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TARGET: a major European project aiming to advance the personalised management of atrial fibrillation related stroke

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Conflict of Interest: • SOM is the Principal Investigator of the TARGET project on health virtual twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244) and senior investigator in the ARISTOTELES project on artificial intelligence for the management of chronic long-term conditions (grant agreement no. 101080189), both funded by the EU's Horizon Europe Research & Innovation programme. She is also a member of the board of the ART (Ageing Research Translation) of Healthy Ageing Network funded by the Biotechnology and Biological Sciences Research Council (BBSRC).

• IO is the methodological lead of the TARGET project on health virtual twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244) and partner lead in the ARISTOTELES project on artificial intelligence for the management of chronic long-term conditions (grant agreement no. 101080189), both funded by the EU's Horizon Europe Research & Innovation programme.

• MO is the coordinator of the TARGET project on health virtual twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244). He is also the program leader for CAISR Health, funded by the Swedish Knowledge Foundation (grant number 20200208 01 H), a significant Swedish initiative on information-driven care that involves several industrial partners, a regional healthcare provider and Halmstad University.

• GYHL is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement no. 899871), TARGET project on health virtual twins for personalised management of atrial fibrillation and stroke (grant agreement no. 101136244) and ARISTOTELES project on artificial intelligence for the management of chronic long-term conditions (grant agreement no. 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme.

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Abstract:
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TARGET: a major European project aiming to advance the personalised management of atrial fibrillation related stroke via the development of health virtual twins technology and artificial intelligence

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Atrial fibrillation (AF) is the most prevalent heart arrhythmia globally, resulting in severe complications, substantial financial costs, and significant resource use(1). AF frequently goes unnoticed until the patient presents with AF-related complications (e.g. stroke, heart failure, dementia and hospitalisations), particularly with brief episodes of AF that spontaneously revert to sinus rhythm.

In Europe, stroke (a major complication of AF) is a leading cause of death and the top cause of disability. The pathophysiology of AF-related stroke (AFRS) involves severe neurological deficits which considerably worsens prognosis. While risk factors for poor stroke outcomes are known, current AF prediction models have limitations and fail to account for dynamic changes in risk profiles (2,3). In addition, the importance of various stroke risk factors in AF may have changed over the years, for example, sex differences in AFRS risk(4,5). This has had implications for stroke risk stratification, concerning the use of the well-validated CHA_2DS_2-VASc score or a non-sex version (CHA_2DS_2-VA)(6–8). Nevertheless, recognising the residual cardiovascular risks associated with AF despite anticoagulation, the management of this condition has moved towards a more holistic or

integrated care approach, which has been associated with better clinical outcomes(9,10). This has led to such an approach recommended in contemporary guidelines(11–14).

Stroke prevention is central to AF management (15). Indeed, oral anticoagulant treatment in AFRS presents a dilemma: early initiation may increase haemorrhagic transformation risk, while delays can lead to recurrent ischemic strokes. Post-stroke rehabilitation, crucial for reducing risks and improving outcomes, lacks consensus on effective protocols, particularly personalised approaches based on functional outcomes in AFRS patients. This uncertainty can result in the exclusion of patients who would benefit from rehabilitation or the inefficient use of healthcare resources on those unlikely to help.

Given this background, the European Union, through the Horizon Europe research programme, has funded the "Health Virtual Twins for the Personalised Management of Stroke Related to Atrial Fibrillation" (TARGET) project (grant agreement no. 101136244). TARGET's consortium involves nineteen partners including universities, hospitals, companies and a charity. The project kicked-started in January 2024 under the scientific leadership of Prof Sandra Ortega-Martorell (Principal Investigator, Liverpool John Moores University, LJMU), the methodological leadership in AI and virtual twins of Prof Ivan Olier (LJMU), the clinical leadership in AF and stroke of Prof Gregory Lip (University of Liverpool), and the coordination of Prof Mattias Ohlsson (Lund University).

TARGET aims to address several clinical challenges within the AFRS disease pathway by focusing on a three-pillar approach: *Pillar I) Risk Prediction* and dynamic, longitudinal monitoring of AF and the subsequent risk of developing AFRS; *Pillar II) Diagnosis and Management* of AFRS, including early identification of stroke aetiology, prediction of outcomes and risk of stroke recurrence; and *Pillar III) Rehabilitation*, focusing on identifying predictors of functional independence and quality of life in AFRS survivors and facilitating personalisation of rehabilitation. The project will be underpinned by the development of virtual twins of patients, which will be used to model novel, causal AI models embedded into decision-support tools for point-of-care applications. These novel models and tools will be evaluated via in-silico simulated clinical trials and on newly collected data from clinical observational studies.

Figure 1 summarises the main activities of the project.

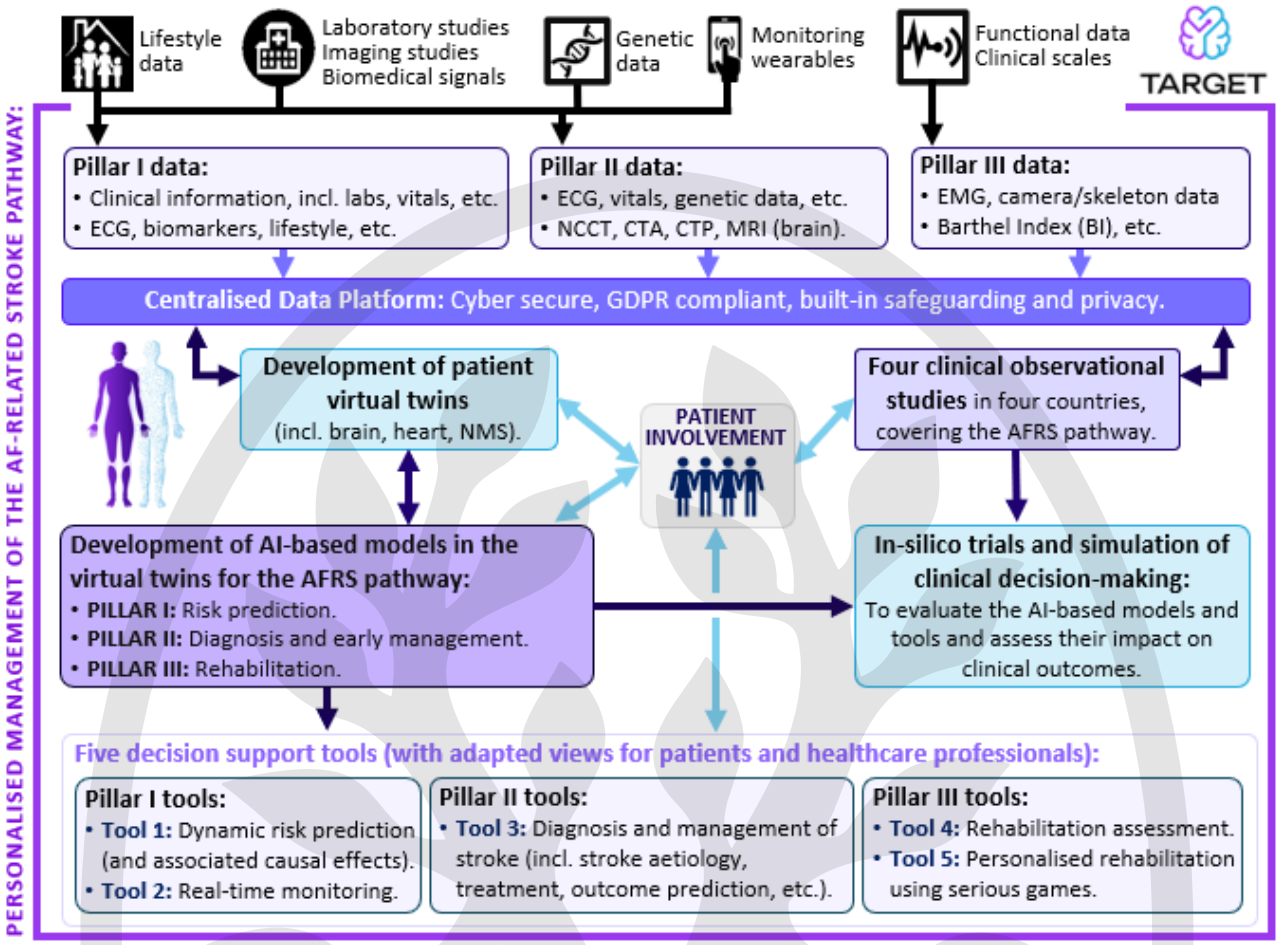

Figure 1. Summary of main activities of the EU project TARGET.

TARGET has a strong focus on the personalisation of health technologies for improved and more cost-efficient solutions in disease prevention, diagnosis, treatment and monitoring, better patient outcomes and well-being in the AFRS disease pathway, and reduced disease burden. TARGET will work closely with healthcare professionals (HCPs) and patients, who will be at the core of the research and the project, to co-develop the tools and ensure their acceptance and adoption.

For Pillar I, one of the tools (Tool 1) will embed TARGET models to provide HCPs with personalised risk prediction scores along with the causal factors; and help patients understand how modifiable factors, e.g., lifestyle changes, could impact risk (e.g. increase or decrease) over time (dynamic, longitudinal monitoring of risk). TARGET will also build on Isansys' (partner) Patient Status Engine (PSE) to integrate and evaluate personalised risk prediction models when monitoring patients. The PSE is an end-to-end medical device (CE Class IIa) and a configurable platform that generates and analyses real-time physiological data. TARGET will adapt the PSE dashboard (Tool 2)

embedding novel risk prediction and AF detection models, to dynamically estimate patients' clinical trajectories and monitor AF.

The tool for Pillar II (Tool 3) will provide HCPs with information about stroke aetiology, personalised outcome prediction and recurrence risk scores (including the dynamic changes in the risk) along with associated causal effects or factors, and optimised recommendations for oral anticoagulation resumption in AFRS. For patients, it will be limited to personalised outcome prediction and recurrence risk scores, where considered that this information would benefit patients.

For Pillar III, one of the tools (Tool 4), will provide HCPs with personalised predictions of functional outcomes along with associated causal effects or factors, the individual rehabilitation needs of patients, and a dynamic and personalised assessment of independence level and health-related quality of life after rehabilitation. Patients will use this tool to learn their personalised prediction of functional outcomes, and how treatment adherence could impact their recovery trajectory over time (dynamic assessment). A second tool (Tool 5) will be a serious game, which will recommend personalised therapeutic sessions involving specific rehabilitation goals and motivation mechanisms; game genres suitable for stroke patients' rehabilitation, with visually appealing and intuitive environments; capturing patients' gestures and gait during gameplay to provide real-time feedback; and inclusion of different types of exercises/movements into the games that gradually increase difficulty and complexity as patients' rehabilitation progresses.

Before wider implementation into clinical practice, external validation of the novel virtual twins-based AI models and tools is required. To this aim, TARGET will perform the four prospective cohort studies (Table 1) in four countries (Figure 2), where clinical and non-clinical information will be collected from the participants.

Table 1. Brief summary of TARGET's four clinical observational studies.

CS 1	Name:	I*n*telligent m*o*nitoring *t*o pr*e*dict *a*trial *f*ibrillation (NOTE-AF)
	Setting:	Liverpool University Hospital NHS Foundation Trust (LUHFT). Liverpool, United Kingdom
	Leader:	Prof Ingeborg Welters

	Description:	This study will validate Pillar I novel models and tools (Tools 1 and 2) for prediction of clinically relevant AF episodes in patients hospitalised for elective surgery or with acute illness. Continuous monitoring will be performed using the Isansys PSE.
CS 2	Name:	Using virtual twin-based AI models to detect AF and improve stroke outcomes (TAILOR)
	Setting:	Stroke Unit at Hospital del Mar (IMIM). Barcelona, Spain. Radboud (RUMC). Nijmegen, The Netherlands.
	Leaders:	Dr Eva Giralt-Steinhauer (IMIM) and Dr Anil Tuladhar (RUMC)
	Description:	This multi-centric study will validate Pillar II novel models embedded into Tools 2 and 3, on patients with ischaemic stroke and no history of AF. The study aims to enhance AF detection using Tool 2, find novel image markers, identify AFRS aetiology and predict stroke outcomes (e.g. at 3 months) using Tool 3.
CS 3	Name:	Improving recovery: a new screening tool for selecting high-intensity and moderate-intensity AFRS rehabilitation programs (PEARL)
	Setting:	Rehabilitation Unit at IMIM. Barcelona, Spain.
	Leader:	Dr Esther Duarte
	Description:	This study will determine differences in rehabilitation needs of acute post-stroke patients and 1, 3 and 6 months post-stroke outcomes (i.e. body structure and function, activity and participation outcomes). Outcomes will be assessed at baseline (stroke unit discharge) and will be compared with Tool 4 assessments.
CS 4	Name:	Follow-up study of stroke patients using sensors for the evaluation of functional ability and compensatory movements (FOSTER)
	Setting:	Revalidatieziekenhuis Inkendaal (RI). St-Pieters-Leeuw, Belgium
	Leader:	Prof Degelaen
	Description:	This study will follow up stroke patients admitted to RI after hospital

discharge, to assess the use of sensor measurements obtained by Tool 5 to quantify patient recovery, which will be compared with standardised clinical assessments. We will also assess whether sensors can help detect compensatory strategies during daily life-based activities.

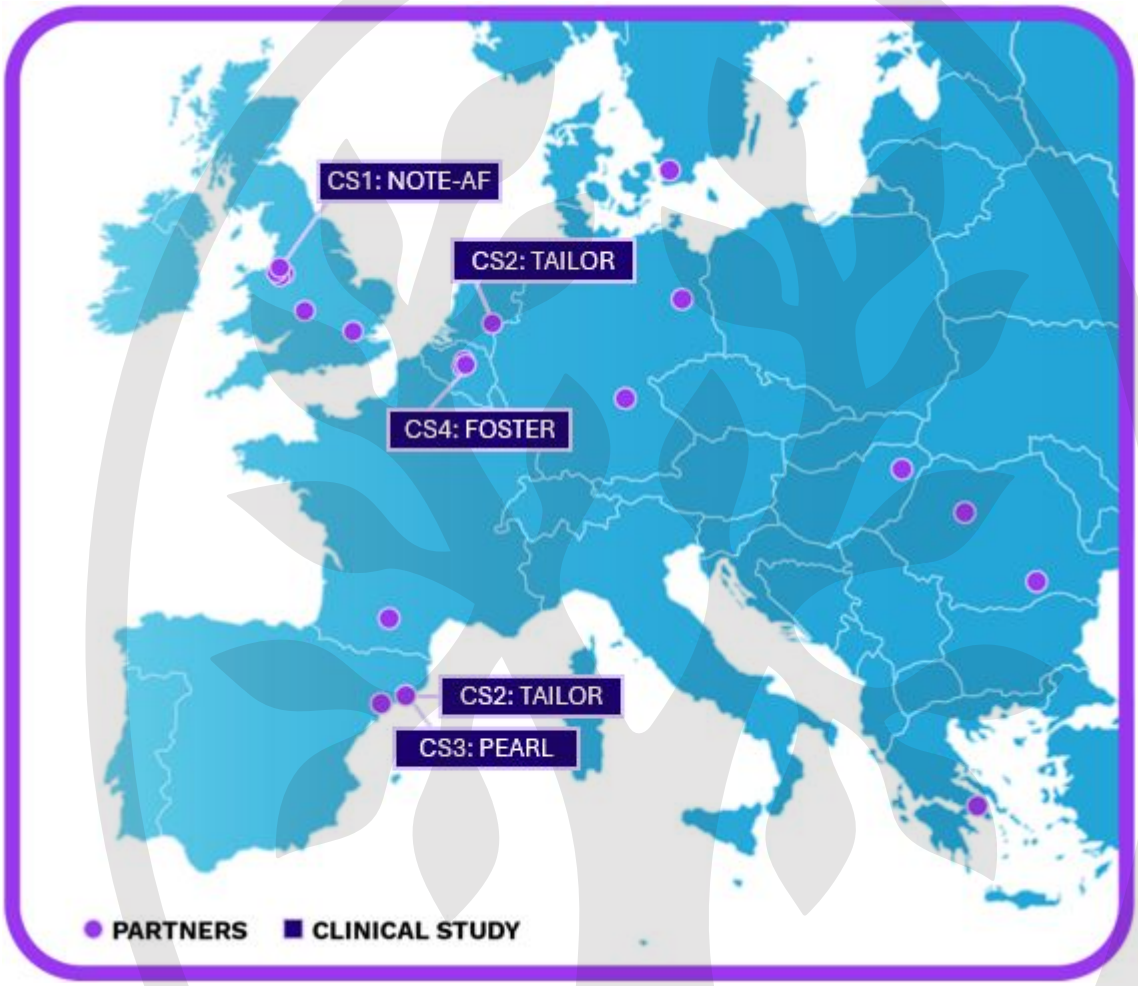

Figure 2. TARGET will conduct four prospective observational clinical studies (CS) in 4 countries. Purple dots represent the nineteen partners of the TARGET Consortium.

In-silico clinical trials will be employed to accelerate the translation of the virtual twin models developed. They will be developed based on TARGET's clinical observational studies to allow for further evidence generation on the effect of these models and their impact on translational outcomes covering the AFRS disease pathway (Pillars I-III). For this, virtual populations of patients will be derived from data collected in the observational clinical studies, as well as from held-out data used for the development of the virtual twins. The in-silico clinical trial simulations will then test candidate virtual twin-based AI models in scenarios such as: i) predicting onset of AF episodes (CS1), ii)

predicting stroke outcomes (CS2), and ii) improving selection of therapy intensity (CS3). Whereas the real-world studies are observational, the in-silico trials will be interventional to determine the impact of the tools on clinical decision-making relevant to the clinical studies and whether improved outcomes are observed.

TARGET will generate a high societal, scientific, technological, and economic impact; and foster translational biomedical research into practice by increasing and accelerating our understanding of the drivers of AF and AFRS, enhancing the knowledge of the disease onset and progression, and developing better tools for improved care management and treatment of AFRS patients.

Supplementary material

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