FDA/MDIC
Symposium on Computational Modeling and Simulation

Generating Regulatory In Silico Evidence

Panel Discussion: Towards Good Simulation Practices

Wednesday, April 17th
10:30 AM – 12:00 PM

Noel Colon
NC MedTech Solutions, LLC
Founder & Consultant

#ModSim2024

MDIC Medical Device Innovation Consortium

Background

- Education
  - Bachelors – Mechanical Engineering
  - Masters – MBA, Finance
- Experience - 32 years in MedTech
  - 17 years in Guidant/Boston Scientific – Operations, Quality and R&D
  - 15 years in Medtronic - Operations, Quality and R&D
    - VP & GM, Medtronic Energy & Component Center – 2012 to 2017
    - VP, Global Quality Medtronic Neuroscience – 2017 to 2019
    - SVP, Chief Quality Officer – 2020 to 2023
    - SVP, Research and Development – 2023 to 2024
  - Started consultancy business

Background

Expertise – Medical technology executive

- Strategy deployment
- Global Regulations
- Regulatory compliance & GxP
- Pre-market design assurance

- Design validation & verification
- Patient safety & risk management
- Design for Reliability and Manufacturability (DFSS)

- Product development process
- R&D productivity
- Lean manufacturing
- Manufacturing automation

Perspective - Good Simulation Practices

- **Adoption**: Embracing Good Simulation Practices (GSP) is critical for the successful execution of CM&S strategies.
- **Global**: A uniform and global adoption of GSP will facilitate essential CM&S investments.
- **Resource Synergy**: It's imperative to demonstrate how CM&S enhances and supports technological advancements like AI/ML and Digital Twin amidst fierce resource competition.
- **Foundational Principles**: There's no necessity to reinvent the wheel; foundational principles from GxP are integrated in the GSP framework.
- **Implementation Roadmap**: The path to adopting GSP involves a structured approach: dissemination, training, pilot projects, and scaling utilization.
- **Expedited Process**: An empowered MDIC work group with a definitive mandate can fast-track this adoption process.

Tina M. Morrison, PhD

BACHELORS

Mechanical Engineering & Applied Mathematics

MASTERS

Mechanical Engineering – Nonlinear Dynamics

DOCTORAL & POST DOCTORAL TRAINING

PhD Theoretical & Applied Mechanics and Applied Mathematics
Post Doc Cardiovascular Biomechanics

WORK EXPERIENCE

3 years Pratt & Whitney Aircraft – Applied Mechanics Laboratory
1 year Boston Scientific – Endovascular Devices
16 years at U.S. Food and Drug Administrator
- 7 yrs Cardiovascular Devices (lead reviewer & expert consultant)
- 5 yrs Deputy Division Director, Applied Mechanics
- 4 yrs Director, Office of Regulatory Science and Innovation

Tina M. Morrison, PhD

EXPERTISE IN MEDICAL DEVICES & SIMULATION

- **Led and Engaged in Standards & Guidance Development**
  - Assessing Credibility of Computational Modeling Studies – FDA Guidance
  - ASME V&V 40 - 2018 Standard
  - Reporting Computational Modeling Studies – FDA Guidance
  - ISO 25539-1:2017 Cardiovascular implants — Endovascular Devices
    - FEA, *in vitro* testing, durability assessment
  - Several ASTM-F04 Test Methods
    - Radial and non-radial durability, fatigue-to-fracture, sample size
  - Medical Device Development Tool Qualification – FDA Guidance
    - Nonclinical assessment models
- **Community Building & Engagement**
  - Reagan Udall Foundation, Regulatory Science Accelerator
  - Avicenna Alliance – FDA as Observer Member
  - FDA Modeling & Simulation Working Group – co-founder
  - ASME V&V 70 Subcommittee ML/AI – co-founder
  - ASME V&V 40 Subcommittee CM&S in Medical Devices – co-founder
  - Interagency Modeling & Analysis Group (IMAG)
    - Credible Practice of Simulation in Healthcare
    - Digital Twins in Healthcare
- **Research publications** on numerical methods, simulation approaches, boundary condition development, and credibility assessment approaches

www.fda.gov/FARS

Tina M. Morrison, PhD

PERSPECTIVE

- Over the last 10-15 years, **FDA has helped address gaps**:
  - *Tell us what you've done* – Reporting Guidance
  - *Tell us why we should trust it* – Credibility Assessment Guidance
  - *Work together in precompetitive space* – MDIC CM&S Workstream
  - Scores of publications on computational approaches, regulatory science tools, and assessment frameworks from scientists and engineers across the Office of Science and Engineering Laboratories

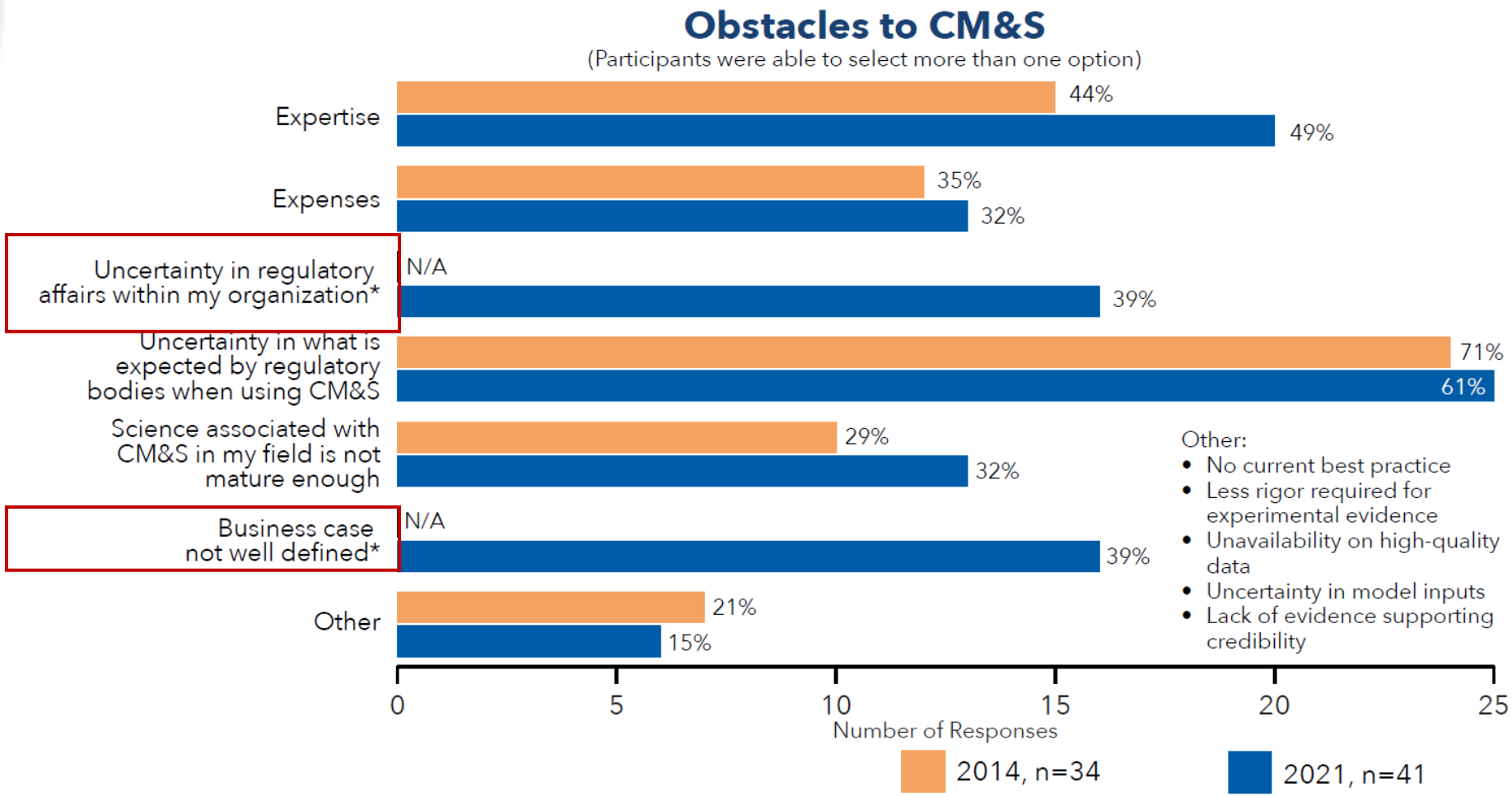
- We had planned to host a GSP Workshop in March 2020 …

- In 2023, we convened a **GSP cluster in our Regulatory Science Accelerator**
  - In 100+ membership inquiries, almost all said: *Yes! We need GSP.*

  - But after several sprints identifying gaps, the consensus changed:
    - NO! We don't need GSP (not now anyway – too many documents)
    - We **need to engage *regulatory affairs personnel***
    - We **need to engage *business leaders and decision-makers***

Tina M. Morrison, PhD

THIS ALSO ALIGNS WITH THE RESULTS FROM THE MDIC LANDSCAPE REPORT & IINDUSTRY SURVEY (2023)



www.fda.gov/FARS

Tina M. Morrison, PhD

www.fda.gov/FARS

PERSPECTIVE

- Over the last 10-15 years, **FDA has helped address gaps**:
  - *Tell us what you've done* – Reporting Guidance
  - *Tell us why we should trust it* – Credibility Assessment Guidance
  - *Work together in precompetitive space* – MDIC CM&S Workstream
  - Scores of publications on computational approaches, regulatory science tools, and assessment frameworks from scientists and engineers across the Office of Science and Engineering Laboratories

- We had planned to host a GSP Workshop in March 2020 …

- In 2023, we convened a **GSP cluster in our Regulatory Science Accelerator**
  - In 100+ membership inquiries, almost all said: *Yes! We need GSP.*

  - But after several sprints identifying gaps, the consensus changed:
    - NO! We don't need GSP (not now anyway – too many documents)
    - We **need to engage *regulatory affairs personnel***
    - We **need to engage *business leaders and decision-makers***

  - **Team shifted to write an "In Silico Technologies" Activation Paper**
    - Coming soon … Junes 2024

ASHLEY PETERSON, PhD

Vice President, Head of Life Science, Applied Science

- Bachelors:

  Mechanical Engineering

- PhD:

  Fluid Dynamics – Multiphase CFD

- Selected employment history:

  10 yrs. device development in Medtronic Aortic R&D

  5 yrs. industry consulting for Thornton Tomasetti

ASHLEY PETERSON, PhD

Vice President, Head of Life Science, Applied Science

- Computational Modeling Experience/expertise:
  - Wrote CFD solver for unsteady multiphase flows
  - Structural analysis (FE) on numerous devices
  - Fluid dynamics (CFD) on many devices
  - Fluid-Structure (FSI) on some devices
  - Authored and contributed to copious Class I, II, III device related regulatory submissions

ASHLEY PETERSON, PhD

Vice President, Head of Life Science, Applied Science

- Perspective:

  Computational modeler, and sometimes experimentalist, who has been extensively involved in cardiovascular device development.

  Experienced and contributed to the total medical device development lifecycle from both an internal and external standpoint.

  Current lead of Thornton Tomasetti's Life Science team.

Mark Palmer, MD, PhD

CTO for Healthcare
Ansys Fellow
Lead Chief Technologist

BACHELORS

Mechanical & Aerospace Engineering

MEDICAL SCIENTIST TRAINING PROGRAM

M.D. Medical Doctor
Ph.D Mechanical Engineering/Computational Mechanics

WORK EXPERIENCE

5 years founder of modeling and simulation startup
5 years as faculty member, University of Michigan
9 years leading human simulation and enterprise strategy, Medtronic
1 year leading life science technology strategy, Ansys

Ansys

Mark Palmer, MD, PhD
CTO for Healthcare
Ansys Fellow
Lead Chief Technologist

EXPERIENCE & EXPERTISE

- Authored fully coupled, multiscale, solid mechanics code with emphasis on active, composite materials & tissues
- Forensic simulations for injury mechanisms
- Image-based modeling of surgical procedures
- Develop and deploy new simulation capabilities across product lines and business units
- Implement enabling technologies and platforms with ROI in the $10'sM (does not include revenue impact)
- Partner on regulatory policy

Ansys

Mark Palmer, MD, PhD
CTO for Healthcare
Ansys Fellow
Lead Chief Technologist

EXTRACURRICULAR

- 50+ papers and refereed journal publications including Nature Scientific Reports and cover of IEEE Biomedical & Health Informatics
- Over 40 international keynote presentations
- Representative on MDIC CM&S Steering Committee, ASME VV40, ASME VV70 , NAFEMS
- Elected to board of Avicenna Alliance for International Working Group. Continued engagement supporting global harmonization.
- Industry Advisory Board for ASME and CompBioMed
- NAFEMS Americas Steering Committee, Business Impact Working Group/Assess Initiative

Ansys

Mark Palmer, MD, PhD
CTO for Healthcare
Ansys Fellow
Lead Chief Technologist

PERSPECTIVE

- Causal modeling can **contribute significantly** to safety & effectiveness, of interventions as well as the health and wellbeing for all of us
- A lot of the heavy lifting around VVUQ and model credibility is done. We need to **transition the conversation**.
- We have an **ethical imperative** to leverage CM&S and GSP to improve the safety and efficacy of devices.
- Burden of CM&S and GSP cannot rest solely on the modeler and the regulatory reviewer. **We need an ecosystem** so that regulator can focus on the evidence.
- The industry needs a CM&S ecosystem where **risk and burden are commensurate** with other evidence generation methods
- Need for a **global regulatory standard**

Ansys

Emmanuelle M. Voisin
PhD
Founder and CEO

voisin@voisinconsulting.com

EU: +33 (0)6 60 28 47 02
US: +1 617 955 9102

A regulatory landscape shift for in silico clinical trials

Keeping up with innovation, the challenge for regulators

Toward Good Simulation Practice:
- Possible Qualification Pathways for In Silico Methodologies
- Possible Health Technology Assessment Pathways
- Ethical Review of In Silico Methodologies

© VCLS

Highlights

- Founder & CEO of Voisin Consulting Life Sciences - VCLS
- 25+ years of experience in advising Biotech, Medtech & Pharmaceutical companies on global Regulatory, Market Access (CMC/Nonclinical/Clinical development)
- Interactions with FDA, EMA and NMPA
- Pioneer in ODD, ATMPs and *in-silico* approaches

Expertise

- Design of drug development plans Europe & USA nonclinical and clinical
- Creative regulatory strategies to speed-up access to the market
- Regulatory toxicology
- Due diligence and negotiations for licensing/acquisition

Memberships

- Ex Leader of Policy Development WG, Avicenna Alliance & Founder of the In Silico Application - ISA WG, AA
- Consortia: EDITH, InnovaHeart, METASTRA
- Member of Scientific Advisory Board of AC Immune SA and Endodiag SAS
- Board Member of Orphalan SA
- Chair of Neighborhood

Experience

- **PhD in Pharmacology**, Institut Gustave Roussy, Villejuif, France
- **Servier**, Non-clinical drug development
- National Institute of Mental Health (**NIMH**), collaboration with Servier
- Reviewing Pharmacologist and Toxicologist, US **F**ood & **D**rug **A**dministration, Division of Antiviral Drug Products
- General Manager, **IQVIA** France & Spain
- **VCLS** since 1997

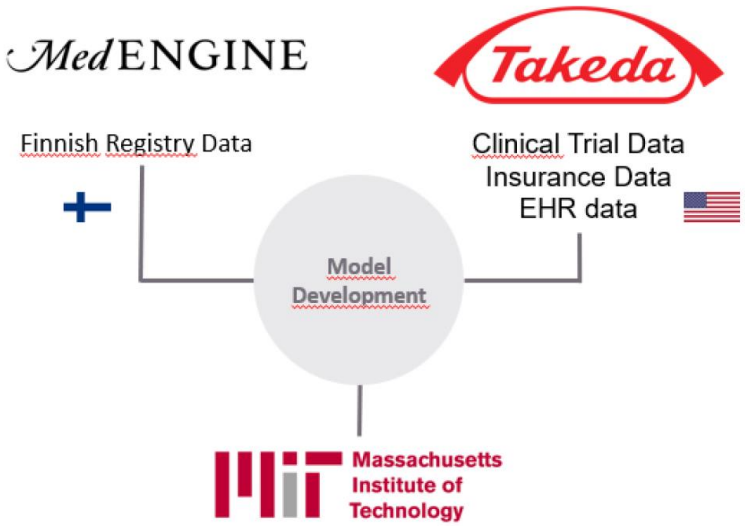
© 2024 VCLS - All rights reserved – Confidential, do NOT distribute without written approval from VCLS.

Why CM&S? To Bring HealthTech Products to Patients

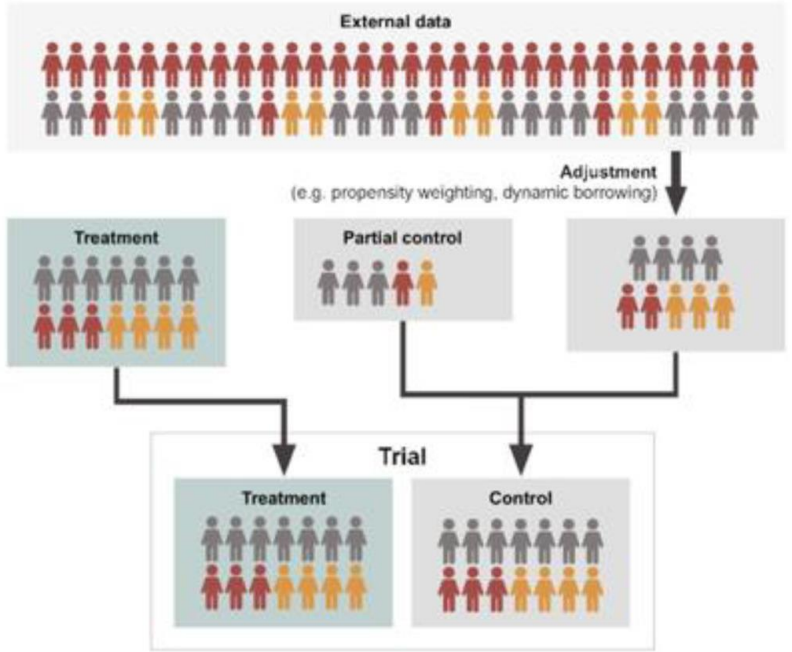
- From watching early modelling “for fun” to …
- Observing Critical Path Initiative
- “Lobbying” around to promote in silico modelling in medical device and drug clinical development
- Avicenna Alliance
  - Policy Development WG former leader
  - In Silico Application WG co-leader
- Leveraging Modeling capabilities within VCLS
  - Translation of modeling into regulatory arguments
  - Acquiring talent in-house Biomodeler
  - Acquiring know-how via MedEngine:
    - Modeling synthetic arm in clinical trials
    - Use of RWD in Regulatory Science and Market Access
    - And beyond…

© 2024 VCLS - All rights reserved – Confidential, do NOT distribute without written approval from VCLS.

MedEngine Modeling & Simulation



External control arms as part of clinical trials



MedENGINE

BAYER

ML-based algorithms in IBD

1. To predict non-responders or suboptimal responders to various therapies
2. To predict disease progression risk
3. To predict IBD diagnosis among undiagnosed individuals

© 2024 VCLS - All rights reserved – Confidential, do NOT distribute without written approval from VCLS.

Patient Portrait in 2035: Regulatory evolution = f(e^x)

PATIENT

- Patrick has a rare disease and uses telemedicine
- He is remotely enrolled into a clinical trial
- Uses smart phone a SaMD (behavioral health app) powered by AI-enabled algorithm
- Data are automatically and securely sent to MD and MedTech
- Active member of an online patient community

INDUSTRY

- PharmaA and MedtechB merged: Digi-Pharm
- Patient-centricity approach: partnership with patient community to understand patient behavior & expectations
- Clinical studies: *via in silico* clinical trial
- Uses AI programs to spot abnormal patterns
- Missing clinical data => replaced by digital evidence from *in silico* trial
- Regulatory submission of dataset via AI-based portal, abnormalities cleared

REGULATOR

- Regulatory agency is global
- Data scientist and behavioral analysts
- *In silico* technologies = standard to evaluate endpoints & surrogates
- Uses AI to provide review reports
- Blockchain mechanisms to use with data sources from regulators across the globe
- Works with payers and industry to shape an adaptive real-world trial

© 2024 VCLS - All rights reserved – Confidential, do NOT distribute without written approval from VCLS.

Perspectives: Multidisciplinary Approach

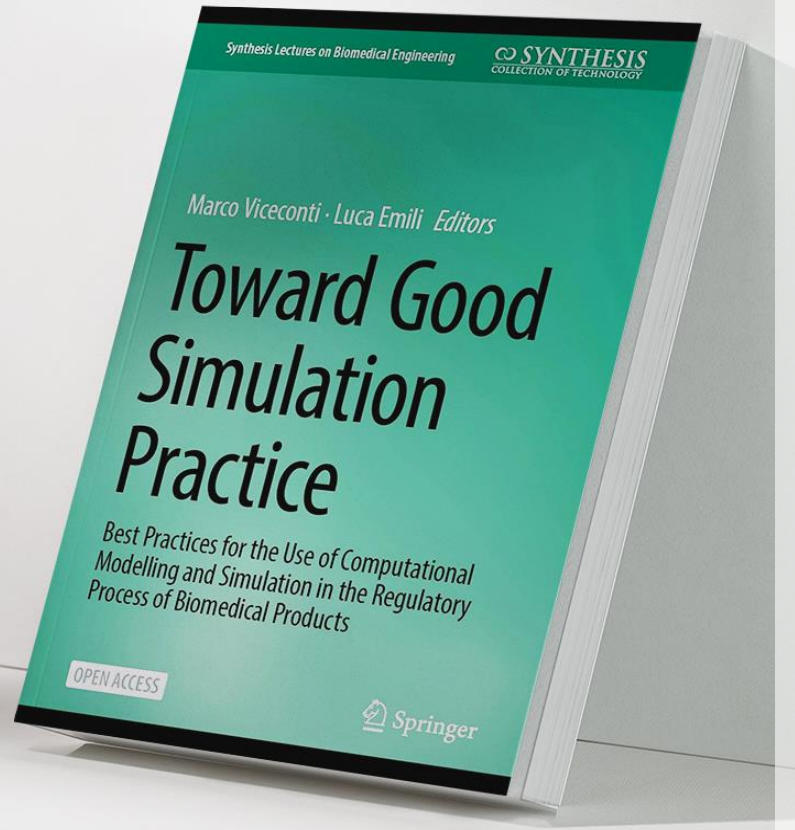
- In silico in HealthTech product development: yes!
- Hurdles: yes…
- Delays: yes…
- Skepticism: yes…
- Success: in the future, yes!
  - When predictive model accepted as much as human model is
  - When modelling accepted at all stages of product development & life-cycle:
    - Discovery (done)
    - CMC
    - Nonclinical
    - Exploratory & confirmatory clinical development
    - Around & post-market life-cycle
  - When all – numerous – stakeholders operate together
  - When Reviewers are also Data Scientists

© 2024 VCLS - All rights reserved – Confidential, do NOT distribute without written approval from VCLS.

Toward Good Simulation Practice

The Book

A consolidated set of industrial practices that render the development and use of *In Silico Trials* solutions easier and reliable.



Co-editors: **Luca Emili** (InSilicoTrials) and **Prof. Marco Viceconti** (University of Bologna)

138 experts from academia, industry, and regulatory agencies (including 13 M&S experts from FDA' s ModSimWG) from all over the world involved in the consensus process in the last 2 years

Published **Open Access** by Nature Springer on 2 Feb., **18K accesses by April 15th**

First milestone toward the **standard creation by regulators**

InSilicoTrials VPH Institute Building the Virtual Physiological Human INSILICO WORLD Avicenna Alliance Association for Predictive Medicine

FDA/MDIC Symposium on Computational Modeling and Simulation

Generating Regulatory In Silico Evidence

Panel Discussion: Towards Good Simulation Practices

Wednesday, April 17th
10:30 AM – 12:00 PM

- What does GSP mean to you?
- In what ways should M&S follow the path of other fields (GLP, GMP, GCP) to enable adoption?
- What are some lessons learned from other GxP domains? What should GSP avoid?
- How do we spread the burden of M&S quality across the other parts of the ecosystem so that Regulatory can focus on the data?
- What are expectations now that GSP is published?
- How do we see GSP applying across pharma and medical devices?

#ModSim2024

MDIC Medical Device Innovation Consortium

GLP Principles (OECD)

1. Test Facility Organisation and Personnel
- 1.1 Test Facility Management's Responsibilities
- 1.2 Study Director's Responsibilities
- 1.3 Principal Investigator's Responsibilities
- 1.4 Study Personnel's Responsibilities

2. Quality Assurance Programme
- 2.1 General
- 2.2 Responsibilities of the Quality Assurance Personnel

3. Facilities
- 3.1 General
- 3.2 Test System Facilities
- 3.3 Facilities for Handling Test and Reference Items
- 3.4 Archive Facilities
- 3.5 Waste Disposal

4. Apparatus, Material, and Reagents

5. Test Systems
- 5.1 Physical/Chemical
- 5.2 Biological

6. Test and Reference Items
- 6.1 Receipt, Handling, Sampling and Storage
- 6.2 Characterisation

7. Standard Operating Procedures

8. Performance of the Study
- 8.1 Study Plan
- 8.2 Content of the Study Plan
- 8.3 Conduct of the Study

9. Reporting of Study Results
- 9.1 General
- 9.2 Content of the Final Report

10. Storage and Retention of Records and Materials

GCP (ICH – 2016)

1. Clinical trials should be conducted in accordance with ethical principles.
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society.
3. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.
4. Available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in clear, detailed protocol.
6. Trials should be conducted with approved IRB protocol
7. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP).
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.