Protocol Title:	**S**econdary Pr**e**vention of **C**ardiovasc**u**la**r** Disease in the **E**lderly (SECURE), a prospective randomized clinical trial comparing a polypill versus standard of care treatment strategies in post MI elderly patients
CNIC Principal Investigator:	Valentin Fuster, MD, PhD
CNIC Co-Investigator:	[redacted]
	Centro Nacional de Investigaciones Cardiovasculares (CNIC) Address: c/Melchor Fernandez Almagro 3, Madrid 28029, Spain Telephone: [redacted] Fax: [redacted]

PATIENT INFORMATION SHEET

A. INTRODUCTION

You are invited to take part in this clinical trial based on your medical history. The purpose of this research study is to test whether a pharmaceutical formulation including three drugs in one (polypill) is useful to decrease the number of subsequent cardiovascular events. This research study will gather information on the use of different medications for cardiovascular prevention in patients who have suffered a myocardial infarction. This information is necessary to improve the treatment of patients who have suffered an acute myocardial infarction. It is important that you read and understand the following instructions before signing this document and thus giving your consent to participate in this study.

1. Participation in this study is voluntary.
2. By participating in this study you might or might not obtain personal benefits, but the knowledge that may be acquired through your participation may benefit other patients
3. You can withdraw your consent at any time and withdraw from the study, without this affecting or causing the loss of any benefit or any right to receive medical care to which you are entitled.
4. Both treatments compared are bioequivalent, that is, they reach the same concentration in your body. Therefore, if you receive treatment with Trinomia (the cardiovascular polypill), you will be treated with the same components as the control group, the only difference being that the polypill includes the three pills received by the control group in a simple once-daily pill formulation in order to evaluate compliance to treatment.

B. BACKGROUND AND PURPOSE

As your doctor already explained, you have suffered an acute myocardial infarction. At the time of hospital discharge, after the acute episode, the doctor prescribed a number of medicines to be taken regularly. It has been shown that patients struggle to obtain and take all medication as prescribed. This decreased adherence (compliance) in medication has been shown to affect patient recovery and the prevention objectives. In parallel, data from different studies has demonstrated that including several drugs into a single pill facilitates patient adherence to treatment. Hence, patients taking the polypill, through their increased adherence, are expected to present fewer events after a myocardial infarction. It is this hypothesis that this study is set out to prove.

Study Objective

The purpose of this study is to evaluate whether taking the polypill compared to the standard therapy, reduces the risk of recurrent cardiovascular events.

C. STUDY DESIGN

There will be a minimum of 2514 participants in this study across Europe, namely in Spain, Italy, France, Germany, Czech Republic, Hungary and Poland.

Your doctor will verify that you meet all the required criteria in order to be included in this study. Once all the requirements are met, you will be invited to participate in this study and to sign the consent form.

After the consent form is signed, you will be "randomized" into one of the two study groups (polypill or standard therapy). Randomization means that you are placed into one of two groups by chance (like when flipping a coin). Neither you nor the research doctor will choose the group where you will be included.

The study groups are:

1. Polypill: combining all three drugs into one pill.
2. Standard treatment: which includes the same treatment but taken separately in three pills.

The polypill will be provided to you for free by your doctor.

The standard therapy of all three drugs separately will be covered by your health insurance.

D. STUDY VISITS AND PROCEDURES

Screening

If you are over 65 and have recently suffered a myocardial infarction (within the last 6 months), you may be eligible to enter the SECURE study. The site investigator will review your history to see that you meet all eligibility criteria.

If and when you decide to enter the study, the site investigator will explain the objectives, expectations, expected risks, expected benefits, visiting schema and duration of the study. Should you decide to enroll in the SECURE study, after signing this informed consent form, you will be randomized to either one of the two study arms.

Randomization

Randomization will be carried out by the investigator using a computer software**.**

Baseline

The site investigator will gather information regarding the acute event, your current list of medications, weight, height, blood pressure and blood analysis, all of which are standard practice following a myocardial infarction. Additionally, the site investigator will run questionnaires regarding medication adherence, treatment satisfaction, and quality of life.

Planned Follow-up

Patients will be invited for a return visit at the hospital for the following reasons outlined below:

1. Medication Refill: Patients taking Polypill will be given medication every 3 months to be refilled at the hospital pharmacy.

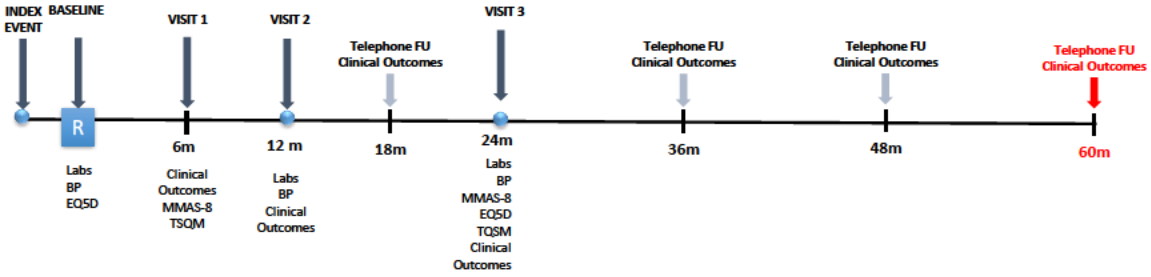
2. Patients randomized to standard treatment will refill medication at their local pharmacy.

.

The study visits will be:

- On-site follow up visits: that will take place at months 6, 12 and 24 from the start of the study. These will be Visit 1, Visit 2 and Visit 3.

- Telephone follow up calls: at months 18, 36, 48 and 60. These will be Call 1, Call 2, Call 3 and Call 4.



E. DESCRIPTION OF PROCEDURES

The following procedures will be performed during the study:

Physical examination/Weight: at baseline. Also, measurement of vital signs at all study visits. A follow-up will be performed at every visit of all concomitant medication taken and all adverse events occurring.

Non-fasting Blood Sample will be collected and analyzed by the local laboratory for: full blood count, full lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol), HbA1c (glycated hemoglobin), serum creatinine and creatinine clearance, CK and liver function tests (ALT, AST, alkaline phosphatase). All of these measurements are standard, guideline recommended follow up measurements after a myocardial infarction. They will be performed at baseline and during Visit 2 and Visit 3.

Quality of Life Questionnaire: this will be assessed using the validated EQ-5D questionnaire. You will complete a Quality of life questionnaire at Baseline and during Visit 3 (24 months of treatment).

Adherence to Treatment will be assessed by the self-reported Morisky-Medication Adherence Scale (MMAS-8), an eight-item Questionnaire, which has been validated in various CV treatment scenarios as an indirect, self-reported measure of adherence. Adherence will be measured at Visits 1 and 3 (6 and 24 months of treatment).

Treatment Satisfaction Questionnaire for Medication (TSQM) is a validated scale that measures patient preference to medication. You will fill in this questionnaire at Visit 1 (6 months of treatment) and at Visit 3 (24 months of treatment).

Major adverse cardiovascular events (MACE) include cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke and urgent coronary revascularization. Together they are the primary endpoints of SECURE. They will be assessed throughout all the visits of the study.

F. RISKS AND BENEFITS OF BEING IN THE STUDY

The three drugs (Aspirin, Statin, and ACE Inhibitor) used in this study are prescribed to all patients who have suffered a myocardial infarction. The benefits of taking these drugs after a coronary event have been shown in several studies and are highly recommended in the current therapeutic guidelines.

Trinomia combines aspirin, a statin (that reduces cholesterol) and an ACE inhibitor (an antihypertensive) into a single pill, which is bioequivalent to the standard treatment and that has been approved by the European Regulatory Authorities. Trinomia is currently commercialized in 18 countries and will be commercialized in several other countries next year. Clinical trials have shown that this drug poses no added risk compared to taking the components thereof as separate drugs. The expected benefit of this new polypill is the improvement of the prevention of coronary episodes, through improving treatment adherence (treatment compliance), which has also been shown to be significant in other clinical trials.

Risks

Acetyl salicylic acid Side effects
Evidence of an adverse event related to treatment with low-dose aspirin

- Clinically significant gastrointestinal bleeding has been reported in up to 3% of the patients treated: 23 elderly patients. The risk of experiencing dyspepsia events (that is, epigastric pain, heartburn, nausea, ulcers) is low in patients with no previous gastrointestinal symptoms who receive low-dose aspirin.
- Renal side effects have included reduced glomerular filtration rate (in particular in patients on sodium restriction or with reduced effective volume of arterial blood, such as patients with advanced heart failure or cirrhosis), interstitial nephritis (kidney tissue inflammation), papillary necrosis (cell destruction in the kidney), increased serum creatinine and increased BUN, proteinuria (abnormal loss of proteins in urine), hematuria (blood loss in urine) and kidney failure.

Side effects of hypersensitivity have included bronchospasm (airway narrowing), rhinitis (inflammation of the nasal mucosa), conjunctivitis (inflammation of the eye conjunctiva), urticaria (skin reaction associated with itching), angioedema (inflammation of body areas such as the lips, ears, nose) and anaphylaxis (generalized allergic reaction that causes reduced blood pressure and is life-threatening). About 10% to 30% of asthmatic patients are sensitive to aspirin (with the clinical triad of sensitivity to aspirin, bronchial asthma and nasal polyps, that are swollen tissue masses similar to the sacs lining the nasal mucosa) 0.24

Ramipril Side Effects

- The side effects were generally mild and transient and were not related to the total dose within the range of 1.25 mg-20 mg.

- Treatment discontinuation due to a side effect is required in about 3% of the US patients treated with ramipril.
- Common side effects include headache (5.4%), light-headedness (2.2%), and fatigue or asthenia (2.0%), but only the latter was more common in patients taking ramipril than in patients receiving placebo.
- Dry cough can also occur (in 3% of the patients randomized to placebo and 7% of the patients randomized to ramipril in the HOPE study) 0.26
- Angioedema, a severe inflammation of the lips, tongue and throat, can occur .01-.1% of the patients taking ramipril.

The most common reasons for discontinuation were: cough (1.0%), light-headedness (0.5%), and impotence (0.4%).

Atorvastatin Side Effects
Most common adverse reactions in patients treated with atorvastatin leading to treatment discontinuation and occurring at a higher rate than with placebo were in ACE data and were as follows:

- Myalgia (muscle pain) (0.7%)
- Diarrhea (0.5%)
- Nausea (0.4%)
- Increased liver enzymes (0.4%).

G. ALTERNATIVES TO BEING IN THE STUDY

Taking part in this research study is voluntary. If you do not wish to be part of this study, an alternative treatment will be available to you, which will use other types of drugs available in the market.

H. VOLUNTARY PARTICIPATION

You have the right to choose not to sign this consent form. If you decide not to sign this form, you will not participate in this research study.

Your participation in this study is completely voluntary and you may choose to withdraw from the study at any time. You can withdraw from the study by simply notifying the research doctor. Your decision to not be part of the study will not affect your medical care or your treatment.

I. COMPENSATION AND EXPENSES ASSOCIATED WITH PARTICIPATING IN THE STUDY

No economic compensation will be given for participating in this research study. Your participation will not entail any additional costs to you.

J. CONFIDENTIALITY

If you decide to participate in this study, your personal medical history will be collected. The information collected will be processed manually and electronically by the CNIC (Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain) and by other designated investigators who work in the study. Your name will not be registered; therefore, the study information does not identify you. Your information will be solely collected for research purposes and the database holding your information will be retained for at least 15 years, according to the legislation of the Health Authorities. We guarantee that your identity will be protected during these procedures. If you would like to participate

and then withdraw from the study, all of your information regarding this study will be removed from the database. When the study results are published, no identifying information of any patient will be included.

According to European and Spanish laws, the processing, communication, and transfer of personal data regarding all participating data subjects shall comply with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and the Organic Law 3/2018 of December 5th on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. According to the provisions of the mentioned legislation, you may exercise your rights of access, rectification, opposition, portability, treatment limitation and cancellation of data, with such requests being directed to your research doctor. In case of transfer of the study data to third countries having a confidentiality protection level different from that provided by the Spanish law, the sponsor will ensure a protection that is at least equivalent to that provided by the of Regulation (EU) 2016/679 and the Organic Law 3/2018. To exert your rights you may contact your Doctors at the hospital, the principal investigator of the trial or the Data Protection Officer of the Sponsor at dpo@cnic.es). In addition, you have the right to contact the Spanish Data Protection Agency (www.agpd.es) if you are not satisfied.

K. APPROVAL

This study will be conducted following local regulations, as well as the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

This clinical trial has been revised and approved by the Ethics Committee of the Hospital Clínico San Carlos as Reference Committee and the Research Ethics Committee of your local hospital and is performed under the center's agreement and acknowledgement.

L. INSURANCE

In compliance with the provisions of RD223/ 2004, which regulates requirements of the clinical trials' conduct, the sponsor has signed an insurance policy to cover any damages resulting from the study for a guaranteed minimum amount of 250,000 Euros per subject, with a maximum capital insured of 2,500,000 Euros per clinical trial and year. The insurance policy has been taken out with the company HDI, under policy number 08051053-14145.

In case you have private insurances, you should review whether your participation in the trial could affect their coverages.

M. QUESTIONS ABOUT THE STUDY

In case you have further questions about the treatment and/or study, please contact your doctor at the following numbers:

Name: _____

Phone: _____

Thank you very much for reading this information sheet.

If you agree to participate in this study, you will be given a copy of this sheet and a signed copy of the consent form.

CONSENT FORM

Protocol Title: Secondary Prevention of Cardiovascular Disease in the Elderly Population (SECURE)

My signature below indicates that:

- I have read and understood all of the information provided by the patient information sheet of this study;
- my doctor has responded to all of my questions to my satisfaction;
- I have had enough time to read the consent and think about participating in this study;
- I am willing to participate in this study;
- I am aware that my participation is voluntary and that I can withdraw at any time;
- I am aware that I can decide to withdraw from this study by communicating my decision to my doctor:
  - ✓ Any time I want
  - ✓ Without having to give any explanation
  - ✓ Without this affecting my medical care dispositions

- I understand and agree that my personal data will be collected from my medical records, used and processed (manually and electronically) by the study investigator, co-investigators or by any other designated party who is involved in the study (medical staff, regulatory authorities, ethics committees).
- The confidentiality of the data provided will be maintained and my name or other identifying characteristics will not be used in any publication.

I have spoken with _____
(Name and Surname/s of Investigator)

I freely give my consent to participate in this study

_____	_____	_____
Print Participant's Name	**Participant's Signature**	**Date**
_____	_____	_____
Print Investigator's Name	**Participant's Signature**	**Date**