From Engineering Metrics to Clinical Endpoints

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SIMCor

In Silico Clinical Trials Predict Clinical Endpoints

Virtual cohort

- Synthetic pulmonary arteries of heart failure patients

Virtual device

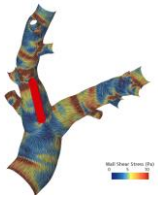
- FEM model of pulmonary artery pressure sensor

Virtual implantation

- Virtual device deployment for FEM and CFD simulations

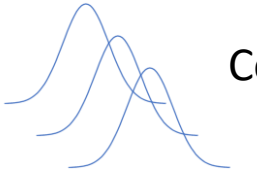
Device effect simulation

- Structural device-vessel interactions
- Blood flow field



Prediction of engineering metrics

- Radial and axial fixation forces
- Thrombosis-related indices



Prediction of clinical endpoints

- Migration
- Perforation
- Thrombosis / pulmonary embolism

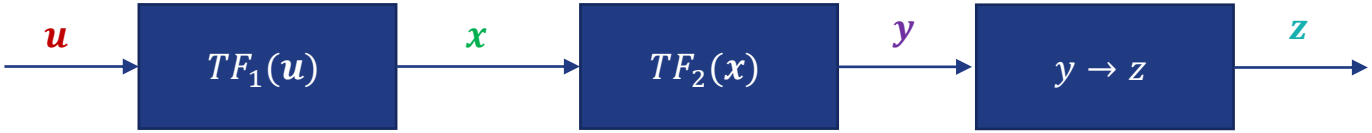
Complication-free rate

How Are Engineering Metrics and Clinical Outcome Related?

We need to define acceptance criteria for the engineering metrics to meet the clinical endpoints.

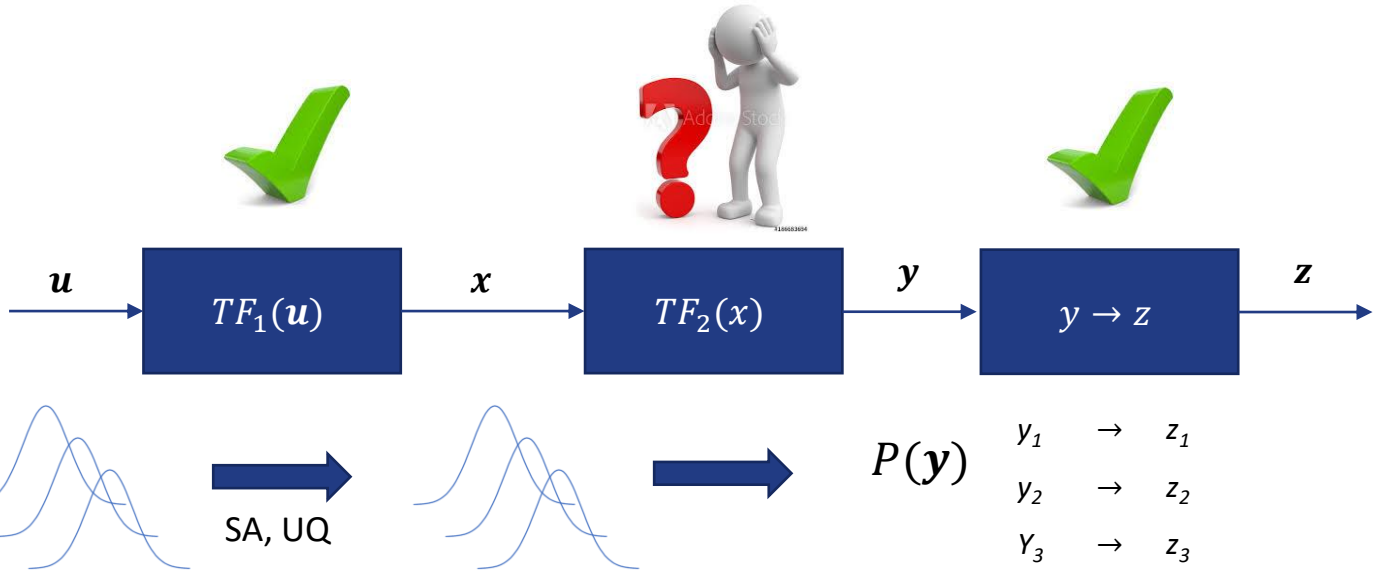
Engineering Metric	Clinical Endpoint	Acceptance Criteria
Axial retention force (F_a) in PA	Freedom of Migration	F_a > XX mN
Radial contact pressure (p_r) between device fixation and PA tissue	Freedom of Perforation	P_r < XX Pa
Blood flow indices: • Wall shear stress (WSS) • Oscillatory shear index (OSI) • Recirculation volume (RCV) • Blood residence time (BRT)	Freedom of Thrombosis / Pulmonary embolism	XX Pa < WSS < YY Pa OSI < XX RCV < XX ml BRT < XX s

A Chain of Transfer Functions Links Model Inputs to Clinical Outcome



u	x	y	z	$TF_1(u)$	$TF_2(x)$	$y \rightarrow z$
Model inputs	**Engineering metrics**	**Clinical endpoints**	**Adverse events**	**Physics-based model**	**Data driven model**	**Mapping**
PA geometry, PA material properties, properties of fixation loops, disturbance forces	Axial retention force margin	**Migration**	Impaired measurement function, pulmonary embolism	Structural mechanics model	Probability of migration at given axial force margin	Pulmonary embolism *due to* occlusion of a PA branch
PA geometry, PA material properties, properties of fixation loops	Maximal contact stress	**Perforation**	Bleeding, haemoptysis	Structural mechanics model	Probability of perforation at given contact stress	Bleeding *due to* vessel puncture
PA geometry, implant location, flow rate	OSI, WSS, residence time, size of recirc. region	**Thrombosis**	Pulmonary embolism	CFD model	Probability of thrombosis at given OSI etc.	Pulmonary embolism *caused by* thrombosis

How to Translate Engineering Metrics to Clinical Outcome?



Probabilistic distribution of model input parameters

Probabilistic distribution of model output

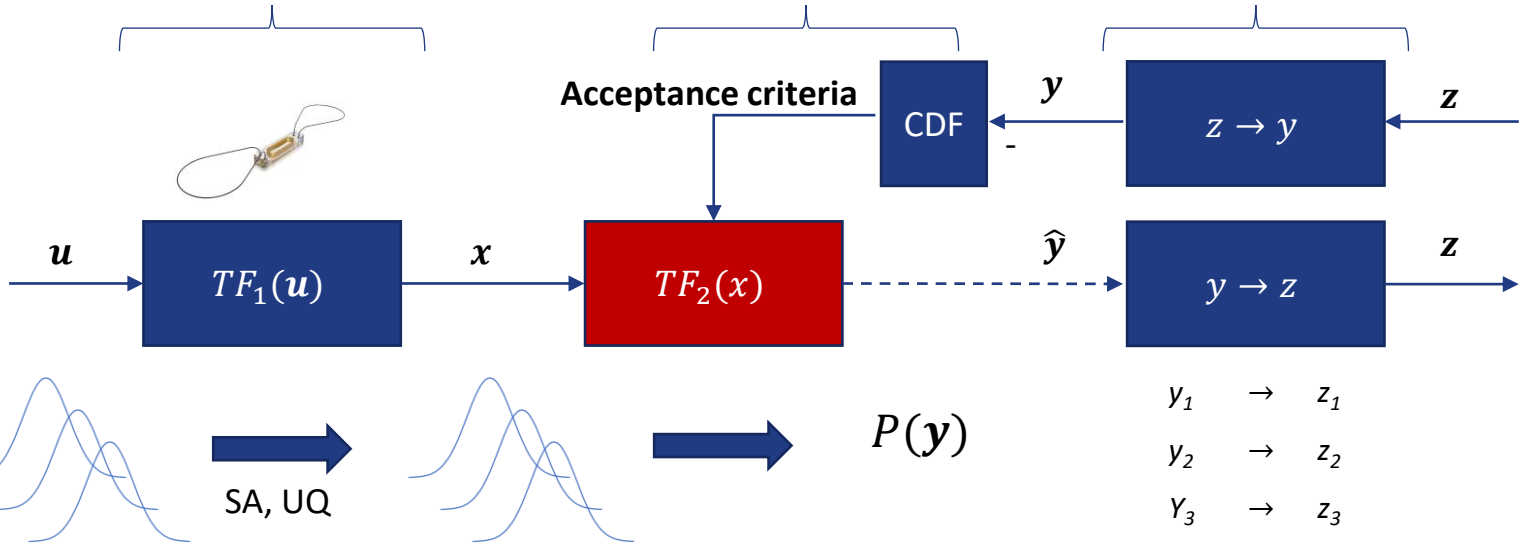
Complication-free rates

Match Model Predictions for Known Device with Clinical Data

Reference model
- Known device
- Intended use

Estimate TF_2
- Match CDF of engineering metrics with complication-free rate

Clinical data
- RCT data
- RWD (registry, complaints, recalls)



How Is the Level of Clinical Evidence?

Device novelty

Novel device, first of its kind

Improved version of existing device

Level of clinical evidence

Sparse or not accessible clinical data

Comprehensive and accessible clinical data

+ Case-specific endpoint mapping possible
+ Comprehensive data available (CT, MRI, additional sensor data)
– Small sample size

Map engineering metrics to pre-clinal data

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Map engineering metrics to clinical data

Translate
- Vessel mechanical properties
- Thrombosis propensity
- Behavioural data

Translation from pre-clinal data to clinical data

Model calibration
Derivation of acceptance criteria

– Population-based endpoint mapping only
+ Large sample sizes

Mapping Engineering Metrics via Pre-clinical Studies

In Silico Pre-Clinical Trial

Perform chronic animal study

- Observe endpoints (device effects)
- Measure engineering metrics, if possible
- Obtain geometrical and mechanical data

"Personalise" simulation model

- Model target device
- Assimilate image data
- Assimilate mechanical properties
- Apply boundary conditions

Predict mechanical output variables

- Perform "personalised" device effect simulations
- Predict non measurable engineering metrics

(Pre-) Clinical outcomes

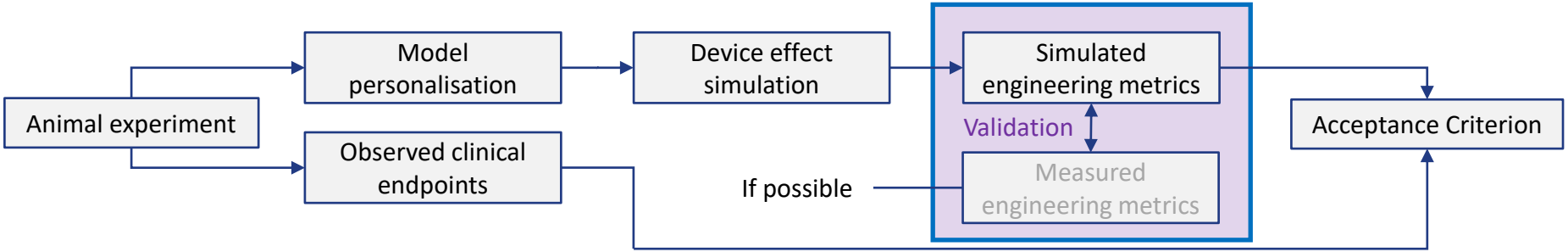
Model calibration

- Individual-based comparison
- Statistical analysis
- **Derive acceptance criteria**

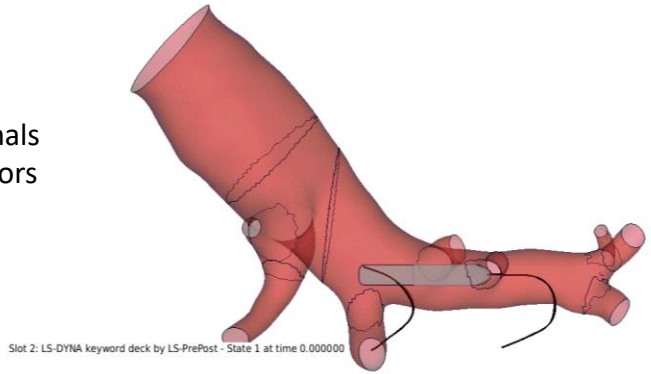
Engineering metrics

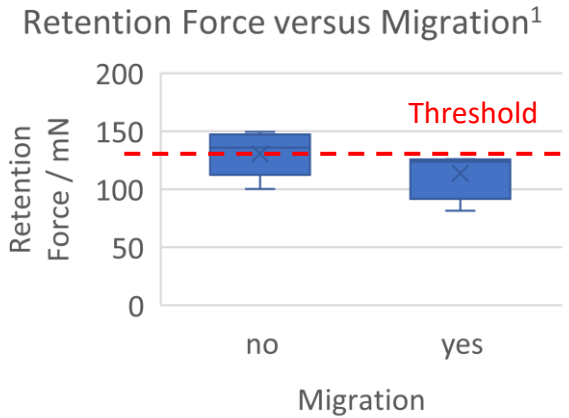
Translate to human case

Example PAPS Migration: Model Calibration with Preclinical Data



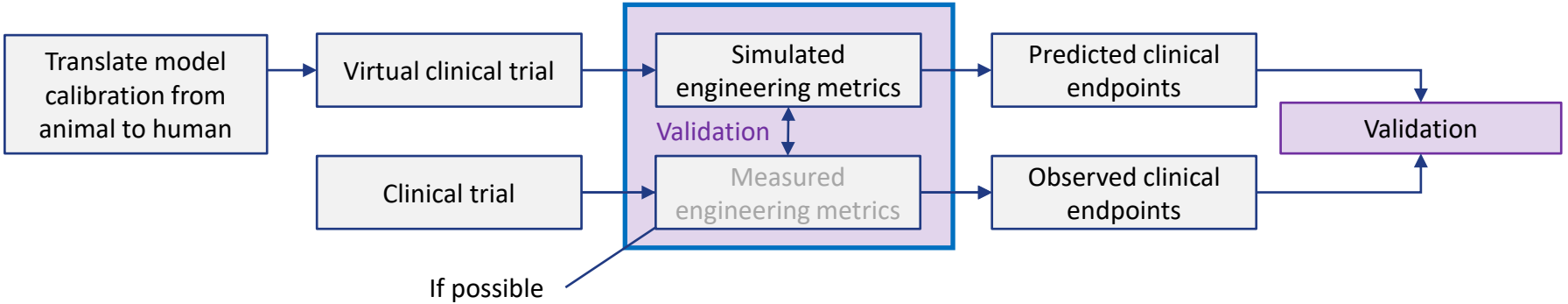
N=10 animals
N=20 sensors



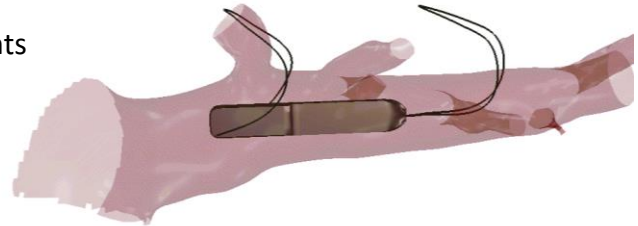


1 Hypothetical data. Real data processing still in progress.

Example PAPS Migration: Model Validation with Clinical Data



N=100 patients



Validation result
Predicted migration rate *versus* observed migration rate

Note
Validation is population-based because individualised simulations are usually lacking the input data (CT scans etc.)

Example PAPS Migration: Systematic of Model Calibration and Validation

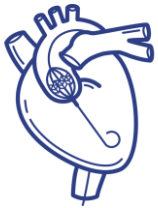
Calibration: Chronic animal trial + In silico animal trial

	Engineering metrics measured	Engineering metrics simulated	Clinical outcome observed	Clinical outcome simulated
Individual comparison		x	x	
Population-based comparison				

Validation: Clinical trial + In silico clinical trial

	Engineering metrics measured	Engineering metrics simulated	Clinical outcome observed	Clinical outcome simulated
Individual comparison				
Population-based comparison			x	x

Mapping Engineering Metrics via Clinical Studies



In Silico Clinical Trial

Model reference device

- Assess geometrical and mechanical properties
- CAD model
- FEM model

Virtual implantation in virtual cohort

- Generate virtual cohort matching clinical study cohort
- Virtual device implantation
- Apply boundary conditions

Predict mechanical output variables

- Perform device effect simulations
- Predict non measurable engineering metrics

PDF of engineering metrics

Clinical outcomes from literature

- Cohort-based measures

Model calibration

Derive acceptance criteria for engineering metrics to match their probability measure with clinical outcomes

Translate to new device

Example TAVI Thrombosis: Model Calibration/Validation with Clinical Data

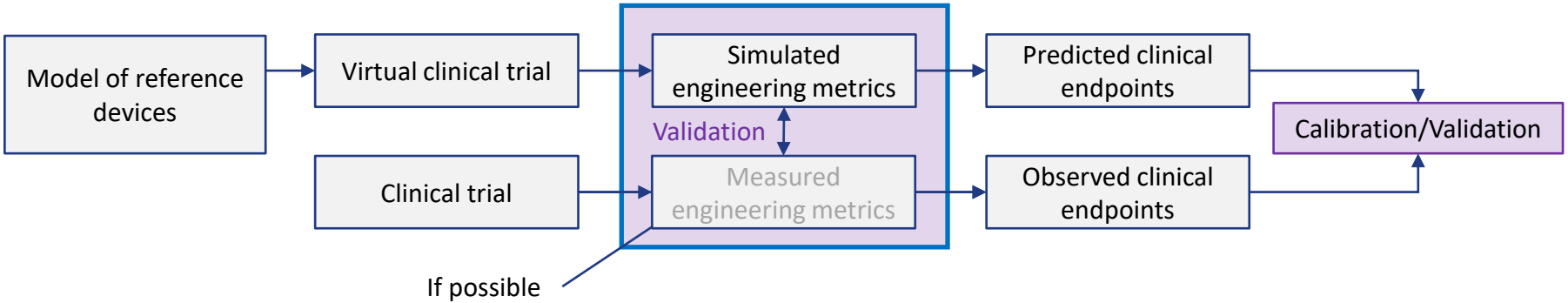


Figure to be inserted after disputation of PhD thesis by Finja Borowski

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Finja Borowski. Contributions to the development of aortic valve prostheses - Analysis of thrombogenic potential based on fluid dynamic studies. PhD dissertation 2023, under review

Example TAVI Thrombosis: Systematic of Model Calibration and Validation

Calibration: Clinical trial + In silico clinical trial

	Engineering metrics measured	Engineering metrics simulated	Clinical outcome observed	Clinical outcome simulated
Individual comparison				
Population-based comparison		**x**	**x**	

Validation: Clinical trial + In silico clinical trial

	Engineering metrics measured	Engineering metrics simulated	Clinical outcome observed	Clinical outcome simulated
Individual comparison				
Population-based comparison			**x**	**x**

Conclusions

1. Link between engineering metrics and clinical outcome can be established through preclinical and clinical trials
2. Individual comparison gives more insight than population-based comparison
3. Measurement of engineering metrics is often not possible in clinical trials and even not always in chronic animal trials
4. A calibrated model must be validated with independent, clinical data (if at all possible)

Further Reading & Acknowledgement

- Jeff Bodner and Vikas Kaul. A framework for in silico clinical trials for medical devices using concepts from model verification, validation, and uncertainty quantification (VVUQ). Proceedings of the ASME 2021 Verification and Validation Symposium

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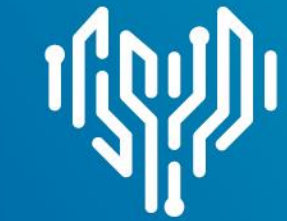

Thanks!

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