COMFORTage

Prediction, monitoring and personalized recommendations for prevention and relief of dementia and frailty

Digital Twins for Personalised Treatme and Monitoring I

Working Paper

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Definitions, Acronyms and Abbreviations

Abbreviation	Description
AAL	Ambient Assisted Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AI	Artificial Intelligence
CDA	Clinical Document Architecture
CDSS	Clinical Decision Support System
CERTH	Centre for Research and Technology Hellas
CING	Cyprus Institute of Neurology and Genetics
CUT	Cyprus University of Technology
DADD	Digital Alzheimer's Disease Diagnosis
DICOM	Digital Imaging and Communications in Medicine
DT(s)	Digital Twin(s)
EEG	Electroencephalogram
EHDS	European Health Data Space
EHR(s)	Electronic Health Record(s)
ELSA	English Longitudinal Study of Ageing
EU	European Union
FHIR	Fast Healthcare Interoperability Resources
GAIA-X	European initiative for federated and secure data infrastructure
GAN(s)	Generative Adversarial Network(s)
GDPR	General Data Protection Regulation
GUI	Graphical User Interface
GXFS	GAIA-X Federation Services
HRS	Health and Retirement Study
HL7	Health Level Seven (International)
ICML	Integrated Care Model Library
IDS	International Data Spaces
IHE	Integrating the Healthcare Enterprise
IKB	Integrated Knowledge Base
IMU(s)	Inertial Measurement Unit(s)
IoT	Internet of Things
iPSC	Induced Pluripotent Stem Cell
LIME	Local Interpretable Model-agnostic Explanations
MRI	Magnetic Resonance Imaging
NLP	Natural Language Processing
PDT(s)	Patient Digital Twin(s)
PET	Positron Emission Tomography
PINN(s)	Physically Informed Neural Network(s)
RBAC	Role-Based Access Control
SDM	Sequential Decision-Making
SDX	Sovereign Data Exchange
SHAP	SHapley Additive exPlanations

SNOMED CT	Systematised Nomenclature of Medicine - Clinical Terms
SSI	Self-Sovereign Identity
TIHM	Technology Integrated Health Management (Dataset)
VHP	Virtual Healthcare Platform
VHT	Virtual Human Twin
VR	Virtual Reality
XAI	Explainable Artificial Intelligence (AI)

Executive Summary

This working paper presents the COMFORTage project's first comprehensive account of developing and deploying Patient Digital Twins to support personalised treatment and monitoring for dementia and frailty. By combining real-time clinical, sensor, genetic, and lifestyle data, the PDTs act as dynamic, individualised virtual models that enable healthcare professionals to simulate patient trajectories, anticipate risks, and deliver tailored interventions. The document details the system's layered architecture, encompassing data integration, advanced modelling and simulation, explainable AI-driven recommendations, and intuitive clinician dashboards. It illustrates the system's integration within the broader COMFORTage platform, including the Clinical Decision Support System and opt-in digital health tools. The approach is validated across thirteen European pilot sites, ensuring robustness, scalability, and practical relevance.

Beyond the technical foundation, the working paper emphasises strong ethical, legal, and regulatory compliance, alignment with emerging European standards (GAIA-X, European Health Data Space (EHDS)), and stakeholder involvement from design through deployment. The result is a transformative, user-centred digital health solution that supports proactive, personalised care for ageing populations, establishing COMFORTage as a leader in the application of digital twins for real-world healthcare improvement.

This working paper is the first version of a series of working papers entitled "Digital Twins for Personalised Treatment and Monitoring" that seek to encapsulate and describe the work conducted in the context of the task – "Digital Twins for Personalised Treatment and Monitoring".

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1 Introduction

As healthcare systems across Europe seek to tackle the growing burden and challenges of dementia and frailty in ageing populations, there is an urgent need for more proactive, personalised, and data-driven care solutions. Digital Twin technology, that is encapsulated into the introduction of virtual representations of individual patients that are dynamically informed by real-world data, offers a powerful means to simulate health trajectories, predict risks, and optimise treatment decisions. This working paper presents the COMFORTage project's first in-depth attempt of developing and operationalising Patient Digital Twins (PDTs) in that context. The core of these applications consists from the real-time integration of clinical records, sensor data, genetic information, and lifestyle inputs. To this end, these PDTs are designed to support tailored interventions while enhancing transparency, adaptability, and clinical relevance.

This document outlines the system's modular architecture, detailing each layer from secure data ingestion and multimodal fusion to advanced modelling, explainable AI-based recommendations, and user-friendly clinician interfaces. It also highlights how PDTs are embedded within the broader COMFORTage ecosystem, including integration with the Clinical Decision Support System (CDSS) and the Integrated Care Model Library (ICML), ensuring seamless interoperability and exchange of information and results across these core components of the project. The PDTs will be validated across thirteen diverse pilots to highlight their robustness, added-value and performance, as well as their alignment with standards and initiatives such as the GAIA-X and EHDS.

1.1 Structure of the document

This working paper is organised into six main sections to provide a comprehensive overview of the development, integration, and evaluation of PDTs for personalised treatment and monitoring within the COMFORTage project.

1. **Section 1** introduces the scope and objectives of the document, outlines its structure, and describes its relation to other project activities and working papers.
2. **Section 2** presents the core concepts and the current state of Patient Digital Twins, including a literature review, the relevance of DTs in dementia and frailty, and the identification of key research gaps.
3. **Section 3** details the methodology and architecture for the development of PDTs, including the use of population databases, conceptual and modular system architecture, personalised recommendations, and an overview of the COMFORTage DT platform.
4. **Section 4** describes the integration of PDTs within the broader COMFORTage ecosystem. This includes their connection with the CDSS, the ICML, Explainable AI (XAI), the Virtual Healthcare Platform (VHP), and opt-in tools. Furthermore, it discusses PDT usability across all pilot studies and addresses the ethical and legal considerations involved.
5. **Section 5** focuses on future perspectives, providing a roadmap for further development and testing, platform evolution, alignment with the GAIA-X framework, and the key performance indicators (KPIs) and evaluation methods relevant to the implementation of PDTs.
6. **Section 6** offers conclusions and discusses current limitations and challenges, summarising the main achievements and providing directions for future work.

This structure ensures a logical flow from conceptual foundations and technical implementation to integration, validation, and future outlook, providing a clear reference for both technical and non-technical stakeholders.

1.2 Relation to other activities and working papers

The development of this working paper,"Digital Twins for Personalised Treatment and Monitoring I" is closely aligned with several key working papers across the COMFORTage project. The table below, **¡Error! No se encuentra el origen de la referencia.**, highlights the related working papers and their corresponding work packages (WPs), reflecting the technical, clinical, ethical, and co-design foundations that underpin the Digital Twin system. These linkages ensure coherence with the project's reference architecture, data infrastructure and AI models, clinical decision support tools, pilot co-design, and ethical and legal compliance.

2 Patient Digital Twins (PDTs) and Scope

This section defines the concept of PDTs within the context of the COMFORTage project and outlines their intended scope and functionality. It explores key technological, methodological, and clinical advances that inform the COMFORTage project's design choices, focusing on how PDTs are being used to enable personalised treatment, monitoring, and risk prediction in healthcare. Particular attention is given to use cases relevant to ageing-related conditions such as dementia and frailty that are the main focus of the project, while also examining enabling technologies including multimodal data integration, AI-driven simulation, and real-time patient modelling. The review provides a critical foundation for defining the scope and direction of the PDTs implemented within COMFORTage.

2.1 PDTs in COMFORTage

2.1.1 Core concepts of DT in COMFORTage

DTs represent virtual models of individuals, continuously updated with real-time data from diverse sources, enabling accurate simulation, monitoring, and prediction of health trajectories. In the context of dementia and frailty, DTs hold significant potential to enhance personalised care by integrating multidimensional data—including clinical assessments, biomarkers, genetic information, sensor inputs, and lifestyle factors—into dynamic models. Within COMFORTage, DTs substantially expand the scope and add value to healthcare interventions by allowing proactive, tailored treatments, early detection of deterioration, and optimised resource allocation.

2.1.1.1 Personalised treatment in dementia and frailty

Personalised treatment is pivotal in managing dementia and frailty, conditions characterised by considerable variability in progression and response to interventions. The adoption of personalised care approaches—including biomarker-driven stratification, pharmacogenomics, AI-driven predictive modelling, and digital health tools—enables tailored interventions matching individual patient profiles.

Recent literature highlights the significant benefits of personalised care in dementia and frailty management. Biomarkers play an essential role in identifying distinct patient subgroups, aiding clinicians in targeted and timely interventions. For instance, research under the Alzheimer's Disease Neuroimaging Initiative (ADNI) demonstrated that integrating biomarkers such as amyloid-beta, tau proteins, and neuroimaging data significantly enhances the precision of disease staging and progression prediction [1]. Similarly, pharmacogenomics has increasingly informed medication selection by aligning treatment plans with genetic profiles, reducing adverse reactions, and optimising drug efficacy [2].

The use of Artificial Intelligence (AI) further augments personalised treatment through predictive modelling. Projects such as the VirtualBrainCloud under Horizon 2020 emphasise AI-driven personalised brain simulations, which enable clinicians to better understand patient-specific progression and responses to treatments, effectively guiding therapeutic decisions[1]. Furthermore, the EU-funded FrailSafe initiative leveraged wearable sensors and data analytics to deliver personalised care plans, significantly improving preventive strategies and quality of life outcomes for frail older adults[2].

DT technology substantially enhances the capacity for personalised treatment by creating dynamic, continuously updated virtual replicas of patients. COMFORTage, a Horizon Europe initiative, exemplifies the utilisation of DTs to integrate real-time data from clinical assessments, lifestyle

[1] https://virtualbraincloud-2020.eu/
[2] https://frailsafe-project.eu/

monitoring, and sensor-based technologies. This integration provides actionable, individualised insights into disease trajectory, risk factors, and optimal intervention strategies. Through such predictive and proactive capabilities, DTs enable personalised, precise, and timely interventions that significantly improve patient outcomes and enhance healthcare efficiency.

In conclusion, personalised treatment, supported by biomarker integration, pharmacogenomics, AI-driven modelling, and DT technology, presents a robust framework to substantially improve healthcare delivery for individuals with dementia and frailty. This approach aligns with European healthcare priorities and demonstrates tangible benefits in care outcomes, resource efficiency, and patient well-being.

2.1.1.2 Personalised monitoring in dementia and frailty

Personalised monitoring is essential for the effective management of dementia and frailty, conditions characterised by progressive decline and significant individual variability. Continuous, individualised monitoring enables early detection of changes in health status, facilitating timely interventions that can slow disease progression and improve quality of life.

DT technology enhances personalised monitoring by creating dynamic, virtual representations of individuals that integrate real-time data from various sources, including wearable sensors, electronic health records, and patient-reported outcomes. These virtual models allow for the simulation and prediction of health trajectories, enabling proactive and tailored healthcare strategies.

The COMFORTage project exemplifies the application of DTs in personalised monitoring. By aggregating data from 13 pilot sites across Europe, COMFORTage develops PDTs that reflect the unique health profiles of individuals with dementia and frailty. These PDTs are continuously updated with data from clinical assessments, biomarkers, and sensor technologies, providing clinicians with real-time insights into patient health and facilitating personalised care plans.

COMFORTage's Virtual AI-based Healthcare Platform (VHP) integrates various components such as the CDSS, ICML, and Explainable AI (XAI) to support healthcare professionals in making informed decisions. The platform's architecture ensures secure data handling and interoperability, aligning with the European Health Data Space (EHDS) initiatives.

Other EU-funded projects also highlight the significance of personalised monitoring. The SERENADE [3] project focuses on sensor-based, explainable detection of cognitive decline, utilising AI to analyse behavioural changes in individuals with mild cognitive impairment. Similarly, the ADMarker project employs a multi-modal federated learning system to monitor digital biomarkers of Alzheimer's disease, demonstrating the potential of advanced analytics in personalised health monitoring.

In conclusion, personalised monitoring, facilitated by DT technology and supported by EU research initiatives, offers a transformative approach to managing dementia and frailty. By enabling continuous, individualised health tracking, these technologies empower healthcare providers to deliver proactive, tailored interventions, ultimately enhancing patient outcomes and QoL.

2.1.2 Literature review

2.1.2.1 Literature review methodology

A systematic literature search was carried out to identify key publications on DT applications in dementia and frailty. Comprehensive searches were conducted across major scientific databases—including PubMed, IEEE Xplore, Scopus, and Web of Science—using targeted keywords such as “digital twin”, “virtual patient”, “Alzheimer* or dementia”, “frailty or geriatric”, and “healthcare”. The search focused on literature published from 2010 to 2024, corresponding with the growing adoption of DT in healthcare. Priority was given to peer-reviewed journal articles and conference proceedings that presented original research, frameworks, or reviews relevant to DT technology for

patient care, particularly in the context of ageing. Additional resources, such as project reports and authoritative reviews, were included when they provided valuable context or highlighted current trends and real-world applications.

The selection process involved a stepwise review of titles and abstracts to pinpoint studies that explicitly addressed DT applications in dementia (e.g., cognitive evaluation, care planning, decision support) or frailty (e.g., monitoring functional decline, predicting falls, supporting rehabilitation). For each included study, relevant details were extracted regarding the study's aims, methodologies (including simulation models, AI techniques, and clinical datasets used), and primary results. Throughout the review, duplicate and overlapping material was excluded, while care was taken to retain essential content, figures, and tables from the source documents.

2.1.2.2 DTs in health

DTs have proven effective in the manufacturing sector by enhancing predictive capabilities and enabling tailored solutions, leading to more efficient and effective resource deployment. Various DT initiatives have been underway in the industry, government, and military, but DT in healthcare is still in its early stages. Building on this success and with the growing prevalence of chronic conditions and increasing pressure on healthcare systems to deliver high-quality, cost-effective care anytime and anywhere, this approach aligns well with the principles of value-based healthcare. DTs enable easy visualisation, reasoning, experimenting, and forecasting of certain aspects of a physical world entity in a way that is both efficient and cost-effective.

These digital models are continuously updated with real-time data and can simulate various processes, predict outcomes, and support decision-making in healthcare. DTs hold thus significant promise for transforming healthcare.

Many healthcare institutions are conducting proof-of-concept studies to explore the potential benefits and feasibility of DTs in various medical applications but their development and deployment in healthcare are still in the nascent stages; significant progress has, however, been achieved in relation to personalised medicine to predict disease progression and to optimise treatment plans, medical device and equipment management to monitor and manage medical equipment, ensuring optimal performance and maintenance and surgical planning and simulation allowing surgeons to practice and refine procedures before actual operations. The main advantage of a DT is that it is more than just a digital replica of a physical system; it is designed to faithfully mirror the real-world system in real-time.

When considering the clinical domains where DTs are implemented, the following ones are today considered as the most mature:

- **Cardiovascular care:** DTs are particularly advanced in cardiovascular applications, such as simulating cardiac electrophysiology, planning interventions like valve replacements, and predicting outcomes of surgical procedures. These applications benefit from rich datasets and validated computational models.
- **Orthopedics and musculoskeletal modelling:** Significant progress has been made in using DTs to personalise orthopedic interventions, for instance, in joint replacements or spinal surgeries. These applications leverage detailed biomechanical models tailored to individual patients.
- **Cancer care (particularly breast and prostate cancer):** DTs are also relatively advanced in oncology, especially for modelling tumor growth, predicting treatment responses, and optimising radiotherapy plans.

Physical Entity	Entity	Mechanism	Endpoint
Lung	Lexma[12]	Runs simulations of blood and oxygen flow	Predict ventilation requirements
Heart	Dassault[13], Medtronic, Boston Scientific, FDA;	Simulates the structure and physiologic function of the heart	Customization and optimization of cardiac devices
Heart	Siemens Healthineers[23]	Simulates the structure and physiologic function of the heart	Cardiac resynchronization
Heart	Heart Navigator[40]	simulated TAVR implantations with different aortic prosthesis	Surgical planning
Spine	Ahmadian et al.[42]	Predict Vertebral Fracture after Stereotactic Body Radiotherapy	Optimal radiation plan to minimize treatment side effects
Alzheimer's disease	Unlearnai[14]	Predicting the individual outcome in neurological diseases	DT of controls of clinical trial and ultimately clinical interventions
Breast lesions	VICTRE trial[51]	Image based virtual patients comparing digital mammography to tomosynthesis	Determine which imaging tool is better at detecting breast lesions
Oropharyngeal cancer	Tardini et al.[61]	Optimal treatment selection	Determine optimal treatment plan for oropharyngeal cancer
Type 2 Diabetes	Cleveland Clinic Twin Health NCT05181449[58]	Disease reversal in type 2 diabetes	Randomized control trial examining twin precision treatment vs. standard of care
Mental health	MindBank AI[65], IBM[66], Babylon[67], DigiTwin[68]		Wellness
Pharma Lab	Atos, Siemens, GSK[23,36]		Optimize drug manufacturing
Biomanufacturing	Teva and AG Pharmaceuticals[37]	Adjust input conditions Key and Critical Process Parameters	Predictive biomanufacturing
Drug Discovery	Takeda[34]		Drug Discovery
Hospitals	GE Care command[24]; Siemens Healthineers[23]		Earlier response times for critical patients, supply chain management, workflow

Figure 1: Major companies utilising DTs [4]

As one can notice from Figure 1 listing major companies which make use of the technology, DTs still remain currently associated with a specific physical entity or process and are not yet capable of representing entities with complex interactions, such as the human being in its full complexity and integrity. There are DT types of one body system, or body organ (i.e., lung or heart), or body function, or finer body component levels (cellular, subcellular), or of the entire human body. Similarly, DTs can be created for a specific disease or disorder. Composite DTs may integrate two or more of the different types of DTs. Continued research, technological advancements, and collaborative efforts are essential to fully realise their potential.

The key challenges related to the use of DTs are related to data. The integration of physiological, biological, and chemical models into DT simulations that capture the underlying pathways and disease processes will enable a much higher degree of customisation and adaptability but the lack of (use of) standards, the lack of alignment between standards, the privacy constraints restricting access to high quality longitudinal data, the data biases and a number of ethical issues have an important impact on the wide acceptance of the technology. As the number of individuals living with dementia continues to rise sharply, innovative solutions like DTs are vital to addressing this urgent challenge.

Dementia diagnosis and management are currently suboptimal due to short patient-provider interactions, multi-symptom presentation, co-morbidities, and barriers such as illiteracy and sensory loss. There's a need for more accurate, early, and individualised intervention strategies.

Utilising Virtual Human Twins (VHTs) to simulate the progression of Alzheimer's disease in patients offers several key benefits:

- Reduced healthcare costs thanks to early detection
- Improved quality of life: Early, personalised care to delay the progression of the disease, relieving the emotional and financial burden on carers
- Maintaining economic productivity: Reducing care-related absenteeism

- Contribution to medical research: Collection of data for the development of new treatments and therapies

Although DT models of the human brain are not yet possible, it is hoped that future DT technology will greatly improve the current practice of clinical psychopharmacology.

2.1.3 DTs in dementia

DTs are typically defined as integrated, continuously updated virtual replicas of physical entities that merge live data feeds with statistical models to inform evidence-based decision-making [5][6], [7][4],[8].

In the context of health, DTs are dynamic, evolving models of individuals, organs, or biological systems. These systems synthesise multimodal datasets including electronic health records (EHRs), environmental data, behavioural metrics, and continuous streams from wearable devices and biosensors to simulate internal physiological processes, monitor health status, and forecast clinical trajectories [6]. In contrast to traditional digital health tools such as dashboards or isolated record systems, DTs enable real-time adaptation by learning from incoming data and refining their models through big data and machine learning techniques [9][10].

DT systems in healthcare typically involve the acquisition of high-frequency, multimodal data from clinical record systems, wearables, imaging modalities, and real-time modelling and simulation of individualised virtual representations. The application of machine learning for pattern detection, forecasting, and intervention planning, and feedback loops continuously refine the virtual models in response to new data inputs [11]. DTs have demonstrated broad applicability potential across medical specialties, including cardiology, oncology, orthopedics, and perioperative medicine [5], [6]. Their capacity to integrate heterogeneous data sources and simulate patient-specific clinical pathways positions DTs as particularly valuable tools in the new paradigms of dementia management, where personalised and adaptive care is essential [12].

Tailoring DT applications to dementia care

Dementia, clinically classified as a major neurocognitive disorder in current diagnostic systems, is a syndrome characterised by a significant decline in one or more cognitive domains that interferes with independence in everyday functioning. Dementias severely threaten the well-being of older people, their families, and communities. Current limitations in prevention, diagnosis and treatment of dementia have prompted growing interest in data-driven and patient-centred approaches, including the application of DT technologies [5], [10], [12].

DT technologies hold unprecedented potential to transform dementia care by addressing critical limitations of conventional models through highly personalised, adaptive, predictive, context-aware, and continuously learning systems. By generating dynamic, data-rich representations of a patient's evolving cognitive and physiological status, DTs offer a paradigm shift from reactive care to proactive, fine-tuned, and anticipatory intervention strategies [4], [13].

DTs can simulate individualised dementia trajectories by integrating multimodal inputs from electronic health records, wearable and ambient sensors, behavioural data, neuroimaging, and contextual information. These models enable fine-grained risk stratification, support early and differential diagnosis, and provide longitudinal tracking of cognitive decline and functional deterioration. Their ability to reflect the heterogeneity of disease progression and accommodate comorbidities, lifestyle factors, and social determinants situates them at the forefront of precision medicine for neurodegenerative conditions [14], [15], [16], [17].

In clinical settings, DT frameworks enable the simulation of expected responses to pharmacological and behavioural interventions, allowing care teams to preemptively assess benefit-risk ratios and

personalise therapeutic approaches. Through real-time integration of multimodal data, DTs detect clinically relevant deviations from baseline functioning and support adaptive decision-making across diverse care contexts. This includes optimising medication regimens, tailoring behavioural strategies, and configuring assistive technologies, with embedded feedback mechanisms that continuously update recommendations to align with the patient's dynamic status [11], [18].

Table 2 shows a representative spectrum of digital-twin applications in dementia research and care. All projects aim to exchange episodic, retrospective management for continuous, data-driven support tailored to individual trajectories. Reported outcomes include improved diagnostic discrimination, more precise prognoses, better-targeted caregiver guidance, and streamlined trial designs, suggesting that digital-twin approaches are steadily gaining practical relevance across the dementia continuum [4], [11], [14].

The emerging evidence base points to two strategic priorities. First, the field must channel its methodological diversity into modular and interoperable architectures able to accommodate heterogeneous data sources without sacrificing reproducibility or scalability. Second, wide adoption will depend on rigorous external validation, transparent benchmarking and governance that anticipates privacy, bias and equity concerns. Addressing these priorities is essential if DTs are to mature from promising prototypes into dependable instruments of precision dementia care.

Table 1: DTs use cases in dementia

DT implementation	Purpose in dementia	Source
CloudDTH: cloud-based digital-twin healthcare framework integrating wearable devices.	Continuous monitoring, diagnosis and prediction of health status for personalised management of older adults.	Liu et al., 2019 [16]
Synthetic-control patient "DTs" to replace placebo arms in clinical trials (UnlearnAI platform).	Accelerates enrolment and resolves ethical issues by simulating disease progression in Alzheimer's Disease and producing a virtual control group.	Armeni et al., 2022 [14]
DT-based Cognitive Building framework for Ambient Assisted Living (AAL).	Real-time scenario awareness and anomaly detection to support independent living and proactive assistance for older adults with cognitive impairment.	Binni et al., 2022 [19]
Algorithm for discovering DTs via phase-matching of MMSE decline trajectories.	Identifies closest historical progression patterns to support personalised prognosis and care decisions.	Wickramasinghe et al., 2022 [12]
Communication-robot + ambient-sensor + wearable digital-twin system for daily behavior monitoring.	Detects early dementia signs by analysing life-function and cognitive-function behavior changes without interviews.	Kobayashi et al., 2021
Smartwatch-based digital-twin agent (avatar) plus in-home sensors for	Monitors daily activities and social engagement; provides mental-health support and early anomaly detection for cognitively frail older adults.	Kobyashi et al., 2022

constructing an elderly "digital twin".		
AI rehabilitation robot integrating visual cognition and motion control via a digital-twin framework.	Personalised cognitive-motor rehabilitation and progress monitoring.	Tao et al., 2024
Metaverse-based anti-ageing healthcare platform integrating AI, blockchain, IoT devices and digital-twin avatars.	Personalised monitoring and interventions to delay cognitive decline and dementia onset.	Mozumder et al., 2024 [20]
Digital-twin–enabled community elderly-care service system with five-layer architecture.	Optimise resource allocation, real-time monitoring and personalised services to support older adults with cognitive decline.	Ye, 2024
DT Immersive Design Process (DT-IDP) combining digital-twin modelling with VR immersion.	Captures real-time user feedback to optimise age-friendly healthcare spaces and reduce stress for dementia patients.	Kemkomnerd & Tirapas, 2024 [21]
Deep-learning NLP digital twin built from clinical notes and multimodal patient data.	Tracks cognitive decline, predicts relapses, and personalises dementia care.	Mikołajewska & Masiak, 2025
Digital Alzheimer's Disease Diagnosis (DADD) digital-twin model built from non-invasive EEG recordings.	Generates personalised biomarkers that predict CSF Alzheimer's pathology and conversion from subjective cognitive decline to clinical impairment.	Amato et al., 2025 [8]
Precision-medicine multiscale digital-twin framework that integrates multi-omics and clinical data.	Simulates disease mechanisms to uncover drug targets, guide repurposing and de-risk Alzheimer's clinical trials.	Ren et al., 2025 [17]
Organoid-based patient-specific digital twin integrating iPSC-derived 3D brain organoids, organ-on-a-chip interfaces and AI analytics.	Real-time modelling of Alzheimer's pathology and personalised drug response to guide precision therapies.	Dolciotti et al., 2025 [9]

2.1.3.1 Strategic priorities for DT deployment

DTs represent a promising paradigm shift in dementia care, enabling proactive, personalised, and data-informed interventions. Longitudinal research and cross-sector partnerships are vital to ensure scalable and equitable implementation [22]. With sustained efforts, DTs could fundamentally improve how we understand, monitor, and support individuals living with dementia.

Turning this promise into routine practice demands a concerted focus on interoperable data standards, transparent benchmarking, and rigorous external validation across heterogeneous populations and care settings. Harmonising multimodal inputs—from non-invasive EEG and

multimorbidity profiles to organoid-based phenotypes—will be essential for mitigating the methodological variability now evident in the literature and for distilling generalizable clinical heuristics [4], [17]. Parallel development of ethical, regulatory, and explainability frameworks that address privacy, bias, and accountability concerns [23] are equally critical to foster stakeholder trust and facilitate regulatory approval. Embedding these priorities within adaptive learning health-system infrastructures will enable DTs to evolve from fragmented proofs of concept into reliable, cost-effective pillars of precision dementia care.

2.1.4 DTs in frailty

Frailty is a complex, dynamic, and multidimensional condition characterised by reduced physiological reserves, increased vulnerability to stressors, and higher susceptibility to adverse outcomes such as falls, hospitalisation, disability, and mortality [24], [25], [26], [27], [28], [29], [30]. Once narrowly associated with physical deterioration, frailty is now widely recognised as a multidimensional condition encompassing interrelated biological, cognitive, nutritional, psychological, and social components that evolve dynamically over time [31], [32], [33].

DT technology offers a promising framework to address these complexities. DTs are real-time, adaptive virtual representations of individual health profiles, integrating data from EHRs, wearables, environmental sensors, and patient-reported outcomes [6], [11], [34]. By simulating patient-specific dynamics, DTs support predictive analytics, early detection, and evidence-based interventions [4], [5]. Their modular, scalable architecture facilitates integration into clinical workflows and health information systems.

DTs in geriatric health settings

DTs provide a dynamic, integrative approach to frailty modelling. By aggregating diverse inputs such as gait speed, nutritional indices, sensor data, and polypharmacy profiles, DTs simulate physiological resilience and predict frailty progression in real time [6], [31]. This supports early intervention, personalised care planning, and the safe testing of treatment scenarios.

DTs are especially useful for tracking transitions from robustness to pre-frailty and frailty. In frailty-friendly systems, DTs support predictive alerts and adaptive monitoring. Their integration with AI platforms enables automated triage, real-time stratification, and caregiver coordination [35]. They also simulate contextual and psychosocial influences such as health literacy (Kim et al., 2024), caregiver stress [36], or environmental strain, further individualising care.

In clinical environments, DTs facilitate the dynamic representation of an older adult's frailty trajectory, enabling continuous assessment rather than episodic evaluations. By integrating multimodal biomarkers such as heart rate variability, inflammatory profiles, and mobility fluctuations, DTs provide clinicians with real-time dashboards that enhance situational awareness and risk prediction. These tools support shared decision-making by aligning predictive outputs with patient-centred goals, particularly in complex cases involving multimorbidity or polypharmacy. As the ageing population grows more heterogeneous, DTs offer scalable personalisation across diverse care settings, from home-based monitoring to acute care wards.

2.1.4.1 Personalised use cases in frailty care

Emerging applications of DTs in frailty care illustrate their versatility across a spectrum of clinical and preventive functions. These implementations leverage real-time data to detect early signs of vulnerability, personalise interventions, and support longitudinal care strategies tailored to diverse ageing populations. By simulating physiological, behavioural, and environmental variables, DTs provide actionable insights into multiple frailty domains, ranging from nutritional decline and cognitive deterioration to social isolation and polypharmacy risks. Table 3 presents representative

use cases of DT integration in frailty care, showcasing their clinical objectives, methodological focus, and associated evidence.

Table 2: DTs use cases in frailty care

DT implementation	Purpose in frailty care	Source
Gait speed monitoring with sensor integration	Early fall risk prediction and balance deterioration	Chehrehgosha et al., 2021 [34]
Nutritional tracking via metabolic biomarkers and wearables	Detection of sarcopenia and malnutrition	Veninšek & Gabrovec, 2018; Li et al., 2023 [24]
Simulation of cognitive-motor decline using multimodal data	Prediction of dementia onset and hospitalisation risk	Song et al., 2024; Mello et al., 2021 [37]
Drug interaction modelling in polypharmacy contexts	Optimisation of deprescription strategies	Pullen et al., 2023; Lyu et al., 2021 [26]
Oral health status and social engagement simulation	Identification of oral frailty and isolation	Zhu et al., 2024; [38] Doi et al., 2023 [39]
Remote monitoring in post-ICU COVID-19 recovery	Functional status restoration post critical care	Seixas et al., 2023
DT-enabled AI platforms for care coordination	Integrated intervention planning in community settings	Kouroubali et al., 2022 [35]
Multimorbidity profiling through hemoglobin and comorbidity data	Risk stratification for functional disability	Liu et al., 2021 [30]
Health literacy-based decision frameworks	Improved health-related quality of life via tailored education	Kim et al., 2024 [28]
Simulation of frailty trajectories in emergency settings	Frailty-informed acute care triage	Mooijaart et al., 2022 [29]
Real-time wearable integration for chronic monitoring	Adaptive risk modelling and personalised alerts	Johnson et al., 2024 [11]

2.1.4.2 Future directions and challenges for DTs in frailty care

DTs represent one of the most promising innovations to transform frailty care in older adults. By integrating clinical, behavioural, social, and environmental data into dynamic virtual representations, DTs enable real-time simulation and prediction of individual health trajectories, allowing for truly personalised, proactive, and person-centred care.

Their potential to anticipate risks, tailor interventions, and provide personalised clinical recommendations opens the door to a new paradigm in geriatrics—one in which ageing is supported by empathetic and intelligent technology, and clinical decisions are informed by integrated and contextualised data.

To ensure that DTs evolve from proof-of-concept to robust tools in geriatric care, future research should focus on longitudinal validation, cost-effectiveness analyses, and real-world implementation. In doing so, DT can become a cornerstone in the shift toward smarter, more preventive, and more human-centred care for older adults.

2.1.5 DT methodologies

Various global and EU projects have advanced DT methodologies in dementia and frailty care, integrating real-time data, AI-driven analytics, and decision support to personalise treatments and monitoring.

Key Examples:

- **NeuroTwin**: Uses individualised brain models integrating neuroimaging (MRI, EEG) with biophysical simulations and AI to optimise personalised neuromodulation therapies for Alzheimer's disease.
- **VirtualBrainCloud**: A cloud-based platform creating personalised brain simulations from multi-modal data (clinical, neuroimaging, multi-omics). Utilises high-performance computing and AI to forecast disease progression, enabling personalised diagnostics and risk reduction strategies.
- **NTT Bio-DT**: Incorporates extensive biomedical data (PET scans, genetic, biomarkers) into predictive AI models to personalise dementia diagnosis and treatment, enabling early intervention and virtual drug testing.
- **Unlearn.AI DTs**: AI-generated virtual patient profiles for clinical trials, simulating individualised disease trajectories to reduce reliance on placebo groups, enhancing prognostic insights.
- **FrailSafe**: Employs wearable and IoT sensors to continuously monitor frailty indicators (mobility, physiological data), using big data analytics to predict frailty progression and deliver personalised intervention recommendations.
- **My-AHA**: Integrated middleware platform aggregating multi-domain health data (physical, cognitive, social), processed through an AI-driven Decision Support System to provide personalised frailty risk assessments and tailored preventive interventions.
- **e-VITA**: Virtual coaching system utilising ambient sensors and comprehensive user profiles to offer personalised daily guidance and preventive recommendations, laying foundations for future full-fledged DTs.

Drawing from these projects, the DT methodology that is proposed by also from the Literature Review of the previous sections, should include:

1. **Data integration layer**: Secure aggregation of multimodal patient data—clinical, genetic, biomarker, sensor-derived, and lifestyle information.

2. **Knowledge base layer**: Structuring integrated data into standardised knowledge graphs supporting personalised patient profiling and continuous data fusion.
3. **AI and simulation layer**: Combining predictive machine learning models with physiological simulations to forecast dementia progression, frailty trajectories, and personalised treatment responses.
4. **Decision support and user interface layer**: Presenting actionable insights and tailored interventions through intuitive digital dashboards for healthcare providers, carers, and patients, enabling proactive, personalised healthcare.

This methodology aligns COMFORTage's objectives with best practices, ensuring predictive, preventive, and personalised care for individuals experiencing dementia and frailty.

2.1.6 Research gaps and objectives

From the previous sections, another key point that could be extracted is the research gaps that all methodologies and studies have imposed and how COMFORTage can be in the state-of-the-art frontier by tackling these gaps through addressing them as objectives.

Table 3: Communication and dissemination team of each WP8 partner/Style 1

Research gap	How to tackle	COMFORTage alignment
Lack of standardised multimodal data integration	Establish comprehensive data ingestion platforms with standardised data formats, ensuring seamless integration of diverse health data streams (biomarkers, sensor data, EHRs, genetic profiles).	Highly aligned, as COMFORTage emphasises integrating multidimensional, multimodal data for personalised dementia and frailty management.
Limited scalability and reproducibility	Develop modular and interoperable architectures that facilitate scalability and ensure the reproducibility of digital twin implementations across diverse populations and care settings.	Strongly aligned; COMFORTage aims to deploy scalable DTs across 13 European pilot sites, requiring standardised and replicable solutions.
Insufficient longitudinal validation	Conduct rigorous long-term validation studies to ensure reliability and effectiveness of DTs in predicting disease progression and treatment outcomes.	Highly aligned; COMFORTage intends continuous updates and validations based on longitudinal patient data to refine predictive accuracy.
Inadequate integration of predictive AI and mechanistic modelling	Integrate hybrid modelling approaches combining AI-driven predictive analytics with mechanistic, knowledge-based simulation models for accurate and explainable insights.	Directly aligned; COMFORTage specifically advocates for combining AI predictions with physiological and mechanistic simulations.
Limited personalised decision support capabilities	Enhance DTs with sophisticated, AI-driven decision support tools providing personalised recommendations for proactive healthcare interventions.	Precisely aligned; COMFORTage explicitly supports personalised interventions through its integrated CDSS.

Privacy and ethical concerns regarding data handling	Establish transparent governance frameworks, data privacy protocols (GDPR compliance), and ethical standards for data usage and patient privacy protection.	Aligned; COMFORTage prioritises secure data handling and compliance with European Health Data Space (EHDS) standards, ensuring privacy and ethical data use.
Absence of user-friendly interfaces for patients and clinicians	Develop intuitive dashboards and interactive digital twin interfaces facilitating ease of use, real-time monitoring, and actionable insights for both clinicians and patients.	Strongly aligned; COMFORTage incorporates user-facing interfaces to translate digital twin insights into actionable, easily interpretable guidance for care teams and patients.

3 PDT Development and Architecture

This section details the development process and architectural design of the PDT system within the COMFORTage project. Building on the insights from the state-of-the-art analysis implemented in the previous section, it outlines the core components, data flows, and technical infrastructure required to implement a dynamic and scalable PDT framework. The architecture integrates multimodal data sources, including clinical records, sensor data, lifestyle inputs, and genomics, with advanced modelling techniques and explainable AI modules. Emphasis is also placed on modularity, interoperability, and alignment with European data and interoperability standards, ensuring the system can be deployed and adapted across diverse healthcare settings.

3.1 Concept and methodology

The PDT that will be developed within the COMFORTage project represents an advanced, data-driven approach to the personalisation and optimisation of dementia and frailty care in ageing populations. Central to this concept is the aggregation and harmonisation of a large-scale, heterogeneous dataset, derived from thirteen distinct pilot studies across Europe, in conjunction with open-access datasets, established research cohorts, and biobanks. This comprehensive repository enables the creation of DTs—virtual, evolving representations of individual health status—capable of simulating disease trajectories, risk profiles, and personalised intervention scenarios.

The scientific foundation of this approach rests on the integration of diverse, multi-modal data streams. Each pilot study within COMFORTage addresses specific aspects of the dementia and frailty continuum, ranging from community-based multi-modal prevention and omics-enabled health assessments to advanced biomarker and imaging studies, frailty and sarcopenia detection, and longitudinal digital phenotyping through mHealth technologies. Data collected encompasses clinical and neuropsychological assessments, biomarker and genetic profiles, neuroimaging, physiological signals, behavioural and lifestyle metrics, and digital outcomes produced by innovative assessment tools.

Harmonisation protocols are systematically employed to ensure data quality, semantic interoperability, and compliance with regulatory standards such as GDPR. Standardisation of variables, ontological mapping, and robust pseudonymisation strategies underpin the ethical integration and exchange of data across pilot sites and secondary sources, preserving both the richness of the data and the privacy of participants.

Building on this harmonised foundation, digital twin models are constructed for each participant using state-of-the-art machine learning, simulation, and statistical inference methodologies. These individualised models are inherently dynamic, assimilating new information as it becomes available from ongoing pilot activities, wearables, clinical follow-ups, and user-engaged digital tools. This continuous updating enables real-time monitoring of cognitive, physical, and psychosocial domains and facilitates the early detection of deviations from normative trajectories.

A core methodological feature of the digital twin framework is its capacity for individualised scenario simulation. By leveraging predictive analytics and causal inference techniques, the system can forecast the impact of various interventions or lifestyle modifications on future health outcomes. This allows for the exploration of scenarios at both the individual and subgroup level, enabling clinicians and participants to jointly consider the risks and benefits of potential prevention or treatment strategies.

The translation of model insights into actionable, context-aware recommendations is achieved through integration with a CDSS. The CDSS acts as a bridge between the data-driven models and

clinical practice, operationalising recommendations in the form of care plans tailored to the unique needs, preferences, and objectives of each individual, while also considering the specific infrastructure and resources available at each pilot site.

A distinguishing aspect of the COMFORTage methodology is the incorporation of an ecosystem of opt-in digital tools. These tools, provided by consortium partners, enable the assessment of cognitive, linguistic, physical, nutritional, and psychosocial domains through engaging and validated digital formats. Examples include digital cognitive training platforms, linguistic games for neuropsychological assessment, virtual supermarkets for functional evaluation, mHealth applications for activity and nutrition tracking, and platforms targeting social connectivity and loneliness. Participation in these tools is strictly voluntary and governed by transparent consent processes, ensuring respect for autonomy and user empowerment.

Continuous stakeholder engagement is embedded throughout the methodological workflow. Older adults, carers, clinicians, and social scientists participate in the co-design, implementation, and evaluation of the digital twin system and its components. Feedback loops enable iterative refinement of both the underlying models and the user-facing interfaces, enhancing usability, trust, and real-world impact.

By uniting large-scale, multi-modal data integration, individualised simulation, predictive analytics, and co-created digital assessment tools, the COMFORTage digital twin methodology represents a significant advance in the scientific landscape of dementia and frailty prevention and care. This integrated framework not only facilitates early identification and mitigation of risk but also enables adaptive, person-centred intervention strategies that are robust, explainable, and scalable across the heterogeneity of European healthcare systems.

3.2 Population databases

Developing a population-level DT for dementia and frailty necessitates access to comprehensive, high-quality datasets that capture the multifaceted aspects of ageing. Open datasets play a pivotal role in this endeavour, offering rich, diverse, and longitudinal data essential for modelling individual health trajectories. These datasets encompass various domains, including clinical assessments, cognitive evaluations, genetic information, lifestyle factors, and sensor-derived measurements. By integrating such data, researchers can construct dynamic and personalised DTs that simulate disease progression, predict health outcomes, and inform tailored interventions.

Table 4: Datasets for dementia and frailty DT

Dataset Name	Description	Access Information
Alzheimer's Disease Neuroimaging Initiative (ADNI)	A longitudinal study collecting clinical, imaging (MRI, PET), genetic, and biospecimen data from individuals with Alzheimer's disease, mild cognitive impairment, and healthy controls.	ADNI Website
Health and Retirement Study (HRS)	A biennial longitudinal survey of Americans over age 50, covering health conditions, cognitive status, and socioeconomic factors.	HRS Website
Cambridge Centre for Ageing and	A large-scale, cross-sectional dataset covering the adult lifespan (ages 18–88), including MRI (structural,	CamCAN Website

Neuroscience (CamCAN)	functional, diffusion), MEG, and extensive behavioural and cognitive data. Designed to investigate healthy cognitive aging.	
English Longitudinal Study of Ageing (ELSA)	A study of adults aged 50 and over in England, collecting data on health, cognitive function, and social participation.	ELSA Website
Study on Global Ageing and Adult Health (SAGE)	A WHO-led study collecting data on adults aged 50+ from six countries, focusing on health and well-being.	SAGE Website
UK Biobank	A large-scale biomedical database containing genetic, lifestyle, and health information from 500,000 UK participants.	UK Biobank Website
GSTRIDE Dataset	Contains health assessments, functional and frailty variables, and gait metrics from elderly adults, using inertial measurement units (IMUs).	GSTRIDE Dataset
TIHM Dataset	Provides multi-sensor data (audio, video, wearable sensors) for monitoring individuals with dementia in real-life settings.	TIHM Dataset
Dem@Care Dataset	Offers multi-sensor data for monitoring individuals with dementia, including audio, video, and wearable sensor data.	Dem@Care Dataset

In summary, leveraging widely used and known datasets (open or after receiving appropriate license) is instrumental in advancing the development of DTs for dementia and frailty. The integration of diverse data sources enables a more accurate and individualised representation of health states, facilitating early detection, personalised care planning, and improved patient outcomes. As the field progresses, the continued availability and utilisation of open datasets will be crucial in refining DT models and enhancing their applicability in pilot clinical settings.

3.3 Conceptual architecture

In a layered view, the DT system is organised into functional layers that handle data flow from collection to insight. This separation of concerns aligns with current digital health frameworks, where layers manage complexity by consolidating distinct functionalities [40]. Below we describe each layer relevant to prototyping a DT for an elderly individual with dementia/frailty and the conceptual architecture is presented in Figure 2.

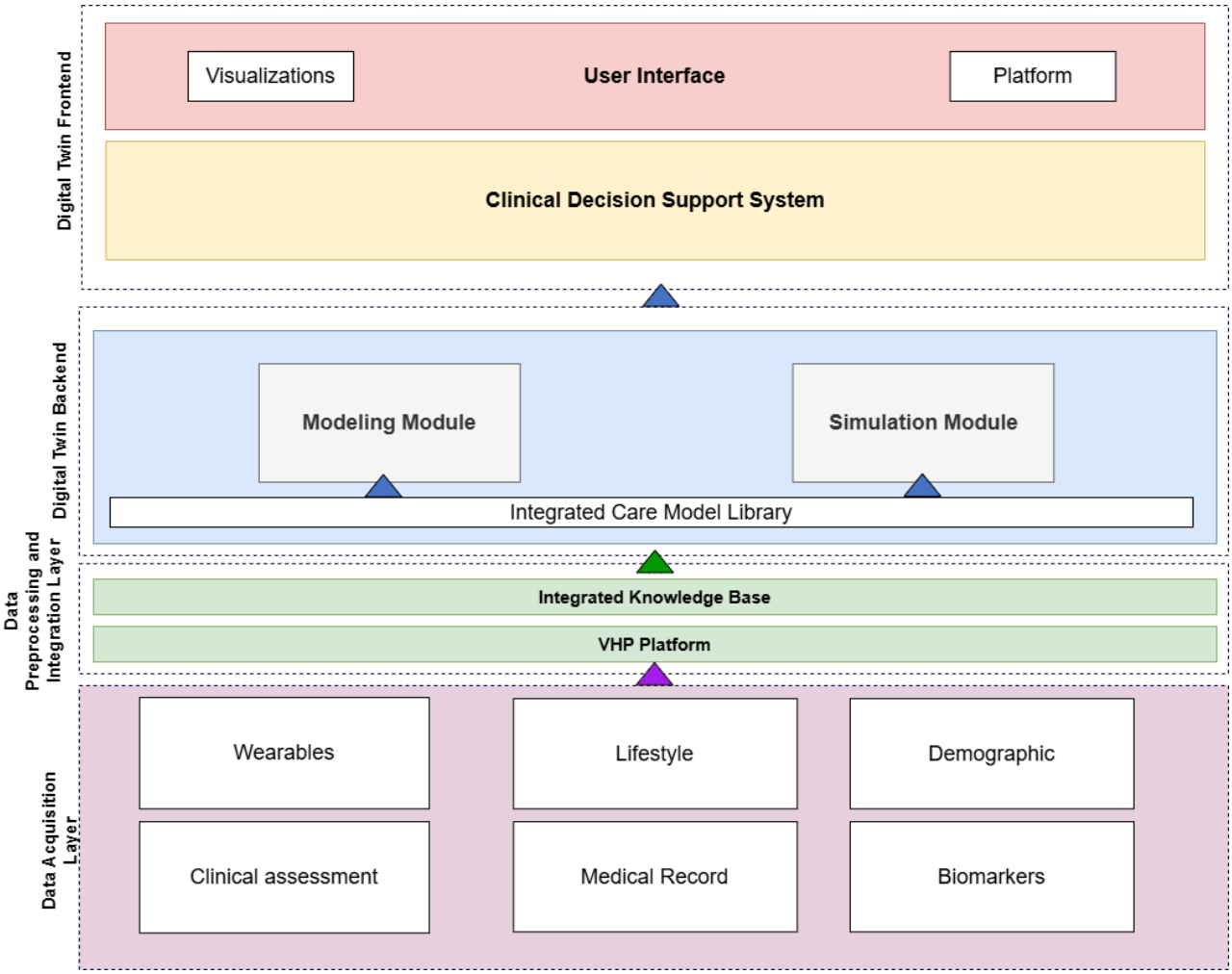

Figure 2: PDT conceptual architecture

3.3.1 Data acquisition, preprocessing and integration layer

This bottom layer interfaces with the physical world, collecting raw data from the patient's daily life. It includes wearables, clinical assessment records, lifestyle data, medical records, demographic data, and biomarkers. The PDT will be integrated in the VHP Platform of the COMFORTage project, and the data will be collected directly from the integrated knowledge base, and the preprocessed data will be forwarded to the main Backend component of PDT. (For more information about the data ingestion, the VHP Platform and Integrated Knowledge Base, please refer to D3.1, D2.8, and D3.5). Finally, all datasets from 3.2 will be integrated to populate the database with already extracted knowledge to enhance the data correlation.

3.3.2 Modelling layer

In the modelling layer of a dementia and frailty DT, state-of-the-art data-driven models simulate disease progression, functional decline, and cognitive deterioration based on large-scale population data. Machine learning (ML) and statistical methods are employed to capture the complex trajectories of cognitive decline in dementia and the multifactorial nature of frailty. These population-level models are built from rich cohort datasets (section 3.2) and all the 13 Pilots of the project, learning how features like biomarkers, cognitive scores, gait speed, and comorbidities evolve over time. More specifically, the initial literature review demonstrated four different algorithms or ML models that are able to capture the variations of the data and provide a risk factor analysis for dementia and frailty.

1. **Physically Informed Neural Networks (PINNs):** PINNs integrate physical laws (e.g., differential equations describing disease mechanisms or physiological decline) into neural network training, enabling robust simulation of disease progression even with sparse or noisy data.
2. **Generative Adversarial Networks (GANs):** GANs are deep learning models that generate realistic synthetic patient data by pitting a generator against a discriminator, allowing the modelling of complex distributions and the creation of DTs that mirror real patient trajectories.
3. **Markov chains:** Markov chain models capture the probabilistic transitions between discrete health states (e.g., healthy, pre-frail, frail, demented), providing interpretable and mathematically grounded tools for forecasting disease trajectories over time.
4. **What-if scenarios:** What-if scenario modelling leverages the digital twin to simulate the potential impact of hypothetical interventions (e.g., exercise programs, medication adjustments) on future health outcomes, supporting personalised decision-making.

These models were initially designed to serve the purpose and objectives for which they were intended. Due to the population databases collection and the ongoing research for this core-component the AI analysis and the performance metrics will be stated under the final form " Digital Twins for Personalised Treatment and Monitoring II" in M36.

3.3.3 Simulation layer

On top of the static model, the simulation layer enables dynamic what-if experimentation. Here, the DT's models are executed forward in time or under hypothetical scenarios to project disease progression, functional decline, or recovery trajectories. Using the personalised model as a starting point, this layer can run simulations of neurodegenerative progression (e.g. cognitive decline over the next year) or frailty progression (e.g. muscle strength loss under certain conditions). It can also test interventions in silico: for example, adjusting a medication, introducing a balance training ageing, or other therapy, and then simulating the outcome on the patient's cognitive and physical health. This capability mirrors current research platforms where digital patient models are used to predict future states and evaluate interventions. In the VirtualBrainCloud neuro-twin, for instance, researchers could simulate the effect of deep brain stimulation on a virtual patient's brain network to predict the treatment's outcome before trying it in real life. By iterating simulations, clinicians and researchers can explore scenarios in a risk-free environment, which is invaluable for personalised planning in dementia care and frailty prevention.

3.3.4 Analytics and decision support layer

Building on simulation outputs and the up-to-date model, the analytics layer provides interpretation and decision support. It employs AI and statistical tools to derive insights such as risk assessments, anomaly detection, and outcome predictions. For an elderly patient, this layer might compute a frailty risk score or predict the probability of rapid cognitive decline, falls, or hospitalisation based on the twin's state. By comparing the patient's trajectory against known disease progression patterns (built into the DT's knowledge base), the system can flag concerning changes or emerging risks that merit attention. For example, if the DT detects a faster-than-expected drop in cognitive performance (given baseline and model expectations), it could alert clinicians to possible upcoming clinical deterioration. Similarly, leveraging machine-learning on simulation data can uncover hidden patterns or disease mechanisms and improve prognostic accuracy. The goal of this layer is to transform raw simulations into actionable information – e.g., identifying early warning signs, providing personalised decision support for interventions, and optimising care plans. Notably, a recent study showed that incorporating digital twin simulation data improved classification of patients across different neurodegeneration stages exemplifying the analytic power of such systems [41].

3.3.5 Visualisation and interaction layer

At the top, the DT system presents information to end-users (researchers, clinicians, or patients) through visualisation and interaction tools. This layer includes dashboards, visual analytics, or even VR environments that allow users to inspect the twin's status and explore scenarios. For a research prototype, a web-based dashboard might display the patient's vital trends, cognitive assessments, and simulation-predicted outcomes in intuitive charts. An example in practice is an older patient's diabetes DT platform that provides real-time web interfaces for patients and doctors to view health data trends and predictions. Similarly, a dementia/frailty twin could visualise the patient's current frailty index, forecasted functional decline curves, or the expected impact of a proposed therapy, thereby aiding understanding. This layer ensures the complex "internals" of the DT are accessible and interpretable, closing the loop from data to user [42]. It also enables feedback: clinicians might modify parameters (e.g. simulate a different intervention) via the interface, which feeds back to the simulation layer. In summary, the visualisation layer turns the DT's rich data and analytics into a usable decision-support tool for humans.

From a modular perspective, the same system can be described as a set of core components or engines, each responsible for specific functionalities, and all interacting to realise the DT's capabilities. The key modules for a dementia/frailty DT prototype might include the following:

- **User modelling module:** This module maintains the digital profile of the elderly individual. It aggregates all personal data (medical history, sensor data, assessments) and encodes the patient's current state in a computable form. Essentially, it is the knowledge base or memory of the DT – containing, for example, the patient's current cognitive status, comorbidities, medications, mobility level, etc. – and is continually updated with incoming data. The user model provides the foundation on which other modules build, ensuring that any simulation or analysis starts from a patient-specific baseline [43]. In practice, this could be implemented as a dynamic database plus a set of parameterised models (e.g. a personalised physiological model) representing the individual. Other modules query and update the user model via defined interfaces.
- **Disease progression simulation module:** This is the engine that drives what-if analyses and temporal forecasts. Given the current user model and embedded disease models, it simulates how the person's health might evolve. For dementia, it could simulate the progression of cognitive decline or neuronal loss; for frailty, the trajectory of functional impairments or sarcopenia. The module may use systems modelling (e.g. differential equations for disease spread in the brain, or agent-based models of daily functioning) and/or machine learning predictors to step the patient's state forward in time. It can operate at multiple scales – for instance, modelling molecular pathology progression as well as macroscopic functional decline. Crucially, this simulation module allows the DT to project future states under various conditions. It interacts heavily with the user model, using it as initial conditions and updating it with simulated changes, and provides outputs to the risk and scenario modules. Contemporary research, such as a graph-based digital patient twin, demonstrates how forecasting modules can predict the evolution of vital health indicators over time, underscoring the importance of this component.
- **Risk assessment engine:** This module analyses the data from the user model and simulation to estimate risks of adverse events or outcomes. It serves as the DT's prognostic and warning system. For example, based on current trends and simulated trajectories, it might calculate the risk of falls in the next month, the likelihood of transition from mild cognitive impairment to Alzheimer's dementia in a year, or the risk of hospitalisation due to frailty-related complications. The engine combines patient-specific data with medical knowledge (e.g. known disease progression models and population statistics) to generate these risk scores employ

statistical risk models or AI classifiers trained to detect early signs of deterioration. As noted in a policy report, a digital twin equipped with prior knowledge of disease progression can flag changes in health status and potential risks that warrant intervention. In our modular setup, the risk engine pulls inputs from the user model (current state) and simulation module (predicted future states) to produce interpretable risk indicators. These risk outputs can then be visualised for clinicians or trigger automated alerts in the DT system.

- **Scenario generator and intervention module:** This component enables exploration of hypothetical scenarios and personalised interventions. Working closely with the simulation module, it allows users to pose *"What if?"* questions to the twin. For instance, the scenario generator can create a virtual scenario where the patient begins a new physical exercise regimen, or adjusts a certain medication, or receives a cognitive training ageing. It then runs the simulation module under those modified conditions to predict outcomes (e.g. will the exercise slow down frailty progression? How much might it improve balance scores?). Essentially, this module systematically varies inputs or parameters in the user model to emulate interventions or environmental changes, thereby providing a sandbox to test therapeutic strategies. Such "virtual trial" capability is a hallmark of digital twin systems – the ability to simulate different treatments and see which is most effective for the individual. The module's outputs (predicted outcomes for each scenario) feed into the analytics and visualisation layers for comparison. In a research prototyping context, this component is invaluable for evaluating intervention efficacy before real-world implementation, aligning with the DT's role as a decision-support tool.
- **Cognitive state predictor:** Given the focus on dementia, a dedicated module can be assigned to predicting and monitoring cognitive status. This is a specialised analytics component (often AI-driven) that takes data from the user model (e.g. recent cognitive test scores, daily activity patterns, neuroimaging markers) and produces an estimate or forecast of the patient's cognitive condition. For example, it might predict the patient's score on a standard memory test 6 months from now or determine the probability that the patient's dementia will progress from moderate to severe within a year. Such predictions can be made using machine learning models trained on longitudinal data, or mechanistic models of neurodegeneration. The cognitive predictor enhances the twin's ability to track neurological decline and evaluate the impact of interventions on cognitive outcomes. Notably, advanced digital twin platforms have demonstrated improved classification of neurodegenerative disease stages by incorporating ML analysis of twin data[3]. Our cognitive module would similarly leverage the integrated data to classify the patient's current dementia stage and predict future changes. It interacts with the user model (for input features), and its outputs inform the risk engine (for dementia-related risks) and the scenario module (to see how an intervention might alter cognitive trajectory).

These modules are highly interdependent and communicate through well-defined interfaces. For instance, the user modelling module provides the initial state and ongoing updates to the simulation module; the simulation module provides future state projections to the risk engine and scenario generator; the risk engine and cognitive predictor feed their findings back into the user model (updating the knowledge of likely outcomes) and up to the visualisation layer. All modules draw from the same underlying data repository (the user model) ensuring consistency. Crucially, a secure data exchange backbone underpins these interactions (though details of data pipelines or external integration are beyond our focus). Modern digital health twin frameworks emphasise such modular designs, where components like simulation, prediction, and data management are decoupled but

[3] https://cordis.europa.eu/article/id/447334-brain-digital-twins-transform-neurodegenerative-disease-care

interoperable. This modularity is especially useful in a research prototype: each component (e.g. the disease model or the risk algorithm) can be refined or replaced without overhauling the entire system, enabling rapid iteration.

In summary, the layered perspective delineates vertical slices of functionality – from data acquisition up to visualisation – while the modular perspective zooms in on specific engines and their interplay – from the user model to simulators and predictors working together. Both views converge on a state-of-the-art DT system that can continuously assimilate an older patient's data, simulate their health trajectory, and provide predictive insights. Such architecture, grounded in current research and experimental platforms (e.g. brain simulation avatars for dementia or IoT-driven twins for chronic disease management) offers a robust foundation for developing personalised decision support in dementia and frailty care. By clearly defining layers and modules, researchers can build and iterate on each aspect of the twin – from sensing to AI analytics – accelerating progress toward a future where virtual patient twins help optimise real-world elder.

3.4 Personalised recommendations

A central innovation of the COMFORTage PDT framework is its ability to generate personalised recommendations for dementia and frailty care. Leveraging continuously updated, multi-modal patient data and sophisticated simulation models, the PDT translates complex analytics into actionable, context-aware guidance for both clinicians and older adults. This capability shifts clinical practice from reactive to proactive, supporting individualised prevention, timely intervention, and optimised resource utilisation.

Personalised recommendations are generated through a multi-step process as demonstrated in Figure:

- **Data integration:** The PDT aggregates up-to-date clinical records, wearable sensor streams, lifestyle metrics, and self-reported outcomes.
- **Simulation and prediction:** Advanced modelling and simulation layers forecast health trajectories and the impact of various intervention scenarios for the individual.
- **Risk assessment:** The system continuously monitors for deviations from expected health trajectories and identifies risk factors such as impending cognitive decline, heightened fall risk, or nutritional deficits.
- **Decision support:** The analytics layer synthesises these findings to produce tailored recommendations, delivered through a CDSS and user-facing dashboards.

Figure 3: Recommendations generation flow

Table 5: Recommendations and examples

Recommendation type	Input data sources	Example system output / recommendation
Early detection and intervention	Cognitive test scores, wearable activity data	"Recent data suggest a faster-than-expected decline in short-term memory. Consider early intervention with cognitive stimulation therapy."
Adaptive medication management	Pharmacogenomic profile, medication adherence, side-effect reporting	"Pharmacogenomic profile indicates increased risk for side effects with current medication. Alternative therapy is recommended."
Fall prevention	Gait speed, step count, mobility metrics, environmental sensors	"Mobility patterns suggest elevated risk of falls. Recommend a physical therapy assessment and home safety review."
Nutrition and lifestyle support	Activity data, nutrition metrics, patient-reported outcomes	"Recent weight loss detected; protein intake below recommended threshold. Suggest nutritionist referral and tailored meal planning."
Personalised scenario simulations	Simulation models, what-if scenario generator	"Model predicts a 15% improvement in frailty index with adherence to proposed 20-minute daily exercise routine."
Social and psychological wellbeing	Data from digital social tools, engagement/activity levels	"Reduced social engagement detected over the past month. Recommend enrollment in group activities or digital social programs."

Personalised recommendations need to be delivered through intuitive dashboards for clinicians to assist on the careplan decisions. These dashboards translate analytics into clear, actionable insights—such as risk scores, alerts, and progress trends—and empower shared decision-making. The system also supports two-way interaction, enabling users to adjust preferences or simulate the effects of potential lifestyle changes, thereby increasing engagement and adherence.

3.5 COMFORTage DT Platform

A critical gap identified in the literature and current digital twin initiatives is the lack of user-friendly, integrated platforms that provide healthcare practitioners with actionable insights, real-time data access, and intuitive interfaces for clinical decision support. Existing solutions are often fragmented, technically complex, and not designed with end-user needs in mind, limiting their adoption in real-world healthcare settings. The COMFORTage DT Platform was developed specifically to bridge this gap, delivering a comprehensive, user-centric environment that consolidates all essential patient information, analytics, and intervention tools in a single, easy-to-navigate interface.

The COMFORTage platform enables clinicians and researchers to access, manage, and act on the full spectrum of data generated by the pilot study. Key features include:

- **Visual analytics dashboards** for at-a-glance interpretation of patient status and cohort trends.
- **PDT recommendations** generated by advanced AI modules directly supporting personalised intervention planning.
- **Device management** for tracking all medical and sensor devices allocated to each patient.
- **Comprehensive patient records**, including clinical data, cognitive assessments, care plans, and adherence metrics.
- **Access to validated opt-in digital tools**, supporting multidomain assessment and intervention for dementia and frailty.
- **Integrated notifications and alerts** to prompt timely clinical action.
- **Multilingual and role-based interfaces** ensuring accessibility for all pilot site users.

Below, each screenshot illustrates a core component of the COMFORTage platform as experienced by healthcare professionals.

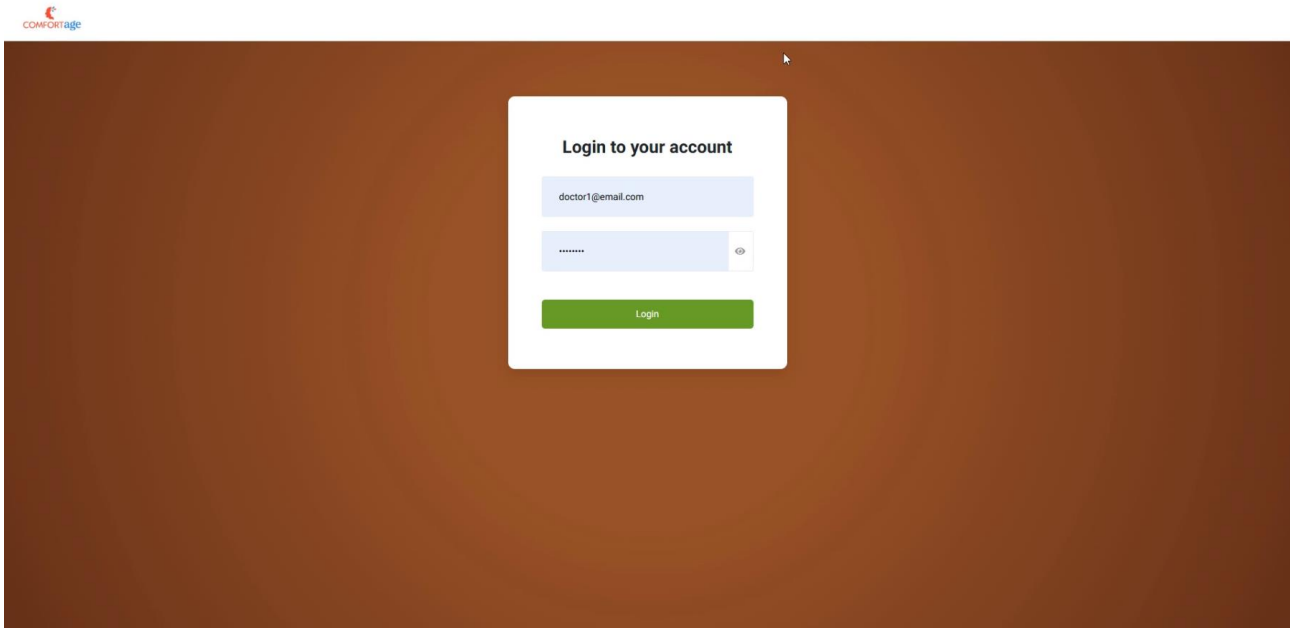

Figure 4: Log-in page of PDT platform

The secure log-in page provides access control, ensuring that only authorised practitioners and pilot personnel can view and manage sensitive patient data. Credentials are authenticated via a modern, streamlined interface.

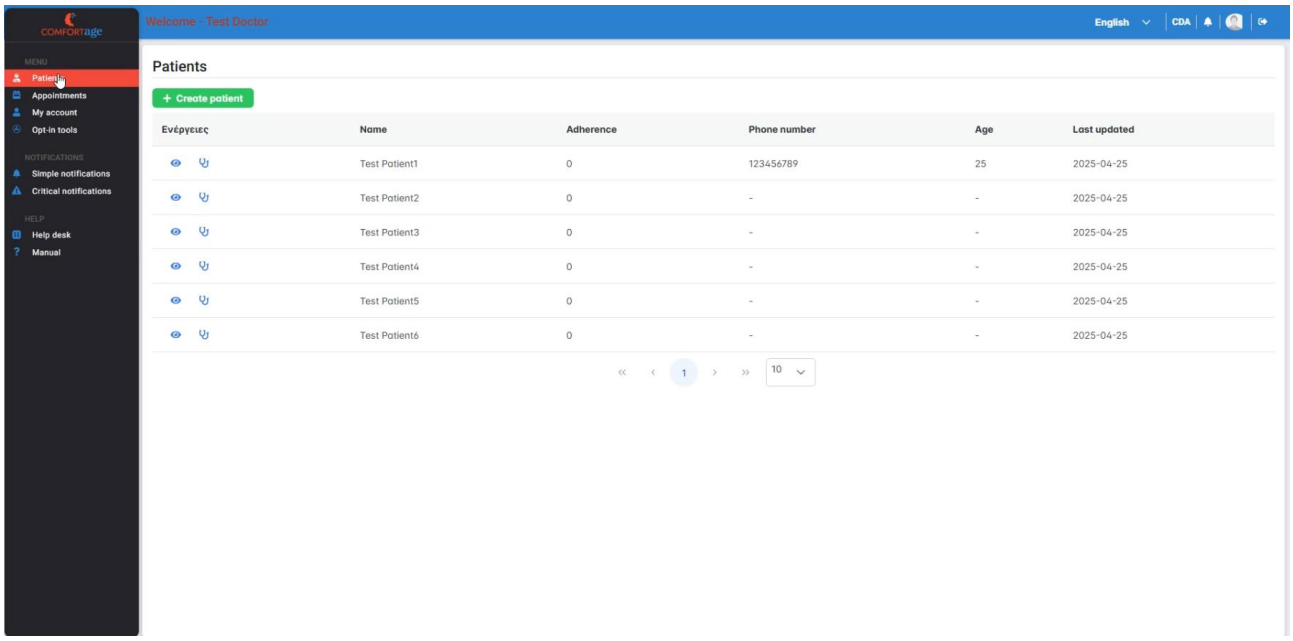

Figure 5: Patients overview

The main dashboard lists all enrolled patients in the pilot, displaying key metadata such as adherence, contact information, and last update. This page allows clinicians to quickly select a patient, create new profiles, or navigate to individual patient files. The menu on the left provides access to appointments, opt-in tools, notifications, and help resources.

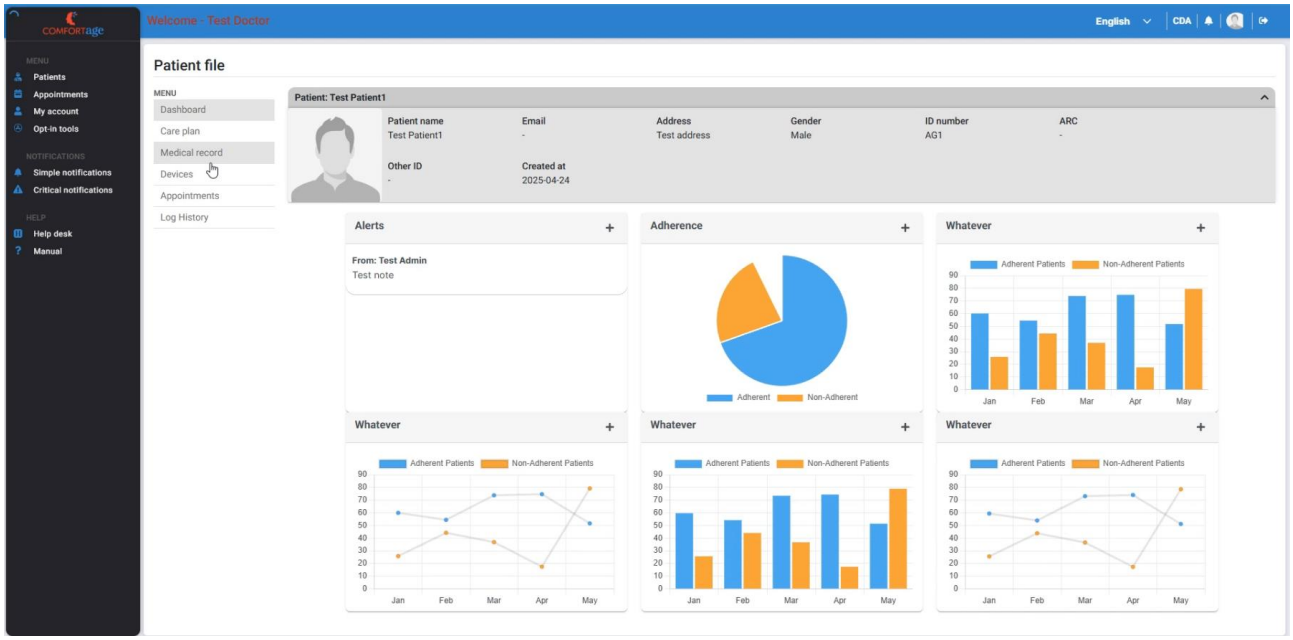

Figure 6: Patient file dashboard

Upon selecting a patient, the platform displays a comprehensive analytics dashboard: demographics, alerts from the clinical team, adherence data, and visualisations of health and intervention trends. Custom charts track adherence over time, enabling the practitioner to identify patterns and respond proactively.

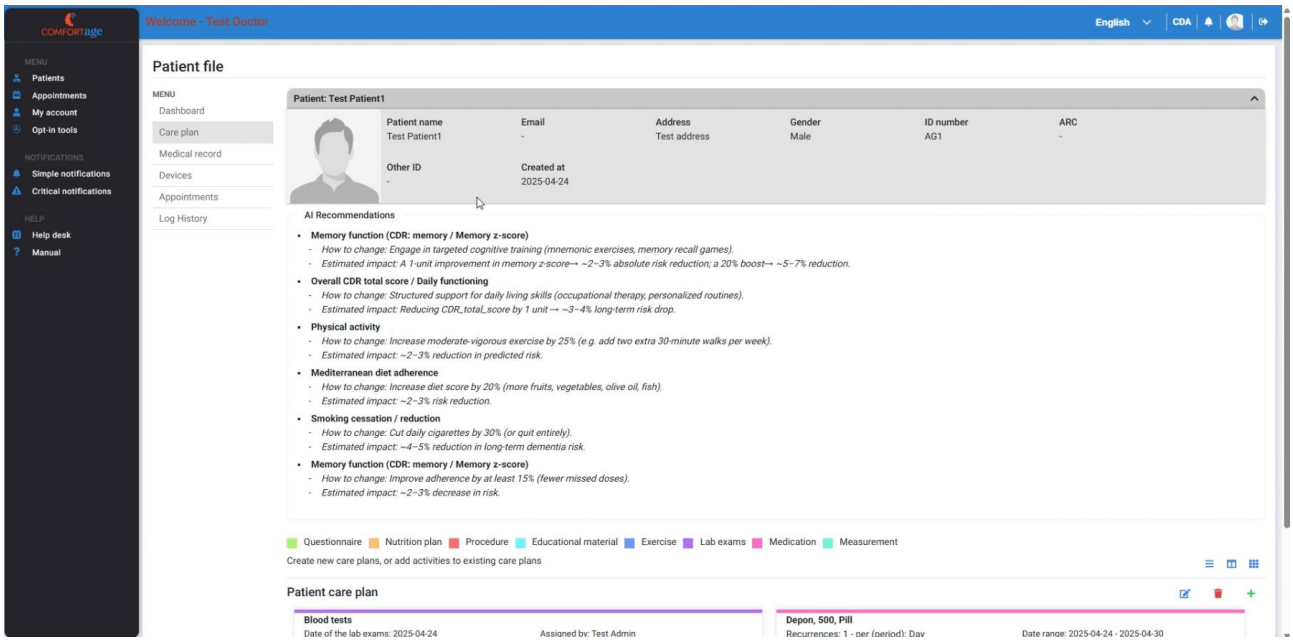

Figure 7: PDT AI recommendations and care plan

This section showcases AI-generated recommendations from the PDT. Personalised suggestions target memory function, physical activity, diet adherence, and other health domains, each linked to estimated impacts (e.g., reduction in risk scores). The care plan area enables clinicians to create or update intervention activities, with options for nutrition, exercise, medication, and educational materials—directly translating PDT insights into actionable care pathways.

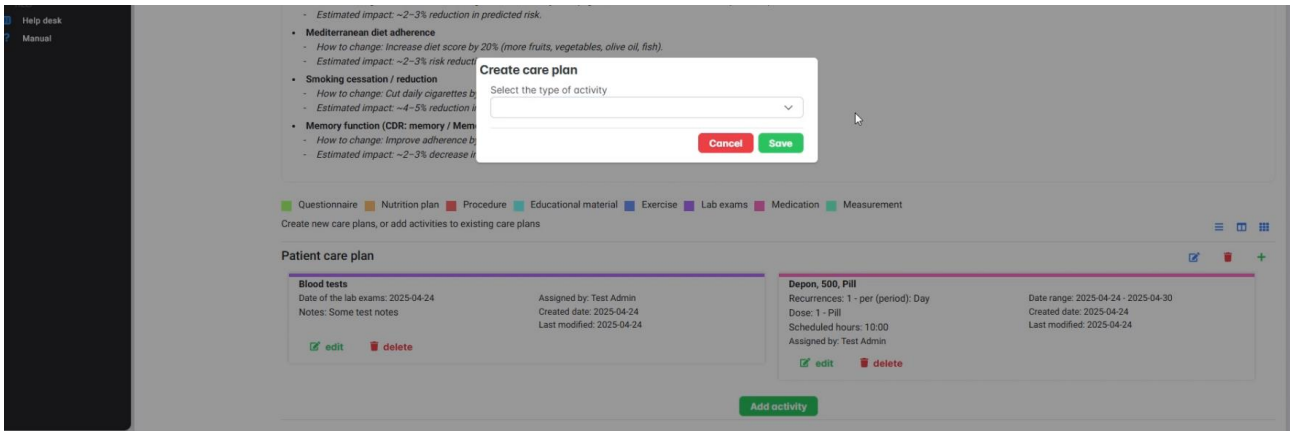

Figure 8: Editing or creating a care plan

The care plan editor allows practitioners to customise activities or interventions for each patient. Drop-down menus provide standardised activity types, ensuring consistency and ease of use in planning, updating, or documenting care processes.

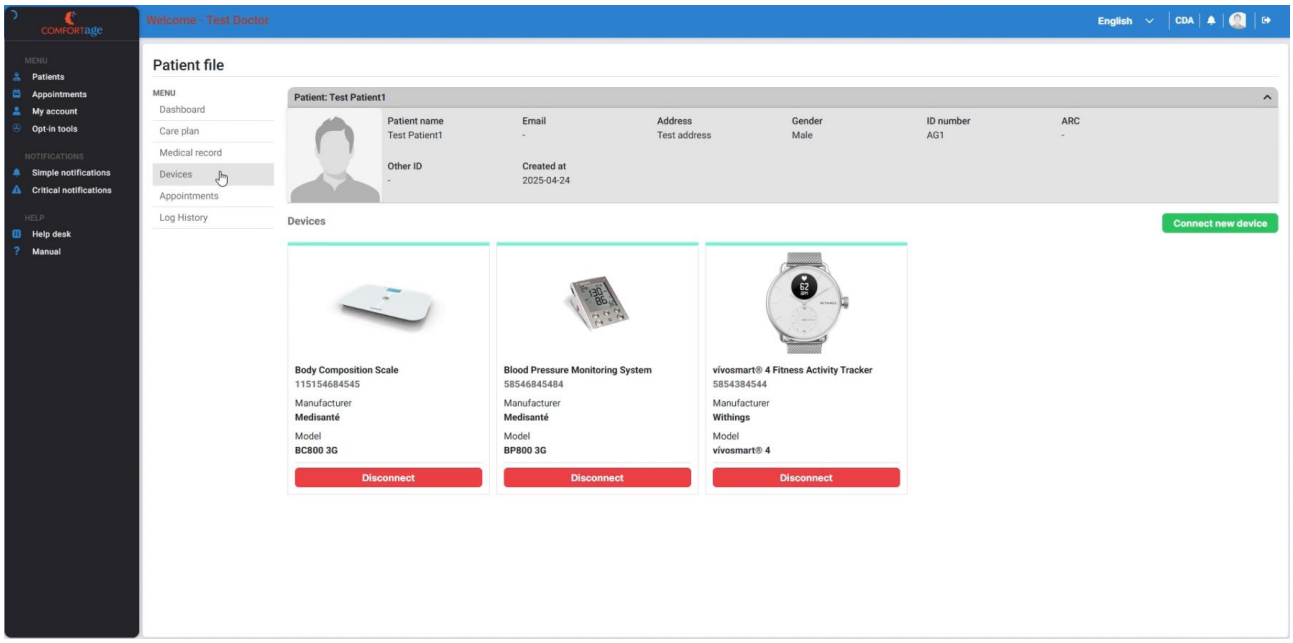

Figure 9: Devices management

Device management is integral for tracking all medical and wellness devices (e.g., activity trackers, blood pressure monitors, body composition scales) assigned to patients. The platform displays device details, manufacturer, and provides options to connect or disconnect equipment—ensuring data continuity and accountability.

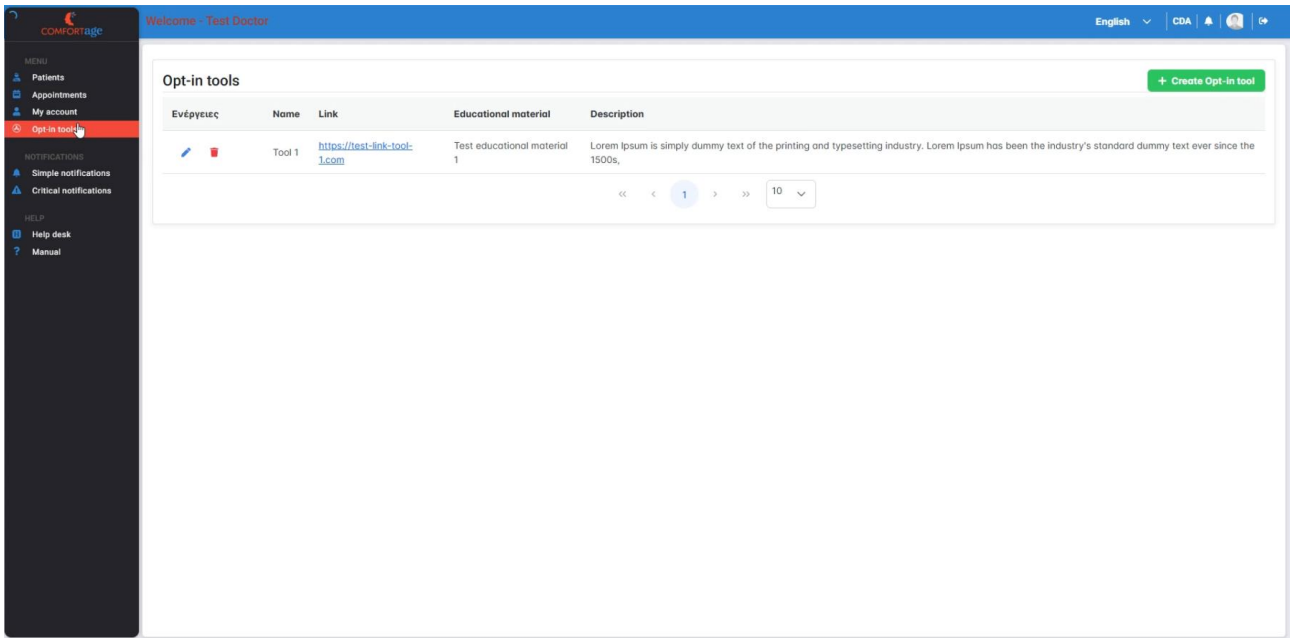

Figure 10: Opt-in tools

Clinicians can access a curated set of validated opt-in tools for cognitive assessment, educational intervention, or social engagement. Each tool includes a description, access link, and usage guidance, supporting both research needs and patient empowerment within the pilot.

By directly addressing the research gap in user-centred clinical platforms, the COMFORTage DT Platform offers a holistic, visually intuitive, and actionable environment for healthcare professionals. It allows seamless visualisation of all relevant patient data, real-time analytics, device tracking, and integration of digital health tools—ensuring that the power of the PDT is fully accessible and practically usable in everyday clinical workflows. This commitment to usability,

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interoperability, and actionable insight is foundational to the COMFORTage approach and central to driving the adoption of digital twin technology in dementia and frailty care.

4 PDT integration in COMFORTage

This section describes how the PDT framework is integrated into the broader COMFORTage platform to support personalised, data-driven care for ageing populations. It highlights the technical and functional connections between the DT system and key COMFORTage components, including the CDSS, the ICML, the ageing-focused EHDS and IKBs infrastructure, and digital health tools for patients and caregivers. The section also explains how interoperability, real-time data exchange, and user-centric interfaces are achieved to ensure seamless interaction between clinicians, patients, and the digital twin environment.

4.1 CDSS Integration and Decision Making

4.1.1 The workflow of intervention planning from the CDSS perspective

The software architecture of the COMFORTage platform, [1], and the user-interaction concept, in [2], specifies the PDT as the leading subsystem for patient-specific AI-driven decision-making about individualised medical and lifestyle interventions. The CDSS attains the role of a lower-level subsystem with the following core functionality and technological integration with the PDT:

- The CDSS allows for the planning of intervention based on crucial core data about patient cases. It receives this data from the Integrated Knowledge Base (IKB) via a data connection running through the PDT. For this purpose, the CDSS provides a connector module to the PDT to interact with.
- Based on the considered case data, the CDSS triggers AI requests for the identification of interventions suited for the considered case and receives the corresponding AI results of analysis. The processing of AI requests and creation of AI results is done by the AI-related components of the COMFORTage platform, namely the Explainable Artificial Intelligence (XAI) framework and the ICML. This communication and data transfer between the CDSS and the AI components also runs through the PDT, which for this purpose interacts with an AI connector contained in the CDSS.
- The received AI results of analysis form the data input for the identification of relevant intervention options and their exploration in the search of the most suitable ones. For this planning step, the CDSS provides a graphical user interface (GUI) plugin with the required visual and functional features, and a method module for the PDT to interact with. The most suitable options are then provided to the PDT for a further comparison and adaptation of the options and the selection of interventions for their subsequent application.
- The finally adapted and selected interventions are then transferred back to the CDSS, where they are documented and thereby serve as data input for the next step in the sequential decision-making (SDM) process of intervention planning. For this documentation step, the CDSS provides a GUI plugin with the needed features, and a method module for the PDT to interact with.

4.1.2 Technological and functional integration of the CDSS

The specified workflow features a natural distribution of decision-making tasks to the COMFORTage subsystems of the PDT and the CDSS:

- The PDT attains the role of the leading system for intervention planning, which allows for detailed assessment of intervention options based on the complete case data and prognoses of the further courses of cases, and the individualised adaptation and final selection of intervention options for subsequent application.

- The CDSS assists the PDT by an automated identification of case-relevant intervention options based on the corresponding AI results of analysis, the exploration of these options for further examination in the PDT and the documentation of the final decisions as information input for further decisions.

This distribution of tasks is reflected in the recently conducted research and development tasks. A first prototype of the COMFORTage CDSS was created on the technological basis of the configurable CDSS DiADeMa and most recently adapted to the COMFORTage branding. Figure **11** shows the survey of an electronic patient record in this CDSS with exemplary case data in text format. This visualisation also contains features for the documentation of patient cases and selected interventions in terms of their crucial parameters, and for an automated quality management assuring data completeness and consistency.

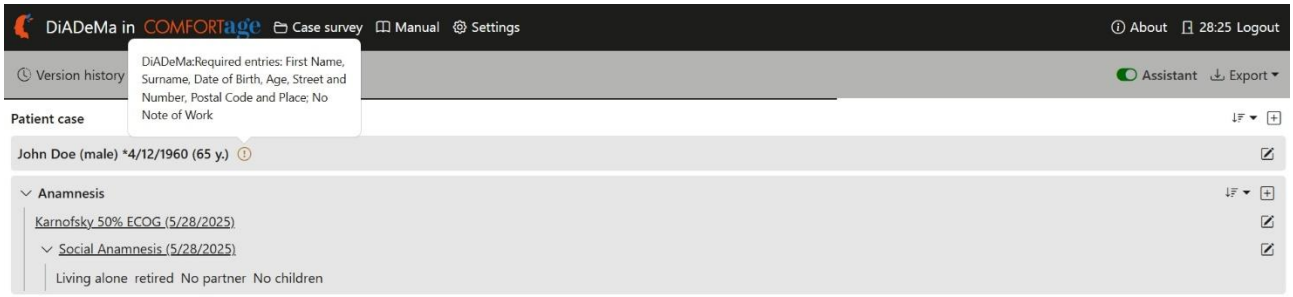

Figure 11: Screenshot of COMFORTage CDSS prototype with an electronic patient record for an artificial patient case with exemplary content data. The text plugin indicates missing case data identified in the automated quality management

The main tasks addressed with the CDSS are the exploration of intervention options, which were identified as relevant based on the AI results of analysis, and the selection of the most suitable one for further processing in the PDT. Figure **12** shows the visual and functional elements of the CDSS for these tasks. This visualisation features a ranking of relevant intervention options, which come along with explanatory context information about the reasoning for these suggestions. The actual format and contents of this context information are a topic of ongoing conceptual work on the interaction of the CDSS and the COMFORTage AI components. The ranking of options colored according to the COMFORTage branding and the displayed text plugin for one intervention option may thus be considered as current exemplary approaches for the integration of explainability features into the AI-assisted decision-making process.

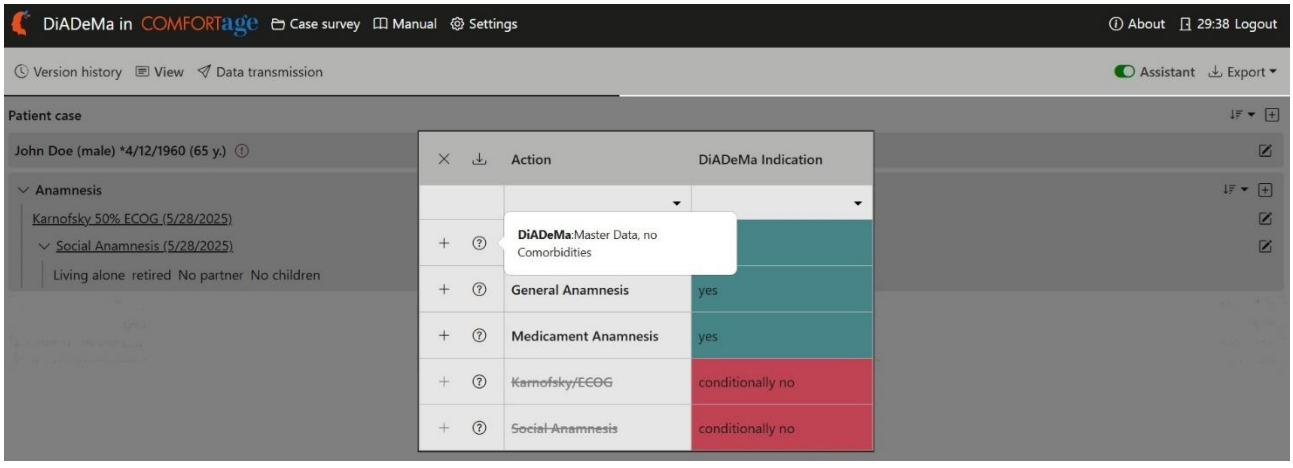

Figure 12: Screenshot of CDSS prototype with the graphical features of the planning of interventions based on automated suggestions and Elementary explainability features. The text

plugin provides explanatory context information about the reasoning of the suggested intervention option.

The list of relevant options shown in Figure 12 is a natural visual and functional component for supporting the generic intervention planning process aside of the more advanced planning addressed by the PDT. Furthermore, this component can essentially be used independently from the underlying case data. Hence, software design and implementation works have started on the provision of this component as a GUI plugin, which allows for a direct integration into the graphical frontend of the PDT.

4.2 ICML and Explainability Integration and hosting

Within the COMFORTage platform, the PDT serves as the central AI-driven module for real-time, personalised care planning and risk assessment in dementia and frailty. A core strength of the PDT lies in its seamless integration with both the ICML and the platform's XAI capabilities, ensuring that every AI-generated recommendation is robust, transparent, and clinically actionable.

The ICML acts as a comprehensive repository of advanced AI and statistical models, covering domains such as risk prediction, disease trajectory simulation, and intervention outcome forecasting for the target populations. When new patient data—such as sensor inputs, clinical assessments, or patient-reported outcomes—are recorded, the PDT automatically invokes the appropriate models from the ICML to update risk scores, health status projections, and tailored intervention options. In practical terms, this allows the PDT to provide clinicians and care teams with dynamic, up-to-date insights into a patient's likelihood of cognitive decline, fall risk, or response to specific interventions. The ICML also supports scenario analysis; for example, clinicians can use the PDT to simulate the impact of a proposed exercise ageing or medication change, with the relevant models in the ICML running these individualised "what-if" analyses in the background.

Crucially, the PDT does not simply present raw predictions—it also leverages XAI tools to generate interpretable explanations for each recommendation. After the ICML models produce their outputs, the PDT automatically calls the XAI modules, which apply techniques such as feature attribution or local interpretability (e.g., SHAP, LIME) to clarify which data points or clinical factors most influenced the model's decision. These explanations are visualised within the PDT interface, enabling clinicians to quickly understand why, for instance, the system has flagged a particular patient as being at high risk of falls or cognitive deterioration. This transparency not only fosters trust and acceptance among healthcare professionals but also facilitates shared decision-making and communication with patients and carers. For more information regarding the XAI visualisations, please refer to D3.8 ' Integrated AI-based Care Model Library II' that will be delivered on M32.

From a technical perspective, the integration of PDT, ICML, and XAI is achieved through standardised APIs and secure data exchange protocols, hosted within the Virtual Health Platform (VHP). The PDT interacts with these back-end services both on-demand—when a user requests a new risk assessment or intervention simulation—and continuously, whenever new data is ingested. The result is a unified, user-friendly interface where all predictive analytics and their underlying explanations are accessible to end-users without requiring separate interactions with the ICML or XAI components.

Overall, the combination of the ICML and XAI within the PDT architecture ensures that COMFORTage delivers explainable, evidence-based, and practically actionable recommendations for dementia and frailty care. This approach directly addresses the challenge of trust and transparency in clinical AI, supporting wider adoption and more effective, individualised interventions across diverse care settings.

4.3 VHP Platform

Working paper D2.8 - Reference Architecture and Integration of VHP Platform I provides a detailed description of each component comprising COMFORTage's virtualised healthcare platform (VHP). Specifically, section 3.3.2 of D2.8 describes the interface details for the personalised PDTs component, outlining the interaction of the component with other components of the platform – namely, Integrated Knowledge Base (IKB), CDSS, ICML, Trainings Recommender and People-centric Assistive Applications/opt-in tools. Furthermore, section 5.3.2 of D2.8 describes several technical specifications of the PDTs component in the form of open interfaces, communication patterns, information flows and design principles. These specifications provide critical details for guiding the design and development of the PDTs component, as well as its integration with other components in the VHP.

Figure 13 shows the component interaction diagram representing the overall COMFORTage VHP system architecture. As part of the platform's patient treatment and monitoring tools, the PDTs component is a front-end application that will make use of digital simulation technologies to generate several personalised virtual models of older individuals. Through these customised and precise models, users will be able to carry out various clinical tasks, such as the generation of health trajectories, the creation of AI-based optimal therapy scenarios, in addition to prognosis and diagnosis.

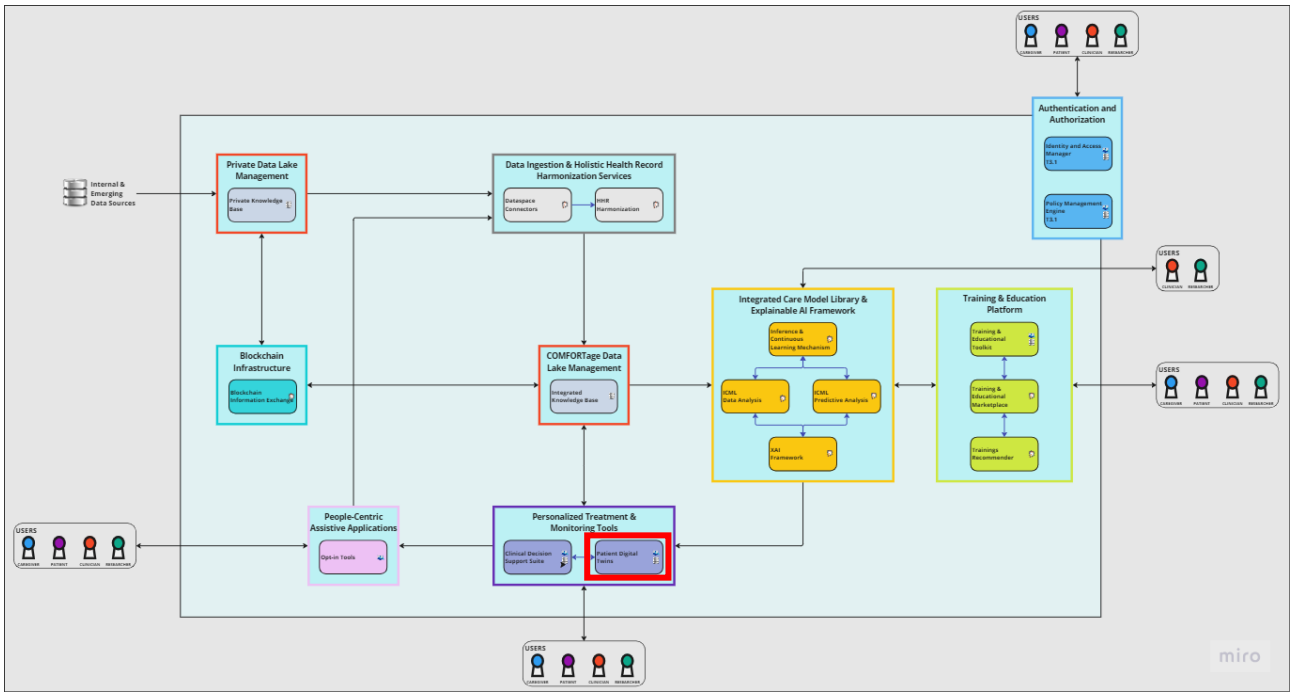

Figure 13: Component interaction diagram representing COMFORTage virtualised healthcare platform system architecture

Specifically, the component interacts with the IKB to retrieve patient data and store any data/results the component generates for each individual. The PDTs component also interacts with both the ICML (in order to provide analytics and visualisations to users that result from the execution of the different AI/ML models) and the XAI framework (for providing explanations of the models' results to clinicians). Clinicians will be required to approve/reject the targeted recommendations (prevention/intervention measures), which necessitates interfacing with the various assistive applications and opt-in tools of the platform, as well as the Training Recommender of the Training and Education Toolkit. Finally, access to the component and its various features will be governed by the requirements of each pilot study.

4.4 Opt-in tools data sharing

Within the COMFORTage platform, opt-in tools constitute an essential ecosystem of digital resources designed to engage patients in their own health management. These tools—ranging from cognitive training games and linguistic assessments to nutrition trackers, physical activity applications, and social engagement platforms—offer validated, user-friendly formats for collecting multidimensional health data beyond traditional clinical environments. Data sharing from these opt-in tools plays a pivotal role in enriching the PDT, ensuring that each digital replica is informed by a comprehensive and dynamic set of inputs reflecting the patient's daily life, functional abilities, and behavioural patterns.

The rationale for sharing data generated by opt-in tools is rooted in the ambition to enable truly holistic and personalised care. Integrating these rich, real-world data streams with clinical, sensor, and self-reported inputs allows for continuous updates of the PDT, supporting real-time risk assessment, proactive intervention planning, and adaptive care pathways. For example, insights gleaned from digital cognitive games can inform early detection of cognitive changes, while physical activity trackers and nutrition apps provide a granular view of lifestyle factors that influence frailty progression. Data from these tools, once consent is provided, are securely transmitted to the COMFORTage platform—typically via encrypted APIs or secure data exchange protocols—and are systematically mapped to each participant's PDT profile for unified analytics and decision support.

Participation in opt-in tools, and the sharing of their data, is strictly voluntary and governed by transparent, informed consent procedures. Patients are presented with clear explanations regarding what data will be shared, the intended uses, and who will have access. The platform enables users to manage their participation preferences at any time, including opting in or out of data sharing or revoking consent for specific tools or data types. All data processing fully complies with GDPR, EHDS, HHRs and related regulatory standards, employing robust pseudonymisation, access control, and data minimisation measures to safeguard privacy and ensure ethical handling. Patients are empowered with intuitive dashboards to review shared data, adjust their preferences, and monitor data flows, reinforcing their role as active stewards of their own health information.

The benefits of this data sharing framework are multifaceted. For clinicians and researchers, it enables the construction of richer and more accurate DTs, facilitating the timely identification of health changes and the personalisation of care plans. For patients, it means tailored recommendations and interventions grounded in their real-world behaviours and preferences. Additionally, aggregated and anonymised data from opt-in tools contribute to ongoing scientific research, supporting the continuous refinement of care models and the development of innovative interventions for dementia and frailty.

To guarantee data security and trust, all transmissions employ state-of-the-art encryption and role-based access, ensuring that only authorised professionals involved in the patient's care can access sensitive information. Comprehensive audit trails document all data interactions, promoting transparency and accountability. Data is shared solely as necessary for direct clinical care, platform improvement, or—where separately consented—research purposes.

In summary, opt-in tools data sharing within COMFORTage balances the empowerment of patient engagement with the highest standards of privacy and data protection. As the platform evolves, future iterations aim to further enhance interoperability with external health applications and expand the repertoire of supported opt-in tools, deepening the integration of digital participation in personalised dementia and frailty care.

4.5 Pilot studies usability

The integration of the PDT into all 13 COMFORTage pilot studies marks a significant advancement in the delivery and evaluation of personalised care for older adults with dementia and frailty. The PDT acts as a digital bridge, bringing together multidimensional health, behavioural, and environmental data to create a continuously updated, individualised profile for each participant. This unified platform empowers care teams to monitor health trajectories, detect early warning signs, and coordinate interventions across a diverse spectrum of real-world settings—from primary care and memory clinics to home environments, assisted living facilities, and day-care units.

By consolidating data from electronic health records, wearable sensors, clinical assessments, and patient-reported outcomes, the PDT ensures that care is not only data-driven but also context-aware and tailored to the unique circumstances of each pilot site. For healthcare professionals, the platform streamlines access to actionable information, supports risk stratification, and enables the simulation of "what-if" scenarios to optimise intervention strategies. For patients and their carers, the PDT offers greater transparency, engagement, and opportunities for proactive management of health and wellbeing.

Furthermore, the PDT platform facilitates the standardised collection and sharing of pilot data, enabling cross-site analytics and harmonised evaluation of outcomes. This harmonisation supports robust multi-site research, comparative effectiveness studies, and the scaling of best practices across Europe. The seamless integration of opt-in digital tools within the PDT further supports cognitive assessment, physical activity tracking, and social engagement, enhancing the comprehensiveness and real-world relevance of the pilot interventions.

In summary, the PDT transforms the pilot study landscape in COMFORTage by delivering an adaptable, user-friendly, and scientifically robust digital environment that meets the needs of clinicians, researchers, patients, and carers alike.

4.5.1 Pilot #1: UNIMAN

In the first COMFORTage pilot, the PDT serves as a pivotal tool for integrating and analysing the complex interplay of lifestyle, genetic, and biological factors associated with dementia risk in a large, "at risk" population. Each participant's PDT aggregates baseline health data—including polygenic risk scores, blood-based biomarker profiles, comorbidities, and results from health and lifestyle questionnaires—into a dynamic, personalised digital profile.

During the intervention, the PDT continuously updates this profile with longitudinal data from both e-health support systems and omics feedback, depending on the participant's randomisation group. The platform's simulation and analytics modules allow clinicians and researchers to track changes in key risk indicators, such as biological age (via methylation indexes), cognitive performance, and health behaviours, throughout the 9-month follow-up period. By providing individualised risk estimates and visual analytics, the PDT empowers health coaches to deliver tailored advice and adjust preventive strategies in real time.

Additionally, the PDT supports outcome evaluation by enabling direct comparison of pre- and post-intervention biomarker levels and lifestyle metrics within each digital twin. For trial monitoring and research, the harmonised data infrastructure of the PDT facilitates the assessment of intervention effects across all four groups, ensuring that both the impact of health coaching and epigenomic profiling can be rigorously analysed. The result is a highly personalised, adaptive approach to dementia prevention that leverages digital twin technology to maximise the effectiveness of lifestyle and genetic interventions.

4.5.2 Pilot #2: NKUA

In Pilot #2, the PDT platform is primarily utilised by clinicians as an advanced analytics and monitoring environment, supporting the identification of early risk factors for dementia during the preclinical stage. The pilot consolidates large-scale, longitudinal data from established studies such as HELIAD and ALBION, as well as new participants enrolled in COMFORTage, to create a comprehensive repository of retrospective and prospective health information.

The PDT does not serve as an intervention tool in this pilot. Instead, clinicians leverage its powerful visualisation capabilities to track and analyse a wide range of biological, lifestyle, and cognitive data over time. This includes monitoring subtle changes in cognitive performance, following the evolution of biomarkers, and mapping trajectories of at-risk individuals before symptoms appear. The system supports the exploration of associations between various health markers and future cognitive decline, enabling clinicians to generate hypotheses, support ongoing research, and facilitate early detection efforts.

Ultimately, the PDT's role in Pilot #2 is to enhance scientific understanding of the mechanisms underlying dementia risk and progression, rather than to deliver or recommend interventions. The platform supports clinicians in making sense of complex, multidimensional datasets, identifying patterns, and sharing actionable insights with the research community for future prevention strategies.

4.5.3 Pilot #3: ACE

In the third pilot, the COMFORTage PDT is deployed to enable the integration and individualised analysis of complex, multimodal health data—ranging from genetic and neuroimaging markers to clinical, digital, and functional assessments. For each participant, the PDT creates a dynamic, living model that assimilates neurological and nursing evaluations, MRI imaging, plasma and CSF biomarkers, genotyping results (including polygenic risk scores and ApoE), and innovative digital biomarkers such as spontaneous speech analysis.

By aggregating these diverse datasets into a unified digital profile, the PDT supports the core aim of the pilot: to identify individuals at high risk of cognitive decline and deliver precisely tailored prevention and intervention strategies. Through advanced simulation and AI-driven analytics, the PDT allows clinicians and researchers to monitor cognitive and functional changes in real time, evaluate the biological impact of interventions, and forecast the likely benefit of different strategies for each individual.

The randomised controlled trial design of this pilot—contrasting an actively supported group using COMFORTage digital tools (such as the PUNTO app for speech monitoring) with a control group receiving standard care—enables direct measurement of the PDT's value in both outcome prediction and care personalisation. PDT-based analytics will track cognitive, biological, and functional outcomes longitudinally, helping to elucidate the interplay between intervention, genetic risk, brain imaging findings, and digital markers.

Additionally, the PDT's integrated platform ensures secure and standardised data sharing across partners through Data Transfer Agreements, supporting both privacy and interoperability. This comprehensive approach empowers the ACE pilot not only to measure cognitive improvement and quality of life (QoL) gains, but also to advance the predictive science of digital and biological markers in dementia prevention—driven by the actionable insights generated by the PDT.

4.5.4 Pilot #4: FPG

In Pilot #4, the PDT is central to enabling precision medicine for individuals with subjective cognitive decline (SCD) or mild cognitive impairment (MCI). By continuously integrating and harmonising data

from blood-based biomarkers, genetic risk factors, advanced imaging, and comprehensive clinical assessments, the PDT creates a detailed and dynamic digital profile for each participant.

This unified model empowers clinicians and researchers to identify those at heightened risk of progression to dementia, years before clinical symptoms become pronounced. The PDT leverages its AI-driven analytics and simulation capabilities to stratify individuals based on their biological, genetic, and connectivity markers, supporting targeted decision-making for early, personalised prevention strategies. For example, if a participant's PDT model indicates elevated amyloid levels or high polygenic risk scores, it can trigger a recommendation for tailored interventions such as nutritional counseling, specific physical exercise regimens, or cognitive training.

Throughout the two-year intervention period, the PDT will not only monitor the impact of these personalised plans on cognitive performance and quality of life (QoL) but also dynamically update risk profiles and recommendations as new data becomes available. This feedback loop ensures that interventions remain optimally matched to each participant's evolving risk landscape.

Moreover, the PDT platform will facilitate the tracking of metabolic and cardiovascular risk management, adherence to interventions, and patient satisfaction, providing both the research team and participants with transparent, actionable feedback. This approach directly addresses the pilot's objectives: to evaluate the impact of personalised interventions versus standard care, and to better understand the interplay between lifestyle, biomarkers, and cognitive health outcomes.

By operationalising advanced prevention strategies through the PDT, Pilot #4 not only enhances early detection and individualised care but also exemplifies the COMFORTage vision for scalable, adaptive, and evidence-based dementia prevention.

4.5.5 Pilot #5: MUL

In Pilot #5, the PDT is employed by clinicians as a centralised data monitoring and analytics system to investigate familial and lifestyle-related risk factors for dementia prevention. The focus of this pilot is on at-risk individuals—such as those with a family history of dementia or early cognitive complaints—and on understanding how lifestyle and educational interventions might affect long-term health outcomes.

Within this observational context, the PDT is not used to generate or prescribe new interventions. Rather, clinicians utilise the platform to aggregate participant data—including demographic details, medical history, neurocognitive assessments, laboratory results, and self-reported behaviours—into an accessible, interactive dashboard. The PDT's visualisation tools enable clinicians to follow each participant's physical and cognitive trajectories, assess adherence to community education and lifestyle programs, and compare baseline and follow-up results.

The primary function of the PDT in this pilot is to empower clinicians and researchers with clear, longitudinal views of how changes in lifestyle, social engagement, and educational initiatives may influence dementia risk profiles. By providing timely, comprehensive insights into participant outcomes, the PDT underpins the pilot's goals of raising awareness, reducing risk factors, and supporting research into effective prevention strategies—while all clinical decisions remain the responsibility of the care team, outside the direct scope of the PDT system.

4.5.6 Pilot #6: AUTH

In Pilot #6, the PDT plays a central role in supporting clinicians as they deliver, monitor, and personalise a complex, remote multimodal intervention aimed at reducing frailty and cognitive decline in older adults. Given the digitally enabled nature of the trial—including the integration of cognitive training, wearable sensors, mHealth applications, and nutritional monitoring—the PDT provides a unified, clinician-facing environment for comprehensive participant management.

Throughout the trial's six phases, clinicians use the PDT to view real-time data streams from digital tools such as BrainHQ, smartwatches, smart scales, and mHealth apps. The platform aggregates neuropsychological assessments, physical and nutritional evaluations, medical history, and biometric readings, making longitudinal tracking seamless across all five assessment points (from baseline to 21 months follow-up). This continuous data integration allows the clinical team to visualise trends in cognitive and physical performance, monitor adherence to training protocols, and rapidly identify individuals who may benefit from tailored intervention adjustments.

The PDT's simulation and analytics features allow clinicians to compare individual progress against expected trajectories and stratification factors (e.g., sex, education, frailty level). For the intervention group, personalised recommendations can be generated based on current and predicted states, such as alerts to increase activity, reinforce nutritional intake, or intensify cognitive training. For the control group and healthy controls, the PDT facilitates unbiased monitoring and benchmarking of natural progression versus intervention response.

In the post-intervention and long-term follow-up phases, the PDT continues to support clinicians by visualising comparative outcomes, quantifying the sustained impact of the intervention, and helping interpret multi-domain improvements (or declines). Furthermore, the system's dashboard enables documentation of participant engagement with educational content, adherence to physical and cognitive programs, and overall well-being.

In summary, the PDT acts as the clinical command center for Pilot #6: enabling data-driven decision-making, intervention adaptation, and outcome evaluation in a complex, technology-rich clinical research setting. By consolidating digital health data, analytics, and intervention management into a single platform, the PDT not only increases efficiency and accuracy for the clinical team but also helps deliver more personalised, responsive care to older adults at risk of frailty and cognitive decline.

4.5.7 Pilot #7: MFU & VSTE

In Pilot #7, the PDT serves as an integrated digital platform to assist clinicians in the complex management of participants at risk for cognitive decline, with a special emphasis on novel risk factors such as oral frailty and oral microbiota. Given the pilot's focus on multidimensional risk assessment—including neuropsychological tests, EEG, sleep quality, activities of daily living, diet, blood pressure, glucose, and oral health—the PDT consolidates and visualises this array of data in a single, user-friendly dashboard accessible only to clinicians.

Clinicians use the PDT to continuously monitor changes in participants' oral and general health profiles, linking these markers with cognitive and functional outcomes. For example, the platform can present longitudinal visual analytics tracking oral health scores, patterns in sleep quality, physical activity, and nutritional status, and correlate them with neuropsychological and EEG findings. As new data streams in from COMFORTage digital tools and clinical assessments, the PDT allows for real-time risk assessment and trend analysis, helping clinicians identify early warning signs of cognitive deterioration or declining oral function.

Moreover, the PDT supports the planning, adaptation, and evaluation of individualised interventions. For participants identified at higher risk—whether due to oral health issues, family history, or abnormal biomarker patterns—clinicians can use the platform's recommendations engine to tailor and document preventive strategies, such as social learning interventions, nutritional adjustments, and physical activity plans. The dashboard enables efficient tracking of intervention adherence, participant engagement, and outcome progression over time.

Through its comprehensive data integration and analytics capabilities, the PDT empowers clinicians to better understand the interplay between oral health, lifestyle factors, and cognitive trajectories,

ultimately facilitating the implementation and continuous refinement of innovative, multi-domain preventive interventions. By making complex, heterogeneous data actionable and easy to interpret, the PDT enhances clinical decision-making and personalised care in this pilot targeting novel dementia risk markers.

4.5.8 Pilot #9: CING

In Pilot #8, the PDT acts as a central platform for clinicians to aggregate, monitor, and analyse complex longitudinal data across three distinct participant groups—patients with Alzheimer's disease, individuals with Mild Cognitive Impairment (MCI), and healthy controls. As this pilot is observational, clinicians use the PDT primarily as an advanced data integration and visualisation tool, rather than for direct intervention planning.

The PDT collects and organises the multi-domain assessments conducted at baseline and at the two-year follow-up, including neurological examinations, neuropsychological assessments, swallowing function questionnaires (such as MASA, EAT-10, DHI, FOIS), and instrumental evaluations like EEG, MRI, and video fluoroscopy. Blood-based biomarkers, DNA, proteomic, and metabolomic data are also stored and visualised within the digital twin interface. By presenting this wide range of information in a unified and structured manner, the PDT enables clinicians to track each participant's cognitive and physical trajectories over time.

Clinicians leverage the PDT's analytics features to identify trends and correlations between cognitive decline and swallowing impairment, as well as to examine the broader interplay between neurodegenerative progression, malnutrition, and functional abilities. For example, by visualising how changes in cognitive scores align with evolving swallowing difficulties or biomarker profiles, clinicians gain a clearer understanding of disease mechanisms and progression patterns.

The PDT's capacity for cohort-level visualisation also allows researchers to compare subgroups (Alzheimer's, MCI, controls) on specific outcomes, facilitating hypothesis generation and supporting the refinement of future study protocols. Additionally, by streamlining data access and longitudinal patient tracking, the PDT improves follow-up processes, ensuring that clinical teams can more efficiently monitor disease progression and schedule timely assessments.

Overall, in this observational pilot, the PDT enhances data management, supports hypothesis-driven research, and empowers clinicians with holistic, real-time views of each participant's status, ultimately contributing to a more nuanced understanding of the links between cognition, swallowing, and neurodegenerative disease in older adults.

4.5.9 Pilot #9: ANA

In Pilot #9, the PDT will serve as a dynamic, clinician-facing platform to support the design, delivery, and monitoring of interventions tailored to the five core components of frailty: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity. Throughout the study, the PDT enables clinicians to consolidate all relevant participant data—from baseline assessments to longitudinal follow-ups—into a unified digital profile for each enrolled individual.

During the initial co-creation phase, the PDT will help clinicians capture qualitative feedback and usability insights from the first 25 participants, informing refinements to the digital solution prior to the larger pilot. As the pilot progresses, the PDT becomes the primary tool for real-time tracking and visualisation of participant status, integrating monthly self-reported data (falls, hospitalisations, weight loss), physical performance measures, and clinical assessments. The system's dashboard functionality provides clinicians with clear overviews of each participant's frailty indicators and alerts for clinically significant events (e.g., a new fall or marked weight loss), ensuring timely follow-up and intervention.

Importantly, the PDT's analytics layer supports personalised intervention planning by synthesising current and historical data to identify evolving risks and guide care decisions. Clinicians can use the platform to create, document, and adjust individualised care plans based on observed changes in frailty status, as well as to monitor adherence to prescribed interventions. For example, a drop in walking speed or an episode of unintentional weight loss, flagged by the PDT, could prompt the care team to intensify physical activity programs or coordinate nutritional support.

Beyond individual-level management, the PDT also facilitates group-level analysis, enabling clinicians and researchers to evaluate the impact of the intervention across the pilot population and iteratively improve the digital solution's features. The system's role in streamlining data collection, analysis, and intervention documentation ultimately enhances the effectiveness and scalability of frailty-targeted care in the COMFORTage project.

4.5.10 Pilot #10: AMI

In Pilot #10, the PDT will play a pivotal role in supporting clinicians to monitor, analyse, and optimise the impact of sensorimotor interventions, such as exercise and Transcutaneous Electrical Nerve Stimulation (TENS), on postural control and walking capacity among adults aged 40–75 years. The PDT will act as a clinician-facing digital environment where each participant's multimodal data—including proprioception measures, postural control metrics, walking ability, force steadiness, and neurophysiological biomarkers—are aggregated, visualised, and tracked longitudinally.

During the study, clinicians will use the PDT to record baseline and follow-up assessments from a variety of sources: standardised clinical tests of balance and gait, wearable sensor outputs, neurophysiological data reflecting spinal and corticospinal adaptations, and participant-reported outcomes on independence and daily function. This comprehensive data integration allows the PDT to provide real-time analytics, identifying trends and subtle improvements or deteriorations in sensorimotor performance throughout the intervention.

The platform's simulation and analytics modules support personalised tracking by comparing individual trajectories to expected patterns of adaptation. If the PDT detects that a participant is not responding as anticipated (e.g., limited improvement in force steadiness or persistent gait instability), clinicians can use this information to tailor rehabilitation plans or adjust intervention intensity. Furthermore, group-level analytics within the PDT can support researchers in evaluating the differential effects of exercise versus combined exercise-TENS protocols, as well as the predictive value of force steadiness as a biomarker for intervention response.

Ultimately, by consolidating all assessment data and intervention history, the PDT empowers clinicians to deliver highly individualised rehabilitation and preventive care, closely monitor participant progress, and document intervention outcomes for research and quality improvement. This functionality will not only advance clinical practice within the pilot but also generate critical evidence to inform future strategies for preserving mobility and independence in older adults.

4.5.11 Pilot #11: INTRAS

In Pilot #11, the PDT will function as a powerful data integration and visualisation platform to support both sub-studies, focusing on enhancing technology acceptance among older adults and validating novel digital tools for early detection and wellbeing. Since this is an observational pilot, clinicians and research staff will use the PDT primarily for advanced data analysis, real-time monitoring, and cohort-level insights, rather than for direct intervention planning.

For Sub-study #1 (Enhancing technology acceptance and user experience with assistive technologies), the PDT will aggregate individual-level data regarding participants' engagement with various assistive technologies, their feedback on usability, satisfaction, perceived usefulness, and impact on quality of life (QoL) and social engagement. The platform will allow clinicians and

researchers to visualise changes in subjective wellbeing and technology adoption patterns over time, supporting the evaluation of co-creation strategies and nudging interventions implemented throughout the pilot. This holistic perspective will help identify which motivational strategies are most effective for promoting technology acceptance and improving wellbeing among older adults.

For Sub-study #2 (Enhancing acceptance and validation of an early detection VR tool), the PDT will serve as a central repository for longitudinal neuropsychological and behavioural data generated from the use of the GRADIOR DLA PREVENTION VR tool. The PDT will enable clinicians to visualise cognitive screening results, track neuropsychological marker changes, and identify early signs of cognitive decline in participants. By consolidating VR-based assessment results with other available health and lifestyle data, the PDT will help clinicians and researchers gain a comprehensive understanding of how digital tools perform in real-world settings and how user acceptance evolves over time.

Across both sub-studies, the PDT will empower researchers to conduct advanced analytics on technology adoption trends, participant satisfaction, and the longitudinal impact of digital tools on health and wellbeing. The platform's dashboard functionalities will facilitate both individual and group-level monitoring, supporting evidence generation for future digital health solutions aimed at ageing populations.

4.5.12 Pilot #12: CERTH

In Pilot #12, the COMFORTage PDT will play a central role in orchestrating, monitoring, and evaluating multifaceted interventions delivered within the nZEB Smart House Digital Innovation Hub. This state-of-the-art living lab leverages a rich ecosystem of intelligent IoT devices, robotics, AR/VR platforms, and behavioural analytics to create a highly interactive, real-world testbed for older adults at high risk of dementia and frailty.

Within this pilot, clinicians will utilise the PDT platform to comprehensively visualise and manage all intervention activities. The PDT will integrate data streams from health-related IoT sensors, smart home devices, virtual reality training games, and social robots, presenting a unified dashboard that displays behavioural, physiological, and cognitive performance metrics for each participant. For example, the PDT will continuously update with ambient sensor readings—such as activity levels, sleep quality, and environmental parameters—as well as results from cognitive virtual games (like the Virtual Supermarket, Memory AR and Linguistic games), enabling longitudinal tracking of functional and cognitive changes over the course of the intervention.

Through the PDT, clinicians can monitor the effects of AR/VR-based cognitive and physical exercises, analyse behavioural patterns, and detect early deviations that may signal emerging risks or intervention needs. The integration with the SmartHome platform and data analytics tools allows for the dynamic assessment of physiological measurements—such as heart rate, movement, and sleep—directly within the living environment. Social robots and virtual coaching agents also interact with participants, and their data (including engagement metrics, detected emotional states, and conversational logs) are reflected in the PDT, providing a holistic view of patient well-being.

Most importantly, the PDT enables clinical professionals to personalise care plans in real-time, adapting interventions based on the rich, multi-domain data captured in the smart home setting. They can review adherence to prescribed cognitive and physical activities, receive alerts regarding abnormal behaviours or sudden changes in health status, and evaluate the overall impact of the smart home interventions on quality of life and independence. The PDT's data visualisation and decision support features empower clinicians to fine-tune intervention strategies, maximise participant engagement, and optimise health outcomes for each individual.

By serving as the digital backbone for integrating, analysing, and translating smart home data into actionable clinical insights, the PDT in Pilot 12 demonstrates how digital twin technology can enable highly personalised, technology-enhanced dementia and frailty care in real-world environments.

4.5.13 Pilot #13: AUTH

In Pilot #13, the COMFORTage PDT will serve as a vital clinical interface for monitoring and optimising participatory educational interventions aimed at enhancing digital and health literacy among older adults. Deployed within the Thessaloniki Active and Healthy Aging Living Lab (Thess-AHALL), the PDT platform enables clinicians to integrate, visualise, and analyse a wide array of health and engagement data collected throughout the four phases of the pilot—needs assessment, co-design, implementation, and evaluation.

During the needs assessment and co-design phase, clinicians will leverage the PDT to collect and synthesise baseline demographic, health, and digital literacy information from participants. This data, securely managed within the PDT, will inform the customisation of educational content and help tailor ageing delivery to the individual needs of each participant. As the educational ageing unfolds, the PDT will track participants' progress, engagement levels, and any reported health or behavioural changes, presenting clinicians with real-time analytics and trends. For instance, data from the COMFORTage TET platform and Healthentia digital tools—such as attendance, activity completion, and health self-reports—will be aggregated within the PDT, allowing for continuous monitoring of individual and group outcomes.

As the pilot transitions into the optimisation and digital guidance phase, the PDT's dynamic data integration capabilities will facilitate the personalisation of training activities and the adaptation of digital guidance based on participant feedback and ongoing assessments. Clinicians will use the PDT to identify individuals who may require additional support or targeted interventions, adjusting training materials and guidance accordingly. Throughout the evaluation phase, the PDT will serve as a centralised resource for analysing intervention impact—enabling clinicians to assess improvements in digital and health literacy, autonomy, and quality of life, and to document outcomes that will inform future recommendations.

By providing an integrated clinical dashboard for data-driven decision support, participant monitoring, and outcome evaluation, the PDT empowers clinicians to personalise and optimise educational interventions in real time. This fosters a more responsive and effective approach to digital and health literacy training, ultimately enhancing health autonomy and well-being among older adults in the Thess-AHALL living lab environment.

4.5.14 PDT KPIs and evaluation framework across pilots

The evaluation of the PDT within the COMFORTage pilots is guided by a set of KPIs that capture the multifaceted impact and success of the platform across all deployment scenarios. These KPIs are designed to reflect both the core technical functionalities and the broader clinical and research objectives of each pilot, ensuring that the PDT delivers measurable value in real-world healthcare environments.

The KPIs encompass domains such as data integration, AI-powered analytics, usability and satisfaction for clinicians, effectiveness in risk stratification and patient management, and the capacity for supporting advanced research (e.g., longitudinal monitoring, cross-site analysis, and harmonised data sharing). They also address the specific requirements of both interventional and observational pilots, recognising the different roles the PDT plays—from supporting clinical decision-making and intervention delivery to enabling advanced data analytics and hypothesis generation.

Table 6: PDT KPIs per Pilot study

Pilot No.	Pilot Lead / Title	KPI Domains Evaluated
1	UNIMAN	Quality and accuracy of individualised risk profiles; Visual analytic use
2	NKUA	Comprehensiveness of trend visualisation; Clinician engagement
3	ACE	Biomarker identification through population analysis; Actionable recommendations per individual
4	FPG	Population-based risk biomarker factor identification; Adherence tracking
5	MUL	Long-term participant monitoring; Visual reporting for awareness
6	AUTH	Use of scenario-based tools; Personalisation in intervention
7	MFU & VSTE	Multi-factor analysis of daily activities and clinical data to create intervention plans; Uptake of preventive plans
8	CING	Usability of visualisation tools for clinicians; Cross-group analysis
9	ANA	Physical intervention plan effectiveness; Intervention documentation
10	AMI	Completeness of sensorimotor data logs; Clinical response to graphs
11	INTRAS	Satisfaction with visual feedback; Change in technology adoption
12	CERTH	Breadth of integrated data streams and in-house technologies; Intervention planning for Quality of Life
13	AUTH	Visualised progress for individuals; Uptake of educational guidance

4.6 Ethical and legal considerations

The implementation of the PDT in COMFORTage pilots brings forth a range of ethical and legal considerations, given the sensitive nature of the data processed, the use of AI, and the involvement of vulnerable populations such as older adults and individuals with cognitive impairment. Ensuring that the design, deployment, and use of PDT are ethically sound and legally compliant is a core requirement of the project and is addressed through a robust ethics management framework established within COMFORTage.

4.6.1 Compliance with European and national regulations

PDT operations strictly adhere to the European Union's General Data Protection Regulation (GDPR), the Clinical Trials Regulation (CTR), and the Medical Device Regulation (MDR), as well as national laws in participating countries. All data processed through PDT, including health, lifestyle, and genetic data, are handled in accordance with the seven key principles of data protection: lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality, and accountability that are handled in VHP Platform. Before any processing, explicit informed consent is obtained from participants or their legal representatives, with clear communication of data uses, risks, and rights—including the right to withdraw at any stage.

4.6.2 Ethics by design and trustworthy AI

The PDT incorporates "ethics by design" principles in alignment with the EU Ethics Guidelines for Trustworthy AI. This means that at each step—from system design to implementation and

operation—ethical aspects such as human autonomy, prevention of harm, fairness, transparency, and explicability are embedded. The PDT is subject to explainability analysis as described in 4.2.

4.6.3 Data privacy, security, and secondary use

All PDT-related data flows are mapped and subject to privacy-by-design measures. Data are pseudonymised or anonymised wherever feasible, and strong security protocols are implemented to prevent unauthorised access, ensuring confidentiality and integrity. The secondary use of data (for research beyond the original purpose) is permitted only with explicit participant consent and subject to review by ethics committees. Data sharing is governed by strict Data Processing Agreements between partners, and all transfers outside the EU are subject to adequacy requirements or additional safeguards.

4.6.4 Transparency, explainability, and human oversight

The AI components of the PDT, including predictive models and explainability tools, are subject to transparency and accountability requirements under the forthcoming EU AI Act. Clinicians using the PDT receive clear information on how model outputs are generated and are empowered to override automated recommendations, maintaining human oversight at all times. Results are communicated to users and participants in an understandable manner, with appropriate attention to the risk of stigma or discrimination arising from AI-based risk assessments. (see section 4.2)

4.6.5 Oversight, auditing and continuous ethical monitoring

Ethical oversight is maintained through the COMFORTage Ethics Manager and the independent Ethics Advisory Board (EAB), which includes experts in bioethics, law, and clinical care. All clinical studies utilising the PDT are subject to review and approval by the relevant institutional ethics committees. The ethics oversight mechanisms encompass not only study approval but also ongoing monitoring, with regular ethics audits, compliance checks, and stakeholder engagement activities ensuring that ethical and legal standards are continuously met. Findings from data protection audits and ethical reviews are used to drive corrective actions and improvements, reinforcing the project's commitment to responsible and trustworthy AI in healthcare.

5 Future PDT Versions

This section outlines the planned evolution of the PDT framework within the COMFORTage project, focusing on enhancements that will improve its scalability, adaptability, and clinical impact. It presents a roadmap for future DT versions, including expanded data modalities, more sophisticated simulation capabilities, and greater personalisation through adaptive learning and patient feedback loops. The section also explores integration with emerging technologies and standards, such as federated learning and the European Health Data Space, to support broader deployment across healthcare systems. These future developments aim to strengthen the DT's role in proactive, precision care for dementia, frailty, and beyond.

5.1 Roadmap and testing plan

The development of the PDT within the COMFORTage project follows a structured, iterative roadmap (Figure 14) that ensures alignment with clinical objectives, technical requirements, and regulatory standards. As visualised in the provided workflow diagrams, the roadmap begins with the clear definition of project objectives and scope, emphasising the early identification of use cases such as risk prediction, disease progression modelling, and individualised intervention planning. This is followed by comprehensive data acquisition and integration, drawing on heterogeneous sources—including neuroimaging, cognitive assessments, electronic health records (EHRs), bi-omarkers, and IoT-enabled devices—collected across all thirteen pilot sites.

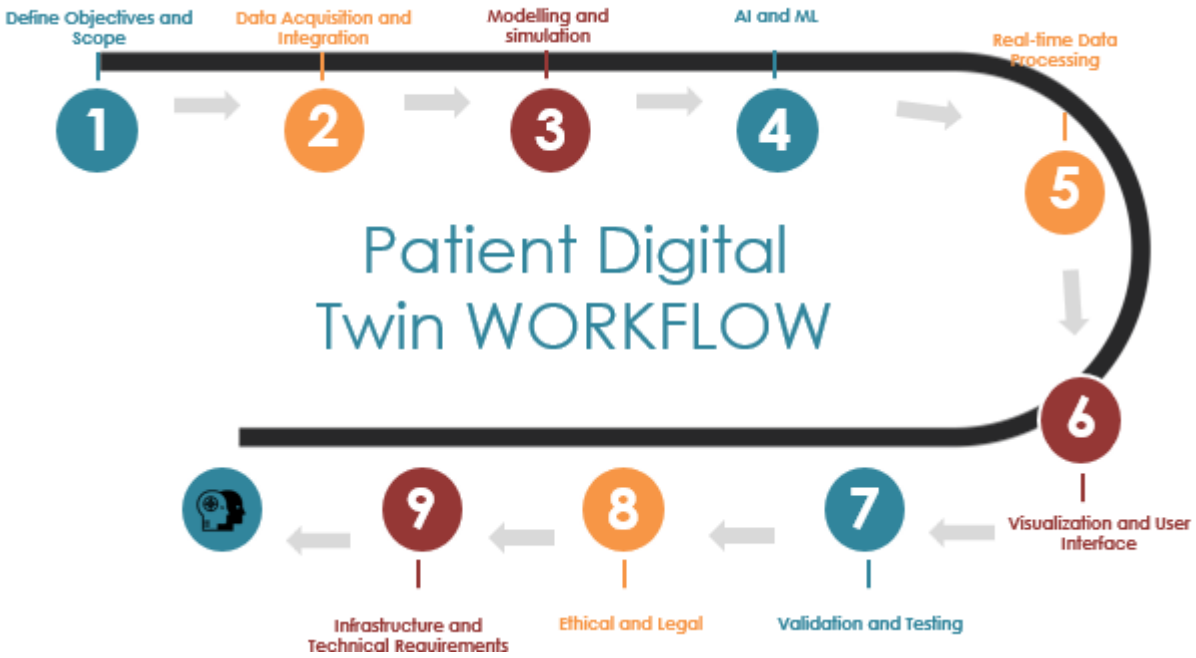

Figure 14: PDT roadmap in milestones.

Currently, the project is in the stage of large-scale data collection and platform design. Special emphasis is placed on harmonising data streams from different pilot studies, ensuring semantic interoperability, and developing robust technical infrastructure capable of secure data management and real-time integration. Parallel to data integration efforts, modelling and simulation activities are underway, utilising state-of-the-art machine learning and physiological modelling approaches to capture disease trajectories and simulate intervention scenarios. More specifically, the actual time plan can be seen in Figure 15.

#	Activity	YEAR 1				YEAR 2				YEAR 3			
		M06			M12				M24				M36
1	Define Objectives and Scope												
2	Data Acquisition and Integration												
3	Modelling and Simulation												
4	AI and ML												
5	Real-time Data processing												
6	Visualization and User Interface												
7	Validation and Testing												
8	Ethical and Legal												
9	Infrastructure and Technical Requirements												

Figure 15: PDT implementation time plan.

The next phases in the roadmap involve the deployment and integration of advanced AI modules and XAI tools, primarily within the context of the ICML and the COMFORTage VHP. Real-time data processing capabilities will be implemented to support dynamic model updating and continuous risk monitoring. Subsequent stages will focus on developing intuitive visualisation and user interface components to ensure the accessibility and usability of the PDT by clinical professionals at each pilot site.

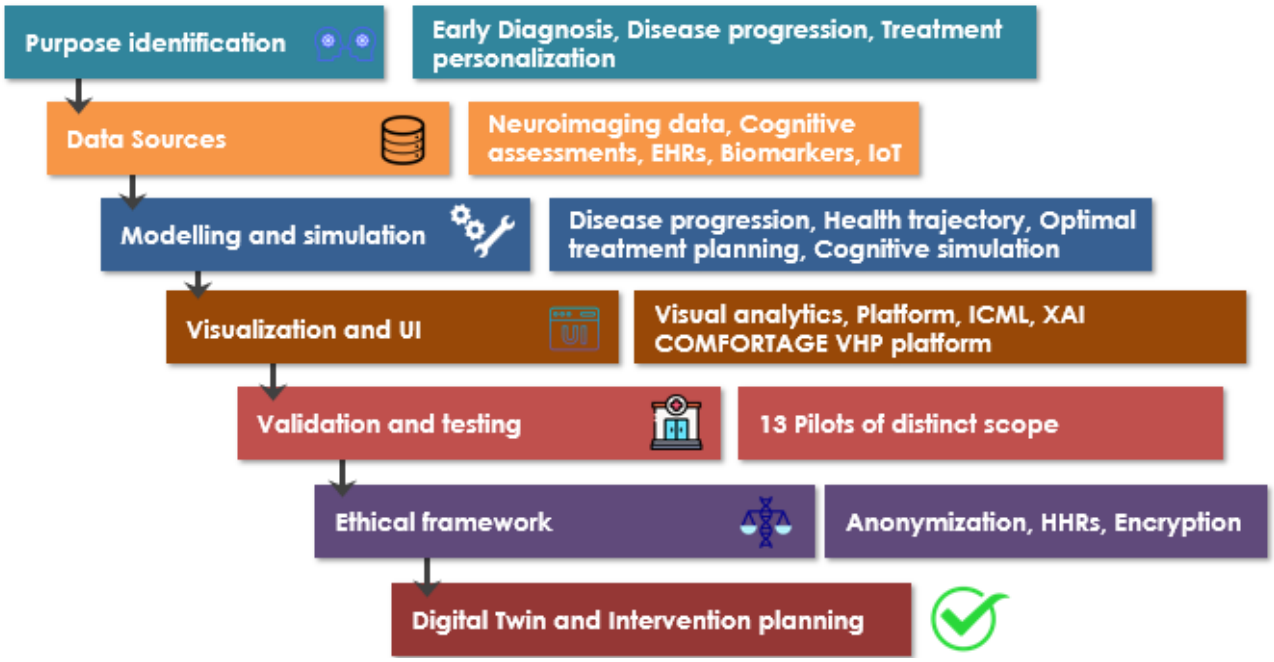

Figure 16: Implementation of milestones into actions

A key milestone in the roadmap is the systematic validation and testing of the PDT across all pilots. This phase includes both technical validation (ensuring data quality, system reliability, and integration across the CDSS, ICML, XAI, and VHP platforms) and clinical testing (assessing predictive

accuracy, decision support effectiveness, and impact on clinical workflows). Ethical and legal compliance is continuously monitored, with particular attention to anonymisation, data security, and adherence to GDPR and EHDS standards.

The final steps of the roadmap involve infrastructure optimisation, continuous stakeholder feedback loops, and progressive scaling for broader clinical use. The PDT platform is envisioned as an adaptive, modular system, enabling the iterative refinement of models, workflows, and interfaces based on pilot site experiences and user feedback.

The testing plan for the PDT is comprehensive and multi-layered, encompassing both technical and clinical validation. During the initial technical integration phase, testing will focus on data ingestion, semantic mapping, and secure transfer between pilot-specific databases and the central VHP. Integration tests will ensure seamless communication between the PDT, CDSS, ICML, XAI framework, and other COMFORTage platform components. Unit and system tests will verify core functionalities, including data acquisition, model training, simulation, and user interface rendering.

Pilot-specific testing will be carried out at all thirteen sites, with each pilot responsible for verifying that the PDT correctly ingests and represents local clinical data, provides accurate analytics, and supports the intended clinical workflows. For interventional pilots, additional tests will validate the effectiveness of the PDT in supporting intervention planning and monitoring, as well as user experience and decision support quality. For observational pilots, emphasis will be placed on the reliability of analytics, longitudinal tracking, and integration with site-specific research protocols.

All testing activities will be conducted in compliance with ethical and legal requirements, including data anonymisation and informed consent protocols. User acceptance testing will be performed with end-user clinicians to evaluate usability, interpretability of XAI outputs, and the overall impact on clinical efficiency and patient care. Continuous feedback from pilot sites will inform further iterations, ensuring the platform remains robust, secure, and fit for purpose as it advances toward full-scale deployment.

5.2 Integrated features and platform evolution

The current PDT platform as shown in the provided screenshots already supports a wide range of essential functionalities for clinicians, including secure log-in, patient management, structured medical records, care plan design, device integration, and opt-in educational tools. The interface is intuitive, supporting easy navigation between patient records, appointments, device connections, and care activities, with clear dashboards for data visualisation and patient adherence tracking.

To further advance clinical decision-making and research within the COMFORTage framework, the PDT platform will be substantially extended with several core features:

- **Integration of CDSS**

A robust CDSS module will be embedded into the PDT platform to provide real-time, evidence-based recommendations to clinicians during patient assessment and care planning. This will leverage both structured and unstructured data within the platform—including clinical, behavioural, and lifestyle information—enabling personalised guidance for diagnosis, intervention selection, and risk assessment. The CDSS will interface with AI-derived insights as well as established clinical pathways, ensuring that the support provided aligns with the latest best practices.

- **Explainable AI (XAI) features**

To foster clinician trust and transparency in AI-driven recommendations, the platform will incorporate advanced XAI capabilities. For every recommendation or risk prediction generated by the AI models, the clinician will have access to explanations detailing the underlying data and logic that contributed to the suggestion. This includes visual indicators of key contributing features (e.g., specific biomarkers, trends in adherence, or lifestyle changes) and textual rationales, making it easier for clinicians to interpret and communicate results to patients and families.

- **Simulation testing scenarios: What-if analysis**

Another innovative upgrade will be the introduction of simulation testing scenarios, often referred to as "What-if analysis." This feature will allow clinicians to explore and test the potential outcomes of different interventions or lifestyle modifications before applying them in practice. By adjusting modifiable risk factors—such as medication, exercise frequency, nutrition, or cognitive training—the platform will dynamically simulate and present the projected impact on patient outcomes, such as cognitive decline risk, frailty status, or adherence. This empowers clinicians to tailor care plans based on personalised, predictive insights, reducing trial-and-error and optimising patient management.

- **Interoperability and Integration**

The platform will be designed for seamless interoperability with other major components of the COMFORTage ecosystem, including integration with the ICML, the VHP, and the Opt-in tools. Data flows will be standardised and secured, supporting both multi-site pilot studies and longitudinal data collection.

- **Continuous platform evolution**

Alongside these major enhancements, the PDT platform will continue to evolve, incorporating new data visualisation tools, enhanced patient engagement modules, advanced notification and alerting mechanisms, and further support for integration of medical devices. All new features will be developed in close collaboration with clinicians and researchers, ensuring usability and alignment with the diverse needs of the COMFORTage pilots.

In summary, the evolution of the PDT platform will transform it into a comprehensive, clinician-focused digital environment supporting advanced clinical decision support, explainable AI, interactive simulation, and robust integration—driving innovation in dementia and frailty care across the COMFORTage pilot network.

5.3 PDT alignment with GAIA-X framework

We think it is useful to begin with two definitions: First, the GAIA-X framework is a European initiative focused on creating a secure, transparent, and interoperable data infrastructure that ensures digital sovereignty. Second, a PDT is a highly sensitive and deeply personal DT infrastructure that relies on secure, ethical, and highly trusted environments for health data exchange. So, it can be easily understood that PDT is a prime and critical candidate for GAIA-X compliance. Achieving full compliance for a PDT involves aligning its architecture and operations with GAIA-X's core principles and technical specifications, with an amplified focus on patient data sovereignty, privacy, and ethical considerations. We will see below how a PDT infrastructure can achieve full GAIA-X compliance:

5.3.1 Core GAIA-X principles and their application to a PDT

GAIA-X's principles are fundamental to its compliance framework. A PDT infrastructure must embody these principles with the highest possible standards:

1. **Data sovereignty and self-determination (*elevated criticality*):**
    - **PDT application:** This moves from paramount to central and non-negotiable. The patients must have ultimate, granular control over *their own* health data. This includes:
        - **Dynamic, granular consent management:** Beyond simple "yes/no" consent, patients need to define who can access specific data points (e.g., genetic data, medication history, lifestyle data), for what purpose (e.g., treatment, research, personalised health advice), for how long, and under what conditions. This requires sophisticated consent dashboards and potentially blockchain-based consent registries for immutability and auditability.
        - **Right to erasure and rectification:** Patients must be able to request correction of inaccurate data and, where applicable, the erasure of data, in line with GDPR.
        - **Transparency of data flow:** Patients need clear, understandable information about every instance their PDT data is accessed, by whom, and for what reason. This calls for highly detailed audit logs and user-friendly interfaces for patients to monitor their data's journey.
        - **"My data, my choice" principle:** The PDT must be designed from the ground up to empower the patient as the primary data controller, not just a data subject.
2. **Transparency and trust (*major requirements*):**
    - **PDT application:** Trust is foundational in healthcare. So:
        - **Unprecedented self-description:** Every component of the PDT – from the sensors collecting data to the AI models processing it and the visualisation tools presenting it – must provide crystal-clear, machine-readable self-descriptions. This includes not just technical specs but also detailed information on data privacy measures, ethical considerations, and algorithmic transparency (e.g., how AI models derive predictions).
        - **Accredited certification (GAIA-X label level 3 is almost a must):** For a PDT, lower GAIA-X label levels might not suffice. A PDT handling highly sensitive medical data will likely require GAIA-X label level 3 (*the highest level*), ensuring exceptional data handling, security, and legal control by European providers, and guaranteeing European control over the digital infrastructure to avoid extra-territorial data access claims (e.g., from the US Cloud Act and its implications for Europe).
        - **Explainable AI (XAI):** Given the use of AI in PDTs for diagnosis, prognosis, or treatment recommendations, XAI becomes critical. Patients and clinicians need to understand *why* a certain prediction or recommendation was made, not just *what* it is. This is crucial for trust and accountability.
3. **Security and data protection (*highest standards possible*):**
    - **PDT Application:** This is where the bar is set exceptionally high.

- **Zero-trust architecture:** A PDT infrastructure must implement a zero-trust model, where no entity (user, device, application) is trusted by default, regardless of its location.
- **Advanced cryptography:** Beyond standard encryption, we should consider of homomorphic encryption or secure multi-party computation for certain analyses, allowing computations on encrypted data without decrypting it, further safeguarding privacy.
- **Data minimisation, pseudonymisation, anonymisation:** Strictly adhering to data minimisation principles. Where possible, data should be pseudonymised or anonymised *before* being used for research or secondary purposes. The process and re-identification risk of pseudonymised data must be clearly documented.
- **Compliance with GDPR and EHDS:** A PDT must comply with GDPR's strict requirements for personal data, ***and*** with the specific provisions of the recently entered into force European Health Data Space (EHDS, 26/3/2025). The EHDS aims actually to facilitate the secure and trusted exchange of health data across the EU for both primary (healthcare delivery) and secondary (research, innovation, policy-making) uses, empowering individuals with control over their data. This involves:
  - **Electronic Health Record (EHR) exchange formats:** Adherence to standardised EHR formats (e.g., HL7 FHIR) for interoperability.
  - **Health data access bodies:** Interaction with national health data access bodies that will govern secondary use of data.
  - **Pan-European health data infrastructure:** The PDT will need to be part of this wider infrastructure.

4. **Interoperability and portability (*medical specifics*):**
   - **PDT application:** Interoperability is crucial for a holistic view of patient health.
     - **Healthcare-specific standards:** Mandatory adoption of international and European healthcare data standards (e.g., HL7 FHIR, SNOMED CT, LOINC for clinical terminology and messaging; DICOM for medical images).
     - **Semantic interoperability:** Use of common ontologies and clinical terminologies to ensure that data from different medical devices, hospitals, labs, and research institutions can be semantically understood and integrated into the PDT.
     - **Model portability:** Not just data, but also the computational models (e.g., physiological models, disease progression models) that constitute the "twin" must be portable and interoperable.
5. **Federation and open ecosystem (*data spaces for health*):**
   - **PDT application:** This means participating in dedicated healthcare data spaces.
     - **Health data spaces:** The PDT infrastructure must be designed to integrate with and contribute to existing and emerging GAIA-X compliant European Health Data Spaces. Projects like "HEALTH-X dataLOFT" and "Dataspace4Health" are already demonstrating how GAIA-X principles apply to health data and can be consulted if needed.
     - **Collaboration with research and clinical networks:** Facilitating secure, governed data sharing with research institutions, clinical trial networks, and public health authorities, always under strict patient consent.

5.3.2 Criteria a PDT should meet for GAIA-X compliance

It was shown in the previous section what are the fundamental principles of GAIA-X framework in relation to PDTs. Let's see now what are the criteria which a PDT should meet to comply with the GAIA-X framework.

1. **Patient-centric consent framework:**
    - **Dynamic & granular consent:** Allowing patients to grant, revoke, and manage consent for specific data types, purposes, and timeframes through a user-friendly interface.
    - **Explicit consent for secondary Use:** Allowing clear separation of consent for direct care vs. research, public health, or commercial uses.
    - **Blockchain-based consent audit trail (*recommended*):** Allowing immutable, verifiable records of consent actions.
2. **Robust security and privacy by design:**
    - **GAIA-X label level 3:** Achieving the highest GAIA-X compliance label for critical health data.
    - **State-of-the-art encryption:** For both data at rest and in transit.
    - **Homomorphic encryption/secure multi-party computation:** Suitable for privacy-preserving analytics on sensitive data.
    - **Strict access control:** Role-based access control (RBAC) and attribute-based access control (ABAC) with strong authentication (e.g., multi-factor authentication, eIDAS-compliant identities).
    - **Data minimisation:** Collecting and processing only the absolutely necessary data.
    - **Pseudonymisation/anonymisation:** Implementing robust techniques to protect patient identity for secondary use, with careful re-identification risk assessment.
3. **Full Interoperability with Healthcare standards:**
    - **HL7 FHIR compliance:** Meant for structured exchange of clinical data.
    - **SNOMED CT, LOINC, DICOM:** Towards semantic interoperability and medical imaging.
    - **IHE (Integrating the healthcare enterprise) profiles:** For consistent data workflows.
4. **Transparency and explainability:**
    - **Comprehensive self-descriptions:** Clear, auditable documentation of data sources, processing algorithms, data privacy safeguards, and security measures.
    - **Explainable AI (XAI) capabilities:** Providing insights into how AI models arrive at their conclusions, making them interpretable for clinicians and understandable for patients.
    - **Clear data provenance:** Tracking the origin and transformations of every data point within the PDT.
5. **Ethical guidelines integration:**
    - **Ethical review and oversight:** Establishment of ethical review boards and ongoing ethical assessments of the PDT's development and deployment.
    - **Bias detection and mitigation:** Establishment of active measures to identify and mitigate algorithmic bias in AI models that could lead to discriminatory outcomes.
    - **Fairness and non-discrimination:** Ensuring that the PDT's benefits are accessible to all, and it does not exacerbate existing health inequalities.

5.3.3 How the PDT should be improved in case it is not yet aligned

One should ask what the necessary actions are so that a currently operational PDT gets compliant to GAIA-X framework. The below multi-faceted approach should be followed:

1. **Fundamental architectural redesign (*high extent*):**
    - **Shift from isolated to federated:** The PDT should move away from silo-data systems to a distributed, federated architecture that can connect with other GAIA-X compliant services and data spaces.
    - **Edge/Cloud continuum:** Some re-design should be needed for processing sensitive data close to the source (edge computing) while leveraging federated cloud resources for complex analytics, ensuring data sovereignty.
    - **Modular and composable services:** A breakdown of the PDT into modular services that can be independently described, certified, and combined, adhering to GAIA-X's composability principles.
2. **Implementation of GAIA-X federation services (GXFS) (*high extent*):**
    - **Identity & trust management:** GXFS should be adopted for secure, verifiable digital identities (e.g., self-sovereign identities - SSI for patients, clinicians, organisations).
    - **Federated catalogue:** The PDT's services and datasets should be integrated into the GAIA-X federated catalogue for discoverability and trust.
    - **Sovereign data exchange (SDX) connectors:** IDS connectors or similar GAIA-X compliant mechanisms should be implemented for secure, policy-controlled data sharing.
3. **Legal and governance framework alignment (*highest extent*):**
    - **GDPR and EHDS compliance:** Thorough legal audits should be conducted and all necessary technical and organisational measures should be implemented to meet these stringent regulations. This includes data protection impact assessments (DPIAs) specific to PDTs.
    - **Data usage agreements:** Robust, machine-readable data usage agreements should be developed that reflect patient consent and GAIA-X principles.
    - **Clear accountability:** Clear roles and responsibilities should be defined for all stakeholders involved in the PDT ecosystem regarding data processing and security.
4. **Certification and auditing (*continuous extent*):**
    - **Pursue GAIA-X label certification:** Need to actively work towards obtaining GAIA-X label level 3 for the PDT services. This involves self-assessments and external audits by Conformity Assessment Bodies (CABs).
    - **Regular security audits and penetration testing:** Need for continuous assessment of the PDT's security posture.
    - **Transparency reports:** Need for periodically publish reports on data usage, security incidents, and compliance status to maintain trust.
5. **Human-centric design and ethical integration (*crucial extent*):**
    - **Patient empowerment interfaces:** Intuitive interfaces should be developed that give patients meaningful control over their data and transparency into its use.
    - **Ethical AI development:** Ethical considerations should be embedded throughout the AI lifecycle, from data collection to model deployment and monitoring.
    - **Informed consent education:** Clear, accessible information should be provided to patients about what a PDT entails, how their data will be used, and their rights.

In order to summarise the above analysis to a central message, we should note that to align a PDT with GAIA-X framework is not something small. Instead, it requires a deep, systemic transformation across technology, legal frameworks, governance, and ethical considerations. In other words, placing the patients at the absolute centre of the data ecosystem, and ensuring their sovereignty, privacy, and trust are the paramount design principles here. The effort is indeed significant, but it's essential for building a truly trustworthy and ethically sound digital health infrastructure. i

5.4 KPIs and Evaluation

The following tables present key performance indicators (KPIs) and evaluation objectives associated with the development, deployment, and impact assessment of the PDT framework within COMFORTage. Table 8 outlines quantitative KPIs related to PDT implementation, visualisation features, and integration of data/AI assets, along with their evaluation methods and monitoring frequency. In addition, Table 9 complements this by detailing qualitative evaluation objectives focused on clinician usability and the PDT's impact on patient management, providing a holistic view of the system's effectiveness across technical and clinical dimensions.

Table 7: KPIs related to PDT and Evaluation method

KPI Code	KPI Description	Target	PDT Contribution/Asset	Evaluation Method	Frequency
2.1	Instances of PDTs Modelling & Implementation	≥ 5	Deployed PDTs per pilot/site	Platform deployment & pilot reports	Quarterly
5.4	Different Visualisations Developed	≥ 5	Dashboards, trend charts, risk projections	UI/UX review, user feedback	Quarterly
-	Data/AI Assets Integrated with VHP	1200	Digital Healthcare Plans, AI recs, datasets	Asset registry, integration reports	Semi-annual

Table 8: PDT objectives and evaluation

Objective	Objective Description	Target	PDT Contribution/Asset	Evaluation Method	Frequency
QA	Clinician Usability & Satisfaction	Qualitative	Visualisations, recommendations	Survey/interview analysis	Pilot end
Impact	Improvement in Patient Management/Risk Stratification	Qualitative	End-to-end PDT workflow	Pilot outcome data analysis	Annual

6 Conclusions

This working paper has presented a comprehensive overview of the conceptualisation, development, integration, and early evaluation of PDTs as part of the COMFORTage project, aiming to advance personalised treatment and monitoring for dementia and frailty. The document began by identifying the critical research gaps in the state of the art, particularly the lack of user-friendly, integrated platforms that can effectively translate the potential of digital twin technology into actionable insights for healthcare professionals. Through an in-depth literature review and analysis of global initiatives, the relevance and transformative potential of PDTs in addressing the multidimensional challenges of dementia and frailty care were established.

The core methodology adopted in COMFORTage emphasises the integration of multi-modal, longitudinal data from both retrospective cohorts and ongoing pilot studies, leveraging advanced AI and simulation models to deliver real-time, personalised risk assessments and intervention recommendations. The layered and modular architecture of the PDT system was described in detail, outlining the flow from data acquisition and modelling to analytics, simulation, and visualisation. The incorporation of a wide range of validated opt-in tools, spanning cognitive, functional, and social domains, ensures comprehensive and holistic assessment of the older adult population.

A central contribution of this work is the design and implementation of the COMFORTage Digital Twin Platform, explicitly developed to overcome usability and interoperability barriers that have hindered the adoption of similar technologies in healthcare. The platform brings together all relevant patient data, AI-driven recommendations, device management, and decision-support functionalities within an accessible, role-based interface tailored to the needs of clinicians. The inclusion of the CDSS, ICML, XAI, and the VHP further enriches the decision-making environment, fostering collaborative, evidence-based, and transparent clinical workflows.

Importantly, the document outlined the planned and ongoing integration and usability testing of the PDT platform across thirteen diverse pilot studies. These pilots span interventional and observational designs, different settings, and a range of target populations, providing a robust testbed for validating the utility and generalizability of the PDT approach. For each pilot, specific examples were provided to illustrate how the platform supports clinicians in data-driven decision-making, personalised care planning, risk stratification, and the monitoring of intervention outcomes.

A thorough discussion of the ethical and legal considerations was also included, with particular focus on data governance, privacy, consent management, and alignment with the evolving EHDS and GAIA-X frameworks. The roadmap and testing plan presented a clear pathway for future platform enhancements, integration of advanced simulation and explainability features, and the structured evaluation of KPIs to measure impact and guide iterative improvements.

Overall, the working paper demonstrates that the COMFORTage PDT framework represents a significant advancement in digital health technology, addressing major gaps in personalisation, integration, and clinical utility. By uniting data-driven modelling, advanced analytics, and a user-centred design philosophy, the platform sets a new standard for real-world implementation of digital twins in dementia and frailty care. The work conducted to date lays a solid foundation for future scaling, sustainability, and cross-European adoption, ultimately aiming to improve patient outcomes, care quality, and system efficiency in the management of complex age-related conditions. This working paper is the first version of a series of working papers entitled “Digital Twins for Personalised Treatment and Monitoring” that seek to encapsulate and describe the work conducted in the context of the task – “Digital Twins for Personalised Treatment and Monitoring”. A second and last version of this document “Digital Twins for Personalised Treatment and Monitoring II” is planned to be submitted on M36 of the project.

6.1 Limitations and challenges

Despite the significant advancements described in this working paper, several important limitations and challenges remain for the PDT approach in COMFORTage. One of the foremost challenges is the complexity of integrating heterogeneous data from diverse sources and pilot sites. Each site may use different protocols, data formats, and clinical workflows, making harmonisation and standardisation a continuous effort. Achieving high-quality, interoperable data streams is essential for the reliability of the digital twin models, but this process is both time-consuming and technically demanding.

A related issue is the generalisability of the PDT platform across varied healthcare settings. Although COMFORTage benefits from testing in thirteen different pilots, each with its unique population and operational context, there is always a risk that models and workflows optimised for one site may not transfer seamlessly to another. This requires ongoing customisation, site-specific adaptation, and continuous engagement with clinical teams to ensure relevance and usability in real-world conditions.

User adoption and usability represent another key area of concern. While the platform has been designed with clinician needs in mind, real-world environments often present unexpected barriers to effective use, such as limited digital literacy, workflow constraints, or resistance to change. Continuous feedback from end users, as well as comprehensive training and support, are crucial to foster trust, encourage sustained use, and optimise the clinical value of the system.

Ethical and legal considerations also pose ongoing challenges. The collection and processing of sensitive health data requires strict adherence to data privacy regulations, including GDPR, the EHDS, and the GAIA-X framework. Ensuring dynamic and granular consent, robust data security, transparency, and accountability is complex, particularly as the platform expands in scope and capability. Any failure to maintain the highest standards in data governance could undermine user trust and legal compliance.

On the technical front, some of the platform's more advanced features—such as real-time simulations, ICML/XAI modules, and interactive "what-if" scenario testing—are still under development and require further validation. Ensuring that these tools deliver meaningful, interpretable, and actionable insights for clinicians, while maintaining high performance and data security, remains a significant task for future work.

Finally, a major challenge lies in the rigorous evaluation and validation of the platform's impact on patient outcomes, clinical workflows, and system-level efficiencies. Longitudinal data collection, harmonised assessment protocols, and collaborative analytics across all pilot sites are necessary to demonstrate real-world value. Furthermore, ensuring sustainability and widespread adoption beyond the project lifecycle will require ongoing investment, integration with broader healthcare infrastructure, and adaptation to emerging standards and user needs.

In summary, while the COMFORTage PDT platform sets a new benchmark for the implementation of digital twins in dementia and frailty care, its future success will depend on continuous efforts to overcome these technical, clinical, regulatory, and organisational challenges. Addressing these limitations will be central to ensuring that the benefits of personalised, data-driven care are realised across diverse European healthcare environments.

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