Statistical Analysis Plan (SAP)

EFFECTIVENESS OF AN MHEALTH INTERVENTION, BASED ON REHABILITATION AND A PERSONALISED NUTRITION PLAN, IN THE RECOVERY AND IMPROVEMENT OF DYSPHAGIA IN PATIENTS DIAGNOSED WITH STROKE

Principal Investigator:	Antonio-Jesús Marín-Paz Principal Investigator Assistant Professor Faculty of Nursing. University of Cadiz Algeciras, Spain

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Abbreviations

- BIA: Bioelectrical Impedance Analysis.
- BMI: Body Mass Index.
- CG: Control Group.
- CONSORT 2025: Consolidated Standards of Reporting Trials 2025.
- CSI: Caregiver Strain Index.
- EG: Experimental group.
- EQ-VAS: EuroQoL visual analog scale.
- ICC: Intraclass Correlation Coefficient.
- MNA: Mini-Nutritional Assessment.
- OR: Odds Ratio.
- PI: Principal Investigator.
- SAP: Statistical Analysis Plan.

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1. Introduction

Stroke represents a major global health challenge, serving as a primary cause of mortality and long-term disability while significantly increasing socio-sanitary expenditures. Among its common complications, oropharyngeal dysphagia stands out, affecting up to 80% of post-stroke patients, a condition that is particularly acute in the elderly population due to age-related physiological changes in the swallowing response. This condition acts as a critical predictor of adverse health outcomes, including malnutrition, dehydration, aspiration pneumonia, and increased mortality rates. Furthermore, dysphagia significantly diminishes the patients' perceived quality of life and imposes a substantial burden on their caregivers.

Currently, evidence suggests that early detection and the continuity of care after hospital discharge are essential to reducing the negative consequences and high costs associated with this condition. In this context, m-Health technology emerges as a transformative tool that can facilitate the monitoring of patients and empower both individuals and their families in health management. Consequently, the general objective of this study is to evaluate the efficacy of a multidisciplinary m-Health intervention, based on a personalized program of nutritional measures and swallowing rehabilitation exercises, as a complement to standard clinical practice for the recovery of dysphagia in post-stroke patients.

This study aims to analyze the intervention’s impact on clinical complications, nutritional status, and quality of life, as well as its economic implications. This Statistical Analysis Plan (SAP) provides a comprehensive framework for the assessment of study outcomes and the corresponding analytical methodologies. It outlines the procedures for evaluating primary and secondary variables, ensuring a robust and transparent analysis of the intervention's impact on dysphagia recovery and associated socio-economic factors.

2. Methods

2.1. Study design

The study is designed as an open-label parallel randomized controlled trial (RCT) featuring a blinded third-party evaluation to ensure the objectivity of the results. The CONSORT 2025 recommendations will be followed. The primary aim is to compare the effectiveness of a multidisciplinary m-Health intervention against standard clinical practice for the recovery of dysphagia in post-stroke patients. Participants will be allocated into two distinct arms: the Control Group (CG), which will receive conventional care provided by the hospital center, and the Experimental Group (EG), which will utilize a mobile device equipped with an ad hoc developed m-Health application both during hospitalization and after discharge. This application provides a personalized program encompassing nutritional measures, compensatory strategies, and swallowing rehabilitation exercises supervised by a specialized multidisciplinary team.

To maintain balance between the study arms and mitigate potential biases, participants will be assigned using block randomization. The randomization sequence will be generated through random permutations within blocks of an appropriate size, ensuring that the number of patients in each group remains equal periodically. Although the study is open-label due to the nature of the technological

intervention, the use of blinded third-party evaluators for outcome assessment will be implemented to safeguard the internal validity of the trial.

2.2. Sample size calculation

The sample size was determined based on the primary outcome variable, defined as the improvement and recovery from dysphagia (a dichotomous qualitative variable: Yes/No). The calculation was performed using the statistical software R and the pwr package, considering a comparison of proportions between the two study arms. Based on existing literature, which indicates that post-stroke dysphagia improvement occurs in approximately 35% of cases under standard conditions, the study aims to detect an increase to 70% improvement in the EG.

For the estimation, the following parameters were established: a 95% confidence level (α=0.05), a statistical power of 80% (β=0.20), and a bilateral contrast. The initial calculation required 31 patients per arm; however, to account for an expected attrition rate of 20% due to potential losses in follow-up or changes in the participants' health status, the sample size was adjusted. Consequently, the final requirement is 37 participants per arm, resulting in a total study population of 74 subjects. This cohort will be recruited via consecutive sampling from patients hospitalized at the Hospital Punta de Europa (Algeciras) who meet the inclusion criteria, specifically being over 18 years of age and presenting oropharyngeal dysphagia to liquids following a stroke.

3. Outcomes

This section outlines the primary and secondary outcomes established to evaluate the effectiveness of the m-Health intervention. Data for all variables will be collected at four specific time points: baseline (Day 1) during the initial 24 hours of hospital admission, and subsequent follow-ups at 3, 6, and 9 months post-stroke.

3.1. Primary outcomes

The primary outcome of this study is Dysphagia Improvement and Recovery, which is defined as a dichotomous qualitative variable (Yes/No). Furthermore, swallowing function will be assessed through the Volume-Viscosity Swallow Test (V-VST), which identifies the safe and efficient combination of volumes (5 mL, 10 mL, and 20 mL) and textures (liquid, nectar, and pudding). This tool utilizes safety markers, such as changes in voice tone, coughing, or oxygen desaturation, and efficiency markers, including labial seal and oral or pharyngeal residue, to determine the clinical status of the patient.

3.2. Secondary outcomes

3.2.1. Nutritional and Anthropometric Status

To assess the nutritional impact of the intervention, the Mini-Nutritional Assessment (MNA) will be employed to categorize patients as having a normal nutritional status, being at risk of malnutrition, or having malnutrition. Additionally, physical and body composition parameters will be measured, including Weight, Height, Body Mass Index (BMI), and circumferences of the arm and calf. Advanced body composition analysis will be performed using Bioelectrical Impedance Analysis

(BIA) to obtain data on Fat Mass, Fat-Free Mass, Total Body Water, and the Phase Angle, the latter serving as an indicator of cellular health and integrity. Furthermore, muscle strength and function will be evaluated via Handgrip Dynamometry and the SARC-F questionnaire to screen for sarcopenia risk.

3.2.2. Clinical Complications and Functional Status

Regarding clinical safety, the study will record the incidence of bronchoaspiration, respiratory infections, and aspiration-derived pneumonia. Functional independence in activities of daily living will be assessed using the Barthel Index, while physical frailty will be determined according to the Fried Criteria (weight loss, exhaustion, weakness, slow walking speed, and low physical activity). The Risk of Falls Detection Scale will also be applied to identify patients requiring preventive measures.

3.2.3. Quality of Life and Caregiver Burden

The perceived quality of life will be measured using the EuroQoL 5D-5L questionnaire and the EQ-VAS visual analog scale, providing insights into five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Considering the impact on the family environment, Caregiver Burden will be evaluated through the Zarit Scale, and Caregiver Strain will be measured using the Caregiver Strain Index (CSI), identifying high levels of perceived stress or effort in the caregiving role.

3.2.4. Economic Impact

Lastly, the economic evaluation will consider the number of hospital admissions, the length of stay (days), and the frequency of visits to primary care, specialists, and emergency departments. The total economic cost will be calculated by multiplying the days of hospitalization by the estimated daily cost of stay, allowing for a comprehensive analysis of the intervention's efficiency within the health system.

4. Study population

The study population will comprise patients hospitalized following a stroke at the Punta Europa University Hospital in Algeciras (Cádiz, Spain). A total of 74 participants will be recruited through consecutive sampling and subsequently assigned in a 1:1 ratio to either the EG or the CG.

Regarding the eligibility criteria, subjects must be 18 years or older and present a confirmed diagnosis of oropharyngeal dysphagia to liquids following a stroke. On the other hand, the study will exclude patients with visual barriers, those receiving terminal palliative care, or individuals in the final days of life. Furthermore, patients with severe cognitive impairment or those facing a language barrier that precludes the effective use of the Spanish-language m-Health application will be ineligible for participation. It is also established that participants will be withdrawn from the study if they revoke their informed consent or if their lack of adherence to the prescribed training plan exceeds 20% of the scheduled sessions.

Finally, baseline data will be collected within the first 24 hours of hospital admission to characterize the study cohort. These initial assessments will include sociodemographic variables such as sex, age, and the presence of a caregiver, as well as clinical and anthropometric parameters. These baseline measurements are essential not only to verify the comparability between the two study arms but also to facilitate subsequent multivariate analyses aimed at adjusting for potential confounding factors.

5. Data analysis

An external researcher, expert in univariate and bivariate statistics, including effect size determination, will perform the database recording and statistical analysis. This investigator will be blinded to participant group allocation and will have full access to all collected data.

To meet the study objectives, the researcher will use the latest version of the statistical analysis plan (SAP), as published in the protocol registered on *ClinicalTrials.gov* (NCT07267468), to derive the necessary statistical results for the outcomes.

The statistical analysis will be conducted using a comprehensive approach, beginning with a descriptive characterization of the study population. Quantitative variables will be expressed as mean and standard deviation or median and interquartile range, depending on their distribution. Qualitative variables, on the other hand, will be represented through frequencies and percentages. To determine the appropriate use of parametric or non-parametric tests, the Shapiro-Wilk test will be applied to assess the normality of the data distribution for all quantitative variables.

Regarding bivariate analyses, comparisons for qualitative variables will be performed using the Chi-square test, provided that at least 80% of the cells in the contingency tables have expected frequencies greater than 5; otherwise, Fisher's exact test will be utilized. To measure the strength of association for clinical outcomes, 2x2 contingency tables will be constructed to calculate the Odds Ratio (OR) and its corresponding 95% confidence interval via the Mantel-Haenszel method. For quantitative comparisons between the EG and CG (independent samples), the Student's t-test will be employed for normally distributed data, while the Mann-Whitney U test will be used for non-normal distributions.

To evaluate the intervention’s effectiveness across four time points (baseline, 3, 6, and 9 months), a Repeated Measures ANOVA or Linear Mixed Models will be used for parametric data, while the Friedman test will be applied for non-parametric data, followed by post-hoc comparisons to pinpoint exactly when significant changes occurred. Furthermore, the relationship between continuous variables will be explored through Pearson or Spearman correlation coefficients. The Intraclass Correlation Coefficient (ICC) will be used to assess concordance between measurements at different stages where necessary.

Finally, to account for potential confounding factors, multivariable analysis will be conducted. Depending on the nature of the dependent variable, linear, logistic, or Cox proportional hazards regression models will be implemented to adjust the intervention's effect for sociodemographic and clinical variables, such as age, sex, and the presence of a caregiver.

All statistical tests will be performed with a significance level of alpha=0.05. Effect sizes will be calculated according to the statistical tests used. Data management and analytical procedures will be executed using R and SPSS (version 25). The analysis is scheduled to be conducted in September 2026.

6. Missing data

Given the longitudinal nature of this study, which includes a follow-up period extending up to 9 months post-stroke, the research team acknowledges the potential for missing data and participant attrition. According to the risk assessment, losses related to the health status of the participants or the extended study duration are considered a high-probability and high-impact risk. To mitigate this, the sample size calculation explicitly incorporated an expected 20% attrition rate, increasing the required enrollment from 31 to 37 participants per arm (totaling 74 subjects) to ensure that the study maintains sufficient statistical power even if losses occur.

Regarding the management of withdrawals, it is established that participants who revoke their informed consent will be classified as a "loss" and will not be replaced by new subjects. Furthermore, a lack of adherence to the prescribed training plan—defined as missing more than 20% of the scheduled sessions—will also constitute a criterion for withdrawal from the study. To minimize the occurrence of missing data related to intervention adherence, the m-Health application includes an integrated treatment diary. This tool allows both patients and caregivers to report daily activity, providing the multidisciplinary team with real-time information to monitor compliance and implement corrective actions if necessary.

Finally, the statistical handling of missing values will be performed with rigor. For participants who complete the baseline assessment but fail to attend subsequent follow-ups, the reasons for attrition will be documented and reported in accordance with CONSORT 2025 guidelines. While the study aims for maximum data completeness through the digital monitoring of the intervention, any remaining missing data for the primary and secondary outcomes will be analyzed to determine if they are missing at random, and the appropriate imputation or analysis methods will be applied to maintain the integrity of the results.

7. References

Bath, P. M., Lee, H. S., & Everton, L. F. (2018). Swallowing therapy for dysphagia in acute and subacute stroke. *Cochrane Database of Systematic Reviews*, *10*(10), CD000323. https://doi.org/10.1002/14651858.CD000323.pub3

Benfield, J. K., Wilkinson, G., Everton, L. F., Bath, P. M., & England, T. J. (2021). Diagnostic accuracy of the Dysphagia Trained Nurse Assessment tool in acute stroke. *European Journal of Neurology*, *28*(8), 2766-2774. https://doi.org/10.1111/ene.14900

Díaz Fernández, A. I., & González Álvarez, M. A. (2017). Prevalencia de disfagia tras Ictus. Visión desde Atención Primaria. *Enfermería Comunitaria*, *5*(1), 38-56.

Dziewas, R., Michou, E., Trapl-Grundschober, M., Lal, A., Arsava, E. M., Bath, P. A., et al. (2021). European Stroke Organization and European Pantheon for Swallowing Disorders guideline for the diagnosis and treatment of post-stroke dysphagia. *European Stroke Journal*, *6*(3), LXXXIX-CXV. https://doi.org/10.1177/23969873211039721

Espinosa, J. M., Rodríguez, S., et al. (2017). *Examen de salud para mayores de 65 años*. Consejería de Salud, Junta de Andalucía. https://www.enbuenaedad.es/sites/default/files/2018-04/examen-salud-mayores-65.pdf

Fang, W. J., Zheng, F., Zhang, L. Z., Wang, W. H., Yu, C. C., Shao, J., & Wu, Y. J. (2022). Research progress of clinical intervention and nursing for patients with post-stroke dysphagia. *Neurological Sciences*, *1–10*. https://doi.org/10.1007/s10072-022-06191-9

Fried, L. P., Tangen, C. M., Walston, J., et al. (2001). Frailty in older adults: Evidence for a phenotype. *Journal of Gerontology*, *56*(3), M146-M156. https://doi.org/10.1093/gerona/56.3.m146

García Almeida, J. M., García García, C., Bellido Castañeda, V., & Bellido Guerrero, D. (2018). Nuevo enfoque de la nutrición. Valoración del estado nutricional del paciente: Función y composición corporal. *Nutrición Hospitalaria*, *35*(spe3), 1-14. https://doi.org/10.20960/nh.2027

Guillén-Solá, A., Marco, E., Martínez-Orfila, J., Donaire Mejías, M. F., Depolo Passalacqua, M., Duarte, E., et al. (2013). Usefulness of the volume-viscosity swallow test for screening dysphagia in subacute stroke patients in rehabilitation income. *NeuroRehabilitation*, *33*(4), 631-638.

Hernández, G., Garin, O., Dima, A. L., et al. (2019). EuroQol (EQ-5D-5L) Validity in Assessing the Quality of Life in Adults With Asthma: Cross-Sectional Study. *Journal of Medical Internet Research*, *21*(1), e10178. https://doi.org/10.2196/10178

Jones, C. A., Colletti, C. M., & Ding, M. C. (2020). Post-stroke Dysphagia: Recent Insights and Unanswered Questions. *Current Neurology and Neuroscience Reports*, *20*(12), 61. https://doi.org/10.1007/s11910-020-01081-z

Kim, D. Y., Park, H. S., Park, S. W., & Kim, J. H. (2020). The impact of dysphagia on quality of life in stroke patients. *Medicine*, *99*(34), e21795. https://doi.org/10.1097/MD.0000000000021795

King, D., Wittenberg, R., Patel, A., Quayyum, Z., Berdunov, V., & Knapp, M. (2020). The future incidence, prevalence and costs of stroke in the UK. *Age and Ageing*, *49*(2), 277-282. https://doi.org/10.1093/ageing/afz163

Krajczy, E., Krajczy, M., Luniewski, J., Bogacz, K., & Szczegielniak, J. (2019). Assessment of the effects of dysphagia therapy in patients in the early post-stroke period: A randomised controlled trial. *Neurologia i Neurochirurgia Polska*, *53*(6), 428-434. https://doi.org/10.5603/PJNNS.a2019.0053

Li, C., Qiu, C., Shi, Y., Yang, T., Shao, X., & Zheng, D. (2022). Experiences and perceptions of stroke patients living with dysphagia: A qualitative meta-synthesis. *Journal of Clinical Nursing*, *31*(7-8), 820-831. https://doi.org/10.1111/jocn.15995

Lim, M. L., Yong, B. Y. P., Mar, M. Q. M., et al. (2018). Caring for patients on home enteral nutrition: Reported complications by home carers and perspectives of community nurses. *Journal of Clinical Nursing*, *27*(13-14), 2825-2835. https://doi.org/10.1111/jocn.14347

Lucena-Antón, D., Luque Moreno, C., Heredia-Rizo, A. M., & Moral-Muñoz, J. A. (2019). Aplicaciones móviles en el abordaje terapéutico del ictus: Revisión en repositorios comerciales y búsqueda de evidencia. *Revista Española de Salud Pública*, *93*, e201906035.

Marin, S., Serra-Prat, M., Ortega, O., & Clavé, P. (2020). Healthcare-related cost of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: A systematic review. *BMJ Open*, *10*(8), e031629. https://doi.org/10.1136/bmjopen-2019-031629

Marin, S., Serra-Prat, M., Ortega, O., Fericgla, M. A., Valls, J., Palomera, I., et al. (2021). Healthcare costs of post-stroke oropharyngeal dysphagia and its complications: Malnutrition and respiratory infections. *European Journal of Neurology*, *28*(11), 3670-3681. https://doi.org/10.1111/ene.14998

Martín, M., Salvadó, I., Nadal, S., Miji, L. C., Rico, J. M., & Lanz, M. I. (1996). Adaptación para nuestro medio de la Escala de Sobrecarga del Cuidador de Zarit. *Revista de Gerontología*, *6*, 338-346.

Ollero Baturone, M. (2018). *Atención a pacientes pluripatológicos. Proceso asistencial integrado*. Consejería de Salud, Junta de Andalucía. https://www.juntadeandalucia.es/export/drupaljda/salud_5af1956d9925c_atencion_pacientes_pluripatologicos_2018.pdf

Pierpoint, M., & Pillay, M. (2020). Post-stroke dysphagia: An exploration of initial identification and management performed by nurses and doctors. *South African Journal of Communication Disorders*, *67*(1), e1-e13. https://doi.org/10.4102/sajcd.v67i1.625

Sánchez-Rodríguez, D., Marco, E., Dávalos-Yerovi, V., et al. (2019). Translation and Validation of the Spanish Version of the SARC-F Questionnaire to Assess Sarcopenia in Older People. *The Journal of Nutrition, Health & Aging*, *23*(6), 518-524. https://doi.org/10.1007/s12603-019-1204-z

Sánchez Torralvo, F. J., Porras, N., Abuín Fernández, J., et al. (2018). Normative reference values for hand grip dynamometry in Spain. Association with lean mass. *Nutrición Hospitalaria*, *35*(1), 98-103. https://doi.org/10.20960/nh.1052

Shimizu, A., Fujishima, I., Maeda, K., et al. (2021). Delayed Dysphagia May Be Sarcopenic Dysphagia in Patients After Stroke. *Journal of the American Medical Directors Association*, *22*(12), 2527-2533.e1. https://doi.org/10.1016/j.jamda.2021.07.013

Sura, L., Madhavan, A., Carnaby, G., & Crary, M. A. (2012). Dysphagia in the elderly: Management and nutritional considerations. *Clinical Interventions in Aging*, *7*, 287-298. https://doi.org/10.2147/CIA.S23404

Teasell, R., Salbach, N. M., Foley, N., et al. (2020). Canadian Stroke Best Practice Recommendations: Rehabilitation, Recovery, and Community Participation following Stroke. *International Journal of Stroke*, *15*(7), 763-788. https://doi.org/10.1177/1747493019897843

Vellas, B., Guigoz, Y., Garry, P. J., et al. (1999). The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*, *15*(2), 116-122. https://doi.org/10.1016/s0899-9007(98)00171-3

Zarit, S. H., Reever, K. E., & Bach-Peterson, J. (1980). Relatives of the impaired elderly: Correlates of feeling of burden. *The Gerontologist*, *20*(6), 649-654.