Historical milestones in coronary stents

1964

The stent is conceptualized

1993

Stents are acceptable as treatment option

1994

Bare Metal Stents approved in US

2003

Technology shifts to Drug-eluting stents

2015

FDA approves first Bioabsorbable drug-eluting stents

[1] Tomberli B et al., A Brief History of Coronary Artery Stents, Rev Esp Cardiol (Engl Ed). 2018 May;71(5):312-319.

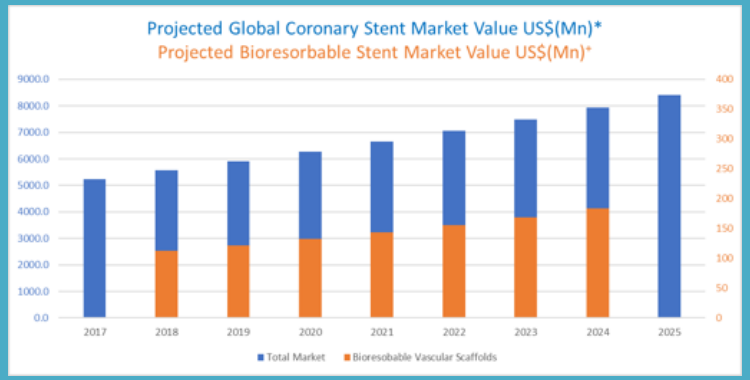
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Stent market

150 million

The global bioresorbable Coronary stents market size is estimated currently at 150 million

Global Coronary Stent Market CAGR 6.1%



Bioresorbable Stent Market CAGR 8.5%

MARKET PLAYER

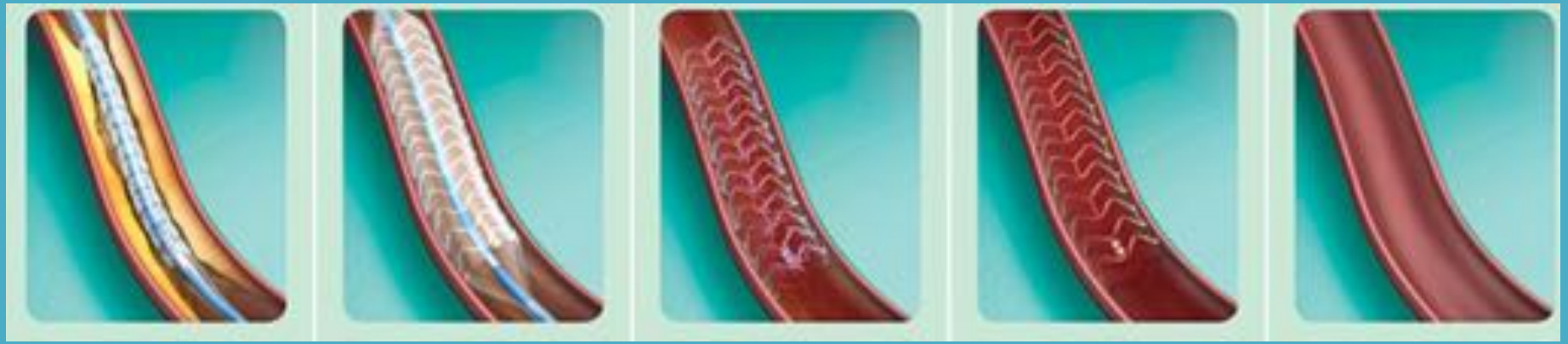
Boston Scientific, Biotronik, Elixir Medical Corporation, Johnson and Johnson, REVA

[1] Coronary Stents: Market Size, Share and Global Trend By Deployment (Self and Balloon-expandable), Stent Type (Drug Eluting Stent, Bioresorbable Stent, Bare Metal Stent, Covered Stent and Others), End User (Hospitals, Ambulatory Surgical Centers, Specialty Clinics, Catheterization Labs) and Geography Forecast till 2025. Fortune Business Insights; May 2019

[2] Bioabsorbable Stents Market - Growth, Trends, and Forecast (2019 - 2024). Research and Markets; February 2019

How it works?

Absorb
Bioabsorbable
drug-eluting stent



The scaffold is inserted into the artery on a balloon at the end of a thin flexible tube

The scaffold is expanded by inflating the balloon, pushing the plaque against the artery to enable blood flow

The balloon is removed, leaving the scaffold to slowly release medication to the diseased area

Blood flow is restored and the scaffold begins dissolving

Over time, the scaffold dissolves into the blood vessel, which remains open without support

[1] https://greaterkansas.mdnews.com/absorb-dissolving-heart-stent-opens-heals-disappears

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Pre-clinical testing and clinical studies

Preclinical testing (*in vitro* and *in vivo*) includes the testing of materials and stents before being tested in humans.

Clinical studies

Stent design (length, strut thickness, diameter, etc)

Type of drug

Type of biodegradable polymer

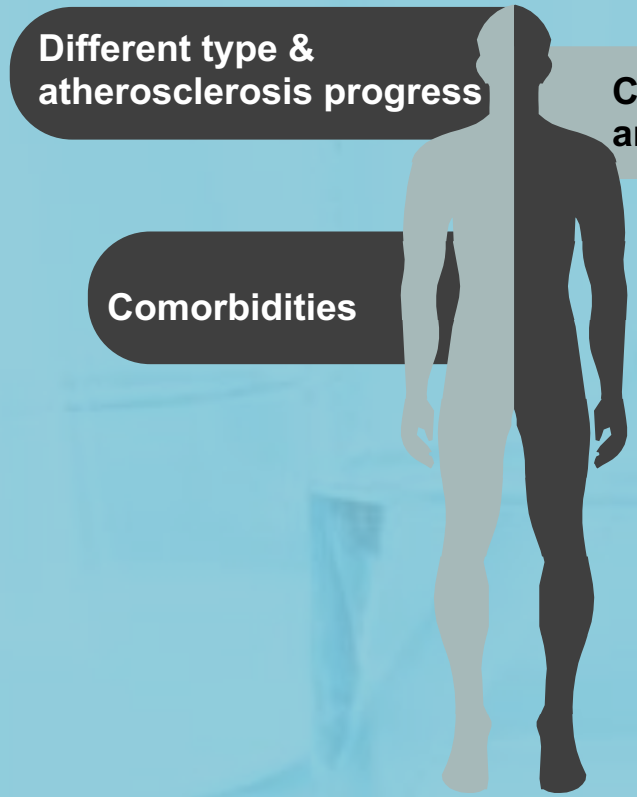
Patient-specific characteristics (gender, diabetes)

Type of vessel (long lesions, number of stenosis, plaque composition)

Stenting technique (two versus one stent)

FACTORS IN CLINICAL STUDIES

Limitations of clinical studies



Some patients are expected to improve after implantation

Some patients present adverse effects (In stent restenosis, stent thrombosis) or even die.

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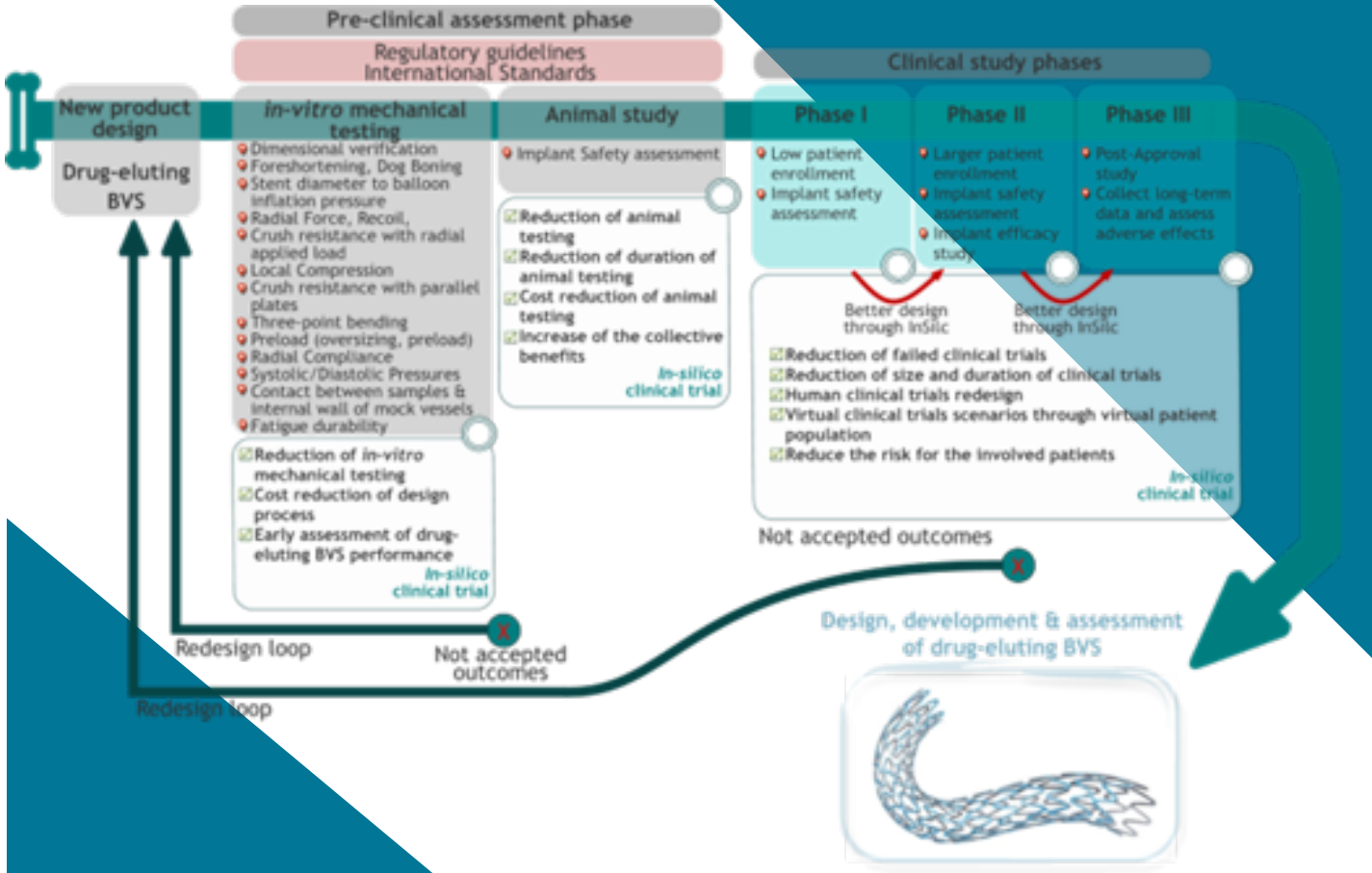
- Percutaneous coronary intervention with stents is the most widely performed procedure for symptomatic coronary disease treatment
- Despite major developments , in stent restenosis remains between 5 -10%.
- These long-term limitations of conventional stents may be overcome to a degree by using drug-eluting BVS.

WHY InSilc?

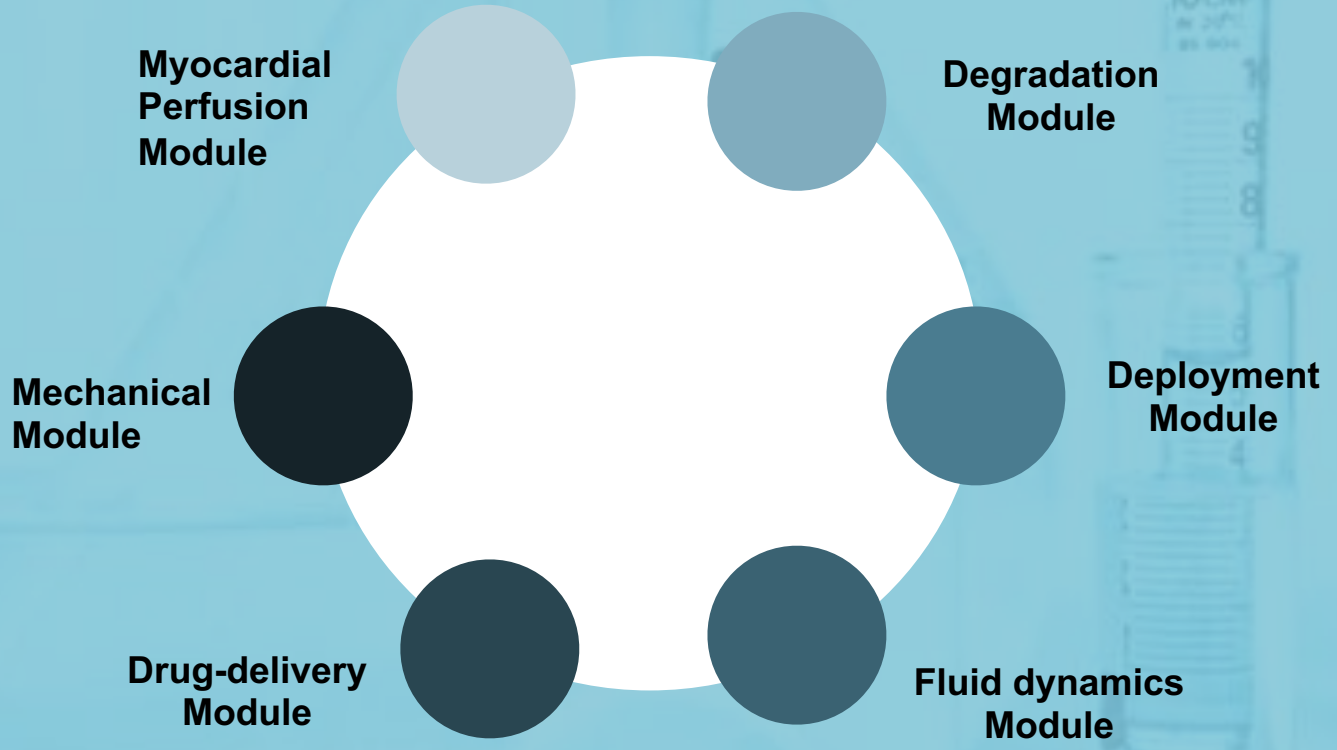
[1] Pan et al., Interv Cardiol. 2019 Feb;14(1):10-16. doi: 10.15420/icr.2018.39.1.

InSilc develops an **in-silico clinical trial (ISCT) platform** for **designing**, **developing** and **assessing drug-eluting bioresorbable vascular scaffolds (BVS)**, by building on the comprehensive **biological** & **biomedical knowledge** and **advanced modelling approaches**



Overall concept

InSilc platform is based on the extension of existing multidisciplinary and multiscale models that simulate the drug-eluting BVS performance



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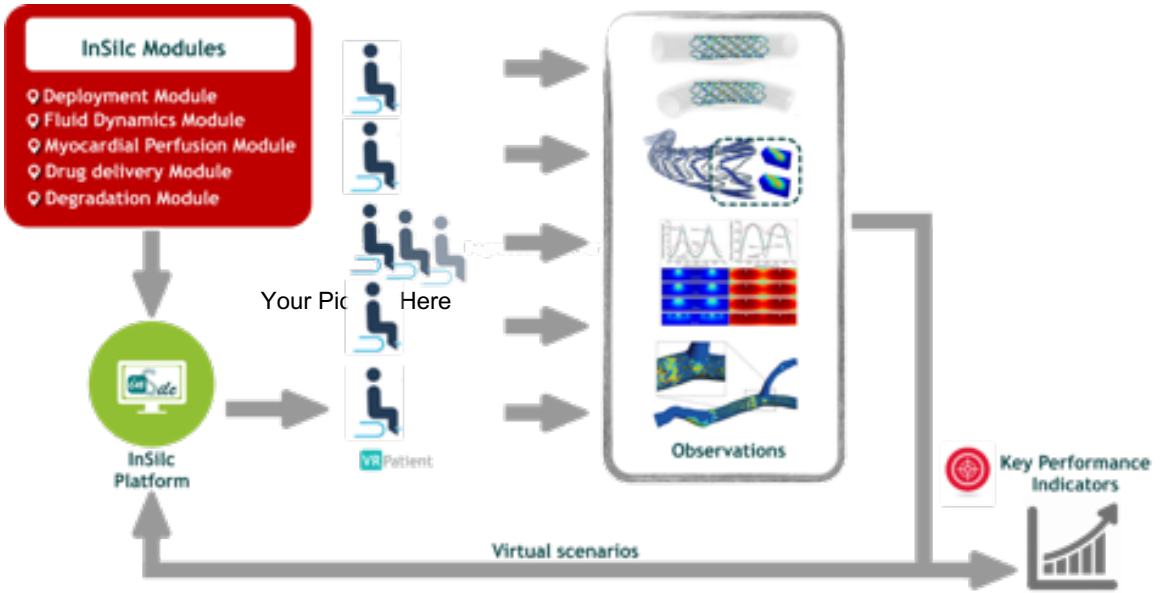
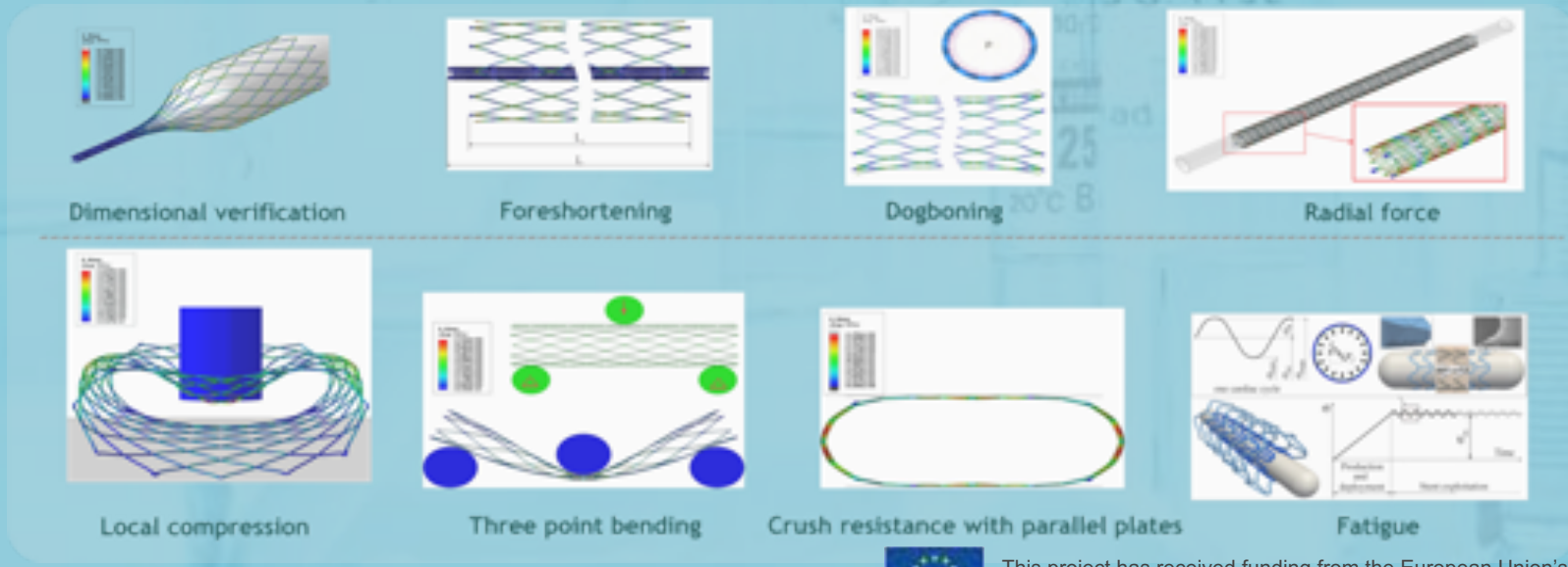
InSilc Modules



Mechanical modelling Module

- Replace all the mechanical *in vitro* tests required for the BVS by technical standard:



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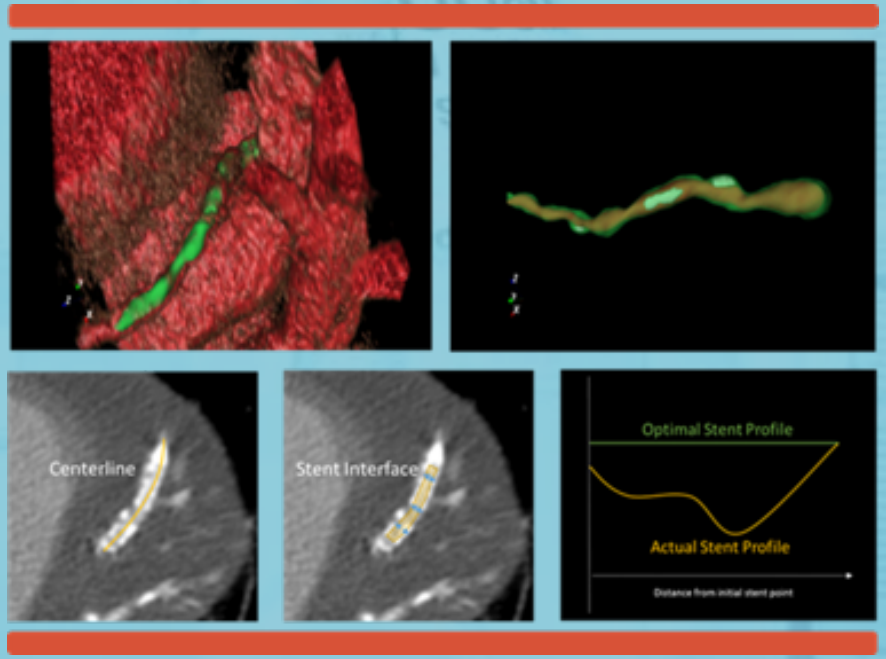
3D Reconstruction and plaque characterisation tool

- The 3D Reconstruction and plaque characterisation tool incorporates a state of the art method for 3D arterial tree reconstruction based on level set methods developed in SMARTool project.
- The method is able to accurately reconstruct the arterial tree including lumen, outer wall, calcified and non-calcified plaques.



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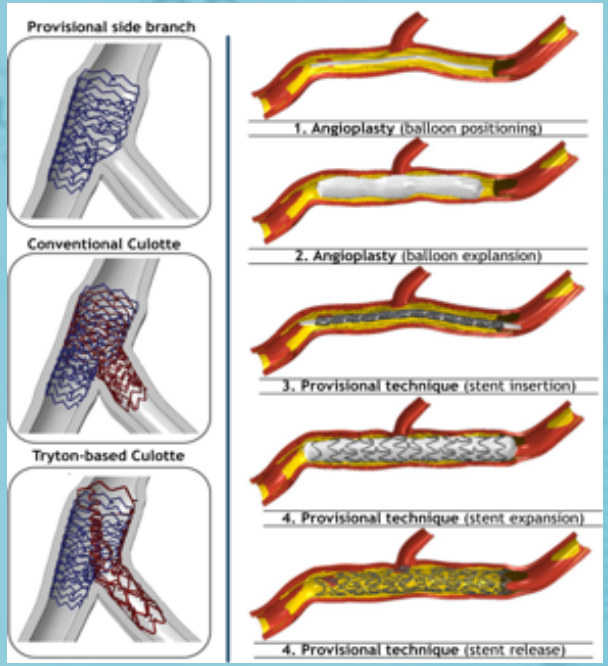
Deployment Module

- “Virtual” deployment in single stenosed or bifurcated coronary arteries:
  - Advanced modelling with device-specific material properties for BVS and patient-specific models for the stenosed coronary artery.
  - Coupling with Fluid Dynamics Module and Degradation Module, provides information regarding the drug-eluting BVS performance and efficacy in short term.



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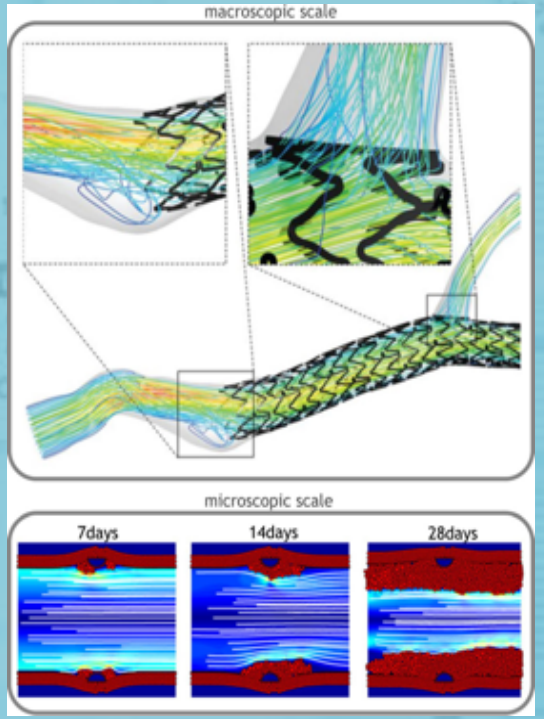
Fluid Dynamics Module

- Two different levels:
  - **Macroscopic scale:** blood is treated as a continuum.
  - **Microscopic scale:** multiscale models for describing the process of in stent restenosis.
- Blood components and vessel wall are included on a cellular level, and endothelial denudation, thrombus formation, SMC migration and the impact of the several laminae on the process of ISR is studied.



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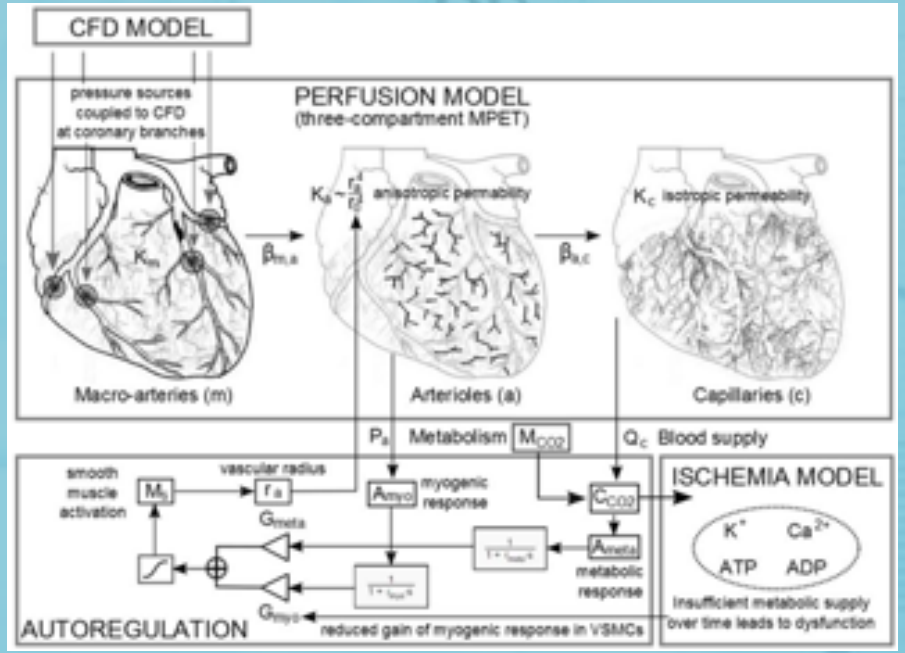
Myocardium perfusion Module

- A whole-heart myocardial perfusion model provides predictions of myocardial perfusion in the cardiac muscle.
- The Myocardial perfusion model is based on the “myocardium as a poroelastic medium” –with multiple overlapping compartments representing different scales of (micro)vasculature.



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Drug-delivery Module

- The drug-delivery module includes 3D modelling of drug release employing most novel types of anti-proliferation drugs through:
  - flow-mediated convection of drug
  - transmural delivery of drug by plasma
  - effective diffusion inside the carrying polymer
  - porous tissue with anisotropic distribution of transport properties.
- Controlled transient release of drug from different layers of polymer include the phase change, diffusion and depletion.

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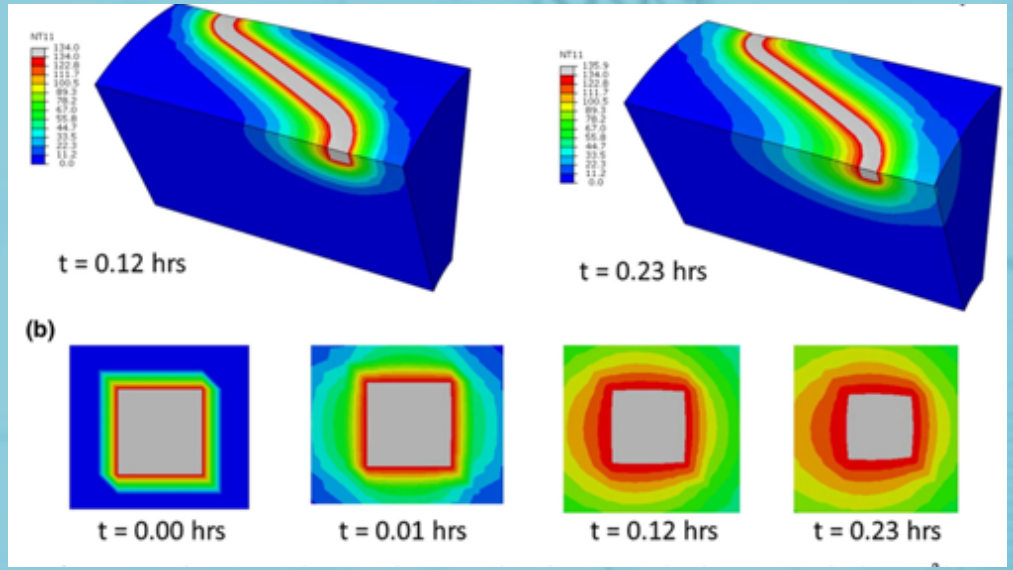
Degradation Module

- Physico-chemical processes that are responsible for material degradation
- Multiphysics progression of degradation processes
- Models of the interaction of the degrading material with the surrounding environment



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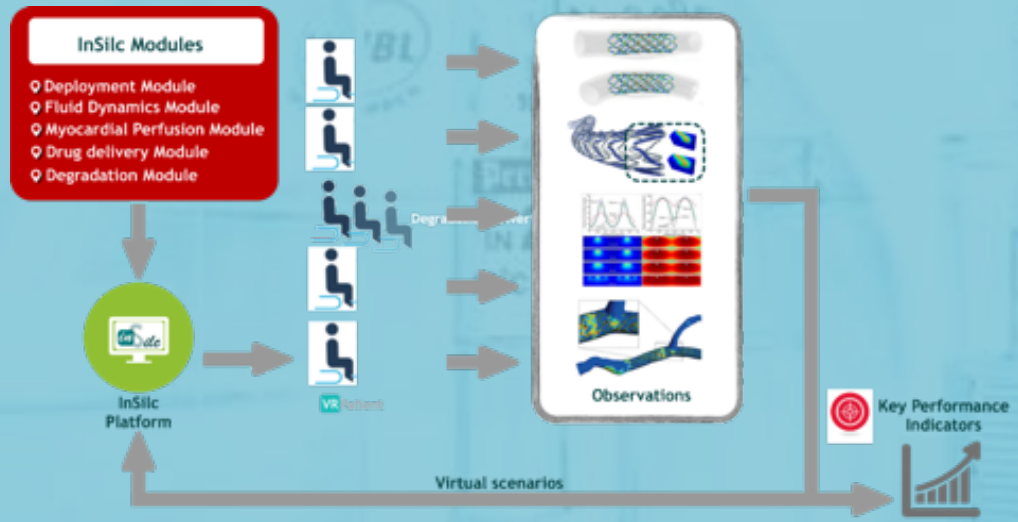
Virtual population

- “Virtual” patients to simulate the drug-eluting BVS performance.
- “Virtual” scenarios include the alteration of the scaffold parameters to evaluate functional characteristics



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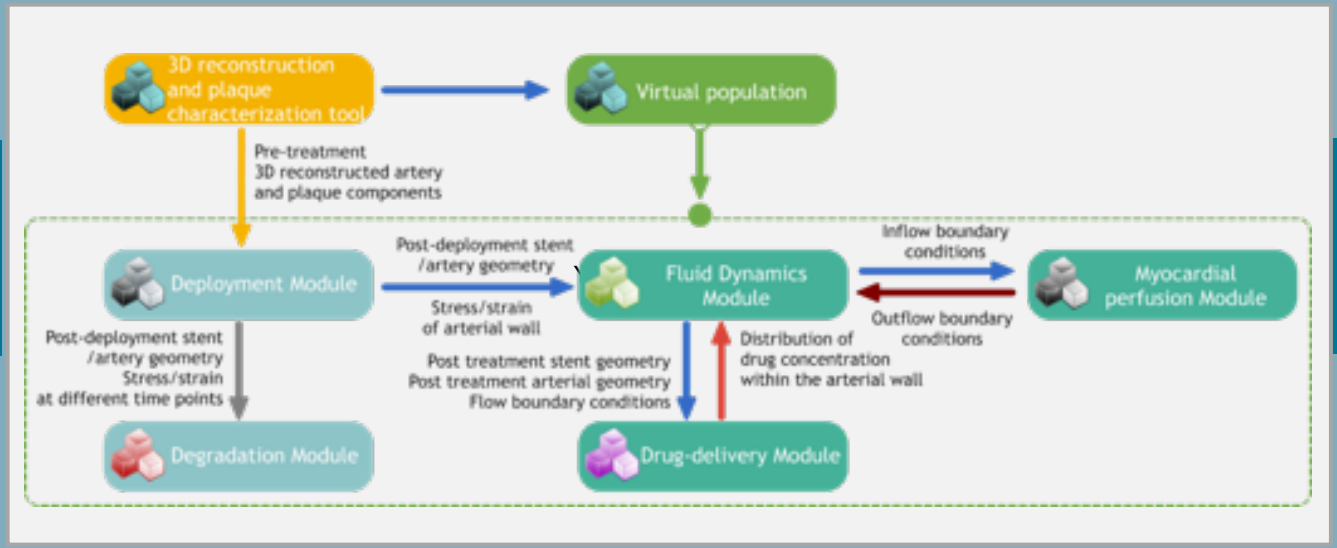

InSilc Scenarios

InSilc Scenarios

01 Compare existing stents

02 Compare anatomy configurations and patient conditions

03 Compare different clinical procedures

04 Design new stents

05 Pre-clinical testing assessment

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Virtual Population

- Virtual population is accessible as a database within InSilc platform.
- Each virtual patient's arterial geometries can be selected through a filtering tool.

1	Arterial segment type
2	Presence of bifurcation
3	LDL and HDL values ranges
4	Comorbid condition • Diabetes • Hypertension • Tachycardia
5	Degree and Length of Stenosis
6	Type of lesion

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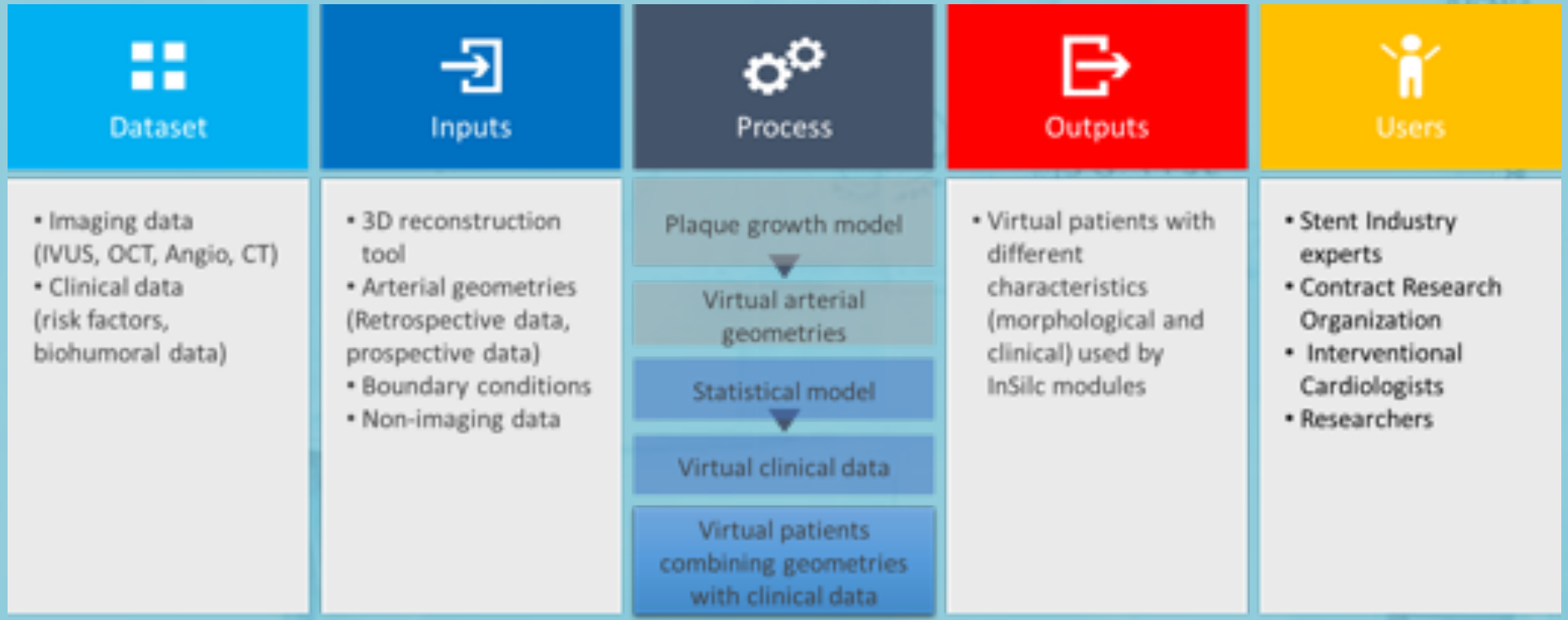
Virtual Population



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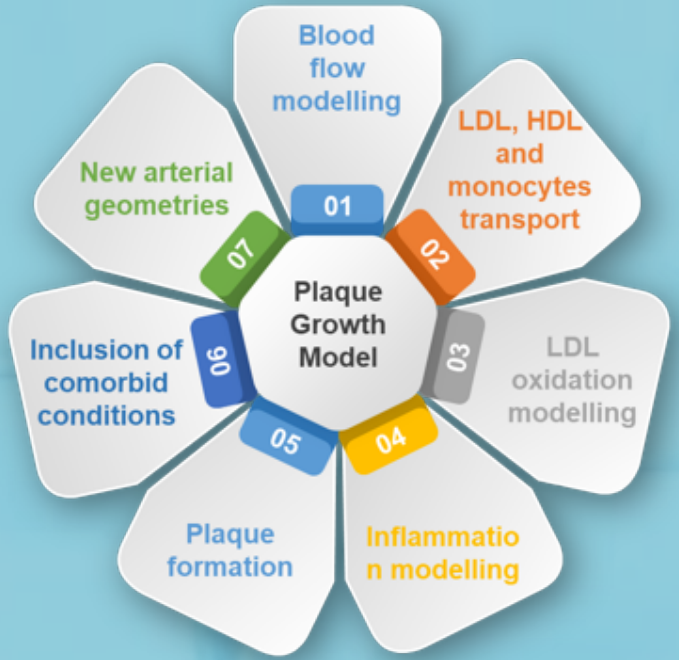
Plaque Growth Model Development



- Based on a previously developed model during SMARTool project.
- Simulation of main mechanisms of atherosclerosis.
- Utilisation of patient-specific data.
- Inclusion of comorbid conditions (diabetes, hypertension, tachycardia)
- Employment of FEA.
- Creation of new arterial geometries.

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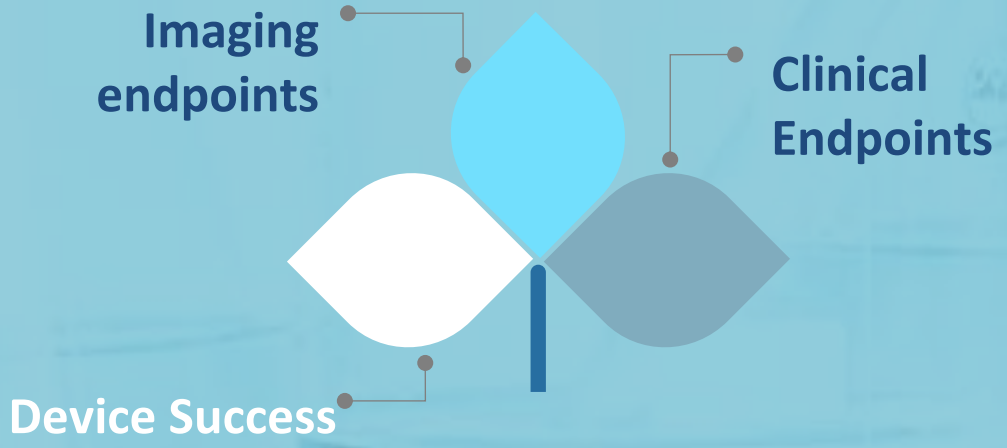
Clinical trials Objective Performance criteria



Device Success

- Successful delivery and deployment (post)
- Attainment of a final residual stenosis of the target lesion ≤ 30% (post)

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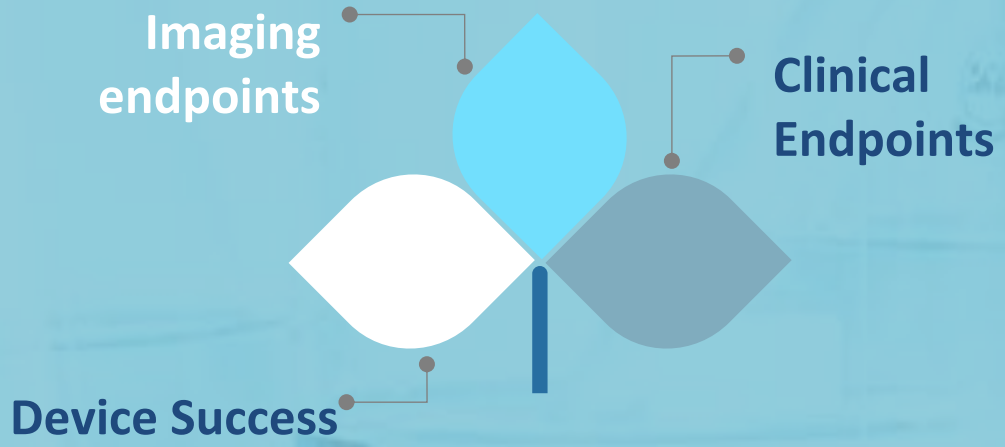
Clinical trials Objective Performance criteria



Imaging endpoints

- Minimal lumen diameter (MLD) mm (pre)
- Reference vessel diameter (RVD) mm (pre, post, fu)
- Percentage diameter stenosis (in-stent/segment) (pre, post, fu)
- Lesion length (pre)
- Plaque burden (pre)
- Minimal stent area (MSA) (post)
- Stent expansion index (post)
- Stent underexpansion (post)

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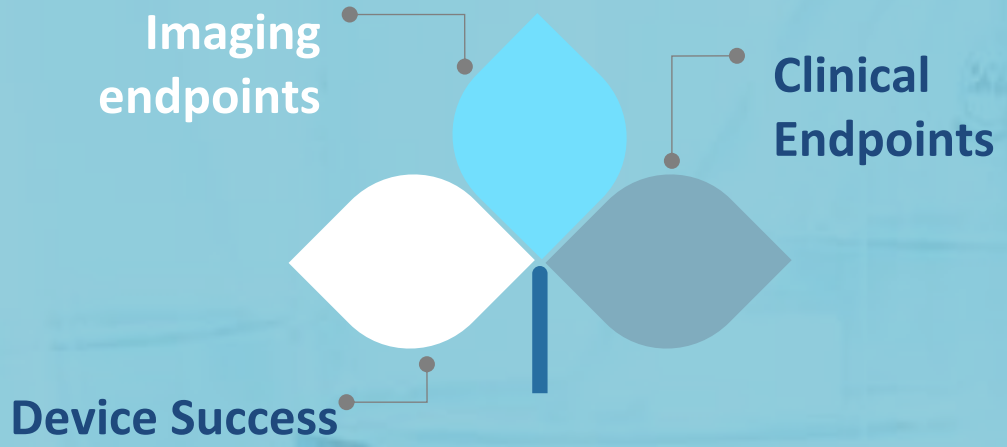
Clinical trials Objective Performance criteria



Imaging endpoints

- Minimal lumen diameter (MLD)
  Post-procedural lumen eccentricity (post)
- Post-procedural lumen asymmetry (post)
- Malapposed stent struts (post)
- Stent edge dissection (post)
- Stent fracture (post)

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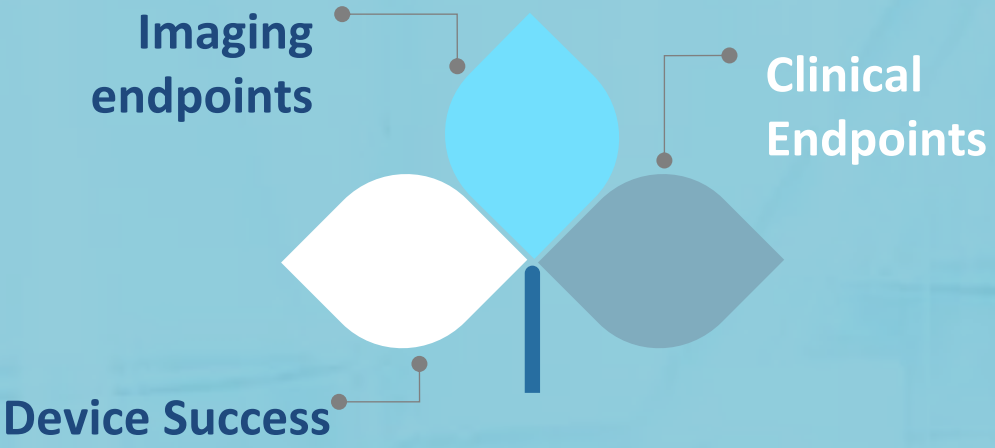
Clinical trials Objective Performance criteria



Clinical endpoints

- Cardiac Death (surrogate)
- Myocardial Infarction (surrogate)
- Revascularisation during in stent restenosis (surrogate)

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InSilc Scenario 1 - Compare existing stents

Clinical Relevance

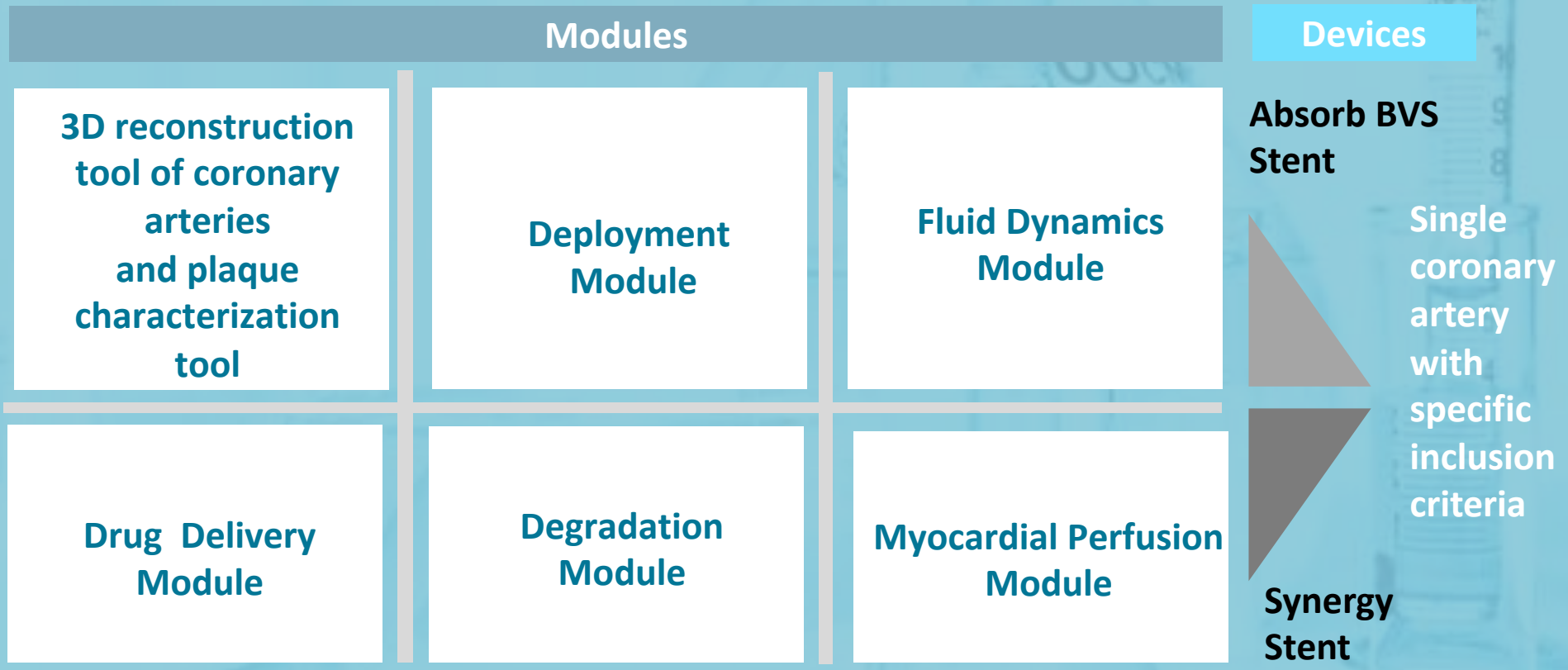
- Polymer-based BVS performance may be different compared to permanent metallic DES.
- This scenario directly compares behaviour of both BVS and DES devices in the same coronary artery and provides clinically relevant insight into key features.

Related clinical trials		
Trial	**N**	**Comparison**
Ellis et al. 2015	*2008*	Everolimus Eluting BVS vs Everolimus Eluting Stent
Chevalier et al. 2015	*501*	Everolimus Eluting BVS vs Everolimus Eluting Stent
Cassese et al. 2015	*3738*	Everolimus Eluting BVS vs Everolimus Eluting Stent
Puricel et al. 2015	*240*	Everolimus BVS vs Everolimus or Biolimus Eluting Stent
Kereiakes et al. 2015	*1684*	Synergy vs Everolimus ES
Byrne *et al.* 2019	262	Everolimus Eluting BVS vs Everolimus Eluting Stent

[1] Ellis *et al.*, *N. Engl. J. Med.*, vol. 373, no. 20, pp. 1905–1915, Nov. 2015.
Chevalier et al., Eurointervention 2018;13: 1561-1564
[2] Cassese *et al., The Lancet*, vol. 387, no. 10018, pp. 537–544, Feb. 2016.
[3] Puricel *et al.*, *J. Am. Coll. Cardiol.*, vol. 65, no. 8, pp. 791–801, Mar. 2015.
Kereiakes *et al.*, *Circ. Cardiovasc. Interv.*, vol. 8, no. 4, Apr. 2015.
[4] Byrne et al., European Heart Journal (2019)

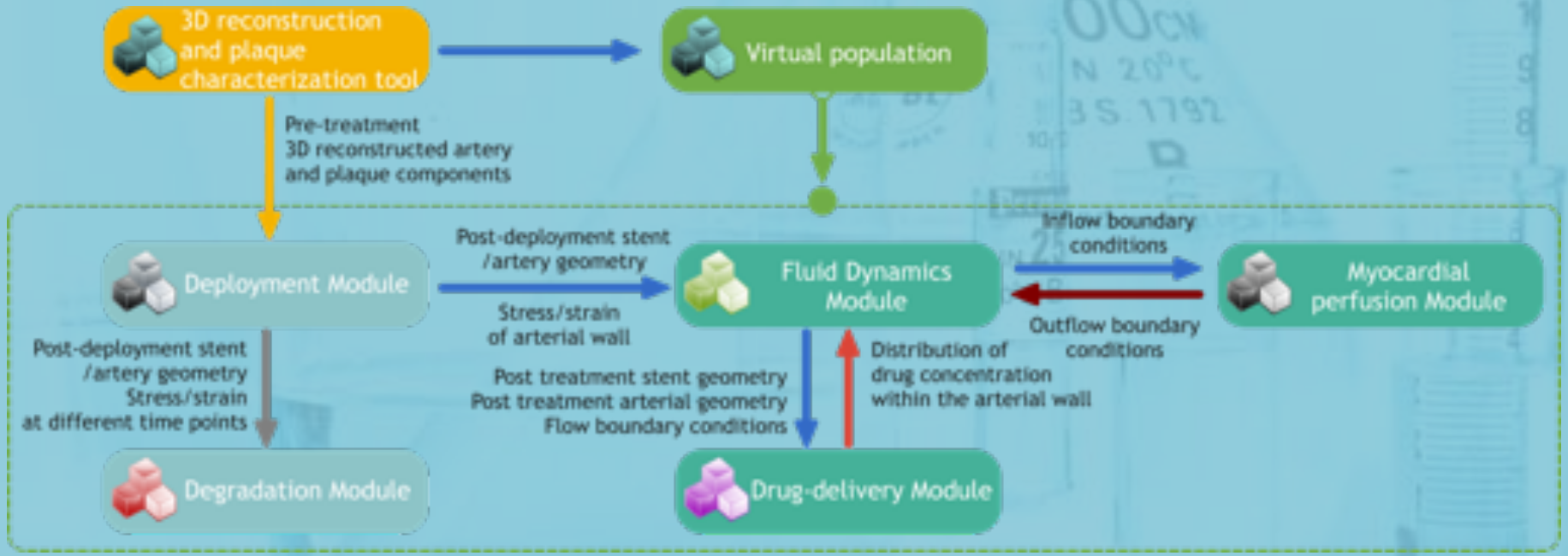
InSilc Scenario 1 - Compare existing stents

In Silico approach



InSilc Scenario 1 - Compare existing stents

In Silico approach



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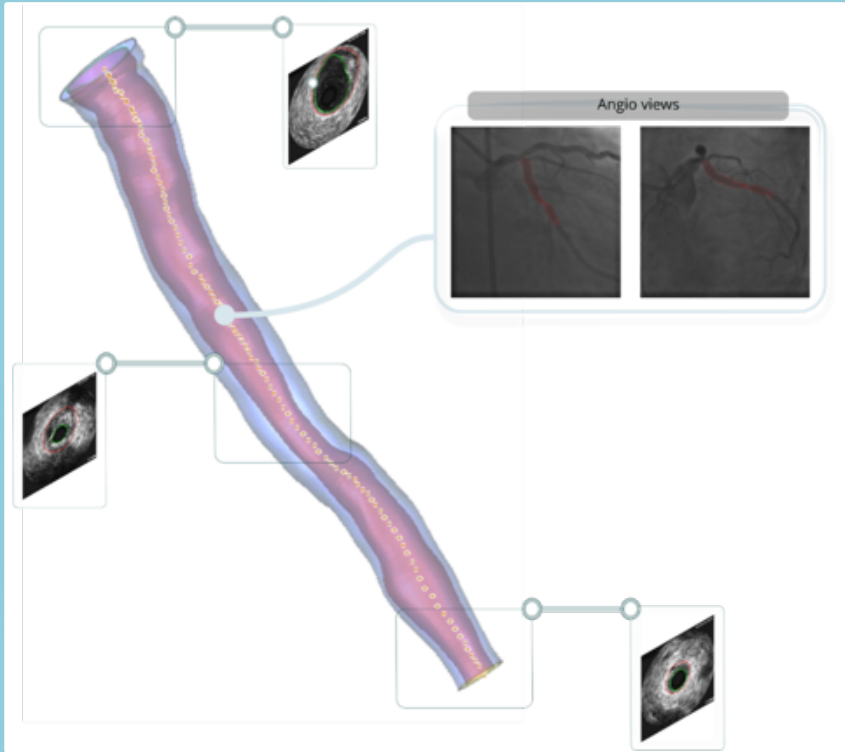
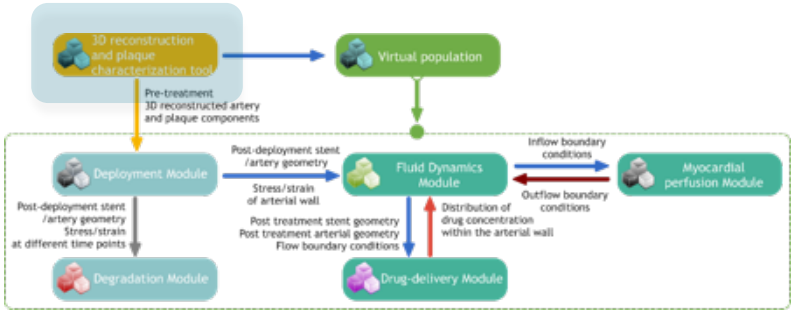
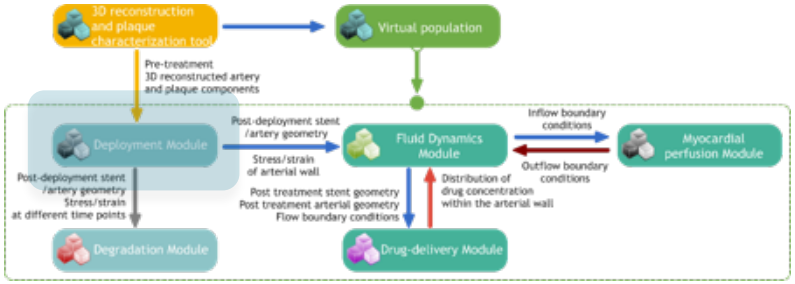
InSilc Scenario 1
Clinical trials Objective Performance Criteria





Vessel Characteristics	
Vessel length (mm)	44
RVD (mm)	3.52
Lesion length (mm)	17
MLD (mm)	1.65
Percentage diameter stenosis	54%

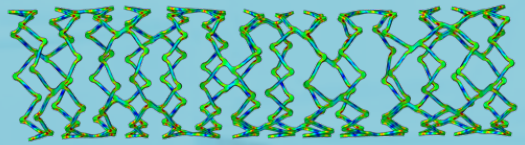
InSilc Scenario 1
Clinical trials Objective Performance Criteria

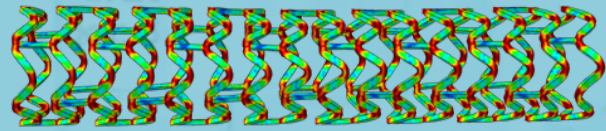


Synergy

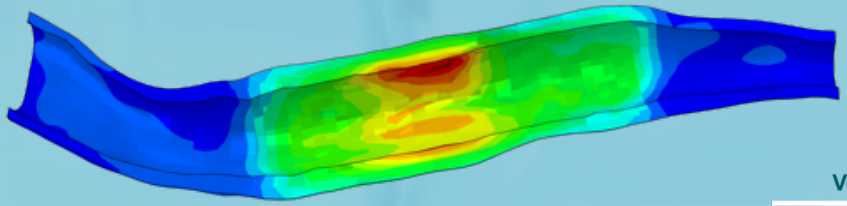
Absorb

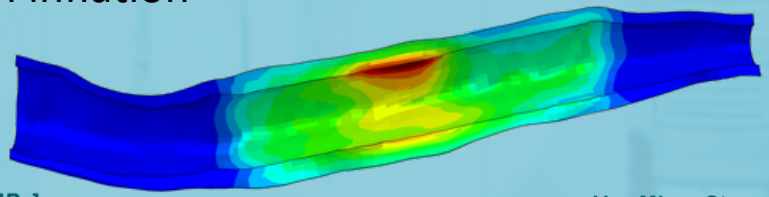
Post-deployment



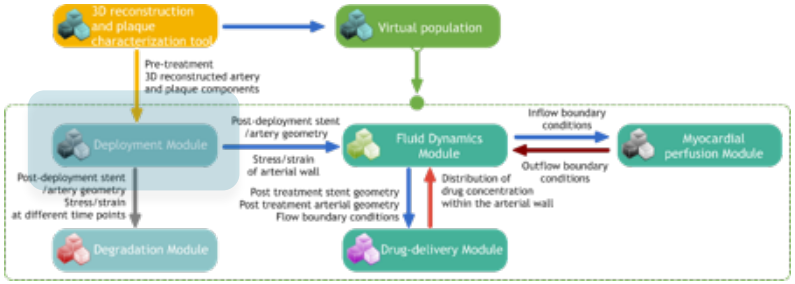


Maximum balloon inflation





InSilc Scenario 1
Clinical trials Objective Performance Criteria

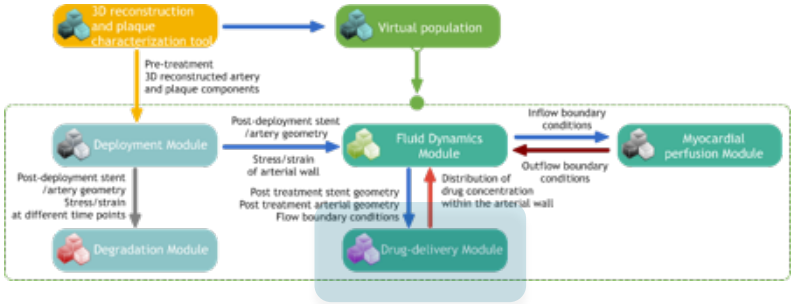


Short-term behaviour: post-deployment

	Synergy	Absorb
Successful delivery and deployment	YES	YES
Final residual stenosis < 30% of the target	YES	YES
MLD - post-procedural [mm]	3.7	3.1
Diameter stenosis post-procedural [%]	0	12
Minimal stent area [mm2]	10.7	7.5
Stent expansion index [-]	1.10	0.77
Eccentricity index - EI [-]	0.96	0.96
Asymmetry index - AI [-]	0.08	0.09
Malapposed strut surface [%]	0	0
Stent edge dissection	NO	NO
Stent fracture	NO	NO

*MLA=minimum lumen area

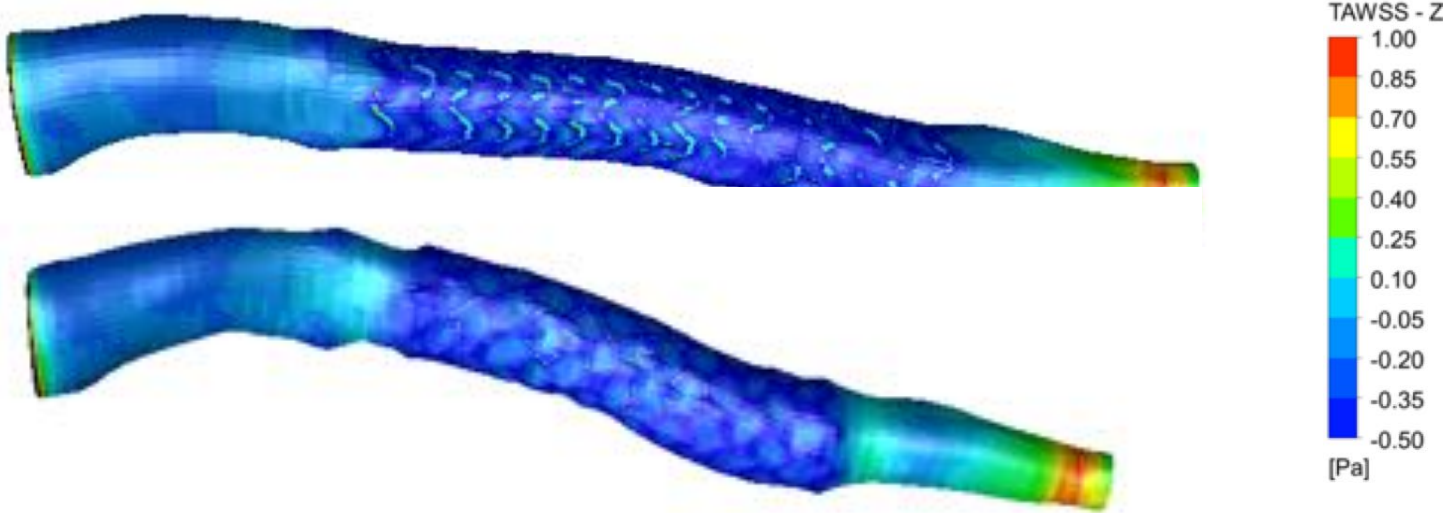
InSilc Scenario 1
Clinical trials Objective Performance Criteria



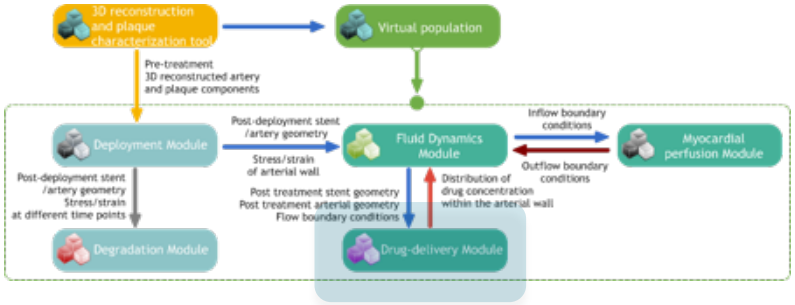
3D shear stress maps of the two stents (qualitative)

Absorb

Synergy



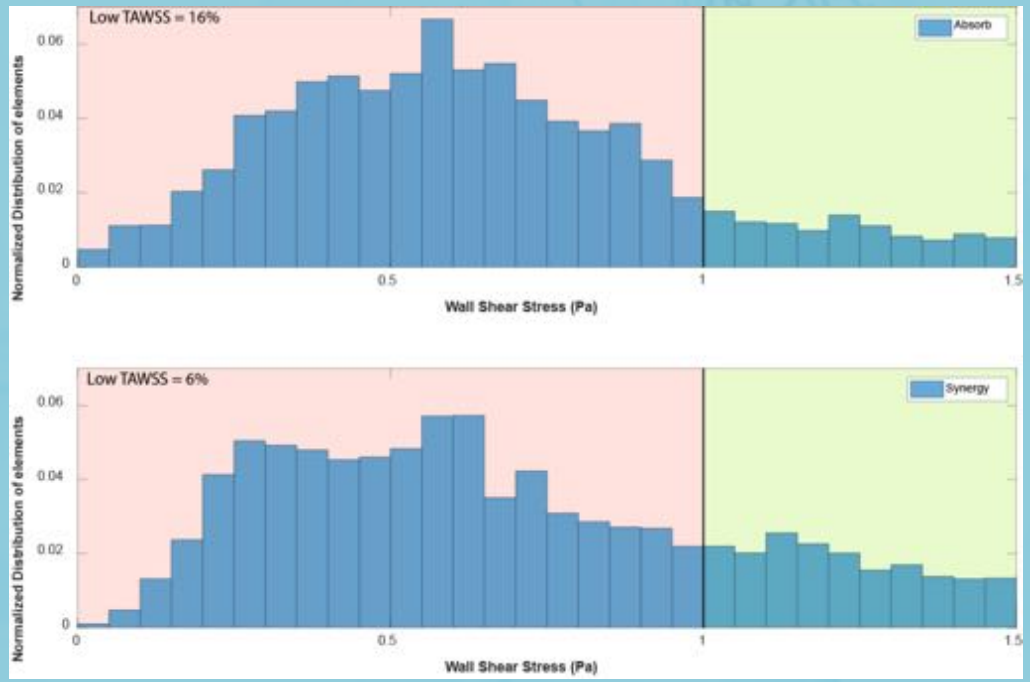
InSilc Scenario 1
Clinical trials Objective Performance Criteria



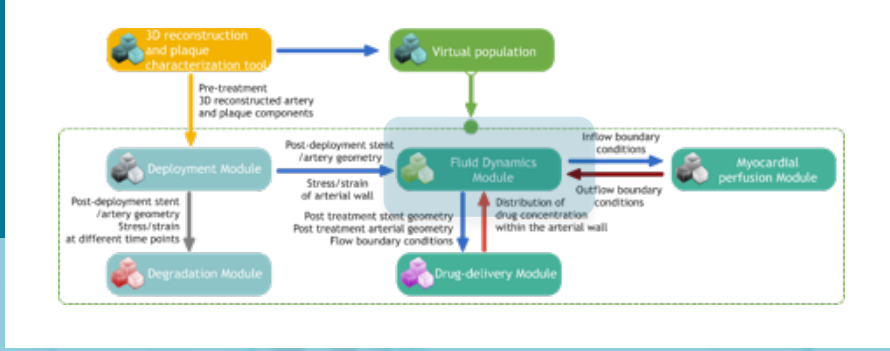
3D shear stress maps of the two stents (quantitative)

Absorb

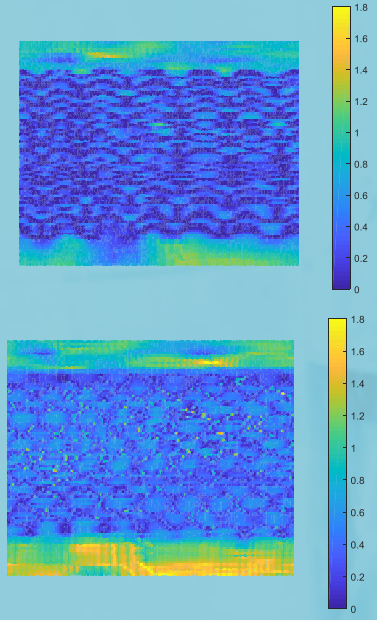
Synergy



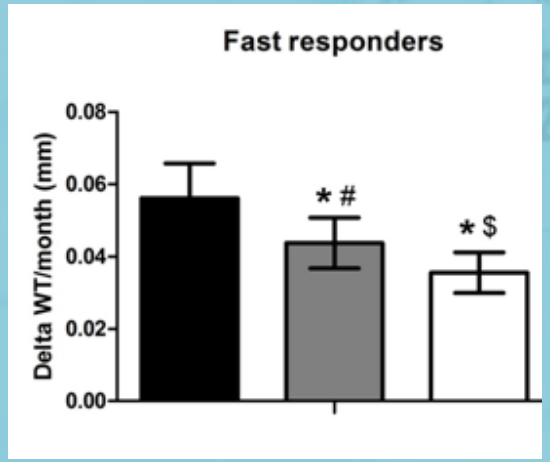
InSilc Scenario 1
Clinical trials Objective Performance Criteria

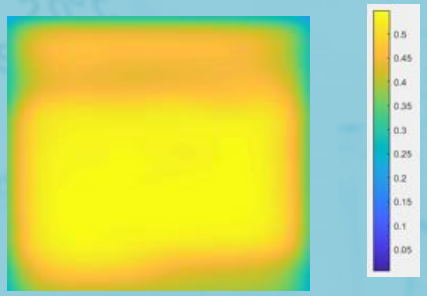


2D shear stress maps and predicted intima growth

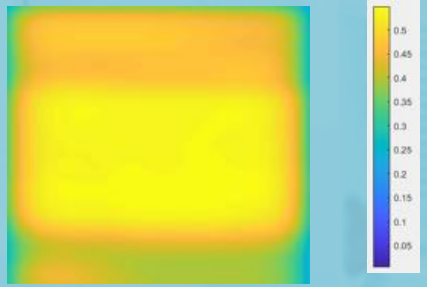


WSS (Pa)



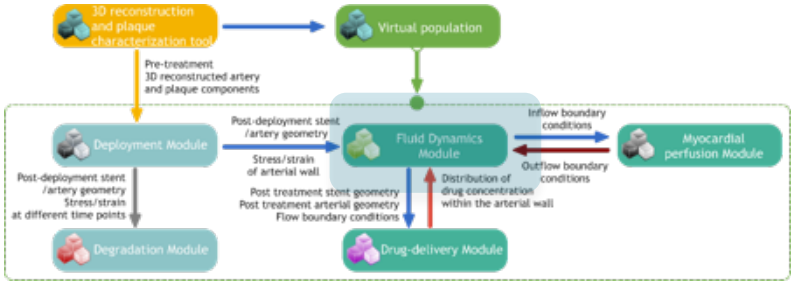


Thickness (mm)



Thickness (mm)

InSilc Scenario 1
Clinical trials Objective Performance Criteria

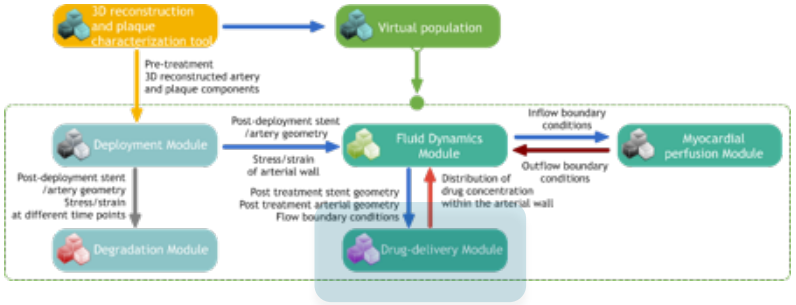


Predicted imaging follow-up data

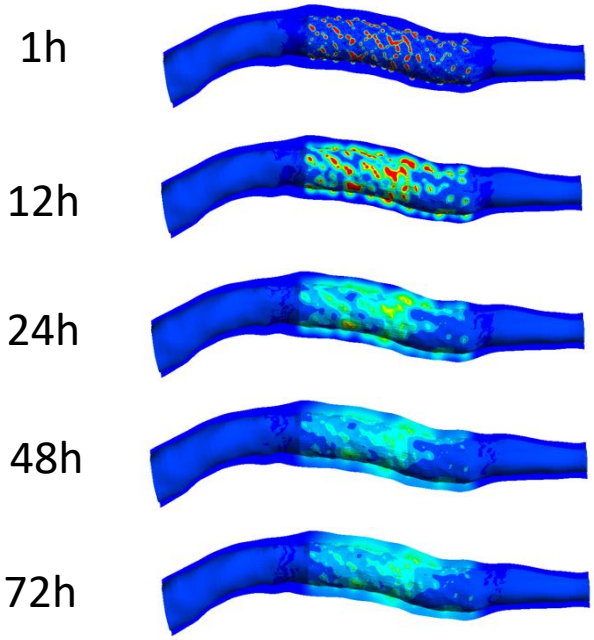
Absorb	neo-intimal thickness	0.41 mm
	MLA	7.8 mm^2
	in-stent volume obstruction	24%
Synergy	neo-intimal thickness	0.4 mm
	MLA	11.6 mm^2
	in-stent volume obstruction	20%

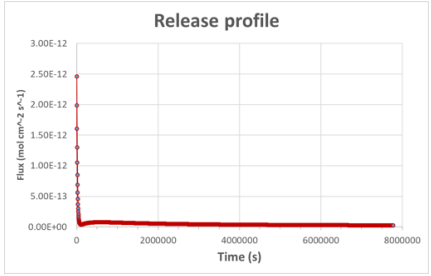
InSilc Scenario 1
Clinical trials Objective Performance Criteria

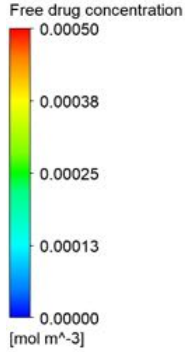
Free drug concentration at different times



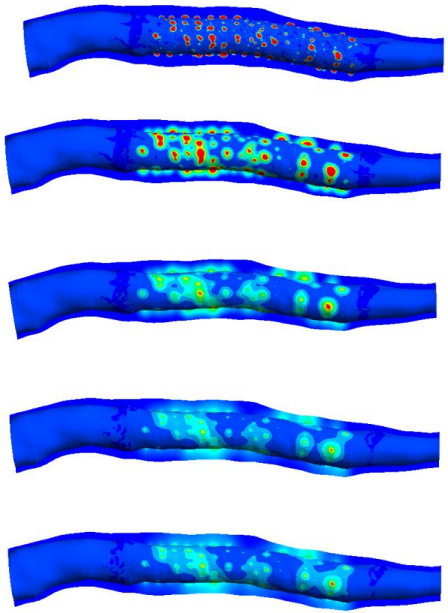
SYNERGY



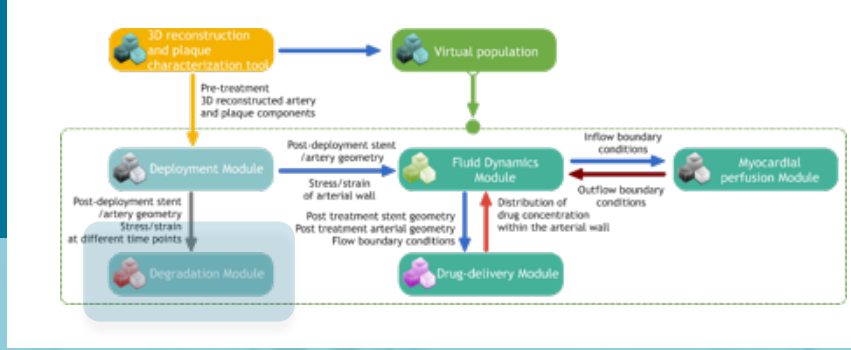


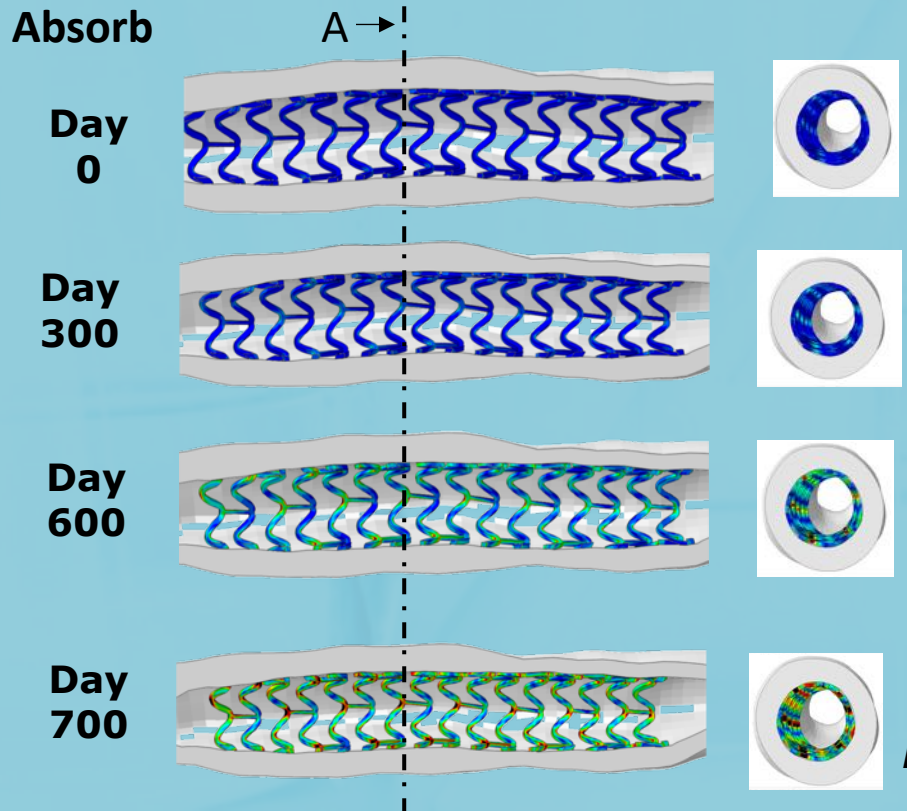


ABSORB



InSilc Scenario 1
Clinical trials Objective Performance Criteria



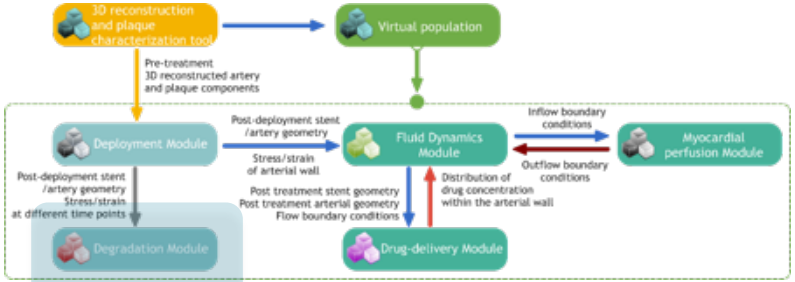


Degradation variable describes ratio of current Von-mises stress (σ_e) to current yield stress ($\sigma_y(t)$).

$$\frac{\sigma_e}{\sigma_y(t)}$$

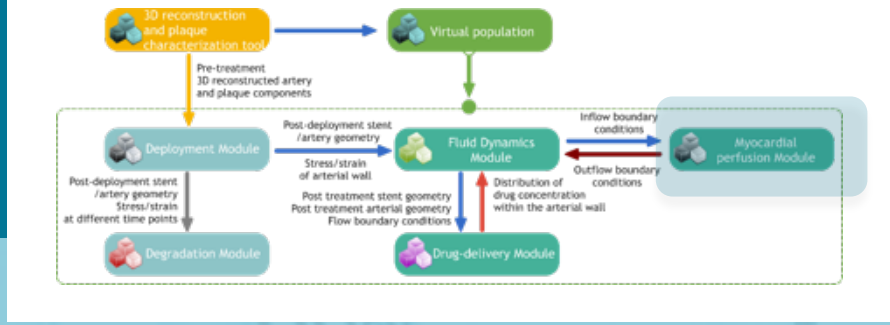
Damage due to degradation initiated ~Day 600

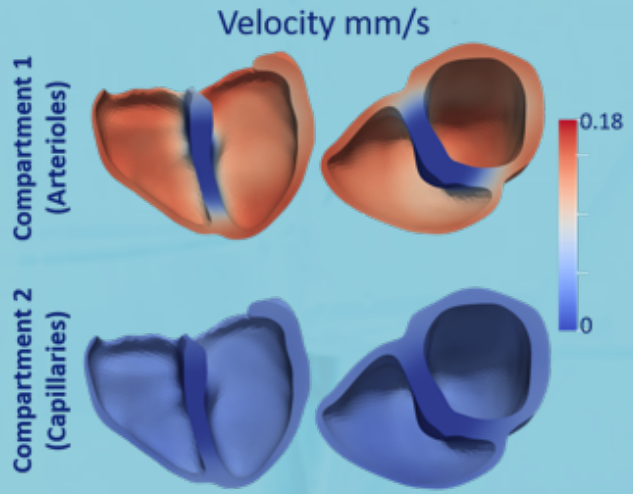
InSilc Scenario 1
Clinical trials Objective Performance Criteria

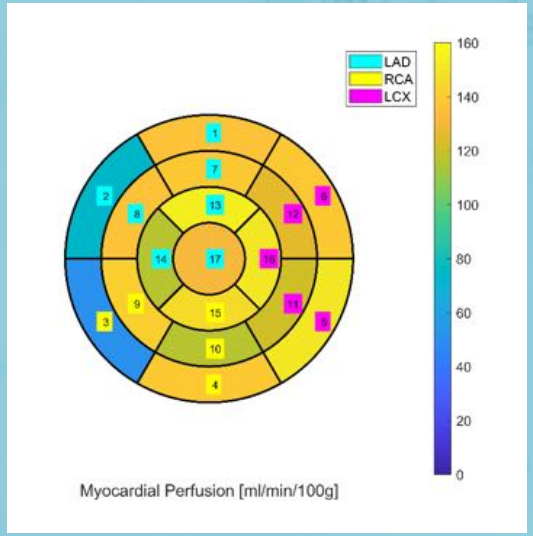


MODEL INPUT	Day 0	Day 300	Day 600	Day 700
Percentage diameter stenosis	n/a	n/a	n/a	n/a
Minimal stent area (MSA) (post)	Unchanged	Unchanged	98.4%	90.1%
Malapposed stent struts (post)	Unchanged	Unchanged	Unchanged	Unchanged
Stent fracture (post)	No	No	No (mild damage)	No (mild damage)
Late loss: in-stent and in-segment luminal loss (fu)	No	No	Minor	Minor
Strut discontinuity or dismantling	No	No	No	No

InSilc Scenario 1
Clinical trials Objective Performance Criteria







Myocardial perfusion [mL/min/100g] is used as surrogate to predict major adverse cardiac events (MACE)

What did we learn?

Both stents successfully implanted, without any critical post-deployment condition. Synergy performs slightly better in terms of stent expansion and lumen opening.

Deployment module

Fluid dynamics module

Bigger struts of ABSORB scaffold induce larger regions exposed to low wall shear stress, potentially leading to more in stent restenosis

Drug delivery module predicted a slightly better performance of Synergy in drug delivery to the tissue as a result of superior apposition and hemodynamics

Drug delivery module

Degradation module

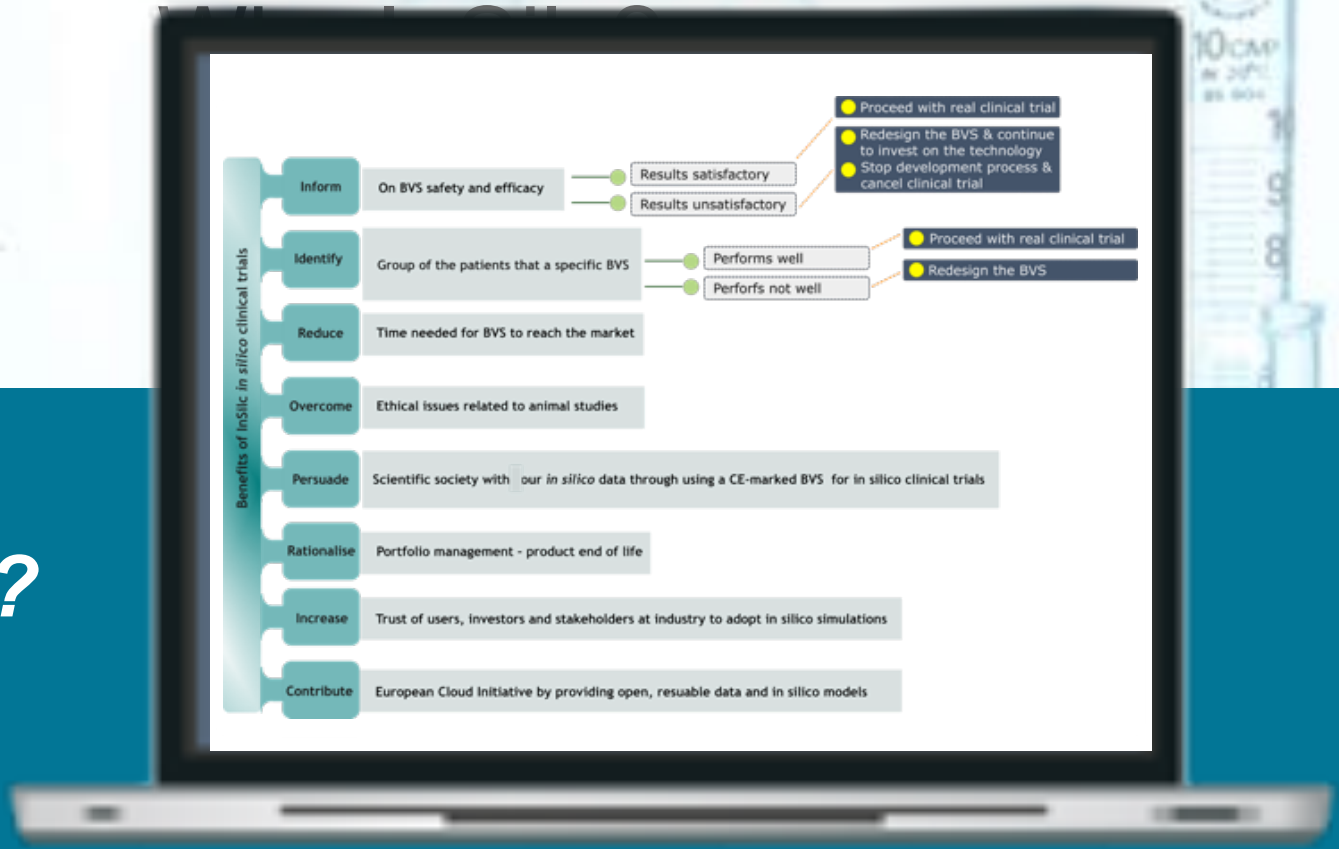
Degradation module predicted onset and progression minimal stent damage at 600 Days, leading to slight reduction in lumen geometry.

Ongoing. This module will be able to compare the post-intervention myocardial reperfusion for different stents.

Myocardial Perfusion Module

Why *in silico* clinical trials?

Why InSilc?



Regulatory road map and actions

- Identify the requirements for the certification of in silico trials for drug-eluting BVS
  - Provide evidence of the increase in the statistical power of InSilc by simulating more homogeneous and more «virtual» patients
  - Show the benefit in terms of clinical trials costs and duration
  - Estimate the reduction in animal testing
  - Define the target selection criteria of the patient population for reducing the need of complex and lengthy trials
- Study all regulatory issues which could prompt a transformation
  - Regeneration of the Stent Biomedical Industry to promote in silico trials
  - Explore the societal consequences of InSilc platform adoption
  - Investigate the standards to be taken into consideration
  - Define the ethical, privacy, secure data storage and management issues.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777119

Regulatory road map and actions

In silico clinical trial platform

Software as a medical device (SaMD) = software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device –

➢Simulation as a medical device

for designing, developing and assessing

Intended use/ intended purpose = the objective intent of the manufacturer regarding the use of a product, process or service …»

Fundamental in the determination of its classification

drug-eluting bioresorbable vascular scaffolds (BVS)

Class III medical device

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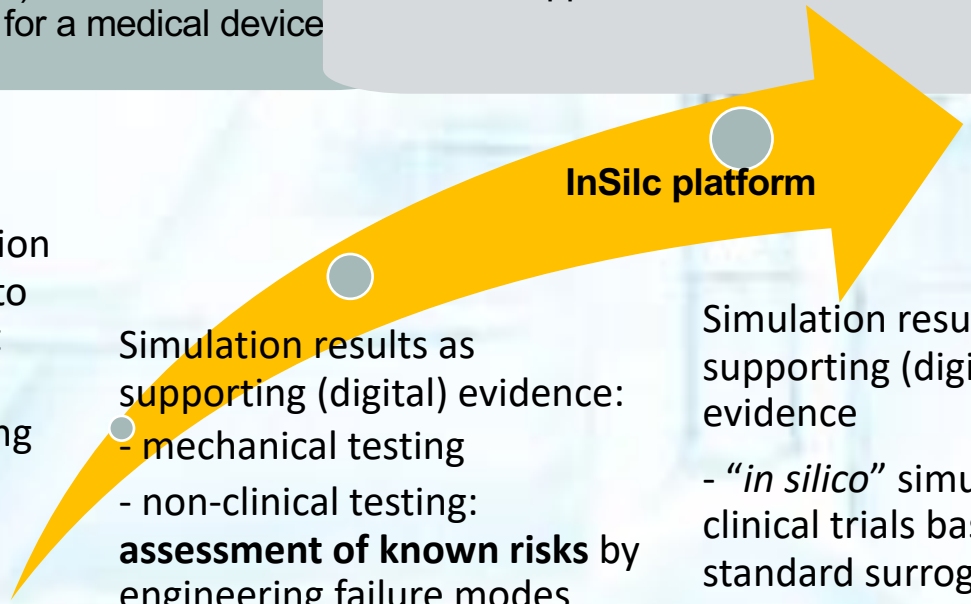
Regulatory road map and actions

Computational modeling can be part of a regulatory submission in two ways*:

when simulation results serve as supporting (digital) evidence in a marketing application for a medical device

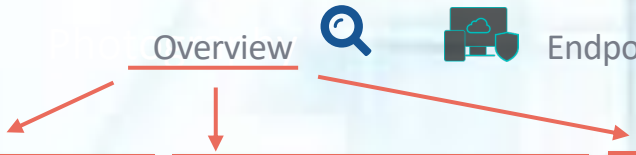
when simulation is a medical device, such as for clinical decision support; this is “software as a medical device.”



Regulatory road map and actions

What is needed to document validation and acceptance of computer modelling and simulations (CM&S) applied to the InSilc platform

Preliminary adoption of the platform for in silico trials with BVS



Current/incoming regulatory pathways for clinical investigations with medical devices → coronary stents

Regulatory aspects related to the acceptance of the models

Regulatory aspects related to the platform

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Regulatory road map and actions

REGULATION (EU) 2017/745
Art 62 General requirements regarding clinical investigations conducted to demonstrate conformity of devices

Guidelines for the conduct of clinical trials with coronary stents

Report of an ECS-EAPCI Task Force on the evaluation and use of bioresorbable scaffolds

FDA - 2016 Guidance
Reporting of Computational Modeling Studies in Medical Device Submissions

American Society of Mechanical Engineers (ASME) verification and validation (V&V) subcommittee on computational models of medical devices (ASME V&V 40 subcommittee)

Medical Device Innovation Consortium

FDA's Office of Science and Engineering Laboratories (OSEL)

IMDRF International Medical Device Regulation Forum

What we could conclude?

- Regulatory requirements and reference guidance for clinical investigations with BVS well established
- Regulatory guidelines for the acceptance of the models partially available, but adaptation to InSilc models is needed.
  - Main question for regulators: define the accepted level of accuracy and reproducibility
- Regulatory guidelines related to the platform as SaMD available

CRITICAL POINTS for the adoption of the platform for in-silico trials with BVS

- Clinical trial requirements for in silico trials are not existing
- Previous experience is missing
- The targeted clinical condition and the treatment have too many variables to be considered to allow for accurate and reliable simulations

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Current regulatory activities

- Extensive collection and review of regulations, guidelines and publications
- Definition of the recognised short/mid-term surrogate endpoint to be tested in the modules
- Consulting with Prof. Viceconti (ex Insigneo Institute for *in silico* medicine – Avicenna Alliance) and liaison with other in silico projects
- Consulting with invasive cardiologists members of ESC/EAPCI (ex task force on BVS)
- Contacts with European Forum for Good Clinical Practice
- Preliminary contacts with FDA and EMA

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Future regulatory activities

- Work closely with:
  - Experts from the Medical Device Coordination Group and FDA
  - Notified Bodies
  - ISO experts
  - Avicenna Alliance
  - ESC/EAPCI
  - European Forum for Good Clinical Practice
  - EUCROF (European CRO Federation)

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