INSILICO UK

Royal Academy of Engineering

Medicines & Healthcare products Regulatory Agency

making science work for health | PHG FOUNDATION

Journeys, experiences and best practices on computer modelled and simulated regulatory evidence

Cross-regulator workshop report

Authors

Elizabeth Redrup Hill, Colin Mitchell, Puja Myles, Richard Branson, & Alejandro F Frangi

December 2023

Cross-Regulator Workshop on Computational Modelling and Simulation—Workshop Report

Acknowledgements

With thanks to the Royal Academy of Engineering for organisational support and to KPMG for assistance with meeting logistics. We are also grateful to Zeike Taylor (University of Leeds), Sheena Macpherson (University of Leeds) and Eliot Gillings (Royal Academy of Engineering) for their research and notetaking during the event.

URLs in this report were correct as of December 2023

How to cite this report

Redrup Hill, E., Mitchell, C., Myles, P., Branson, R., & Frangi, A.F. (2023). Cross-Regulator Workshop: Journeys, experiences and best practices on computer modelled and simulated regulatory evidence— Workshop Report. InSilicoUK Pro-Innovation Regulations Network. https://doi.org/10.5281/zenodo.10121103

Contents

Key points

- Computational modelling and simulation (CM&S or in silico trials) have considerable potential to refine or, in some cases, replace a significant proportion of late-stage human clinical testing, benefitting patient safety and outcomes and the economy. However, a critical barrier to adopting and scaling CM&S methods of evidence generation (hereon 'CM&S methods') for life sciences has been identified as uncertainty about regulators' expectations and requirements for CM&S evidence. This workshop sought to discuss those uncertainties across industry and UK regulatory and certification agencies to see what lessons could be learnt to address remaining ambiguity on its appropriate use for life sciences.
- There is significant appetite for a consistent effort across UK regulatory agencies to address uncertainties on using and accepting CM&S methods across government and regulatory bodies. Cross-Government work is already underway on new approach methodologies (NAMs), which might provide a platform for further coordination. In addition, industry, academia, and broader stakeholders recommended that regulators work towards a high-level consensus statement, signalling their openness towards considering CM&S evidence.
- A set of general principles for quality model assurance would support good simulation practices and the further adoption of CM&S as an evidence-generation tool. The principles contained in HM Treasury's Aqua Book (proportionality, quality assurance, verification and validation, analysis with RIGOUR) provide an excellent starting point and could be tailored to improve their suitability for the regulation of CM&S methods now and in the future while remaining generalisable across sectors.
- Further engagement with policymakers and the public to understand perceptions of both current (non-simulated) and CM&S methods will assist in identifying optimal language for communicating their risks and benefits, identify sensitivities around their use, and assist in the appropriate development of trusted regulatory approaches.
- New approach methodologies (NAMs) such as CM&S methods and their capacity to generate further evidence are highly topical given the burgeoning and international interest in AI. The insights from the workshop map out some of the barriers that exist and, in some cases, demonstrate how other industries and sectors have addressed them to help ensure that CM&S methods' potential to support patient outcomes and safety are not missed in the health sector.

1. Background

Computational modelling and simulation (CM&S) uses programming languages, numerical methods and high-performance computing to create either numerical representations of first-principles equations or hybrid models (using a mix of first principles and empirical data to map correlations and draw conclusions), to reduce, refine or even replace experimental and clinical research.* Modelling and simulation have been used in biomedicine for many decades, but CM&S methods have gained momentum as computer processing power and data availability have developed, and there is now widespread interest in its economic, social and health benefits across several sectors. However, some sectors are further ahead than others in accepting CM&S methods as an evidence-generation tool. Therefore, the workshop identified an opportunity for cross-regulatory learning and discussion.

Additionally, interest in AI is surging, and there is a well-known need for increased data availability and accessibility for its effective training. New approach methodologies (NAMs) offer differing ways of doing this; for example, synthetic data can be used to gap-fill missing data needed to train AI, in some contexts.† Alternatively, CM&S methods for health can be used to generate virtual populations or to simulate organs or complex and interrelated biological systems. It, therefore, offers a way to test the efficacy of medicinal products and technologies in a manner often impossible via traditional clinical trial methods due to various ethical, legal and practical limitations. CM&S is an important evidence-generation tool in the context of AI's increasing presence in health.

However, a key barrier to their further adoption and scaling is uncertainty on regulators' expectations and the extent to which regulatory bodies will accept CM&S-generated evidence.‡ To begin to address this, the Medicines and Healthcare products Regulatory Agency (MHRA) and the Royal Academy of Engineering jointly convened a cross-regulator workshop to learn how CM&S methods are being used and regulated in other sectors as an established evidence tool for safety and performance evaluations.

---

* National Institute of Biomedical Imaging and Bioengineering (NIBIB). Computational Modelling. 2020 [cited 12 Nov 2020]. https://www.nibib.nih.gov/science-education/sciencetopics/computational-modeling

† Colin Mitchell and Elizabeth Redrup Hill. Are synthetic data 'personal data'? 2023. PHG Foundation Report Commissioned by the MHRA. https://www.phgfoundation.org/report/are-synthetic-health-data-personal-data

‡ Medical Device Innovation Consortium, Landscape Report & Industry Survey on the Use of Computational Modelling & Simulation in Medical Device Development, 2023. https://mdic.org/wp-content/uploads/2023/01/CM&S_Landscape_Report.pdf

Workshop aims

1. To promote a better understanding of CM&S methods, and to promote consistent effort to address uncertainties in their use and acceptance across UK regulatory and certification agencies.
2. To identify actions conducive to raising awareness and trust in CM&S methods as a basis for assessing risk and performance of interventions with an emphasis on healthcare.
3. To identify areas of priority to develop good simulation practices and standards that support sound regulatory evidence with an emphasis on CM&S methods for healthcare products.

Workshop overview

The opening and welcome addresses were provided by Professor Dave Delpy CBE FREng (Bioengineer and Emeritus Professor at University College London), Dr Glenn Wells (Chief Partnerships Officer at the MHRA), and Professor Alejandro F Frangi FREng (Bicentennial Turing Chair in Computational Medicine at the University of Manchester).

The workshop was divided into three main parts. First, regulators and representatives from six different sectors gave flash presentations on the extent and form to which CM&S methods are used in their evidence-generation activities. Then, a panel of wider stakeholders from industry bodies, academia and the public sector were invited to provide their initial reflections and perspectives on the barriers and opportunities associated with increased adoption of CM&S methods. Finally, delegates (n 55) were divided into breakout groups and tasked with identifying generalisable principles to ensure the credibility and quality of CM&S methods and, in turn, to generate key priorities for the short, medium, and long terms to support their increased adoption as a form of acceptable regulatory evidence.

An invited keynote presentation was also provided by Dr Miguel Lago, a visiting scientist at the US Food and Drug Administration (FDA), who provided an overview of the measures being taken by a range of actors to trial and demonstrate the value of their increased acceptance in medical technological developments and regulatory pathways in the United States.

In this report, we summarise the presentations and discussions from the workshop and draw out key points, themes, conclusions, and recommendations for a range of stakeholders in their further adoption of CM&S methods in regulatory pathways.

Any opinions in this report should not be taken as policy statements for any of the organisations represented.

The agenda and delegate list are included in the Appendix.

2. Workshop summary

2.1. Opening and setting the stage

This section covers

- setting the stage from a cross-regulatory perspective on acceptability of CM&S methods
- introduces the InSilicoUK Innovation Network and the bases for convening the workshop

Key themes include

- fragmentation in the regulatory landscape and its impact on cross-regulator communication
- regulatory uncertainty on the acceptability of CM&S methods and how to validate such models
- the importance of capacity and capability building

Setting the stage. What is needed and why?

Keynote from the MHRA - Dr Glenn Wells, Chief Partnerships Officer, MHRA

Dr Wells provided an overview of the regulatory and policy environment within the UK and discussed why this workshop is important. He noted that the UK Government has indicated strong support for life sciences research and innovation, and highlighted the importance of this workshop in that it brought together six regulators from different industries to discuss what is needed to further the acceptance of CM&S methods within their regulatory pathways (with a specific focus on medical and life science innovation). Dr Wells picked out four key interrelated drivers and barriers:

1. ***Fragmentation*** is a notable barrier with regulators rarely engaging with each other on these issues which ultimately delays the safe delivery of innovation in all sectors, including for patients in health. This can be due to the ever-changing regulatory landscape where it is difficult to define regulators' roles and to identify and address any overlaps.
2. ***Greater engagement*** is required both among and between regulators and wider stakeholders to guard against overregulation and to ensure regulators play an enabling role for safe innovation.
3. ***Greater capacity and capability*** are necessary both nationally and internationally. Such collaborations and partnerships can help build information and knowledge on improving regulatory capability and enabling innovation.

4. ***The CERSI (Centres of Excellence in Regulatory Science and Innovation) model*** has proved effective in the United States at providing additional expertise to regulators and the wider system and provides a clear example of how such collaborations could be highly beneficial within the UK.

Dr Wells encouraged workshop participants to explore cross-sectoral challenges, barriers and solutions collaboratively and emphasised the importance of aligning systems to improve understanding of regulatory roles and, in turn, to enable better collaboration on specific issues.

Welcome and plan for the day

Professor Alejandro Frangi, Bicentennial Turing Chair in Computational Medicine at the University of Manchester

Professor Alejandro F Frangi FREng introduced the plan for the day and the work that InSilicoUK have been undertaking on CM&S methods in life sciences and medical innovation. He particularly emphasised the important role that CM&S methods can play in reducing, refining, or replacing experimental and clinical research aspects. He also outlined the workshop's aims (set out above) and introduced the Aqua Book, which contains guidelines for fit-for-purpose analysis developed by the HM Treasury in 2015. He explained that the Aqua Book expounds four principles relevant to CM&S methods and that the workshop's breakout sessions would outline what they are and seek stakeholders' feedback on their effectiveness.

In particular, he noted that InSilicoUK is a grassroots group of 1,800 stakeholders that formed three years ago with support from the Innovate UK Knowledge Transfer Network. It aims to make the UK the best environment for delivering medical innovations using CM&S methods otherwise known as in silico evidence. To date, the network has produced a series of open reports which successively build the case for adopting computational modelling and simulation as an innovation-friendly tool for modern design and regulatory evidence.§

They have also found via surveys that the top three barriers to increased acceptance for CM&S methods from regulators are: (1) uncertainty of their regulatory acceptability, (2) uncertainty about how to validate such models or to trust them, and (3) that a skills gap exists, limiting communication between regulators, industry, and academics. This workshop responds to these barriers and, in particular, goes some way to start addressing the first noted barrier.

§ Alejandro F Frangi and others, Unlocking the Power of Computational Modelling and Simulation Across the Product Lifecycle in Life Sciences: A UK Landscape Report, 2023. https://zenodo.org/record/7723230; A F Frangi, T Denison and J Lincoln, The Economic Impact of In-Silico Technology on the UK and its Lifesciences Sector, 2023. https://zenodo.org/record/7558649

2.2. State of play across regulatory sectors - Flash presentations

This section covers

Summaries of the brief presentations that representatives from regulatory and technical authorities across six different sectors (food standards, health and safety, medicinal products, product safety, defence and medical devices) provided, outlining the:

- current position of CM&S methods in their sector, including the scientific evidence sources that are recognised and have been adopted by their relevant regulatory agency, and
- existing and required skill sets on CM&S methods' assessment and validation

Key themes include

- the wider context of evidence generation methods, such as its uses for AI,
- the need for regulatory champions,
- common uncertainties in CM&S methods' acceptance and validation procedures, and
- regulatory appetite for CM&S methods and use cases

Dr Olivia Osborne, Food Standards Agency (FSA)

Dr Osborne described the role of the Science, Evidence and Research Division (SERD) of the Food Standards Agency (FSA) in providing strategic analysis, insight, and evidence across the FSA's remit to underpin the development of policies, guidance, and advice on food safety. Approaches to CM&S methods were situated within the broader context of a range of new approach methodologies (NAMs) that can be used to predict risk more accurately, rapidly, and efficiently. The FSA and Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) are currently developing a UK roadmap towards scientific acceptance and integration of these NAMs (including predictive toxicology methods using computer modelling) into safety and risk assessments for regulatory decision making. Further steps are required, including stakeholder engagement, research into the most promising technologies, validation through case studies and developing relevant skills and training. Dr Osborne highlighted that work is underway to set up a Cross-Whitehall working group to exchange information in this area and stressed the importance of ensuring public confidence in CM&S methods through increased public engagement.

Dr George Loizou, Health and Safety Executive (HSE)

Dr Loizou gave an overview of the development of computational modelling and simulation in the context of physiologically-based pharmacokinetic modelling (PBPK) used by the HSE in assessing environmental and occupational chemical risk. As early as 1995, new modelling approaches were being discussed across Government, and cautious steps were being taken towards regulatory acceptance at national and international levels. However, Dr Loizou emphasised the importance of champions within the government who are willing to make the case for new approaches and highlighted progress slowing when champions fall away. Several current initiatives and promising developments were highlighted, including recent draft guidance assessing the credibility of CM&S methods in medical device submissions from the US's FDA and the UK Government's developments towards integrating NAMs in regulatory decision-making.

Ms Sue Cole, Medicines and Healthcare products Regulatory Agency (MHRA)

Sue Cole presented on the role of modelling in new drug applications made to the MHRA, drawing on her expertise as leader of the Clinical Pharmacology group which provides support in pharmacokinetic and pharmacodynamic assessments of new drug applications (among other functions). She stated that whilst the MHRA appreciates the mechanistic understanding that it provides, modelling is actively encouraged in applications and within regulatory guidance, and added that in the case of PBPK models, it has been used to replace clinical studies. Regarding PBPK modelling, she noted that there are some helpful frameworks and guidance on how to attain qualification and assess the predictive performance of models for regulatory acceptance from the European Medicines Agency (EMA) and FDA. She also highlighted that a range of activities are underway to further explore the usability of models in specific areas such as paediatrics. Ms Cole highlighted a range of potential benefits including better informed benefit/risk decisions, and ethical advantages, including potentially replacing or reducing reliance on animal studies or clinical trials. However, barriers still exist, including the wide variability in types and applications of current PBPK, Population or Disease Models, the complexity of the software used, inconsistent levels of model validation and reporting, and limited resources such as specialist staff to assess CM&S methods.

Dr Charlotte Hall, Office of Product Safety and Standards (OPSS)

The OPSS is the UK's product regulator and is responsible for most consumer goods, excluding food, medicines, and vehicles. The OPSS currently recognises a range of scientific evidence, but more capability and capacity building are needed to adopt CM&S methods effectively and to improve regulatory effectiveness at assessing and validating them. A range of potential benefits were identified, including adopting CM&S methods as an improved way to analyse risk, improve understanding of consumer behaviour, and to support proactive risk identification. However, there are barriers, including time and resource requirements for data cleaning and categorisation, and there is a lack of expertise and validation methods. Several enablers were identified which would support their adoption, including enhanced digital transformation capabilities, resources, and expertise to keep pace, and validated methods for risk assessment.

Dr Joe Gillard, Defence, Science and Technology Laboratory (DSTL)

The DSTL is the principal government organisation providing scientific and technological support in the defence and security sector. Evidence for military use are drawn from multiple sources: laboratory data, data extracted from field trials, real-world military operations and historical data, data generated from CM&S modelling, academic journals and expert judgement. Dr Gillard noted that CM&S methods are widely accepted in this sector as a source of advice and is routinely used to support research and procurement of military equipment, planning and policymaking, as well as providing operational advice for real-time deployments. CM&S methods are an accepted approach for extrapolating experimental data for real-world and hypothetical scenarios. This enables quantification of uncertainty, encapsulates expert knowledge, encourages interdisciplinary collaboration, highlights knowledge gaps, helps derive more value from experimental data, and provides an auditable source of evidence. The enablers for CM&S methods' increased acceptance include the availability of data to develop or validate models, quality assurance processes and systems, access to suitably qualified modellers, and appropriate CM&S software (as well as the suitability of the underpinning IT infrastructure). Within the DSTL, there is a wealth of modelling experience and methods relevant to modelling, such as differential equations, finite element modelling, uncertainty analysis, bioinformatics, software engineering, and physics-based models, among many others. The level of quality assurance (e.g., testing, review, documentation, or audit) required for a CM&S tool depends on the tool's maturity and the importance of the decision being informed by its outputs. For instance, a model which is developed to maturity and supports critical decision-making will be subject to more stringent quality assurance processes than an immature research prototype. A level of quality assurance is required in all cases, but this level must be commensurate with the maturity and context in which the model is to be used. Moreover, how CM&S results are communicated is important: results should be presented as evidence rather than facts and should be supplemented with clear statements on any underlying uncertainty, ambiguity and limitations in the results, such as the specific context the results apply to.

Rob Turpin, British Standards Institution (BSI)

Rob considered the development of standards in relation to CM&S methods in medical device and health contexts. The BSI has a catalogue of 37,000 standards and publishes approximately 2,000 new standards each year, 90 per cent of everything they publish is produced internationally by bodies such as ISO. He explained that generally, regulations are mandatory. In contrast, standards are voluntary in nature as a helpful way of describing how you might meet the differing obligations contained in regulations and standards. However, he added that 5,000 UK and EU standards hold a legal presumption of conformity (i.e., are effectively held on an equal footing with regulatory obligations), particularly for standards in high-risk domains. He also noted the UK's strong history of influencing global standards and that it has developed 'good practice' guidance, providing the basis for international consensus on appropriate standards. He also outlined the BSI's role in defining governance of new technologies such as AI,

where the BSI has been supporting an AI Standards Hub with the Alan Turing Institute for AI as Medical Devices (AIaMD). He also stated that in terms of in silico methods or CM&S-related standards, three phases are required. First is a landscape mapping exercise, including analysis of real-world applications and identifying knowledge gaps. Second, an accelerated consensus is required to agree on approaches to address gaps in best practices and third, the development of full global consensus standards. He highlighted that the first two phases are already partially funded and are underway in this context, and that the third phase will form part of normal 'business as usual' activities whilst working towards a long-term ambition of global standardisation.

2.3. Analysis – Benefits, barriers, and enablers across sectors

This section covers

- synthesis of key themes raised by the flash presentations and summarised in Section 2.2, and
- provides an outline of what the identified benefits, barriers and enablers are to the further acceptance of CM&S methods from a regulatory perspective

Key themes include

- differing levels of acceptability and advancement of CM&S methods across sectors,
- examples of where CM&S methods provide unique opportunities for evidence generation,
- the need to further explore what new risks CM&S methods might introduce, and
- upskilling is needed to improve communication of risks and benefits across stakeholders and the public

The flash presentations provided an excellent snapshot of the state of play for CM&S methods across various sectors and subsectors. In most cases, its use is well established as one of a range of methods of evidence generation. Still, the precise place of CM&S methods in regulatory pathways and the specific standards for validating models to satisfy regulatory requirements are yet to crystallise. In some sectors (such as defence), implementing CM&S methods may be more advanced in generating evidence where limited feasible alternatives are available. In other sectors (including health), increased acceptance of CM&S methods will require a shift from traditional approaches of evidence generation. As such, it was recognised that a wide range of potential benefits and opportunities were associated with such a shift, and that CM&S methods' common barriers and enablers were identifiable.

Benefits

Common to all sectors is the acknowledgement that CM&S methods could provide an improved way to analyse and predict performance and risk where alternatives are problematic. For example, in health, their beneficial uses include where there are gaps in or low availability of data, its use to test previously untestable populations or where a drug or device is particularly high risk for human or animal experimentation. The benefits in other industries included an improved understanding of consumer behaviour, an improved understanding of the effects of weaponry and strategic planning in defence, and to pre-emptively solve problems at the design stage in the automotive industry. CM&S methods could help reduce ethically or financially high-cost measures arising from testing a product in the real world and for health. This could reduce reliance on animal studies or clinical trials.

Barriers

Generally, the same barriers to the further adoption of CM&S methods are present across sectors. These include limited resources and a skills gap in training and expertise required to scrutinise CM&S methods and outputs fully. In particular, the acceptability of outputs and the need for guidance presents a significant barrier. Other mentioned barriers include availability of suitable data, the nature of the underpinning IT infrastructure, data protection challenges and the resource intensiveness of data cleaning and categorisation required to train CM&S methods. Moreover, CM&S methods (much like any new form of evidence generation) will introduce new kinds of risk. Those types of risk may in fact be lesser than the existing risk arising from traditional evidence methods, but both the public and regulators will need to accept and learn how to manage any new forms of risk that it introduces.

Enablers

In all sectors it was identified that increased resources would help to advance the application of CM&S methods in regulatory pathways. Significant enablers, therefore included the increased accessibility of data for evidence building, the catalysing role of regulatory champions to drive progress, enhanced communication and engagement with decision-makers and the public, and the development of appropriate standards and guidance to aid in assessing the acceptability of CM&S outputs. Some of these are already underway and promising developments were also highlighted, including significant cross-government working (for example, on NAMs) and the development of guidance and standards, both in terms of specific areas such as for PBPK modelling and broader, longer-term ambitions like the development of BSI and ISO standards for CM&S methods in the context of health. It also seems that the Department of Health and Social Care's Data Access Policy Update suggests significant movement is being made towards increasing health data accessibility in England's secure data environments.

3. Wider views and perspectives on CM&S methods

This section covers

- the keynote presentation on the US's Food & Drug Agency's progress with CM&S methods acceptability, and
- key reflections and considerations from the multistakeholder panel on all presentations to further inform and broaden discussions

Key themes include

- the importance of earlier, pre-submission conversations for increasing regulatory acceptability,
- the context-specific nature of risk acceptability or 'risk appetite',
- the importance of fostering trust and transparency in communicating its risks and benefits
- the importance of international collaboration for harmonising standards, and
- the importance of understanding (and communicating) CM&S methods' investment value

3.1. Keynote - Dr Miguel Lago, Staff Fellow, US FDA

Dr Lago is affiliated with the Office of Science and Engineering Laboratories (OSEL) which is the research arm of the U.S. Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH). Its mission is to accelerate patient access to innovation by assessing the benefits and risks of the effectiveness, safety and quality of medical products. OSEL provides expertise for regulatory decisions, collaborates with industry and academia, develops standards, and disseminates the science. Dr Lago described the work of OSEL's Division of Imaging, Diagnostics, and Software Reliability (DIDSR) in relation to CM&S methods. Surveys in 2014 and 2021 found that MedTech stakeholders' biggest concerns related to uncertainty in regulatory affairs within their own organisations and importantly on the expectations of regulators.¶ However, Dr Lago highlighted the significant value of CM&S methods for medical devices and the work undertaken at the FDA to advance this area of regulatory science.

¶ See the Medical Device Innovation Consortium's (MDIC) 2023. Landscape Report & Industry Survey on the Use of CM&S in Medical Device Development. https://mdic.org/wp-content/uploads/2023/01/CM&S_Landscape_Report.pdf

For example, a set of Virtual Family models have been developed for whole-body thermal, electromagnetic and fluid dynamic simulations, and have been cited in over 200 regulatory applications for medical devices, contributing to more effective and predictable devices.

Another example is the Virtual Imaging Clinical Trial for Regulatory Evaluation (VICTRE) which generates breast imaging for breast cancer assessment. This technology can generate breast models, compress them, allow examination for in situ lesion growth, and simulate imaging X-ray projection, reconstruction, and model readers. Digital breast tomosynthesis (DBT) (i.e., 3D mammography) was found to be better than digital mammography (DM) (i.e., 2D mammography) in nearly every case for the detection of breast legions. He also noted that DBT cut down the time and costs of running real clinical trials and could simulate the same results within a week.

Further insight was then given into what OSEL is also working on, including their efforts to provide an end-to-end example of using CM&S methods in a medical device regulatory submission (known as 'mock submissions'); to develop and demonstrate industry strategies for performing in silico trials to supplement or enrich clinical trial data; and to extend the credibility assessment processes to patient-specific models (e.g., digital twins). He also outlined how the FDA has approached CM&S methods, explaining that pre-submission discussions on regulatory processes with new devices will include consideration of in silico approaches and that at the premarket submission stage, comprehensive reporting of such techniques is required. However, full guidance has yet to be developed on the submission of CM&S methods for medical device approvals. Nevertheless, it was suggested that in silico trials hold a bright future and that it is hoped that in the next few decades that the use of human and animal trials will have been drastically reduced as confidence in CM&S methods grow.

3.2. Reflections and themes from the multistakeholder panel

Six experts from academia, industry and the public sector provided their initial reflections in a panel discussion on the presentations given (and outlined above) by representatives of regulatory and technical authorities, including on the keynote presentation on developments at the US FDA. The panellists were:

- **Michael Adeogun**, Head of Life Science and Health at the National Physical Laboratory (NPL)
- **Jeff Bischoff**, Senior Director of Zimmer Biomet, and American Society of Mechanical Engineers (ASME)
- **Alison Cave**, Chief Safety Officer at the MHRA
- **Thierry Marchal**, Chief Technologist Healthcare for EMEA, Secretary General of Avicenna Alliance and Industry Director for Healthcare Solutions at Ansys
- **Erman Melikyan**, Principal Clinician at Intertek Medical Notified Body & Consultant Orthopaedic Surgeon
- **Amin Rostami**, Senior Vice President of Research and Development and Chief Scientific Officer at Certara, Director of the Centre for Applied Pharmacokinetic Research (CAPKR) at the University of Manchester

The panel expressed excitement that the presentations demonstrated great convergence in support for CM&S methods. However, some also queried why progress was not being achieved as quickly in some sectors.

Confidence to approach and work with regulators

It was emphasised that stakeholders are encouraged to talk to regulators to discuss proposed approaches for example on analytics, development of skill sets etc. The FDA's support for the medical device sector more generally and their encouragement of CM&S methods was lauded but the challenges of accommodating these evidence gathering approaches under the current regulatory framework in the UK and EU were acknowledged. Such challenges include uncertainty on how to make space for high-risk devices where CM&S methods may be the only available testing technique e.g., for orphan status compounds, which raises the further challenge of how to demarcate the evidentiary standards that must be met in such circumstances. The panel pointed out that the UK has world class capabilities which put it in a position to take a leading role in developing and deploying CM&S methods and submissions in the regulatory context. It was agreed that there would likely be different standards and approaches across different regulatory sectors and that context and the point of use in the product's lifecycle would be highly relevant considerations for such submissions.

Fostering trust and transparency

It was agreed that transparency is a prerequisite for trust and that communication of the strengths and limitations of CM&S approaches is crucial, given that not everyone can or will have the same level of understanding about each model. Models can also build transparency by allowing assumptions and underpinning data to be declared explicitly and can be made auditable as illustrated in other non-healthcare industry sectors. It was also noted that some aspects relating to validation, risk and acceptability may be context specific, and that language and the broader issue of trust will need to be discussed.

Appreciating the importance of international collaboration

There was also discussion of the international efforts to advance CM&S methods in the life sciences context, including the recognition that both coordination and friendly competition between nations are equally beneficial in advancing innovation for patients.

Understanding of its investment value

In terms of industry investment in in silico approaches, it was acknowledged that there might be greater upfront costs than traditional in vivo trials, such as in the development of CM&S models but after that, those costs would dramatically decrease. A further potential efficiency of CM&S methods is that models can be modified through small tweaks to code, allowing for a whole new device to be created or a slightly different trial to be run. However, whilst this may support quicker patient access to innovation in a manner not currently possible in in vivo trials, regulatory safety and certification requirements still need to be met.

4. Identifying principles and next steps

This section covers feedback and responses from the multistakeholder delegates on the two breakout session tasks, including

- consideration of and feedback on a generalisable set of principles to support CM&S methods credibility, and
- identification of priorities for advancing the acceptance of CM&S in the short-, medium- and longer-terms

Key themes include

- consideration of the current landscape CM&S methods exist in and therefore its appropriate role,
- the importance of defining key terminology and clarifying language,
- consideration of the benefits of a joint regulatory statement,
- harmonisation of international standards for CM&S methods' validation, and
- increased recognition of the importance of sustainability in future conversations on its value

The second part of the workshop was interactive. Delegates were given two tasks to work on in small breakout groups of around 10 people each. The first task aimed to determine whether the generalisable principles set out in the Aqua Book can support the credibility of CM&S methods and associated regulatory evidence. The second task aimed to consider specific actions that a range of stakeholders could take to drive forward their acceptance in the short, medium, and longer terms.

4.1. Breakout task one - Identifying principles for quality assurance

While there are wide-ranging products and regulatory contexts where CM&S methods could play a role, it may be helpful to identify a minimum set of principles to support their credibility, quality, and associated regulatory evidence. Rather than beginning from scratch, a starting point could be based on a set of quality assurance principles outlined in 2015 guidance from HM Treasury, known as the Aqua Book (see box below). These principles were developed following a review in 2015 and aimed to provide a set of sensible and achievable principles to guide quality assurance of government analytical models.

The following table of Aqua principles was provided to delegates in the breakout materials for their consideration.

HM Treasury Aqua Principles

No single piece of guidance can provide a route to a definitive assessment of whether a piece of analysis is of sufficient quality for an intended purpose. However, the Aqua Book sets out the following principles of analytical quality assurance that will help to support commissioning and delivery of fit-for-purpose analysis:

- **Proportionality of response**: The extent of the analytical quality assurance effort should be proportionate in response to the risks associated with the intended use of the analysis. These risks include financial, legal, operational and reputational impacts. In addition, analysis that is frequently used to support a decision-making process may require a more comprehensive analytical quality assurance response.
- **Assurance throughout development**: Quality assurance considerations should be taken into account throughout the life cycle of the analysis and not just at the end. Effective communication is crucial when understanding the problem, designing the analytical approach, conducting the analysis and relaying the outputs.
- **Verification and validation**: Analytical quality assurance is more than checking that the analysis is error-free and satisfies its specification (verification). It must also include checks that the analysis is appropriate, i.e. fit for the purpose for which it is being used (validation).
- **Analysis with RIGOUR**: Quality analysis needs to be repeatable, independent, grounded in reality, objective, have understood and managed uncertainty, and the results should address the initial question robustly. In particular, it is important to accept that uncertainty is inherent within the inputs and outputs of any piece of analysis. It is important to establish how much we can rely upon the analysis for a given problem.

Delegates were asked to consider the following questions:

1. **Are these principles suitable for quality assurance of CM&S methods as part of regulatory pathways?**
2. **Are there missing elements or aspects that should be adjusted?**
3. **Are the RIGOUR credibility requirements appropriate and comprehensive for regulators?**

Each group reported back on their conversations in a final plenary session. We summarise these discussions and key points below.

4.1.1. Summary of insights from breakout session one

Positive feedback was received across the breakout groups with a view that the generalisable principles for quality assurance in the Aqua book could also be useful for CM&S methods, even though they were new to many of the delegates. It was noted

that some of the principles reflect those already embedded in current frameworks (e.g., medical device regulation). However, some delegates queried whether the landscape is still aligned with the Aqua principles or if it has moved on since 2015 when they were first developed. It was suggested that further landscaping may be required to see if and how they would need to be further developed (in addition to the points below). Several groups also discussed language and how the same term could have different meanings in different contexts, and therefore, that care should be taken to use precise language when using generalisable principles. In terms of the specific content of the Aqua principles, it was highlighted that some elements would require tweaking to suit the context of CM&S methods in medical device or similar regulatory pathways. For example, it was noted that in terms of 'proportionality', financial impacts are not relevant to the assessment of risk in health. Delegates highlighted several key points arising from their breakout discussions and outlined the principles that they felt may need to be adjusted or are missing.

First principle: Proportionality of response

It was highlighted that understandings of both risks and potential benefits would need to be tailored to the specific context that CM&S methods are operating in to achieve a proportionate response. For example, it was highlighted that accounting for benefits may be relevant to some regulatory areas but not all. For example, the MHRA's focus tends to be on benefit versus risk whereas other regulators focus on risk and less on benefit e.g., the Food Standards Agency (FSA). There was also discussion of what the requirements were for CM&S methods and what could be considered 'fit for purpose'. It was noted that this could require consideration of the limitations and interdependencies existing in each context and to consider modelling data in conjunction with other clinical or real-world data. Some groups emphasised that risk of harm and patient safety are missing from the Aqua book formulation and that proportionality should acknowledge that risk levels may change over the lifecycle of the product.

Second principle: Assurance through the development

Some groups considered the term 'quality assurance' and while contributors were positive that the principle acknowledged the importance of assessing analysis throughout its lifecycle, there was confusion expressed over what quality assurance meant in the context of CM&S methods regulation. For example, whether the term would refer to or include confidence in the technique and/or data. Contributors noted that this principle should state that analysis needs to continue until the end of its lifecycle (i.e., throughout post-market use). They also added that assurance considerations should consider that model performance is constantly changing, and that data and the populations reflected in those data are also in a state of constant flux. There were also discussions on the impact of other sources of evidence on the validity of evidence derived from models and the effect this may have on credibility requirements. For example, if the model is the main source of evidence and other sources are hard to come by, the influence of this evidence will

be more significant. Consequently, it was felt that a question arose on whether this means that model credibility requirements should rise and fall in line with such influence. Some also felt that the Aqua principles miss a key question of interest which asks what the nature of the problem is that needs to be solved, as well as the recognition of the importance for multistakeholder engagement throughout the development process.

Third principle: Verification and validation

There was a general view that further discussion is needed on what appropriate verification and validation means for a given model and that querying how far the science has been developed is necessary to understand what appropriate verification or validation approaches will realistically require. Contributors also stated that appropriate statistical verification is needed and that they felt this was adequately reflected in the principle of verification. Some felt that the importance of the independence of testing and the validation data should be better reflected in the principle. As with proportionality, there was discussion about the extent to which purpose may alter over time and that verification and validation would also need to be nimble to ensure that a model is 'fit for purpose'. Some felt that a reference to keeping pace with the 'state of the art' should also be included.

Fourth principle: Analysis with RIGOUR

Participants felt that this principle was expanding on principles one (proportionality) and two (assurance). They also expressed uncertainty over what was meant by 'managing' uncertainty and were curious about why 'communicating' uncertainty was not mentioned. More broadly, contributors noted the importance of language in the context of emerging technologies where it is often found that new fields, language can serve as the first set of standards. There was also a sense that while the RIGOUR principles were themselves not particularly problematic, they offered regulators little support in adapting to the speed at which in silico approaches are evolving.

Possible missing elements

Some additional elements were raised for further consideration of the Aqua book principles. One was (noted above) that there should be consideration of the limitations and interdependencies involved in terms of where modelling data fits within the context of wider relevant clinical or real-world data. Another is that any assumptions involved should be made explicit. Ethical proportionality was also raised as a potential addition, requiring consideration of ethical risks and benefits of adopting CM&S methods.

4.2. Breakout task two - Where do we go next?

In the second task, delegates were asked:

1. **How can we drive adoption of CM&S in regulatory pathways?**
2. **Who are the key stakeholders and what are the short-, medium- and long-term priorities?**

Delegates were provided with a grid that they could use to set out priorities according to timeframes and different actors. Participants were prompted to think beyond the principles and consider further actions, for example, wider standards or best practice that could be considered to operationalise the principles. Within these future-facing conversations, the groups suggested a wide range of priorities for action which can be categorised into broad themes. The key themes of those discussion are outlined below.

4.2.1. Key themes for future work

1. **Enhanced collaboration between regulators, industry, government and other stakeholders**

Several suggestions and priorities related to building on current collaborations, as well as developing new collaborations between regulators, industry and other stakeholders to progress on CM&S methods' acceptance.

Short-term

- **Ensuring all relevant stakeholders are involved in these discussions:** Delegates considered if there are stakeholders who should be approached by those seeking to drive forwards CM&S methods. For example, investors were identified as a potentially powerful group who could shape industry behaviour. Additionally, regulatory officers in industry were identified as potentially crucial because they have been found to prevent the use of CM&S methods out of fear that submissions will be rejected, possibly highlighting a key disparity between the excitement of researchers wishing to use them more and the trepidation felt in the regulatory space. Such stakeholders may also require persuasion on the benefits of CM&S methods and indications on where these could be used appropriately. Finally, it was noted that other stakeholders, such as rare disease patient groups, could play a powerful role in championing the benefits and necessity of CM&S methods.

Medium-to-long-term

- **Demonstrating the incentives of CM&S methods adoption for industry:** Some delegates emphasised the importance of demonstrating incentives for industry, for example, being able to indicate how CM&S methods will assist in obtaining approval or in saving time and resources. Piloting CM&S methods and health economic analyses in the medium-to-longer term would likely provide significant impetus for further industry adoption.

2. Public engagement and communication

A set of related priorities for action were also identified as important to advance CM&S methods through engagement and communication of innovative technologies to wider groups and the public.

Short-term

- **Exploring public perceptions of CM&S methods:** It is important to engage with the public to determine levels of acceptance and confidence in CM&S methods. This could involve both short- and longer-term engagement, enabling regulators and other stakeholders to address sensitivities and take action to maintain high levels of confidence.
- **Continuing to work on the appropriate language for explaining CM&S methods:** Several groups considered the importance of language and how terminology can have differing meanings depending on the audience or context.

Medium-to-long-term

- **Developing a programme of patient/public engagement on CM&S methods:** The importance of patient/public input and support for CM&S methods requires sustained efforts to drive improved public and patient involvement (PPI). In addition, the importance of communicating to the public who ultimately must have confidence in them, suggests that communication to lay people needs to be clearer and more effective. Getting this right was considered crucial for the ultimate success of their adoption.
- E**mphasising compatibility with sustainability goals:** The potential benefits of CM&S methods for sustainability are likely to become increasingly important and this is an important message to communicate to governments and publics. For example, there is an interesting conversation to be had about resource demands created by increased reliance on computing and data servers and how this could be balanced against the carbon savings of not having to conduct trials across dispersed populations.

3. Setting standards and defining regulatory requirements

Standard setting and defining regulatory standards will be essential for driving their adoption.

Short term

- **Regulators' consensus statement:** Several groups suggested that regulatory openness to CM&S methods could be evidenced through a regulatory joint statement, taking the form of a high-level statement indicating that CM&S methods are being explored and where such a statement could also initiate the development of a White Paper or more developed position.
- **Beginning the standard setting process:** Considerable encouragement was expressed for standard-setting organisations beginning the necessary process of debating and agreeing standards relating to CM&S methods both at generalised and more specific levels.

Medium-to-long-term

- **Developing mock or pre-submission processes for CM&S methods:** One concept that echoes the approach taken by the FDA and described in the Keynote Presentation is for regulators to enable pre-submission support and mock applications to help clarify regulatory expectations for applicants.
- **Agreeing standards at an international level:** In the longer term, it was expressed that a priority is to harmonise standards relating to CM&S methods at an international level.

4. To advance relevant education and skills for CM&S methods' assessment

A final key area relates to upskilling and education in relation to CM&S methods.

Short-term

Developing and expanding training programmes: Some universities are already offering regulatory training. However, it was felt that these programmes should be expanded to include part-time courses to assist professionals who are in full-time work. Moreover, the delegates expressed a desire for further cross-over between the public and private sector, both in terms of conversations and personnel, to limit the siloing of expertise.

5. Conclusions and recommendations

Computational modelling and simulation methods for evidence generation have the potential to significantly improve and increase the development of safe and effective medical devices, medicines and a wide range of technologies that could ultimately benefit patients and the public. This cross-regulator workshop demonstrated encouraging support for the further acceptance of CM&S methods across UK (and international) regulatory and allied agencies. Agencies across sectors, from defence to product safety and medicines or medical devices, have already adopted many of these methodologies as a source of evidence for new technologies. Additionally, the representatives of many agencies involved in this workshop outlined a wide range of ongoing activity within and across regulatory boundaries that explore CM&S methods and the development of best practices.

Different language may be used to describe some of these approaches (e.g., CM&S methods, in silico trials or NAMs), and the precise nature and requirements for validation, quality assurance and other dimensions will depend on context, but general parameters in common exist for drawing on models and simulated evidence.

Key themes that emerged over the course of this workshop included:

- recognition of **fragmentation** in the regulatory landscape and differing levels of CM&S acceptance and advancement across agencies
- **uncertainty** on the acceptability of CM&S methods and how to validate such models
- the importance of **capability and capacity building**
- the need to **explore** what **new risks** CM&S methods might introduce
- the importance of **building and supporting confidence** in having earlier discussions with regulators to **foster trust and transparency** needed for increased acceptance
- recognition that risk and **risk appetites are context-specific**
- consideration of the **wider landscape CM&S methods exist in** and therefore what its appropriate role is
- the need **to clarify language** to foster better communications with all stakeholders and the public
- **increased harmonisation** of international standards for its validation
- the **utility of developing generalisable principles** to further CM&S methods' regulatory and public acceptance

Some conclusions and recommendations were developed by the workshop delegates which can be related directly to the workshop aims:

1. **To promote a better understanding of CM&S methods, and to support a consistent effort to address uncertainties in their use and acceptance across UK regulatory and certification agencies**

There is significant appetite for a consistent effort across UK regulatory agencies on CM&S methods acceptance. Cross-government working is already underway on new approach methodologies (NAMs) more generally which might provide a platform for further sector-specific development. In addition, industrial, academic and wider stakeholders recommended that regulators work towards a high-level consensus statement signalling their openness toward CM&S methods for evidence generation.

2. **To raise awareness and trust in CM&S methods as a basis for assessing risk and performance of interventions (with an emphasis on healthcare)**

A clear conclusion of this workshop is the importance of exploring public acceptance of and confidence in CM&S methods and sources of evidence within regulatory pathways. This requires engagement with patients and members of the public now, to identify sensitivities and issues for regulators and for CM&S advocates to address. More sustained engagement could also help to earn trust and confidence in the long-term and to help develop appropriate language to describe and communicate CM&S methods for varying audiences. There may also be wider groups who could be engaged on this topic, for example, in the context of health, rare disease groups may even act as champions for the patient and public benefits of CM&S methods.

3. **To further explore the public acceptance and trust of CM&S methods and evidence within regulatory pathways**

Exploring public acceptance and trust on CM&S methods and evidence within regulatory pathways should be a top priority for future work. In particular, a positive and vital future step will be to run a Citizen's jury event to better understand what views and attitudes the public have towards CM&S methods.

4. To prioritise the development of good simulation practices and standards that support sound regulatory evidence, with an emphasis on CM&S methods in healthcare products

There was a consensus that a set of general principles for quality assurance would be useful and could further support good simulation practices and thereby the further acceptance of CM&S methods. The principles contained in HM Treasury's Aqua book (proportionality, quality assurance, verification and validation, analysis with RIGOUR) provide an excellent starting point that could be tailored to create principles that are up-to-date, flexible enough to keep pace with the ever-developing technology and are generalisable across sectors. There was also considerable support for standard-setting organisations' initial steps to begin the process of debating and agreeing standards relating to CM&S methods, and for their efforts to work towards standardisation at an international level.

5. To continue collaborative efforts to take forward the identified priorities and to consider further sector specific reflections raised on CM&S methods

The diverse stakeholders involved in this workshop were keen to maintain the momentum of the collaborative discussions generated by this workshop. They expressed support for further cross-sector meetings (including further key stakeholders) with the aim of taking forward the priorities identified in this report, and to consider further sector- or subsector-specific reflections.

Appendix

Event details

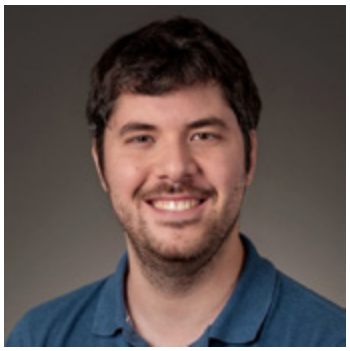
The Computational Modelling and Simulation Cross-Regulator Workshop was conceived and organised by Alejandro Frangi (University of Manchester), Puja Myles (CPRD at MHRA), Richard Branson (MHRA) with support from the Royal Academy of Engineering and PHG Foundation. The event was kindly hosted by KPMG's Life Sciences Team at Canary Wharf on Monday 10th July 2023.

Agenda

1.	09:00-10:00	**Registration and networking**
2.	10:00-10:10	**Opening and welcome** Professor Dave Delpy CBE FREng FRS FMedSci
3.	10:10-10:20	**Keynote from MHRA - Setting the stage. Why and what is needed** Dr Glenn Wells, MHRA
4.	10:20-10:30	**Plan for the day** ◆ Professor Alex Frangi, University of Manchester ◆ Dr Puja Myles, MHRA ◆ Dr Colin Mitchel, PHG Foundation
5.	10:30-11:15	**Flash presentations - Regulators view and the state of play** ◆ Olivia Osborne, FSA ◆ George Lazhou, HSE ◆ Sue Cole, MHRA
6.	11:15-11:30	**Break**
7.	11:30-12:15	**Flash presentations - Regulators view and the state of play** ◆ Charlotte Hall, OPSS ◆ Joe Gillard, DSTL ◆ Rob Turpin, BSI Focus on Standards & Guidelines
8.	12:15-13:00	**FDA invited keynote** Dr. M Lago, OSEL/CDRH/FDA
9.	13:00-13:45	**Networking lunch**
10.	13:45-14:15	**Roundtable/panel discussion - Stakeholder's perspective**
11.	14:15-15:30	**Break out group activities - Identifying principles and next steps**
12.	15:30-15:45	**Break**
13.	15:45-17:00	**Plenary panel and brainstorming - Where do we go next?**
14.	17:00-18:00	**Networking drinks and nibbles**
15.	18:00	**End**

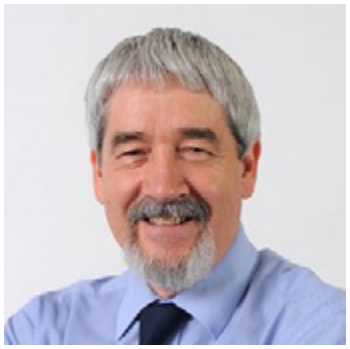
Presenters and panellists

Keynote



Dr Miguel Lago, DIDSR, OSEL, CDRH, FDA

Dr Miguel Lago is a Staff Fellow at the US's Food and Drug Administration (FDA). His research interests are in medical image perception, medical image quality assessment, in silico clinical trials and computational modelling.

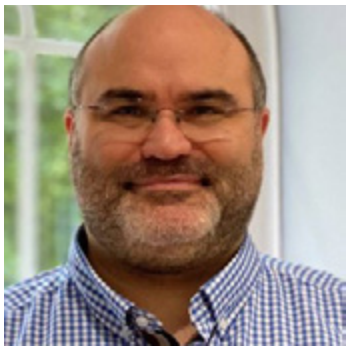


Professor David Delpy, CBE FRS FMedSci FREng

Professor David Delpy is a bioengineer and Emeritus Professor of Medical Photonics at University College London. He is currently Honorary Treasurer at the Institute of Physics, Chair of the RAEng Healthcare Community of Interest, a member of the Home Office Science Advisory Council and Brunel University Council.

Dr Glenn Wells, MHRA

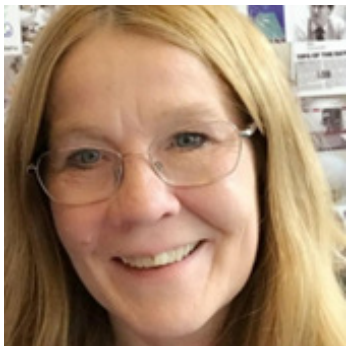
Dr Wells is the Chief Partnerships Officer at the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and leads their work on building and developing partnerships to deliver the best innovations and care for patients. He is also the Director of Strategy and Planning at the Medical Research Council and is a Board Member of Health Data Research UK.



Professor Alejandro F Frangi, FREng, University of Manchester

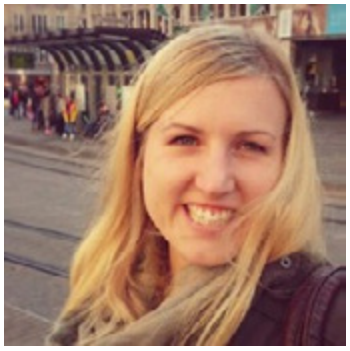
Professor Alejandro Frangi is the Bicentennial Turing Chair in Computational Medicine at the University of Manchester, with joint appointments at the Schools of Computer Science and Health Sciences. He is the Director of the Christabel Pankhurst Institute for Health Technology Research and Innovation and a Turing Fellow at the Alan Turing Institute. He is a Royal Academy Chair in Emerging Technologies focusing on Precision Computational Medicine for in Silico trials of Medical Devices.

Presenters



Ms Sue Cole, MHRA

Susan Cole is an expert Pharmacokinetics Assessor and Head of the Clinical Pharmacology group in the Innovative Medicine Group at the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

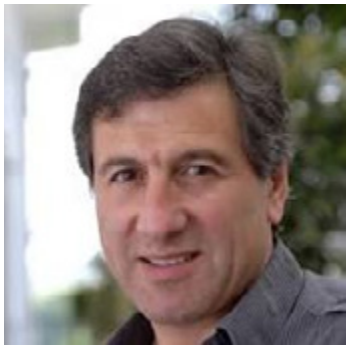


Dr Charlotte Hall, OPSS

Dr Charlotte Hall is the Head of Science at the Office of Product Safety and Standards (OPSS).

Dr Joe Gillard, DSTL

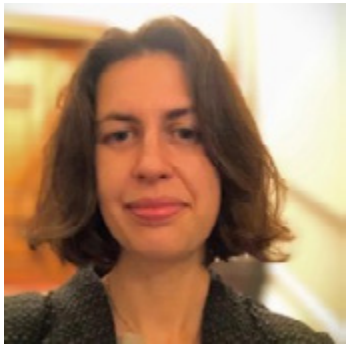
Dr Joe Gillard works at the Defence, Science and Technology Laboratory (DSTL) using computer modelling and simulation methods to help provide the best defence capabilities for the UK.



Dr George Loizou, UK HSE

Dr George Loizou is a biochemical toxicologist with over 30 years' experience in quantitative, mechanistic chemical toxicology. He is an experienced computer simulation scientist, using physiologically-based pharmacokinetic and pharmacodynamic modelling to analyse and explain toxicological data at the UK Health and Safety Executive (UK HSE).

Presenters



Dr Olivia Osborne, FSA

Dr Olivia Osborne is a multidisciplinary (eco) toxicological chemical risk assessment scientist in the fields of human health and the environment. Dr Osborne works on chemical risk assessment and new approach methodologies (NAMs) in the Science Evidence and Research Division of the UK's Food Standards Agency (FSA).

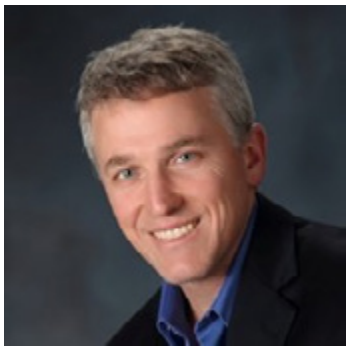
Rob Turpin, BSI

Rob Turpin is Head of Sector for Healthcare at the British Standards Institution (BSI).

Panellists

Michael Adeogun, NPL

Michael Adeogun is Head of Life Sciences and Health at National Physical Laboratory.



Jeff Bischoff, Zimmer Biomet and ASME

Jeff Bischoff is the Senior Director of Biomechanics Research at Zimmer Biomet.

Alison Cave, MHRA

Alison Cave is the Chief Safety Officer at the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

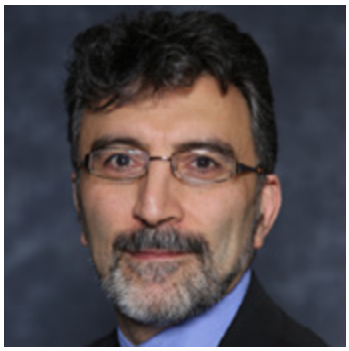
Thierry Marchal, EMA and Avicenna Alliance

Thierry Marchal is the Chief Technologist Healthcare for the European Medicine's Agency (EMA) and works for the CTO Office at Ansys.

Panellists

Erman Melikyan, Intertek

Erman Melikyan is the Principal Clinician at Intertek Medical Notified Body Consultant and is an Orthopaedic Surgeon.



Amin Rostami-Hodjegan, Simcyp Certara and the University of Manchester

Professor Amin Rostami-Hodjegan is the Professor of Systems Pharmacology and Director of the Centre for Applied Pharmacokinetic Research at the University of Manchester. He is also Senior Vice President of Research and Development and Chief Scientific Officer at Certara.

Workshop participants

	First Name	Surname	Organisation
1	Michael	Adeogun	*National Physics Laboratory*
2	Jeff	Bischoff	*Zimmer Biomet*
3	Richard	Branson	*Medicines and Healthcare products Regulatory Agency*
4	Ian	Brotherston	*UK Research and Innovation*
5	David	Brown	*Medicines and Healthcare products Regulatory Agency*
6	Rebecca	Bryan	*Synopsys*
7	Mike	Bryant	*University of Leeds*
8	Alfonso	Bueno-Orovio	*University of Oxford*
9	Andrew	Butler	*British Standards Institution Group*
10	Alison	Cave	*Medicines and Healthcare products Regulatory Agency*
11	Susan	Cole	*Medicines and Healthcare products Regulatory Agency*
12	David	Delpy	*University College London*
13	Timothy	Denison	*University of Oxford*
14	Louise	Earley	*National Physics Laboratory*
15	Eliot	Gillings	*Royal Academy of Engineering*
16	Alejandro	Frangi	*University of Manchester*
17	Rebecca	Ghosh	*Medicines and Healthcare products Regulatory Agency*
18	Joe	Gillard	*Defence Science and Technology Laboratory*
19	Charlotte	Hall	*Office for Product Safety and Standards*
20	Anna	Hands	*Academy of Medical Sciences*
21	Brittany	Hseih	*Royal Academy of Engineering*
22	Ross	Hughes	*Vehicle Certification Authority*
23	Essam	Kerwash	*Medicines and Healthcare products Regulatory Agency*
24	Michael	Kipping	*Element Materials Technology*
25	Miguel	Lago	*US Food and Drug Administration*

	First Name	Surname	Organisation
26	Carol	Lane	*Philips*
27	Mark	Littlewood	*Innovate UK KTN*
28	George	Loizou	*Health and Safety Executive*
29	Sheena	Macpherson	*University of Leeds*
30	Thierry	Marchal	*Avicenna Alliance*
31	Erman	Melikyan	*InterTek*
32	Colin	Mitchell	*PHG Foundation*
33	Mehran	Moazen	*University College London*
34	Tim	Morris	*NAFEMS International Association for the Engineering, Modelling, Analysis and Simulation Community*
35	Puja	Myles	*Medicines and Healthcare products Regulatory Agency*
36	Johan	Ordish	*Roche*
37	Olivia	Osborne	*Food Standards Agency*
38	Gavin	Quigley	*British Standards Institution Group*
39	Jess	Radcliffe-Craggs	*Department of Health and Social Care*
40	Elizabeth	Redrup Hill	*PHG Foundation*
41	Amin	Rostami	*University of Manchester*
42	Jamie	Soames	*Medicines and Healthcare products Regulatory Agency*
43	Marta	Soares	*University of York*
44	Paul	Stewart	*University of Leeds*
45	Ian	Symington	*NAFEMS International Association for the Engineering, Modelling, Analysis and Simulation Community*
46	Zeike	Taylor	*University of Leeds*
47	Rob	Turpin	*British Standards Institution Group*
48	Simon	Walker-Samuel	*University College London*
49	Glenn	Wells	*Medicines and Healthcare products Regulatory Agency*
50	Zoe	Wright	*Department for Business, Energy and Industrial Strategy*

How to cite this report

Redrup Hill, E., Mitchell, C., Myles, P., Branson, R., & Frangi, A.F. (2023). Cross-Regulator Workshop: Journeys, experiences and best practices on computer modelled and simulated regulatory evidence— Workshop Report. InSilicoUK Pro-Innovation Regulations Network. https://doi.org/10.5281/zenodo.10121103

INSILICO UK

Medicines & Healthcare products Regulatory Agency

Royal Academy of Engineering

making science work for health | PHG FOUNDATION