Our experience in developing an in silico clinical trial in the medical device industry

Philippe Favre, PhD
Research Associate Director
Switzerland

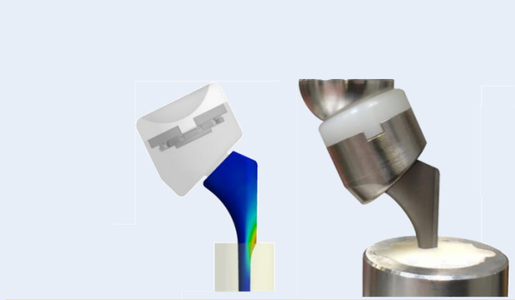
ZIMMER BIOMET
Moving You Forward.™

CADFEM ANSYS SIMULATION
CONFERENCE RAPPERSWIL 2023
15. June 2023

Medtech industry

Mission: improve the patients' quality of life
Significant potential for hazards
Manufacturer must demonstrate safety and efficacy

Establish product safety and efficacy



Product launch

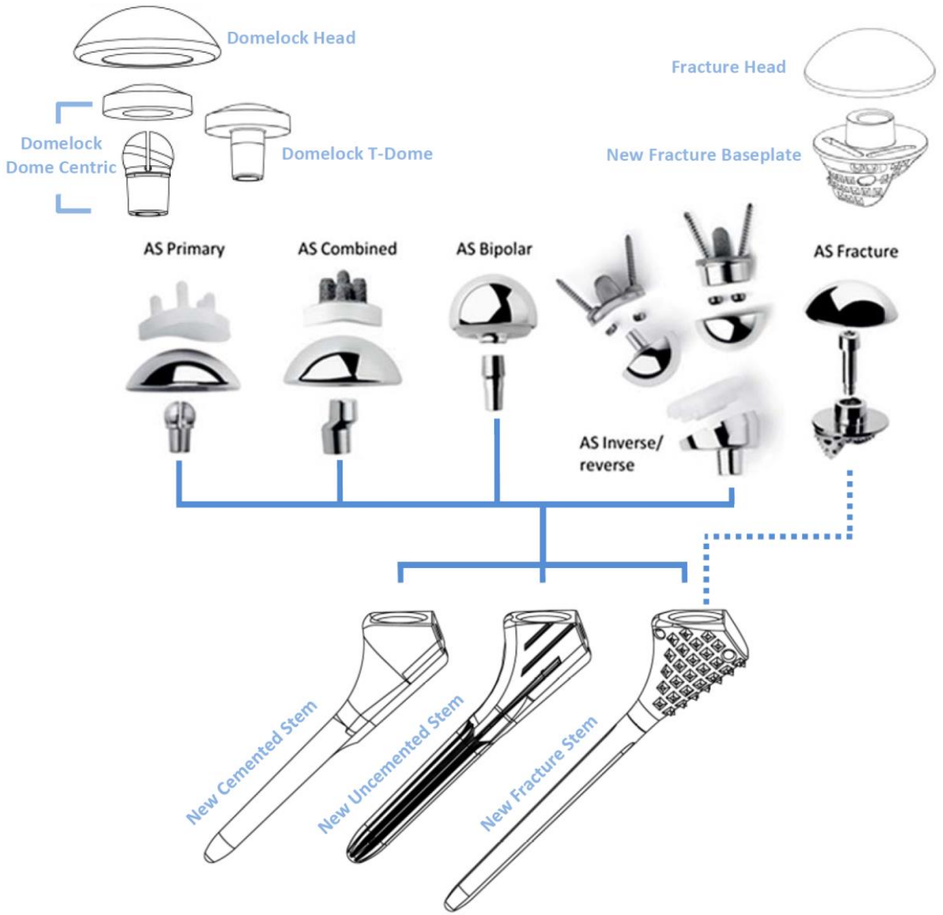
Pre clinical testing

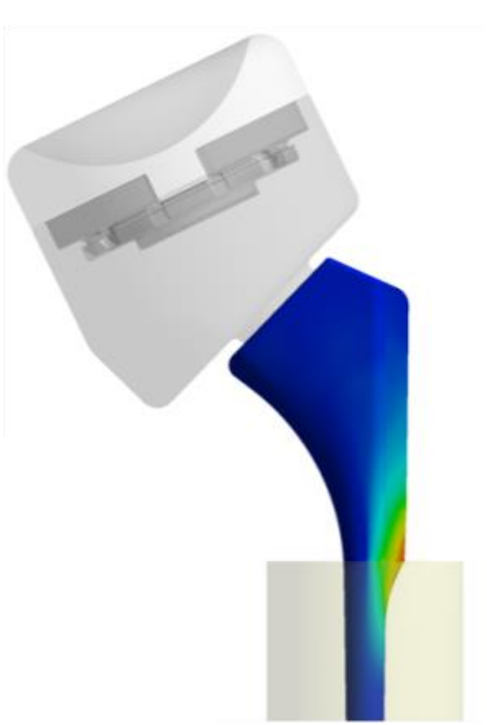
Clinical follow up

Post market surveillance

Worst-case identification

FEA - Finite element analysis

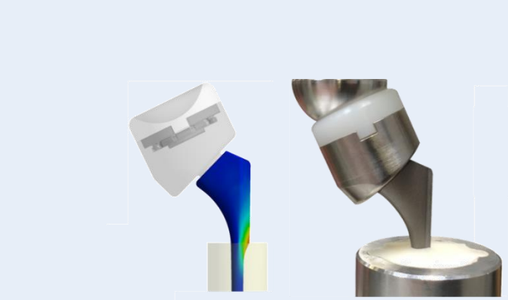




> 100 FEA simulations of combinations

1 physical test of worst-case

Establish product safety and efficacy



Product launch

Pre clinical testing

Clinical follow up

Post market surveillance

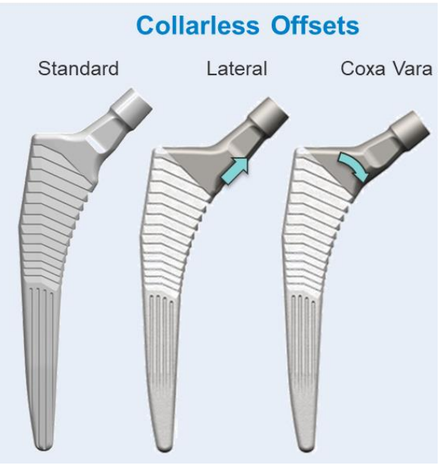
Challenges with clinical data acquisition

Increasing burden to effectively provide clinical data to satisfy expanding regulatory requirements (ex. EU MDR)

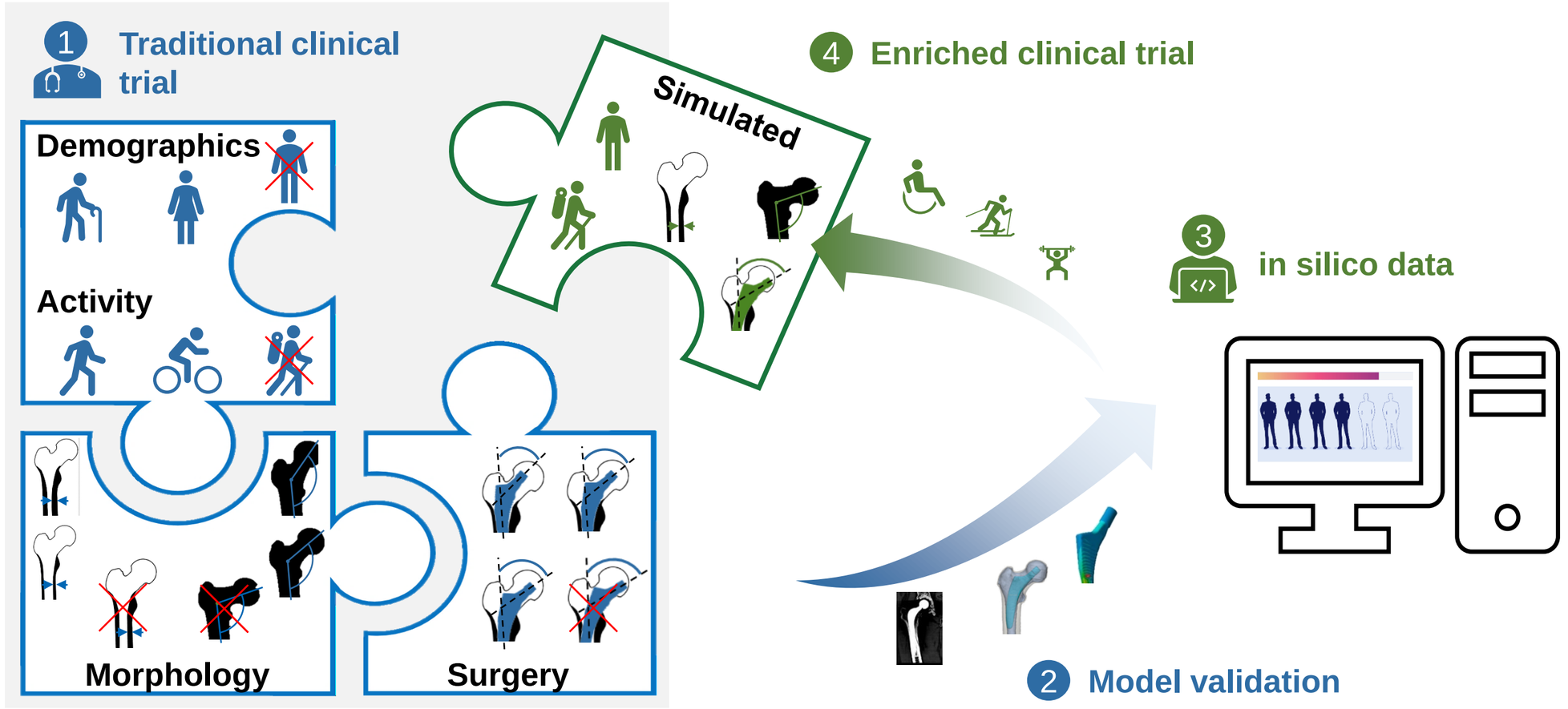
1. Difficult to find patients for
   - rare demographics (eg. XS and XL patients)
   - rare use (rare pathologies)
   - rare surgical procedure (hemiarthroplasty)

2. Drop rate

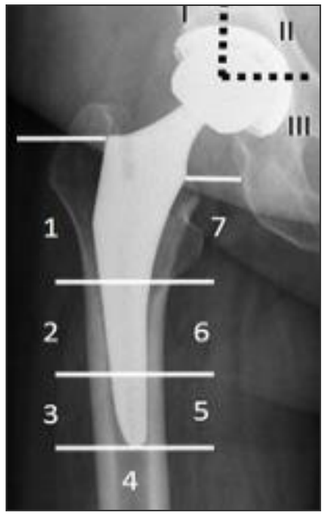
3. Different clinical studies can be required for variants of a same implant



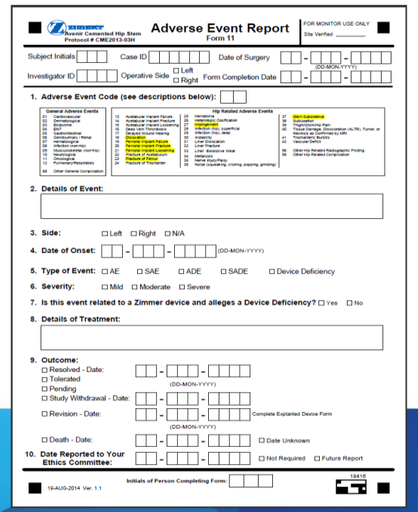
Concept of in silico clinical trials (ISCT)

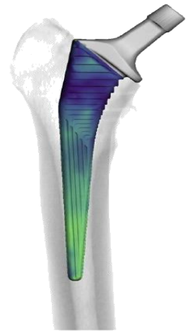


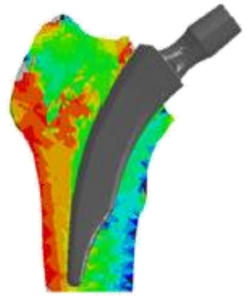
In Silico Methods are here



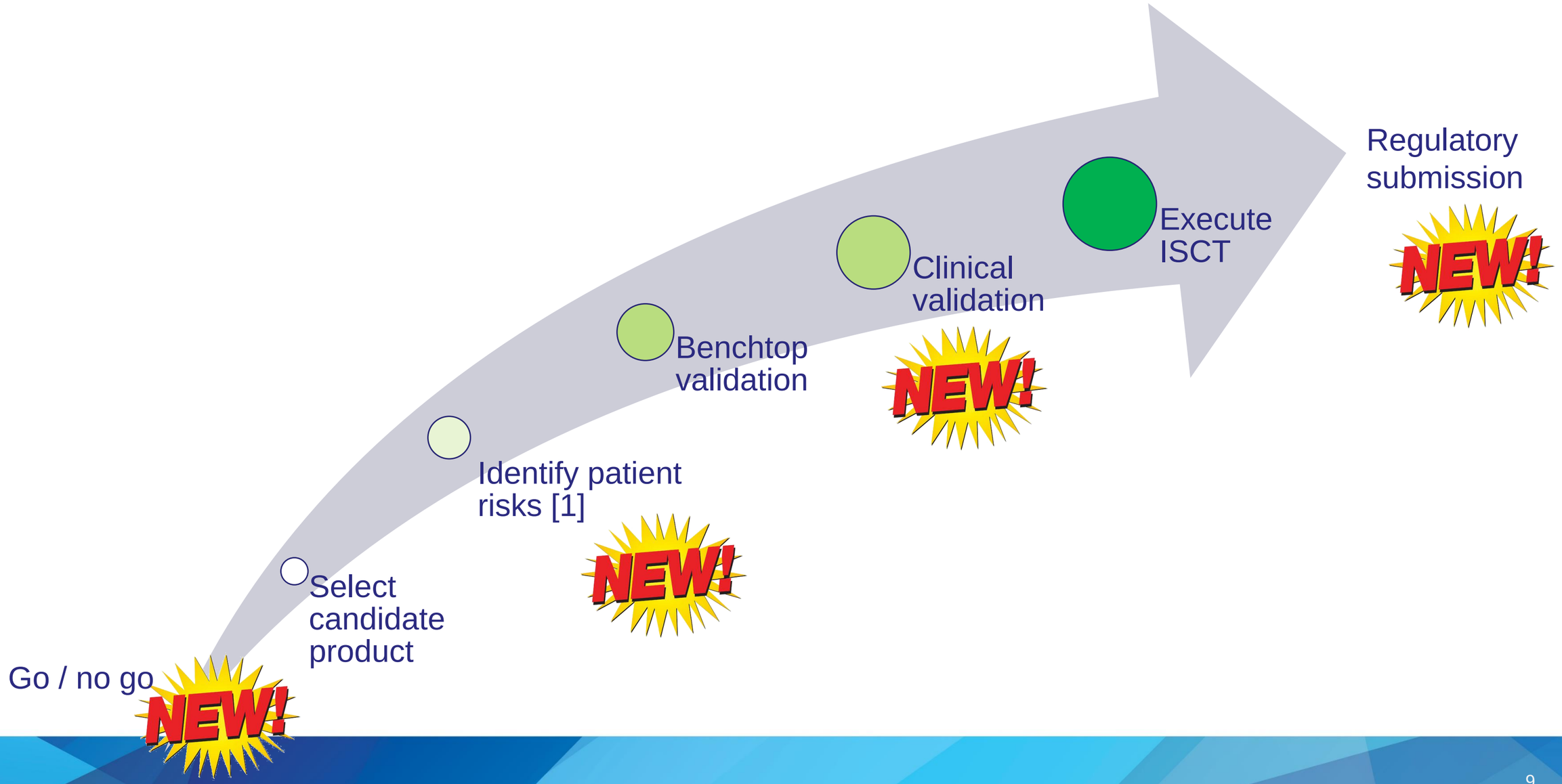
Clinical		In silico
Aseptic loosening	↔	Micromotion and interface strain
Stem subsidence	↔	Permanent displacement
Bony atrophy/hypertrophy	↔	Change in bone stress
Intra/post OP bone fracture	↔	Bone ultimate/fatigue stress
Stem fracture	↔	Implant fatigue stress
Impingement/dislocation	↔	Range of motion
VARIABILITY	↔	VARIABILITY


Adverse Event Report
Form 11





The journey towards ISCT in a regulatory submission



The journey towards ISCT in a regulatory submission

Benefits for everyone

€
Cost/benefit analysis

→ Increases confidence in expected device performance
→ Leads to safer and better products
→ Gets product to patients, faster
→ Reduces cost throughout healthcare system

Benefits patients, healthcare system, industry and regulators

Financial considerations

€
Cost/benefit analysis

- Personnel
- Software licenses
- Data storage
- Acquisition of clinical data for validation

Model development costs

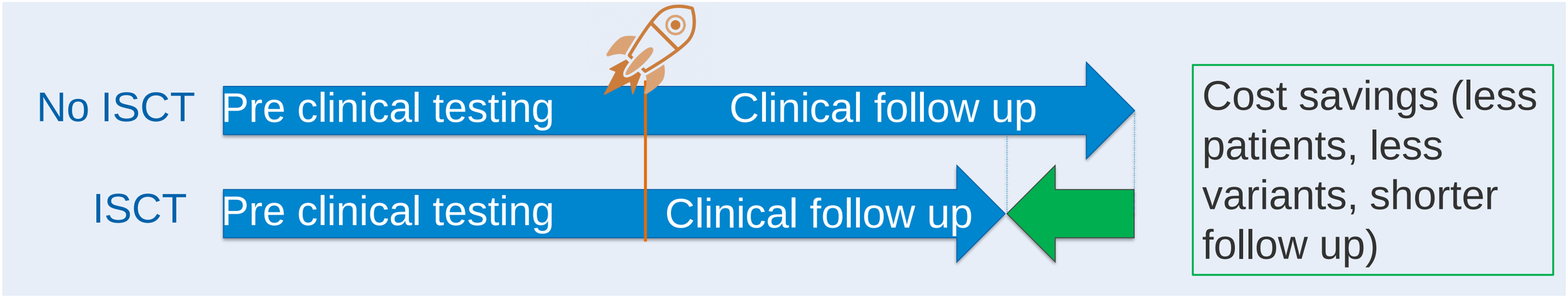
- Reduction on clinical study costs
- Reduction of risk of recall
- Earlier launch

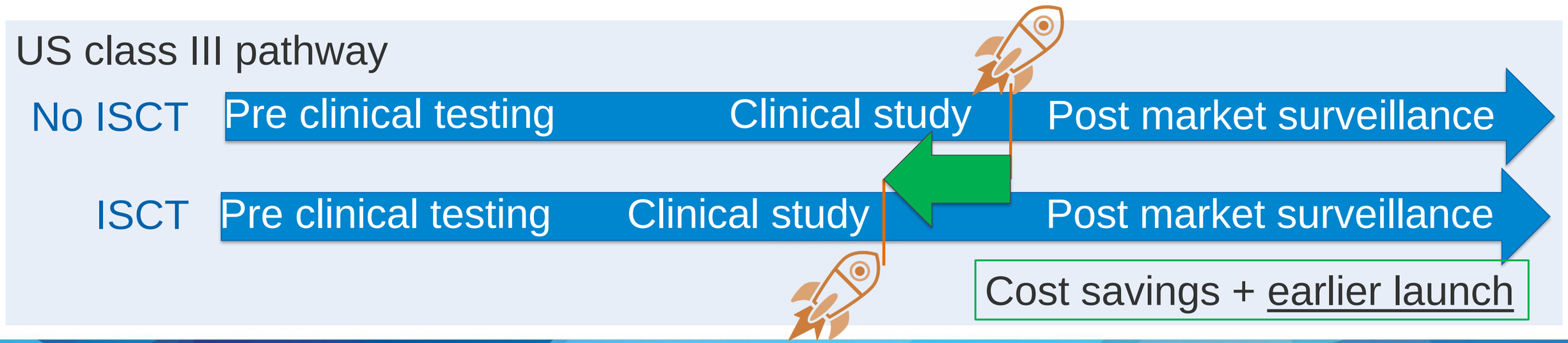
Revenue

12

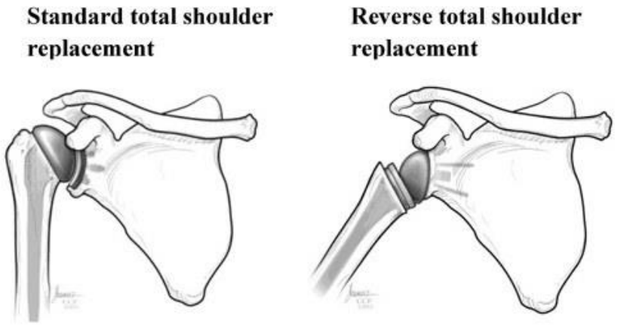
Business case

€
Cost/benefit analysis





The journey towards ISCT in a regulatory submission



Humeral stem

Select candidate product

Go / no go

NEW!

Identify patient risks

NEW!

Benchtop validation

Clinical validation

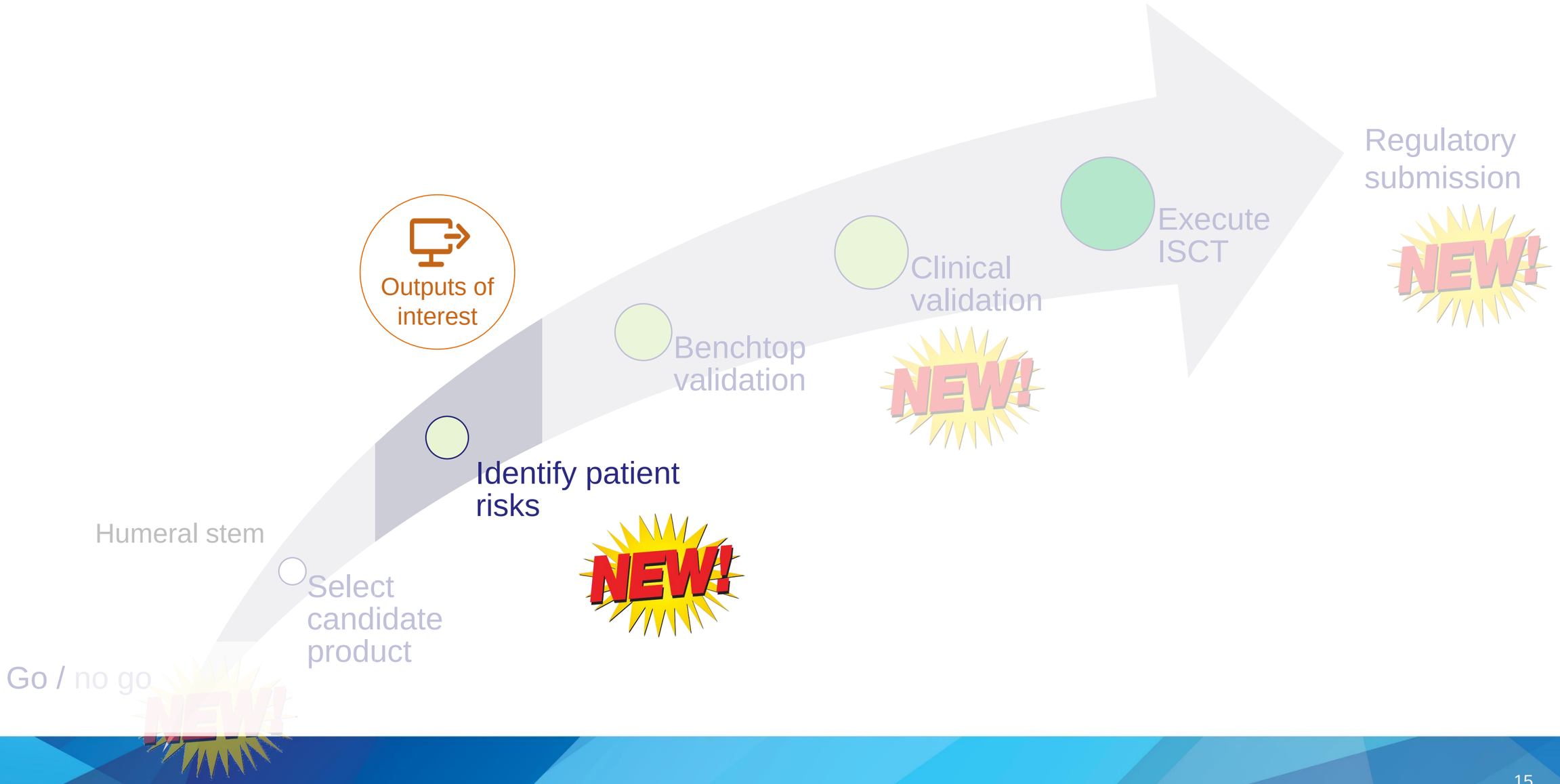
NEW!

Execute ISCT

Regulatory submission

NEW!

The journey towards ISCT in a regulatory submission



Clinical outcome measures

Outputs of interest

- Radiolucency
- Osteolysis
- Stem subsidence
- Bony atrophy/hypertrophy
- Osteophytes formation
- Heterotopic ossification grade (Brooker grading)
- Scapular Not
- Range of mot
- Rotator cuff Defects
- Osteoarthritis progression in the glenoid (hemi)
- Intraoperative bone fracture
- Component disassembly
- Polyethylene dislocation / disassembly
- Polyethylene wear
- Pain
- Strength at 90° Abduction
- Assessment of Daily Activities
- Joint instability
- Patient satisfaction
- Superficial Infection
- Deep Vein Thrombosis
- Delayed Wound Healing
- Dislocation
- Fracture of Glenoid
- Fracture of Humeral Neck
- Fracture of Humeral Shaft
- Fracture of Proximal Humerus
- Glenoid Implant Fracture
- Glenoid Implant Loosening
- Humeral Implant Fracture
- Humeral Implant Loosening
- Polyethylene Fracture
- Skin Slough
- Subluxation
- Vascular Deficit
- Wound Dehiscence
- Wound Drainage

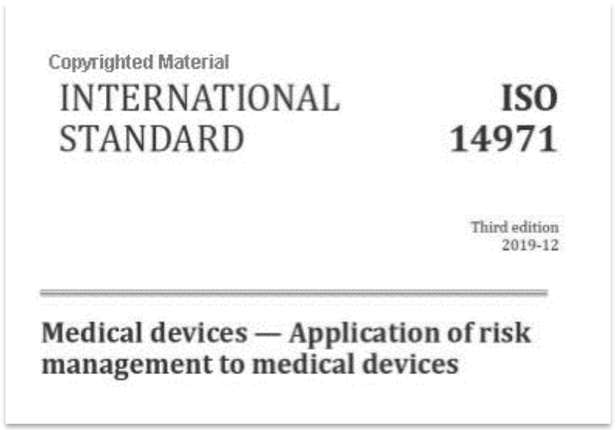
Which patient harms do we include in an ISCT?

What risks to include in ISCT?

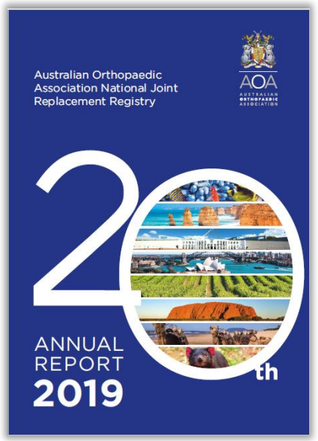
Outputs of interest

Decision based on existing standards and published data, where applicable

Risk management



National Registries

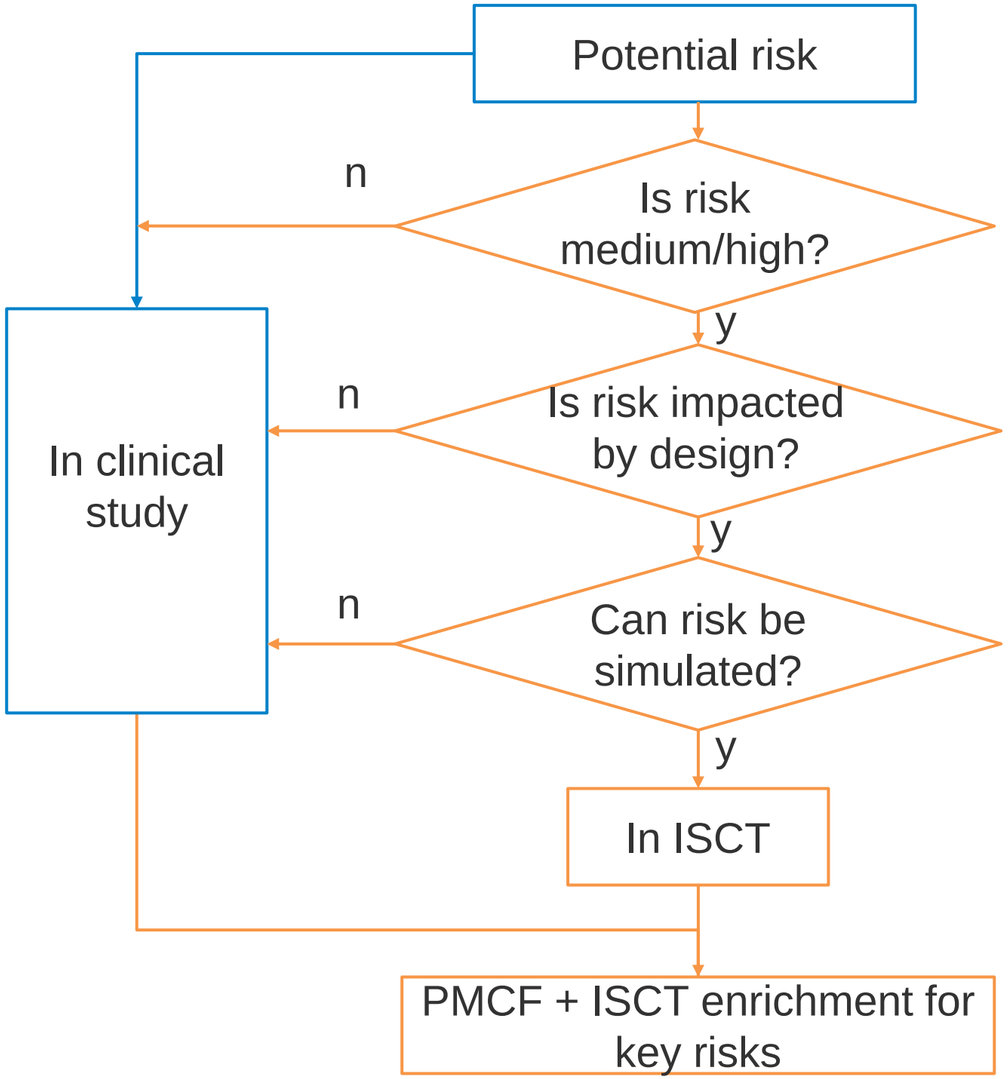


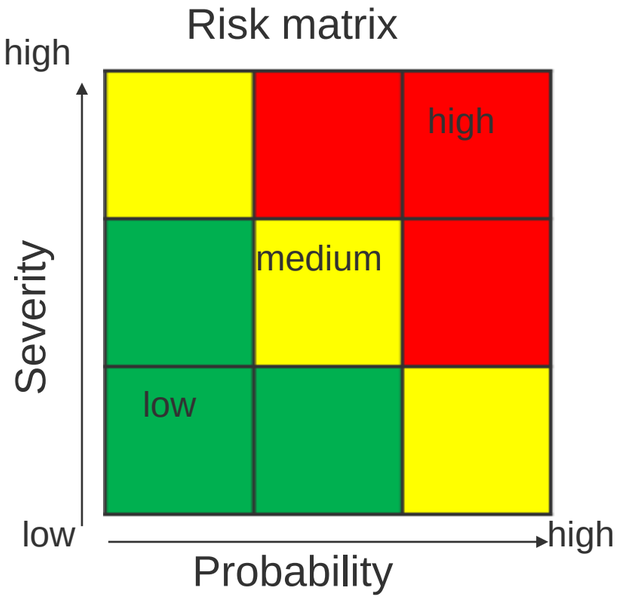
Complaints

Post market surveillance review

Literature

Decision tree



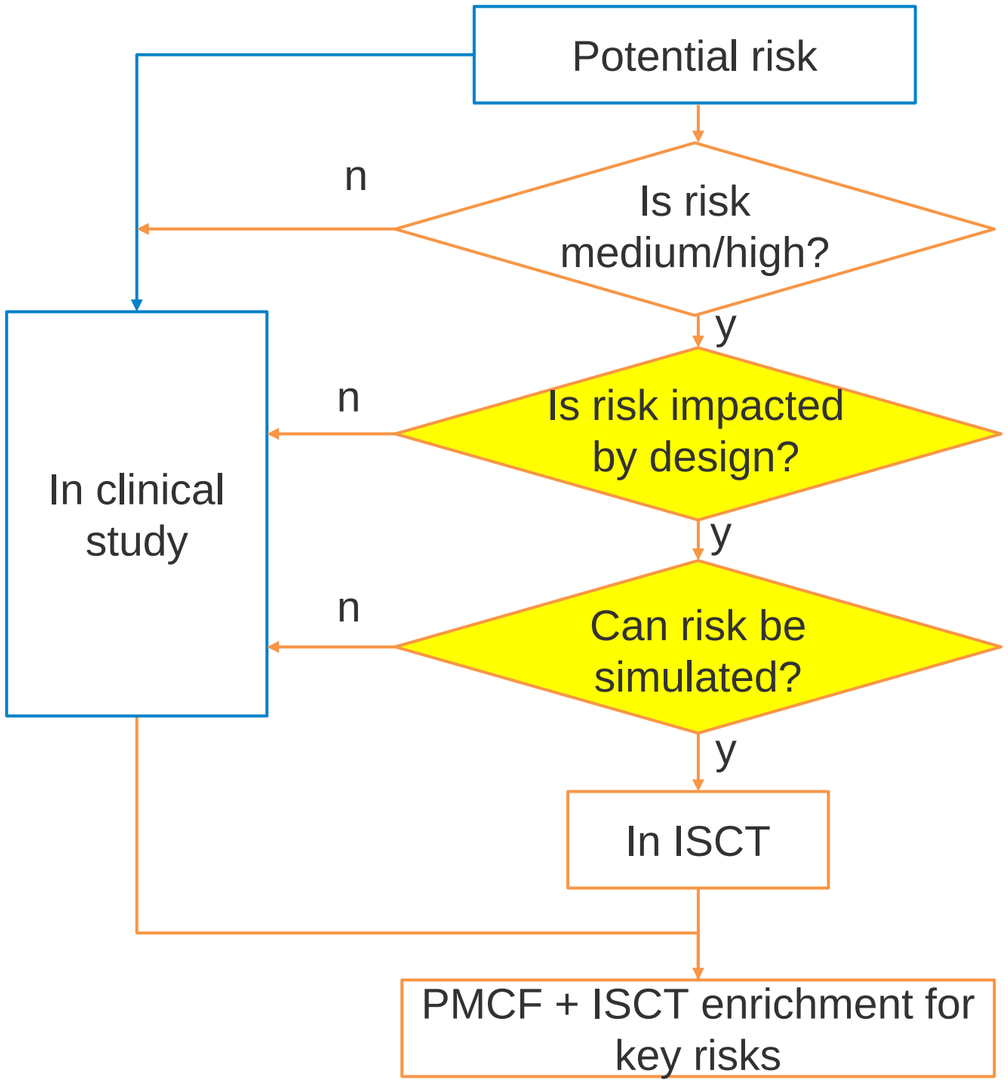


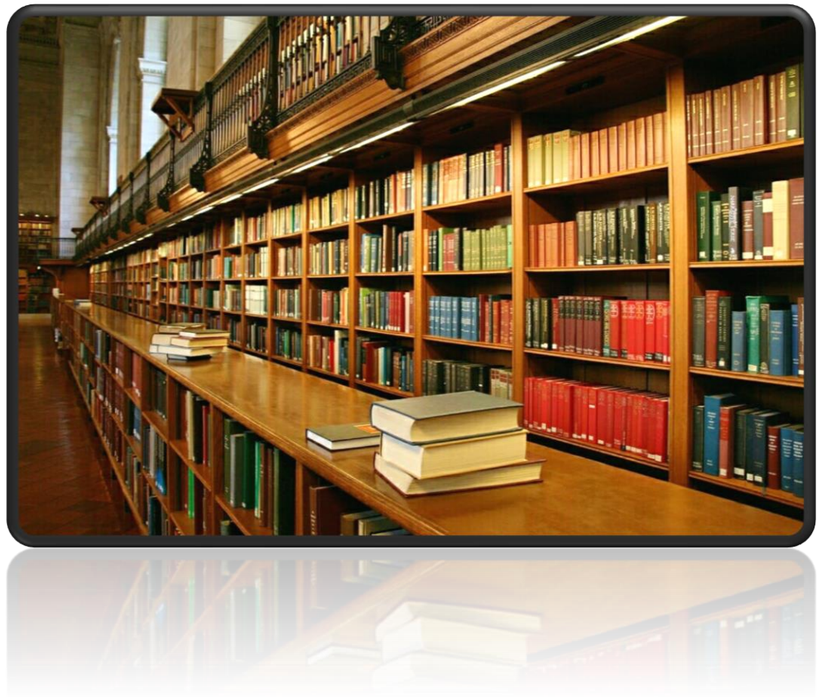
ISO 14971 Medical devices — Application of risk management to medical devices

Outputs of interest

Can risk be simulated/is risk impacted by implant design

Outputs of interest



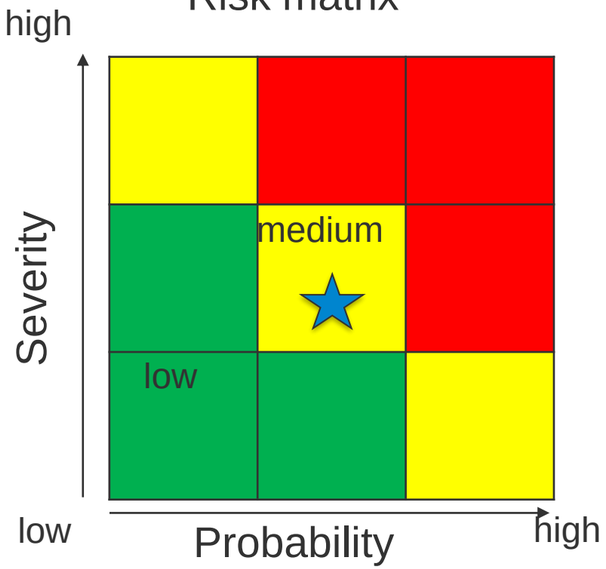


Example: stress shielding

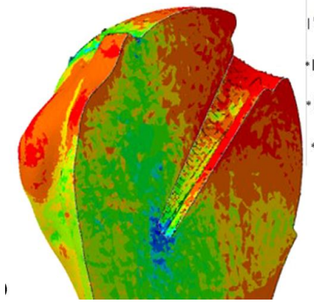
Outputs of interest

Is risk medium/high?

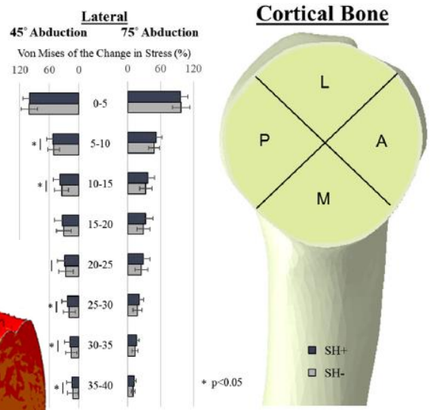
Risk matrix



Can risk be simulated?

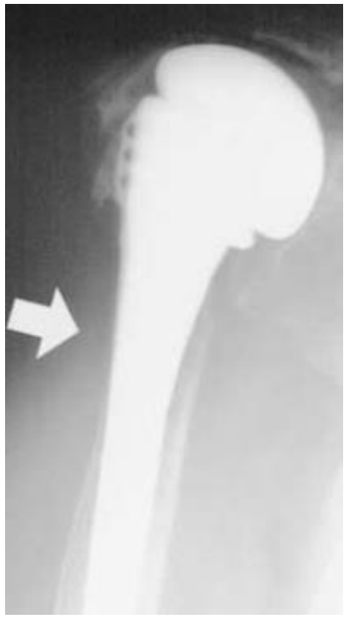


Schmidutz et al.
J Biomech 2014



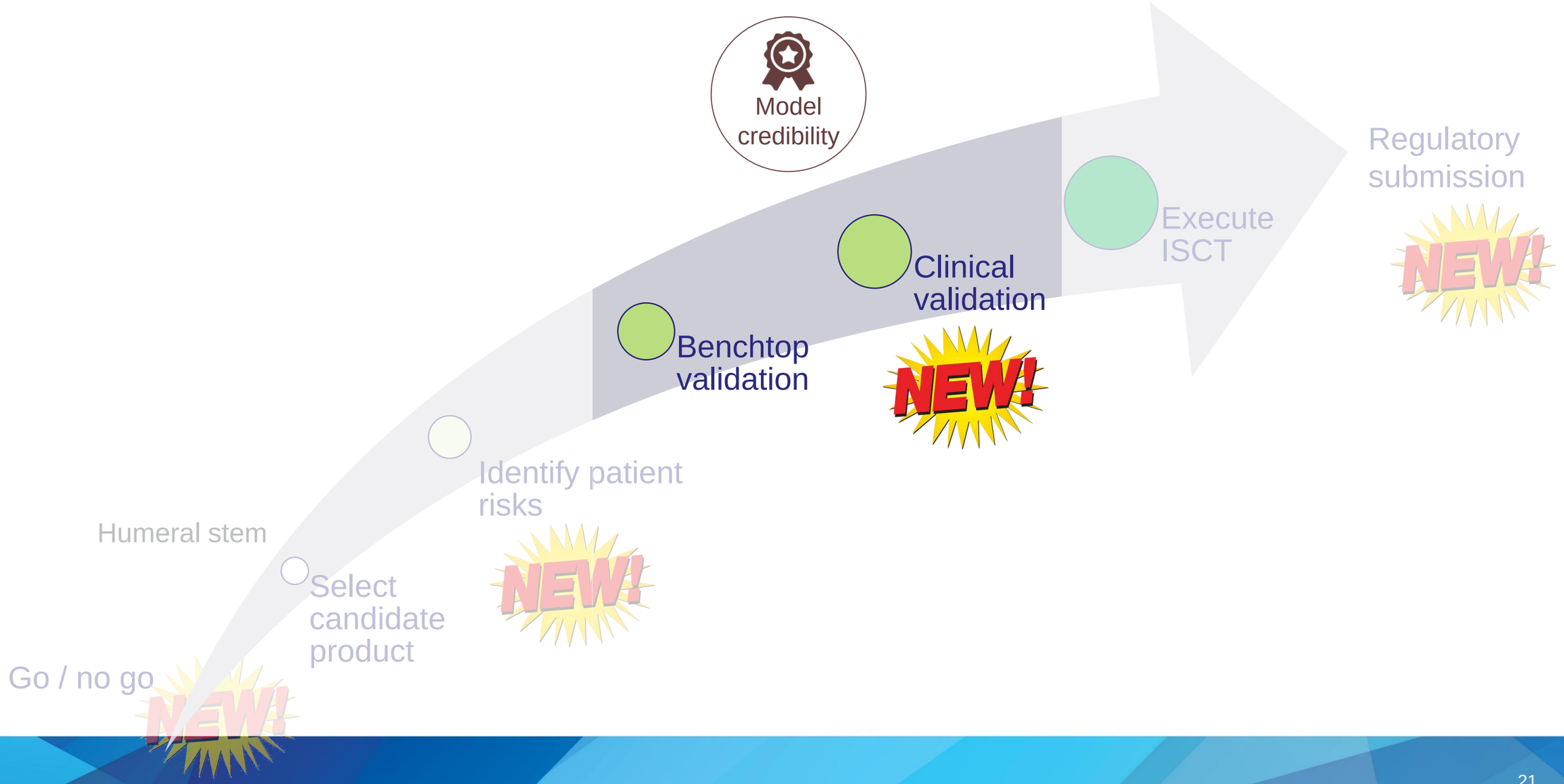
Langohr et al.
JSES 2020

Is risk impacted by design?

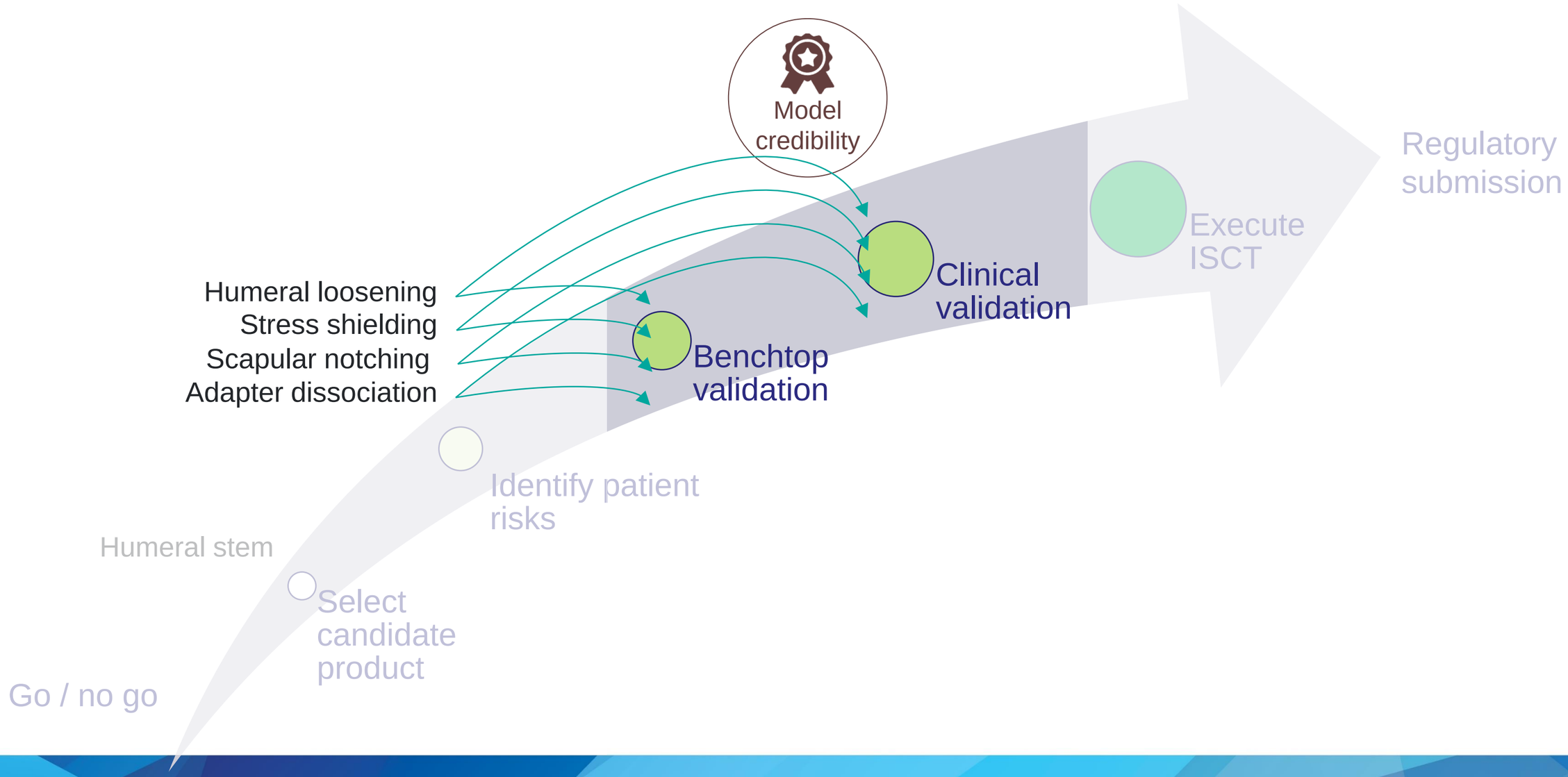


Nagels et al.
JSES 2003

The journey towards ISCT in a regulatory submission



The journey towards ISCT in a regulatory submission

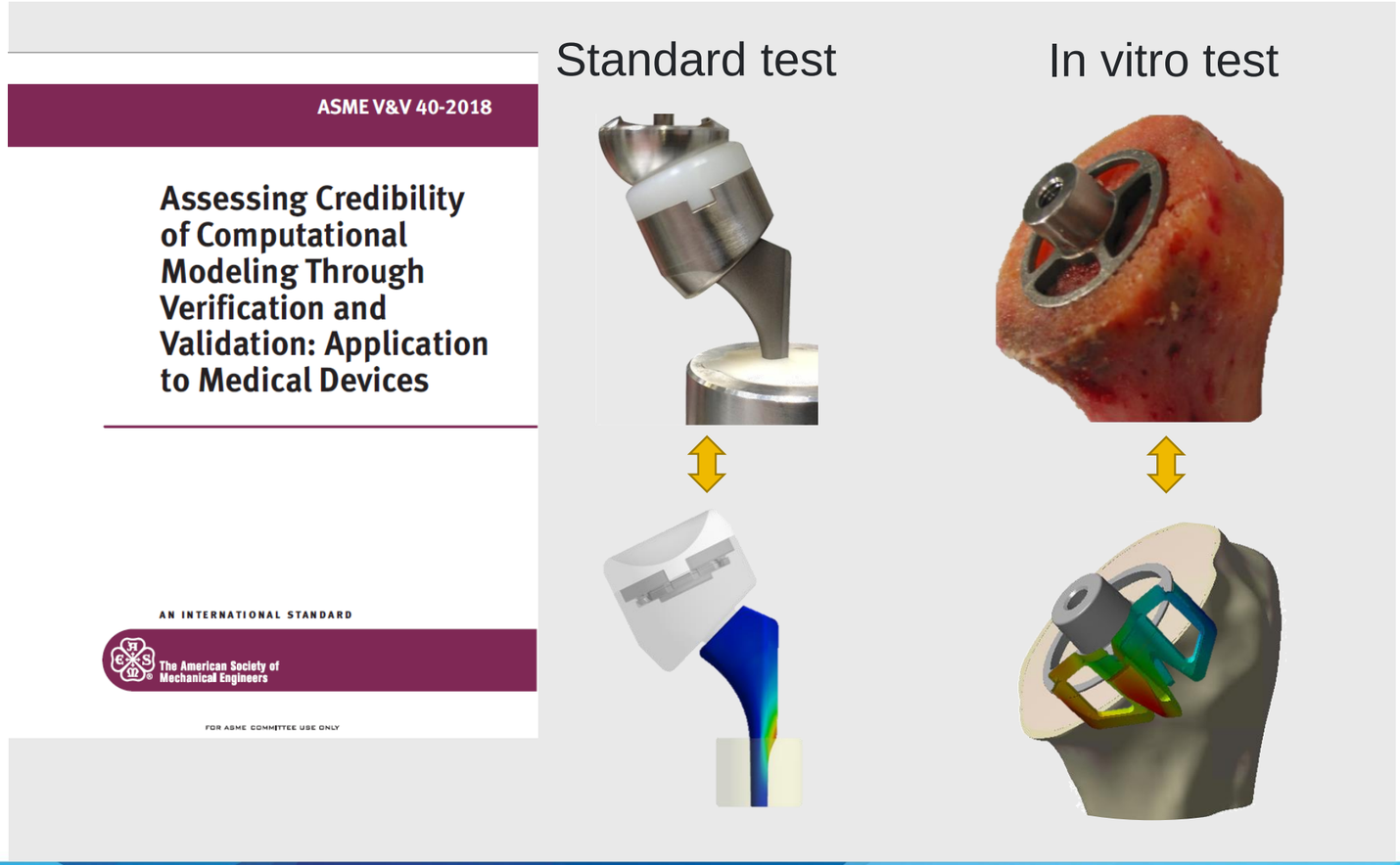


Model validation

Model credibility

Well controlled and characterized data

Increasing consideration of in vivo variability

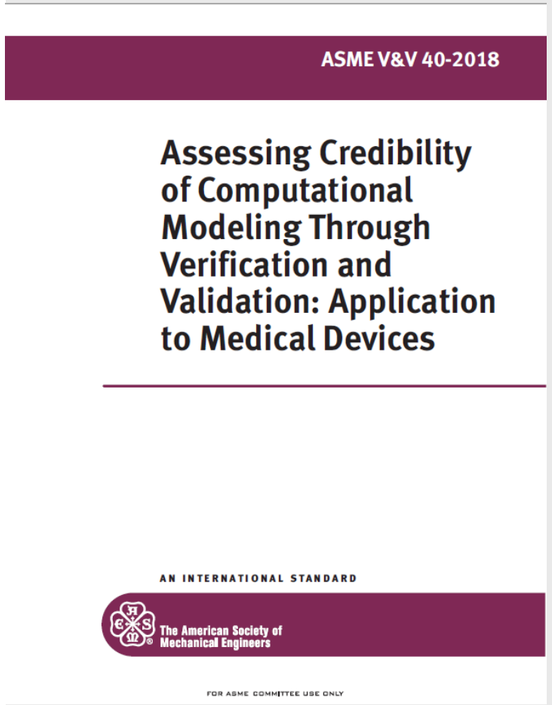


Model validation

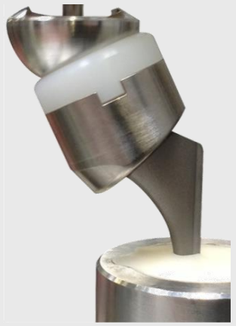
Model credibility

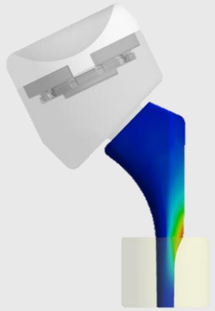
Well controlled and characterized data

Increasing consideration of in vivo variability

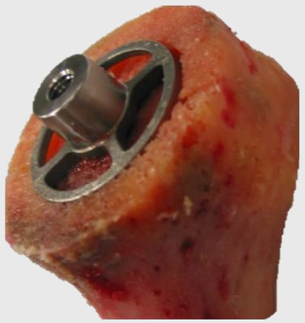


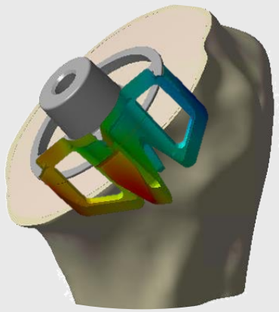
Standard test



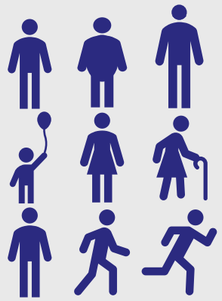


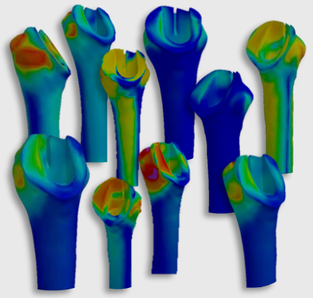
In vitro test





Clinical trial





ISCT Model validation

Model credibility

Model validation strategy

Clinical validation	- *Clinical literature data* - *PMCF data*
Benchtop validation	- *Technical literature data* - *Internal test data*
Model verification	- *Mesh convergence* - *Buddy checks*
Code verification	- *Unit tests* - *Software quality assurance*

Clinical comparator:

- Ensure aspect of implant survivorship can be predicted appropriately
- Reproduce clinically significant differentiation in outcomes b/w different designs, variants, sizes, etc

Benchtop comparator:

- Ensure physics are modeled correctly
- Best addressed with tight control over test conditions

Model validation

Model credibility

Model validation strategy

Clinical validation	- *Clinical literature data* - *PMCF data*
Benchtop validation	- *Technical literature data* - *Internal test data*
Model verification	- *Mesh convergence* - *Buddy checks*
Code verification	- *Unit tests* - *Software quality assurance*

Patient risks	Benchtop	Clinical
Adapter dissociation	[1]	N/A
Scapular notching	[2]	[5]
Humeral loosening	[3]	[6]
Stress shielding	[4]	[7]

[1] Internal benchtop testing
[2] Roche et al., JSES 2009
[3] Internal benchtop testing
[4] Eberle et al., Med Eng Phys 2013
[5] Simovitch et al., JBJS 2007 – Statistically significant relationship of PSNA, DSNA, and PGRD on the incidence of scapular notching (N=186, Delta III)
[6] Morwood et al., JSES 2017 – Increased incidence of humeral loosening for grit blast stems as compared to porous coating (N=118, Aequalis Ascend stems)
[7] Nagels et al., JSES 2003 – Greater relative stem size results in increased proximal lateral humeral cortical thinning (N=70, Biomodular stems)

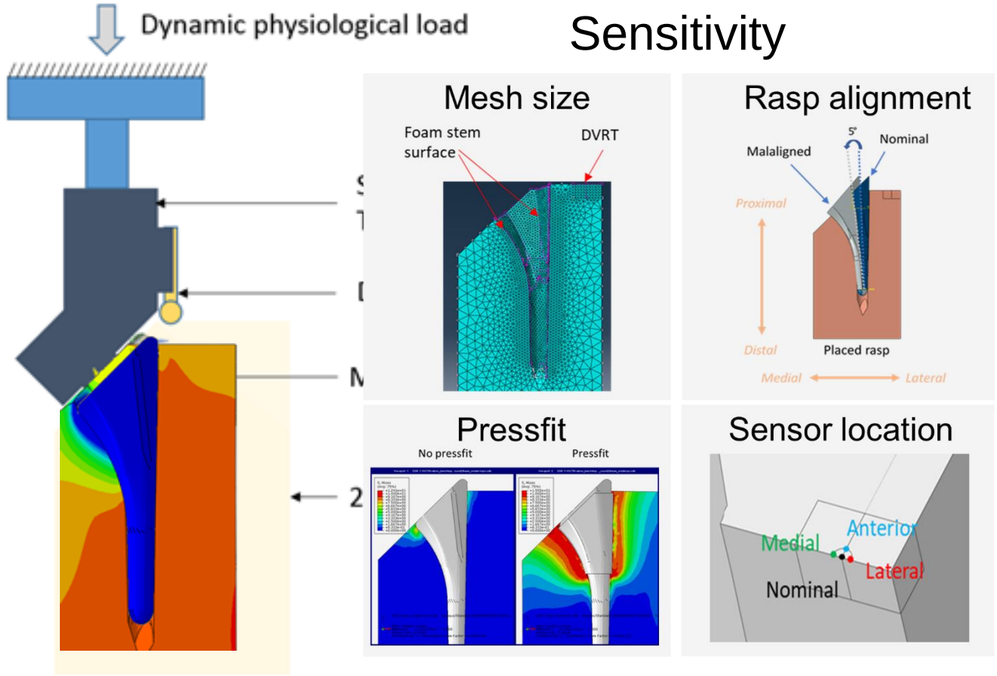
Benchtop testing – humeral loosening

Model credibility

Comparator

n=6

Model

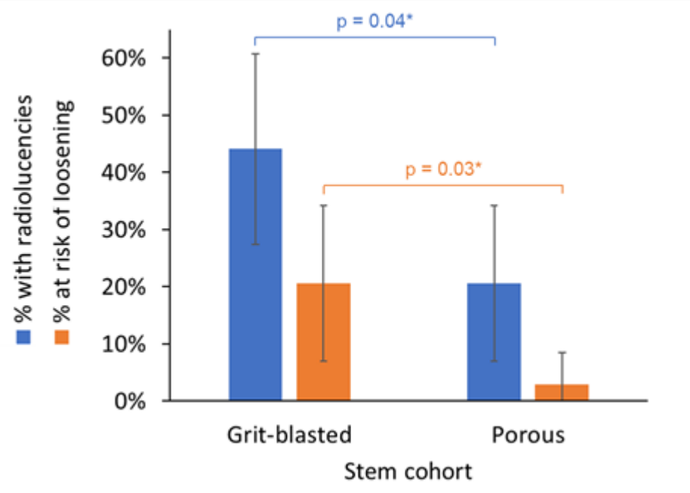


Comparison

Clinical validation – humeral loosening

Model credibility

Comparator

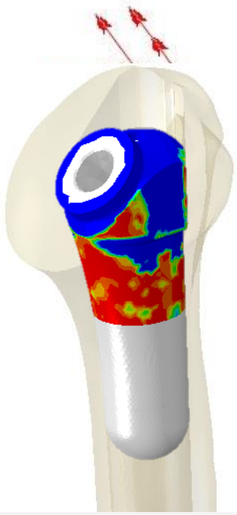


Statistically significant higher incidence of radiolucencies and risk of stem loosening with grit-blasted stems compared to porous coated stems @ 2+ years post-op (N=34).

Morwood et al., JSES 2017

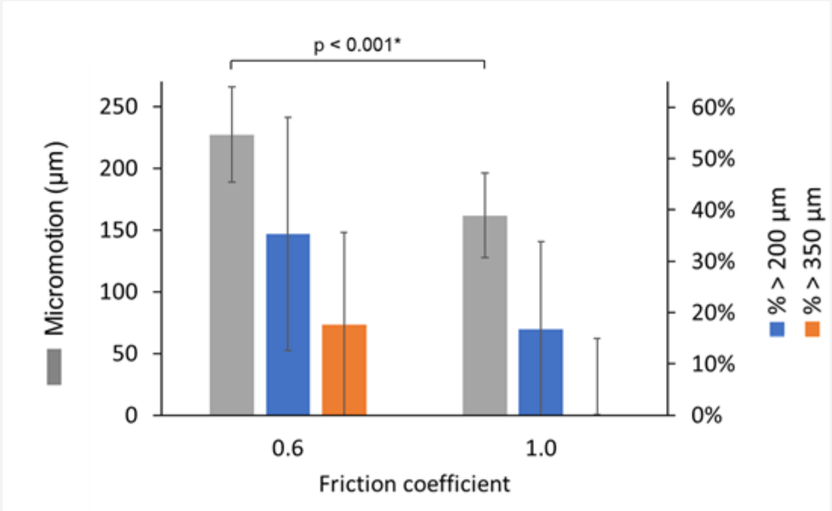
Model

N=18
Comprehensive Micro



Sensitivity
Friction coefficient
Mesh size
Loading
Contact stiffness
Bone mat prop
etc

Comparison



Significantly higher interface micromotions with low friction coefficient (grit-basted) compared to high friction coefficient (porous-coating).

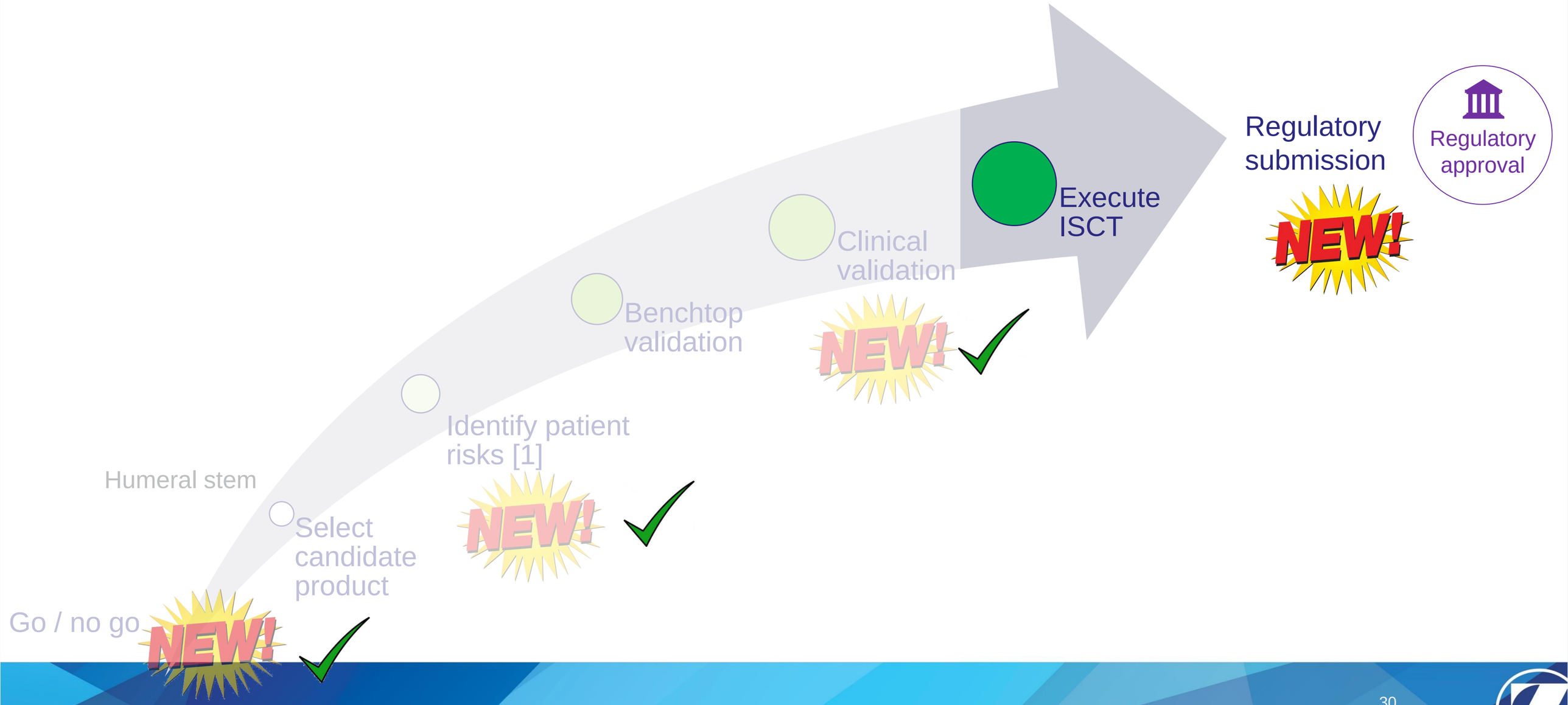
Percentage of models with a micromotion above 200 and 350µm compared well with % of patients with radiolucencies and at risk of stem loosening.

Model Credibility

Model credibility

ASME V&V40			Low	High	Loosening	Stress shielding	Scapular notching
Activity		**Credibility factor**					
Validation	Computational model	Model form	Representative configuration	Comprehensive variability	**High**	**High**	**Medium**
		Model inputs					
	Comparator	Test samples	Clinical trends	Statistical significance	**Medium**	**Medium**	**High**
		Test conditions	Key attributes not measured, spanning limited range	Key attributes measured, spanning clinical conditions range			
	Assessment	Equivalency of input	Consistency in ranges	Patient-specific models	**Low**	**Low**	**Low**
		Output comparison	Qualitative agreement	Quantitative agreement			
	Applicability	Relevance of val activities to COU	Similar device	Subject device	**Low**	**Low**	**Low**
Verification					**High**	**High**	**High**
Credibility					**Medium**	**Medium**	**Medium**

The journey towards ISCT in a regulatory submission



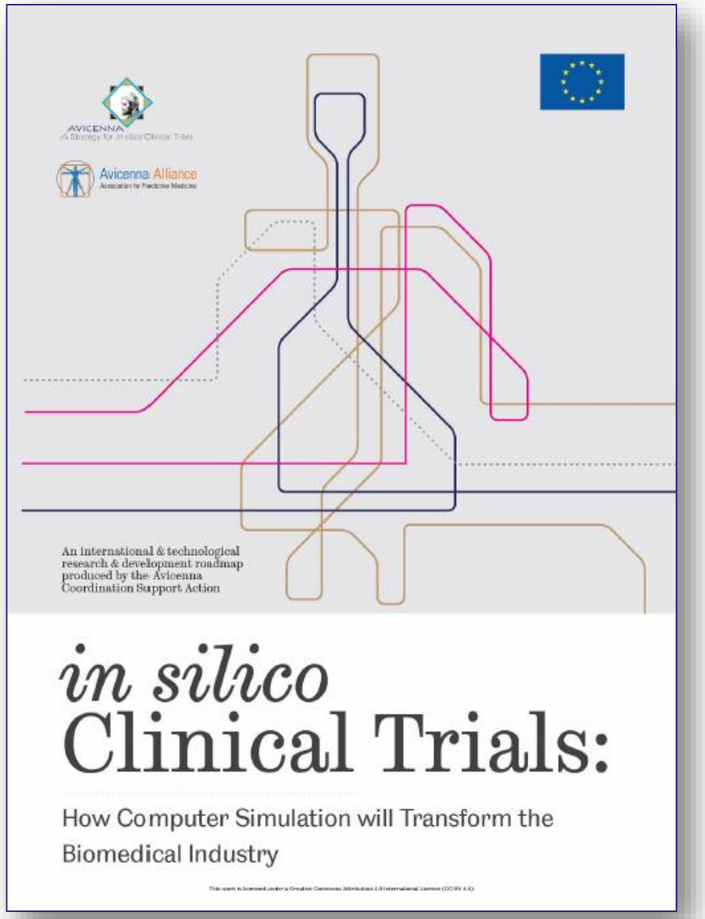
The Regulatory Environment is Receptive

Avicenna Alliance
Association for Predictive Medicine


IEEE JOURNAL OF BIOMEDICAL AND HEALTH INFORMATICS, VOL. XX, NO. X, XXX 201X 1

TOWARD A REGULATORY PATHWAY FOR THE USE OF IN SILICO TRIALS IN THE CE MARKING OF MEDICAL DEVICES

Francesco Pappalardo, John Wilkinson, Francois Busquet, Antoine Bril, Mark Palmer, Barry Walker, Cristina Curreli, Giulia Russo, Thierry Marchal, Elena Toschi, Rossana Alessandrello, Vincenzo Costignola, Ingrid Klingmann, Martina Contin, Bernard Staumont, Matthias Woiczinski, Christian Kaddick, Valentina Di Salvatore, Alessandra Aldieri, Liesbet Geris, and Marco Viceconti



The Regulatory Environment is Receptive

U.S. FOOD & DRUG ADMINISTRATION

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

***In Silico* Clinical Trials.** *In silico* clinical trials are an application of CM&S where device performance is evaluated using a 'virtual cohort' of simulated patients with realistic anatomical and physiological variability representing the indicated patient population. *In silico* clinical trials can complement real world clinical trials (e.g., augment or reduce the size of, or provide improved inclusion-exclusion criteria), rather than replace them.[12]

The VICTRE trial: an in-silico replica of a clinical trial for evaluating digital breast tomosynthesis as a replacement for full-field digital mammography

MARCH 14, 2019

frontiers in Medicine

Front Med (Lausanne). 2018; 5: 241. PMCID: PMC6167449

Published online 2018 Sep 25. doi: 10.3389/fmed.2018.00241 PMID: 30356350

Advancing Regulatory Science With Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories

Tina M. Morrison,* Pras Pathmanathan, Mariam Adwan, and Edward Margerrison

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials

Owen Faris, Ph.D., and Jeffrey Shuren, M.D., J.D.

In the future, computer-based modeling may change the way we think about device validation in other ways, allowing for much smaller clinical trials, or may change the way we think about running trials, in that some "clinical" information may be derived from simulations.

Towards regulatory approval

Regulatory approval

Chances of acceptance by the regulator increased by:

Following guidelines for clinical studies and computational modelling

[ISO 14155. Clinical investigation of medical devices for human subjects — Good clinical practice, 2011.]

[Guidance for Industry and Food and Drug Administration Staff. Reporting of Computational Modeling Studies in Medical Device Submissions, 2016.]

[ASME V&V40]

[DRAFT - Guidance for Industry and Food and Drug Administration Staff. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions. 2021.]

Open and regular communication with the regulator

Conclusions

- Strong interest from scientific community, industry and regulators in ISCT – the time is now!
- Still many novel aspects
  - Identify the risks to be included → approach based on data
  - Validation against clinical comparator → ASME V&V40 standard philosophy is adaptable to clinical comparator
  - Submission to Regulatory body → ongoing
- Standardization for ISCT is greatly needed (e.g. ASME V&V40, FDA V&V draft guidance, Avicenna)

THANK YOU!

ZIMMER BIOMET

Moving You Forward.™