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Prospective evaluation of atrial fibrillation-related stroke patients in rehabilitation programme (PEARL), clinical study for the 'Health virtual twins for the personalised management of stroke related to atrial fibrillation (TARGET)' project: a protocol for a prospective cohort analysis

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ABSTRACT

Introduction Rehabilitation is recognised as a cornerstone of recovery in the stroke care pathway, and the intensity of therapy is closely related to functional recovery. However, longitudinal studies investigating differences in short- and long-term outcomes between ischaemic and haemorrhagic strokes remain scarce. In particular, it is not yet clear whether atrial fibrillation-related stroke (AFRS) entails specific rehabilitation needs or leads to different functional outcomes compared with non-AFRS. Identifying aetiology-specific recovery patterns may support the development of predictive models of stroke recovery and optimise the use of rehabilitation resources.

Methods and analysis In this prospective observational cohort study, patients with stroke will be recruited from the Stroke Unit of a tertiary hospital. Patients discharged from the unit who require inpatient rehabilitation will be allocated to one of two rehabilitation centres offering programmes of differing intensity: high-intensity (three to five sessions daily) or moderate-intensity (one to two sessions daily). Allocation criteria are based on standard clinical parameters, including age, prior functional level, neurological impairment and cognitive and medical status. The primary outcome is functional recovery, measured using the Barthel Index at 6 months post-stroke. Rehabilitation needs, the time course of disability and final outcomes will be compared between AFRS and non-AFRS groups.

Ethics and dissemination The study has received approval from the local Research Ethics Committee of Hospital del Mar, Barcelona, Catalonia, Spain (Ref. 2023/11172/I). Written informed consent will be obtained from all participants prior to inclusion. Study findings will be disseminated through peer-reviewed publications, conference presentations and communication activities aligned with the TARGET project dissemination strategy.

Trial registration number NCT07253974.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A prospective cohort design with standardised, multidimensional assessments enables consistent measurement of functional status, participation and quality of life across rehabilitation domains.
⇒ Inclusion of both patients with atrial fibrillation-related stroke (AFRS) and non-AFRS allows comparison within a single, systematically collected dataset.
⇒ Allocation to rehabilitation intensity is based on predefined clinical criteria, reflecting routine practice but without randomisation.
⇒ The single-centre design may limit generalisability to other healthcare settings.
⇒ Exclusion of patients not admitted to the rehabilitation programme may introduce selection bias.

INTRODUCTION: BACKGROUND AND RATIONALE

Stroke rehabilitation and prognosis

According to the World Stroke Organisation,[1] stroke is the second-leading cause of death and the third-leading cause of death and disability combined worldwide, with nearly 50% of survivors experiencing chronic disability.[2] The global burden of stroke has increased substantially in recent decades due

to population growth, ageing, improved survival rates and a rising prevalence of multiple modifiable risk factors.[3]

Stroke care encompasses rehabilitation, which is recognised as a cornerstone of the recovery period. Rehabilitation is a patient-centred process delivered by a multidisciplinary team, including physiotherapists, occupational therapists, speech therapists, nurses, social workers and neuropsychologists, and led by physicians trained in Physical Medicine and Rehabilitation.[4] The intensity of rehabilitation therapy is directly related to functional recovery; however, there is considerable variability in both the amount of time of therapy delivery and the techniques applied in therapy sessions.[3] There remains a need for improved description and standardisation of stroke rehabilitation protocols to enhance our understanding of current clinical practices and to strengthen both the internal validity and generalisability of clinical trial findings.

Following discharge from the acute stroke unit, post-acute inpatient care for patients with stroke may include inpatient rehabilitation facilities and long-term care hospitals.[4] Intensive inpatient rehabilitation programmes provide hospital-level care and deliver rehabilitation at a minimum of 3 hours of therapy per day, 6 days a week,[5 6] to restore lost body functions and promote autonomy/independence in activities of daily living (ADL). Patients treated in these inpatient rehabilitation facilities demonstrate better functional outcomes and higher rates of return to community living than those treated in general wards or long-term care hospitals.[4 7–10] In contrast, long-term care centres and skilled nursing facilities offer moderate-intensity programmes that consist of one to two daily rehabilitation sessions.

Among patients with moderate-to-severe acute post-stroke deficits, substantial inter-individual variability in recovery trajectories makes outcome prediction challenging.[11] Evidence suggests that both initial motor impairment and long-term motor recovery are influenced by the severity of corticospinal tract damage and the integrity of alternative motor pathways.[12–14] Advanced neuroimaging techniques, including MRI, diffusion tensor imaging and functional MRI, provide comprehensive in vivo assessments of microstructural and functional brain connectivity. Despite these advances, no validated gold standard currently exists for predicting functional outcomes after stroke in routine clinical practice. To date, 21 stroke registries across 19 different countries have been documented, and some clinical trials aimed at developing data-driven prediction models are ongoing.[15] These efforts reflect increasing interest among rehabilitation teams in optimising interventions across the stroke care continuum.

Differences between aetiology

Most published studies do not differentiate between stroke aetiologies; at best, they classify events as ischaemic or haemorrhagic. Longitudinal studies assessing short- and long-term outcomes according to stroke aetiology remain scarce, particularly in the context of post-acute rehabilitation.

Atrial fibrillation (AF) affects approximately 1–2% of the general population and is associated with a five-fold increased risk of stroke. Strokes related to AF are predominantly cardioembolic in origin and are frequently characterised by greater initial severity. An analysis of 14 662 patients from the Nationwide Danish Stroke Registry demonstrated that individuals with AF-related stroke (AFRS) experience more severe strokes and face higher morbidity and mortality compared with patients without AF.[16] Consequently, these patients were more likely to have significant disability by hospital discharge.

Despite the recognised clinical severity of AFRS, limited information is available regarding the specific rehabilitation needs and long-term functional outcomes of this patient group. It remains unclear whether patients with AFRS demonstrate distinct recovery trajectories or differential responses to rehabilitation compared with patients with non-AFRS. Emerging research indicates that AF subtype and related cardiac structural and functional markers may predict poorer functional and cognitive outcomes following ischaemic stroke.[17]

Identifying differences in stroke aetiology and recovery patterns may support the development of predictive models of rehabilitation outcomes and facilitate more efficient and personalised allocation of rehabilitation resources. Improved understanding of these differences is particularly relevant in healthcare systems with limited rehabilitation capacity, where optimisation of intensity and timing of therapy is critical.

The role of PEARL in the TARGET project

The PEARL study is part of the TARGET project, a Horizon Europe-funded programme focused on risk prediction, diagnosis, management and rehabilitation of AFRS (https://target-horizon.eu/)[18 19] (Grant Agreement No. 101136244). TARGET aims to advance personalised stroke care through the integration of clinical data, artificial intelligence and digital twin technologies.

One of the core objectives of the TARGET project is to identify predictors of functional independence and quality of life (QoL) in AFRS survivors, with the ultimate goal of facilitating personalised and optimised rehabilitation strategies. In this context, PEARL is designed as a prospective observational cohort study conducted over a 2-year period within a tertiary Rehabilitation department. The study focuses on characterising recovery trajectories following acute ischaemic stroke, with particular emphasis on comparing patients with AFRS to those without, in terms of functional outcomes after admission to either high- or moderate-intensity inpatient rehabilitation programmes.

Patients are not randomised but allocated to treatment arms based on predetermined clinical and functional criteria, consistent with routine clinical practice and based on the 2008 Catalan Stroke Rehabilitation Plan,[20] developed through expert consensus. Although a revised

framework was approved in 2022, it has not yet been fully implemented, and current allocation continues to rely on established clinical protocols. These criteria ensure appropriate territorial distribution across designated rehabilitation centres in Catalonia and consider clinical variables such as the National Institutes of Health Stroke Scale (NIHSS) score at admission, premorbid modified Rankin Scale (mRS) and cognitive status.

Data generated within the PEARL study will contribute both to the primary study objectives and to the broader TARGET consortium activities. Specifically, PEARL will provide real-world longitudinal rehabilitation data to support the development, calibration and validation of digital optimisation tools and digital twin technologies aimed at improving rehabilitation planning and outcome prediction in patients with AFRS.[21]

Hypothesis

We hypothesise that there will be a significant difference in functional outcomes at 6-month post-stroke, as measured by the Barthel Index, between patients with AFRS and non-AFRS enrolled in high- and moderate-intensity rehabilitation programmes.

Objectives

Given the distinct characteristics of AFRS and the potential for differential rehabilitation trajectories, this study aims to address the following objectives:

Primary objective

To compare functional outcomes at 6-month post-stroke, measured using the Barthel Index,[22] between patients with AFRS and non-AFRS within high-intensity and moderate-intensity rehabilitation programmes.

Secondary objectives

- To evaluate differences in occupational therapy, physiotherapy, speech therapy and cognitive outcomes between patients with AFRS and non-AFRS.
- To assess the efficacy and efficiency of rehabilitation according to stroke aetiology (AFRS vs non-AFRS) and rehabilitation intensity.
- To identify clinical and functional predictors of favourable rehabilitation outcomes in patients with AFRS .

METHODS

Study design and setting

The PEARL study (conducted within the framework of the EU TARGET project) is a prospective observational cohort study conducted at the Rehabilitation Department of Hospital del Mar, Barcelona, Catalonia, Spain. This tertiary rehabilitation centre serves a catchment population of approximately 500 000 inhabitants and admits 200–250 patients with stroke annually for comprehensive rehabilitation.

Based on predefined clinical and functional criteria, patients will be allocated to one of two study arms corresponding to rehabilitation programmes of different intensity: high-intensity rehabilitation (3–5 therapy sessions daily) or moderate-intensity rehabilitation (1–2 therapy sessions daily).

Patient inclusion started in November 2024 for high-intensity rehabilitation and in January 2025 for moderate-intensity rehabilitation.

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[23] statement to ensure transparency in reporting the findings of this prospective cohort.

Participants

Inclusion criteria

Screening criteria for both programmes, based on current clinical criteria, are as follows:

For both:

- Age≥18.
- First-ever intracerebral ischaemic stroke.

For the high-intensity rehabilitation programme:

- NIHSS score between 3 and 13.
- Previous mRS score 1–2.

For the moderate intensity rehabilitation programme:

- Any NIHSS score.
- Previous mRS score≥3.
- Cognitive or medical status that does not allow participation in high-intensity therapy.

Exclusion criteria

For both modalities of rehabilitation, exclusion criteria include intracranial haemorrhage, symptomatic haemorrhagic transformation, new infarcts occurring after the initial stroke, or other neurological or psychiatric conditions that could interfere with rehabilitation participation or outcome assessment.

All patients with ischaemic stroke admitted to the Stroke Unit-Hospital del Mar (average of 488 stroke admissions per year) will be screened by the rehabilitation team. A member of the rehabilitation team will prospectively follow every included patient throughout the inpatient rehabilitation programme until completion of the 6-month post-stroke follow-up is reached. Assessments will be performed in each of the two rehabilitation centres, to minimise missing data, ensure consistency and completeness of data collection and enhance fidelity.

Sample size calculation

Sample size calculations were performed separately for each rehabilitation intensity arm. Based on the observed prevalence of AF in the local stroke registry, an AFRS to non-AFRS ratio of approximately 1:3 in the high-intensity rehabilitation arm (ARM 1) and 1:1 in the moderate-intensity rehabilitation arm (ARM 2) was assumed. These sample sizes were planned to detect a 10-point difference in 6-month Barthel Index change between patients with AFRS and non-AFRS within each rehabilitation arm, assuming a common SD of 15, assuming alpha risk of 0.05 and a power of 0.8 in a two-tailed test.

For the high-intensity ARM 1, 90 subjects are necessary in the AFRS group and 30 in the non-AFRS, assuming a

dropout rate of 20% that has been anticipated, resulting in a total sample size of 120 patients required in this arm. For the moderate-intensity ARM 2, 48 subjects are necessary in the AFRS group and 48 in the non-AFRS, assuming a dropout rate of 25% anticipated in this arm, resulting in a total sample size of 96 patients required in this arm.

The total planned sample size across both rehabilitation intensity arms is 216 patients. The sample size provides adequate statistical power to detect clinically meaningful differences between patients with AFRS and non-AFRS within each rehabilitation intensity level, while accounting for anticipated attrition. The GranMo Sample size and power calculator (V.7.12) was used for all calculations

Study interventions and variables

Rehabilitation will begin in the acute care setting. After discharge from the stroke unit, all patients requiring inpatient rehabilitation will undergo standard multidisciplinary rehabilitation therapies, including physiotherapy, occupational therapy, speech therapy, social work and neuropsychology, delivered in an Intensive Inpatient Rehabilitation Facility (IRF) or a Skilled Nursing Facility (SNF). The choice of rehabilitation setting will depend on age, functional level before stroke, stroke impairment severity and cognitive and medical status, in accordance with routine clinical practice.

High-intensity rehabilitation programme in IRF

In the high-intensity rehabilitation programme in IRF, patients will receive a minimum of 3 sessions daily of Inpatient Physiotherapy (PT), Occupational Therapy (OT) and Speech-Language Pathologist (SLT). It implies periodic reviews that include evaluation of the patient's need for collaborative goal setting and cooperation in therapeutics. Each patient will be managed by an assigned team (physician, PT, OT and SLT). PT sessions address global mobility, balance, transfers and walking. During PT sessions, body functions such as movement, sensation, perception and cognition are trained, as well as ADL. SLT sessions are focused on dysphagia management, enhancing language skills and recovering from motor speech disorders. Sessions are individual, tailored to the patient's needs and graded by difficulty. OT sessions are sometimes performed in the patient's room, especially when training in dressing, eating, toilet use, personal hygiene and transfers. Otherwise, sessions are carried out in the physical, occupational or speech therapy rooms, where, although working individually, patients are together and can share their difficulties and progress with each other, promoting peer support.

Therapy sessions are distributed throughout the day and delivered on an individual basis, tailored to the patient's tolerance and needs, and special attention is paid to provide sufficient rest periods during the day. Patients may receive visits from caregivers, family members and friends. During the inpatient stay, patients and caregivers are invited to attend a 1 hour educational session led by an occupational therapist. This session aims to provide information, training and support on how to manage stroke deficits and consequences. This information and training intervention has been shown to have a positive impact on patients' and caregivers' satisfaction and perceived support.[24] At discharge, patients will be referred to home-based or outpatient rehabilitation services, as needed.

Moderate-intensity rehabilitation programme delivered in SNFs

In the moderate-intensity rehabilitation programme delivered in SNFs, patients will receive approximately one or two sessions of therapy per day, including PT, OT and SLT, when indicated. The criteria for therapy indication and the therapeutic approach will follow the same principles established in the high-intensity programme within IRFs, including individualised, goal-oriented interventions adapted to the patient's needs. Sessions will continue to address core domains such as mobility, functional independence, communication and swallowing, but delivered at a lower intensity appropriate for patients' clinical status and tolerance.

Study interventions and variables

Assessment time points

The assessment will be performed during inpatient rehabilitation at admission (T0), discharge (T1) and at follow-up at 3 months (T2) and 6 months (T3) after the acute stroke event. Inpatient assessments (T0 and T1) will be conducted at the rehabilitation centres. Follow-up assessments at T2 and T3 will preferentially be performed face to face; when this is not feasible, a structured telephone interview will be conducted using validated outcome measures.

The timing and content of all assessments are summarised in table 1.

Baseline assessments (T0)

Evaluation at admission includes epidemiological and premorbid data such as level of education, occupation, premorbid health status, civil status and the presence of a caregiver to support the patient. Event data collected will include the stroke type classification (TOAST and OXFORD), location of the lesion, side of the body affected by paresis, type of treatment received during acute phase and mRS. Clinical evaluation will include assessment of associated comorbidities with Charlson Comorbidity index, neurological deficit with NIHSS, metabolic risk ratio based on blood-analysis performed at admission to the stroke unit and previous sport level. A functional evaluation will include physiotherapy outcomes (Barthel Index (BI), Functional Ambulation Scale (FAC), Trunk Control Test, Berg Scale (BS), Test get-up and go (TUG) and 10-metre walk velocity; occupational therapy outcomes (Box and Block, 9-Hole Peg test (9HPT), Handgrip force), and cognitive and QoL measures (Montreal Cognitive Assessment (MOCA), quality of life evaluation. Speech and language therapy assessment will document the presence of dysphagia and

Table 1 Description and timing of study procedures

	Enrolment	Allocation	Follow-up				
Time-point	Medical interview_t0	0	Baseline (t0)	Discharge (t1)	3 months (t2)	6 months (t3)	Close
ENROLMENT							
Eligibility screen	x						
Informed consent	x						
Demographic data collection	x						
Allocation		x					
Data analysis							x
INTERVENTIONS							
High Intensity rehabilitation			x	x	x		
Medium Intensity Rehabilitation			x	x	x		
FUNCTIONAL ASSESSMENT							
Stroke and epidemiological data			x	x	x	x	
Occupational Therapy outcomes			x	x	x	x	
Physiotherapy outcomes			x	x	x	x	
Cognitive and mood outcomes			x	x	x	x	
Swallow and Language Therapy Outcomes			x	x	x	x	

aphasia. For assessing dysphagia and aphasia, the Volume-Viscosity Swallow Test[25] will be performed at admission, and aphasia will be registered in a dichotomic variable by the SLP.

Discharge assessments (T1)

At discharge from inpatient rehabilitation, functional evaluation performed at admission will be repeated. In addition, patient satisfaction with the rehabilitation treatment received will be assessed using a Likert-type numerical scale. Discharge destination and rehabilitation protocol will be assigned according to final functional status achieved during the IRF/SNF.

Follow-up assessments (T2 and T3)

The follow-up evaluations at 3 months (T2) and 6 months (T3) post-stroke will include a face-to-face evaluation. Functional evaluation will be repeated, and additional scales will be added, including the Hospital Anxiety Depression Scale (HADs) and return to the usual job. When face-to-face follow-up is not possible, a telephone interview will be conducted to assess BI, FAC, QoL and HADs.

Primary and secondary outcome measures

The *primary outcome measure* is functional recovery, defined as the change in BI score[26 27] between admission to inpatient rehabilitation (T0) and 6-month follow-up (T3).

Secondary outcome measures include changes in BI scores between T0 and T1 and between T1 and T3; changes in physiotherapy, occupational therapy, speech and language therapy, cognitive and mood outcomes; rehabilitation efficiency indicators such as length of stay; and final destination at discharge. All outcomes will be compared between patients with AFRS and non-AFRS and across both rehabilitation intensity programmes (IRF and SNF).

Rationale for selected outcome measures based on literature review

For acute care assessment, NIHSS and mRS scales have been chosen as variables. The NIHSS provides an assessment of stroke-related disability and permits monitoring in the acute phase.[28] It is known that elevated NIHSS scores (≥10) at admission correlate with 50% slower gait velocity recovery during rehabilitation.[7 29] Their rehabilitation programmes required greater intensity (≥3 hours/

day) to achieve functional gains comparable to patients with non-AFRS, particularly in addressing deficits in motor function and ADL.[30 31] The mRS[27] is a validated tool for assessing functional outcomes in patients with stroke, measuring disability levels from 0 (no symptoms) to 6 (death). It correlates with independence in daily activities and predicts long-term recovery trajectories, with scores≤2 indicating functional independence. The Catalan stroke registry incorporates mRS alongside metrics such as the BI to stratify disability severity and track rehabilitation progress.[4 31]

For cognitive, which has been correlated with limited functional gains and poor rehabilitation outcomes, mainly in older patients,[32] the MoCA has been chosen as the follow-up test for inpatient patients to 6 month follow-up. MoCA is a rapid 30-point screening tool designed to detect mild cognitive impairment in patients with stroke. It evaluates multiple domains: attention (via serial subtraction or vigilance tasks), executive function (trail-making B, verbal fluency), memory (delayed recall), language (naming, repetition), visuospatial abilities (cube copy, clock drawing), and orientation. A score <26/30 indicates cognitive impairment, with high sensitivity (90%) for detecting post-stroke vascular cognitive deficits.[33 34]

For mood assessment, HADS[35] is one of the most used tools to detect not only depression but also anxiety. Depression has a high prevalence after stroke,[36 37] predicting worse functional outcomes and worse QoL.

With regard to Functional Independence at 6-month follow-up, the BI has shown its usefulness. Patients with AFRS showed lower BI scores (≤60, indicating severe dependency) and reduced community discharge rates compared with their non-AFRS counterparts.[30]

For assessing upper limb function and daily living abilities in stroke rehabilitation, the 9HPT, Box and Block Test (BBT) and Lawton scale have been considered. The 9HPT quantifies fine motor dexterity by timing peg manipulation, where scores>25 s indicate significant impairment correlating with limitations in daily activities like buttoning or writing.[4 38 39] Conversely, the BBT evaluates gross manual dexterity through block transfer counts in 60 s; fewer than 30 blocks/minute predicts challenges in object manipulation (eg, utensil use) and bimanual coordination.[38 40] Together, these tests provide complementary insights: The 9HPT identifies fine motor deficits affecting precision tasks, while the BBT detects proximal arm impairments impacting reach and grasp. Their combined use prognosticates long-term functional independence and guides rehabilitation strategies, with stagnation in scores signalling needs for adaptive devices or intensified therapy.[4 38 40]

The Lawton Instrumental Activities of Daily Living (LIADL) Scale is a widely used tool for assessing more complex daily functions necessary for independent living in patients with stroke, such as managing finances, using transportation, medication management, shopping and housekeeping. In stroke follow-up, the LIADL Scale provides valuable information on a patient's ability to reintegrate into the community and maintain autonomy beyond basic self-care, complementing other functional assessments such as the BI. Its use helps clinicians identify specific areas of instrumental disability, guides tailored rehabilitation interventions and monitors progress or decline in independence over time, supporting comprehensive care planning for stroke survivors.[30 31]

For assessing gait and balance, gait velocity, the BS, TUG, and support devices have been included. Gait velocity, TUG, the Berg Balance Scale, and the test are widely used to monitor mobility and balance during stroke rehabilitation follow-up. Gait velocity, typically measured with the 10-metre walk test, provides a sensitive indicator of walking ability and community ambulation; slower speeds are linked to greater disability and increased fall risk. The Berg Balance Scale evaluates both static and dynamic balance through a series of functional tasks, with lower scores indicating a higher risk of falls and reduced independence. The TUG test assesses functional mobility by timing a patient as they rise from a chair, walk three metres, turn, return and sit down; prolonged times reflect impaired mobility and predict difficulties with daily activities. Regular follow-up with these measures allows clinicians to track recovery, adjust rehabilitation intensity and identify patients at risk for persistent disability or falls, thereby supporting individualised care planning and improved long-term outcomes in stroke survivors.[30 31]

End of study definition

The expected study duration is 24 months, including participant recruitment, completion of the 6-month post-stroke follow-up and results analysis.

The study will be considered complete once all enrolled participants have completed the 6 month (T3) follow-up assessment and the final dataset has been locked for statistical analysis. Following study completion, the final study report will be prepared and submitted to the funder in accordance with the requirements of the TARGET project.

Statistical methods/data analysis

This observational study will describe the functional outcomes of AFRS and non-AFRS of two patient groups undergoing rehabilitation programmes of different intensity over a 6-month period. Comparisons will be performed between groups of rehabilitation and intra-group, also considering AFRS and non-AFRS aetiology. The statistical analysis of the preliminary data will be carried out using the IBM SPSS Statistics V.21 package.

Descriptive analyses

Baseline demographic, clinical and functional characteristics will be summarised using means and SD or medians and IQRs for continuous variables, as appropriate, and frequencies and percentages for categorical variables. Normality of continuous variables will be assessed using Shapiro-Wilk tests and visual inspection of histograms.

Comparative analyses

For secondary analyses, comparisons across time points (admission and discharge or between admission and follow-up moments) will be performed using paired t-tests or Wilcoxon signed-rank tests for continuous variables, while χ^2 or McNemar's test will be used for categorical variables. A further step will involve identifying functional predictor factors for the AFRS and non-AFRS in both therapy arms. Where applicable, univariate analysis will be followed by multivariate logistic regression analysis.

Primary outcome analysis

The primary outcome, change in BI score between admission (T0) and 6-month follow-up (T3), will be analysed by comparing patients with AFRS and non-AFRS high-intensity and moderate-intensity rehabilitation programmes. Multivariable regression models will be used to adjust for potential confounding factors, including age, sex, baseline NIHSS score, premorbid mRS score and comorbidity burden. For this multivariable regression, variables will not be selected solely on the basis of univariable statistical significance. Candidate predictors will be assessed for redundancy and multicollinearity using clinical judgement, pairwise correlations and variance inflation factors. Because baseline differences and distribution of between patients with AFRS and non-AFRS may introduce confounding, all analyses will account for baseline imbalance using Inverse Probability Weighting (IPW).

Secondary outcome analyses

Secondary analyses will examine changes in functional outcomes across intermediate time points (T0–T1 and T1–T3), as well as domain-specific rehabilitation outcomes, length of stay and discharge destination. Where appropriate, univariable analyses will be followed by multivariable regression modelling to identify predictors of favourable rehabilitation outcomes, particularly in patients with AFRS.

Handling of missing data

Analysis will be performed by intention-to-treat condition. Participants who withdraw consent or are lost to follow-up will not be replaced. The sample size calculation accounts for anticipated attrition. Analyses will be conducted using all available data, and the extent and patterns of missing data will be reported. Sensitivity analyses may be performed if missing data exceed expected levels.

Statistical software and significance

Statistical significance will be settled at $p<0.05$, and all tests will be two-tailed.

Methodological and statistical approach will receive external support from the Statistics of IMIM—Institut Municipal d'Investigacions Mèdiques from Hospital del Mar..

EXPECTED RESULTS AND IMPLICATIONS

This clinical study is designed to compare the rehabilitation needs and functional outcomes in patients who experience AFRS versus those with strokes of other ischaemic aetiology undergoing inpatient rehabilitation programmes of differing intensity. By prospectively collecting detailed clinical and functional data across multiple rehabilitation domains, the PEARL study aims to characterise recovery trajectories over the first 6 months following stroke.

Consistent with existing literature, patients with AFRS tend to be older and present with more severe neurological impairments at baseline compared with patients with non-AFRS. Previous studies have reported that the worst prognosis in the AFRS is mainly related to older age and multimorbidity.[41] This aligns with the known cardioembolic nature of AFRS, which are often characterised by larger infarct volumes and more extensive cerebral involvement. As a result, patients in the AFRS group could have greater rehabilitation needs, slower recovery trajectories, poorer functional outcomes and lower levels of independence at follow-up compared with those in the non-AFRS group.

The study is expected to provide insight into whether AFRS is associated with distinct rehabilitation outcomes and whether rehabilitation intensity modifies recovery patterns in this patient group. Identifying differences in functional recovery, rehabilitation efficiency and discharge outcomes between patients with AFRS and non-AFRS may help clarify whether aetiology-specific rehabilitation strategies are warranted. The findings could also highlight the clinical importance of early identification and optimal management of AF. AFRS may benefit from more intensive rehabilitation strategies and closer post-discharge monitoring due to their higher likelihood of functional dependence.

Furthermore, the identification of clinical and functional predictors of favourable rehabilitation outcomes, particularly in patients with AFRS, may support the development of data-driven models for outcome prediction. Such models could inform more personalised rehabilitation planning and optimise the allocation of rehabilitation resources in routine clinical practice.

Within the broader context of the TARGET project, the data generated by the PEARL study are expected to contribute to the development and refinement of digital optimisation tools and digital twin technologies for stroke rehabilitation. By providing high-quality longitudinal rehabilitation data, this study may support future efforts to improve personalised care pathways and long-term outcomes for patients with AFRS.

Ethics and dissemination

The national and international guidelines (World Medical Association, 2024. *World Medical Association Declaration of* Helsinki*: Ethical Principles for Medical Research Involving Human Participants,* 75th WMA General Assembly, Helsinki, October 2024) for research on human beings

have been followed, and the study will comply with the legal regulations on data confidentiality (Organic Law 15/1999, of 13 December, on Personal Data Protection). This study was approved by the Clinical Research Ethics Committee of Hospital del Mar (CEIC-IMIM), approval number (N. 2023/11172/I). Written informed consent is obtained from all participants or legally authorised representatives. The trial has been registered in ClinicalTrials.gov (NCT07253974). Results of the study will be disseminated through publication in peer-reviewed scientific journals and presentation at international conferences.

Risk-benefit assessment

This study involves minimal risk, as all assessments consist of standard clinical evaluations performed as part of routine stroke rehabilitation care. The potential benefits include contributions to evidence-based stroke rehabilitation and the advancement of personalised care approaches. All adverse events and serious adverse events (SAEs) occurring during rehabilitation will be documented in the clinical records and reported to the local ethics committee in accordance with institutional requirements. SAEs will prompt immediate notification to the ethics committee.

Data collection and management

All study data will be collected and managed in accordance with the European Union General Data Protection Regulation requirements and relevant national data protection legislation. Personal identifying information will be stored separately from study data and linked using unique study identifiers.

Clinical data collected will be derived from routine hospital registry systems and prospectively recorded following informed consent from patients or their legally authorised representatives. Data will be entered into a secure electronic database using Research Electronic Data Capture (REDCap), a web application designed to support data capture for research studies. Each participant will be assigned a unique REDCap identification number and a specific trial number to ensure anonymisation.

Data collected at admission and discharge will be registered by members of the rehabilitation team, including physiatrists, physiotherapists, occupational therapists and speech and language therapists. Follow-up data at three and 6 months post-stroke will be collected by two junior researchers using standardised assessment procedures. All users will have private credentials and roles to access the database. Each patient will be associated with a reference REDCap-ID and specific TRIAL number.

Regular data quality checks will be conducted by the principal investigators to ensure data completeness, consistency and accuracy. Given the observational nature and minimal risk profile of the study, a formal Data Monitoring Committee will not be established and no interim analyses are planned. Data will be stored securely on institutional servers, with access restricted to authorised study personnel.

Patient and public involvement

Patient and public involvement (PPI) activities are conducted at the level of the TARGET consortium, within a dedicated work package focused on stakeholder engagement. Patients and representatives of patient organisations contribute to the broader TARGET programme through consultation, dissemination activities and feedback on project objectives and outputs. No additional study-specific PPI activities were undertaken in the design or conduct of the PEARL study.

Generalisability and external validity

The study population represents typical patients with stroke admitted to tertiary rehabilitation centres in Southern Europe. The rehabilitation pathways and intervention intensity reflect routine clinical practice and are aligned with current evidence-based rehabilitation guidelines, supporting the relevance of the findings to similar healthcare systems.

However, differences in healthcare organisation, referral pathways, availability of rehabilitation resources and post-acute care models across countries may limit the direct applicability of the findings to other settings. In addition, the single-centre design and the use of predefined, non-randomised allocation criteria may further constrain generalisability. These factors should be considered when interpreting the study results and when extrapolating findings to other rehabilitation contexts.

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