption of ISTs in the UK. More than two-thirds of respondents pointed to government regulators, policymakers and funders.

A conservative approach by regulators is the most significant impediment to the greater utilisation of ISTs in the UK and the rest of the world. However, the UK has a unique opportunity to modernise its regulatory structure, making it more agile and innovation-friendly. The TIGRR report[180] stated that 'the UK is recognised as one of the global leaders in good regulation,' and 'Our departure from the EU provides us with a once-in-a-generation opportunity to redesign and improve our approach to regulation across the economy' in a manner that, for the first time in forty years, 'is not constrained by what the EU will or will not allow.' This includes the opportunity to develop independent regulatory strategies for developing and evaluating medical products. For example, the MHRA recently launched its Innovative Licensing and Approvals Pathway smoothing the developers' and sponsors' assessment and approval journey for developers and sponsors.[181] The Medicines and Medical Devices Act 2021[182] specifically allows the government to update legislation related to clinical trials, aiming to deliver 'a more streamlined and flexible regulatory regime' that enables 'a thriving clinical research environment in the UK reflecting innovative trial design and delivery.' A modernised regulatory approach to clinical trials can help accelerate the development and introduction of new medicines, diagnostics and medical devices, benefitting patients and the UK economy.

Which stakehkolders are key to driving the UK adoption of ISTs?



Key:

- Regulators & Policy Makers – MHRA, NICE
- Data Guardians & Providers – HDRUK, NHS
- Funders – NIHR, InnovateUK, EPSRC, MRC
- Experts in Health Technology Assessment
- Government – BEIS
- General Public & Patients
- Clinical Trial Methodologists
- Trade Associations – ABPI, ABHI
- Standardisation Bodies

Adapted from a presentation by Prof AF Frangi at the InSilicoUK Innovation Network Launch Event, [183] InSilicoUK Community Survey #1: Enablers and Barriers.

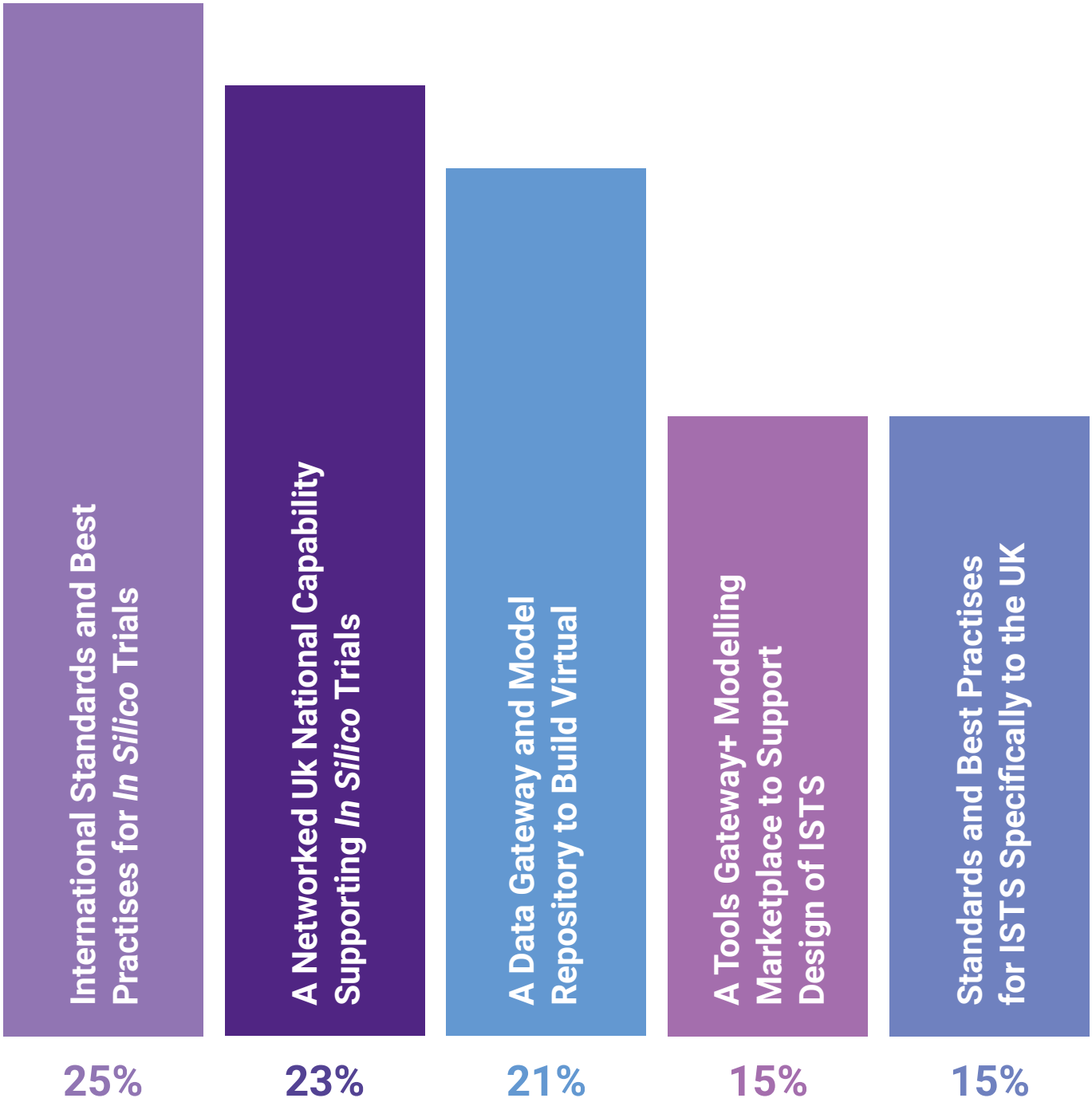
Though the UK landscape for ISTs is less advanced than the US or the EU, it has a mature, sophisticated and dynamic infrastructure, giving it the potential to take a leading role in making good on the promise of CM&S and ISTs. Major contributing factors include:

- Government policy that supports innovation through public R&D funding (£7.8 billion in 2021-22) and is implementing proposals set out in the Taskforce on Innovation, Growth and Regulatory Reform (TIGRR) report[184]
- Strategy objectives for clinical research[185] and data,[186] backed up by a vision for the life sciences[187] that directly complement the proposal for the UK to lead the development of CM&S techniques
- The opportunity presented by MHRA to become a sovereign regulator outside the EU
- Pre-existing and strong ecosystems, including in med-tech, pharma, universities, academic research, translational research, data science/AI, digital technologies, ethics, standards and regulation, relevant to progressing with CM&S methods based in the UK
- Proven track record of forming strategic partnerships in science and industry, as witnessed by the UK's coordinating role in the COVID pandemic response
- Under the NHS, a rich and accessible repository of increasingly well-organised health data and a comparatively streamlined path to clinicians, clinical practice and patients

The thriving UK life sciences sector includes:

- A world-class science base with deep expertise from basic science through to clinical research
- Two of the world's largest pharmaceutical companies[188]
- Approximately 2,600 medical device manufacturers
- Leading academic centres with expertise in medical device innovation, drug design, computational biomechanics and fluid dynamics, imaging sciences, sensors, material sciences and biomanufacturing (e.g. at the Universities of Leeds, Sheffield, Oxford, Cambridge, UCL, Birmingham, Imperial, Glasgow, Strathclyde, Nottingham and King's College London)
- Academic networks, including the BioMedEng Association[189] and the VPHi UK Chapter[190]
- Five Industry Strategy Challenge Centres of Excellence[191] in digital pathology and/or medical imaging with AI
- The Henry Royce Institute has the vision to accelerate the discovery, manufacture and translation of biomedical materials.

How would you prioritise investment in these enablers of IST adoption as a source of regulatory evidence?



Adapted from a presentation by Prof AF Frangi at the InSilicoUK Innovation Network Launch Event, [192] InSilicoUK Community Survey #1: Enablers and Barriers.

Data Science Infrastructure

- OpenSafely[193]
- NHS DigiTrials [194]
- NWeHealth[195]
- Clinical Practice Research Datalink [196]
- UK BioBank [197]
- NIHR Bioresource[198]
- Genomics England[199]
- SAIL Databank (in partnership with Digital Health and Care Wales)[200]
- DiscoverNow[201]
- Scottish Health Research Register[202]
- Generation Scotland[203]
- Precision Medicine Scotland[204]
- The Scottish Biorepository Network[205]
- Scottish Data Safe Havens[206]
- Trusted Research Environments[207]
- Digital Health Care Wales[208]
- electronic Data Research and Innovation Service (eDRIS)[209]
- Digital Health and Care Northern Ireland[210]

This rich patchwork of resources is being aligned under NHS Transformation Directorate's new unitary Data Saves Lives strategy for health and care, currently in draft,[211] which is aligned to the UK's National Data Strategy, published in 2020.[212]

Supporting this, the UK has a rich ecosystem of academic and commercial capabilities in AI and computational science, including the Alan Turing Institute,[213] DeepMind,[214] and various related UKRI-funded Centres for Doctoral Training. This is backed by world-leading computational facilities relevant to *in silico* medicine, including Centres of Excellence in High Performance computing, such as The Science and Technology Facilities Council (STFC)[215] Hartree Centre for Digital Innovation,[216] Edinburgh Parallel Computing Centre,[217] Google Brain by Google Research in Cambridge and the new 'Cambridge-1' AI Supercomputer[218] (which is supported by GSK and AstraZeneca and High-Performance Computing (HPC) software companies like Numerical Algorithms Group Ltd[219]).

Ethical Authority

The benefits of increasing the use of ISTs cannot be realised at the expense of ethical considerations or patient safety. The UK has a reputation for responsible innovation and ethical governance, exemplified in the Human Genome Project[220] and how the Human Fertilisation and Embryology Authority[221] oversees technological development. Equally, the work of UK-based organisations such as the Nuffield Council on Bioethics[222] and, in exploring and driving the ethical use of AI and emerging technologies, the Centre for Data Ethics and Innovation,[223] the Ada Lovelace Institute,[224] the Alan Turing Institute,[225] and Doteveryone,[226] give it considerable authority.

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186 National Data Strategy, Department for Science, Innovation and Technology and Department for Digital, Culture, Media & Sport, 2020, www.gov.uk/government/publications/uk-national-data-strategy.

187 Life Sciences Vision, Office for Life Sciences, Department for Science, Innovation and Technology and Department for Business, Energy & Industrial Strategy, 2021, www.gov.uk/government/publications/life-sciences-vision

188 AstraZeneca and GSK, who have jointly funded the Cambridge Centre for AI in Medicine that aims to transform clinical trials, personalised medicine and biomedical discovery: Cambridge Centre for AI in Medicine – Novel AI to transform healthcare

189 The BioMedEng Association – Association of Biomedical Engineers, Medical Engineers and Bioengineers, www.biomedeng.org.

190 VPH Institute - UK Chapter, www.vphiukchapter.co.uk.

191 Artificial Intelligence to help save lives at five new technology centres, 2018, www.gov.uk/government/news/artificial-intelligence-to-help-save-lives-at-five-new-technology-centres.

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193 OpenSAFELY: The secure analytics platform for NHS electronic health records: www.opensafely.org.

194 NHS DigiTrials - NHS Digital, which offers data services to support clinical trials to reduce the time, effort and cost of developing new drugs, treatments and services.

195 NorthWest EHealth, www.nweh.co.uk.

196 Clinical Practice Research Datalink (CPRD), www.cprd.com.

197 UK Biobank, www.ukbiobank.ac.uk.

198 NIHR BioResource, www.bioresource.nihr.ac.uk.

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200 SAIL Databank - The Secure Anonymised Information Linkage Databank, www.saildatabank.com.

201 Discover-NOW, Imperial College Health Partners, www.discover-now.co.uk.

202 SHARE, The Scottish Health Research Register and Biobank, www.registerforshare.org.

203 Generation Scotland, The University of Edinburgh, www.ed.ac.uk/generation-scotland.

204 Precision Medicine Scotland Innovation Centre, www.precisionmedicinescotland.com

205 The Scottish Biorepository Network, www.biobankinguk.org.

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217 EPCC – Edinburgh Parallel Computing Centre, www.epcc.ed.ac.uk.

218 Cambridge-1:The UK's powerful supercomputer, www.nvidia.com/en-gb/industries/healthcare-life-sciences/cambridge-1.

219 The Numerical Algorithms Group, www.nag.com.

220 The Human Genome, www.genome.gov/human-genome-project.

221 Human Fertilization and Embryology Authority, www.hfea.gov.uk, www.hfea.gov.uk.

222 The Nuffield Council on Bioethics, www.nuffieldbioethics.org.

223 Centre for Data Ethics and Innovation, www.gov.uk/government/organisations/centre-for-data-ethics-and-innovation.

224 Ada Lovelace Institute, www.adalovelaceinstitute.org

225 Alan Turing Institute, www.turing.ac.uk.

226 doteveryone, www.doteveryone.org.uk.

Annex A Case Studies

Early success and adoption

Introduction

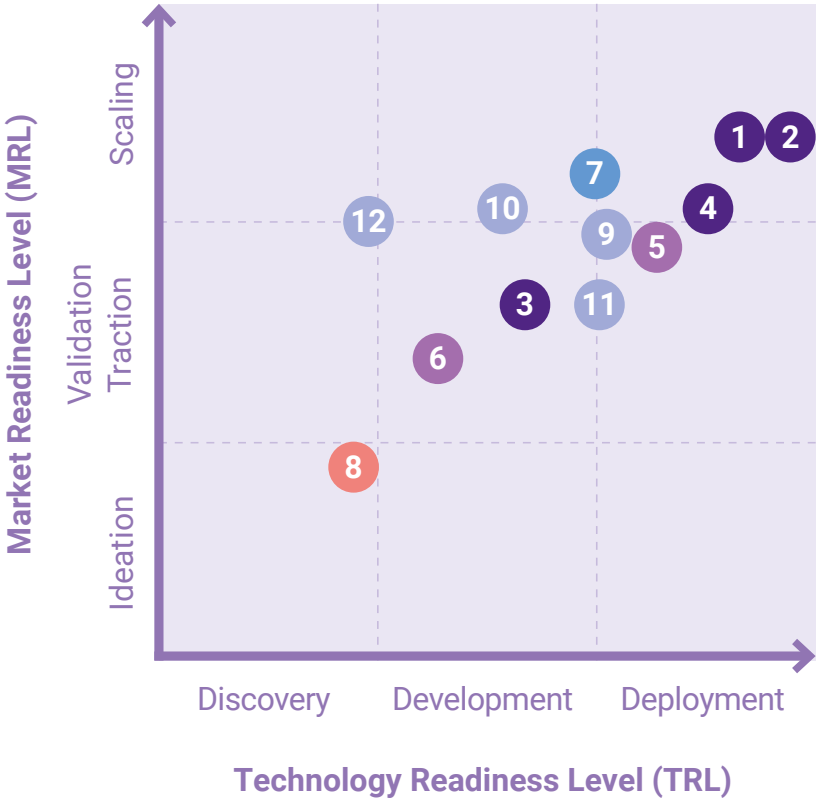
The following pages cover twelve case studies demonstrating how *in silico* trials, simulations and modelling are utilised to boost the development of healthcare technologies and clinical procedures across the UK. A wide range of medical conditions is covered, impacting the heart (arrhythmias), the brain (aneurysms and arterial blockage leading to stroke), the lungs (viral infections such as COVID-19) and the bones (knee and shoulder osteoarthritis, craniosynostosis). In the UK, these conditions cause physical and mental suffering to a significant portion of the population. Annually, 2 million people experience arrhythmias, many of the 1.3 million stroke survivors live with disabilities and 9 million seek osteoarthritis treatment. Whereas most listed diseases impact senior citizens, craniosynostosis is a congenital disability resulting in an unusual head shape in infants. Therefore, the applicability of computer models undoubtedly spans the entire spectrum of health conditions with a potential benefit for society.

Case studies are categorised by the location of the disease of interest:

- Heart
- Brain
- Lungs
- Abdomen
- Bones

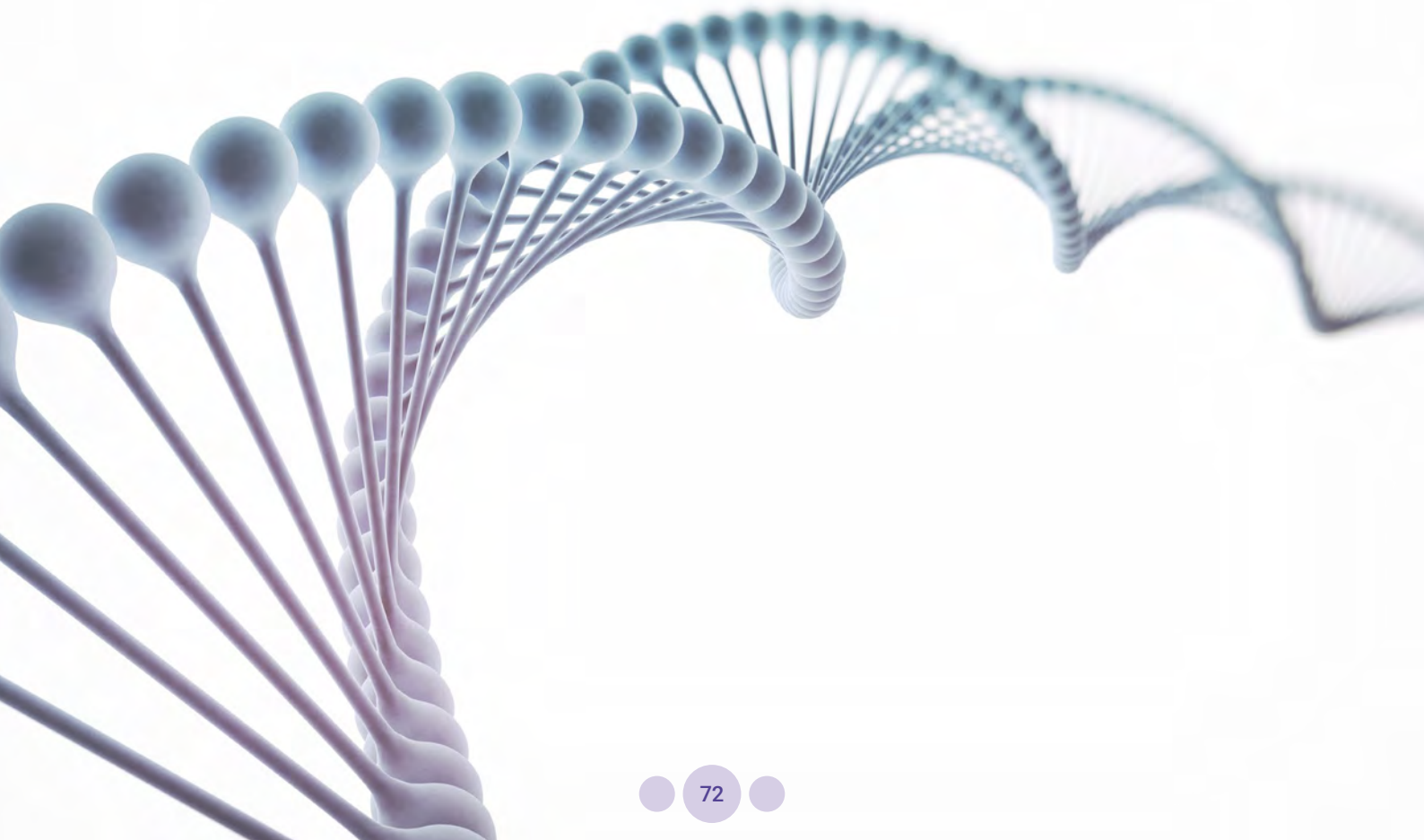
Furthermore, studies investigate the applications of:

- Devices
- Drugs



The investigated treatments and therapies range from joint repairs through pacemakers and stent retrievers to antiarrhythmic drugs like lidocaine. Efficacy and safety testing rely primarily on animal tests and clinical trials. The associated financial and time costs are enormous, measured in years and tens of millions of pounds. Still, only one out of six clinical trials succeed and paves the way for a market-ready medical product. It is anticipated that *in silico* trials could reduce the associated costs by providing a priori safety and efficacy estimation, thus sharpening future clinical trials' focus. The potential of simulation and modelling techniques to accelerate medical device and drug development has been acknowledged by the United States Congress and the European Parliament. The case studies below emphasise that the UK is an international hub at the forefront of the related revolutionary research, development and regulatory processes. The presented studies provide a unique window of opportunity to further and exploit this technology in favour of the UK society and economy.

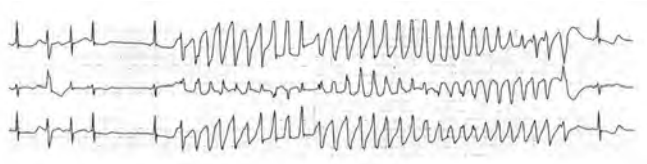
It is worth acknowledging that *in silico* trials are new, emerging technologies which rely on interconnected modelling and simulation modules. The models underlying some of the collected case studies are the product of decades of research, whereas others are the outcome of recent, relatively short projects. In general, the technology and market readiness of modelling and simulation tools in medicine have a huge variance depending strongly on the field of application, as detailed below and shown in the figure above.



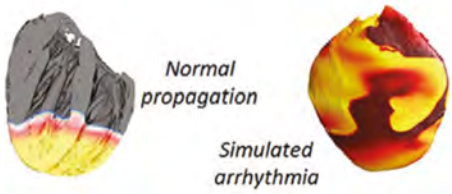
Case Study 1

Industrial Use Of Mathematical Electrophysiology Models For Drug Pro-Arrhythmic Safety Testing

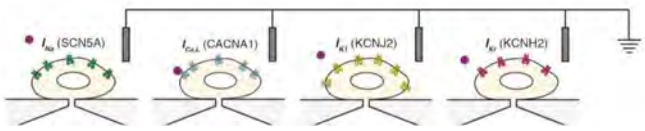
Motivation and problem formulation



Increased **risk of potentially-fatal cardiac arrhythmias** is one of the leading causes of compounds being withdrawn from drug development, and led to the withdrawal of drugs from the market in the 1990s and 2000s at a cost of many £bn.

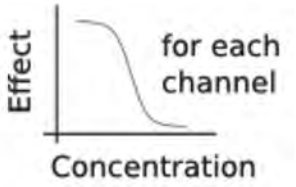


Electrical activity controls the heartbeat, and drug compounds can block a variety of different ion currents in the heart, with the degree of block of different currents conferring different arrhythmic risk.

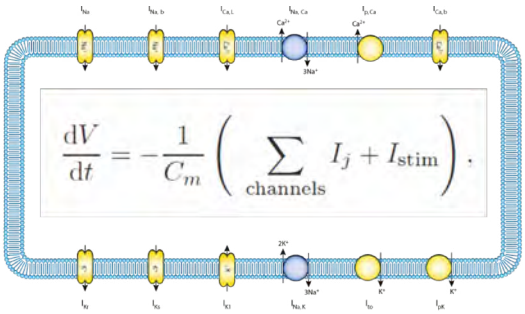


Until recently, most pharmaceutical screening relied on looking at block of one potassium channel (hERG.) But mathematical models are letting us integrate information on block of multiple ion channels to refine clinical risk assessment.

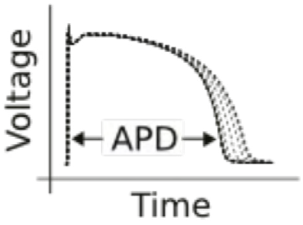
Cardiac Electrophysiology modelling and simulation



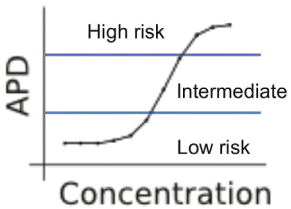
Early pharma experiments in cell lines



Mathematical model of heart cell electrical activity

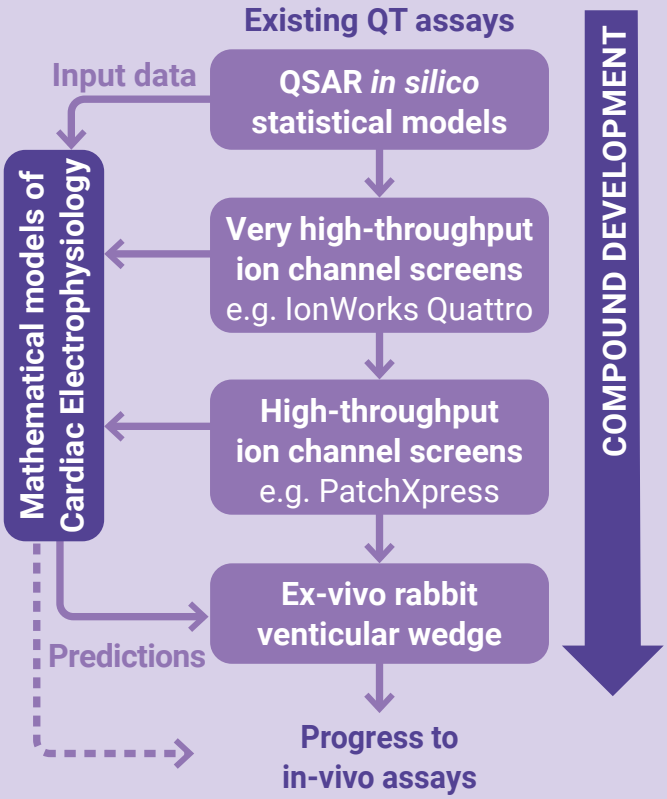


Predict changes to heart electrical activity

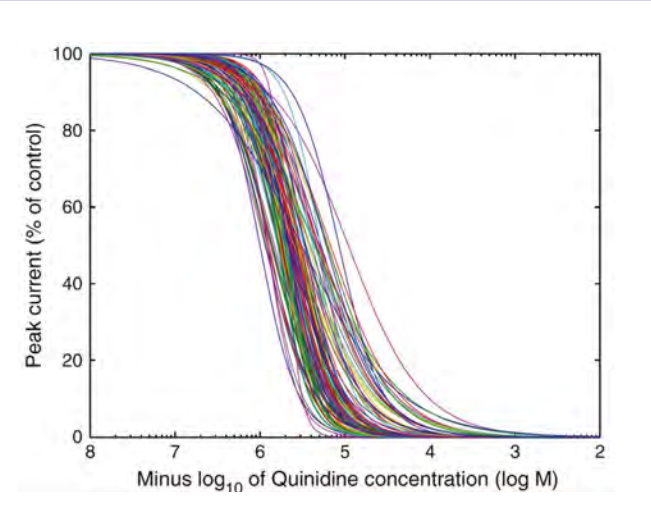


Assess risk of new drug at various concentrations

Predict results of later safety tests; refine concentrations they examine; and aim for replacement of animal-based experiments.



Uncertainty Quantification



Conclusion

Electrophysiology Modelling and simulation is already being used in the pharmaceutical industry to integrate information on how drugs interact with multiple biological targets and to predict both the outcome of animal-based experiments and clinical risk for patients.

Future Challenges

Patient-specific risk assessment based on all the drugs they are being administered, accounting for patient characteristics (sex, age, genetics)

Question or problem addressed

All new pharmaceutical compounds must be carefully screened for unwanted side effects. Nevertheless, many drugs have been withdrawn from the market worldwide because of fatalities due to arrhythmias at the cost of billions of pounds. Even drugs for ailments as mild as hay fever have been withdrawn due to fatalities and an unacceptable increase in arrhythmic risk (e.g. terfenadine), so there is now a huge industrial effort to avoid this situation occurring for new drug compounds. The root cause has been identified as drug molecules binding to and blocking ion channels in the heart. Ion channel block can now be screened in cell lines in a dish (*in vitro*) early in drug development without using animal cardiac muscle tissue. This is the standard screening approach for ion channels in many large pharmaceutical companies.

However, the clinical risk is a complex function of many cardiac ion channels, which are difficult to understand by looking at the results of these screens independently.

Study methods and procedures

The developed mathematical modelling and risk classification offer a way to integrate information from different ion channels *in vitro* screens, to predict the effect on whole cardiac muscle cells. The resulting simulations can provide a more accurate summary of the risk of a new potential drug compound earlier in drug development and more cheaply than the pre-existing approaches. In short, the computational modelling tool, ApPredict, uses the data produced by *in vitro* tests to identify lower-risk compounds to be progressed into translational *in vivo* studies on animals (with a concomitant reduction in the need for animal studies) and ultimately into clinical trials on humans.

Impact on industry and regulatory processes

Cardiac electrophysiology simulation software developed by Nottingham researchers is used in-house by three of the top 10 largest (by revenue) pharmaceutical companies – GlaxoSmithKline Plc (GSK), F. Hoffman-LaRoche (Roche) and Sanofi – for routine compound profiling and pro-arrhythmic side effect safety testing. The simulator is also available via a public portal (https://cardiac.nottingham.ac.uk), where over 140 other companies have used it. The simulator applies mathematical models of the electrophysiology of cardiac muscle cells to predict the side effects of pharmaceutical compounds and assign them a clinical pro-arrhythmic risk class. The system allows the global pharmaceutical industry to focus development on compounds with a lower cardiac risk, reducing the likelihood of failing safety tests during later stages of drug discovery. The ability of the industry to select low-risk compounds using these computer models has enhanced productivity, generated financial savings and decreased reliance on animal-based testing – at GSK, reducing the use of a rabbit heart experiment by over 90%.

Technical abstract

The electrophysiology of cardiac myocytes (muscle cells) can be described with compartmental Ordinary Differential Equation (ODE) models to quantify the compartment ionic concentrations within the cell and the voltages across membranes. Each ionic current can be selective for sodium, potassium, calcium and/or other ions and travels through particular proteins – ion channels – in the cell membrane. Each major type of current is characterised by a separate mathematical sub-model describing how the channels that carry it open and close in response to changes in voltage and ionic concentrations. The voltage itself follows the ODE shown in the figure below. So we have complex non-linear feedback between currents controlling the evolution of voltage and voltage influencing the size of currents. In the study that led to the reduction of rabbit left-ventricular wedge experiments at GSK, the model was assessed by testing it on historic compounds from their development pipeline that had both the ion channel screening data (simulation inputs) and changes to prolongation from

rabbit wedge electrocardiogram recordings (simulation prediction/output). The model was found to be 78% accurate, 72% sensitive and 81% specific when predicting QT prolongation (>10%) using the highest available accuracy (PatchXpress assay) data (77 compounds). Similar levels of predictivity were demonstrated using IonWorks/FLIPR data (121 compounds) with 78% accuracy, 73% sensitivity and 80% specificity. QT shortening (<-10%) was predicted with 77% accuracy, 33% sensitivity and 90% specificity using PatchXpress data and 71% accuracy, 42% sensitivity and 81% specificity using IonWorks/FLIPR data.

Contact:

Gary Mirams, University of Nottingham, gary.mirams@nottingham.ac.uk

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Case Study 2

Human *in silico* trials for drug cardiac testing

Pharmaceutical products are screened for efficacy and safety, with cardiotoxicity being one of the most common adverse drug effects.

Many drugs have been withdrawn from market due to their potential to induce lethal arrhythmias.

Current regulatory guidelines, although effective for safety, are acknowledged too restrictive and impeding potentially beneficial new drugs from entering the market.

Human *in silico* drug trials has high regulatory impact for the assessment of new drug candidates in human-relevant systems, overcoming limitations of animal testing.

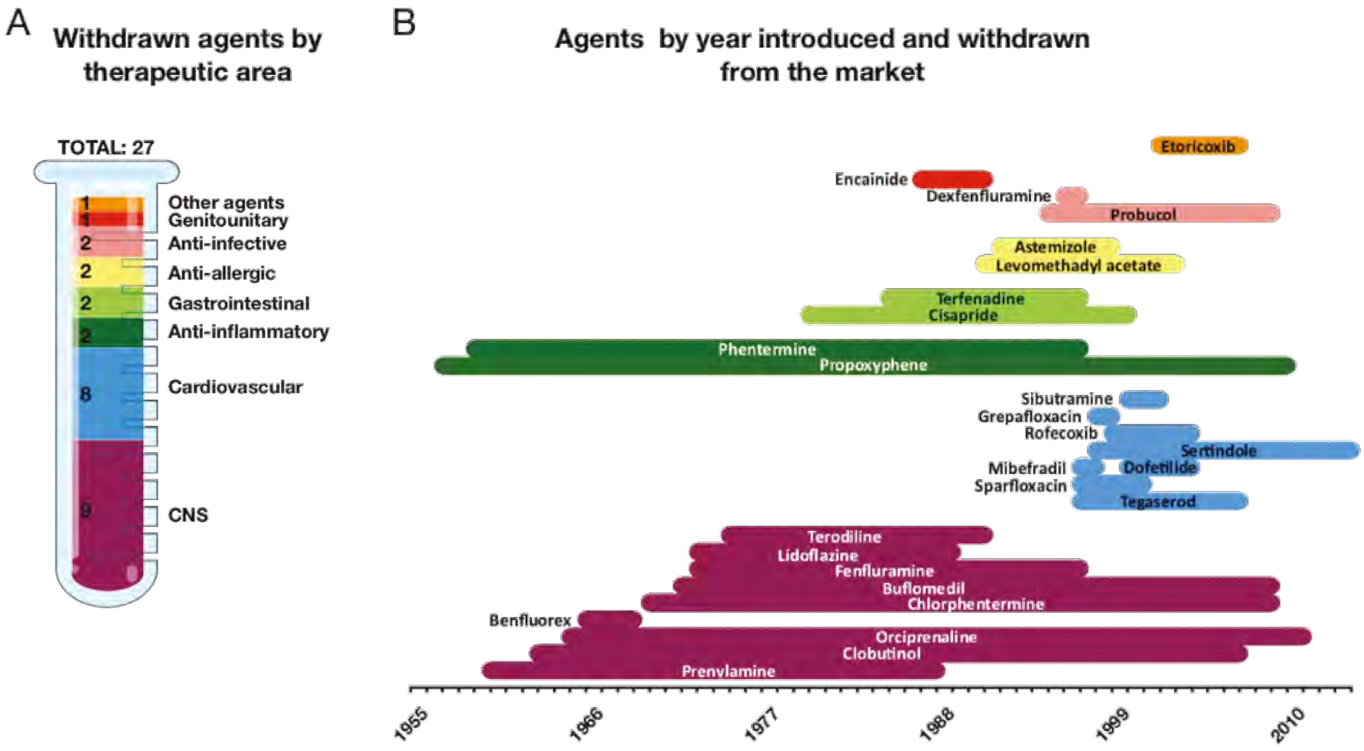
The Virtual Assay software for human *in silico* drug trials

Virtual Assay is a human-based cardiac modelling and simulation framework developed to run human *in silico* drug trials to augment drug cardiac testing.

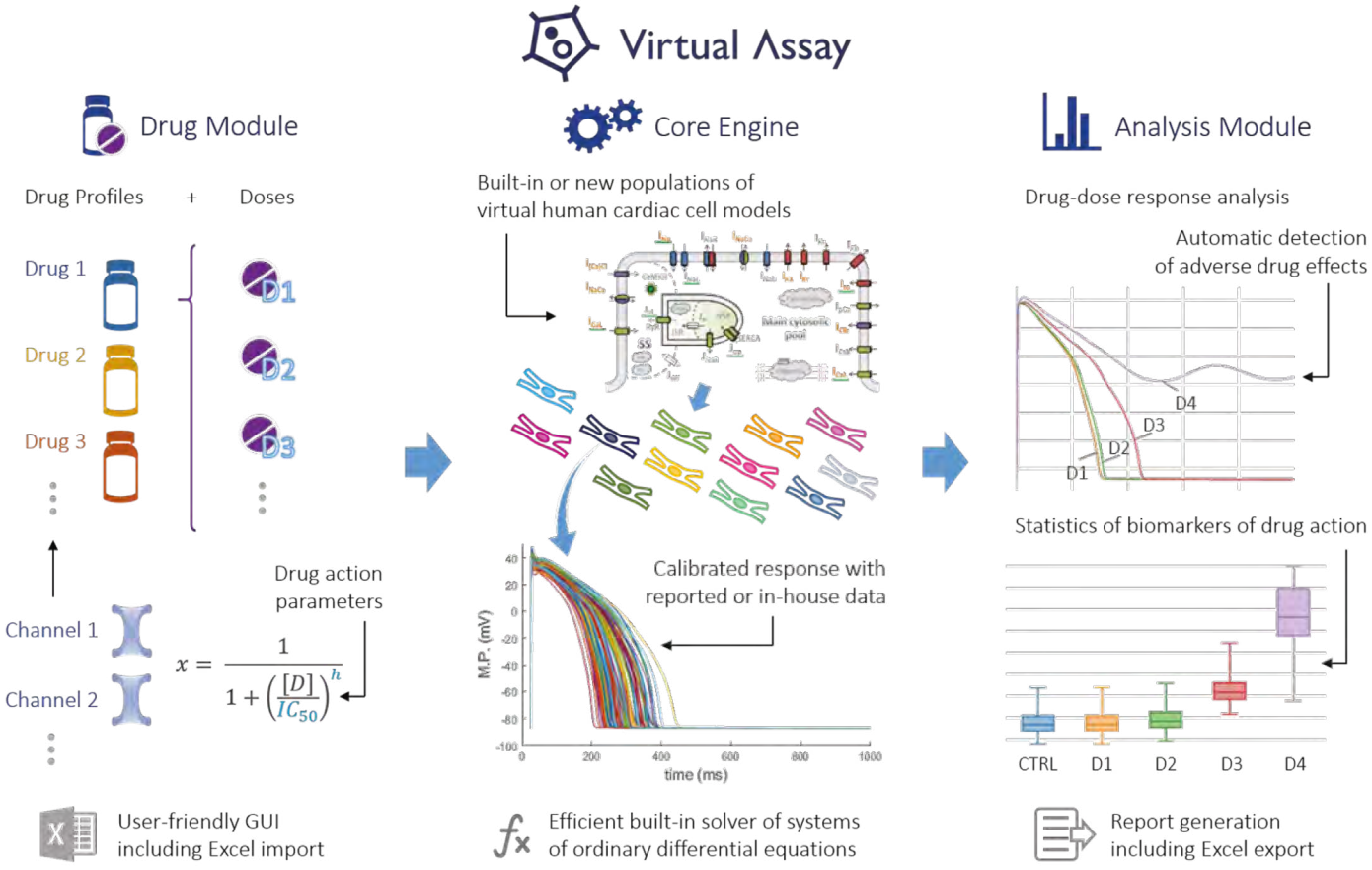
Adverse drug effects are known to depend on the gender, age, and genetic background of the individual. These are taken into account in Virtual Assay by building **populations of virtual cardiac cells.**

Human *in silico* drug trials with Virtual Assay in 62 reference drugs demonstrate an **accuracy of 89%** in safety classification, **overpassing preclinical animal testing.**

These results have been **independently validated in blinded studies** in collaboration with pharma industry.



Drugs withdrawn from market due to cardiotoxicity up to May 2020 [doi.org/10.1016/j.xcrm.2021.100216]. (A) Number of drugs withdrawn according to therapeutic area. (B) Lifespan of withdrawn agents. CNS, central nervous system.



The Core Engine offers a user-friendly graphical interface for creating and using populations of virtual human cardiac cell models. The Drug Module directly converts the drug parameters for their use by the Core Engine in each of the models of the population. The Analysis Module finally generates visual reports of the drug studies, including the automatic detection of adverse drug effects.

Conclusion

- **Virtual Assay** is a human-based technology, able to **predict drug safety and efficacy in humans**
- Virtual Assay **extends** traditional trials for drug cardiac testing by providing **mechanistic insights of drug action,** and **analysis of demographic heterogeneity in drug response**
- Further areas of impact include the **reduction and replacement of animal use** in research and for conventional trials

Question or problem addressed

This study has potential implications for new drug candidates given the regulatory requirement of assessing *in vivo* drug-induced pro-arrhythmic cardiotoxicity and the need for novel effective, safe therapeutic targets for cardiac disease. Cardiac safety assessment focuses on drugs that may be ruled out due to potential false positive signals based on hERG (human ether-à-go-go-related gene) assays and multichannel effects. One of the key questions for human *in silico* clinical trials is whether the drug of interest results in a risk of developing arrhythmias in the human population, even in the context of positive hERG assays and multichannel effects.

Study methods and procedures

The work relies on the Virtual Assay Software, a human-based cardiac modelling and simulation framework developed to run human *in silico* drug trials using populations of human electromechanical cellular models. The core engine provides a user-friendly graphical user interface (GUI) for efficient algorithms for the sampling and solving of populations of virtual human cardiac cell models. The Drug Module directly converts the drug action parameters for their use by the Core Engine in each of the models of the population. The Analysis Module finally generates visual reports of the conducted drug-dose response studies.

Impact on industry and regulatory processes

The Virtual Assay software is in use in many pharmaceutical companies. It is routinely used in at least four major ones to assess drug effects on cardiac electrophysiology and contractility. Several pharma companies, including Janssen, Amgen, UCB, Sanofi and Merck, have published extensive validation studies. As highlighted in publications with the European Medicines Agency and FDA, this study has a high regulatory impact because modelling and simulation results constitute the key source of evidence to answer the question of interest. The proposed approach has high clinical influence given the new Q&A Guidelines: impact on the decision to accept phase 1 to 3 trial designs. Based on this model, waiver of intensive electrocardiogram (ECG) monitoring in confirmatory trials. This is also crucial for the evaluation of cardiotoxicity in cancer

drugs. Wrong model prediction/simulation could expose patients to the risk of lethal arrhythmias following clinical trials due to cardiotoxic drugs. Model predictions have been found superior to animal testing.

Technical abstract

Human-based computer models constitute a fast, cheap and potentially effective alternative to experimental assays. Key challenges include consideration of inter-cellular variability in drug responses and integration of computational and experimental methods in safety pharmacology. We aim to evaluate the ability of *in silico* drug trials in populations of human ventricular cell models to predict the clinical risk of drug-induced arrhythmias based on ion channel information and to compare simulation results against experimental assays commonly used for drug testing. A control population of human ventricular cell models in agreement with experimental recordings was constructed. *In silico* drug trials were performed for 62 reference compounds at multiple concentrations, using pore-block drug models (IC50/Hill coefficient). Drug-induced changes in electrophysiological biomarkers and repolarisation/depolarisation abnormalities were quantified. Simulation results were used to predict clinical risk based on reports of Torsade de Pointes arrhythmias and further evaluated in a subset of compounds through comparison with electrocardiograms from rabbit wedge preparations and Ca2+-transient recordings in human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs). Drug-induced changes *in silico* vary in magnitude depending on the specific ionic profile of each model in the population, thus allowing the identification of cell sub-populations at higher risk of developing abnormal AP phenotypes. Models with low repolarisation reserve (increased Ca2+/late Na+ currents and Na+/Ca2+-exchanger, reduced Na+/K+-pump) are highly vulnerable to drug-induced repolarisation abnormalities.

In contrast, those with reduced inward current density (fast/late Na+ and Ca2+ currents) exhibit high susceptibility to depolarisation abnormalities. Repolarisation abnormalities *in silico* predict clinical risk for all compounds with 89% accuracy. Additional validation studies have been performed independently with data from several companies, reporting similar levels of accuracy.

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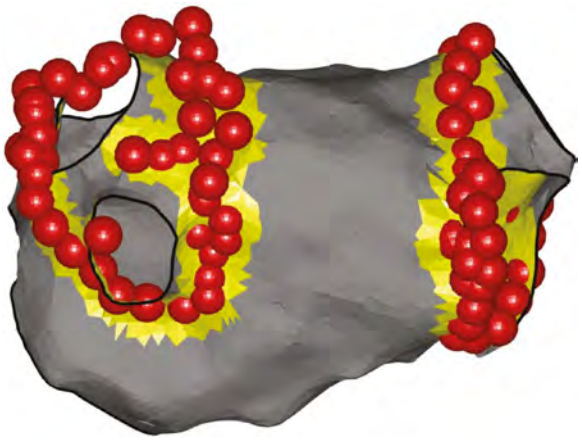
Case Study 3

Predicting atrial fibrillation recurrence in patient-specific left atrial populations

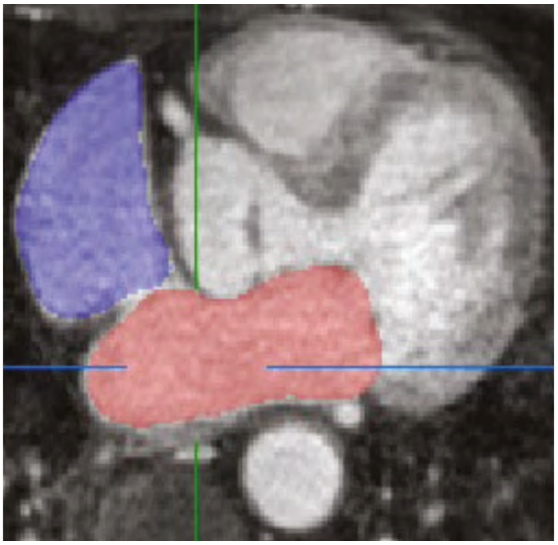
Predicting Atrial Fibrillation Recurrence by Combining Population Data and Virtual Cohorts of Patient-Specific Left Atrial Models

Motivation and problem formulation

Atrial fibrillation (AF) is the most common form of heart arrhythmia, affecting around 1.4 million people in the UK. It can lead to stroke or heart failure. Current treatments for AF, including ablation, have shown mixed results. Each patient responds differently and it is difficult to predict the best possible course of long-term treatment.



Treatment by catheter ablation lesion sets



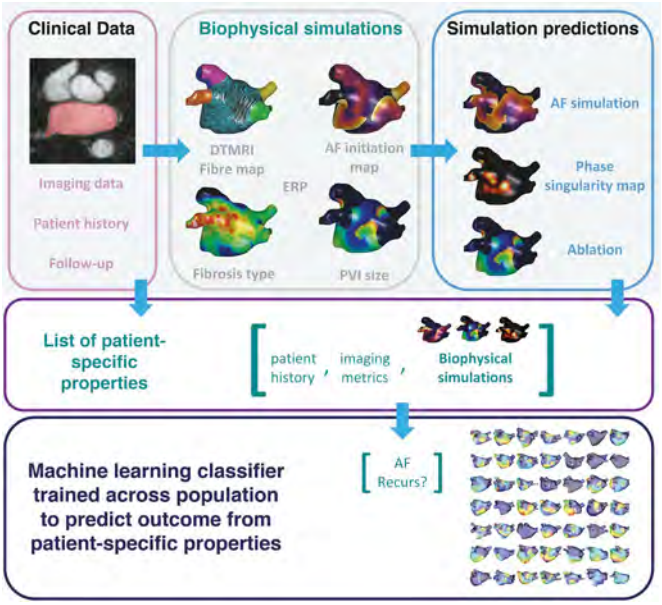
MRI imaging data for personalised models

Aim

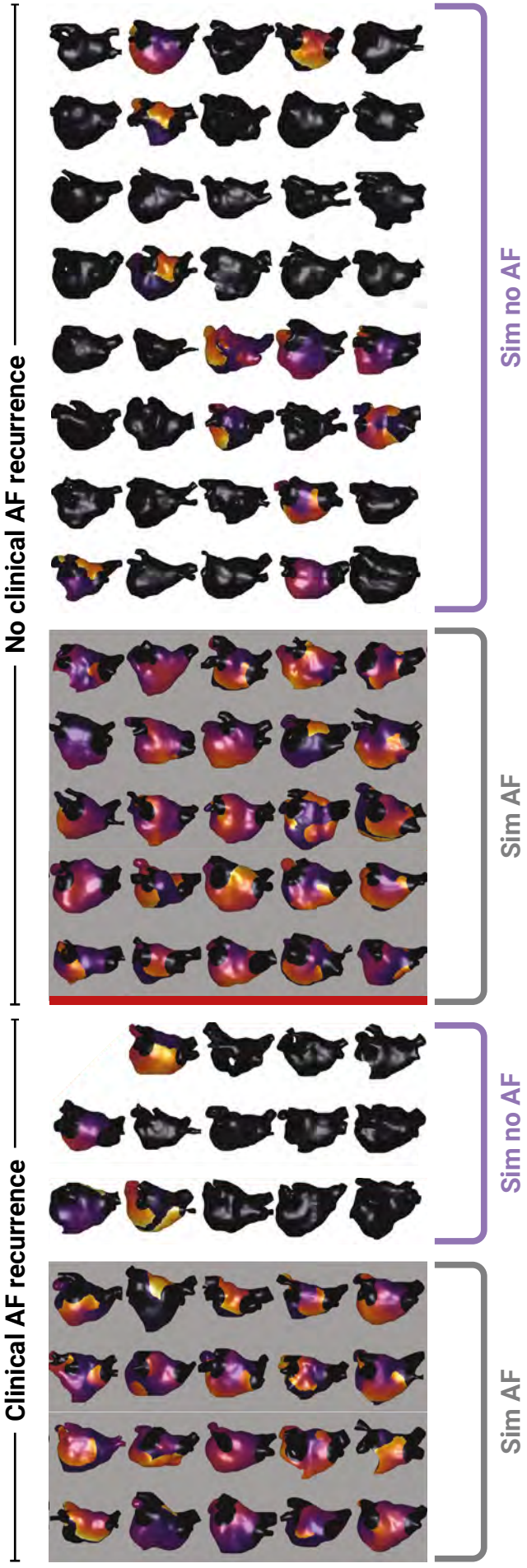
To predict long-term atrial fibrillation recurrence after ablation in large cohorts, by using **machine learning** to complement **biophysical simulations** by encoding more interindividual variability.

Combining Population Data and Virtual Cohorts of Patient-Specific Left Atrial Models

Methodology schematic for combining patient history, imaging metrics and biophysical simulations to predict outcome



Acute response to pulmonary vein isolation ablation across a cohort of 100 models.



Conclusion

- A novel computational pipeline accurately predicted long-term AF recurrence in individual patients by combining outcome data with patient-specific acute simulation response.

Future challenge

- **Applying** machine learning and simulation tools to **optimise** and personalise **AF treatments**

Question or problem addressed

Atrial fibrillation (AF) is the most common form of heart arrhythmia, affecting around 1.4 million people in the UK. AF can lead to stroke or heart failure. Current treatments for AF, including catheter ablation therapy, have shown mixed results. Each patient responds differently and predicting the best possible course of long-term treatment is difficult. We aimed to predict long-term response to ablation therapy for AF in large cohorts using machine learning to complement biophysical simulations in an *in silico* trial.

Study methods and procedures

We constructed patient-specific models for 100 atrial fibrillation patients undergoing the first ablation. The patients were followed for 1 year using ambulatory ECG (electrocardiogram) monitoring. Each patient-specific biophysical model combined different properties, including different fibrosis patterns, fibre orientation maps, electrical properties and ablation patterns, to capture uncertainty in atrial properties and test the tissue's ability to sustain fibrillation. These simulation stress tests of different model variants were post-processed to calculate atrial fibrillation simulation metrics across the *in silico* cohort. Machine learning classifiers were trained to predict atrial fibrillation recurrence using features from the patient history, imaging and atrial fibrillation simulation metrics.

Impact on industry and regulatory processes

Our novel computational pipeline accurately predicted long-term atrial fibrillation recurrence in individual patients by combining outcome data with patient-specific acute simulation response. This technique could help to personalise selection for atrial fibrillation ablation. We performed 1100 atrial fibrillation ablation simulations across 100 patient-specific models. Models based on simulation stress tests alone showed a maximum accuracy of 0.63 for predicting long-term fibrillation recurrence. Classifiers trained in history, imaging and simulation stress tests outperformed those trained in history, imaging, or history alone. This cardiac modelling pipeline is a case study for a Coordination and Support Action Digital Europe project to develop an Ecosystem for Digital Twins in Healthcare led by the Virtual Physiological Human Institute (www.edith-csa.eu/) and recently featured in EETimes Europe (www.eetimes.eu/ee-times-europe-magazine-march-2023/).

Technical abstract

Current ablation therapy for atrial fibrillation is suboptimal and long-term response is challenging to predict. Clinical trials identify bedside properties that provide only modest prediction of long-term response in populations, while patient-specific models in small cohorts primarily explain the acute response to ablation. We aimed to predict long-term atrial fibrillation recurrence after ablation in large cohorts using machine learning to complement biophysical simulations by encoding more interindividual variability. Patient-specific

models were constructed for 100 atrial fibrillation patients undergoing first ablation (43 paroxysmal, 41 persistent and 16 long-standing persistent). Patients were followed for 1 year using ambulatory ECG monitoring. Each patient-specific biophysical model combined differing fibrosis patterns, fibre orientation maps, electrical properties and ablation patterns to capture uncertainty in atrial properties and test the ability of the tissue to sustain fibrillation. These simulation stress tests of different model variants were post-processed to calculate atrial fibrillation simulation metrics. Machine learning classifiers were trained to predict atrial fibrillation recurrence using features from the patient history, imaging and atrial fibrillation simulation metrics.

We performed 1100 atrial fibrillation ablation simulations across 100 patient-specific models. Models based on simulation stress tests alone showed a maximum accuracy of 0.63 for predicting long-term fibrillation recurrence. Classifiers trained to history, imaging and simulation stress tests (average 10-fold cross-validation area under the curve, 0.85±0.09; recall, 0.80±0.13; precision, 0.74±0.13) outperformed those trained to history and imaging (area under the curve, 0.66±0.17) or history alone (area under the curve, 0.61±0.14). A novel computational pipeline accurately predicted long-term atrial fibrillation recurrence in individual patients by combining outcome data with patient-specific acute simulation response.

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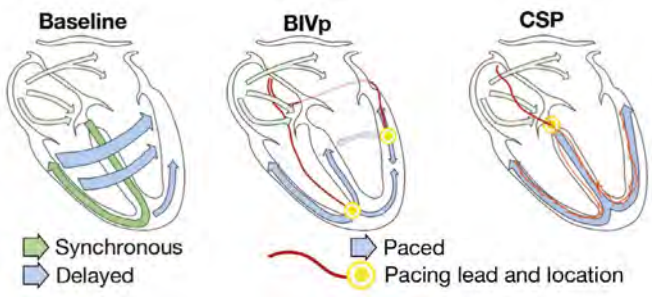
Case Study 4

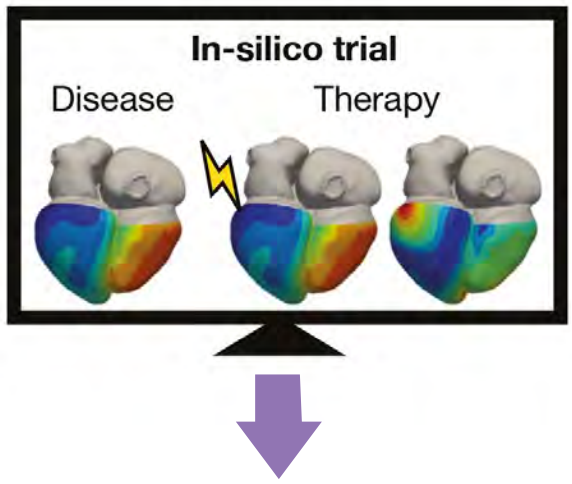
In silico trial to investigate response to conduction system pacing

Response to conduction system pacing (CSP) might be better compared to standard biventricular pacing (BIVp), but it might depend on the **underlying conduction disease.**



Studying this systematically in a **clinical setting** is **challenging**.

***In silico* trials** offer a **systematic framework** to investigate how response to pacing changes with different conduction disturbances.

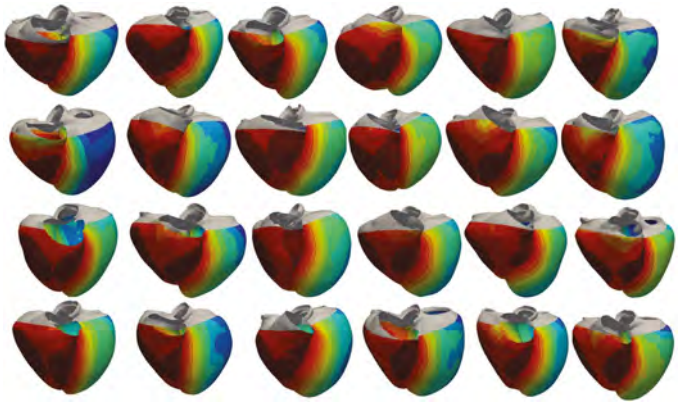


Response assessment

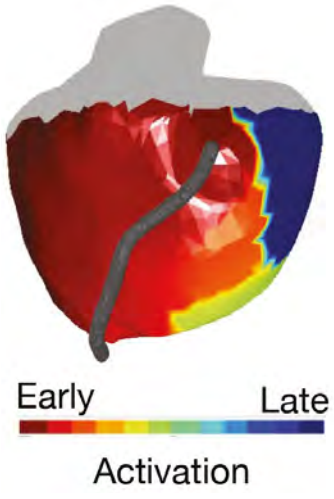
Model development and validation

Activation was simulated on a cohort of patient-specific anatomies. Baseline activation and changes in biventricular (BIV AT) and left ventricular activation times (LV AT) following pacing agreed with measured clinical values.

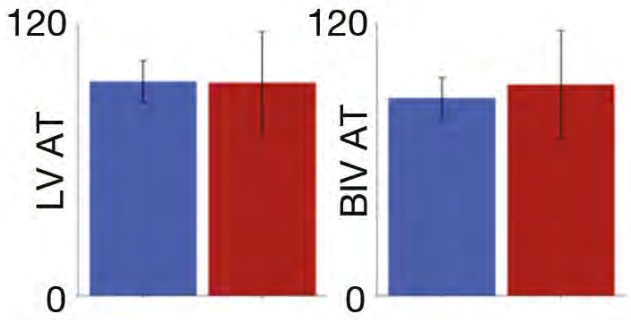
Modelled activation on virtual cohort



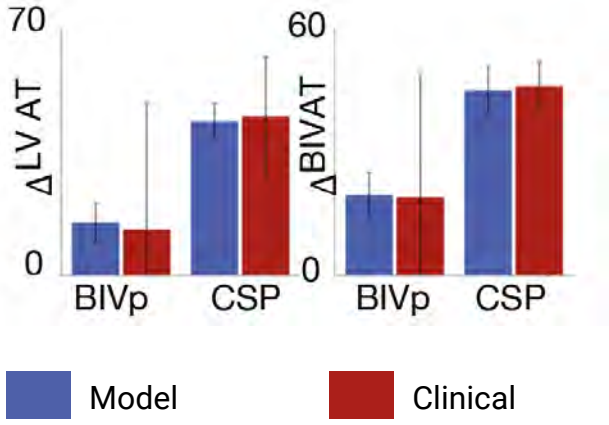
Clinical



Baseline model



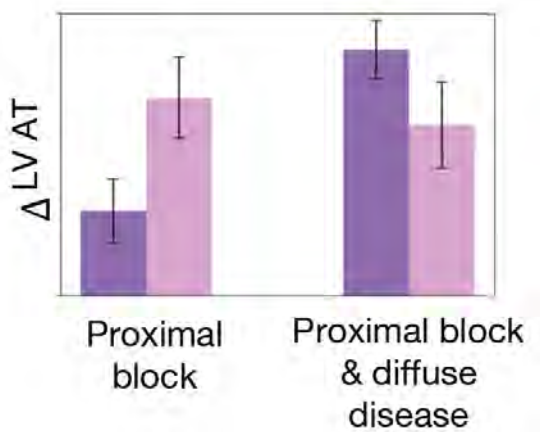
Therapy response

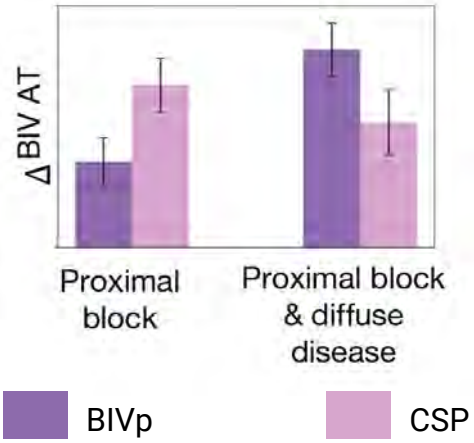


In silico trials clinical applications

Comparison between pacing modalities

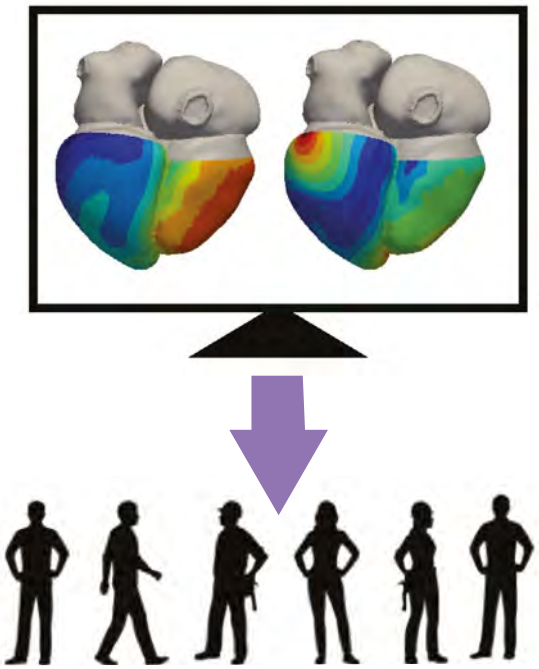
Patients with diffuse conduction disease benefit from BIVp more than CSP, while proximal block alone can be corrected with CSP.





Guiding clinical trials design

In silico clinical trials can **inform clinical trials on patients** in order to **shorten procedure time** and to **accelerate guidelines update.**



Conclusion

Once validated against clinical data, computer modelling and *in silico* trials have the potential to **compare different pacing modalities** and to **guide clinical trials on patients** in order to **improve patient care.**

Question or problem addressed

Cardiac resynchronisation therapy (CRT) is an effective treatment for patients with dyssynchrony. However, patients do not experience target clinical improvements in 30-50% of cases. This led to unnecessary and expensive procedures and increased patient risk. Therefore, identifying novel methods for therapy delivery to improve patient care is a pressing need. Conduction system pacing (CSP) may offer a better response than standard biventricular pacing (BIVp). However, response to CSP might depend on the underlying pathology causing dyssynchrony. Identifying patient subgroups that might benefit from CSP over BIVp is very challenging in a clinical setting, but it would reduce costs and patient risk and improve patient care.

In silico trials performed using computational models offer a systematic framework to investigate how patient response changes in the presence of different conduction disturbances. This ultimately allows for identifying patient subgroups likely to respond to CSP non-invasively and focusing future clinical trials on such patient groups.

Study methods and procedures

We simulated ventricular activation on a cohort of twenty-four virtual anatomies generated from a heart failure patient imaging data. The model's baseline and paced activation pattern and response metrics were validated against clinical data to ensure the simulations reproduced clinical observations. We then introduced different conduction disturbances and simulated baseline (e.g. before treatment), BIVp and CSP activation times and compared acute changes in activation times following pacing.

Impact on industry and regulatory processes

We have demonstrated how computational models can systematically and non-invasively identify patient groups that might benefit from CSP rather than BIVp. This can potentially reduce cost and procedure times, guide future clinical trials focusing on specific patient subgroups rather than large and heterogeneous populations and ultimately accelerate updating guidelines and improve patient care.

Technical abstract

Response to cardiac resynchronisation therapy (CRT) is heterogeneous and sub-optimal in a significant proportion of patients. Therefore, identifying novel methods for therapy delivery to improve patient care is a pressing need. Conduction system pacing (CSP) may offer a better response than biventricular pacing (BIVp). However, testing different pacing methods requires long, risky and expensive procedures.
In silico trials have the potential to reduce costs and procedure times by identifying patient subgroups that are likely to respond to different pacing modalities.
We simulated ventricular activation on twenty-four patient-specific geometries from end-diastolic CT image datasets acquired from heart failure patients. Each heart anatomy included a His-Purkinje network with three left ventricular and two right ventricular fascicles to represent early activation sites during sinus rhythm. We introduced the proximal left bundle branch

block (LBBB) and compared the simulated activation pattern with electrocardiographic imaging data, showing that the model can replicate a typical LBBB activation sequence. Response metrics (such as left ventricular and biventricular activation times) during baseline and how these change in response to BIVp and CSP were compared to encephalographic image-derived metrics from in-house and literature data [doi.org/10.1093/europace/euac245] to verify that the model was able to replicate response observed in patients. We simulated different conduction disturbances and compared BIVp and CSP, showing that patients with diffuse conduction disease of the left ventricle do not experience additional benefits with CSP compared to BIVp. We have demonstrated how *in silico* trials can be used to identify patient subgroups that are more likely to respond to CSP over BIVp. This can shorten procedure time, risk and costs, guide future clinical trials, accelerate updating guidelines and improve heart failure patient care.

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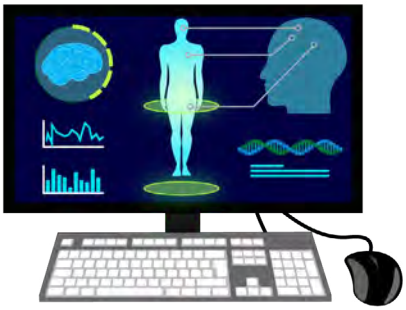
Case Study 5

Intracranial flow diversion devices: *in silico* trial replicates & expands findings of conventional trials

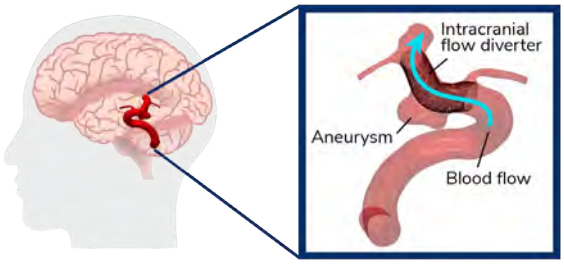
Computer modelling and simulation of virtual cohorts for the development or regulatory evaluation of a medical product, device, or intervention

The virtualisation of patients and their physiology through ***in silico* trials** offers a powerful and ethical alternative to conventional clinical trials.

But can *in silico* trials replicate and expand insights from conventional trials?

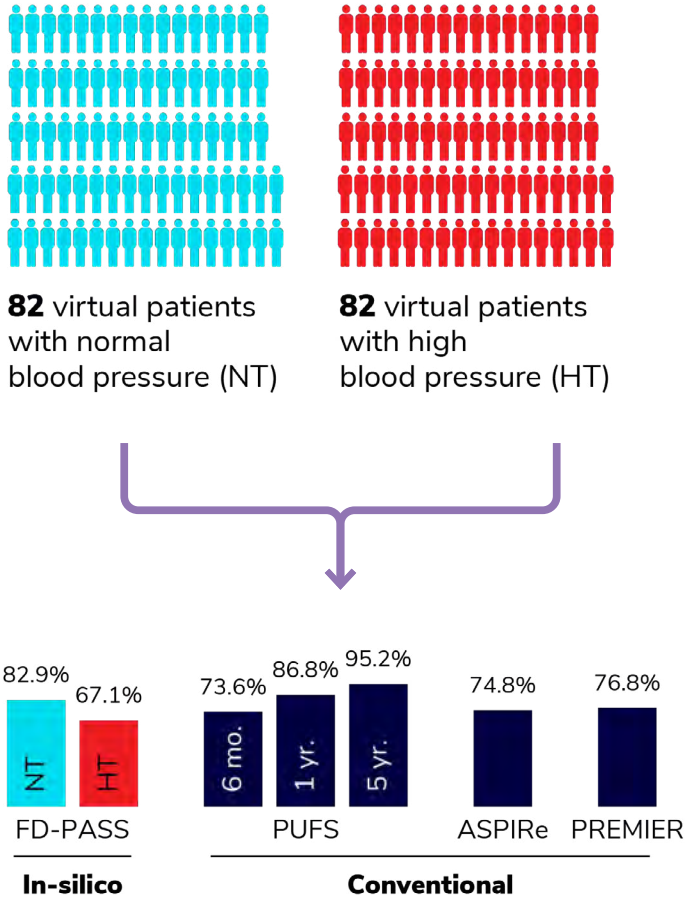


To find out, researchers modelled the treatment of virtual patients with **intracranial flow diverters** (stents designed to redirect blood flow away from brain aneurysms) in the **Flow Diverter Performance Assessment (FD-PASS) *in silico* trial**.

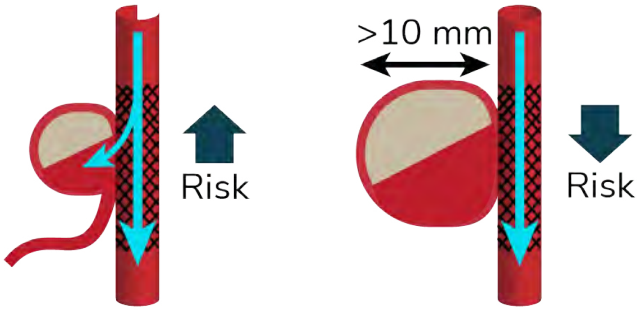


Flow Diverter Performance Assessment (FD-PASS) *In Silico* Trial

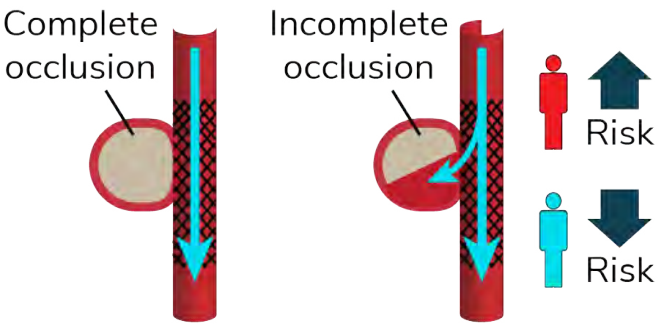
The predicted percentages of successful flow diversion **replicated** values reported in three conventional clinical trials



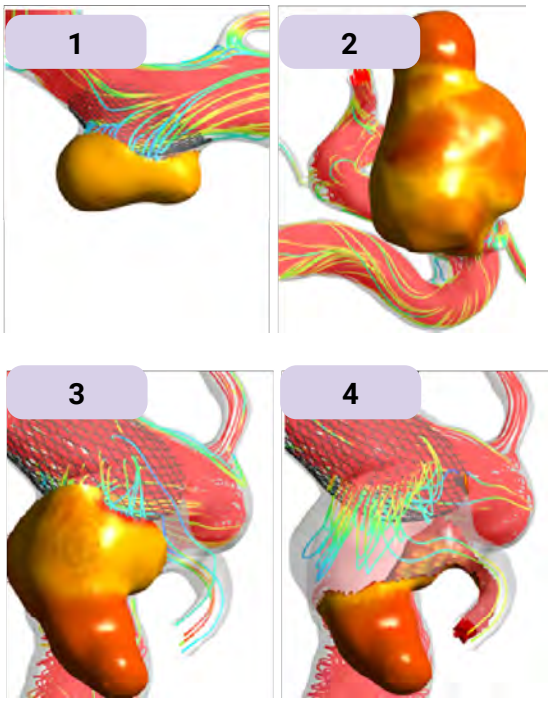
FD-PASS also **extended** clinical findings, providing information that would not usually be available about populations most likely to experience device failure



A higher risk of incomplete occlusion was found among aneurysms with a **branch artery** vs. those larger than 10mm



Patients with **HT** may also experience higher risks of incomplete occlusion



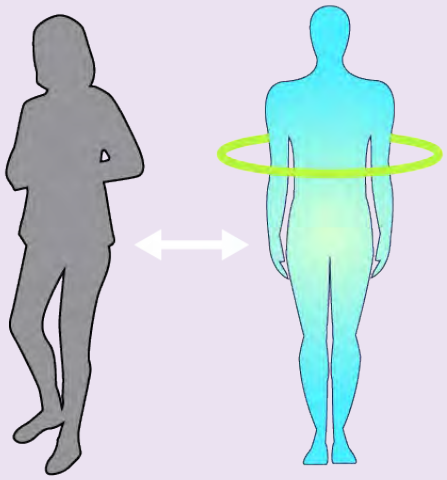
Finally, **blood clot formation** within the treated aneurysm sac was simulated to study stroke risk in 4 virtual patients

Conclusion

- The FD-PASS *in silico* trial indeed replicated and extended findings obtained from conventional clinical trials
- This result indicates that *in silico* trials offer the potential to reduce, refine, and replace conventional trials

Future challenge

- Future work will translate findings from in silico trials to improve device designs and explore combined therapies (drugs/device).



Question or problem addressed

In silico trials may offer solutions to augment regulatory evaluation of medical devices by (I) enabling digital evidence to reduce, refine, or replace bench, animal, or human studies; (II) extending trial cohorts to rare or difficult-to-recruit phenotypes; (III) evaluating devices under practically challenging conditions (i.e. off-label use); and (IV) directly comparing alternative treatments in the same virtual population (reducing the observed effect variance).

Flow-diverter performance assessment (FD-PASS) *in silico* trial (I) determined whether *in silico* trials can replicate outcomes of clinical trials using independent simulated populations that match those of the clinical trials; and (II) in the event of successful replication, demonstrated whether such virtual trials could facilitate exploratory virtual experiments not easily achievable in clinical trials, thus providing new insights and generating new hypotheses.

Study methods and procedures

FD-PASS simulated the treatment of intracranial aneurysms in 164 virtual patients with 82 distinct anatomies (each in hypertensive and normotensive phenotypes) with a flow-diverting stent using computational fluid dynamics (CFD). FD-PASS was performed in approximately three months, compared to the 5-7 years required in the reference clinical trials. The predicted FD-PASS flow-diversion success rates replicated the values reported in three conventional clinical trials on the same device (RCT design: PREMIERE, ASPIRe and PUFS). Through further stratification of virtual cohorts and simulation of complex phenomena, like thrombosis, the *in silico* approach allowed broader investigation of factors associated with insufficient flow reduction than feasible in clinical trials.

Impact on industry and regulatory processes

The findings from the FD-PASS *in silico* trial replicated those of previously published clinical trials, demonstrating the utility of *in silico* trials in informing regulatory decisions based on the clinical trials. The FD-PASS trial offered additional information about populations more likely to experience device failure that would not usually be available from reference clinical trials. We demonstrated the use of advanced modelling and simulation techniques to explain the underlying mechanisms of complications and to advise clinical decisions on a case-by-case basis.

Technical abstract

The cost of clinical trials is ever-increasing. *In silico* trials rely on virtual populations and interventions simulated using patient-specific models and may offer a solution to lower these costs. FD-PASS *in silico* trial simulated the treatment of intracranial aneurysms in 164 virtual patients with 82 distinct anatomies with a flow-diverting stent using computational fluid dynamics. FD-PASS's primary endpoint was based on post-treatment flow reduction, shown in an independent population as an accurate surrogate for complete aneurysm occlusion. The FD-PASS *in silico* trial estimated an occlusion rate of 82.9% in patients with normal blood pressure and 67% in

hypertensive patients, which replicated the occlusion rates reported in the reference clinical trials. *In silico* trials can offer detailed subgroup analysis of the outcomes. For example, FDPASS showed higher risks of incomplete occlusion in aneurysms with a branch vessel (risk ratio (RR): 3.53; CI: 1.21-10.32; p = 0.021) and in aneurysms with size >10mm (RR: 2.15; CI: 0.84-5.51; p = 0.109). For each virtual patient in whom we could maintain the anatomy and the deployed device configuration, we studied the post-treatment haemodynamics with two physiological flow conditions (normotensive and hypertensive). We observed higher risks of incomplete occlusion in hypertensive patients (RR: 1.93; CI: 1.09-3.40; p = 0.023). Such control of sources of variability is not readily available in conventional clinical trials. Clinical trials have been limited in identifying the underlying mechanisms of the increased stroke risk. By simulating post-treatment thrombosis, FD-PASS demonstrated explanations for ischaemic or haemorrhagic strokes in patients with hypertension and complex-shaped aneurysms, respectively. FD-PASS demonstrated that *in silico* trials of endovascular medical devices could: (I) replicate findings of conventional clinical trials and (II) perform virtual experiments and subgroup analyses that are difficult or impossible in clinical trials.

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Royal Academy of Engineering

UNIVERSITY OF LEEDS

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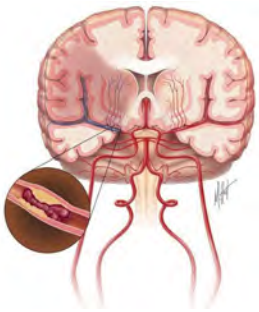
Case Study 6

In silico clinical trials for acute ischaemic stroke treatment

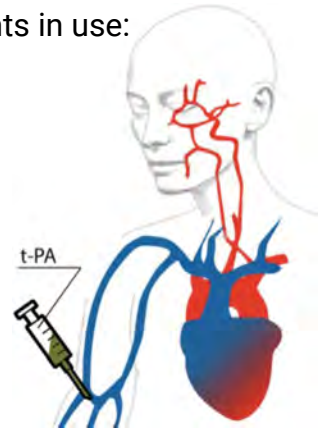
Motivation and problem formulation

Stroke kills 780,000 people annually in Europe and due to population ageing the number of stroke patients is set to increase in the following decades. In 2015, the cost associated with stroke care was £26 billion.

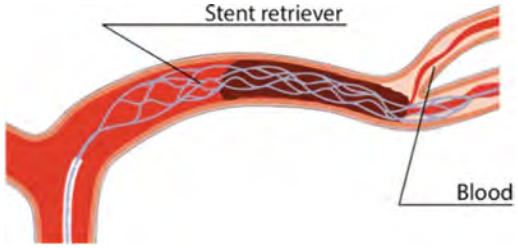


There are two treatments in use:

(I) thrombolysis

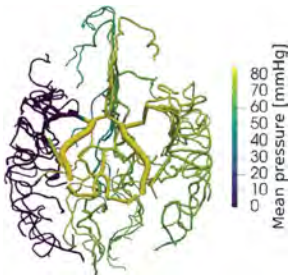


(II) thrombectomy

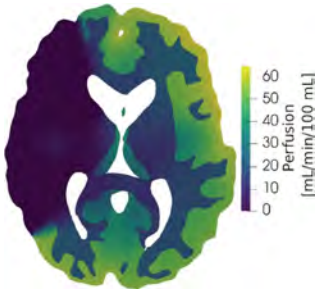


The **INSIST** consortium employs computer **simulations and modelling to better stroke treatments.**

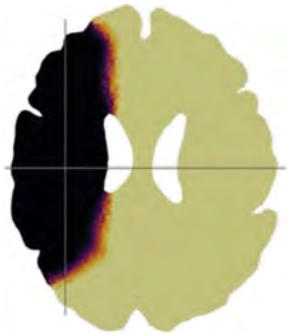
Stroke modelling and simulation



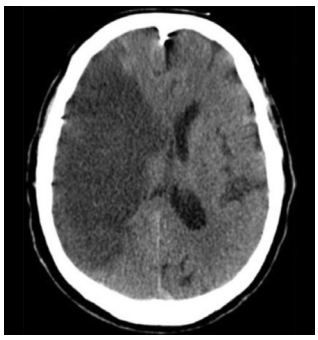
Blood flow in large arteries



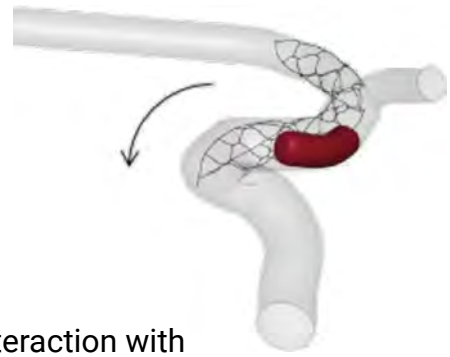
Perfusion of the brain tissue



Infarct formation as function of space and time

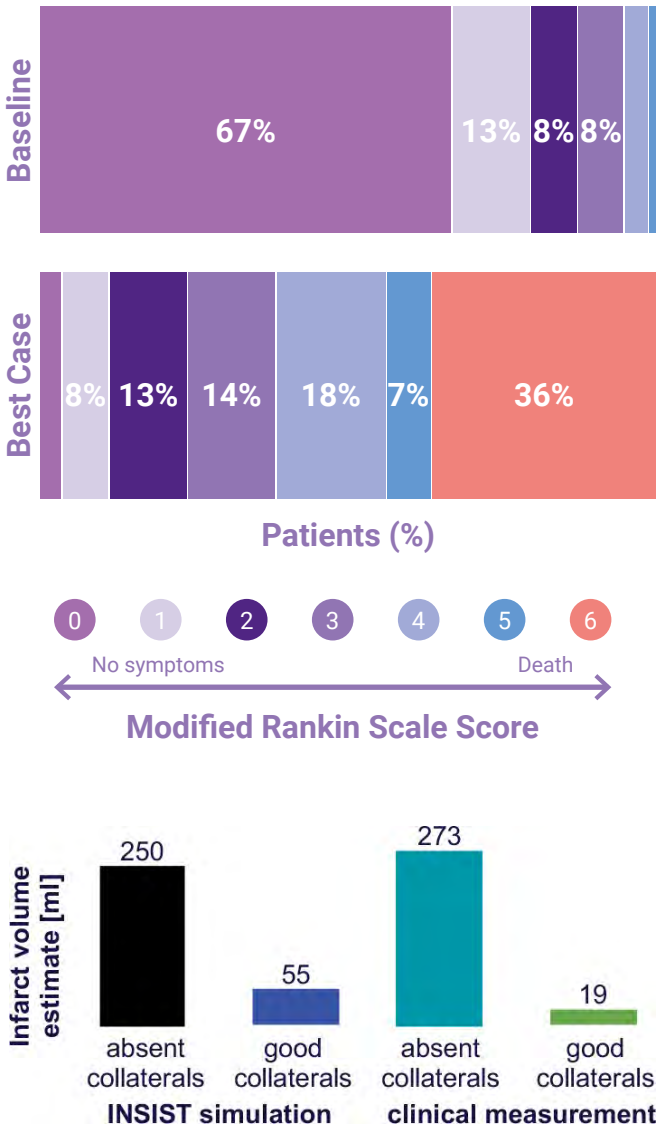


Clinical data integration



Blood clot interaction with medical devices and drugs

Functional outcome estimation



Question or problem addressed

Standard acute ischaemic stroke treatments are based on the chemical resolution of the clot with blood thinner (thrombolysis) and the mechanical removal of the clot with a stent retriever (thrombectomy). These revolutionary techniques improve stroke patients' survival chances significantly. However, about half of stroke patients remain functionally dependent and the mortality rate stagnates at about 20%.

The *in Silico* Clinical Trials for Treatment of Acute Ischaemic Stroke (INSIST, www.insist-h2020.eu) consortium developed the tools needed for stroke simulations and created an event-based stroke simulator. Our long-term goal is to optimise stroke treatments, for example, by accounting for group-specific features. Such features include clot composition (e.g. platelet-rich clots) and the variation of the large arteries (e.g. carotid shape).

Study methods and procedures

INSIST delivered many models to capture stroke as a series of discrete events. The employed mechanistic models quantifying (I) blood flow in large arteries where the thrombus is located before treatment; (II) perfusion of the brain tissue by capillaries; (III) spatiotemporal infarct formation; (IV) stent retriever and clot interaction; (V) blood thinner and clot interaction. The functional outcome of the investigated patient cohort is estimated using a statistical model.

Conclusion

- **Modelling and simulation** is sufficiently mature to capture the key processes in **stroke** and thus **explain clinical observations**
- The **INSIST simulation pipeline can estimate treatment efficacy and patients' functional outcome**

Future challenge

- **Applying INSIST** modelling and simulation tools **to optimise** and personalise **stroke treatments**

Integrating data from multiple sources enabled the generation of 500 virtual patients for stroke simulations. To date, middle cerebral artery occlusions were in the focus of computational studies because this is the most frequent clot location. Statistics regarding virtual patients' anatomical and physiological properties (e.g. vessel diameter and length, blood pressure, brain perfusion, clot composition) were comparable to clinical measurements.

Impact on industry and regulatory processes

The predictions obtained by *in silico* stroke trials overlap with clinical measurements regarding population-level statistics, including spatial perfusion distribution in untreated stroke patients and treatment efficacy. Thrombectomy simulations were suitable for evaluating the thrombus removal success rate of two different stent retrievers, thus estimating the treatment with superior efficacy. Simulations offer the possibility to develop neuroimaging-based diagnostic software which might assist in categorising stroke patients into high-risk and low-risk groups. Furthermore, the INSIST simulation pipeline might assist in determining near-optimal therapies for stroke patients.

Technical abstract

The *In Silico* Clinical Trials for Treatment of Acute Ischaemic Stroke (INSIST) project aimed to model and simulate the impact of thrombolysis and thrombectomy. The effort led to a library of simulation tools, including large arterial blood flow models, brain perfusion, infarct formation and treatments. Parameters were inferred from preclinical measurements and clinical data corresponding to healthy reference subjects and stroke patients from the MR CLEAN registry. Based on 150 middle cerebral artery simulations, the perfusion lesion overlapped with clinical infarct volume (IV) measurements (simulated perfusion lesion: 212±28 ml; clinical IV measurement: 203±28 ml; mean±SD). When parameters were inferred solely from healthy reference subjects, simulations could not capture the IV variability in stroke patients. Therefore, by default, the simulated perfusion lesion distribution had a smaller standard deviation than the clinical data. Adding collateral vessels explained part of the high variability observed in clinical settings: the median infarct volume estimate without collaterals was 250 ml (clinical 273 ml), whereas the median infarct volume estimate with good collaterals was 55 ml (clinical 19 ml). Thrombectomy simulations of a virtual cohort with 500 individuals implied that there is a measurable difference in the performance of various stent retrievers (recanalisation success rate, device A: 85.2±1.4%; device B: 90.8±1.3%; clinical measurement corresponding to multiple devices: 81.9%, CI: 73-91%).

Furthermore, simulations suggest that platelet-rich clots (fibrin content larger than 75%) are more challenging to remove (recanalisation success rate, platelet-rich clot: 81.8±1.5%; red-blood-cell-rich clot: 89.1±1.3%). This project demonstrated that *in silico* trials could (I) explain clinical findings corresponding to hundreds of stroke patients; (II) capture stroke patients' physiological response to large vessel occlusion and treatment; and (III) evaluate different treatment options and give estimates of efficacy. INSIST consortium

members hope their work will benefit stroke patients by accelerating future medical device and drug development.

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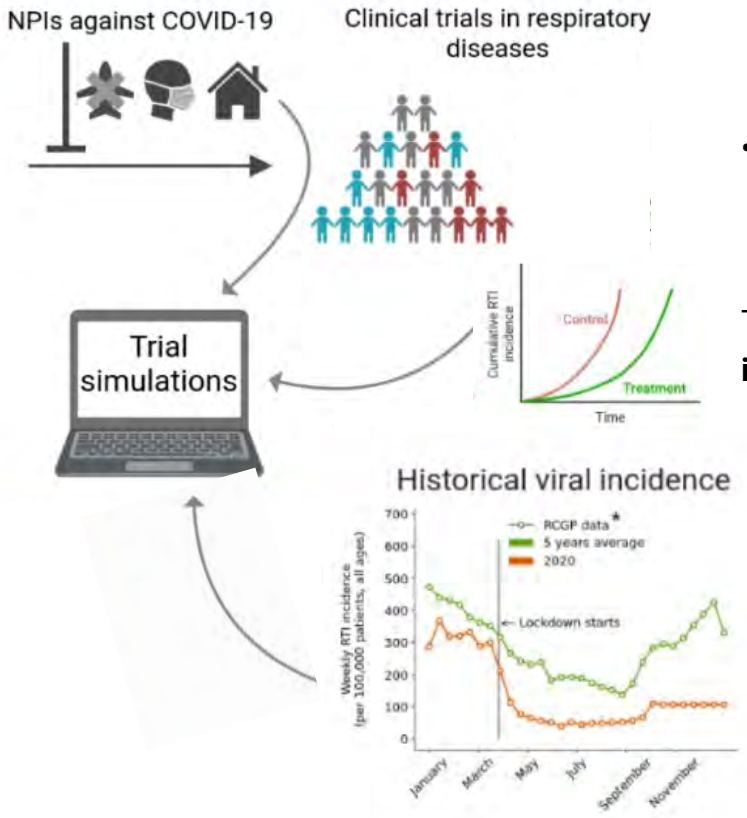
Case Study 7

The challenge of running clinical studies during pandemic lockdowns

Computational modeling and trial simulations for assessing the impact of the COVID-19 pandemic on respiratory diseases clinical trials

Non-pharmaceutical interventions (NPIs) against COVID-19 perturbed patterns of regular viral epidemics putting clinical trials in respiratory diseases at high risk.

Can a trial simulation set-up capture these impacts and suggest ways to mitigate the risks of trial failure?

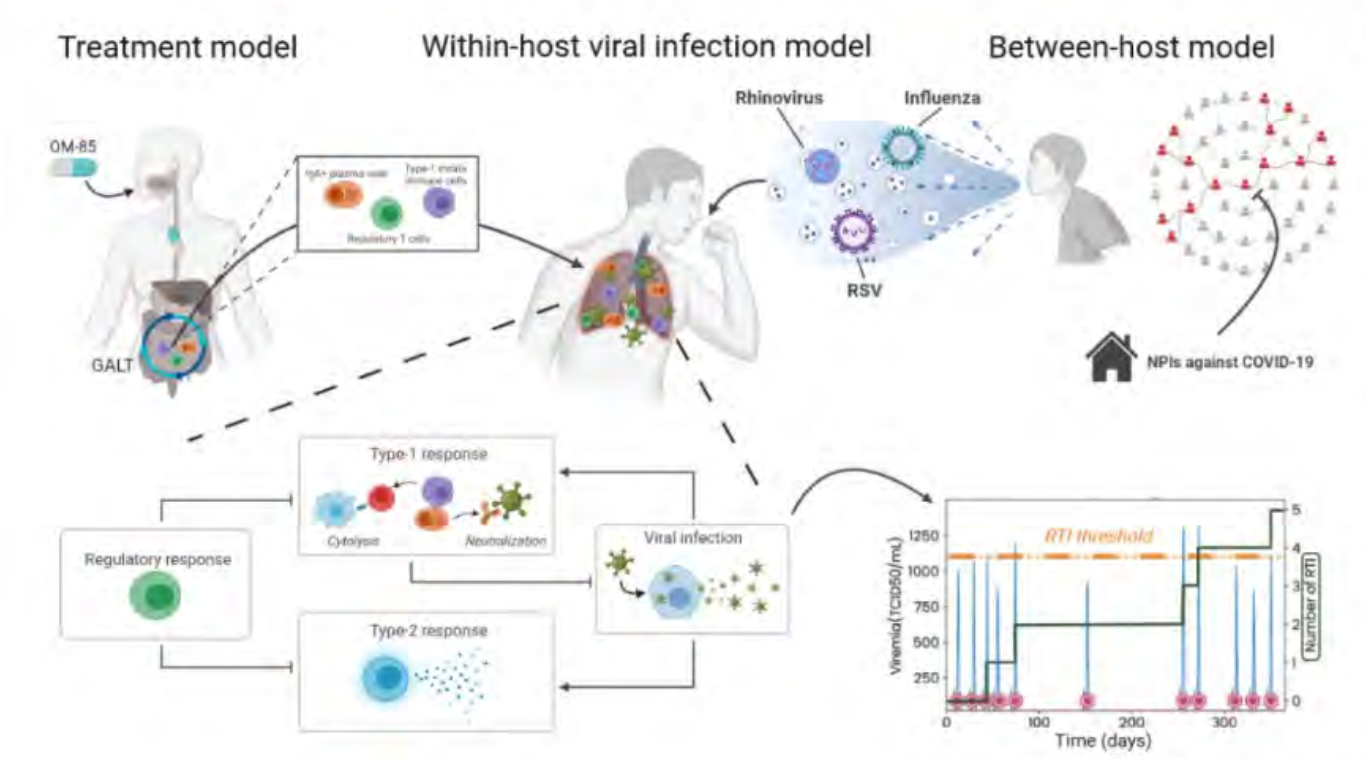


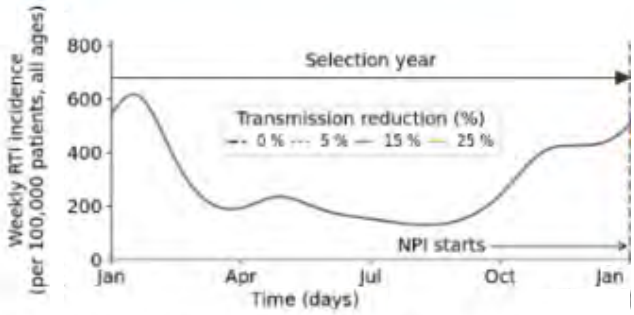
Multi-scale *in silico* approach to incorporate within-host and between-host respiratory tract infection

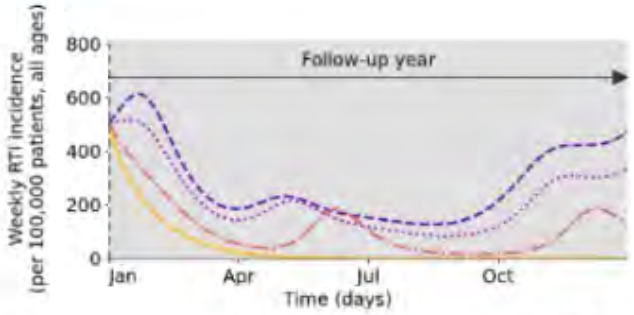
The core element of the computational approach is the coupling of:

- **A within-host mechanistic disease model,** representing the viral and immune dynamics,
- **A between-host disease burden model,** representing the viral dynamics at the population-scale with SIRS framework in the presence or absence of NPIs against COVID-19,
- **A treatment model,** describing the immuno-modulating effect of OM-85 in RTI prophylaxis

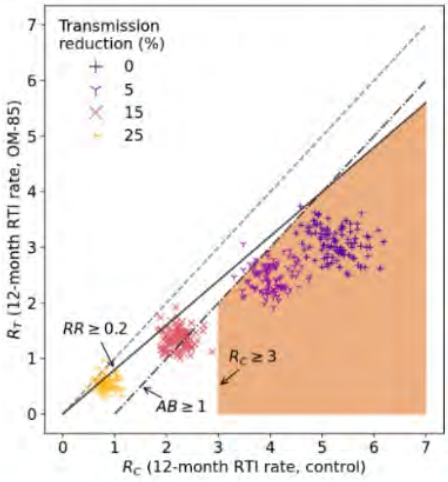
To obtain a **multi-scale RTI and immunomodulation model.**







This multi-scale *in silico* approach is used to simulate trials affected by **NPIs against COVID-19 of increasing strictness** resulting in a more or less affected viral burden.



Simulations showed that NPIs of all strictness are expected to affect **clinical relevance** by decreasing absolute benefit and **recruitment efforts** by limiting the pool of eligible patients.

However, **relative efficacy metrics** are predicted only to be affected by very strong NPIs such as a strict lockdown for example.

Simulations-suggested adaptations of trial design to mitigate failure risks

Question or problem addressed

OM Pharma, the company developing OM-85, an immunomodulatory bacterial lysate treatment used for prophylaxis of respiratory tract infections (RTIs), plans to generate clinical data further supporting OM-85's efficacy. Yet, running an RTI prophylaxis study has become much harder since 2020. The Covid-19 pandemic and associated non-pharmaceutical interventions (NPIs) have severely impacted clinical trial recruitment and execution across the board, while social distancing and lockdowns radically cut RTI incidence in the population.

Given rapidly changing NPI and lockdown patterns across continents and little visibility on how these might evolve, the company needed to understand better: (I) how lockdowns of varying severity impact RTI incidence in the population, (II) how altered RTI incidence impacts the trial size required to show a preventative effect and its clinical significance and (III) the impact of lockdowns on the speed and ease of trial recruitment.

Study methods and procedures

Nova built a multi-scale *in silico* model capturing how NPIs - such as lockdown or mask-wearing - affect rates of infection with the most common respiratory viruses and the impact of the prophylactic treatment OM-85 under different NPI scenarios in the context of an upcoming trial. The model was calibrated and validated using independent population and patient-level datasets. It successfully reproduced UK surveillance data from 2020 on respiratory tract disease burden under lockdown measures.

Impact on industry and regulatory processes

The model was used to calculate the required adjusted sample size and recruitment efficiency under various NPI scenarios, allowing OM Pharma to make informed clinical development decisions and take risk mitigation strategies (such as considering an adaptive design). Furthermore, by quantifying absolute benefit versus event rate ratios, the model helped OM Pharma to identify the optimal analyses and reporting under which clinical trials could be conducted - for instance, with altered eligibility criteria.

Technical abstract

Respiratory disease trials are profoundly affected by non-pharmaceutical interventions (NPIs) against COVID-19 because they perturb existing regular patterns of all seasonal viral epidemics. To address trial design with such uncertainty, we developed an epidemiological model of respiratory tract infection (RTI) coupled with a mechanistic description of viral RTI episodes. We explored the impact of reduced viral transmission (mimicking NPIs) using a virtual population and *in silico* trials for the bacterial lysate OM-85 as prophylaxis for RTI. Ratio-based efficacy metrics are only impacted under strict lockdown, whereas absolute benefit already is with intermediate NPIs (e.g. mask-wearing). Consequently, despite NPI, trials may meet their relative efficacy endpoints (provided recruitment hurdles can be overcome) but are difficult to assess concerning clinical relevance.

These results advocate reporting various metrics for benefits assessment and using adaptive trial design and adapted statistical analyses. They also question eligibility criteria misaligned with the actual disease burden.

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nova
DISCOVERY

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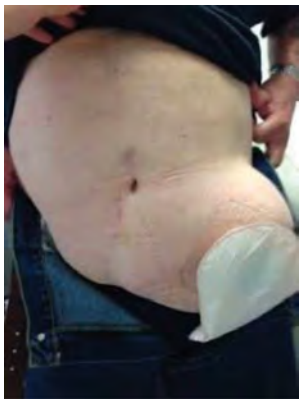
Case Study 8

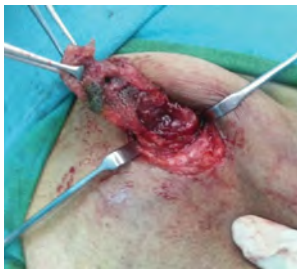
Addressing parastomal herniation through biomechanical simulation

Motivation and problem formulation

Parastomal hernia remains a significant source of post-operative morbidity. Existing surgical solutions have shown limited success while not addressing the biomechanics underpinning parastomal herniation.



Parastomal Hernia



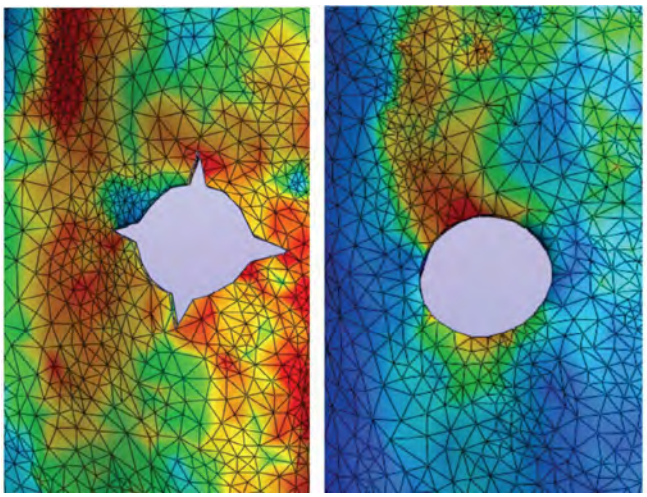
Mesh Erosion

Pathophysiology: Chronic repetitive mechanical stress induces secondary changes in tissue fibroblast function resulting in a chronic non healing wound state. Mesh reinforcement has reduced parastomal hernia rates but its erosion complication has discouraged widespread adoption.

The **primary objective** was to examine the influence of stoma aperture shape on abdominal wall stress and tissue destruction. The **secondary objective** compared mesh designs with respect to abdominal wall stress.

Unanswered Questions:

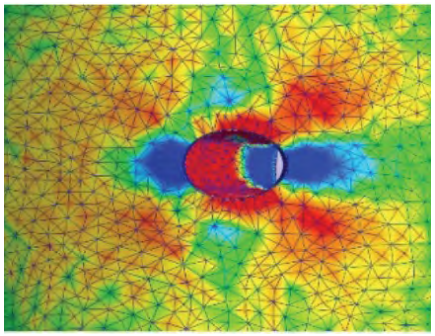
- **How do we reduce tissue stress?**
- **Can we make mesh safer but retain effectiveness?**



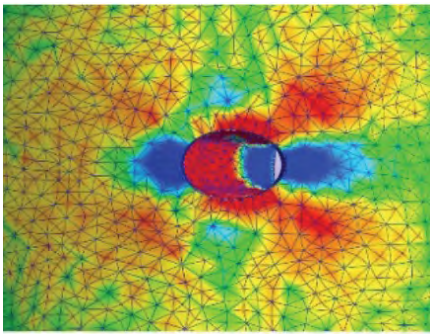
Abdominal Wall Simulation Through Finite Element Analysis

The Circular Stoma design distributed tissue stress more evenly and avoided stress risers compared to the traditional Cruciate design.

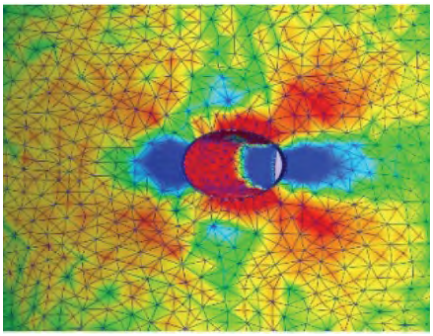
Peak and median tissue stress was significantly lower with the Circular design. ($P<0.01$)



Sugar Baker Mesh Design



Keyhole Mesh Design
1.0x Multiple of Stoma Aperture Diameter

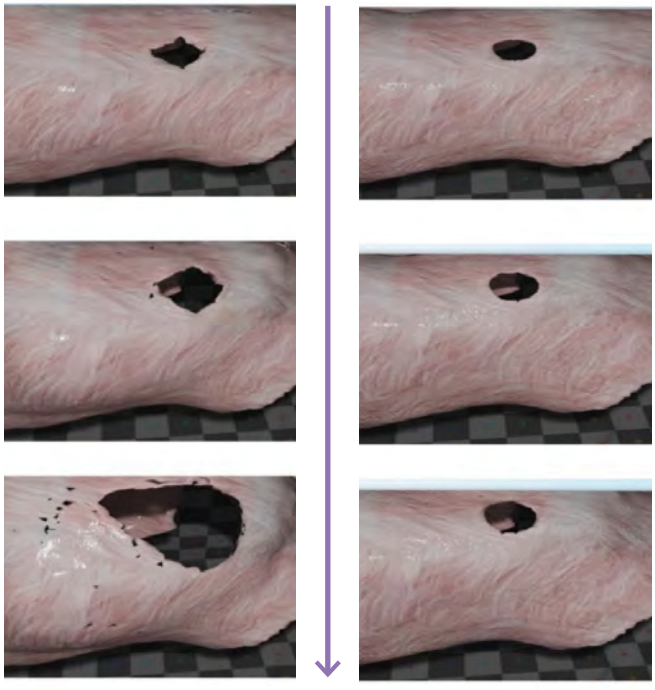


Loose Mesh Design
1.5x Multiple of Stoma Aperture Diameter

Existing and novel mesh designs were compared iteratively to find an improved mesh design with respect to herniation and safety.

A novel loose mesh design was found to reduce abdominal wall stress as effectively as the gold standard keyhole design while avoiding mesh proximity to bowel; potentially avoiding mesh erosion. ($p = 0.223$).

Cruciate Incision **Circular Incision**



The Circular Stoma design better preserved abdominal wall integrity over time compared to the traditional cruciate technique.

Purple arrow indicates passage of time.

Conclusion

- This study has demonstrated that the shape of the fascial incision and mesh design have a significant impact on parastomal hernia formation.
- Novel designs can be used to optimise the stoma. The circular stoma and loose mesh designs are promising avenues for future research.

Future challenge

- Abdominal wall modelling is a promising tool to better understand hernia formation and treatment

Question or problem addressed

A parastomal herniation is a common event following stoma formation. It is a significant source of postoperative morbidity and patients reported poor quality of life.Existing research has not determined the ideal method for preventing and repairing parastomal hernias. Current surgical techniques do not consider the underlying biomechanical principles underpinning the parastomal hernia. Understanding the disease process underlying parastomal hernia has become imperative to tackle this challenging pathology. Insights gained from biomechanical simulations can be used to optimise the design of the stoma to mitigate parastomal herniation.

Study methods and procedures

This study uses a simulation technique to examine the influence of stoma aperture and mesh design on abdominal wall stress and hernia formation. This simulation technique sheds light on the underlying shortcomings of existing techniques, such as the cruciate stoma, keyhole mesh reinforcement and the Sugarbaker mesh technique and compares them to two new designs. This study proposes two novel designs, the circular stoma aperture and loose mesh reinforcement, as alternatives to existing techniques. This study has demonstrated using simulation methods that the fascia incision's shape significantly impacts tissue stress and hernia formation at the stoma site. The circular stoma incision was superior to the traditional cruciate incision for tissue stress and significantly reduced tissue tearing over time. The novel loose mesh design demonstrated similar benefits to the standard keyhole mesh design regarding reducing tissue stress at the stoma aperture and was superior to the Sugarbaker design.

Impact on industry and regulatory processes

The circular stoma and loose mesh designs are promising targets for future clinical research in preventing and repairing parastomal hernia based on biomechanical principles. Developing novel surgical strategies using simulation opens new research avenues to decrease the disease burden of parastomal hernia. From an ethical perspective, the application of future surgical devices, such as novel mesh designs and operative techniques, should be optimised *in silico* before exposing animal and human subjects to potential harm.

Technical abstract

Parastomal hernia remains a significant source of postoperative morbidity. Existing surgical solutions have shown limited success while not addressing the biomechanics underpinning parastomal herniation. The primary objective was to examine the influence of stoma aperture shape on abdominal wall stress and tissue destruction. The secondary objective compared mesh designs concerning abdominal wall stress. Finite element analysis of an abdominal wall model was used to simulate various stoma and mesh designs. The outcome measures were abdominal wall pressure (mmHg) required

to initiate tissue tearing, stress distribution and median and peak abdominal wall stress (N/m2). The simulation demonstrated that the cruciate stoma incision developed high-stress concentration at the apices of the slit incisions. The circular stoma incision distributed stress uniformly. The circular stoma design was more resistant to tissue tearing. The keyhole mesh design demonstrated the lowest median and peak stress at 17.32 and 28.01 N/m2. This was a statistically significant stress reduction compared to the Sugarbaker and no mesh designs ($p < 0.001$). There were no significant differences between the keyhole mesh design and loose mesh designs if the loose mesh design aperture did not exceed 1.5 times the stoma aperture diameter ($p = 0.223$). This study has demonstrated that the shape of the fascia incision and mesh design significantly impact parastomal hernia formation. Simulations can be used to optimise the stoma. The circular stoma and loose mesh designs are promising avenues for future research.

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Salisbury
NHS Foundation Trust

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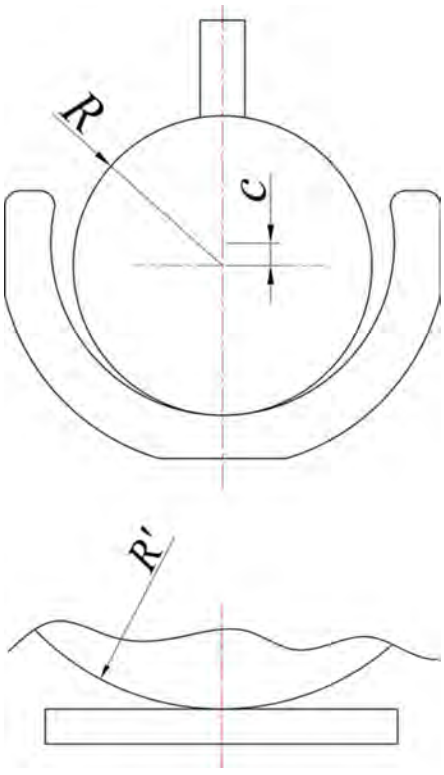
Case Study 9

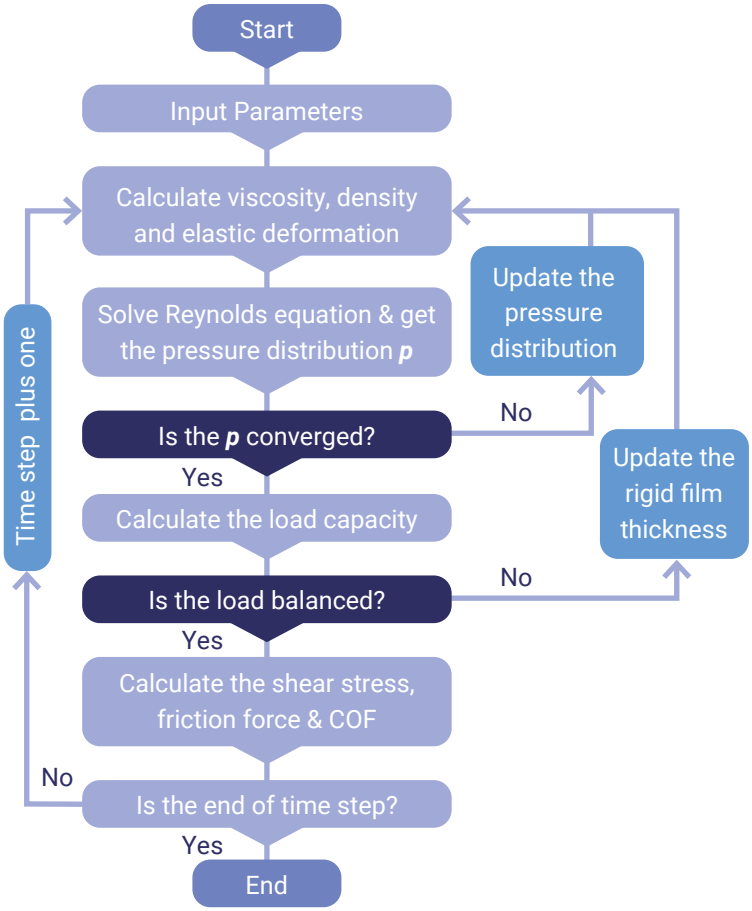
In silico preclinical prediction of friction of total hip replacement bearings

Introduction

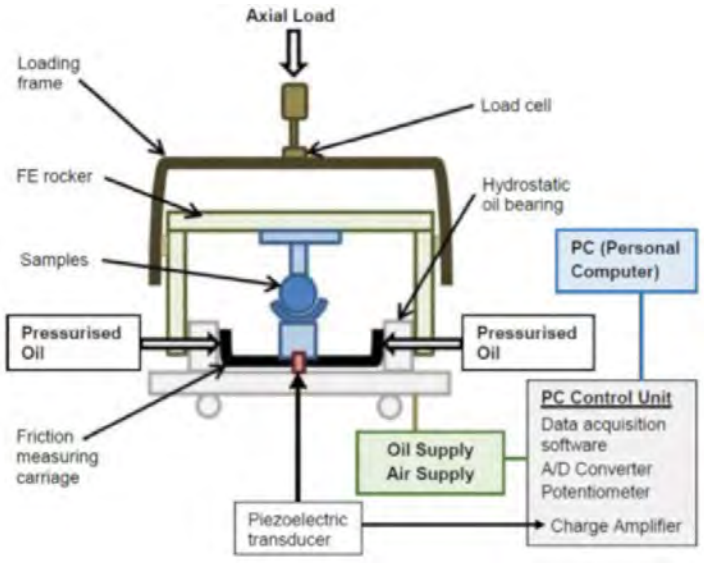
Despite five decades of pre-clinical simulation of total hip replacements, a framework for the accurate prediction of friction when subjected to established pre-clinical testing methodologies does not exist. The aims of this study was to develop a framework for predicting friction for a range of typical motion cycles, which can be represented in a (2D) pendulum friction simulator.

Methodology

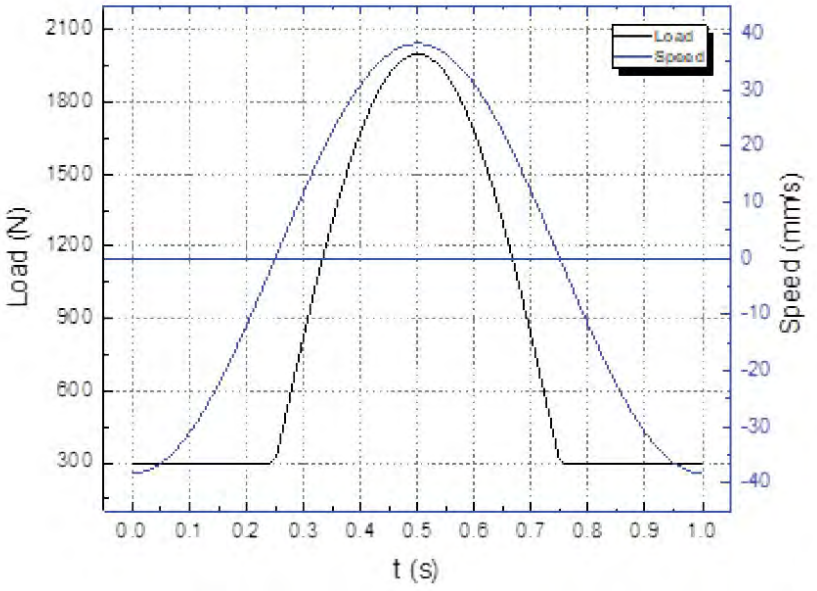




Validation



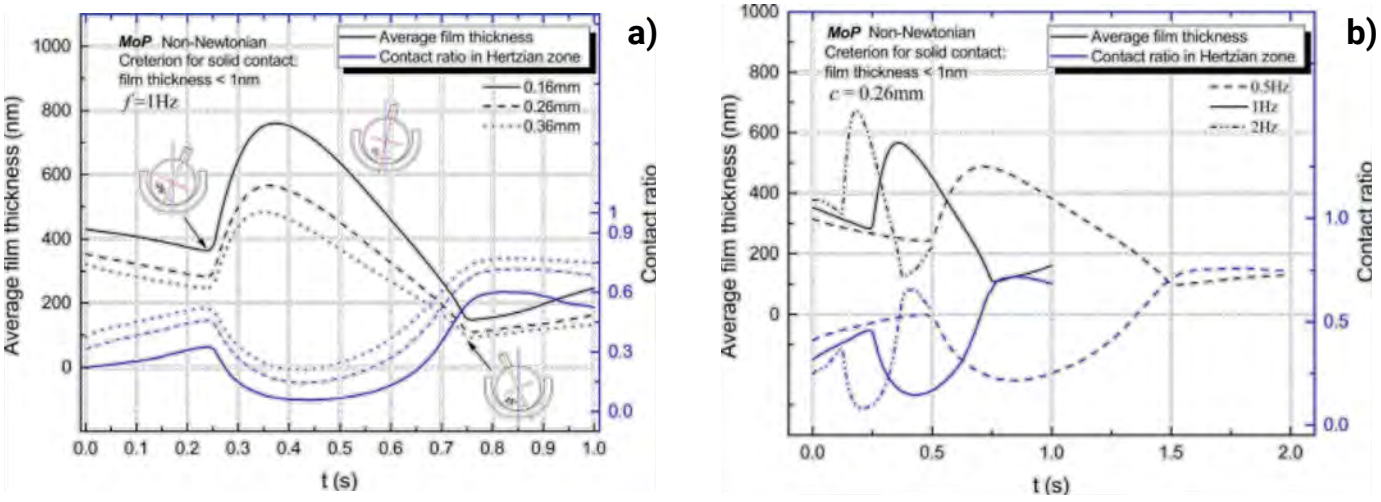
Schematic of pendulum hip simulator



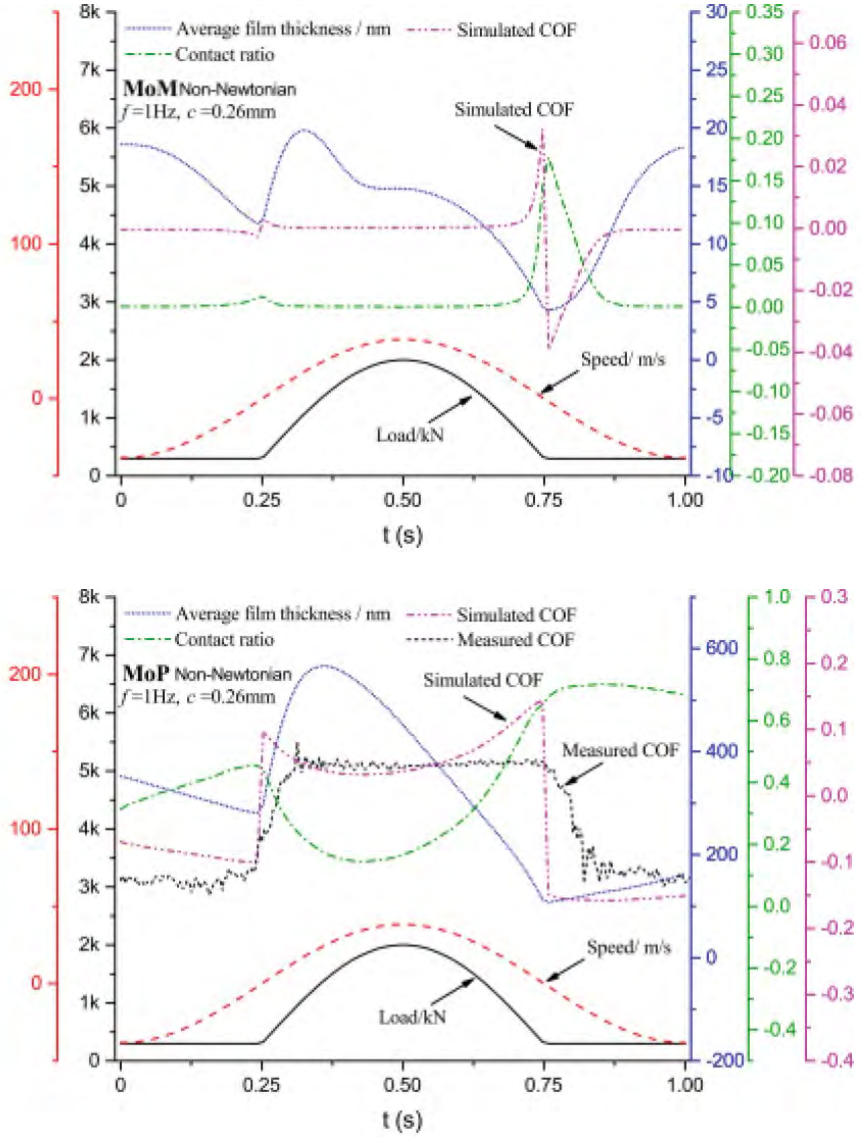
Load and velocity profiles when f = 1Hz

	CoCrMo Head	UHMWPE Cup	CoCrMo Cup
Young's Modulus, E (GPa)	220.0	1.0	220.0
Poisson's Ratio,	0.3	0.5	0.3
S_q *(nm)*	7.0	860.0	8.0
S_{sk}	-5.2	0.8	-5.1
S_{ku}	109.0	8.8	118.0

Results



a) Average film thickness and contact ratio for MoP with different clearance and **b)** Average film thickness and contact ratio for MoP at different input frequencies.



Predicted coefficient of friction and comparison with experimental data for **a)** MoP and **b)** MoM bearings with c = 0.26mm, f = 1 Hz. These simulation results consider non-linear rheological properties of the lubricant.

Conclusion

A novel ab-initio computational framework capable of predicting mixed lubrication and friction has been produced for 2D pendulum friction hip simulator contact. This model uses intrinsic surface, mechanical and rheological properties and does not required experimentally observed tribological quantities for the predictions. This includes the non-Newtonian behaviour of 17 g/L bovine serum lubricant.

Question or problem addressed

The friction of total hip replacements has been the focus of many clinical and preclinical studies, both experimental and *in silico*. Despite five decades of preclinical simulation of total hip replacements, a framework for accurately predicting friction when subjected to established preclinical testing methodologies does not exist.

As orthopaedic technologies progress, there is a need to understand better and predict friction and its systemic effects at other interfaces. Due to the use of larger head sizes, new materials and implant designs, friction at the bearing surfaces (and the systemic effects) has become more relevant for implant interfaces between modular components and the implant fixation to bone, both of which are implicated in the clinical failure of devices.

Study methods and procedures

A transient non-Newtonian elastohydrodynamic lubrication (EHL) computational model was developed to analyse and predict the frictional properties of metal-on-metal and metal-on-polymer hip prosthesis. A range of clearances between the acetabular cup and femoral head were investigated. Different frequency values of the pendulum simulator were also considered. Film thickness and friction values were comparatively analysed with the applied load and speed profiles. Numerical models and friction predictions were validated using an ISO-compliant ProSim pendulum friction simulator (Simulation Solutions Ltd., Stockport, UK).

Impact on industry and regulatory processes

The results presented in this study signify an enhancement and step forward in the current tools available for the preclinical assessment of biomedical devices, specifically tribological processes. A computational model has been developed, considering surfaces with representative surface roughness and non-Newtonian lubricant properties, capable of predicting the transient coefficient of friction for a 2D pendulum hip simulator. A new tool has been developed to streamline and stratify preclinical articulating hip replacement bearings testing. This reduces the need for expensive experimental testing and can be used to identify device performance limits quicker. Future studies will be conducted to scale and translate this interfacial model to whole component systems.

Technical abstract

Preclinical testing of medical devices is both time-consuming and expensive. Furthermore, the complexity and expense of current experimental performance testing methodologies do not lend themselves to an R&D screening and optimisation tool. This study simulated an ISO-standard pendulum hip friction test, an experiment used to demonstrate efficacy before a clinical trial. The primary endpoint was the prediction of friction using realistic surface topographies without the need for experimentally derived constants. This study's predicted transient lubricating film thickness results align with several experimental observations. For MoM bearings, the lowest predicted coefficient of friction was seen to occur at two points of the cycle: The mid-point during initial loading and at max speed/load, where the predicted

coefficient of friction was μ ≈ 0.005. Upon the decrease of loading speed (towards change in direction), an increase in the predicted coefficient of friction to μ ≈ 0.02 was observed. For MoP-bearing couples, the highest predicted COF corresponds to the minimum average film thickness, where the contact ratio is also the largest. A good agreement with simulated and measured data was observed. The results presented in this study signify an enhancement and step forward in the current tools available for the preclinical assessment of biomedical devices, specifically tribological processes. A computational model has been developed, considering surfaces with representative surface roughness and non-Newtonian lubricant properties, capable of predicting the transient coefficient of friction for a 2D pendulum hip simulator.

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UNIVERSITY OF LEEDS

DePuy Synthes
THE ORTHOPAEDICS COMPANY OF Johnson & Johnson

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Case Study 10

In silico trial of personalised high tibial osteotomy

Toka virtual trial

Comparing mechanical safety of personalised versus generic high tibial osteotomy plates.

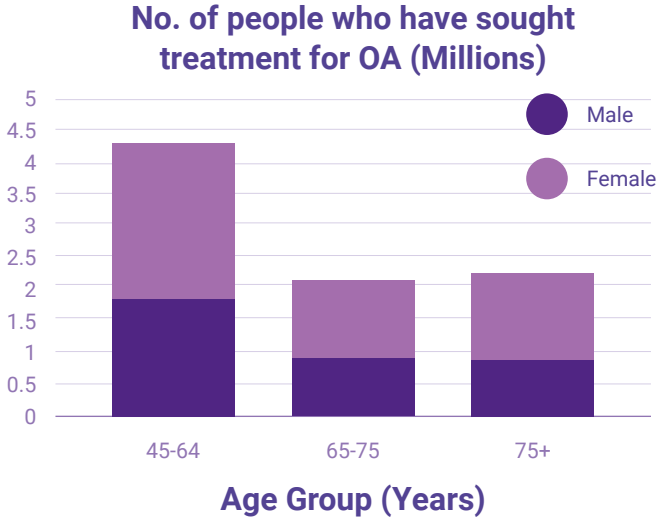
Motivation and problem formulation

Knee osteoarthritis (OA) is very common and causes a great deal of suffering and a considerable socioeconomic burden, UK: ~20% of pop. >45yr has symptomatic knee OA

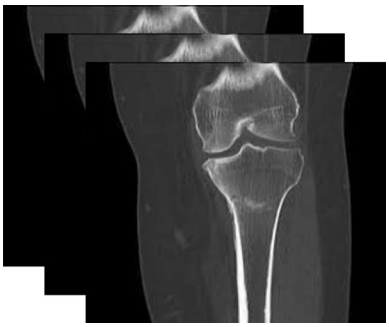
High tibial ostetomy (HTO) is a proven treatment for early knee OA, success depends on correction accuracy. A personalised HTO system has been created (TOKA) which simplifies HTO surgery and improves accuracy. TOKA Virtual Trial.

Aim

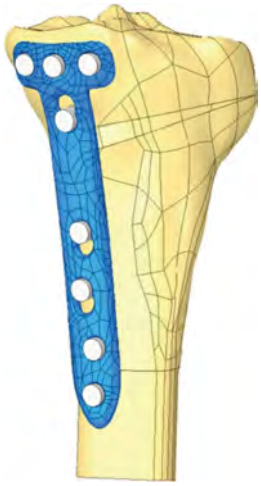
Compare mechanical safety of personalised and generic HTO.



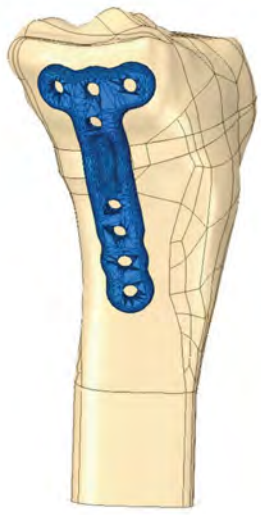
HTO modelling and finite element simulation



knee OA patient CT scans n=28



ARM A Generic n=28



ARM B Personal n=28

3
activities

- Fast walking
- Rise from chair
- Squatting

3 bone
healing stages

- 2, 4, 12 weeks

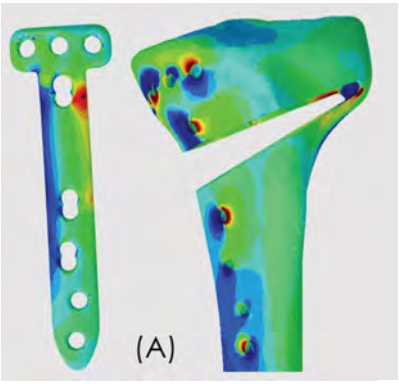
3 screw
configurations

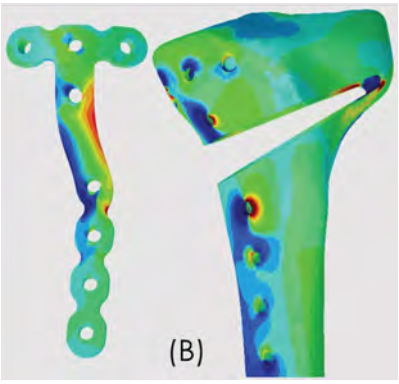
- Long/short spans
- Short plate

7,560
load steps simulated

Results

Solution took 500,477 core hours on HPC cluster.





Odds Ratio (95% CI)	P-value
0.14 (0.01 to 2.73)	0.20

Odds ratio **Personalised vs Generic** for no. of loads steps in which fatigue limit exceeded at final healing stage

Conclusion

Personalised HTO stabilisation plates have mechanical safety equivalence to generic HTO stabilisation plates. *In silico* trials of orthopaedic medical devices can: (i) perform virtual experiments and sub-group analyses that are difficult or impossible in clinical trials, (ii) perform comparative safety assessments between new and existing devices, (iii) determine mechanical factors which are important for healing and device function

Question or problem addressed

Osteoarthritis (OA) of the knee is an increasingly common debilitating musculoskeletal disease that causes great suffering and a considerable socioeconomic burden. In the UK, approximately 20% of the population over 45 years old has symptomatic knee OA. OA is progressive and might take decades to get to end-stage disease, defined by bone-on-bone contact in the knee joint. It is only at the end-stage disease that joint replacement is a viable option, meaning that sufferers can have decades of pain and disability while waiting for joint replacement. High tibial osteotomy (HTO) is a proven effective treatment that can be utilised at much earlier stages of knee OA. However, to be effective, it needs to be accurate. HTO surgery realigns the knee joint, moving the main contact from worn to unworn articular knee surfaces.

With standard methods of performing HTO surgery, achieving the planned alignment correction is challenging. We have designed a new personalised process called TOKA that greatly simplifies the surgery and improves correction accuracy. This method utilises personalised 3D-printed stabilisation plates. To compare the mechanical safety of personalised and generic stabilisation plates, we performed an *in silico* trial.

Study methods and procedures

The TOKA *in silico* trial simulated HTO surgery in a cohort of 28 virtual patients created from CT scans of 28 individual patients with knee OA. This *in silico* trial was prospectively registered at ClinicalTrials.gov (NCT03419598). The virtual cohort was duplicated into two arms, one receiving virtual HTO using a standard generic stabilisation plate and the other receiving virtual HTO using a personalised stabilisation plate. The personalised plates were generated from the TOKA planning system and differed for each virtual patient. The virtual patients were modelled using finite element analysis, with loads simulating fast walking, rising from a chair and squatting at three healing stages, 2, 4 and 12 weeks after surgery. The stresses in the stabilisation plates were calculated for these activities. Failure of these types of devices occurs due to fatigue. The number of load steps for which the plate stresses exceeded the fatigue limits were compared between the generic and personalised arms. The *in silico* study demonstrated that personalised stabilisation plates were comparable in mechanical safety with generic plates. The study also showed that personalised plates were less stiff and thus should promote faster bone healing.

Impact on industry and regulatory processes

The findings from the TOKA *in silico* trial were used in submissions to the Italian regulator and the UK MHRA as part of the approved applications for two clinical trials. The information provided satisfied the regulatory bodies regarding mechanical safety for the personalised device and approvals were given for the two clinical trials. The device is now generally available in the UK and the EU under the EU MDR personalised device framework. The TOKA device has also been submitted for FDA approval, with the findings of the TOKA *in silico* trial as part of the submission.

Technical abstract

The TOKA *in silico* trial simulated the treatment of early-stage knee osteoarthritis using virtual high tibial osteotomy (HTO) surgery in 28 virtual patients with 28 distinct anatomies. The virtual cohort was duplicated into a generic stabilisation plate arm and a personalised stabilisation plate arm. Using finite element modelling, the virtual cohort was subjected to physiological loads simulating fast gait, rising from a chair and squatting at three healing stages (2, 4 and 12 weeks post-surgery). The maximum Von Mises stress in the stabilisation plate was the primary outcome measure. Fatigue is the main failure mode and the maximum stress was compared to the fatigue limit. The TOKA *in silico* trial showed that personalised HTO stabilisation plates had mechanical safety equivalence to generic HTO stabilisation plates. The odds ratio for stress to exceed the fatigue limit in terms of personalised versus generic stabilisation plates by the final considered healing stage was 0.14 (95% CI 0.01 to 2.73). The TOKA virtual trial

has demonstrated that *in silico* trials of orthopaedic medical devices can: (I) perform virtual experiments and sub-group analyses that are difficult or impossible in clinical trials, (II) perform comparative safety assessments between new and existing devices, (III) determine mechanical factors which are important for healing and device function.

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Case Study 11

In silico simulation to advance treatment of craniosynostosis

Background

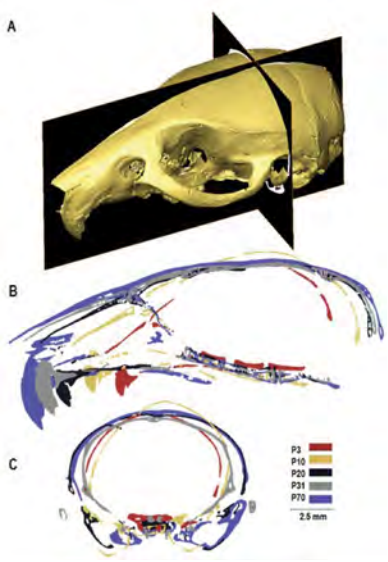
Cranial joints, sutures, allow the skull to expand and accommodate the brain growth in children.

Craniosynostosis is premature fusion of the sutures and occurs in about 1 in 2000 births.

Clinical management of this condition is challenging, especially in cases of multiple suture fusion, and usually requires the child to have several operations.

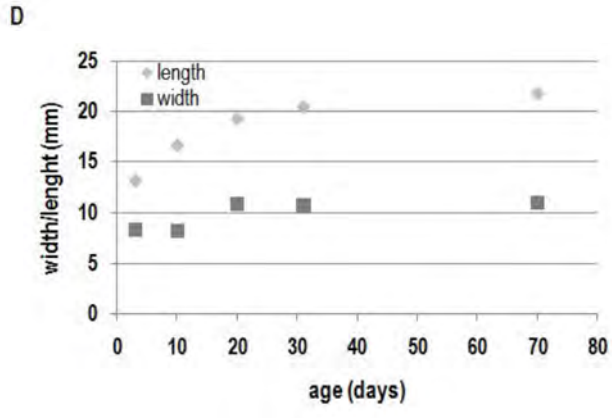
Aim

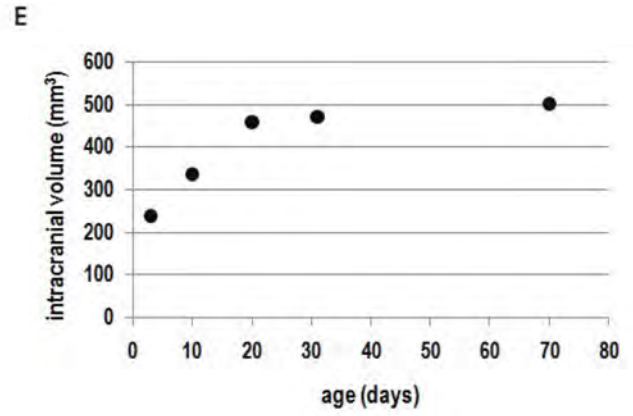
The long term vision of this project is to develop a computational framework to predict the skull growth and virtually compare different treatment options for a patient to ensure the best treatment will be carried out, minimising the complications and potential further operations.

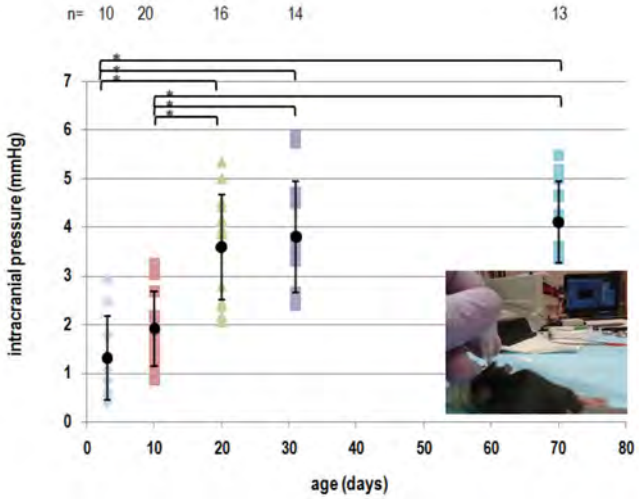


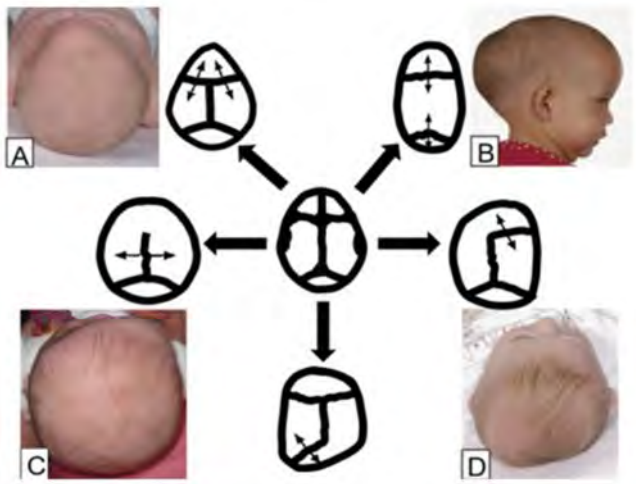
Measuring intracranial pressure during development in wild type mouse.

Biomechanics of mouse skull growth

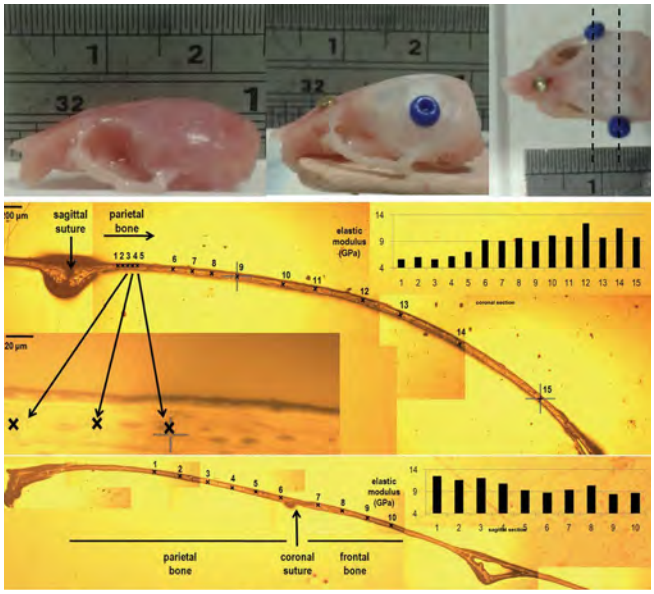




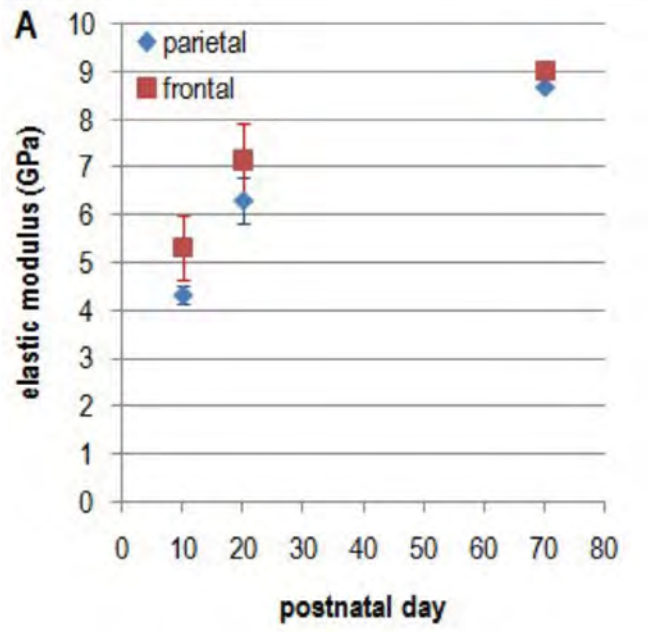


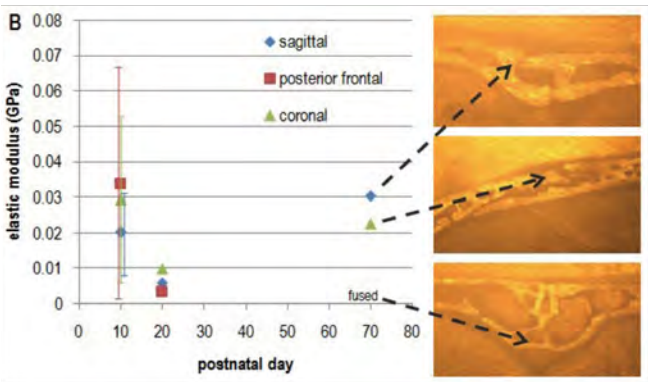


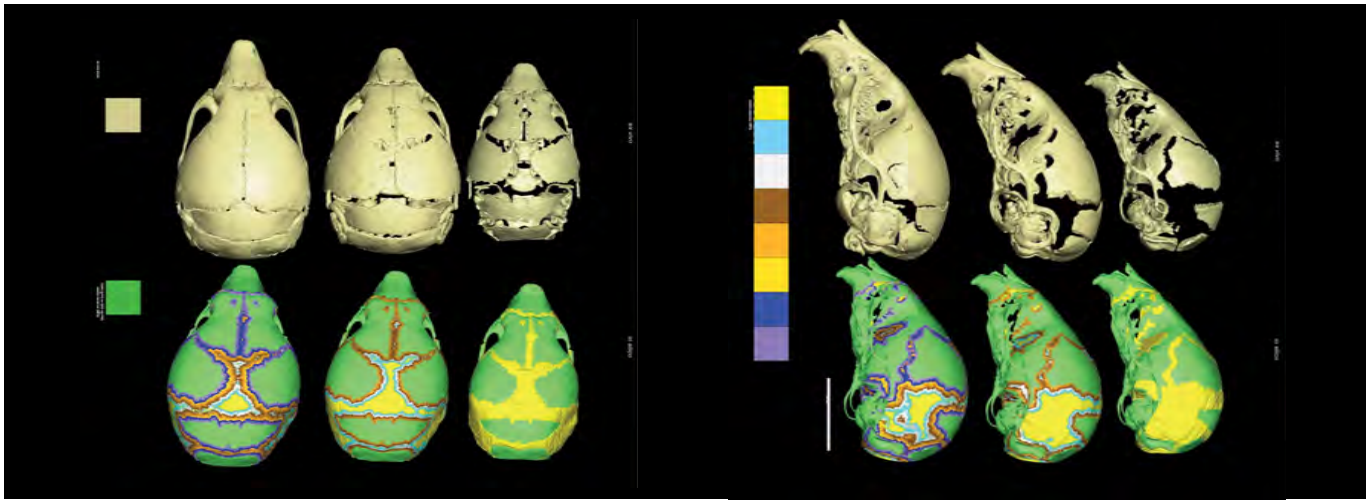
Craniosynostosis: (A) metopic; (B) sagittal; (C) bi-coronal; (D) uni-coronal suture fusion.



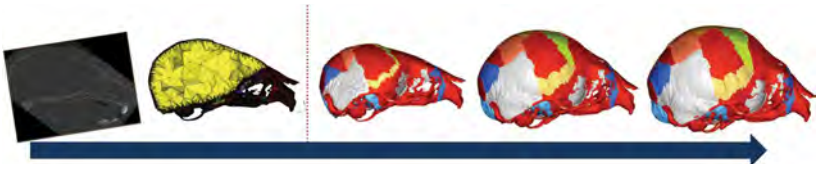
Measuring bone and suture mechanical properties during development in wild type mouse.





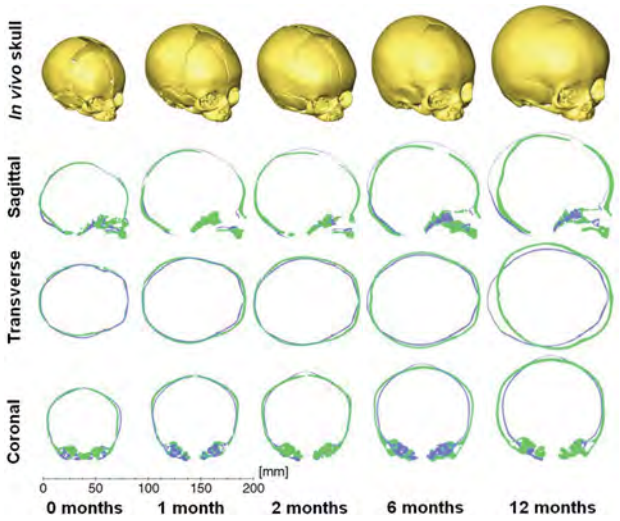


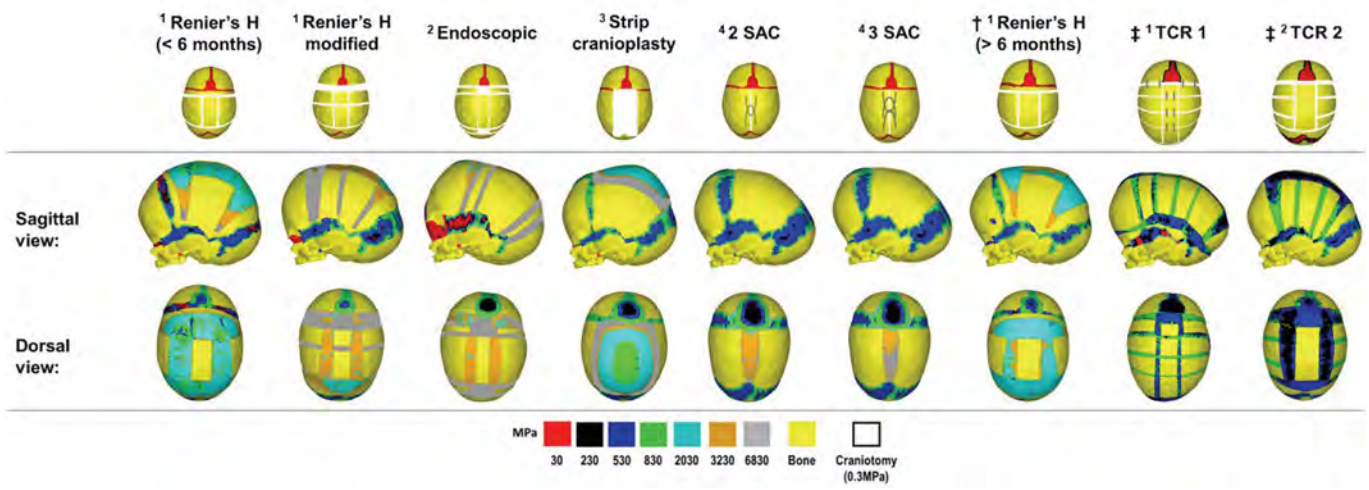
Predicting radial expansion of the skull and bone formation at the sutures at P7 and P10: ex vivo skull compared vs. *in silico* predictions.



Biomechanics of human skull growth & sagittal craniosynostosis treatment options

Predicting normal human skull growth: *in vivo* skull section (green) compared vs. *in silico* predictions (blue).





Predicting skull shape of a child following surgery and virtual comparison of different surgical techniques.

Question or problem addressed

In silico computational models enable us to test different treatment options for various medical conditions virtually. These models allow us to test various "what if?" questions. Generic models can be easily altered to test different scenarios for comparative analysis, while patient-specific and population-based models enable us to capture individual variabilities.

Craniosynostosis (CR) is a rare yet growing medical condition caused by the early fusion of one or more cranial joints. This condition affects children craniofacial system, altering the natural growth and development of the skull. Depending on CR severity, one or multiple surgeries might be required to restore the skull shape. This study aimed to develop a validated computational framework to predict skull growth that can be used to compare different treatment strategies for different forms of this condition.

Study methods and procedures

We initially developed and validated our computational framework in normal and genetically modified mouse models of CR. We then scaled up our approach to the human skull. We first developed a validated finite element model of normal calvarial growth in humans, having characterised morphological changes during the human craniofacial growth in n=241, aged 0-4 years. We then applied our approach to 2 patient-specific CR models predicting calvarial growth following the surgery. We recently used our computational framework to compare 9 different treatment options for managing sagittal CR, i.e. the most prevalent form of CR affecting the joint in the midline of the skull. Our results highlight that different surgical techniques can constrain the growth of the brain in different ways that can potentially impact the neurodevelopment of these children.

Impact on industry and regulatory processes

The computational framework we have developed to predict skull growth has enabled craniofacial surgeons to appreciate the impact of different reconstruction techniques on brain growth and the overall skull morphology years after the surgery. It has built confidence in this key stakeholder that *in silico* models can be trusted and can indeed inform their clinical decision-making.

Technical abstract

The neonate skull consists of several bony plates connected by soft tissues called sutures. Early fusion of sutures is a medical condition known as craniosynostosis. Sagittal craniosynostosis, caused by early fusion of the sagittal suture, is the most common form of this condition. The optimal management of this condition is subject to an ongoing debate in the craniofacial community, while aspects of the corresponding biomechanics and mechanobiology are poorly understood. We developed a computational framework to predict calvarial growth. We used this framework to predict and compare the calvarial growth following ten different reconstruction techniques for managing sagittal synostosis. Our results demonstrated how different reconstruction techniques interact with the increasing intracranial volume.

Further, our data highlighted that the more invasive surgical techniques could potentially lead to a better correction of the skull compared to the less invasive techniques by 76 months of age. Nonetheless, they come at the risk of imposing higher pressure on the growing brain pre-operatively and it is unclear whether this has any functional impact on the brain. The proposed framework can inform near-optimal management of different forms of craniosynostosis, minimising the risk of functional consequences and secondary surgery.

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Team Members

Prof M Moazen; Prof MJ Fagan, Prof AOM Wilkie, Prof ML Cunningham, Prof R Hopper, Prof SW Herring, Prof L Kolby, Dr H Delye, Dr E Pauws, Dr C Babbs, Mr D Johnson, Prof R Khonsari, Dr J Libby, Dr A Marghoub; Dr C Cross; Mr O Malde et al.

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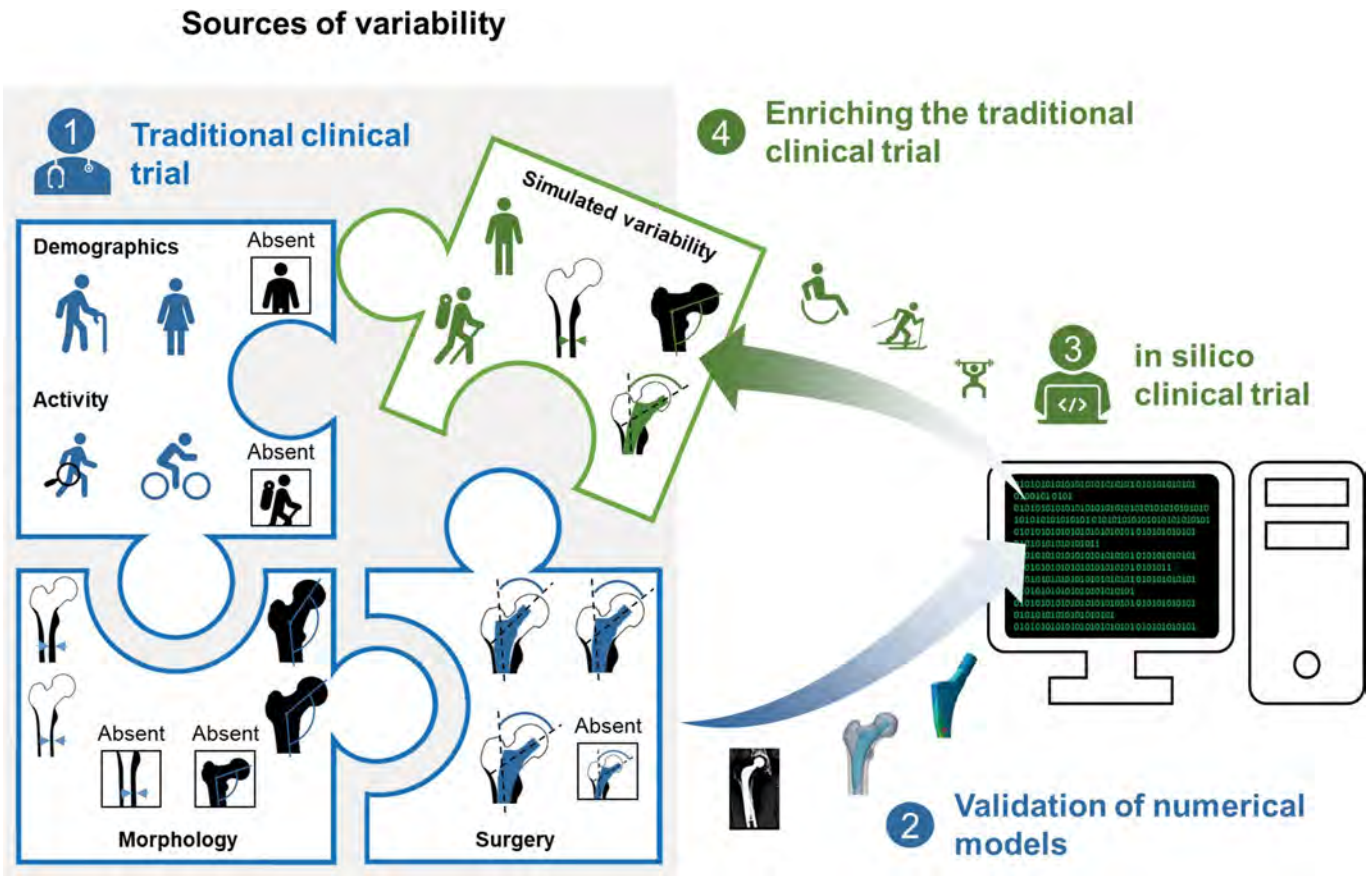
Case Study 12

In silico study of the clinical risk of scapular notching in RSA

Validation of scapular notching risk for an *in silico* clinical trial in support of a regulatory submission

- Regulatory requirements for providing clinical data are increasing.
- Clinical data may be enriched with *in silico* clinical trials (ISCT), where virtual cohorts of clinical patient-specific computer models predict the performance of a medical device.
- Case study: Is it possible to evaluate scapular notching following reverse shoulder arthroplasty via *in silico* trials?

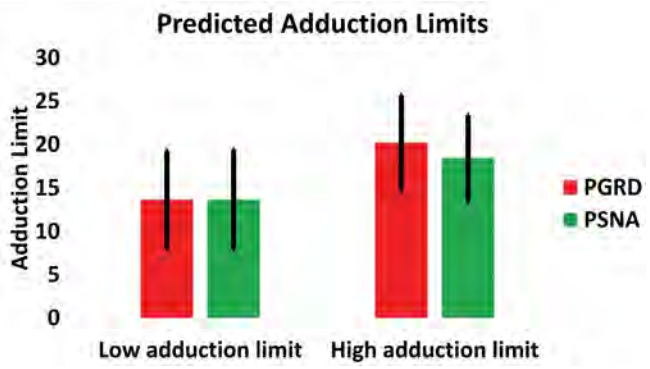


Notching risk assessment following methods used by Simovitch et al.

Clinical study of Simovitch et al demonstrated the clinical impact of anatomical and implant factors on the risk of notching *in vivo*

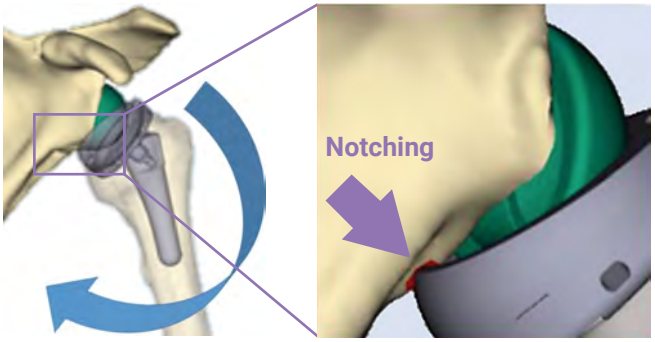
Provides clinical dataset for validation of *in silico* approach

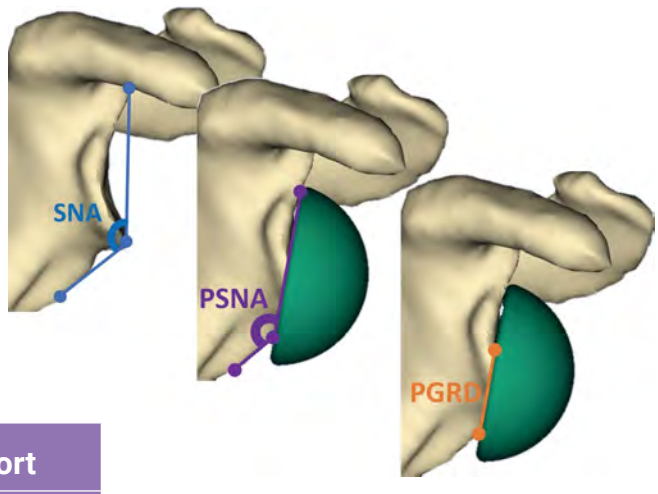
ISCT: Virtual cohort of patients (N=38), allowing for evaluation of the impact of implant placement and surgical variability on shoulder range of motion.



- Clinical study showed statistically significantly increased risk of notching with increased PSNA and PGRD
- *In silico* clinical study showed statistically significant increased adduction limit (representing shoulder range of motion) with increased PSNA and PGRD, p<0.001
- Prediction of adduction limit from ISCT is a viable surrogate for clinical measurement of notching

Simulated adduction





	Clinical Cohort		Virtual Cohort	
	No Notching	Notching	Low Adduction	High Adduction
PSNA, ° (SD)	93 (15)	124 (19)	126.4 (5.5)	135.5 (8.2)
PGRD, mm (SD)	20.1 (2.5)	24.7 (3)	13.2 (0.3)	18.1 (0.1)

SNA: Scapular Neck Angle; PSNA: Prosthesis-Scapular Neck Angle; PGRD: Peg-Glenoid Rim Distance

Conclusion

- *In silico* notching risk assessment **predicted** and **replicated** clinical findings
- Supports use of adduction limits **as *in silico* surrogates** for notching incidence *in vivo*
- Supports hypothesis that it is **possible to use *in silico* method**s to reduce and supplement traditional clinical trials

Question or problem addressed

Clinical trials cannot routinely cover all possible clinical scenarios of contemporary medical devices due to factors such as patient availability for enrolment and patient loss due to follow-up. Additionally, they cannot necessarily provide a physiological or mechanistic explanation for the origin of complications, such as implant loosening or wear. *In silico* clinical trials (ISCT) can augment clinical trials with predictions of clinical performance from a virtual cohort by providing results earlier and more comprehensively than from a traditional clinical trial. ISCT can also provide a more detailed explanation for the root cause of any complications, enabling enhanced patient stratification and implant indications for use. This case study addresses the risk of scapular notching following reverse total shoulder arthroplasty. The humeral implant contacts the scapular bone during normal activities, potentially resulting in various negative outcomes, including erosion of the scapula, damage to the implant components and loosening of the implants.

Study methods and procedures

Numerical models of 38 full shoulders were obtained from segmented and reconstructed CT scans. Each virtual model underwent simulated reverse shoulder arthroplasty (RSA) using generalised implant geometries according to contemporary surgical techniques. Following reconstruction, each joint was subjected to a simulated range of motion assessment to identify the incidence of scapular notching. Perturbations on the inferior overhang and inferior tilt of the scapular implant were included to evaluate the impact of surgical approach and implant design on the risk of notching. The clinical relevance of this *in silico* approach was evaluated by comparing *in silico* predictions to clinical rates of notching measured by Simovitch et al. [Simovitch R, Zumstein MA, Lohri E, Helmy N, Gerber C. Predictors of Scapular Notching in Patients Managed with the Delta III Reverse Total Shoulder Replacement. J Bone Joint Surg 2007;89(3):p 588-600.

Impact on industry and regulatory processes

The present *in silico* assessment of scapular notching risk successfully replicated observations of a previous retrospective clinical study which stratified implant parameters associated with scapular notching. Additionally, the model enabled direct assessment of the impact of implant position and bone resection on a range of motion on a patient-specific basis, adding mechanistic insight beyond what can be obtained via a clinical study. This study provides confidence in the clinical utility of future applications of the proposed

modelling approach for supporting the design of new RSA systems and refining surgical techniques via a comprehensive consideration of patient anatomies, implant characteristics and surgical approaches.

Technical abstract

In silico clinical trials (ISCT) allows for a robust, population-level assessment of postoperative complications that can occur in orthopaedics. The present study simulated reverse shoulder arthroplasty and subsequent joint range of motion following clinical methodologies outlined in Simovitch et al. [doi.org/10.2106/jbjs.f.00226] in 38 segmented and reconstructed full shoulders. The primary goal of the study was to evaluate the risk of scapular notching in a virtual cohort and, in doing so, achieve the following: assess model fidelity for determining the influence of various parameters (including glenosphere inferior tilt, inferior overhang and native scapular neck angle), as well as establish the credibility for adduction limit as an *in silico* surrogate for scapular notching incidence. The clinical study did not report the surrogate measure of adduction limit; rather, only the presence of notching was recorded, along with corresponding implant (inferior tilt, glenosphere inferior overhang) and anatomic (native scapular neck angle) metrics. The numerical models showed statistically significant differences in adduction limit as a function of the influencing parameters ($p<0.001$) when varying glenosphere inferior overhang and inferior tilt, following trends seen in the clinical study. The present study has demonstrated that ISCT can evaluate and assess, on a population level, the risk for scapular notching when considering surgical variation and patient anatomy.

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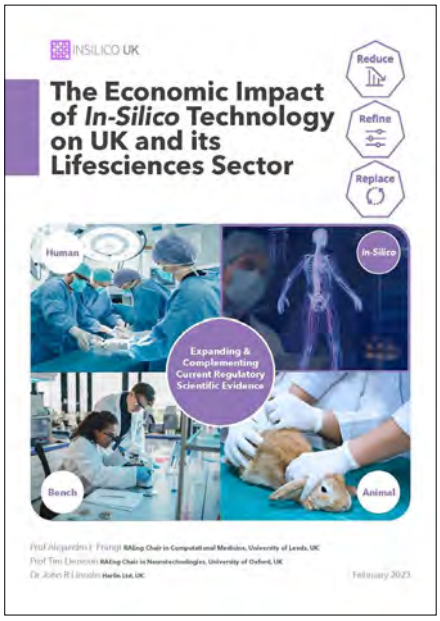
Other Relevant Readings



InSilicoUK Innovation Network

The Economic Impact of In-Silico Technology on the UK and its Lifesciences Sector

By 2025 at least £2.6 billion worth of Pharma and Med Devices underpinned by in-silico methods will be made in the UK, even at our current share of the global manufacturing.

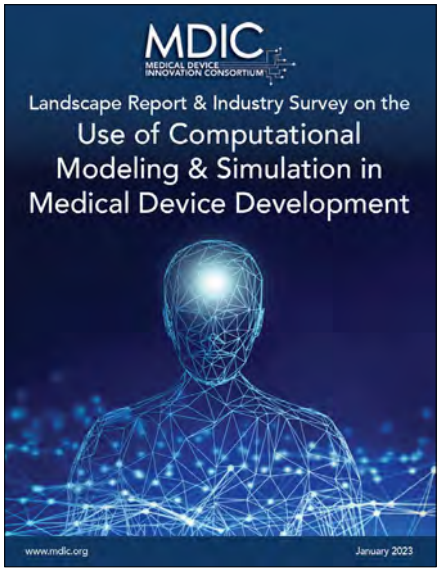
In-silico technologies will be critical to the future of the 111,200 directly employed in 2010 UK manufacturing sites in the Pharmaceutical and Med-Tech sectors.

In collaboration with Beauhurst and InnovateKTN

Researching next-generation life sciences innovations in the UK

On the UK's Public and Private Equity investment in the UK over the past 10 years on *in silico* medicine technologies

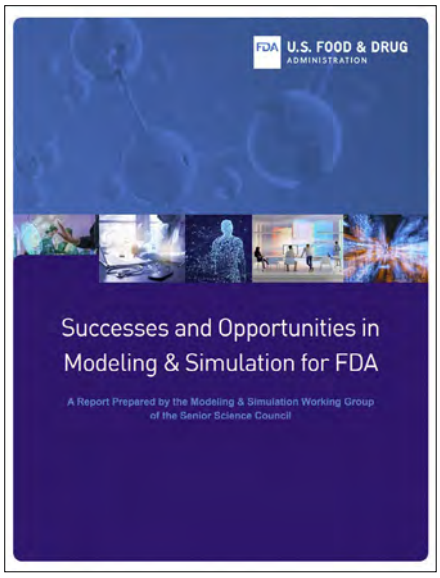
www.beauhurst.com/research/in-silico-medicine/



Medical Device Innovation Consortium

Use of Computational Modeling & Simulation in Medical Device Development

Computational modeling and simulation (CM&S) has numerous applications throughout the medical device life cycle, from product development and testing to clinical evaluation, premarket submissions, and postmarket performance assessment and failure analysis. CM&S has the potential to reduce or eliminate the need for physical prototyping and testing, and to rapidly and cost-effectively evaluate more design and clinical use variations than are feasible using traditional methods.



Modelling & Simulation WG, FDA's Office of the

Successes & Opportunities in Modeling & Simulation for FDA

1. Elucidates how and where M&S is used across FDA, and the type and purpose of M&S used

2. Presents a selection of M&S case studies from across nearly all FDA centers, which demonstrate how M&S is playing a tangible role in FDA fulfilling its mission

3. Identifies opportunities for FDA to better harness M&S in upcoming years by embracing computational advances and new (and big) data streams to develop improved public health solutions

Government Office for Science

Council for Science and Technology

Computational Modelling: Technological Futures

This report, known also as Blackett Review, sets out the findings of a review looking at the rapid evolution of UK computational modelling capability, and how it could be better used in both the public and private sectors.

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How to Cite this Report

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How to Engage with InSilicoUK

We are working to make the UK the best milieu for delivering medical innovations using *in silico* evidence and regulatory science. A well-coordinated and cohesive cross-sectorial community is the key to delivering a national strategy that accelerates adopting *in silico* trials and supports its uptake by the UK's LifeSciences sector. Such a strategy must be adapted to the specific challenges, drivers and opportunities in the UK and engage with international initiatives to achieve faster, safer and more cost-effective innovation for patient benefit.

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