Non-Animal Platform for Nanoparticle-Based Delivery across the Blood-Brain Barrier Interface with Vehicle Evolution

www.nap4dive.eu

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Clinical context & scientific challenge

- **Brain diseases** affect 179 million Europeans, costing 800 billion EUR per year
- **Blood-brain barrier (BBB)** is the major obstacle in efficiently delivering drugs for treatment (only 5% reaching the brain)
- Solution might be the use of **drug delivery vehicles**
  - **Nanoparticles** studied as a solution for BBB-crossing for 30 years, but only 30 NP systems in clinical trials, and majority have already failed
- **Preclinical models (mostly mice) harm animals** and do not successfully mimic human BBB
  - 850 000 animals used annually in the EU in the nervous system research

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NAP4DIVE Solution

- We develop two complementary non-animal tools for biomedical research and drug development:

  1. "**Nanoparticle Design Simulator**", *in silico* model based on machine-learning

  2. High-throughput "**Blood-brain barrier-on-Chip**" model using human cells to mimic human physiology

- This will establish reliable non-animal alternatives for testing, explaining, and predicting nanoparticle-based drug delivery across the human blood-brain barrier.

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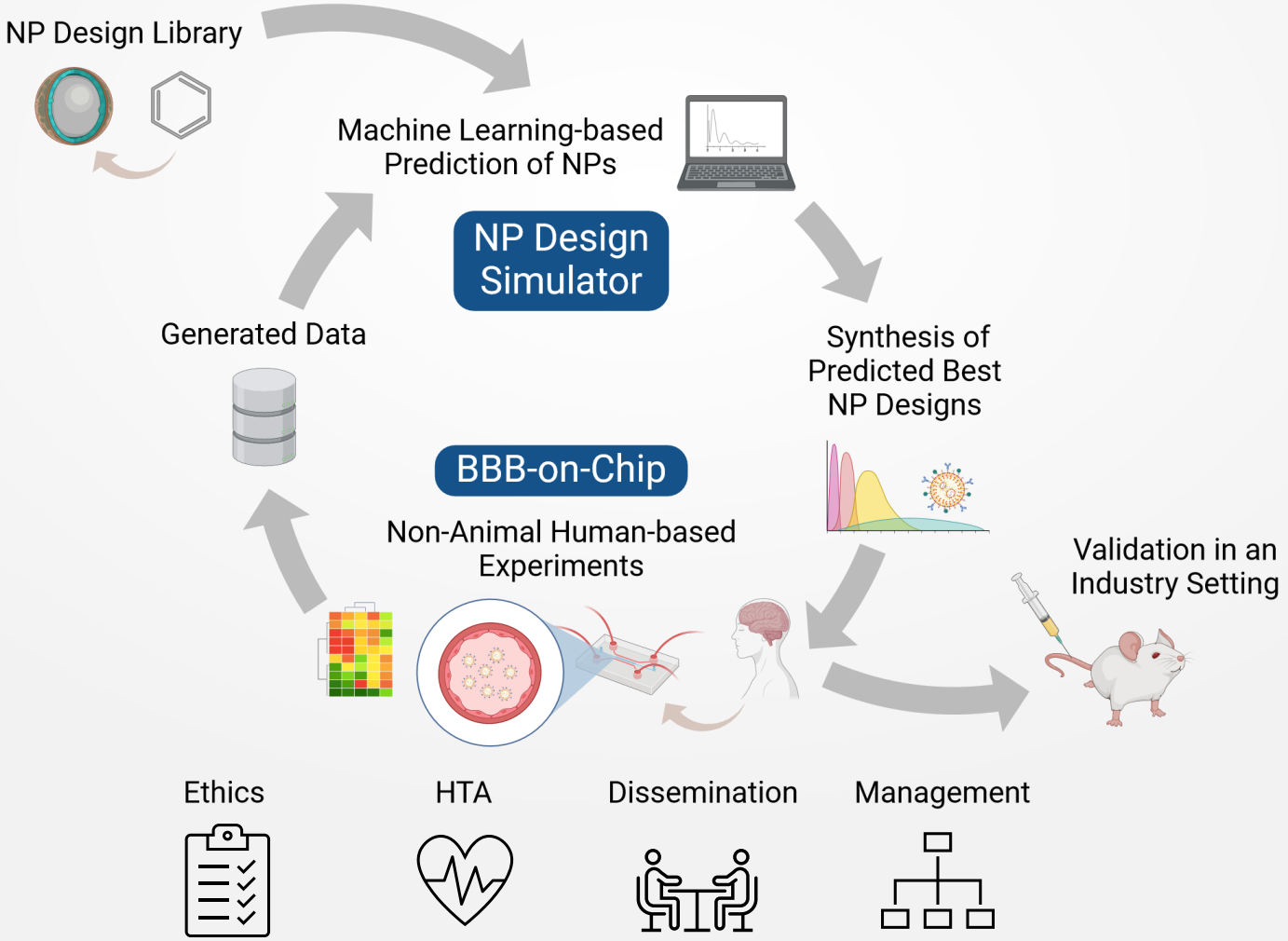
NAP4DIVE overview



BBB = blood-brain barrier
HTA = health technology assessment
NP = nanoparticle

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Consortium expertise

NAP4DIVE

NP design library, digital simulator

Åbo Akademi University

TU Delft

Blood-brain barrier-on-Chip

finnadvance

MIC Microfluidics Innovation Center

NPs (synthetic & biological)

Åbo Akademi University

University of Gothenburg

NP upscaling & manufacturing

HansaBioMed Life Sciences

Ethics

TU/e Eindhoven University of Technology

Cell-NP interaction

Åbo Akademi University

Chalmers University of Technology

Demonstration & validation

AstraZeneca

Health technology assessment

betthera

Management & dissemination

AMIRES

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Support structure

- Ethics board
  - Monitor and report ethics issues (AI and animal research)
  - Meet with partners once a year
  - Ensure all activities follow ethical principles
- External Advisory Board
  - Provide advise and guidance on technological, exploitation, regulatory and clinics aspects of project progress
  - Meet with consortium yearly and provide advice *ad hoc*
- Joint Research Centre (JRC)
  - Provide advice on standardization aspects of developed technologies

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NAP4DIVE Building blocks

- Nanoparticle (NP) design library: characterization and synthesis
- Digital nanoparticle design simulator
- Blood-Brain Barrier-on-Chip
- Demonstration and validation: Identifying safe and efficacious nanoparticles: Triaging on the Blood-Brain Barrier Chip
- Market readiness, health technology assessment
- Ethics

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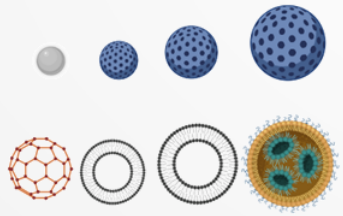
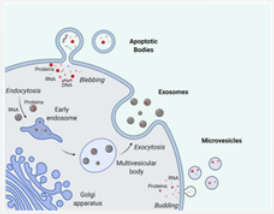
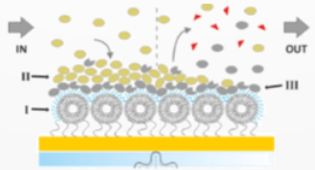
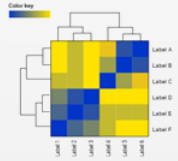
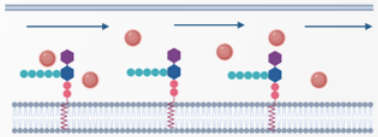
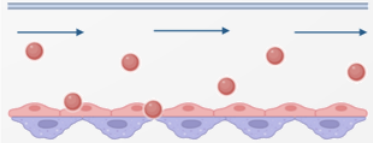
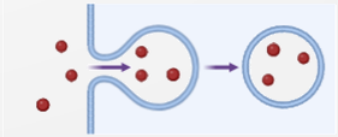
NP characterization and synthesis

Property-functionality relationship

Nanoparticle formulations	Nanoparticle properties and protein corona	Nanoparticle-BBB interactions
• **Synthetic nanoparticles** • *Different core materials* • *Different sizes* • *Different surface properties*  • **Biological nanoparticles** • *Different cell sources* 	**Nanoparticle characterization** • *Size, charge, density* • *Surface ligand, drug load* **Protein corona** • *Static (bulk)* • *Dynamics (surface bound)*  **Composition of protein corona** • *Effect on nano-bio interactions* 	• **Dynamic cell membrane interactions**  • **Dynamic cell interactions and uptake**  
DLS, NTA, TEM, SEM	**WGSM, MP-SPR, Mass spectrometry**	**QCM-D, MP-SPR, WGSM**

Created by Tapani Viitala, modified by Mariana Pacheco B. in https://BioRender.com // Dang, X.T.T. et al Extracellular Vesicles as an Efficient and Versatile System for Drug Delivery. *Cells* 2020, https://doi.org/10.3390/cells9102191 // Kari, O. et al. In situ analysis of liposome hard and soft protein corona structure and composition in a single label-free workflow. *Nanoscale 2020,* https://doi.org/10.1039/C9NR08186K

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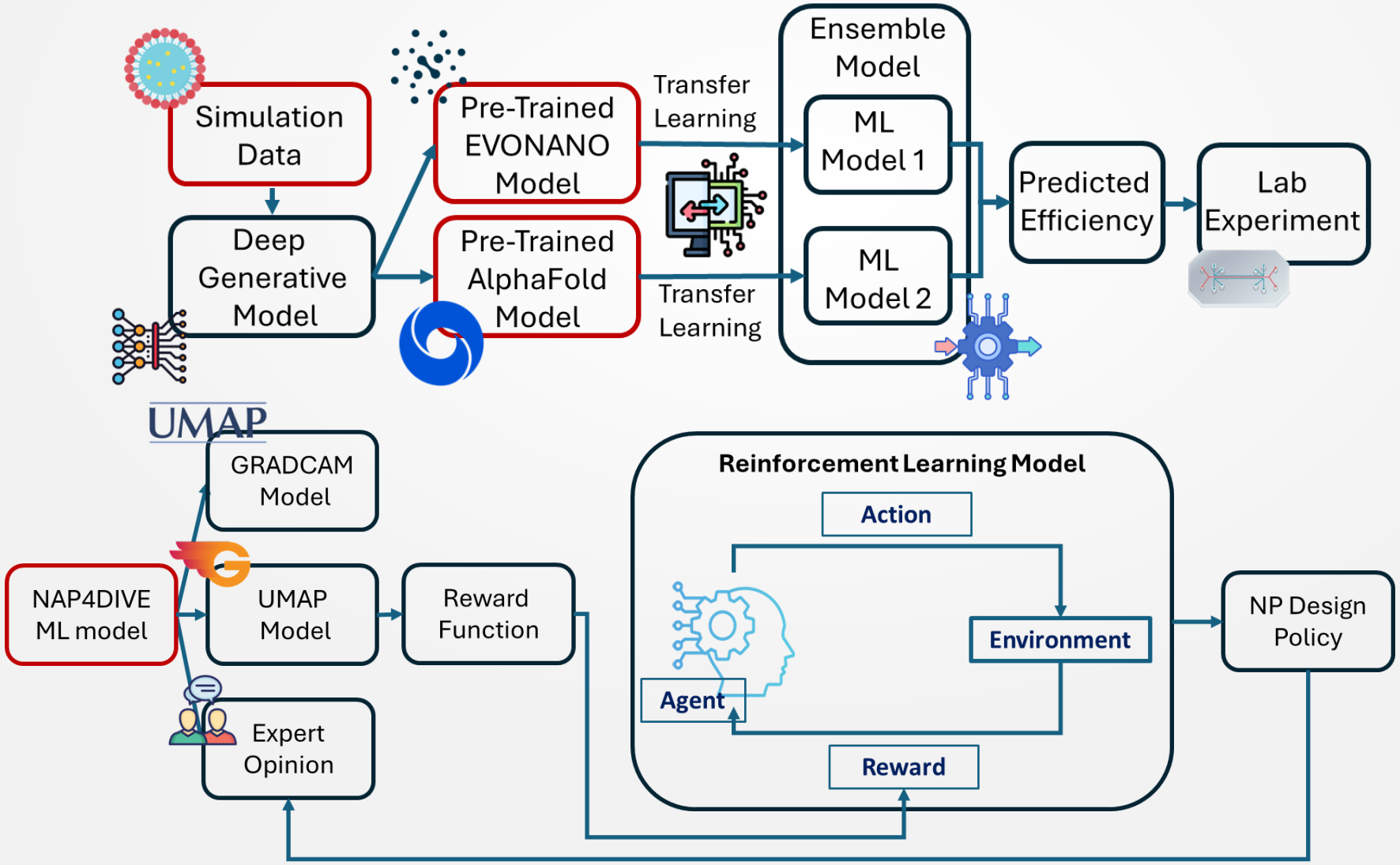
Digital NP design simulator



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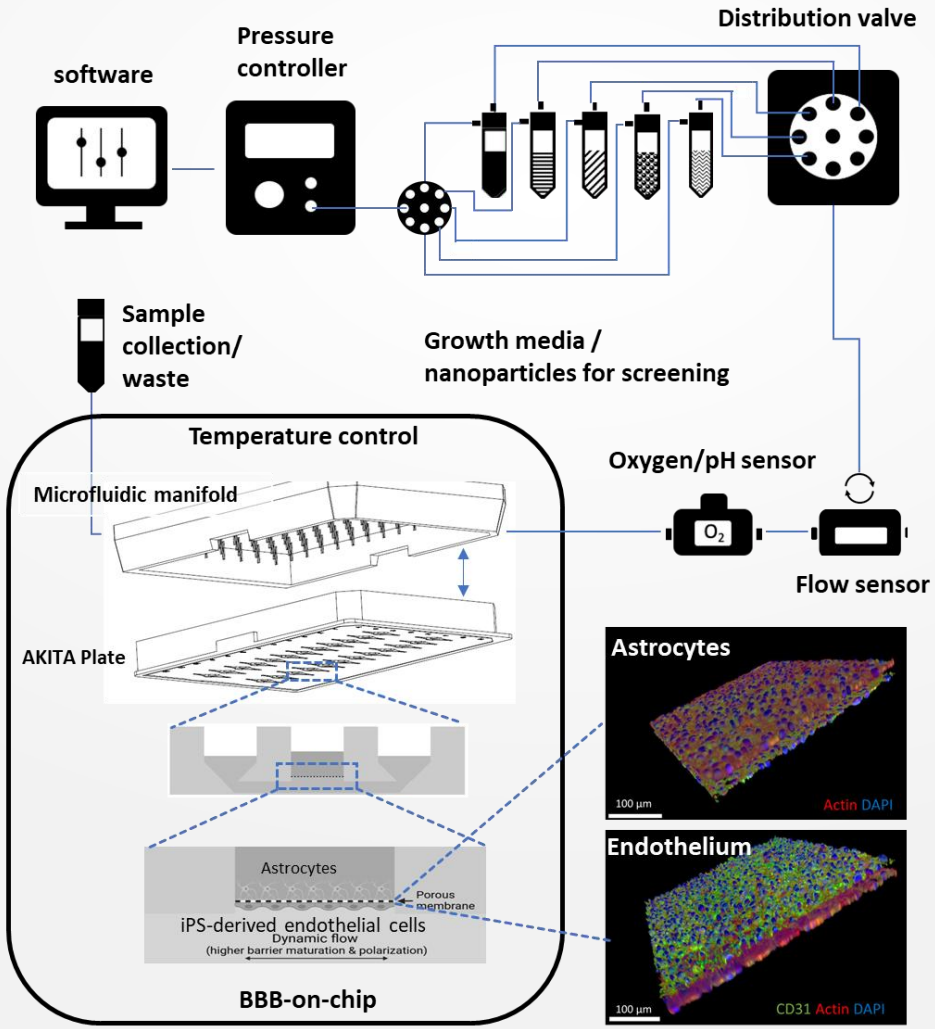
Blood-brain barrier-on-Chip

Optimization for the test of nanoparticles and extracellular vesicles



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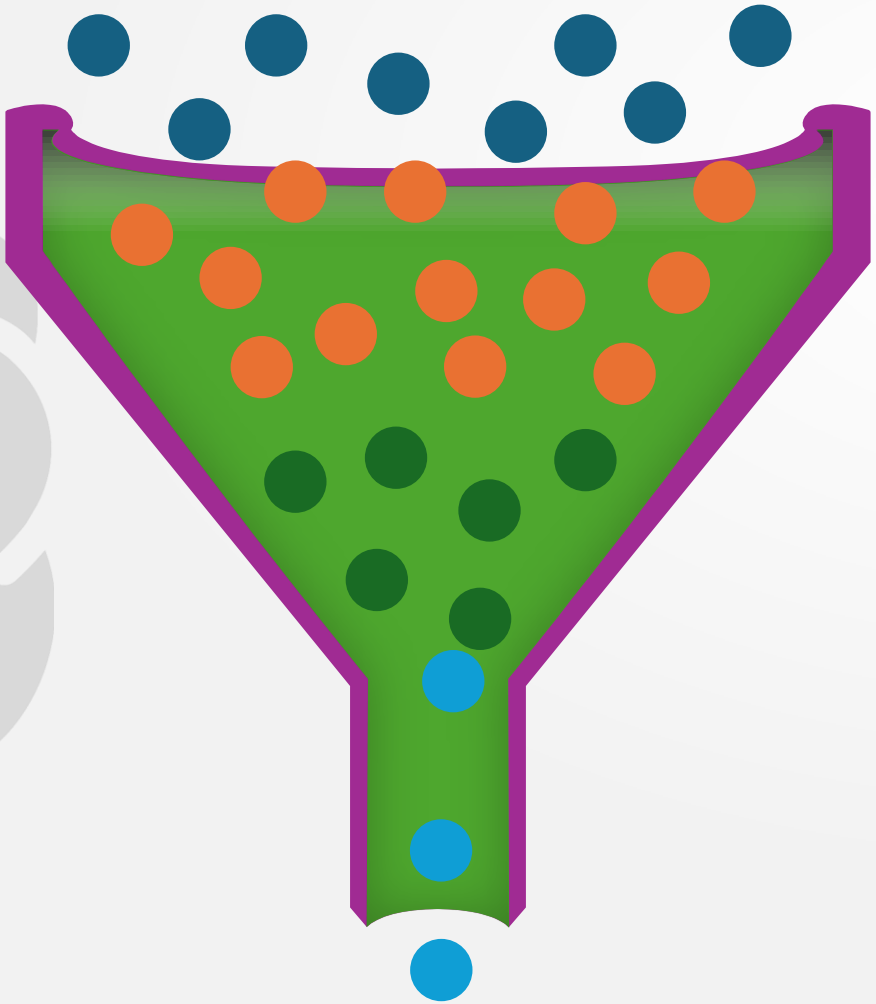
Demonstration and validation

Identifying safe and efficacious NPs, triaging on the BBB-on-Chip



Primary screen — NP libraries applied to BBB-on-Chip to test for permeability

Secondary screen — Permeable NPs tested for cargo delivery

Tertiary screen — NPs tested for safety and toxicity in dose response and time course studies

***in vivo* validation** — 5 NPs selected for downstream *in vivo* studies in mouse models

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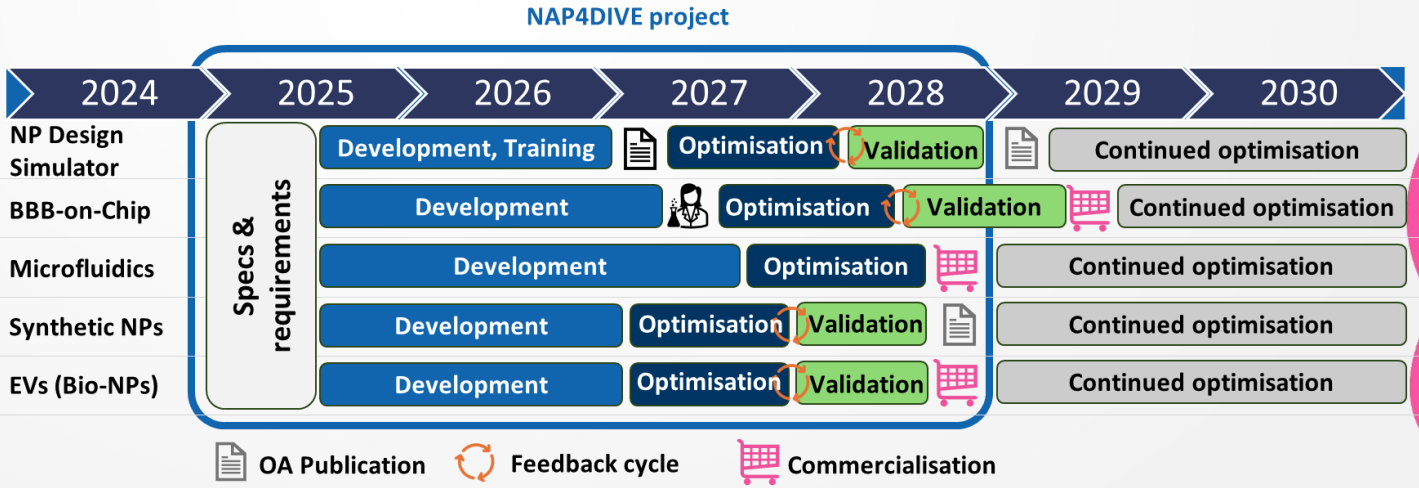
Market readiness & Health Technology Assessment

HTA Core Model domains
1. Description and technical characteristics of the technology (TEC)
2. Health problem and current use of the technology (CUR)
3. Clinical Effectiveness (EFF)
4. Safety (SAF)
5. Cost and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Patient and social aspects
9. Legal aspects



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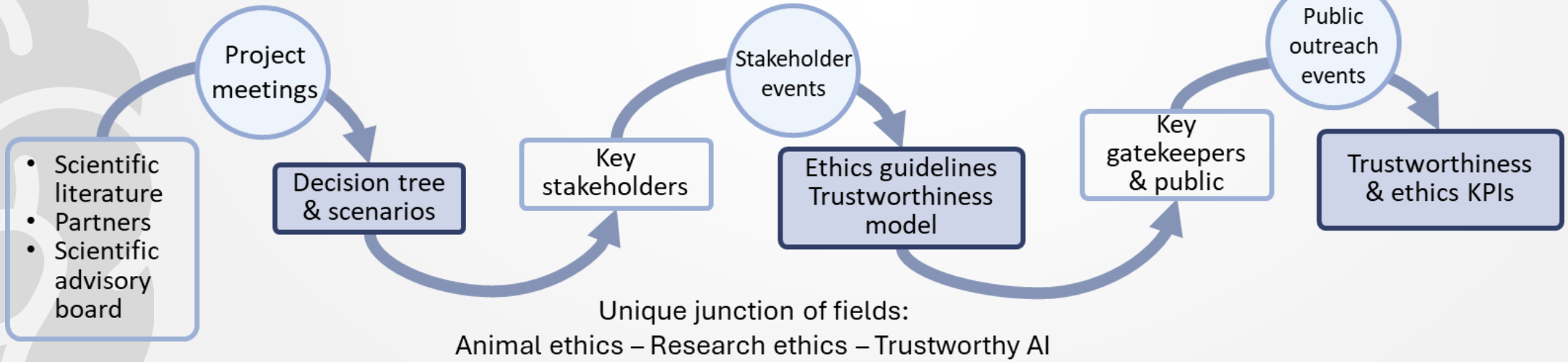
Ethics



Unique junction of fields:
Animal ethics – Research ethics – Trustworthy AI

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