

Study protocol and Statistical Analysis Plan (SAP)

Brief Title: Itaca App vs. Usual Care for Medication Adherence in Older Adults on Polypharmacy

Date: 04/09/2025

1. Background

Medication nonadherence is a significant public health problem. It contributes to morbidity, mortality, hospital readmissions, and reduced quality of life.

Older adults (aged 65 or older) are particularly vulnerable due to multimorbidity, polypharmacy, and physical or cognitive impairments. Traditional medication adherence interventions often have limited effectiveness in this group. Mobile health (mHealth) technologies provide reminders, monitor adherence, and support patient engagement in homecare setting.

This trial evaluates the ITACA mobile application for medication management in older adults versus usual care.

2. Objectives

2.1 Primary Objective

To evaluate whether the use of the ITACA mobile application improves medication adherence in older adults, compared to usual care.

2.2 Secondary Objectives

- To assess the intervention's effect on patient engagement in medication management.
- To assess the intervention's effect on health-related quality of life.
- To evaluate the perceived usability of the ITACA application among participants in the intervention group.

3. Study Design

Design: Single-center, two-arm, parallel-group randomized controlled trial (RCT)

Allocation: 1:1 randomization (intervention vs. control)

Blinding: Blinding of outcome assessors and statistical analysts; no blinding of participants or care providers

Follow-up duration: 3 months

Reporting guidelines: Designed in accordance with SPIRIT 2025; results will be reported per CONSORT 2025

Setting: Local Health Unit, Rome, Lazio, Italy

4. Participants

4.1 Inclusion Criteria

- Age 65 years or older with chronic condition
- Home pharmacological treatment with at least three medications (any route of administration)
- Ability to understand and speak Italian
- Willingness to comply with all study procedures, confirmed by signed written informed consent

4.2 Exclusion Criteria

- Diagnosed cognitive impairment that could interfere with study participation
- Diagnosed psychiatric disorder that could interfere with study participation

4.3 Discontinuation Criteria

- Reduction to fewer than three prescribed medications
- Voluntary withdrawal by the participant

5. Recruitment

Participants will be recruited by general practitioners (GPs) at the Local Health Unit, Italy. The GP will assess eligibility criteria in collaboration with the research team. Eligible participants will receive written information about the study. Participants who agree to participate will sign the informed consent form. Signed consent authorizes the research team to access contact details and proceed with randomization.

6. Randomization and Blinding

Eligible participants will be randomly assigned to the intervention or control group in a 1:1 ratio. The randomization sequence will be generated using dedicated software with a permuted block design. This approach ensures progressive balance between groups throughout the recruitment period. Allocation concealment will be maintained by storing the sequence in a separate, password-protected file. The sequence will be inaccessible to personnel involved in enrollment. A centralized system will determine group assignment at the time of formal enrollment. Blinding of participants and researchers delivering the intervention is not possible due to the nature of the study. Outcome assessors and statistical analysts will be blinded to group allocation throughout the trial.

7. Interventions

7.1 Intervention Group: ITACA Mobile Application

At baseline (T0), the research team will support participants in installing the ITACA application on their personal smartphone. An individual training session will be provided at T0. Medication reminder notifications will be activated according to each patient's prescribed regimen. The application will be used throughout the entire 3-month follow-up period. Researchers will contact participants by telephone at monthly intervals to monitor app use and address barriers. No formal assessments are performed at these contacts. At 3 months (T1), participants will complete the System Usability Scale (SUS) to evaluate perceived app usability.

7.2 Control Group: Usual Care

At baseline (T0), participants will receive and be provided with an explanation of a written medication plan containing prescribed therapies, dosages, and administration schedules. Participants will continue standard clinical follow-up with their GP throughout the 3-month period. No digital tools or additional interventions will be provided beyond routine clinical practice.

7.3 Concomitant Care

There are no restrictions on continuing concomitant care for either group. No serious adverse events are anticipated given the low-risk nature of the intervention. Any adverse event reported by participants will be recorded, assessed for its relationship to the intervention, and reported to the Ethics Committee as required.

8. Outcomes

8.1 Primary Outcome

Medication adherence will be assessed using the Morisky Medication Adherence Scale (MMAS-4). The MMAS-4 is a validated 4-item self-report questionnaire. Each item has a yes/no format. Adherence scores are categorized as follows: low adherence (0–1), medium adherence (2–3), and high adherence (4). It identifies common forms of non-adherence, such as forgetting doses or stopping treatment. The MMAS-4 will be administered subject to prior authorization and/or licensing for use.

8.2 Secondary Outcomes

- Patient engagement: Patient Health Engagement Scale (PHE-s), a 5-item validated scale measuring progressive psychological engagement in health management. The PHE-s will be administered subject to prior authorization and/or licensing for use.
- Health-related quality of life: Short Form Health Survey (SF-12), 12-item questionnaire generating physical and mental component summary scores. The SF-12 will be administered subject to prior authorization and/or licensing for use.
- App usability (intervention group only): System Usability Scale (SUS), a 10-item questionnaire evaluating perceived usability and ease of use. The SUS will be administered subject to prior authorization and/or licensing for use.

Primary and secondary outcomes will be assessed at baseline (T0) and at 3 months (T3) in both groups, with the exception of app usability, which will be assessed only at 3 months, at the end of the intervention period, in the intervention group.

9. Sample Size

Sample size was calculated based on the primary endpoint (MMAS-4 as a dichotomous variable). The baseline proportion of adherent patients is estimated at 39.3%, based on data from Napolitano et al. (2016) in a comparable Italian elderly population.

An absolute increase of 35 percentage points is hypothesized in the experimental group (from 39.3% to 74.3%).

A 5% increase is assumed in the control group (from 39.3% to 44.3%), attributable to a possible spontaneous improvement or usual care effect.

Parameters: two-sided significance level $\alpha = 0.05$; statistical power = 80%.

Minimum required sample size: 41 participants per arm.

Given an expected 15% dropout rate, the final sample size is set at 49 participants per group.

Total sample: 98 participants.

10. Data Collection

Data will be collected by researchers and designated project collaborators.

Questionnaires (MMAS-4, PHE-s, SF-12) will be administered to both groups at T0 and T1 in paper format or via structured interview, subject to prior authorization and/or licensing for use.

Data will be entered into a purpose-built study database.

The SUS will be administered exclusively to the experimental group at T1.

Each participant will be assigned a unique identification code.

Data will be stored in a protected form. Access will be limited to the principal investigator and authorized collaborators.

Data management complies with Regulation (EU) 2016/679 (GDPR) and applicable Italian data protection legislation.

Communications between the application and backend are secured via HTTPS and token-based authentication.

11. Statistical Analysis

Statistical analyses will be performed using STATA version 19.

Analysts will be blinded to group allocation.

The significance level is set at $p = 0.05$.

11.1 Descriptive Statistics

- Continuous normally distributed variables: mean and standard deviation (SD).
- Continuous non-normally distributed variables: median and interquartile range (IQR).
- Categorical variables: absolute frequencies and percentages.

- Normality will be assessed using the Shapiro-Wilk test.

11.2 Primary Analysis

The primary analysis will follow the intention-to-treat (ITT) principle.

All randomized participants will be included, regardless of compliance with the assigned intervention. The proportion of adherent patients at T1 (MMAS-4 score) will be compared between groups using the chi-square test or Fisher's exact test, as appropriate.

A logistic regression model will be used to estimate the adjusted odds ratio, controlling for key baseline covariates.

11.3 Secondary Analyses

Continuous secondary outcomes will be compared between groups using the independent-samples t-test or the Mann-Whitney U test, based on distribution.

Within-group changes from T0 to T1 will be analyzed using the paired t-test or the Wilcoxon signed-rank test.

11.4 Missing Data

Missing data will be handled using complete-case analysis.

If the proportion of missing data exceeds 10%, multiple imputation techniques will be considered.

12. Monitoring and Safety

The principal investigator will continuously monitor the study.

Regular meetings will be held, and data will be reviewed monthly.

Any adverse events will be promptly evaluated.

No Data and Safety Monitoring Committee (DSMC) has been established, given the short study duration, small sample size, and low-risk profile of the intervention.

No interim analyses are planned.

No formal stopping guidelines have been established.

Any decision to terminate the trial prematurely will be made by the principal investigator.

13. Ethics

This study received ethical approval from the Ethics Committee of Lazio Area 3 (Protocol n. 7889).

No modifications will be implemented without prior Ethics Committee approval.

The trial will be conducted in accordance with the Declaration of Helsinki.

The trial will comply with ICH/GCP guidelines.

Regulatory agencies, the Ethics Committee, and authorized personnel may access original study documentation.

Participant confidentiality will be ensured through the use of coded identifiers.

Data management complies with GDPR (EU Regulation 2016/679) and Italian data protection legislation.

14. Data Sharing

De-identified individual participant data, statistical code, and study materials will be available from the corresponding author upon reasonable request.

Requests must comply with ethical and privacy regulations.

The full study protocol and statistical analysis plan are available from the corresponding author upon reasonable request.

15. Dissemination

Results will be published in peer-reviewed national and international journals.

Findings will be presented at scientific conferences.

All results will be reported in aggregate form and will not be attributable to individual participants.

16. Funding and Conflicts of Interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare no conflicts of interest.

17. Key References

1. Patel T. Medication nonadherence: time for a proactive approach by pharmacists. *Can Pharm J (Ott)*. 2021;154(5):292-296.
2. Chan AW, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *Lancet*. 2025;405:e19-e27.
3. Hopewell S, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ*. 2025;389:e081123.
4. Napolitano F, et al. Medication adherence among patients with chronic conditions in Italy. *Eur J Public Health*. 2016;26(1):48-52.
5. Peng Y, et al. Effectiveness of mobile applications on medication adherence in adults with chronic diseases. *J Manag Care Spec Pharm*. 2020;26(4):550-561.