MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

Landscape Report & Industry Survey on the

Use of Computational Modeling & Simulation in Medical Device Development

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The general recommendations in this document:

- *Do not imply FDA concurrence for specific applications*
- *Do not represent the opinion or policy of the FDA or of the companies represented*
- *Do not necessarily reflect the official policy or position of MDIC*

About the Medical Device Innovation Consortium

The Medical Device Innovation Consortium (MDIC) is the first public-private partnership created to advance the medical device regulatory process for patient benefit. MDIC was formed in 2012 to bring the U.S. Food and Drug Administration (FDA) and industry together to share vital knowledge that can help bring safe, affordable, and effective devices to patients and providers more quickly. MDIC membership and participation are open to non-profit, industry, and government organizations that are substantially involved in medical device research, development, treatment, or education; or in the promotion of public health; or that have expertise or interest in regulatory science.

MDIC has been designed to pursue several strategies that support its mission:

- Create a forum for collaboration and dialogue
- Make strategic investments in regulatory science, utilizing working groups to identify and prioritize key issues, and to request, evaluate, and implement project proposals
- Provide and enable implementation of tools from these projects that drive cost-effective innovation

The activities and outputs from MDIC are intended to:

- Ensure that innovative technology is readily available to patients
- Provide industry and government with methods and tools that may be used to expedite medical device development and the regulatory process
- Reduce the risk and expense of clinical research
- Reduce time and cost of medical device development

MDIC members provide guidance and leadership through collaboration to develop solutions for regulatory, scientific, health, and economic challenges within the medical device and diagnostic industry.

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM
Align. Achieve. Accelerate.

MDIC Computational Modeling & Simulation Program

Background

The MDIC Computer Modeling and Simulation (CM&S) Program focuses on regulatory science strategies to achieve the delivery of medical product solutions in a responsible, patient sparing way that relies on computer modeling and simulation as valid scientific evidence to provide increased trust in device performance while limiting the delay in patient access that is commonly associated with elevated certainty.

The vision of the CM&S Program is to aid in the creation and approval of safe and effective medical devices by providing access to:

- Regulatory-grade computational modeling and simulations
- Forums for discussing CM&S topics
- The latest CM&S validation and reporting documents

MDIC CM&S Projects

- Blood Damage Modeling
  - Hemolysis Working Group
  - Thrombosis Working Group
- CM&S Landscape Analysis Report: This report compares the results of the MDIC CM&S surveys that were conducted in 2014 and 2021. The results have been analyzed by industry and regulatory experts to better understand the importance and benefits of CM&S in the MedTech industry.
- Publicly Funded Human Body Simulation Models: Translational research to bridge the gap between NIH and other publicly funded academic research models and models that are credible for development of medical devices and interventions. Assess the credibility of NIH funded human body simulation models for industry contexts of use and develop models with sufficient credibility into a Medical Device Development Tool (MDDT).
- Virtual Patient Project
- ENRICHMNET trial (in silico clinical trial) Project & Industry Advisory Council (IAC)
- External Evidence Methods (EEM)

MDIC member organizations have multiple opportunities to participate in various CM&S projects. These projects are governed by the MDIC CM&S steering committee which is comprised of global thought leaders on medical device CM&S, including industry and regulatory bodies like the US FDA.

Current chair of MDIC CM&S steering committee: Randall Schiestl, Vice President, Research & Development, Global Technology, Boston Scientific

MDIC CM&S Steering Committee

Organization	Team Member
FDA	Edward Margerrison, Zane Arp, Aldo Badano, Brent Craven
NIH	Kris Kandarpa, Grace Peng
Medtronic	Mark Palmer, Alex Caulk
Boston Scientific	Randy Schiestl, David Flynn
BD	Chris Basciano
Edwards	Tina Zhao
Johnson & Johnson	Payman Afshari
Zimmer Biomet	Jeff Bischoff
Dassault Systèmes	Steve Levine
Avicenna Alliance	Thierry Marchal
Cook	Richard Swift
Stryker	Cheryl Liu
FDA/MDIC Liaison	Christina Webber
Google	Yuan Fang
Philips	Olaf van der Sluis
MDIC Staff	Jithesh Veetil, Taylor Metheny, Joe Sapiente

Learn More

Learn more about MDIC and CM&S projects by visiting www.mdic.org or https://mdic.org/program/computational-modeling-and-simulation-cms/

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Executive Summary

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. This technology 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. In a recent MDIC survey, the statements with the highest level of agreement among survey responders, with 69% and 51% respectively of respondents strongly agreeing, were "Modeling and simulation can reduce the time to market for my product" and "Modeling and simulation can reduce the risk of postmarket complications." Despite the potential advantages to manufacturers, patients, and other stakeholders, the medical device industry has been slow to adopt CM&S as regulatory evidence, though it has been widely implemented for decades in many other industries.

This MDIC Landscape Report presents the results of a survey of a diverse group of stakeholders and discusses the potential of CM&S to reduce product development costs, speed up time to market, and better serve patients with safe and effective medical devices. Case studies included in this Report demonstrate tangible evidence of the value of CM&S to both industry and regulators. The Report also discusses current barriers to more widespread adoption and offers recommendations for future actions.

MDIC is committed to advance the awareness and adoption of CM&S in medical product development. MDIC welcomes more discussion on the topics covered in this Report and on CM&S generally. Interested parties can provide feedback on this Report, ask questions, share opinions, and request access reference materials related to CM&S using this link: MDIC CM&S Feedback and Engagement.

In addition, MDIC website and resource library provide a plethora of resources relevant across the total product life cycle of medical devices.

Background and Promise of CM&S

Computational modeling and simulation (CM&S) is the use of computers to create and analyze in-silico models representing physical systems. Investigators can rapidly perform large numbers of simulated tests or experiments by modifying variables, then evaluate the different resulting outcomes without the need to build analogous physical prototypes. Data from simulations can guide more efficient and better targeted development of physical models or studies, and in many cases can evaluate conditions that would be impossible or unethical to test in the physical world. CM&S is used extensively in industries such as aerospace and automotive, and is being adopted in medical device development and evaluation, though its full potential in this field has yet to be realized.

CM&S is a key element of the digital transformation in healthcare. It has the potential to revolutionize the medical device field by replicating real-world use conditions with minimal or no animal or human testing. Medical device developers can use these models to predict performance of new product designs before building and testing physical prototypes. Higher value ideas can be identified and designs can be optimized before they are used in animals or on human subjects. Tomorrow, simulations of virtual physiological patients could eliminate early-stage human trials and replace a significant proportion of late-stage human clinical testing.

By reducing the number of subjects that need to be enrolled in clinical trials, CM&S is beneficial for patients, and can also save organizations millions of dollars in clinical trial costs. CM&S can also help refine study designs, re-evaluate the viability of a clinical trial as new data comes in, and can provide better understanding of specialized patient populations and such topics as pediatrics, gender bias, the elderly, and other subsets. The success of CM&S in product design is clearly resulting in increased confidence in product performance.

The CM&S Initiative was developed by MDIC to help provide solutions that have the potential to increase the predictability of safe and effective device performance while reducing risks to patients and delays in patient access through the use of computational modeling and simulation as valid, regulatory-grade evidence. The MDIC CM&S Steering Committee works across the MedTech Community to increase the utility of CM&S and drive adoption of these techniques throughout the product cycle from early stage research to performance validation.

Case Study:

An In Silico Trial of Breast Cancer Imaging Technologies

Expensive and lengthy clinical trials can delay regulatory evaluation of innovative technologies, affecting patient access to high-quality medical products. Simulation is increasingly being used in product development but rarely in regulatory applications. An *in silico* diagnostic study (VICTRE) used computer-simulated imaging of 2986 digital patients to compare digital mammography and digital breast tomosynthesis and found an improved lesion detection performance favoring tomosynthesis for all breast sizes and lesion types. The findings of the VICTRE trial suggest that the regulatory assessment of the imaging devices based on *in silico* data would have been the same compared to the actual regulatory decision made based on the comparative trial.

See Appendix B.1 for more detail

Case Study:

The Use of Digital Twins in the Patient-Specific Analysis of Heart Failure

Pulmonary hypertension (PH) is a chronic medical condition affecting 1% of the global population. PH affects the arteries in the lungs and the right side of the heart and can be life-threatening. Accurate or early diagnosis and treatment are hindered by the functional dominance of the left side of the heart and gender differences, particularly when the PH is caused by left heart disease. A study suggests that use of a digital twin in pilot human or animal studies can reveal a mechanistic understanding of disease and treatment efficacy, which can facilitate optimal trial design, more reliable interpretation outcomes, and safety risk identification. Longitudinal data could provide long-term outcome prediction, leading to the use of virtual patients as evidence in a pivotal trial.

See Appendix B.2 for more detail

Regulatory agencies rely on models of real-world behavior to judge the safety and efficacy of new treatments. In a landmark paper, "The Role of Computational Modeling

and Simulation in the Total Product Life cycle of Peripheral Vascular Devices"[1], the authors describe the four sources of regulatory evidence. As summarized in Figure 1, each model has benefits and limitations for predicting a range of performance attributes and outcomes in the assessment of peripheral intervention and vascular surgery devices.

CM&S has many strengths where other tools and approaches do not, notably in its flexibility in replicating and controlling for specific patient populations. Its greatest weakness is the inherent need to make many assumptions, either for modeling efficiency or because certain input parameters are not known. History suggests that widespread adoption of CM&S reduces this uncertainty over time as validation data sets grow.

1 Morrison TM, Dreher ML, Nagaraja S, Angelone LM, Kainz W. The Role of Computational Modeling and Simulation in the Total Product Life Cycle of Peripheral Vascular Devices. J Med Device. 2017;11(2):024503. doi: 10.1115/1.4035866. Epub 2017 Jan 23. PMID: 29479395; PMCID: PMC5823268.

Case Study:

In Silico Trial of Flow Diverters of Intracranial Aneurysms

An *in silico* trial of flow diverter performance was intended to determine whether *in silico* trials can enhance the regulatory evaluation of medical devices by a) reducing, refining, or replacing bench, animal, or human studies; b) extending trial cohorts to rare or difficult-to-recruit phenotypes; c) evaluating devices under practically challenging conditions (e.g. off-label use); and d) directly comparing alternative treatments in the same virtual population, reducing the observed effect variance.

See Appendix B.3 for more detail

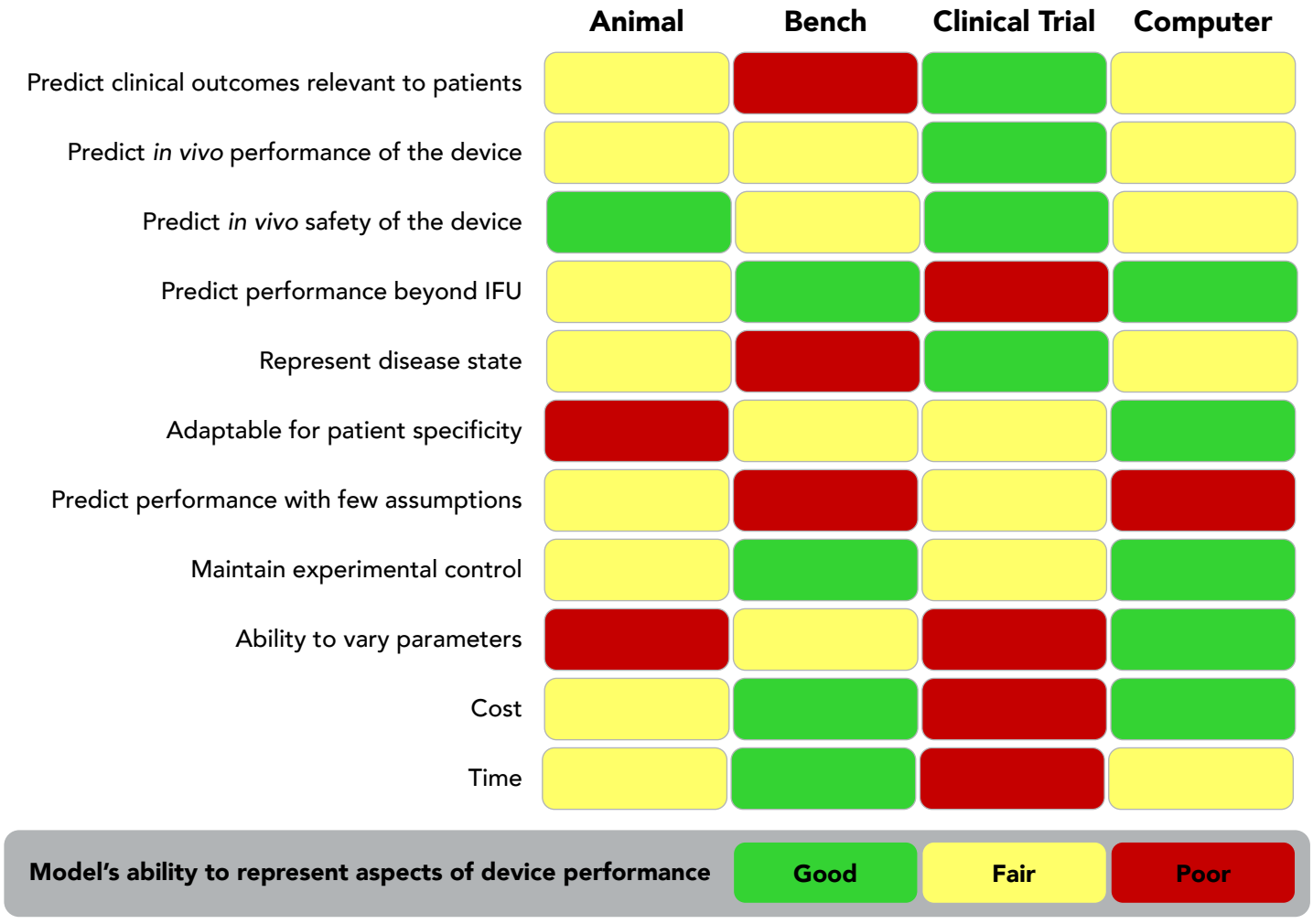


Figure 1. Four different models (top row) can be used for regulatory evaluation of peripheral intervention and vascular surgery devices. The shading represents our interpretation of how well the models can be used for different aspects of performance, as listed in the left column. Note that while cost and time are not attributes of performance, they are important factors to consider when selecting a model for use as scientific evidence. As adapted from Morrison TM et al.[1]

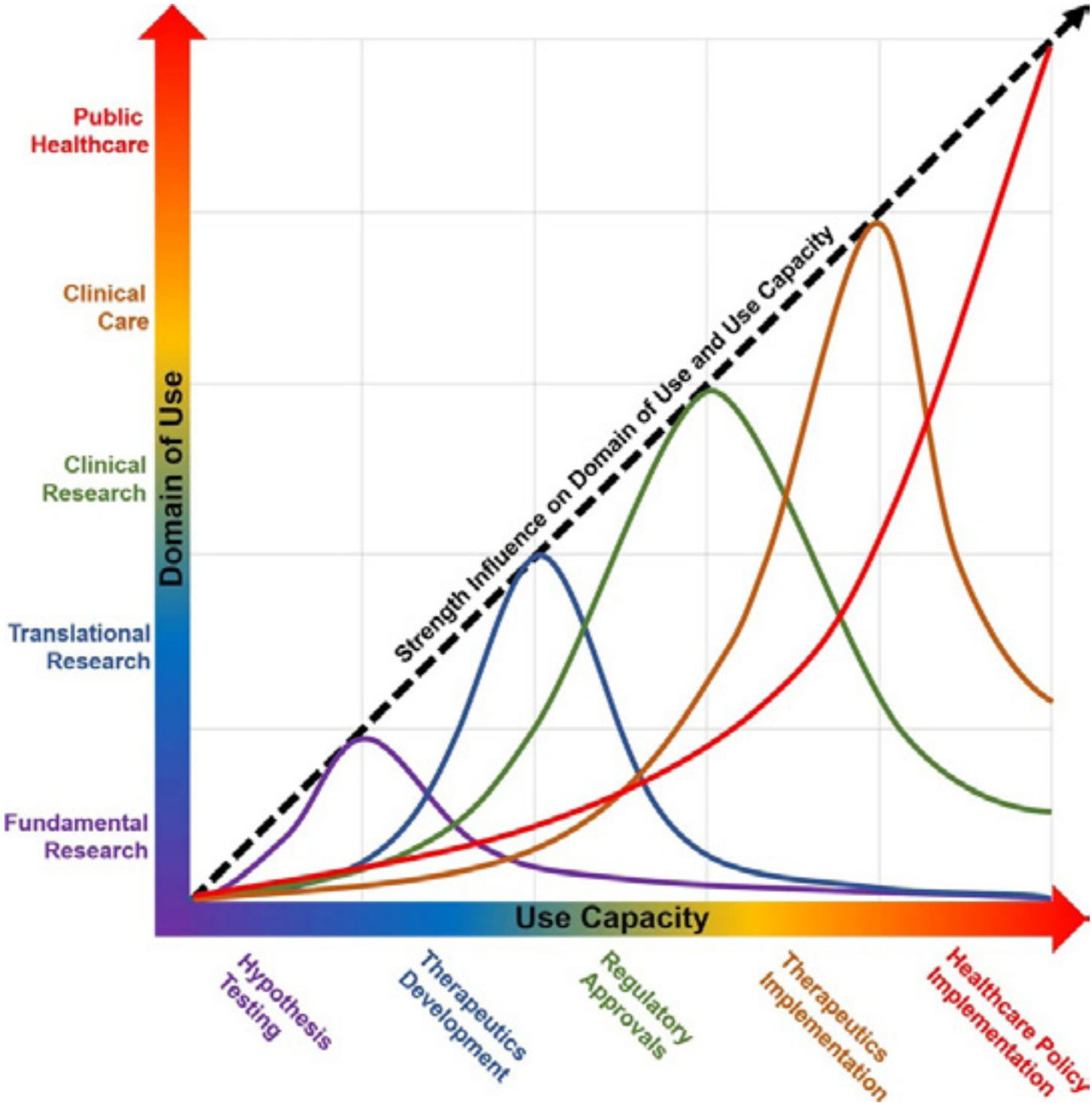


Figure 2. Relation between Model and Simulation Domain of Use, Use Capacity and Strength of Influence. Model and Simulation developed for a specific Domain of Use will typically have the greatest Strength of Influence within a commensurate range of Use Capacity. It may, however, be able to provide inference data for other Use Capacity areas. For example, a modeling and simulation framework specifically intended for translational research (blue line) in pharmaceuticals is likely to have the highest Strength of Influence in therapeutics development (e.g. new drug development). Similarly, a highly vetted epidemiological modeling and simulation to analyze the long-term effect(s) of an FDA-approved vaccine on public health (red line) is likely to be most credible for informing healthcare policy and preventative therapeutics implementation. The Strength of Influence of these examples would likely differ should the Use Capacity involve applications related to regulatory approval, therapeutics development, and hypothesis testing. As adapted from Erdemir, A et al.[2]

Table 1: Rules of good practice

• Use version control	• Make sure your results are reproducible	• Perform appropriate level of sensitivity analysis within context of use
• Use credible solvers	• Define your evaluation metrics in advance	• Use consistent terminology or define your terminology
• Explicitly list your limitations	• Conform to discipline-specific standards	• Get it reviewed by independent users/developers/members
• Report appropriately	• Be a discipline-independent/ specific example	• Provide user instructions whenever possible and applicable
• Document your code	• Learn from discipline-independent examples	• Use traceable data that can be traced back to the origin
• Provide examples of use	• Use appropriate data (input, validation, verification)	• Disseminate whenever possible (source code, test suite, data, etc.)
• Practice what you preach	• Define the context the model is intended to be used for	• Use competition of multiple implementations to check and balance each other
• Develop with the end user in mind		
• Attempt validation within context		
• Follow discipline-specific guidelines		
• Attempt verification within context		
• Attempt uncertainty (error) estimation		

Set of initial 26 rules for credible practice of modeling and simulation in healthcare developed from a comparative analysis as reported by Erdemir, A et al.[2]

In a more recent paper entitled, "Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective"[2], the use of CM&S across the full healthcare lifecycle is summarized in detail. The authors remark that beyond basic verification and validation, other factors affect the credibility and utility of models for specific applications and in different contexts (Figure 2), and recommend twenty-six rules of good practice (Table 1) which were identified as the result of a survey of almost 200 international experts in healthcare CM&S. Further, the authors proposed the top ten from the 26 listed- mostly commonsense, basic rules for credible practice of modeling and simulation in healthcare: (1) Define 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.

A better understanding of the strengths, limitations, and appropriate use of CM&S, and the further development of standards and best practices for its use, will be key to the more widespread adoption of the technology.

MDIC CM&S Roadmap

In 2014, the MDIC CM&S Steering Committee released the roadmap shown in Figure 3 for the use of CM&S as evidence in the regulatory process. It suggested that simulation of bench testing was possible at the time, and the evolution of model credibility would be driven by basic research done in academia. It further hypothesized that it would require 10+ years to develop accredited model libraries of patients and implanted devices with the goal of replacing more than half of the subjects used in a review with computer-based evidence. Eight years later, progress has lagged somewhat behind this roadmap forecast, although there are notable exceptions that are now accepted as regulatory evidence, such as the use of computational models to evaluate MRI safety.

Stakeholder Communities

Stakeholder communities across the device lifecycle

1. Academic Researchers
2. Software and Service Providers
3. Medical Device Manufacturers (by order of CM&S impact)
   a. Cardiovascular

2 Erdemir, A., Mulugeta, L., Ku, J.P. et al. Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective. J Transl Med 18, 369 (2020). https://doi.org/10.1186/s12967-020-02540-4

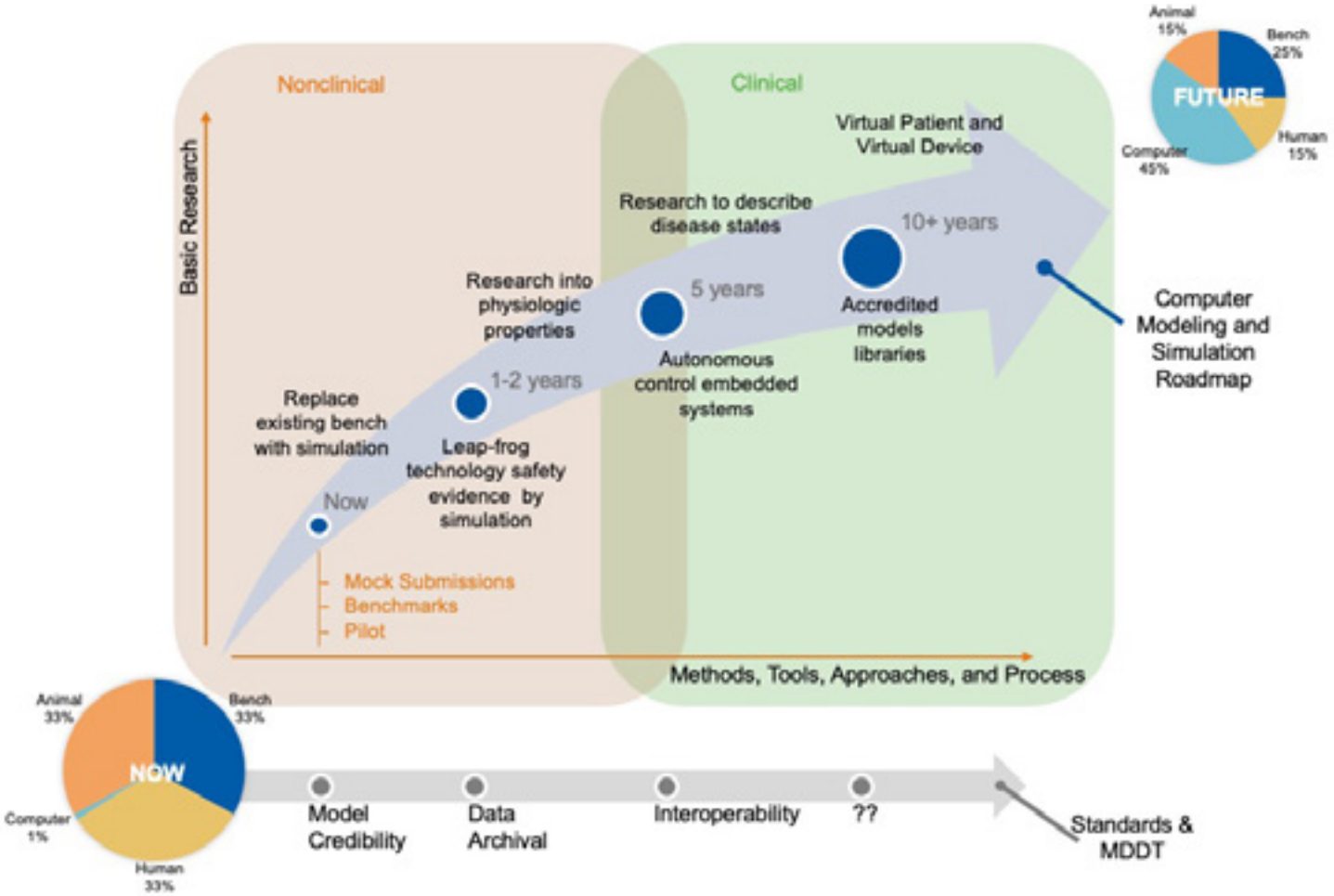


Figure 3. CM&S as evidence in the regulatory process as envisioned by MDIC CM&S steering committee in 2014.

   b. Orthopedic
   c. Neurological
   d. Ophthalmic, Respiratory
   e. Gastro-renal
4. FDA and other regulatory agencies
5. Clinicians
6. Patients
7. Payers

Advances in CM&S have accelerated considerably during the past decade, but its impact has not been uniformly felt among the various stakeholders across the lifecycle. Basic academic researchers have made the greatest use of CM&S. Held to standards of scientific merit rather than worrying about unclear regulatory requirements, they now have sufficient ability to model the real-world behavior of devices, yielding impactful studies, publications, and the development of best practices and/or de facto standards.

Industry reluctance to adopt CM&S has stemmed in large part from concerns about verification and validation as

Case Study

Reducing Regulatory Uncertainty of CM&S through the Use of Guidance and Standards

Uncertainty about regulators' expectations on model credibility is commonly cited by device manufacturers as presenting an unnecessary risk when using CM&S data in regulatory submissions. CM&S data on a stemless total shoulder arthroplasty system submitted to FDA in 2017 – prior to the publication of ASME V&V 40 and an FDA guidance on CM&S documentation – incurred several questions from reviewers. A revised submission incorporating best practices for CM&S verification/validation and documentation was accepted with no questions, indicating that FDA was fully knowledgeable of the standards and expectations of compliance.

See Appendix B.4 for more detail

well as FDA acceptance of modeling and simulation data. These concerns have been somewhat mitigated by the 2016 FDA final guidance document on "Reporting of Computational Modeling Studies in Medical Device Submissions," the 2018 ASME V&V 40 standard on "Assessing Credibility of Computational Modeling and Simulation Results through Verification and Validation: Application to Medical Devices," and the 2021 FDA draft guidance on "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions," which incorporated many elements of the ASME V&V 40 standard. As is seen in the survey results, the industry closely watches FDA expectations, which are now clearly stated for stand-alone device testing.

As the science advances and demand increases, commercial software developers to the medical device industry are incorporating new capabilities into their software and practices, offering more comprehensive solutions that are more readily available to device manufacturers. While still not fully mature, device simulation is now the standard for optimizing design under lab testing conditions, and most midsize and larger device companies have adopted it for at least some applications.

The use of CM&S in medical device development is uneven across different product categories. In a few domains, cardiovascular in particular, data from automated 3D segmentation of organs enables patient-specific structural, fluidic, and electromagnetic simulations. A strong focus in cardiovascular device development and evaluation has been driven by the combination of high-risk devices and their challenging use environments. Orthopedics, while slightly lower risk, has seen significant impact as well because of the challenging use environment. More recently, neurological and respiratory devices have made increasing use of the technology.

Case Study

Simulating the Release Mechanism in Drug-Eluting Stents

Simulated models were created of the complex microstructure of drug-eluting stent coastins. Insight into the drug release process in different conditions can lead to a better understanding of the relationship between processing, microstructure, and release behavior and ultimately give designers more control over the delivery process.

See Appendix B.5 for more detail

From the regulatory perspective, FDA has seen the impact of CM&S most significantly in cardiovascular devices, with companies submitting virtual patient data for review and even using CM&S as the device itself. Despite the Agency's sustained commitment, however, full adoption remains the exception rather than the rule for device submissions. It is important to note that many device development companies are using modeling but not always as part of their regulatory submissions.

In clinical practice, CM&S has recently seen a groundswell of adoptions. While this would typically follow from its use in clinical trials or through device company expert guidance, we note that in challenging surgical environments such as pediatrics and valve replacements, the use of CM&S is being driven directly by clinical need. Further, the clinical availability of several CM&S based Software-as-a-Medical Device (SaMD) services has raised the visibility and understanding of these methods in the medical community.

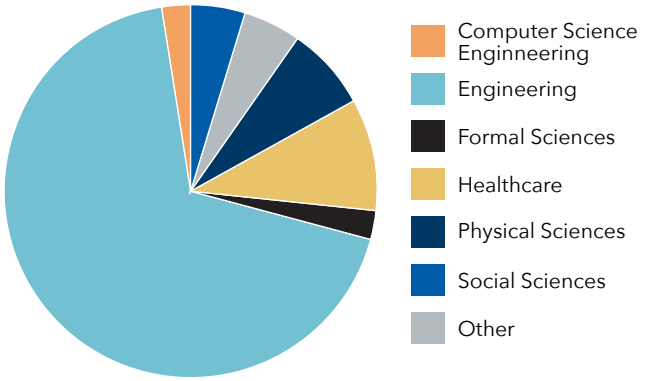
The final two stakeholder groups, patients and payers, are thus far still largely isolated from the impact of CM&S. We anticipate that there will be significant impact in the coming years, but this has not yet been a focus.

MDIC CM&S Survey

Respondent Profile

This document is a comprehensive representation of the data collected from the 2014 and 2021 CM&S surveys. The survey results offer more than 40 expert insights into CM&S, and helps identify the changes that have taken place during the seven years between the two surveys.

Respomdants Primary Field of Academic/Professional Training



The majority of survey respondents are very familiar with CM&S: 73% have more than 10 years of experience in the subject. While most of the respondents have an engineering background (68%), the remaining respondents come from a variety of professional backgrounds, including the physical and social sciences, computer science, and healthcare. Together, the stakeholders have determined the current barriers to greater use of CM&S and the actions that are required to move the industry forward in a way that ultimately better serves patients.

There is variability in the use of CM&S by different organizations (Appendix Figure A.1). In 2014 the highest reported use (68%) was in companies with more than $1 billion in revenues. The second most common organization type for 2014 was organizations under $1 billion (22%). The lowest scoring organization types were reported as pre-revenue (3%), non-profit (3%), and regulation (3%). The 2021 survey showed consistent results, indicating that there had been little change: the top two user organizations were still those with revenues over $1 billion (41%) and those just under $1 billion (17%). In the 2021 survey, 15% of the 41 respondents were affiliated with academic institutions, a category that had not been included in the 2014 survey. There was an increase from 0% to 5% in the percentage of respondents affiliated with a research organization. There was little change in those users from pre-revenue companies (3% in 2014; 2% in 2021), non-profits (3% to 2%), and regulation (3% to 5%). In 2021,12% of respondents reported working as consultants or for CROs, whereas none had fallen into these categories in 2014.

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CM&S Application Areas

There were key similarities in the areas where CM&S was used across the different organizations. (Figures A.7) In 2014, the most common answers were product development and testing (83%), new product discovery (57%), field surveillance and root cause analysis (54%), and manufacturing (51%). There was a shift in the 2021 results. Product development and testing was not included as a possible answer. In other areas, use in new product discovery increased to 69%, field surveillance and root cause analysis and clinical trial development and conditions were both at 41% (as opposed to 17% for clinical trials in 2014), and manufacturing had dropped to 33%. Additional areas of CM&S utilization included disease prognosis, treatment outcome prediction, test plan optimization, and product line extensions.

In a related question on specific types of CM&S use (Figure A.8), there were many similarities and a few interesting differences between the 2014 and 2021 survey results. The most common answers for both years were performance evaluation (83% in 2014; 83% in 2021) and device development (81% and 77%). The use in surrogate tests also remained relatively stable at 58% and 64% in the successive surveys. Significant increases were noted for embedded devices (8% to 21%), medical devices (6% to 18%), and to identify clinical uses (50% to 72%). The use in product sustainment was not asked in 2014, but was selected by 54% of respondents in 2021. Other respondents noted that they use CM&S in research, in-silico test evaluation, and certification.

The 2021 survey asked how organizations leverage CM&S resources. (Figure A.9) Most respondents (72%) claimed that the resources were available internally. 64% of respondents personally apply CM&S regularly as opposed to relying on others. A smaller number rely on the expertise of software companies (36%), regularly use consultants (23%), or personally utilize the technology when specifically required (23%). A few organizations leverage their resources through universities.

In the 2021 survey, organizations identified their primary reason for interactions with CM&S in health technologies (Figure A.10) as product development (56%). Far behind were scientific research (12%), regulatory approval (12%),

clinical research (7%), clinical decision making (12%), and medical training (2%). 2% were not using or not interested in CM&S.

The type of business case that organizations use for CM&S (Figure A.11) were consistent from 2014 to 2021. The most common justification was performance, selected by 69% in 2014 and 74% in 2021. The second highest category was quality, which fell close behind at 61% (2014) and 62% (2021). Next was using CM&S for productivity at 56% (2014) and 54% (2021). These numbers are very close and show little significant change within each category. Other respondents replied that the business case for CM&S within their organization was for revenue growth, therapy development, research, regulatory opportunity, and ROI.

Barriers to CM&S Adoption

In light of the generally acknowledged potential benefits of CM&S, the survey asked about obstacles to its use. (Figure A.12) The greatest barrier to the further adoption of CM&S was reported in both the 2014 (71%) and 2021 surveys (61%) as uncertainty in what is expected by regulating bodies. The second most common obstacle – 48% (2014) and 49% (2021) – is reported as a lack of expertise in CM&S. Another barrier to adoption was a sense that the business case is not well defined (39%). Cost was also a factor (32% in 2021), and another 32% of respondents did not believe that the science associated with CM&S in their field was sufficiently mature.

Responders to the question on barriers to CM&S adoption, disproportionately worked at larger companies that already tended to possess the unique skills and infrastructure requirements needed to adopt CM&S. This may have introduced some unintended bias in the survey results. The responses may have tended to ignore the start-up or scale-up costs that were no longer an issue for large companies, but that present barriers to the many small to medium-sized device companies that could derive significant benefits from CM&S.

Cost is certainly a real consideration for an organization wishing to build internal CM&S capabilities, though the survey responses indicate that these investments return value over time. Trained analysts are needed to ensure

Case Study

Reducing the Time and Cost of Design Verification Testing through Simulation

Design verification (DV) testing often takes significant labor hours and calendar time to execute as a precursor to a device regulatory submission. Moreover, the amount of DV testing is exponentially increased when a collection of relatively small device changes and/or product line extensions occur in a concurrent timeline. Can we use in-silico modeling and simulation to reduce the time and cost of DV testing for hypodermic syringe product updates?

See Appendix B.6 for more detail

reliable use, interpretation, and communication. The computational demands of CM&S may be well beyond the existing IT infrastructure typically found in a medical device company, and require additional investment in hardware. However, in contrast to the state of the industry in 2014, there now exist several effective methods of lowering this adoption barrier, or at least smoothing the path to adoption. Many scalable, cost-effective computational resources are available through high performance computing (HPC) cloud providers specializing in computational modeling. This avoids capital startup expenses and provides a long-term, on-demand ability to increase capacity when needed. Establishing the initial setup can be nearly as easy as setting up an account.

In addition, CM&S for medical devices has matured sufficiently that a number of highly trained service providers offer virtual testing services with rapid turnaround. Many of these organizations have experience with the demands of regulatory evaluation and are able to provide guidance to companies lacking this expertise. Nonetheless, as indicated in the survey results, uncertainty about FDA expectations should encourage caution for any company lacking internal expertise that wishes to submit CM&S data.

The survey asked what CM&S applications respondents felt would have the most positive impact in FDA submissions (Figure A.14). Bench testing was the top application, selected by 91% of respondents in 2014 and 78% in 2021. *In-vivo* animal testing was chosen by 63% in 2014 and 68% in 2021. Expanding indications for use responses increased from 40% to 51%. *In vivo* clinical testing, which was not listed as an option in 2014, was selected by 56% in 2021. Those anticipating an impact on down-classifying devices increased from 2% to 7%. Additional options that were not included in the 2014 survey were supporting CAPAs (24%) and manufacturing and distribution (12%). Other respondents commented that it would be important to expedite review cycles by utilizing validated CM&S.

The majority of survey respondents indicated that device development and early feasibility studies were the most beneficial applications of CM&S (Figure A-13). The 2014 and 2021 results were similar in the rated importance for 510(k) submissions and device discovery, with responses ranging from 50 – 54%. PMA submissions, on the other hand, dropped from 53% in 2014 to 37% in 2021. There was a startling difference in the respondents that selected pre-submission interactions as the most beneficial application: in 2014, 62% of respondents selected this response; in 2021 no one selected this option. It is difficult to explain this change, particularly as the answers to all other options were relatively consistent from one survey to the other, and it may be an artifact of respondent confusion in choosing between submissions and pre-submission interactions. Options that were not asked in the 2014 survey include device manufacturing (41%) and post-market assessment (39%). Other organizations commented that enhancing product quality, decreasing cost, and in-silico clinical trials are the most beneficial aspects of CM&S.

"I would like more objective measurements that show that there is a tangible improvement in the time to gain approval or clearance of IDE, PMA, and 510(K) applications, based on the removal of mutually identified barriers and enhanced effort leading to collection and submission of high-quality data."

(46% of respondents agreed with this statement)

Half of respondents use modeling and simulation at their companies but do not submit the data to FDA (Figure A.22), suggesting a recognition of its value in guiding or refining development or testing efforts without full confidence that it will meet stringent regulatory requirements. It is therefore interesting to note the seemingly contradictory responses that while the top-ranked obstacle to the use of CM&S was "uncertainty in what is expected by regulating bodies" (61% in 2021), 95% of respondents agreed or strongly agreed with statements that FDA supports the use of modeling in regulatory evaluation and that FDA accepts CM&S data in regulatory decision-making, and 80% agreed that FDA will provide useful guidance on its use. On the other hand, 38% agreed, 16% strongly agreed, and 32% disagreed with the statement that "our organization knows what is expected to use modeling and simulation data in regulatory submissions." (Figures A.21 and A.22) It is difficult to conclude that the respondents agree that the FDA's position on CM&S is clear from the guidance, but the majority believe the FDA will clarify their expectations, possibly on a reactive or case-by-case basis. There does seem to be a lack of internal understanding within industry (only 16% strongly agree that they understand), suggesting that adequate comprehension of the regulatory requirements is not yet consistent. Further industry education and

"I would measure success by assessing the quality of the products brought to market, reduction in post-market product issues, and other stakeholder feedback"

(32% of respondents agreed with this statement)

training on CM&S is clearly critical to the further adoption of this technology.

There was overwhelming (90%) agreement among respondents with the statements that modeling and simulation can reduce the time to market for their products and that modeling and simulation can reduce the risk of postmarket complications. (Figure A.21) A majority of respondents (76%) even agreed that, in the future, data used to support health technologies would come more from CM&S than from sources such as animal models and bench testing. (Figure A.22) On the other hand, there was very strong agreement about the need for verification and validation of the software and models, traceability of inputs, understanding of the context of use and the limitations of experimental scenarios, ease of repeatability, and error and uncertainty quantification within the context of use. (Figures A.23 – A.25) 97.3% of respondents agreed on the importance of using appropriate data for input, validation, and verification. One can deduce that concerns about CM&S data reliability in comparison to that generated by traditional testing methods remains an obstacle to expanded adoption of the technology.

With the more widespread understanding and use of the ASME V&V 40 standard, FDA guidance documents, and other publications on credible practices in modeling and simulation, the perceived regulatory and validity concerns will undoubtedly subside with time. Further advances will depend upon the sharing of case studies, data, and models. In the 2014 MDIC survey, 9.7% of respondents stated that they currently had data that their organizations would be willing to share with an open database in order to improve CM&S validation, and 23.3% stated that they would be willing to share models. In the 2021 survey, these percentages were 22.9% and 29.4% respectively (Figures A.18 & A.19), an incremental but encouraging increase.

Future Actions

Survey Priorities

Survey respondents ranked their top three priorities for MDIC's CM&S program. A scoring system was used in order to quantify the importance of each priority. The top priority was for the program to focus on creating collaborations across the MDIC community and academia to advance the use of CM&S in medical device development. Survey respondents were also asked to determine their level of agreement with statements. The statement with the highest level of agreement amongst survey responders, at 69% of respondents strongly agreeing, was "Modeling and simulation can reduce the time to market for my product."

There has been an increase in the ability and willingness of organizations to share data through an open database to improve CM&S and validation. In 2014 only 9.7% of respondents reported that they were able to share data, while in the 2021 survey that number had risen to 22.9%. This could offer valuable insights from real experiments that could be used to help advance CM&S. There has also been a slight increase from 23.3% to 29.4% of respondents stating that their organizations were able to share models to an open database. Though not a large increase, greater sharing of data and models will help verify data integrity and validate CM&S activity within the context of use.

In the 2021 survey, 83% of respondents indicated that products within their company's portfolio would benefit from FDA-qualified Medical Device Development Tools (MDDTs) that FDA/CDRH reviewers should accept for the qualified context of use without the need to reconfirm the suitability and utility of the tool when used in a regulatory submission. 73% of organizations agree that it is very important to define the context in which the CM&S is intended to be used.

CM&S Steering Committee Priorities

The CM&S Steering Committee recognizes that with the growth in capability and adoption of CM&S, both the number and diversity of respondents needs to be improved. The committee will pursue this goal in future surveys.

Appendix A – Survey Results

Computational Modeling & Simulation Survey Results

The following data compares the results of the 2014 and the 2021 survey results.

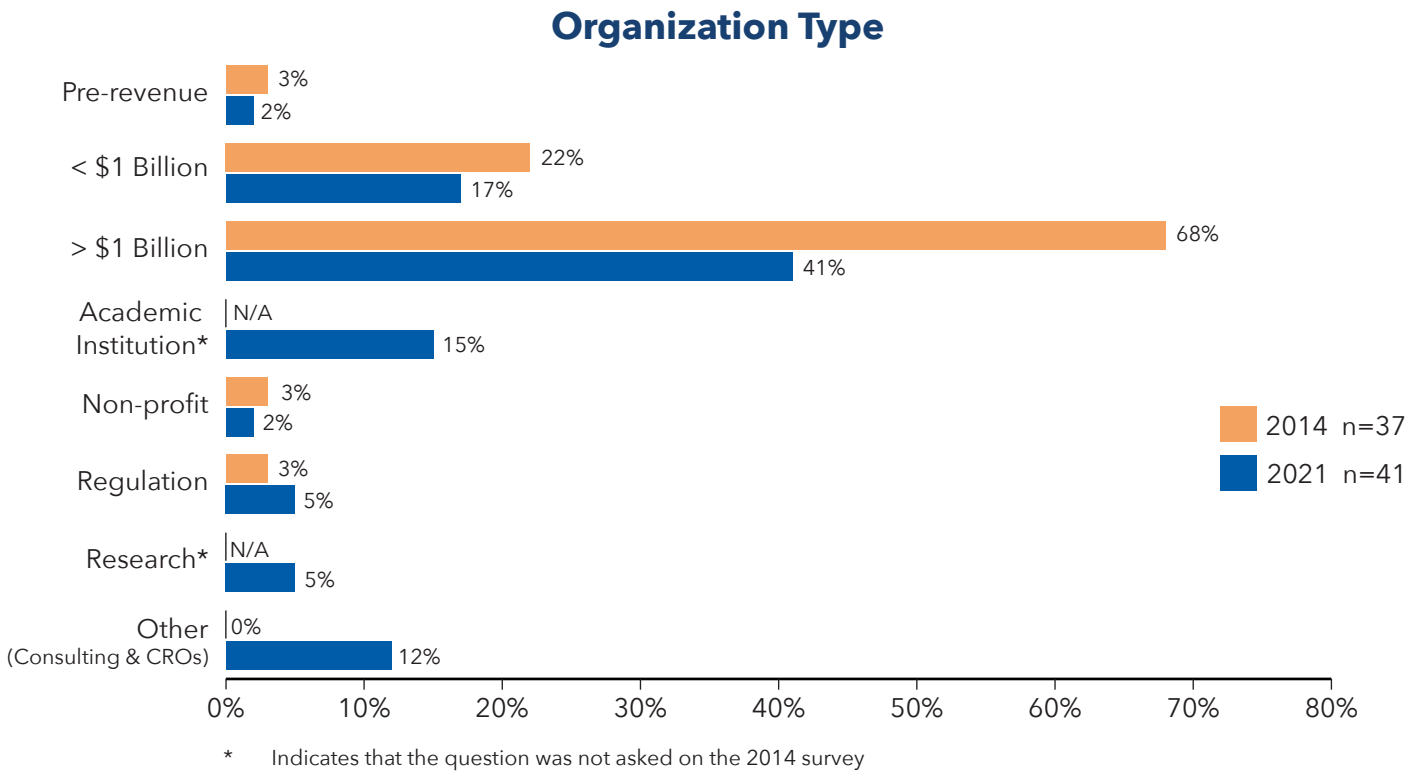


Figure A.1

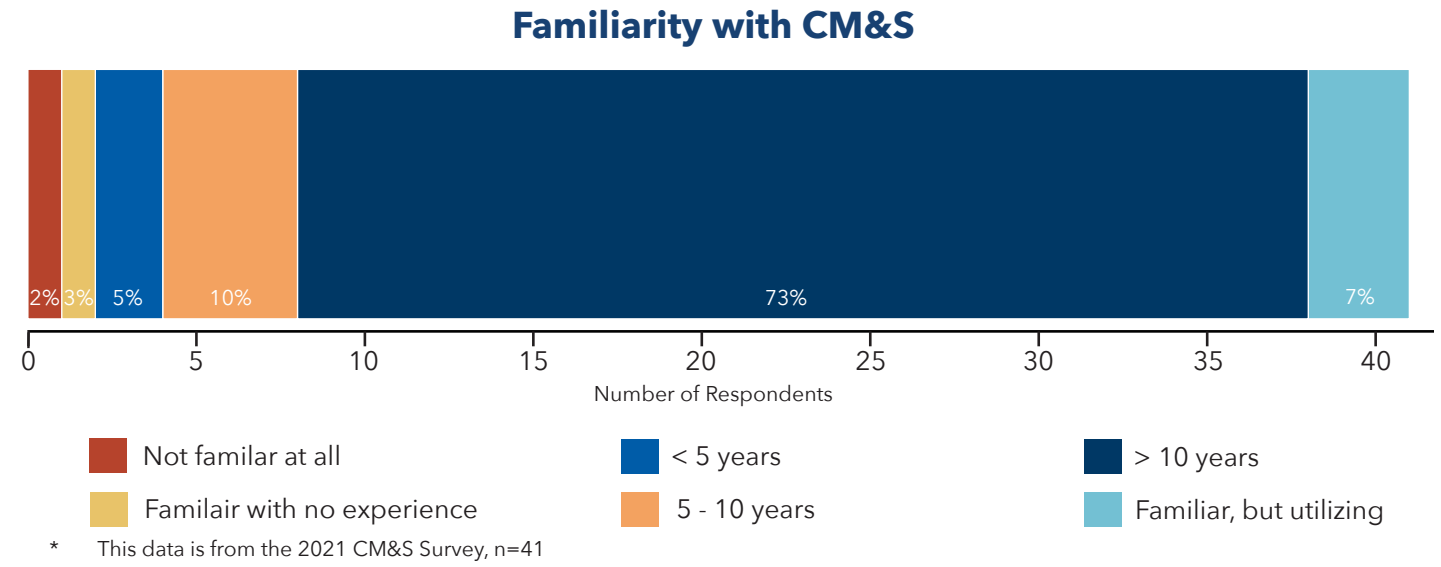


Figure A.2

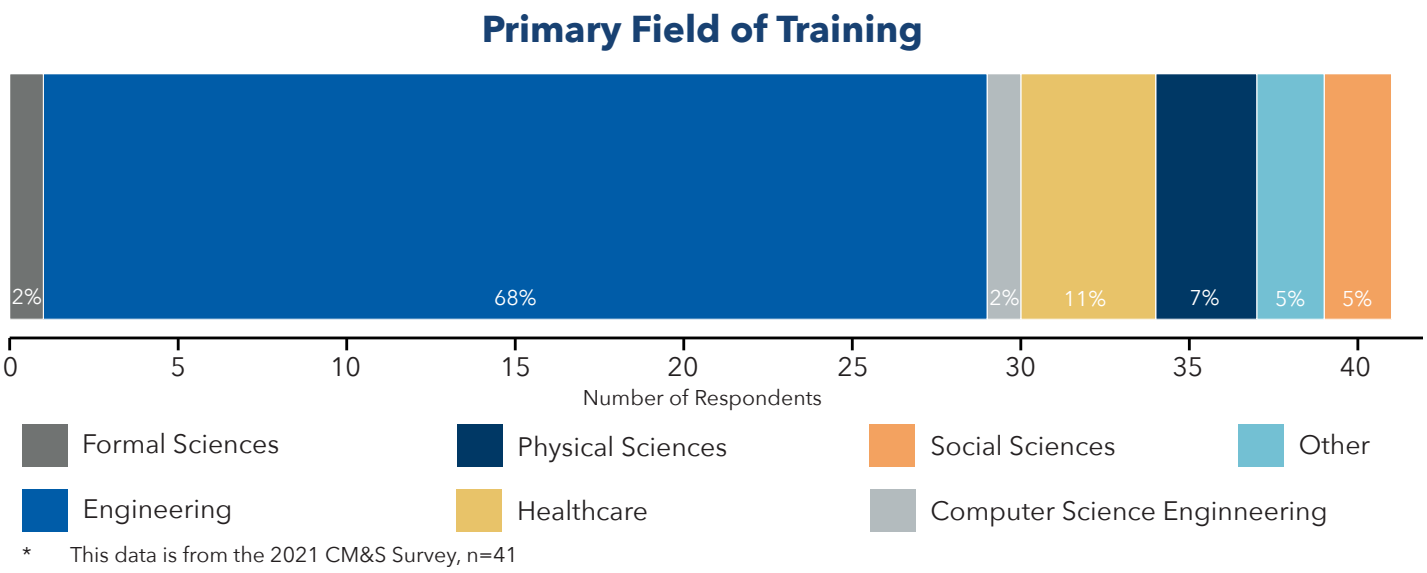


Figure A.3

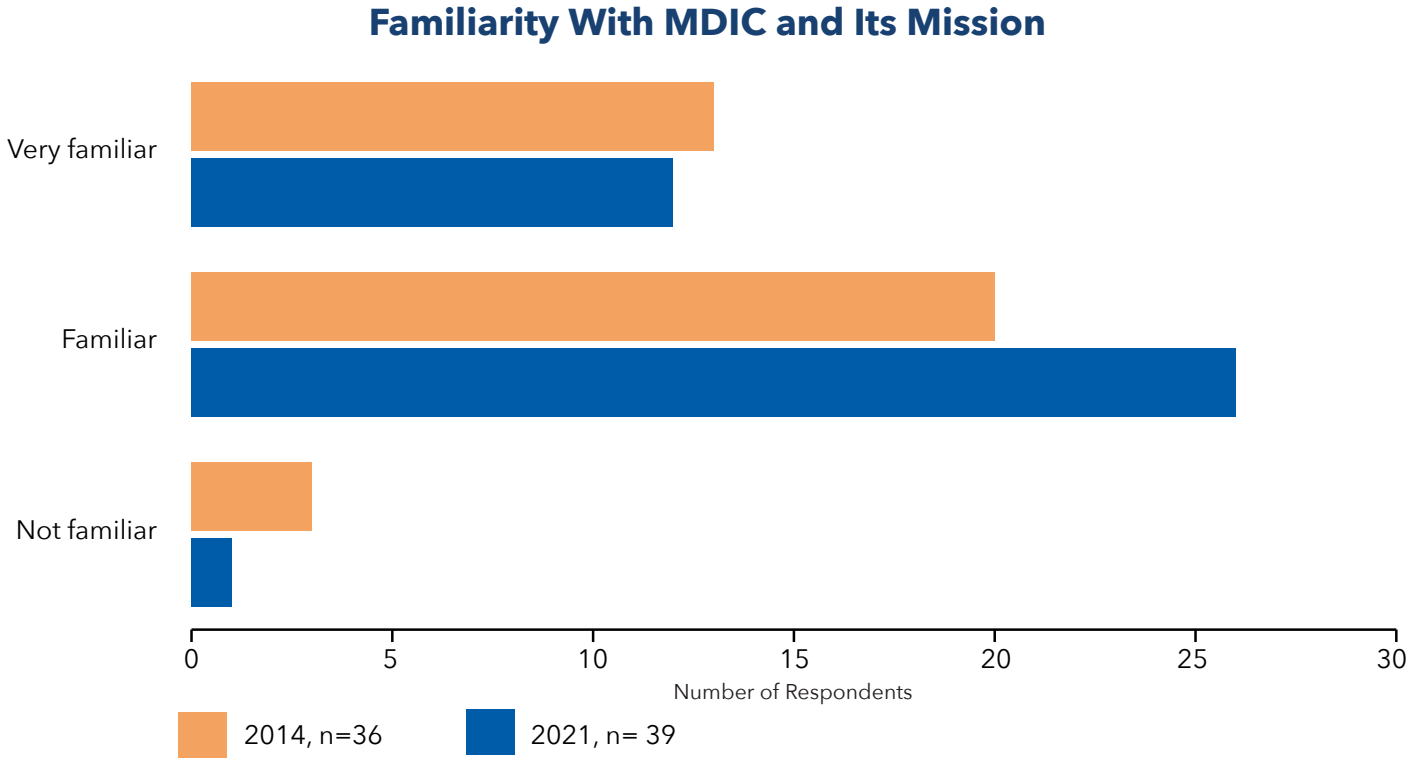


Figure A.4

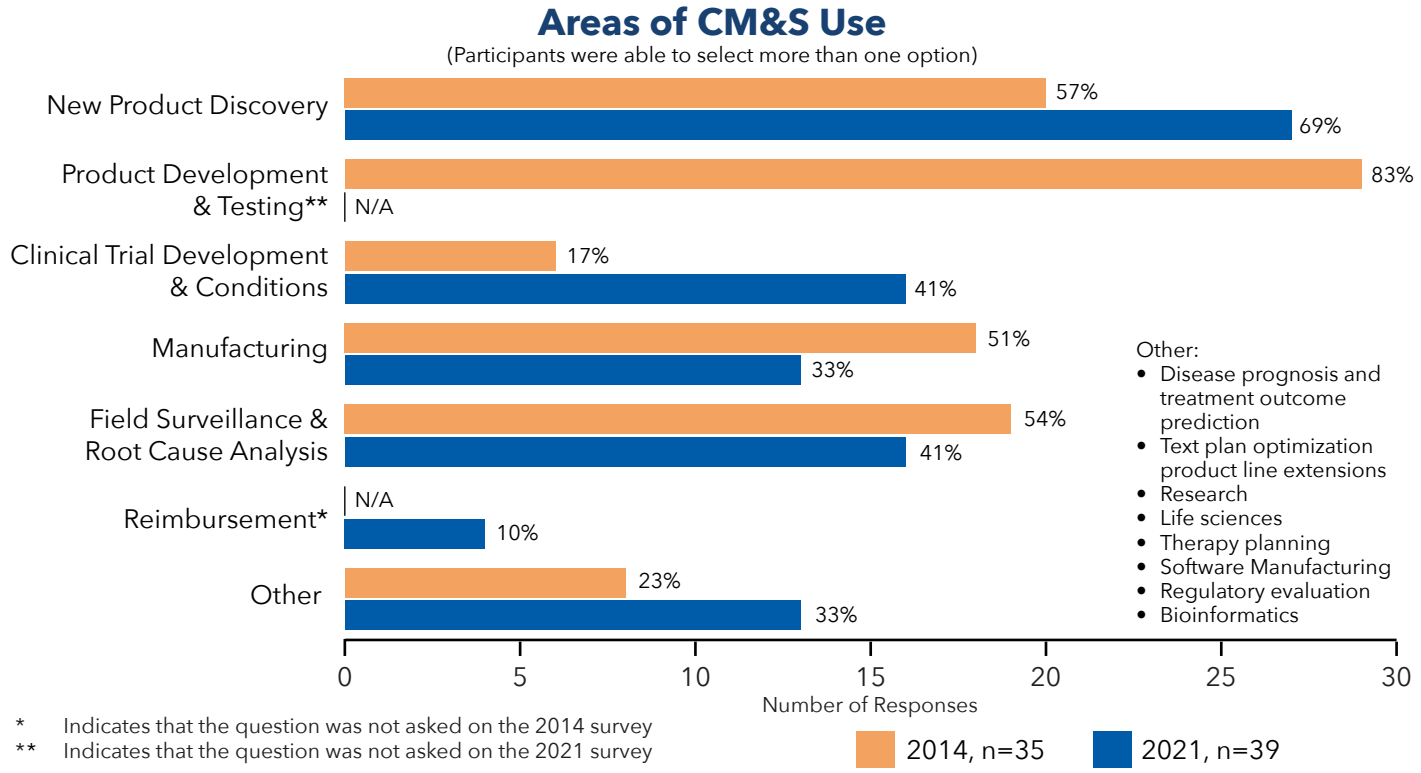


Figure A.5

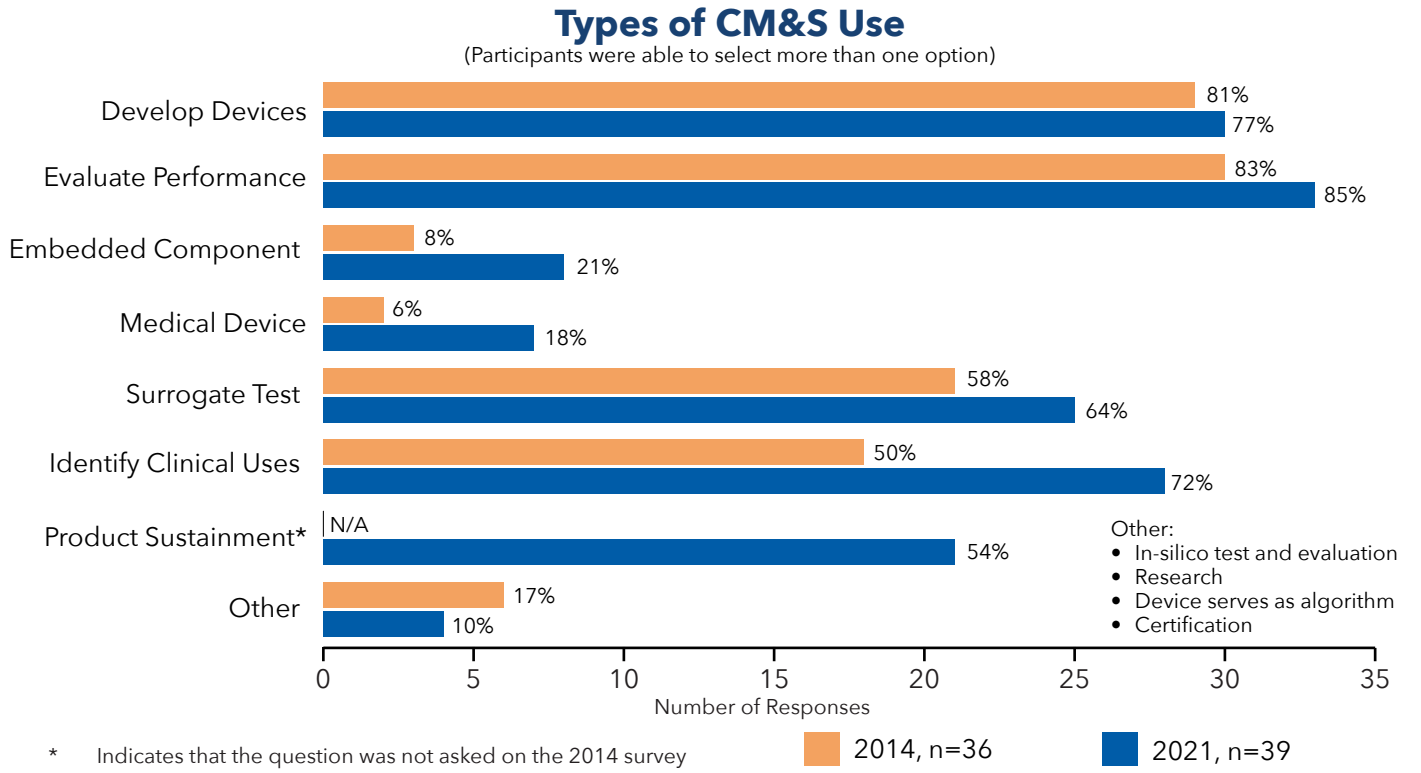


Figure A.6

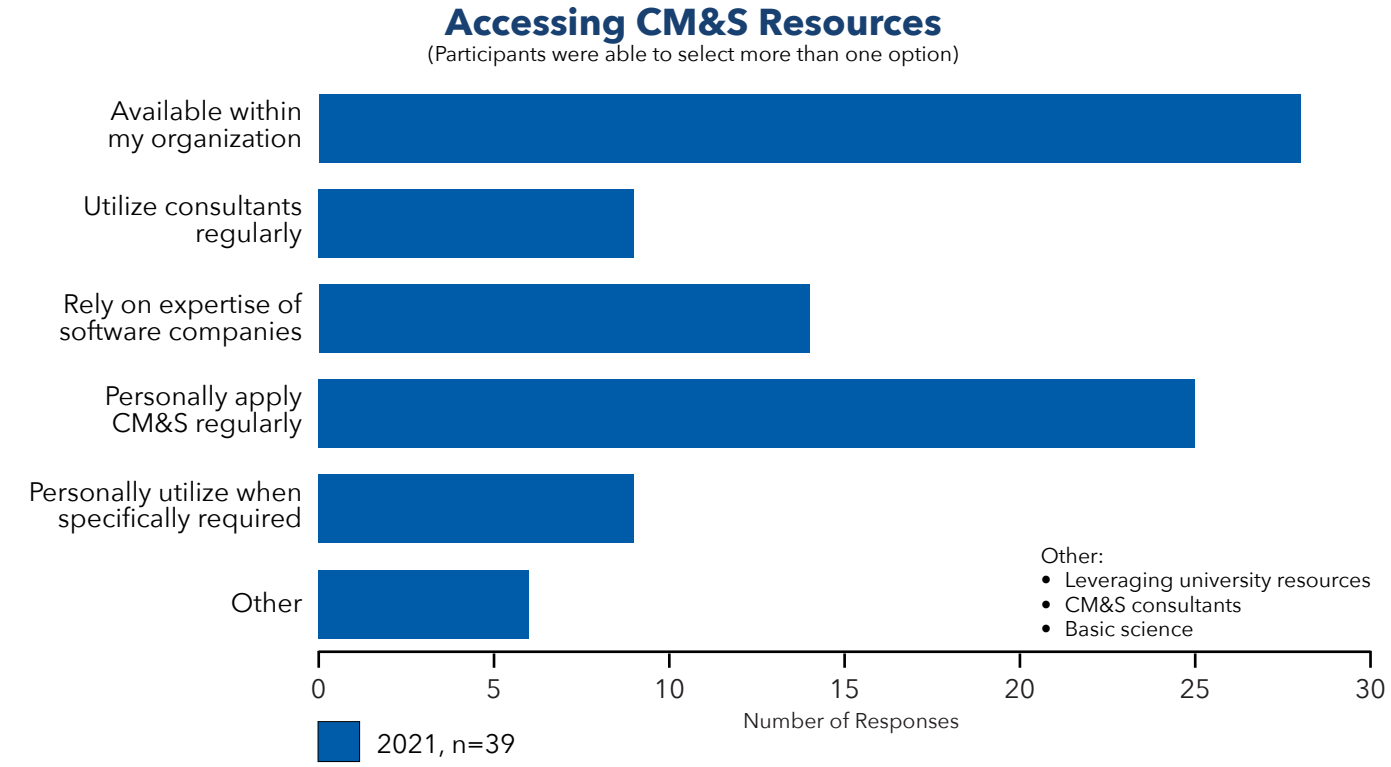


Figure A.7

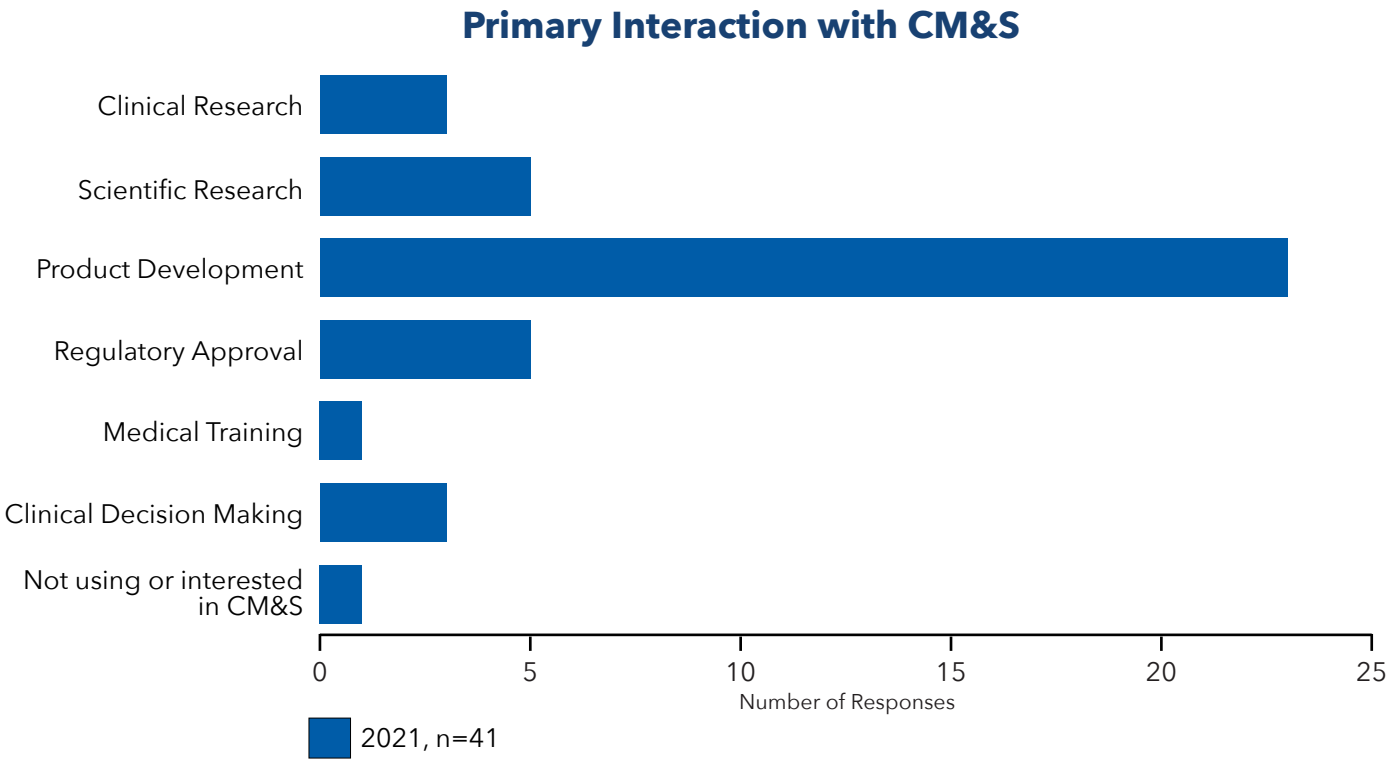


Figure A.8

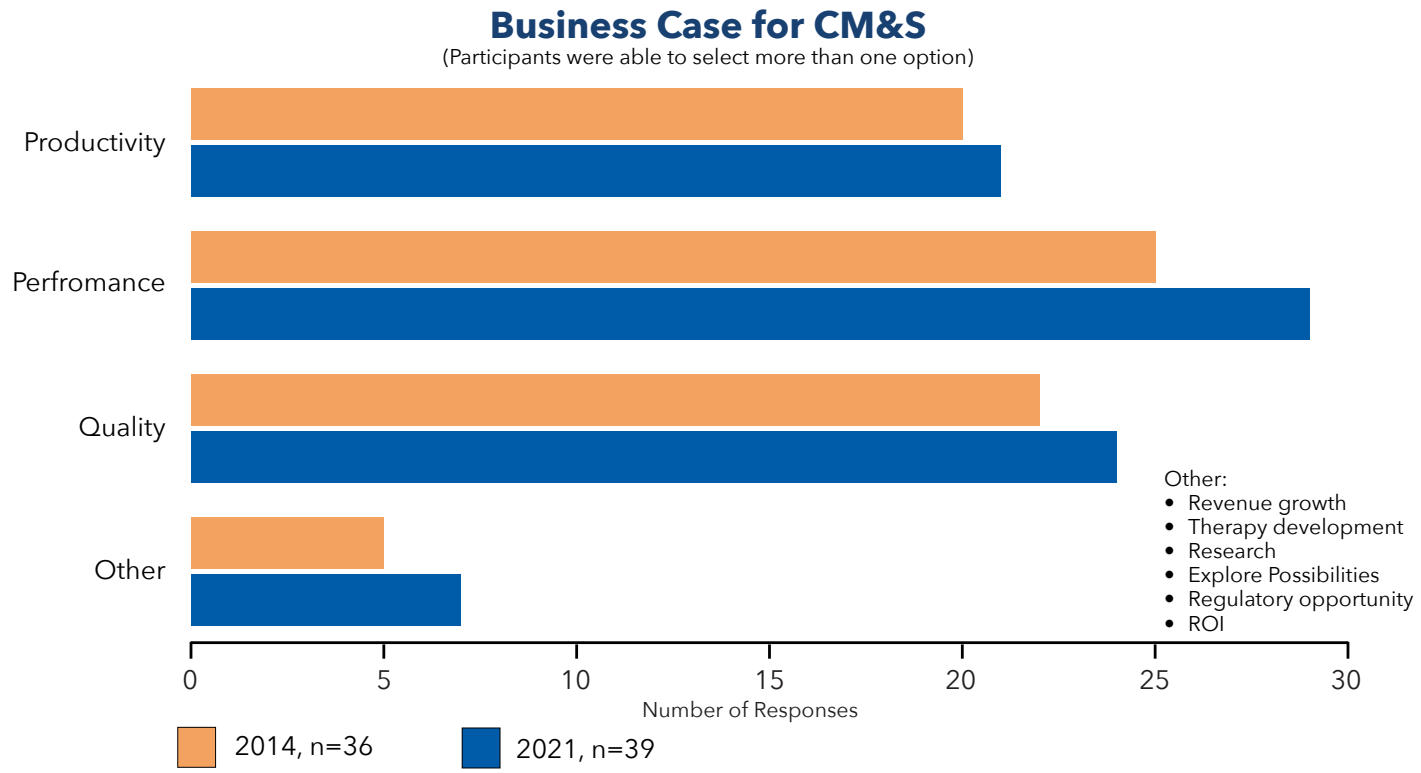


Figure A.9

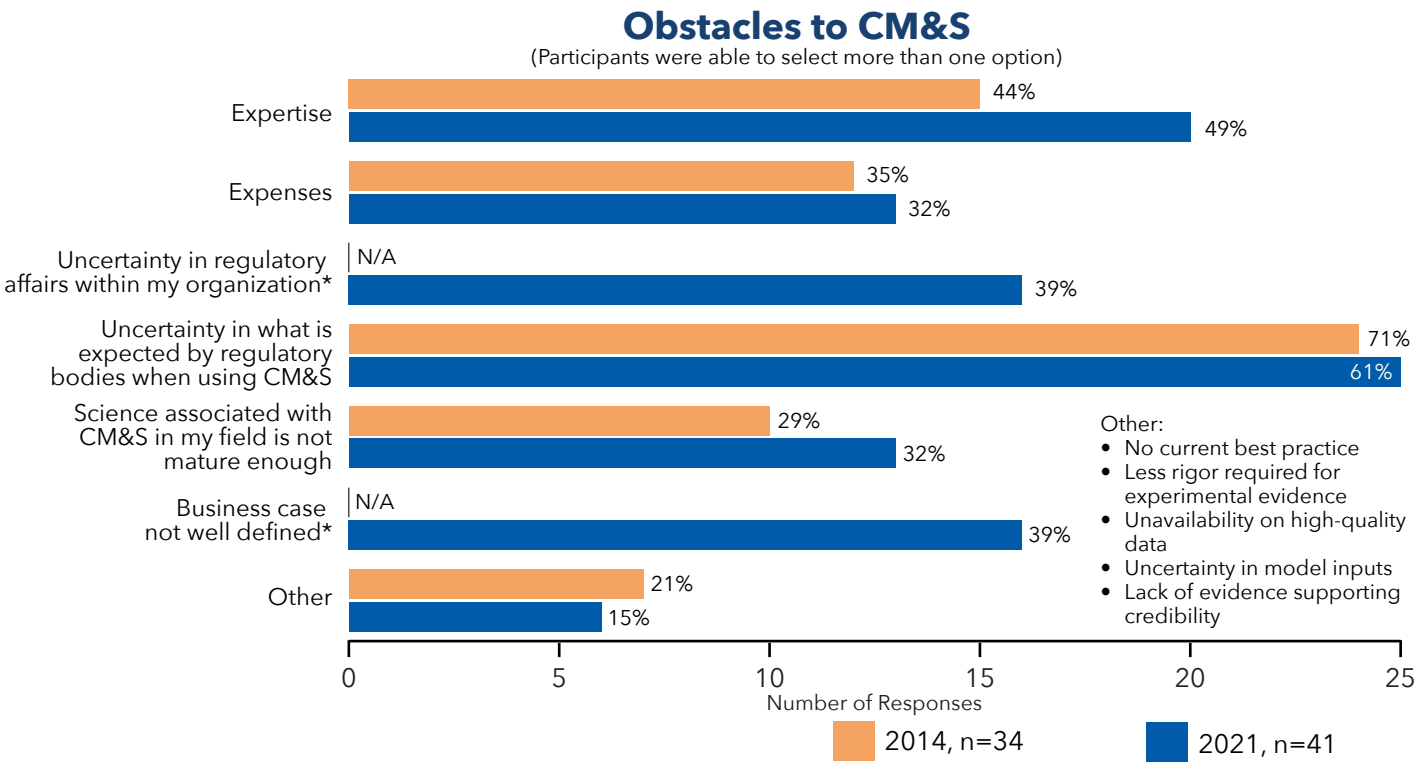
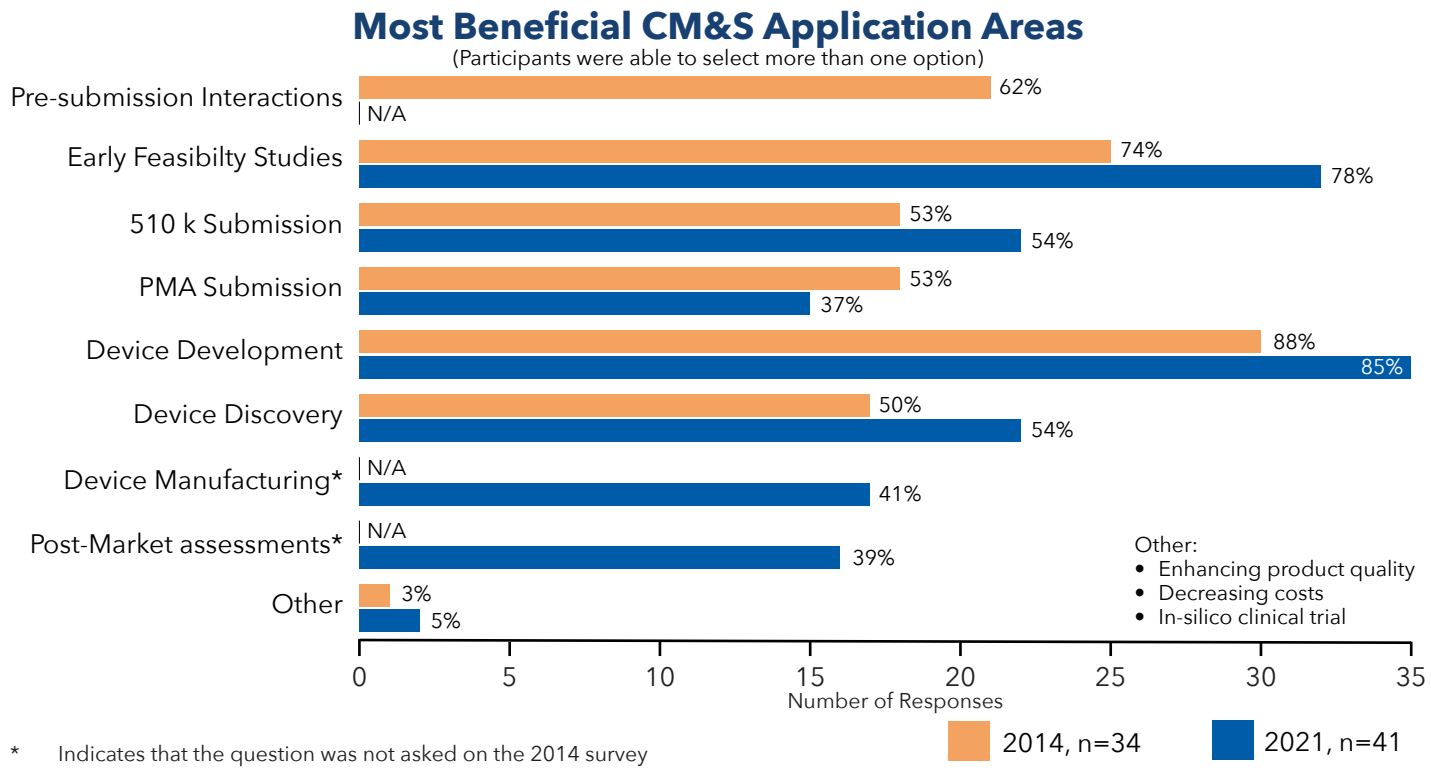
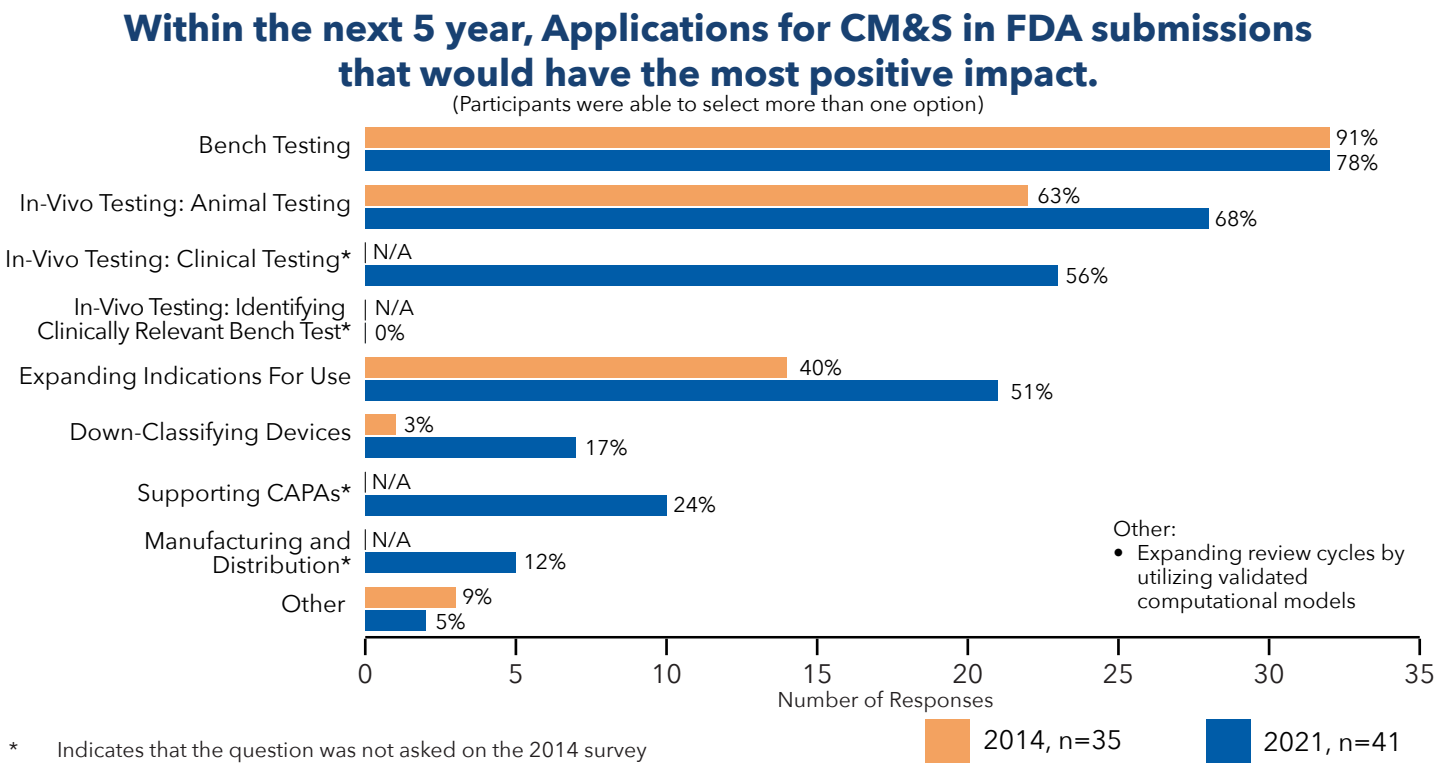


Figure A.10



* Indicates that the question was not asked on the 2014 survey

Figure A.11



* Indicates that the question was not asked on the 2014 survey

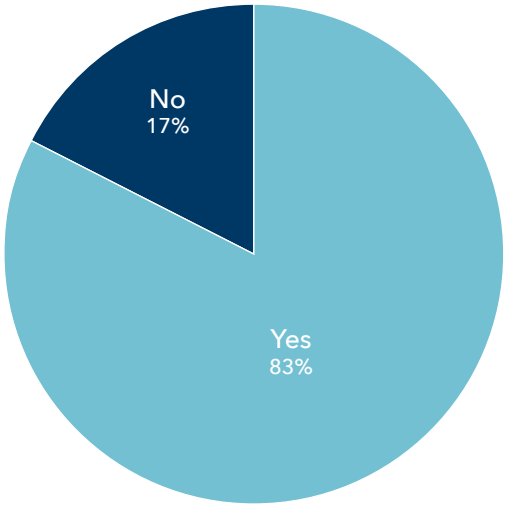
Figure A.12

Most Useful to Participants When Evaluating the Success of CM&S Over the Next Five Years

	Percent
I would measure success by assessing the quality of the products brought to market, reduction in post-market product issues, and other stakeholder feedback	2%
I do not feel that a specific metric is needed to evaluate CM&S success. Having periodic meetings and regular conference calls to facilitate communications would be enough for me.	2%
I would like more objective measurements that show that there is a tangible improvement in the time to gain approval or clearance of IDE, PMA, and 510(k) applications, based on the removal of mutually identified barriers and enhanced effort leading to collection and submission of high quality data.	46%
I would measure success based how my interactions with FDA fare over the next three years with our IDE, PMA, and 510(K) submissions. If my company is able to use CM&S to support these interactions, I would feel that CM&S would be deemed a successful project and I would continue to support it .	44%
Other: • Would like to know when FDA considers CM&S as part of the supporting evidence when making a clearance decision. The evidence that is considered is not currently shared. • I would measure success by the increase in applicability of tools. I believe that FDA wants CM&S to succeed, I believe that if the business case is there then stakeholders will appreciate the value. However, the metric I would use would center around how many FDA submissions include what volume of CM&S information. The more submissions with CM&S, the more applicability the tools are gaining. There is fundamental work to be done to build out capabilities and expand what's possible, not in a theoretical sense but in a translational, actionable way. • Would like to know when FDA considers CM&S as part of the supporting evidence when making a clearance decision. The evidence that is considered is not currently shared.	5%

Figure A.13

Would products in your company's portfolio benefit from FDA-qualified MDDTs which FDA/CDRH viewers should accept for the qualified context of use without the need to reconfirm the suitability and utility of the MDDT when used in a CDRH regulatory submission?



This data is from the 2021 CM&S Survey

n=29

Figure A.14

Do you currently have data that your organization would be willing to share to an open database to improve CM&S and validation?

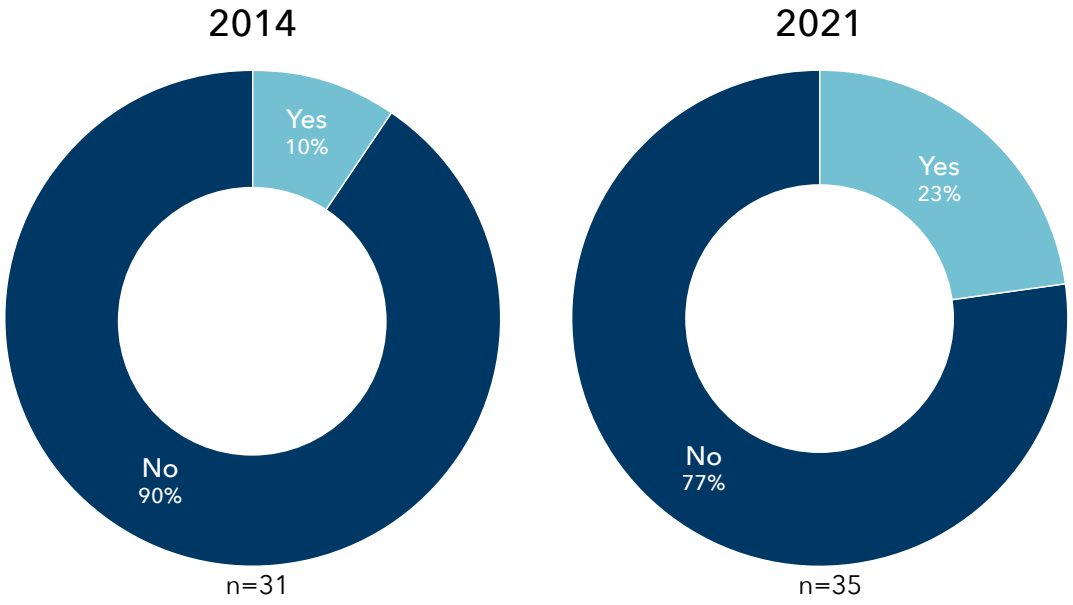


Figure A.15

Do you currently have models that your company would be willing to share to an open database to improve CM&S and validation?

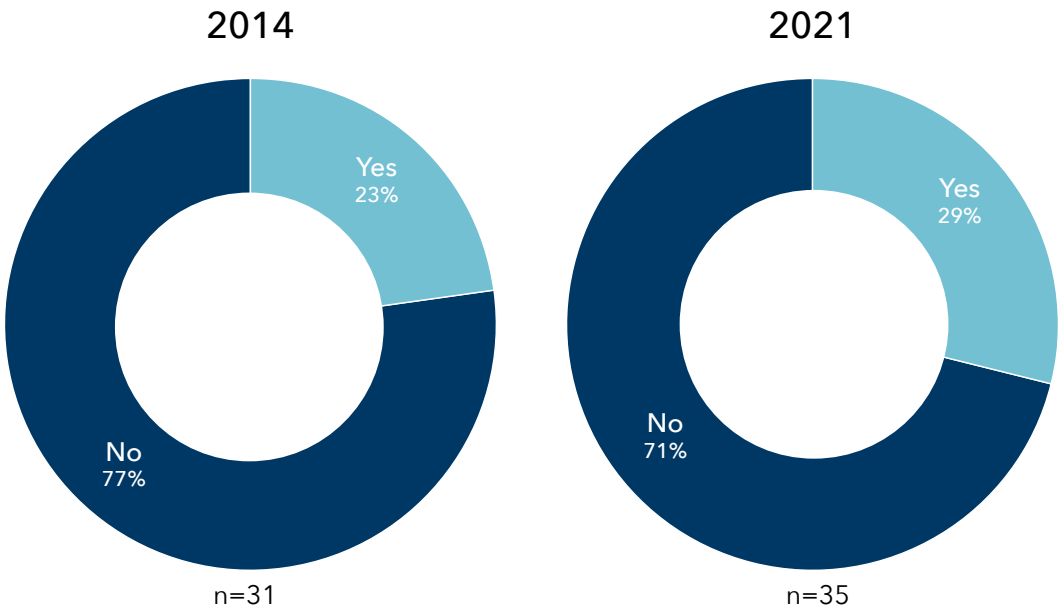


Figure A.16

Top Three Priorities for MDIC's CM&S Project.

	1st	2nd	3rd	Score	Percent
Creating collaborations across the MDIC community and academia to advance the use of CM&S in Regulatory Science	13	7	4	57	48%
Holding workshops and meetings to highlight, educate, and discuss the use of CM&S in Regulatory Science	5	6	7	34	28%
In partnership with standards determining organizations, leveraging the breadth of the MDIC membership to identify CM&S best practices	5	7	6	35	29%
Demonstrating the use of CM&S Validation Requirements	2	3	3	15	13%
Identifying areas for research and research funding	1	3	2	11	9%
Planning and creating a library/repository for CM&S inputs, models, and validation experiment results	7	4	2	31	26%
Envisioning methods to qualify CM&S as a medical device development tool (MDDT)	6	6	4	34	28%
Creating whitepapers to inform the industry and FDA on CM&S and its applicability in specific fields of application	0	4	3	11	9%
Facilitating round robins to demonstrate and improve repeatability and reproducibility of CM&S	0	0	9	1	9%

The score/percentage indicates that the statement was in the individual's top three priorities.
n = 41

Figure A.17

Agreement With the Following Statements

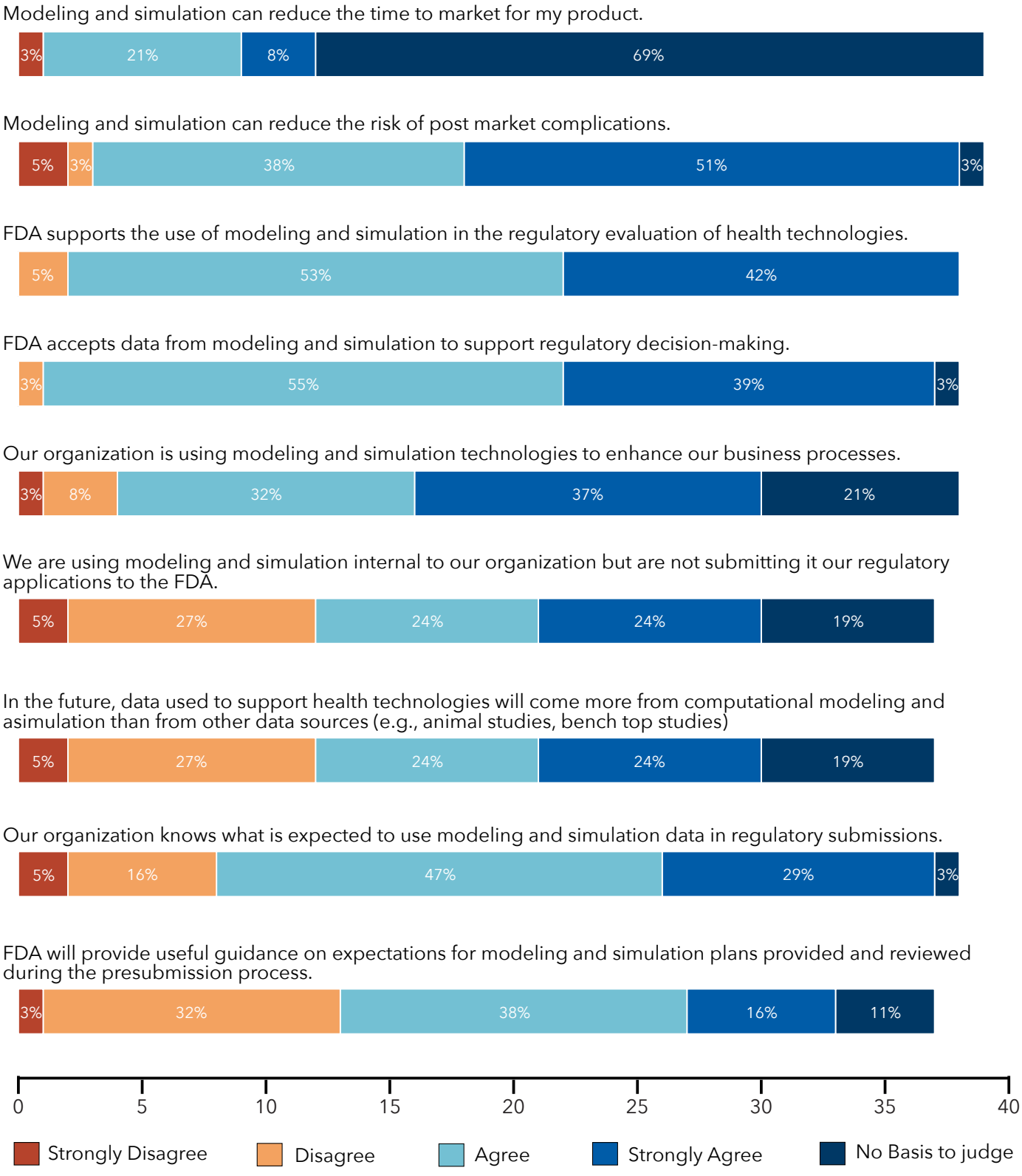


Figure A.18

Level of Agreement With the Following Statements

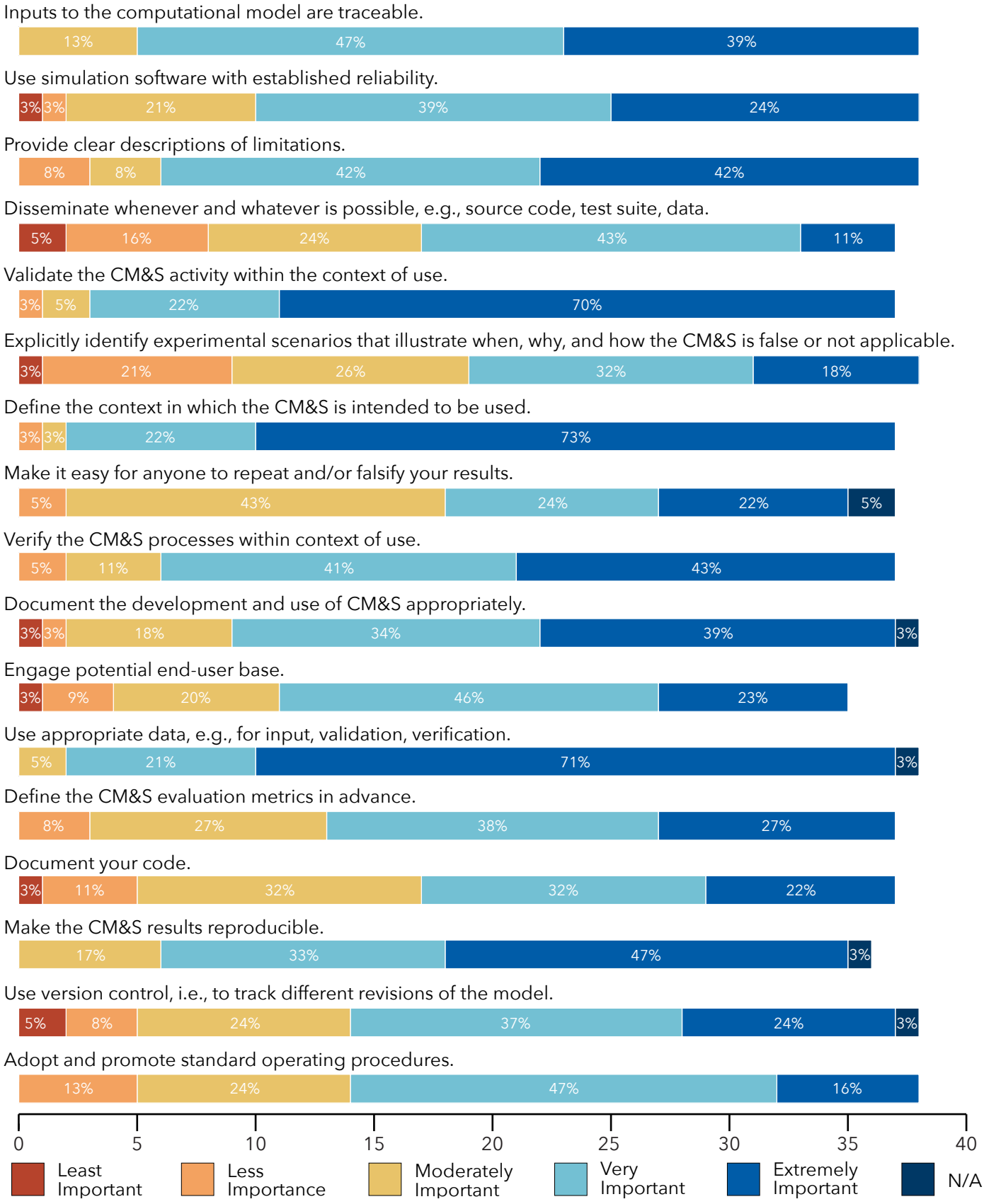


Figure A.19

Level of Agreement With the Following Statements

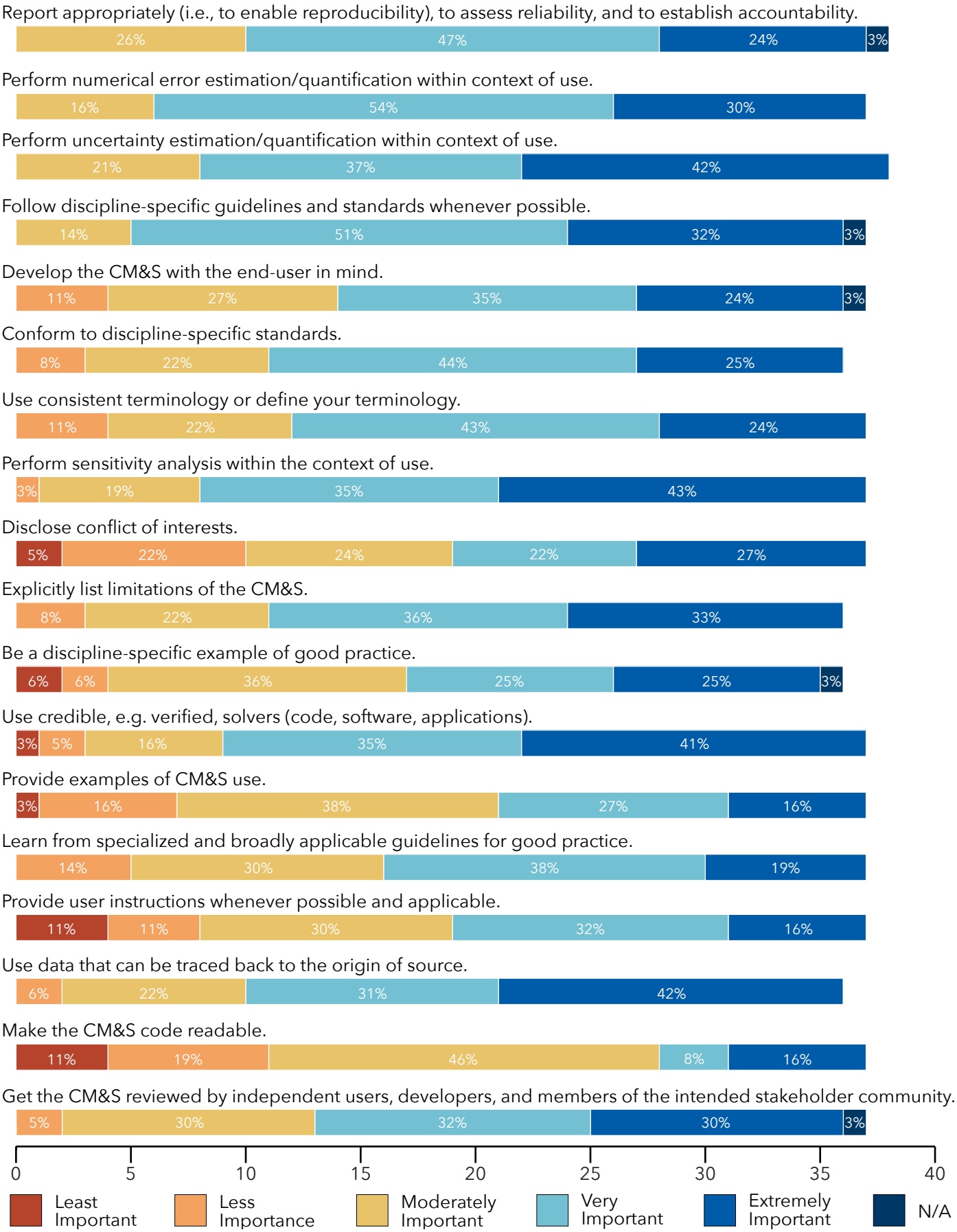


Figure A.20

Appendix B – Case Studies

B.1

CASE STUDY: *In Silico* Trial of Breast Cancer Imaging Technologies

Contact info: Aldo Badano, aldo.badano@fda.hhs.gov

QUESTION OR PROBLEM ADDRESSED

Expensive and lengthy clinical trials can delay regulatory evaluation of innovative technologies, affecting patient access to high-quality medical products. Simulation is increasingly being used in product development but rarely in regulatory applications. Can in silico imaging trials provide digital evidence for the regulatory evaluation of medical imaging products?

STUDY METHODS AND PROCEDURES

An in silico diagnostic study used computer-simulated imaging of 2986 digital patients to compare digital mammography and digital breast tomosynthesis and found an improved lesion detection performance favoring tomosynthesis for all breast sizes and lesion types. The increased performance for tomosynthesis was consistent with results from a large comparative trial using human patients and radiologists. The in silico trial was performed in approximately 2 weeks of computations, compared to the 7 years required for completing the comparative human trial.

IMPACT TO INDUSTRY AND REGULATORY PROCESSES

The findings of the VICTRE trial suggest that the regulatory assessment of the imaging devices based on in silico data would have been the same as to the actual regulatory decision made based on the comparative trial. The VICTRE trial, performed exclusively with open-source computational methods, suggests that increased use of computational modeling tools in the regulatory assessment of imaging systems could significantly decrease the burden of bringing new and improved imaging technologies to market.

TECHNICAL ABSTRACT

The study aimed at conducting a computer-simulated imaging trial evaluating digital breast tomosynthesis (DBT) as a replacement for digital mammography (DM) and to compare the results with a comparative clinical trial. The simulated Virtual Imaging Clinical Trial for Regulatory Evaluation (VICTRE) trial was designed to replicate a clinical trial that used human patients and radiologists. Images obtained with in silico versions of DM and DBT systems via fast Monte Carlo x-ray transport were interpreted by a computational reader detecting the presence of lesions. A total of 2986 synthetic image–based virtual patients with breast sizes and radiographic densities representative of a screening population and compressed thicknesses from 3.5 to 6 cm were generated using an analytic approach in which anatomical structures are randomly created within a predefined breast volume and compressed in the craniocaudal orientation. A positive cohort contained a digitally inserted microcalcification cluster or spiculated mass. The trial end point was the difference in area under the receiver operating characteristic curve between modalities for lesion detection. The trial was sized for an SE of 0.01 in the change in area under the curve (AUC), half the uncertainty in the comparative clinical trial. In this trial, computational readers analyzed 31 055 DM and 27 960 DBT cases from 2986 virtual patients with the following Breast Imaging Reporting and Data System densities: 286 (9.6%) extremely dense, 1200 (40.2%) heterogeneously dense, 1200 (40.2%) scattered fibroglandular densities, and 300 (10.0%) almost entirely fat. The mean (SE) change in AUC was 0.0587 (0.0062) ($P < .001$) in favor of DBT. The change in AUC was larger for masses (mean [SE], 0.0903 [0.008]) than for calcifications (mean [SE], 0.0268 [0.004]), which was consistent with the findings of the comparative trial (mean [SE], 0.065 [0.017] for masses and −0.047 [0.032] for calcifications). The results of the simulated VICTRE trial are consistent with the performance seen in the comparative trial. While further research is needed to assess the generalizability of these findings, in silico imaging trials represent a viable source of regulatory evidence for imaging devices.

B.2

CASE STUDY: The Use of Digital Twins in the Patient-Specific Analysis of Heart Failure

Contact info: Alireza Heidari, alireza.heidari@mcgill.ca

QUESTION OR PROBLEM ADDRESSED

Rapid and accurate interpretation of clinical outcomes can be a major barrier to approval of new medical treatments, leaving some diseases with little or no cure. Pulmonary hypertension (PH) is a chronic medical condition affecting 1% of the global population. It is a type of high blood pressure that affects the arteries in the lungs and the right side of the heart and can be life-threatening. Accurate or early diagnosis and treatment are hindered by the functional dominance of the left side of the heart and gender differences, particularly when the PH is caused by left heart disease. Can virtual patient twins provide necessary insights to expand indications of existing devices or cost-effective development of new ones?

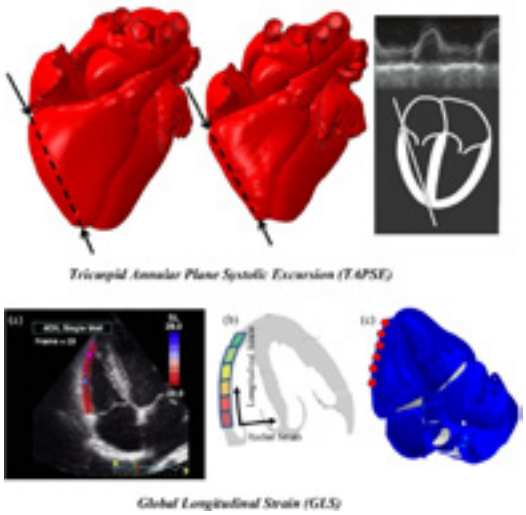
STUDY METHODS AND PROCEDURES

Prospective and retrospective data from two patients were used to create whole heart models of pre and post treatment physiological states. Pre-treatment patient twins were used to identify the root cause of the patient condition and the association between the function and physical states of the left and right sides of the heart. Using the post-operative patient twin, clinically available biomarkers were interpreted in terms of the acute changes in physical conditions, as well as providing additional biomarkers that suggest the effectiveness of the treatment.

IMPACT TO INDUSTRY AND REGULATORY PROCESSES

The findings in the study suggest that use of a digital twin of a patient in pilot human or animal studies could reveal mechanistic understanding of disease and treatment efficacy. Such understanding could be highly effective in optimal trial design, more reliable interpretation outcomes and safety risk identification. Longitudinal data could provide long term outcome prediction, leading to the use of virtual patients as evidence in a pivotal trial.

TECHNICAL ABSTRACT



Pulmonary hypertension (PH), a chronic and complex medical condition affecting 1% of the global population, requires clinical evaluation of right ventricular maladaptation patterns under various conditions. A particular challenge for clinicians is a proper quantitative assessment of the right ventricle (RV) owing to its intimate coupling to the left ventricle (LV). We, thus, proposed a patient-specific computational approach to simulate PH caused by left heart disease and its main adverse functional and structural effects on the whole heart. Information obtained from both prospective and retrospective studies of two patients with severe PH, a 72-year-old female and a 61-year-old male, is used to present patient-specific versions of the Living Heart Human Model (LHHM) for the pre-operative and post-operative cardiac surgery. Our findings suggest that before mitral and tricuspid valve repair, the patients were at risk of right ventricular dilatation which may progress to right ventricular failure secondary to their mitral valve disease and left ventricular dysfunction. Our analysis provides detailed evidence that mitral valve replacement and subsequent chamber pressure unloading are associated with a significant decrease in failure risk post-operatively in the context of pulmonary hypertension. In particular, right-sided strain markers, such as tricuspid annular plane systolic excursion (TAPSE) and circumferential and longitudinal strains, indicate a transition from a range representative of disease to within typical values after surgery. Furthermore, the wall stresses across the RV and the interventricular septum showed a notable decrease during the systolic phase after surgery, lessening the drive for further RV maladaptation and significantly reducing the risk of RV failure.

B.3

CASE STUDY: *In Silico* Trial of Flow Diverters of Intracranial Aneurysms

Contact info: Alejandro Frangi, a.frangi@leeds.ac.uk

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 phenomenon, like thrombosis, the in-silico approach allowed broader investigation of factors associated with insufficient flow reduction than feasible in clinical trials.

IMPACT TO 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 to be 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. To date, 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 sub-group analyses that are difficult or impossible in clinical trials.

B.4

CASE STUDY: Reducing Regulatory Uncertainty of CM&S through the Use of Guidance and Standards

Contact info: Jeff Bischoff, Jeff.bischoff@zimmerbiomet.com

QUESTION OR PROBLEM ADDRESSED

Uncertainty in the expectations of regulatory bodies on model credibility is commonly cited as a factor that impacts the use of CM&S within the medical device manufacturing community. Without common expectations between manufacturer and regulator, the use of CM&S within a device submission historically has presented unnecessary risk to a successful regulatory review. Publication of the 2016 FDA final guidance document on "Reporting of Computational Modeling Studies in Medical Device Submissions" and the 2018 ASME V&V 40 standard on "Assessing Credibility of Computational Modeling and Simulation Results through Verification and Validation: Application to Medical Devices" both may contribute to reducing this uncertainty by providing explicit expectations on documentation and credibility, respectively. This case study demonstrates the impact of adherence to these documents on a device submission.

STUDY METHODS AND PROCEDURES

In the early 2010s, a series of modeling activities was conducted in support of design verification activities for a novel, stemless total shoulder arthroplasty (TSA) system. These activities included the use of finite element analysis to evaluate the primary stability of the proposed TSA design, in order to identify key variables that impact the primary stability of the design and to determine worst case test conditions. Benchtop testing was then conducted within a worst-case test setup to generate final design verification evidence. Comparison of model predictions and benchtop test results showed sufficient agreement to support the use of the model in this context.

Due to the regulatory pathway for this device in the United States, clinical data were required following regulatory review (early 2010s) of the design verification evidence. The device application, now augmented with clinical data, was resubmitted to the FDA in 2017, which included the CM&S reports which had been prepared several years earlier, preceding publication of both the FDA guidance on CM&S documentation as well as the ASME V&V 40 standard. Regulatory review of those CM&S reports, which had not incurred any questions when reviewed prior to initiation of the clinical study, now generated comments or questions including:

- "For additional details regarding model validation please see the computational modeling reporting guidance for FDA's current thinking on reporting numerical simulations."
- "A description of the verification activities (software quality assurance or numerical code verification) to ensure that software/solver is producing credible results for your software installation on your computer could not be found."
- "Please perform and provide a description of the validation performed to ensure that the finite element model provided accurate results within the context of use."

This response prompted a revision to the CM&S documentation by the manufacturer, incorporating best practices both for CM&S verification/validation as well as documentation that had been put in place in the company in the interim years but which had not been used to revise the earlier documentation. With these revisions, there were no further questions from the agency on the adequacy of the CM&S studies.

IMPACT TO INDUSTRY AND REGULATORY PROCESSES

This case study demonstrates the direct utility of adherence to the newly introduced FDA guidance on CM&S documentation and the ASME V&V 40 standard for reducing regulatory uncertainty associated with CM&S. From the manufacturer perspective, adherence of internal CM&S practices to the ASME V&V 40 standard, as well as adherence to FDA expectations on documentation, resulted in confidence that the questions from the FDA on documents which were generated prior to these standards could be sufficiently addressed. Further, the questions from the regulatory body demonstrated that the regulator was fully knowledgeable of these standards with expectations of compliance. With these expectations level set between both manufacturer and regulator, an informed decision by the manufacturer on the use of CM&S to support a submission, balancing the impact of CM&S on the design dossier with the burden to establish the requisite model credibility, can be made early in the process, with good confidence that later review of the CM&S evidence by the regulatory body will adhere to the expectations laid out in these standards.

B.5

CASE STUDY: Simulating the Release Mechanism in Drug-Eluting Stents

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QUESTION OR PROBLEM ADDRESSED

Over time, the coronary arteries that supply blood to heart muscle can become blocked by plaque in the artery wall. This condition is known as stenosis. The symptoms are shortness of breath and chest pain resulting from restricted blood flow to heart muscle. One treatment for this condition is the implantation of a stent. A stent is small mesh tube that is deployed using a balloon catheter. Prior to implant, the stent is crimped onto the balloon. The stent is positioned in the area needing treatment using the balloon catheter. As the balloon is inflated, the stent and balloon reopen the artery. The amount of deformation used to deploy the stent and the material used to make the stent result in the stent being permanently deformed after deployment, keeping the artery open.

It is possible for a stented artery to become blocked again due to tissue growth over the stent. Drug coated stents were developed to reduce this tissue growth. The coating is composed of a drug in a polymer matrix and is designed to provide a controlled release of the drug. It is important to understand how the drug release mechanism works to optimize performance.

STUDY METHODS AND PROCEDURES

Cumulative drug release versus time data were collected in both in vitro and in vivo conditions. The drug is released in 2 phases. The first is a fast release phase were the drug on the surface of the coating is quickly released into the tissue. In the second phase, drug diffuses out of the polymer at a slower rate. An idealized model of the coating microstructure was created. This model consisted of a pattern of cylindrical pores filled with solid drug (fast release) surrounded by a polymer shell also containing drug (slow release). A commercial finite element code with an optimization module was used to find the best fit for both sets of experimental data by varying the shell thickness and retardation coefficient.

IMPACT TO INDUSTRY AND REGULATORY PROCESSES

The modeling approach used is this study offers valuable insight into one type of drug release mechanism. The pore-shell idealization model of the coating microstructure showed very good agreement with both the in vitro and in vivo data sets. Simulation has the potential to give medical device designers more control over the drug delivery process.

B.6

CASE STUDY: Reducing the Time and Cost of Design Verification Testing through Simulation

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QUESTION OR PROBLEM ADDRESSED

Design verification (DV) testing often takes significant labor hours and calendar time to execute as a precursor to a regulatory device submission. Moreover, the amount of DV testing is exponentially increased when a collection of relatively small device changes and/or product line extensions occur in a concurrent timeline. Can we use in-silico modeling and simulation to reduce the time and cost of DV testing for hypodermic syringe product updates?

STUDY METHODS AND PROCEDURES

An in-silico finite element analysis (FEA) of hypodermic syringe-tip interactions and leakage was completed mirroring ISO requirements for physical testing. The FEA investigations included fundamental computational model verification and validation credibility factors such as: model parameter calibration, calculation verification, and model prediction validations. A new DV testing was then developed based on the in-silico data from the FEA investigations and engineering fundamentals.

IMPACT TO INDUSTRY AND REGULATORY PROCESSES

The in-silico data clearly identified the most important conditions to physically test within a DV investigation. Furthermore, the updated DV testing plan drastically reduced the expected number of physical tests and labor hours to a few high-impact cases. Physical testing labor hours were reduced by over two orders of magnitude and enabled a reduced time to patient for updated hypodermic syringe devices.

TECHNICAL ABSTRACT

A detailed technical abstract, as submitted to 2015 FDA/BMES Frontiers in Medical Devices Conferences can be found here.

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