ALDIGO

(ALerts for the Safe Use of DIGoxin in Hospitalized Elderly Patients)

Sponsor	Consorci Sanitari de l'Alt Penedès i Garraf
Investigators	Alejandro Rodríguez Molinero Department of Research Beatriz del Pilar Ortiz Naranjo PhD candidate, Department of Research Consorci Sanitari de l'Alt Penedès i Garraf

Protocol

Code: CSAPG-73	**Version:** 2	**Date:** 16/04/2025

Investigator Signature Page

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Investigator name:	Alejandro Rodríguez Molinero, Beatriz del Pilar Ortiz Naranjo
Hospital:	CSAPG
Address:	_____

I have read and understood the protocol of this trial and all the documentation mentioned therein, and I agree with its content.

I agree to direct and conduct this trial as described in the protocol, taking into account the considerations of the Clinical Research Ethics Committee, the Declaration of Helsinki, the Good Clinical Practice (GCP) guidelines, as well as any applicable regulations.

Full name (in capital letters): _____

Signature: _____

Date: _____

Protocol Synopsis

Title	Alerts for the Safe Use of Digoxin in Hospitalized Elderly Patients
Code	CSAPG-73
Sponsor	Consorci Sanitari Alt Penedès i Garraf (CSAPG)
Study centers	This trial will be conducted on the inpatient wards of the Hospital Comarcal de l'Alt Penedès and the Hospital Residència Sant Camil.
Investigators	Alejandro Rodríguez Molinero, Beatriz del Pilar Ortiz Naranjo. Geriatrics, Consorci Sanitari de l'Alt Penedès i Garraf
Intervention under study	The intervention consists of the introduction of computerized alerts in the CSAPG electronic health record (MIRA software) that are triggered when a physician prescribes digoxin at a dose higher than the recommended one (more than 0.125 mg/day).
Study period	The total duration of the study will be 18 months. Fieldwork at each study center will last 12 months, including a 6-month pre-intervention period and a 6-month post-intervention period.
Main objective	To study the efficacy of a computerized alert, visible to physicians responsible for hospitalized elderly patients who have been prescribed digoxin at a dose above 0.125 mg/day (recommended dose), in reducing the number of patients with inadequate digoxin doses.
Study design	Pre-post intervention quasi-experimental study, in two study centers.
Number of subjects	Accepting an alpha risk of 0.05 and a statistical power above 0.8 in a two-sided test, 2977 subjects are required in the pre-intervention group and 2977 in the post-intervention group, to detect as statistically significant a 25% reduction in inappropriate digoxin prescriptions.
Sample	Eligibility criteria: Men and women older than 64 years. Admitted to the inpatient wards of the study centers during the study period. No exclusion of patients is anticipated.
Statistical analysis	The percentage of patients whose last digoxin dose prescribed during admission is above the recommended daily dose in the elderly will be compared between patients treated during the intervention period and patients treated during the post-intervention period, using the Chi-Square statistic.

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2 Introduction

Inappropriate prescribing is one of the most common problems we face in the older adult population. In the case of Catalonia, its population prevalence has recently been estimated at 89% (3). In addition to being very frequent, it can have various negative consequences for both the patient and the healthcare system. Some of these consequences include a higher probability of adverse effects or interactions, more hospitalizations, a deterioration in quality of life, and an increase in healthcare costs (4).

In the field of Geriatrics this problem is considered of vital importance, being even one of the main geriatric syndromes with one of the greatest impacts on the health of our elders. In recent decades, attempts have been made to create scales to avoid the inappropriate prescribing of medication in the elderly. Among these tools, the most widely used are the STOPP/START criteria (whose first version appeared in 2008 and has been updated up to its latest version in 2023 (2,5)) and the Beers criteria (created in 1991 and updated up to their latest version in 2023 (1,6)). The review of the existing literature shows that various strategies have been used to try to improve medical prescribing to avoid this problem, both with digital tools and through collaboration with the pharmacy service of each hospital (7).

At the Consorci Sanitari del Garraf, a consortium comprising three hospitals in the province of Barcelona, we carried out an exhaustive review of the administration of active ingredients in hospitalized patients during 2017, including the prescribed doses. From this analysis, we identified that one of the drugs most frequently used inappropriately in our center is digoxin. This medication is fundamental in the treatment of certain arrhythmias and heart failure; however, its use in older patients entails a significant risk due to its narrow therapeutic margin and its high probability of toxicity, especially in those with renal dysfunction and polypharmacy. Aging modifies both pharmacokinetics and pharmacodynamics, which increases the risk of serious adverse effects such as bradycardia, nausea, and arrhythmias (8–11). For these reasons, both the Beers criteria and the STOPP/START criteria recommend caution in the prescription of digoxin in older adults and suggest not exceeding a daily dose of 0.125 mg, particularly in cases of heart failure and atrial fibrillation (1,2).

Despite these recommendations and the possible adverse effects, dosing errors remain common, due to the complexity of managing polypharmacy in the elderly. Upon observing that these dosing errors also occur in our hospital, we proposed the possibility of creating a computerized alert system focusing on the use of digoxin. There are already some studies exploring the use of software-based intervention programs, which in some cases have proven useful and in others less so (7,12–14).

The difference we propose in our intervention is to address only one drug with frequent misuse, thus preventing alert fatigue (15). The objective is to verify whether

with these alerts we manage to reduce both the number of times digoxin is used inappropriately, as well as the prevalence of adverse effects associated with digoxin such as nausea and vomiting.

For all these reasons, the importance of this study lies in the need to improve the safety and efficacy of drug prescribing in the elderly population. The implementation of a computerized alert system specific for digoxin could represent a significant advance in the reduction of dosing errors and, consequently, in the improvement of patients' quality of life.

3 Objectives

3.1 Main objective

To study the efficacy of a computerized alert, visible to physicians responsible for hospitalized elderly patients who have been prescribed digoxin at a dose above 0.125 mg/day (recommended dose), in reducing the number of patients with inadequate digoxin doses.

3.2 Secondary objective

- To study whether the implementation of a computerized alert, visible to physicians responsible for hospitalized elderly patients who have been prescribed digoxin at a dose above 0.125 mg/day (recommended dose), is associated with a reduction in the percentage of patients treated with digoxin who receive doses above the recommended dose.
- To study whether the implementation of a computerized alert, visible to physicians responsible for hospitalized elderly patients who have been prescribed digoxin at a dose above 0.125 mg/day (recommended dose), is associated with a reduction in the frequency of nausea and vomiting in elderly patients.

4 Study design

Pre-post intervention quasi-experimental study. Two centers participate in this study, and the intervention will be introduced sequentially, with a 6-month lag, in the centers. Thus, during the first 6 months after the implementation of the intervention in the first center, it will not yet have been implemented in the second center, allowing the concurrent comparison over time of a center without intervention and another center with the intervention implemented (parallel groups period):

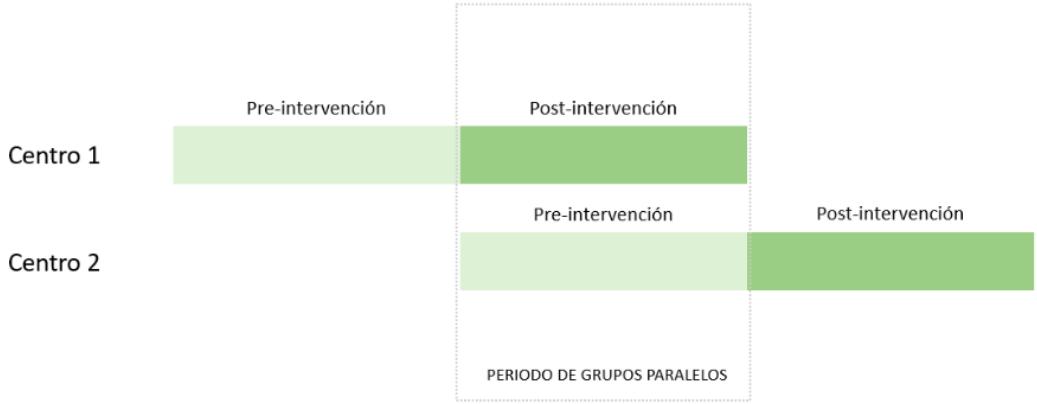


Figure 1: study design

Finally, the intervention will be implemented in the second center, allowing the pre-post group comparison.

5 Description of the intervention

The intervention consists of the introduction of computerized alerts in the CSAPG electronic health record (MIRA software) that are triggered when a physician prescribes digoxin at a dose higher than the recommended one (more than 0.125 mg/day).

On the one hand, an alert appears directed at the physician responsible for the patient on their home screen of the software (figure 2). The responsible physician will receive one alert for each patient with doses prescribed above the recommended level. For these alerts, the following text has been designed:

“HIGH DIGOXIN DOSE. The Geriatrics Service informs you that in persons >65 years it is not recommended to exceed a dose of 0.125 mg/day.”

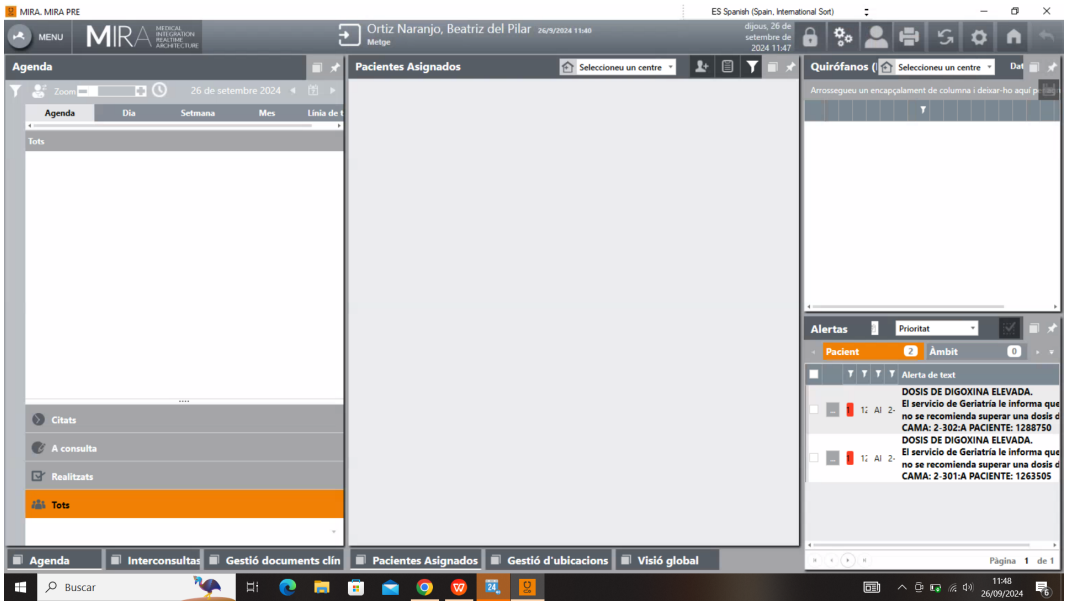


Figure 2. View of the alert on the home screen of the responsible physician's software.

On the other hand, an alert appears, visible to any physician accessing the patient's health record. Next to the medical record number, an icon with a striking color and shape is displayed (figure 3), accompanied by a notice in the corresponding section of the “alerts” tab of that patient's record (figure 4).

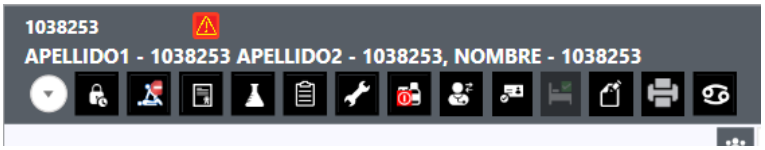


Figure 3. View of the alert next to the medical record number for any physician treating the patient.

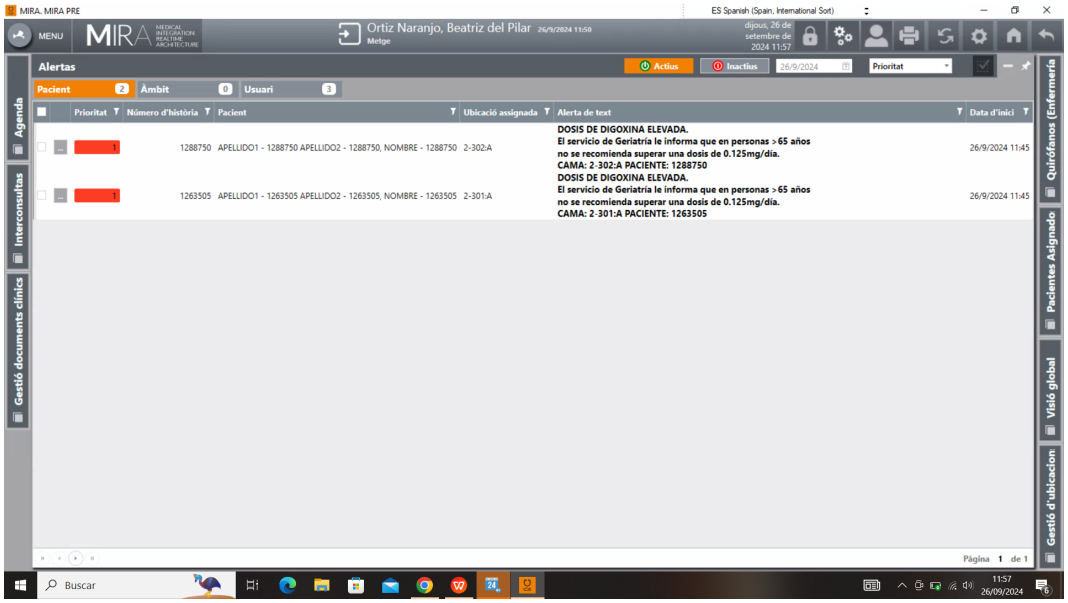


Figure 4. View in the alerts section of the health record.

6 Study subjects

6.1 Eligibility criteria

Patients meeting the following criteria will be included in the study:

- Men and women older than 64 years.
- Admitted to the inpatient wards of the study centers during the study period.
- No exclusion of patients is anticipated.

7 Study period

Fieldwork will last 12 months at each study center, including a 6-month pre-intervention period and a 6-month post-intervention period. In total, the study will last 18 months, which will begin after obtaining a favorable opinion from the Ethics Committee.

8 Scope and study centers

This trial will be conducted on the inpatient wards of the Hospital Comarcal de l'Alt Penedès and the Hospital Residència Sant Camil.

9 Sample size and sampling procedure

Accepting an alpha risk of 0.05 and a statistical power above 0.8 in a two-sided test, 2977 subjects are required in the pre-intervention group and 2977 in the post-intervention group, to detect as statistically significant a 25% reduction in inappropriate digoxin prescriptions. Based on internal data from the study centers regarding inappropriate digoxin prescribing, the rate in the pre-intervention period is estimated to be 6.7%. Hospitalization data from the study centers suggest that the sample size will be reached during the study period.

10 Concomitant interventions

Participants enrolled in another study involving an experimental intervention that directly or indirectly affects digoxin prescribing will be excluded from the analysis during the study period.

11 Outcome criteria, measures and instruments

11.1 Outcome criterion for the primary objective (primary outcome measures)

- Reduction in the percentage of hospitalized patients receiving digoxin above the recommended dose (0.125 mg per day) (1,16) in the post-intervention period compared with the pre-intervention period.

11.2 Outcome criteria for the secondary objectives (secondary outcome measures)

- Reduction in the percentage of admitted patients receiving digoxin above the recommended dose (0.125 mg per day), out of the total of hospitalized patients treated with digoxin, in the post-intervention period compared with the pre-intervention period.
- Reduction in the percentage of admitted patients receiving antiemetics in the post-intervention period compared with the pre-intervention period. Antiemetic consumption will be used as a surrogate indicator of the presence of nausea and vomiting.

11.3 Control and descriptive variables of the sample:

- Sex, collected from the hospital information system.
- Age, calculated from data recorded in the hospital information system.
- Inpatient ward/service.
- Number of patients admitted in each study phase.
- Mean length of stay of hospitalized patients.
- Number of prescribing physicians.

11.4 Sources of information

All study data will be collected from the electronic health record once the pre and post intervention phases have concluded.

12 Quality control

Quality control will be performed on 2.5% of the cases included in the study, selected at random, to manually verify that the automated extraction of data recorded in the information system contains no errors. If errors are found, the problems associated with the extraction will be corrected, or the affected data will be excluded when the problem cannot be solved. If necessary, after the corrective operations, quality control will be repeated on the same percentage of cases, until the absence of errors in the data is confirmed.

13 Data analysis plan

A descriptive analysis of all variables available in the database will be performed. Quantitative variables with a normal distribution will be described using the number of observations, the mean, and the standard deviation. To describe quantitative variables that do not fit a normal distribution, the number of observations, the median, and the interquartile range will be used. Qualitative variables will be described using the number of observations and the percentage of each category.

For the main analysis, the percentage of patients whose last digoxin dose prescribed during admission is above the recommended daily dose in the elderly will be compared between patients treated during the post-intervention period and patients treated during the pre-intervention period, using the Chi-Square statistic.

Similarly, for the analysis of the first secondary objective, the percentage of patients treated with digoxin whose last digoxin dose prescribed during admission is above the recommended daily dose in the elderly will be compared in the post-intervention period versus the pre-intervention period.

For the analysis of the second secondary objective, the percentage of patients who have received antiemetic drugs during the post-intervention period will be compared with respect to patients treated during the pre-intervention period.

Subgroup analyses are planned according to age and sex.

As a sensitivity analysis, it will be checked that the main results do not vary due to time-related factors, repeating all the analyses in the group exposed to the intervention and in the group not exposed to the intervention, exclusively during the parallel groups phase (figure 1).

The characteristics of participants excluded from the analysis for receiving a prohibited concomitant intervention or during quality control will be studied to assess whether they are homogeneous with the rest of the sample or, on the contrary, whether losses and exclusions may introduce bias and/or lack of validity.

The analysts will be blinded to the study period (pre or post intervention). A type I error of 5% is set for all analyses. The statistical analysis will be performed with the R statistical program, version 4.0 or higher.

An additional follow-up analysis may be performed using secondary data obtained from the health record approximately one year after the completion of the intervention. This analysis is not part of the objectives of the study and its execution will require new approval from the Ethics Committee. The purpose of this analysis will be to evaluate the persistence of the effect observed in the study.

14 Ethical aspects and data protection

14.1 Information to the Research Ethics Committee

This study protocol must be reviewed and approved by the corresponding Ethics Committee before the start of the trial. Any change to the protocol that may entail a new risk to the rights of the participant, or that may affect the validity of the study, must be submitted by the sponsor to the Ethics Committee and approved by it before implementation.

14.2 Information to the participant and informed consent

Given that this study collects health record data (secondary data) retrospectively, it is not feasible to obtain informed consent from the participants, so the data will be pseudonymized (see section 14.3).

14.3 Protection of personal data

This scientific study could not be carried out without collecting personal data from the participants treated at the participating centers. The use of the data is legitimized by a mission of public interest (due to the scientific interest of the study and the impact of the knowledge it will produce). No data will be collected until the study and all its documents have been approved by the Ethics Committee.

The data will be processed in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (GDPR), as well as Organic Law 03/2018, of 5 December, on Personal Data Protection and Guarantee of Digital Rights (LOPD-GDD). In line with the data minimization principle, only the data necessary to carry out the research will be collected. In this study, health record data will be collected. The data will be extracted by automatic or semi-automatic means from the information system, retrospectively, once the pre and post intervention phases of the study have ended. This data extraction will be carried out by personnel assigned to the research department of the center, which is independent of the research team, and is specifically designated for tasks related to data processing and coding. The total data and the planned subgroups will be presented to the investigators in pseudonymized form.

The CSAPG is the data controller; any other entity working with the data will act as data processor, for which specific agreements will be signed. Data will not be transferred outside the European Union.

Situations classified as high risk for the rights and freedoms of data subjects are not anticipated, in accordance with additional provision 17.2.f of the LOPD-GDD, so a data protection impact assessment will not be performed.

The investigators and the sponsor will retain the data collected for the study for 5 years after its completion, or the time required by current legislation and the Ethics Committee.

15 Protocol modifications

15.1 Protocol deviations

The instructions and procedures specified in this protocol require diligent attention to their execution. No alterations or changes to this protocol are permitted. However, should any doubt or consideration of a change to the protocol arise, it must be clarified with the sponsor. Any subject treated differently from that established in the protocol, or who is admitted to the study without meeting the protocol requirements, may be unfit for analysis and may therefore compromise the study. The investigator and the research team must comply with national and international laws.

15.2 Protocol amendments

The protocol cannot be amended by the investigators or study personnel without first obtaining the review and approval of the sponsor. Clinically significant amendments (e.g., those affecting the rights of the human subjects participating in the research, the scientific soundness of the research plan, the validity of the data, or the information resulting from the completion of an approved protocol, etc.) cannot be made before their approval by the corresponding Ethics Committee and the regulatory authorities.

16 Publication plan

The results of the study will be disseminated through publication in congresses and scientific journals. Any formal presentation of results will be considered a publication of the study and must have the sponsor's approval.

The list of authors of formal publications will be agreed upon according to the criteria or limits of the journal or congress organization in question. Whenever possible, all study investigators will be included as authors; if this were not possible, priority will be given to investigators with a greater contribution to the study (e.g., in participant recruitment). In any case, the authors included in the publication must meet the authorship criteria of the International Committee of Medical Journal Editors (ICMJE). According to these criteria, all authors must approve the final version of the article and have made substantial contributions in at least one task in each of the following blocks:

- Conception, design, acquisition or generation of data, or analysis and interpretation of data for the publication.
- Drafting of the manuscript and critical review of its content.

Any publication resulting from this study will be carried out in accordance with the Good Publication Practices.

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