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# RATIONALE AND DESIGN OF THE CV-PREVITAL STUDY: AN ITALIAN MULTIPLE COHORT RANDOMISED CONTROLLED TRIAL INVESTIGATING INNOVATIVE DIGITAL STRATEGIES IN PRIMARY CARDIOVASCULAR PREVENTION



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# RATIONALE AND DESIGN OF THE CV-PREVITAL STUDY: AN ITALIAN MULTIPLE COHORT RANDOMISED CONTROLLED TRIAL INVESTIGATING INNOVATIVE DIGITAL STRATEGIES IN PRIMARY CARDIOVASCULAR PREVENTION

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**Short running head:** mHealth in primary CV prevention: the CV-PREVITAL study

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No new data were generated or analysed in support of this research.

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**Abstract**

**Introduction:** Prevention of cardiovascular diseases (CVD) is of key importance to reduce morbidity, disability and mortality worldwide. Observational studies suggest that digital health interventions can be an effective strategy to reduce cardiovascular (CV) risk. However, evidence from large randomized clinical trials is lacking.

**Methods and analysis:** The CV-PREVITAL study is a multicenter, prospective, randomized, controlled, open-label interventional trial designed to compare the effectiveness of an educational and motivational mobile-Health (mHealth) intervention vs. usual care in reducing CV risk. The intervention aims at improving diet, physical activity, sleep quality, psycho-behavioral aspects, as well as promoting smoking cessation and adherence to pharmacological treatment for CV risk factors. The trial enrolls ~80,000 subjects without overt CVD referring to general practinioners' offices, community pharmacies or clinics of research hospitals (IRCCS) affiliated with the Italian Cardiology Network. All participants are evaluated at baseline and after 12 months to assess the effectiveness of the intervention on short-term endpoints, namely improvement in CV risk score and reduction of major CV risk factors. Beyond the funded life of the study, a long-term (7 years) follow up is also planned to assess the effectiveness of the intervention on the incidence of major adverse CV events. A series of ancillary studies designed to evaluate the effect of the mHealth intervention on additional risk biomarkers are also performed.

**Ethics and dissemination:**
This study received ethics approval from the ethics committee of the coordinating center (Monzino Cardiology Center; R1256/20-CCM 1319) and from all the other relevant IRBs and ethics committees. Findings are disseminated through scientific meetings and peer-reviewed journals and via social media. Partners are informed about the study's course and findings by regular meetings.

**ClinicalTrials.gov: NCT05339841**

**Key Words**:
Randomized controlled trial; Digital health; cardiometabolic diseases; study design; gamified mobile app.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- ⇒ The randomized controlled design of the study and the enrollment of a large population of participants (N~80,000) recruited in different real-world settings, including general medicine, community pharmacies and Research Hospitals (IRCCS)
- ⇒ The adoption of a coordinated network strategy that also envisages the creation of an IT infrastructure for communication among health operators
- ⇒ The collection of biological samples for the multisite biobank of the Italian Cardiology Network, according to specific Standar Operating Procedures for sample collection, storage and transfer
- ⇒ The lack of standardization of the equipment used for hematological testing and blood pressure measurement, due to the real world nature of the study, is a possible limitation of the trial
- ⇒ Due to the nature of the intervention, the trial personnel and participants are not blinded to treatment allocation

## INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in developed countries.[1] In Italy, there are 136,353 deaths annually attributed to atherosclerotic CVD, with acute coronary syndromes and ischemic strokes corresponding to about 22% of total deaths.[2] CVD are also among the major causes of chronic disability, affecting millions of people in the world.

CVD are, to a large extent, preventable. Prevention of CVD is of key importance, not only to reduce morbidity, disability and mortality, but also to increase the years of wellness in the growing elderly population, thus contributing to decrease the socio-economic burden imposed by cardiovascular (CV) events. However, according to European data,[3] only a minimal percentage of the health care budget is currently spent on preventive measures. In this context, there is an urgent need for exploring innovative approaches to better address the challenge of CVD prevention. Internet-based tools and smartphone applications could actually be used for remote lifestyle monitoring, diagnosis, self-management of CV risk factors, medication adherence, education and psychological support, playing an important role in CVD prevention. In primary CV prevention, preliminary evidence suggests that digital health interventions can be an easy-to-implement and cost-effective strategy to reduce CV risk.[4] However, there is still a need for more solid evidence, which can only be provided by large controlled trials.

Based on these premises and a specific mandate from the Italian Parliament (Law No. 136, Dec. 17, 2018, and Law No. 145, Dec. 30, 2018), the Italian Cardiology Network (ICN), a network of research hospital ("Istituti di Ricovero e Cura a carattere scientifico", IRCCS) engaged in the CV field promoted by the Ministry of Health, launched the study "Digital Strategies in Primary Cardiovascular Prevention in the Italian Population (CV-PREVITAL)" in 2020.

CV-PREVITAL is a multicenter, prospective, randomized, controlled, open-label interventional trial designed to compare the effectiveness of an educational and motivational mobile health (mHealth) intervention with that of usual care in primary CV prevention. The main study hypothesis is that digital technologies can be used efficiently for improving the control of CV risk factors and detrimental lifestyles and, consequently, for reducing CVD incidence and mortality, compared with usual care. The trial also includes a series of ancillary studies. The purpose of this report is to provide a comprehensive description of the project background and of the study protocol, which is also publicly available at www.clinicaltrials.gov as NCT05339841.

## METHODS AND ANALYSIS

The study protocol follows "The Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013 statement"[5] (**Online Supplemental file 1**).

### Trial organization

CV-PREVITAL consists of a large clinical trial (the parent study) and of a series of ancillary studies. The organizational structure of CV-PREVITAL is presented in **Figure 1**. The organizational structure includes several integrated committees: the Steering Committee (see also **Online Supplemental Material - Supplemental Table 1**); the Central Management Committee, which takes care of organizing and coordinating the whole study (Monzino Cardiology Center); the Scientific Coordination Committee, and nine Technical Committees (TCs). TCs have the responsibility to coordinate the specific activities in the following areas: clinics; hematological analysis; socio-economic status assessment; non-invasive diagnostic techniques; genetic analysis; statistics; artificial intelligence; mHealth, eHealth, and technology platforms; technology transfer.

The list of operative units and their role in the study are shown in **Online Supplemental Material - Supplemental Table 2**. Besides the Institute of Pharmacological Research Mario Negri IRCCS, which acts as monitoring center for the cohort of subjects recruited by general practitioners (GPs), all the other IRCCSs participate in the trial as recruiting centers. The working group also includes Consorzio Sanità (Co.S.), a consortium of cooperatives of GPs working in the National Health Service.

Study data are collected and managed using REDCap electronic data capture tools hosted at the Consortium of Bioengineering and Medical Informatics (CBIM).[6 7]

### Trial design

CV-PREVITAL is a multicenter, prospective, parallel-arm, randomized, open-label interventional study. It encompasses the recruitment of ~80,000 participants (aged ≥45 years) nationwide. Of these, 50,000 subjects are selected among those who daily access the participanting GPs offices. In order to assess whether the mHealth intervention under investigation can be effective also in settings different from the primary care one, several specific cohorts are also enrolled by IRCCSs (**Online Supplemental Material - Supplemental Table 2**). These cohorts include subjects (~34,000) from outpatient clinics, diagnostic centers, blood donor centers, company cohorts, general population and pharmacies. The full list of study sites is available on ClinicalTrials.gov (NCT05339841). A structured summary of the trial based on the WHO Trial Registration Data Set is provided in **Online Supplemental file 2**. CV-PREVITAL data flow is represented in **Figure 2**.

**Eligibility**

Participants of both sexes are eligible to participate in the study if: (a) they are in primary CV prevention, (b) they are ≥ 45 years old, (c) they have a smartphone and (d) they have signed the relevant informed consents. Participants are not eligible for the study if they: (a) refuse to sign the informed consent, (b) have an age lower than 45 years, (c) have a history of overt CVD [myocardial infarction (MI), angina pectoris, stroke, transient ischemic attack (TIA), aortic aneurysm or arteriopathy obliterating lower limbs pathologies, congestive heart failure (NYHA Class III-IV)]. Prior to randomization, participants who meet the eligibility criteria are asked by the study investigators to sign the informed consents (**Online Supplemental file 3**). To encourage participation in all the recruiting settings leaflets and posters promoting the study and explanatory videos on the importance of the correct management of CV risk factors have been realized. The number of subjects screened but not eligible is recorded centrally in the ICN database.

**Randomization**

To verify the effectiveness of the interventions carried out, the subjects are allocated randomly in a 1:1 fashion into two groups: 1) control group, followed by the conventional approach (usual care); and 2) intervention group, to which the mHealth interventions are added to “usual care”. Randomization is carried out in three different ways depending on whether the intervention is carried out on subjects enrolled by GPs, by community pharmacies or by IRCCSs. In the setting of general medicine, the procedure randomises the GPs assuring that in each GPs group practice (namely Centro Sanitario Polifunzionale or CSP) the number of physicians assigned to the control group is balanced with that assigned to the intervention group. In the setting of community pharmacies, the procedure randomises the pharmacies assuring that in each geographic area the number of pharmacies assigned to the control group is balanced with that assigned to the intervention group. In the setting of IRCCSs, the procedure directly randomises the participants. Participants are randomised with a central randomisation service developed in house. Allocation concealment is ensured, as the service does not release the randomization code until the patient is recruited and baseline measurements are completed. Additional details are provided in the **Online Supplemental Material**.

**Intervention**

At baseline, participants allocated to the intervention group (mHealth group) receive, in addition to usual care, a smartphone application (CV-PREVITAL app) capable of managing a personalized primary CV prevention program. The app is designed for: (a) education on CV risk, remote monitoring and self-management of CV risk factors, (b) education on and remote monitoring and self-management of psycho-behavioral variables, and (c) detection and/or modification of harmful lifestyles. The CV risk factors managed by the app include high blood pressure, dyslipidemia, diabetes mellitus, obesity, abdominal obesity, and sleep disorders. Psycho-behavioral variables include stress, depression, anxiety and factors related to aspects of the human sphere relevant for patients’ empowerment, such as risk propensity, self-efficacy and locus of control. Harmful lifestyles include unhealthy diet, excessive alcohol intake, smoking habits and a sedentary lifestyle. The app is organized in several educational sections and tools for monitoring over time the variables under consideration. The app performs a personalized delivery of the

educational contents and guided access to the different sections depending on the subject's profile (e.g. subjects with hypertension or hypercholesterolemia or diabetes, etc.). Profiling is performed through specific algorithms according to data collected at baseline (see below) and recorded in a pseudonymized form on the ICN platform database. The app also allows the participant to self-monitoring, during follow up, the changes of risk factors identified at baseline. The lifestyle monitoring is carried out through an active participation of the subject who provides, periodically, information relevant for its own health, such as dietary habits, assumption of medications, specific anthropometric parameters, sleep quality, level of physical activity practiced and so on. Such monitoring is also assisted by links to native wellness apps that allow, upon permission by the user, the automatic and objective detection of step counts and sleep duration in an interactive mode. The app also provides reminders, personalized motivational feedback and evaluation of tasks and periodic goal achievements. Everything is managed with a gamification logic,[8] i.e. an approach that seeks to create experiences reminiscent of gaming and that implies not only a combination of concepts such as rewards (e.g. points, achievement badges, and challenges), but also the use of narrative storylines, avatar-based self-representation, and onboarding tutorials. Gamification logic has been proposed for a twofold purpose: first, to make the participation to the study including data compilation tasks more enjoyable, and second, to ensure people's long-term commitment to tasks that, some time, are perceived as boring and/or demotivating. The final goal is to help users accomplish all required tasks that, in turn, have the goal to improve health literacy and adhesion to healthy behaviors and/or maintaining healthy habits. Data collected through the app during the follow up are transmitted to the ICN database. This makes information available to the treating doctor so that he/she can use it to personalize further prevention activities.

**Control group**

Participants allocated to the control group are followed by the conventional approach (usual care) based on regular visits respecting the usual schedule dictated by the rules of general practice. As a part of the baseline assessment, they receive counselling and are encouraged to maintain or improve their current physical activity level, dietary habits, medical adherence, etc., depending on their individual goals and needs.

**Hypotheses and outcomes**

The primary hypothesis of the trial is that a personalized intervention of CV primary prevention based on mHealth technology can be more effective than usual care in controlling conventional risk factors and harmful lifestyles in the short term and in reducing vascular events in the long term. The primary outcome used to measure the efficacy of the mHealth intervention at short term (12 months) is the change of a risk score developed *ad hoc* in the Italian population. The score, named "modified Moli-Sani score" (details in **Online Supplemental Material**), was constructed by analysing the combined impact of different modifiable risk factors on the risk of developing CVD in the follow up of the MOLI-SANI study, which collects data from the general population of Molise, a region in south-central Italy.[9 10] A 10% improvement in the modified Moli-Sani score between the baseline and final assessment in the intervention group (App) compared with the score change detected in the control group (Usual care) is regarded indicative of a clinically meaningful intervention effectiveness at short term. The primary outcome used to measure the efficacy of the mHealth intervention at long term (7 years) includes major adverse cardiovascular events (MACE), i.e. CV death, MI, stroke, TIA, peripheral artery disease or new diagnoses of angina, hospitalizations for CVD, and need for revascularization. Several secondary outcomes are also pre-specified. Short-term secondary outcomes include: (a) a combined endpoint including the concomitant change in hypertension, diabetes and hypercholesterolemia; (b) the change of at least one of the risk factors considered in the score; (c) the percentage of subjects who accepts to compile the questionnaires; (d) the percentage of subjects who interrupts the use of the app during the follow up; and (e) the adherence to recommended therapies. Long-term secondary outcomes include: (f) the development and validation of a new algorithm for CV risk estimation; (g) the estimation of the costs and effectiveness of the intervention; and (h) the identification of new socio-economic and behavioral risk factors.

**Measurements performed at baseline and follow-up**

At baseline, subjects identified as potentially eligible for recruitment are given the information material and the forms for signing the informed consent for study participation. Subjects who agree to participate in the study are invited to complete a series of questionnaires. Questionnaires can be completed in two different ways: (a) on site (i.e. at physician's office or pharmacy), after having signed the informed consent, by a direct access to an electronic "Case Report Form" (eCRF) compiled with the help of a healthcare professional; or (b) remotely (via web), after having provided a digital informed consent, through remote access to the electronic eCRF compiled with the assistance of computer tutorials or with phone assistance and using a secure access. This second option was provided to cope with the limitations due to the COVID-19 pandemic, which required social distancing to limit the spread of SARS-CoV-2.

Self-report questionnaires administered at baseline cover the following areas:

1. family and personal history of diseases (cardio- and cerebrovascular disease; metabolic disease)
2. ethnicity, socio-economic status and marital status
3. smoking habits
4. alcohol consumption (PREDIMED questionnaire[11])
5. adherence to Mediterranean diet (PREDIMED questionnaire[11] and Moli-Sani questionnaire–an adaptation of the MEDAS questionnaire[12])
6. salt consumption (MiniSal questionnaire[13])
7. physical activity (IPAQ–International Physical Activity Questionnaire[14])
8. personal history of sleep disorder and sleep quality (PSQI–Pittsburgh Sleep Quality Index[15])
9. psycho-behavioral factors:
   - 9.1 perceived stress (PSS–Perceived Stress Scale[16])
   - 9.2 anxiety and depression (PHQ 4 questionnaire[17])
   - 9.3 self-efficacy (GSE–General Self-Efficacy Scale[18])
   - 9.4 locus of control (Multidimensional Health Locus of Control Scale[19])
   - 9.5 risk propensity (RPS–Risk Propensity Scale[20])
10. personal history of coronavirus disease (COVID-19)

Baseline evaluation is completed by healthcare professionals (nurses or physicians) with the collection of the following data: (a) on ongoing pharmacological treatments (chronic therapies); (b) personal history of organ damage from diabetes and hypertension; (c) measurements of anthropometric parameters (weight, height, body mass index, waist circumference,[21] blood pressure and heart rate); and (d) biochemical variables (total, LDL and HDL cholesterol, triglycerides and glycated hemoglobin) assessed by point-of-care testing or by standard laboratory methods. Based on these data, by using validated algorithms a series of risk scores are estimated, including scores assessing the risk of developing metabolic diseases such as diabetes (Findrisc),[22] and hypertension,[23] and a score assessing the risk of developing vascular events. The latter is calculated on the basis of the aforedescribed modified Moli-Sani score. The risk to develop vascular events is also calculated on the basis of other algorithms and in particular with (a) the Italian algorithm developed within the "Progetto Cuore" framework,[24] (b) the European and the American risk algorithms (i.e. SCORE-Risk[25] and Framingham Risk Score,[26] respectively), and (c) the ASCVD, i.e. the score proposed within the ACC/AHA (American College of Cardiology/American Heart Association Task Force on Practice) guidelines.[27] These algorithms are calculated in order to assess whether the risk calculated with the modified Moli-Sani risk score (and its change due to the intervention) is in line with the corresponding values obtained with other risk estimators.

At the 12$^{th}$ month, all participants are invited back to the recruitment center (GP office, IRCCS facility or territorial pharmacy) to re-complete the questionnaires administered at baseline and to repeat the anthropometric and biochemical measurements made during the first assessment. At 7 years, participants are contacted once again to monitor the possible occurrence of new MACE. In the case of fatal events, information is obtained by contacting the participant's family.

All follow up visits foreseen in the study are those recommended according to routine clinical practice for CV prevention. The reason for discontinuation are collected by an ad hoc eCRF.

A schematic diagram of data collected at the three time points of the study protocol (T0, baseline; T1, month 12; T2, year 7) is shown in **Online Supplemental file 4.**

**Sample size**

The sample size has been calculated for the long-term endpoint (i.e. incidence of CV events). On the basis of the data collected on a sample of about 1,000 Italians (~50% women) aged between 55 and 79 years (Italian groups of the IMPROVE study[28]), the annual incidence of MACE has been estimated. Based on this data, the following sample size calculation was made: assuming an incidence rate of 0.0116/year, we expect, considering 50,000 participants, a total of 3,921 events in 7 years. This sample is enough to detect as significant (alpha=0.05) and with a power of 80% a reduction in MACE incidence in the "intervention group" equal to 8.5%, compared to the "usual care" group (Hazard Ratio=0.915). On the basis of the data of the MOLI-SANI study, i.e. 21,806 subjects with a median follow up of 8.2 years and 862 events, the incidence rate is 0.0048 and the expected number of events in the CV-PREVITAL population is 1,687. This sample size provides a power of 80% to detect as significant (alpha=0.05) a reduction in MACE incidence in the "intervention group" equal to 12.8%, compared to the "usual care" group (Hazard Ratio=0.872). It should be noted that being calculated on the vascular events at 7 years, this sample size yields a very high power (>95%) to detect even extremely small differences in the short-term end-points, in both risk scores and single risk factors (e.g. < 1 mg/dL for total cholesterol and blood glucose, and <1 mmHg for systolic blood pressure). Results obtained from different cohorts, i.e. subjects enrolled by GPs and subjects enrolled in the various IRCCSs, are combined using a meta-analytic approach.

**Statistical analysis**

Continuous data will be presented as means and standard deviations (SDs) and as medians and interquartiles, categorical data as frequencies and percentage.

Three classes of pre-specified statistical analyses are considered. The first class refers to the analyses of variables collected at enrollment. These analyses are performed to estimate the baseline prevalence of the different risk factors and risk conditions in the different recruited cohorts. The second class refers to the analyses of variables collected at the end of the short-term follow up (12-month) aimed at assessing the effectiveness of the intervention (App vs. Usual care) on CV risk. The third class refers to the analyses of variables collected at the end of the long-term follow up (7 years) aimed at assessing the effectiveness of the same intervention on the incidence of fatal and non-fatal CV events.

Cross-sectional analyses on data collected at baseline (analysis of determinants of risk factors and estimation of their prevalence) will be carried out using logistic regression and general linear models (GLMs). The short-term primary endpoint, i.e. the change in CV risk score in the two treatment arms, will be analyzed with GLMs adjusting for potential confounders possibly unbalanced between the two groups. Secondary endpoints, i.e. changes in the level of individual risk factors, will be analyzed with GLMs and Bonferroni correction will be applied to account for the number of tests performed.

The long-term primary end-point, i.e. the incidence of fatal and nonfatal CV events, will be analyzed by Cox regression models adjusting for potential confounders. As long-term secondary end-points, new risk algorithms will be developed using Cox models and validated using ROC curve analysis and reclassification techniques. Results generalizability will be tested with cross-validation approaches.

Subgroup analyses stratified by gender are also planned.

In case of missing outcomes for the primary endpoint, these will be imputed using multiple imputation. A sensitivity analysis on the imputed data will be performed. Drop-outs will not be replaced.

The efficacy analyses will be performed according to the intention to treat (ITT) principle on the full analysis set. A sensitivity analysis will be performed in the population with adherence to protocol (PP analysis).

**Cost-effectiveness assessment**

Cost-effectiveness is assessed for different screening scenarios. The analysis of the economic aspects of digital-health interventions is often a complex process (digital-health interventions have been defined as "complex interventions in a complex system"), while in the intervention involving GPs the costs are limited

to: (a) cost of the implementation and maintenance of the IT platform; (b) cost of the application for smartphones (which, once produced, has virtually no shipping and installation costs); and (c) cost of the time spent by the GP for training, for the use of the IT platform and for the involvement and education of the patient. For an analytical evaluation of the economic aspects of the intervention, cost/efficacy analysis (CEA) and cost/utility analysis (CUA) are applied. The CEA is the simplest and most frequently used form of evaluation in health economics and aims to estimate the relationship between the costs of the resources used and the effectiveness of their use. Effectiveness is estimated by a single measure in two ways: first, as the number of participants reaching the target in the main risk factors (hypertension, diabetes and hypercholesterolemia) and second, as the number of CV events (fatal and non-fatal) avoided during the 7 years of follow-up, related with the costs incurred. The CUA considers not only the duration, but also the quality of life that the participants achieve as a result of the intervention. Quality-adjusted life years (QALYs) are summary measures that allow a more complete appreciation of the full state of health and well-being of the individuals examined. To estimate QALYs, validated instruments such as World Health Organization Quality Of Life (WHOQOL) or similar will be used and administered during the follow-up.

**Web based trial management**

In order to create an effective communication network between GPs and physicians of IRCCSs, all the data collected are stored in the IT platform of the ICN (**Figure 2**). This platform is also integrated with the IT platform of Co.S., i.e. the interface used by GPs participating in the study (**Figure 2**). The ICN database also communicates with the mHealth interface (App for smartphones) dedicated to the population and used for both educational purposes and additional data collection (**Figure 2**).

Data protection measurements have been implemented to accomplish with security recommendations specified by the National Institute of Standards and Technology[29] and European data protection regulations.[30] A detailed description of the web-based system for data management and data protection measures is provided in the **Online Supplemental Material**.

**Staff training, standard operating procedures (SOPs) and quality control**

A detailed description of models for staff training, standard operating procedures (SOPs; available upon request), and quality control activities is reported in the **Online Supplemental Material**.

**Ancillary studies (CV-PREVITAL sub-studies)**

CV PREVITAL also includes a series of ancillary studies that are conducted by the various IRCCSs already participating in the parent study. Ancillary studies were designed to evaluate a series of additional risk biomarkers in groups or selected sub-groups included in the parent study. A detailed description of the specific variables evaluated in each ancillary study is reported in the **Online Supplemental Material**.

The steering committee reviewed all the ancillary study protocols to ensure that the specific objectives did not duplicate or interfere with those of the parent study and that all the adopted procedures were consistent with those established in the main protocol. Beyond the specific aims of single sub-studies, a particularly relevant goal, common to all the sub-studies, is the collection of biological samples (e.g. serum, plasma, DNA or RNA) for the multisite biobank of the ICN. For this purpose, the research consortium developed specific SOPs for collection, storage and samples transfer e.g. towards centers acting as core lab. A brief description of the plan for collection, processing, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies is provided in **Online Supplemental file 5**. A biobank informed consent is obtained to specifically address the collection of these samples.

**ETICHS AND DISSEMINATION**

The CV-PREVITAL study has been approved by all relevant IRBs and ethics committees. Their list and the study approval number-IDs are provided in the supplemental material (**Online Supplemental Material - Supplemental Table 3**). Any protocol amendment is promptly reported to all relevant parties (namely,

investigators, ethical committees/IRBs, ClinicalTrials.gov). Personal data are processed in compliance with the provisions set out in the Regulation (UE) 2016/679 (the "GDPR") and in the Legislative Decree. 196/2003 (Personal Data Protection Code, added by the Legislative Decree 101/2018). Personal information are available to the researchers using password-protected files. In addition, all data for presentations are anonymized and aggregated, so the participants' identity is not revealed in any way. CV-PREVITAL results will be disseminated at conferences, through publication in peer-reviewed journals, and through other channels (e.g. web sites of the ICN and of all the hospital involved, social media) in order to reach a diverse community of researchers, GPs, pharmacists and other stakeholders, including citizen and policy makers.

**DISCUSSION**

To the best of our knowledge, this is the first randomized, controlled trial designed to evaluate the effects of an individualized digital intervention through an app containing tools for education on CV risk, remote monitoring and self-management of CV risk factors, detection and/or modification of harmful lifestyles, and patient empowerment.

Preliminary data show that smartphone applications might actually have a great potential in the remote monitoring and self-management of CV risk factors and in improving therapy adherence in hypertensive, diabetic, and dyslipidemic patients.[31 32] However, there is not yet enough evidence to confirm the effectiveness of such applications in primary CV prevention programs. CV-PREVITAL, by collecting information in a prospective, randomized and controlled way on a large-scale, has the potential to provide strong evidence to support policy makers in making informed decisions about strategic planning and resources allocation in primary CV prevention.

If the proposed intervention proves to be workable and successful, the study will support with robust evidence the idea that digital medicine can be a useful strategy to engage, motivate and empower people towards primary prevention of CVD. In addition, due to the large sample size and the different types of cohorts involved, the study has also the potential to generate reliable evidence useful for the implementation of future digital technology-based CV primary prevention programs not only in general or specialist medicine, but also in other real-world and less explored settings such as companies (occupational medicine), blood donors centers and community pharmacies.

A significant strength of the CV-PREVITAL study design is the adoption of a coordinated network strategy, which includes the presence of IRCCSs with proven experience in primary prevention programs, epidemiology and biomedical statistics, and the involvement of a large number of GPs spread throughout the national territory. We expect that such strategy, which also envisages the creation of an IT infrastructure for communication among GPs and IRCCSs, may provide the basis for their permanent collaboration, increase the opportunity for future real-world research and favor the transfer of competences among health operators.

A special feature of the study is the participation of a large number of pharmacies. We believe that this is another significant strength of the study organisation, by virtue of the widespread distribution of pharmacies throughout the territory and the frequent access of citizens to these facilities, which makes them capable of taking an active role as an outpost of the national health systems for the delivery of health services and the implementation of primary prevention programs. In this regard, it is worth mentioning that it is estimated that approximately 4,000,000 people enter the ~20,000 pharmacies existing in Italy every day.[33]

Another important strength of the study is that it allows to make inference (a) on the level of adhesion to the digital prevention programs, (b) on the rate of drop-outs associated to this type of programs in different cohorts in real-world settings, (c) on the rate of drop-outs in different age and sex classes, and (d) on the barriers that hinder the adequate participation based on individual participants' feedbacks. These issues are of particular importance because they can help decision makers in identifying the different type of barriers (e.g. socioeconomical or psychological) that can hinder the successful implementation of digital health in primary prevention of CVD, including the low digital literacy (especially in older people), the limited access to the Internet and to digital tools, the concerns about privacy and data security and, last but not least, the prejudices on the real usefulness of digital approaches.

A last important aspect of the CV-PREVITAL study is that it was designed in the pre-COVID-19 era, but is in fact being carried out during the pandemic. While this created a number of difficulties that required the reorganization of some of the study activities, it also gave new opportunities. In fact, the pandemic has dramatically highlighted how useful digital tools can be to reach people even when conventional methods do not allow it. Indeed, it has accelerated the adoption and acceptance of remote monitoring and other digital approaches to CVD management across the world.[34]

A possible limitation of the study is that the equipment used for hematological testing and blood pressure measurement has not been standardized (only blood pressure measurement devices validated according to internationally acknowledged validation protocols are used, however).[35] Although aware of the inevitable increase in variability of measurements associated to this type of choice, the decision was made to obtain data better reflecting what happens in real-world prevention programs.

**CONCLUSIONS**

Current evidence suggests that digital health interventions have the potential to improve primary CV prevention and save costs of CVD management. However, as only few digital health tools are already implemented in standard care, more researches, especially within large randomized controlled trials, are needed to prove the effectiveness of such approaches. CV-PREVITAL can significantly contribute to the advance in such field by providing evidence of effectiveness of primary CV prevention strategies based not only on the control of CV risk factors, but also on educational activities related to psycho-behavioural aspects (such as stress, depression, anxiety) and aspects of the human sphere relevant for patients' empowerment (such as risk propensity, self-efficacy and locus of control), to be implemented through the use of digital technologies.

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**Authors contribution**

D.B drafted the manuscript, contributed to the conception and study design, and contributed to the implementation of the working plan.

L.I, M.C.R, Gi.Co, G.R, G.F.G, L.F, P.G.C, A.U, Si.Bo, G.S, M.F, An.Di, G.A, A.C, M.T.L, D.Pr, G.L, E.A, M.Vo, E.T, L.Me, G.P and G.Po contributed to the conception and study design and manuscript revision.

R.B drafted the manuscript and contributed to the implementation of the working plan.

M.A, F.Co, M.P, M.Ba, F.Go, L.A, A.Gi, A.E.M, M.M.C, R.C, V.A, B.P, L.S, J.P.W, S.G, G.B, C.I, A.Di, C.L, A.F, D.R, L.O, A.Fo, A.De, Au.Di, S.S, A.Pi, A.Go, L.V, L.L, A.R and M.B contributed to the implementation of the working plan and manuscript revision.

F.V contributed to the conception and study design, statistical analyses and manuscript revision

A.Bo and C.K contributed to statistical analyses and manuscript revision.

G.F, S.C and M.V contributed to the conception and study design, implementation of the working plan and manuscript revision.

All authors gave final approval for manuscript submission and agree to be accountable for all aspects of the work, ensuring integrity and accuracy of the study.

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**Declaration of conflicting interests**
Authors disclosed the relationships/activities/interests reported below.
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Details are available in the individual ICMJE online disclosure forms (available upon request).

**Patient and public involvement**
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Trial Sponsor**
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**Legends to the figure**

**Figure 1: CV-PREVITAL organizational structure**

Abbreviations: SC: Steering Committee; CMC: Central Management Committee; SCC: Scientific Coordination Committee; TCs: Technical Committees; DMC: Data Management Committee.

**Figure 2: CV-PREVITAL data flow**

Abbreviations: IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico; GP: General practitioner; UPI: Unique Partecipant Identifier; GARR: Gruppo per l'Armonizzazione della Rete della Ricerca; Co.S: Consorzio Sanità; VPN: Virtual Private Network.

**Figure 1**

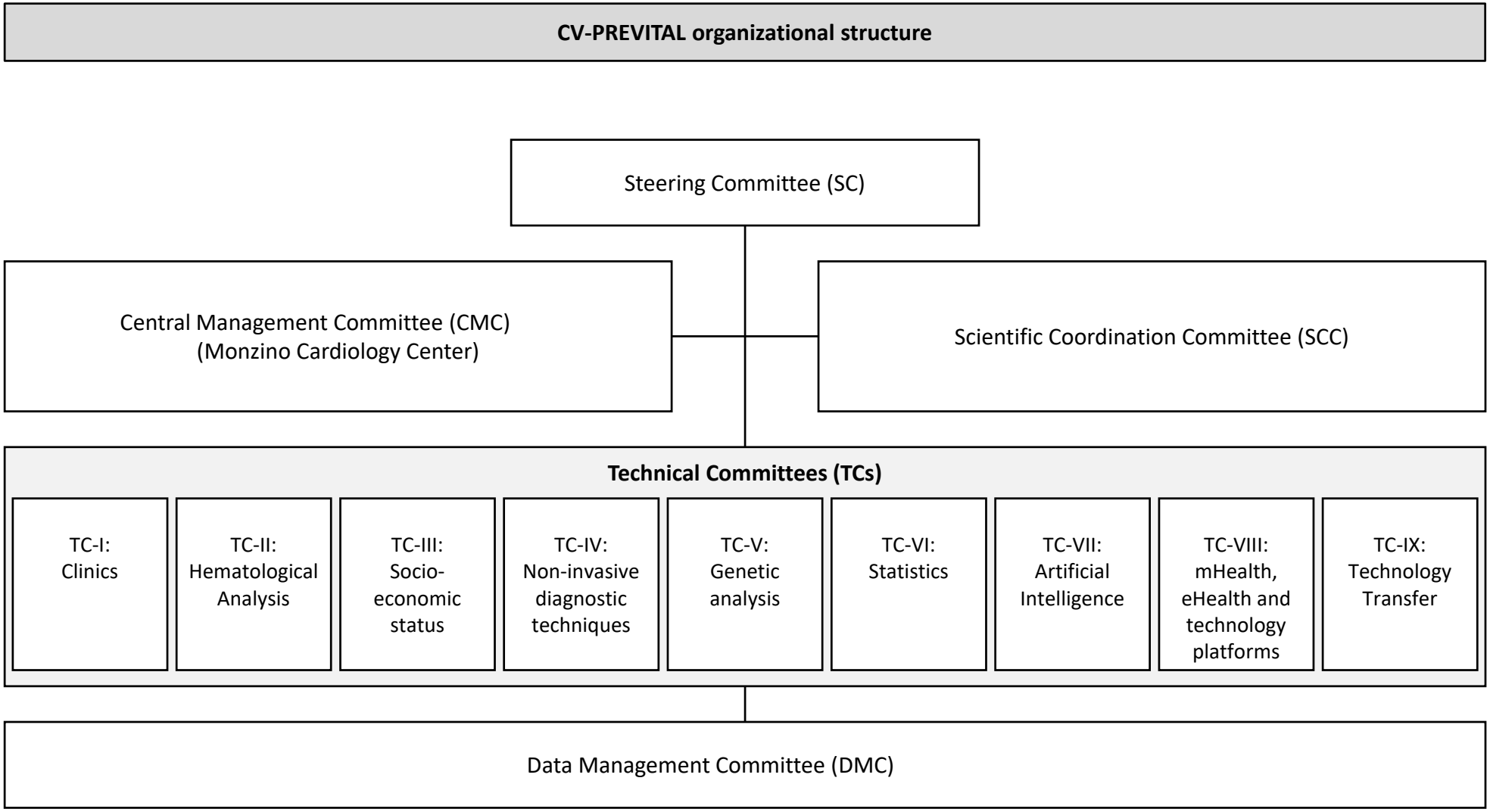
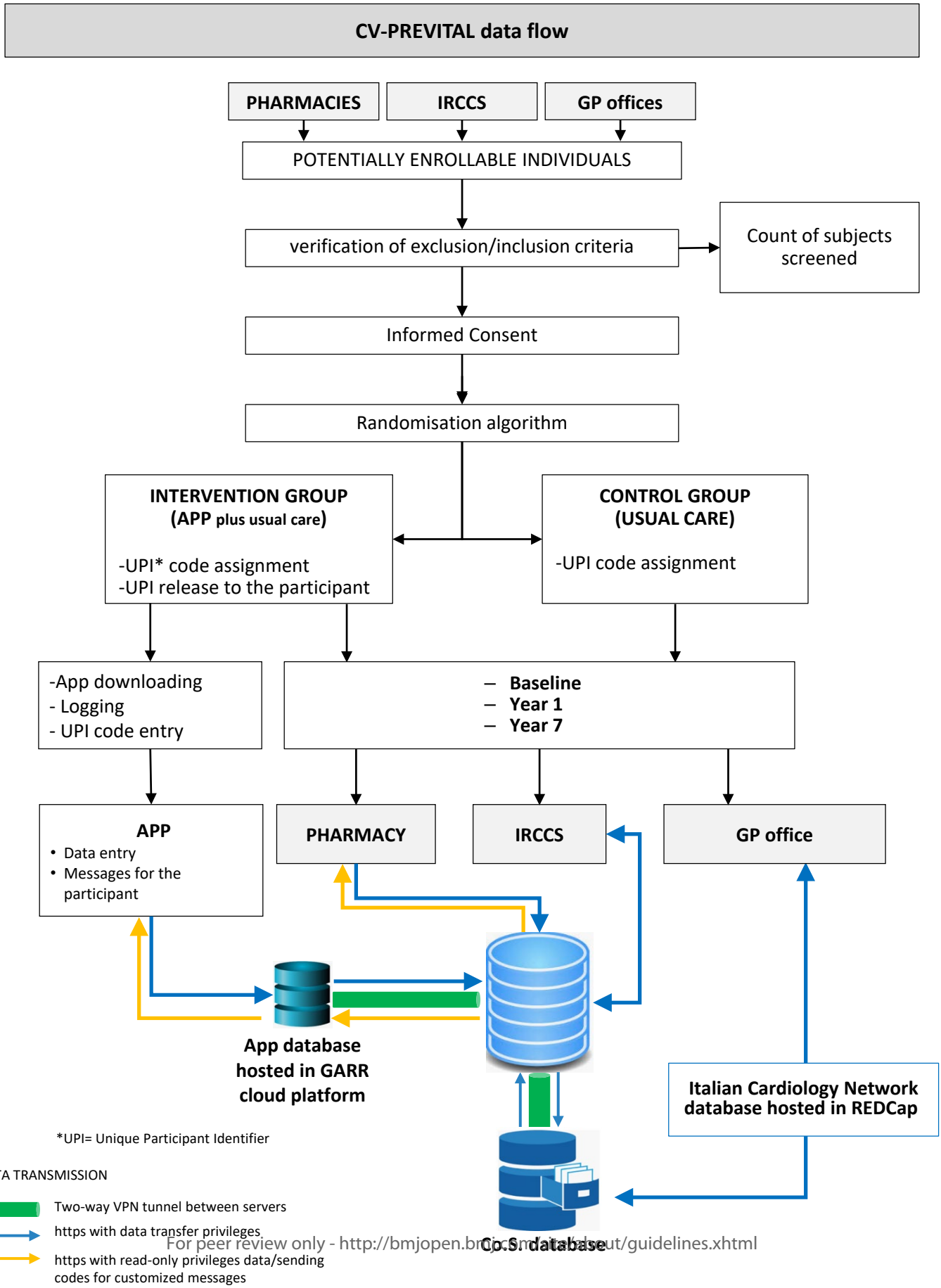

CV-PREVITAL organizational structure
Steering Committee (SC)
Central Management Committee (CMC)
(Monzino Cardiology Center)
Scientific Coordination Committee (SCC)
Technical Committees (TCs)
TC-I: Clinics
TC-II: Hematological Analysis
TC-III: Socio-economic status
TC-IV: Non-invasive diagnostic techniques
TC-V: Genetic analysis
TC-VI: Statistics
TC-VII: Artificial Intelligence
TC-VIII: mHealth, eHealth and technology platforms
TC-IX: Technology Transfer
Data Management Committee (DMC)

**Figure 2**



## ONLINE SUPPLEMENTAL MATERIAL

**Supplemental Table 1. Members of the Steering Committee of the CV-PREVITAL study**

| Institution | Member of the Steering Committee |
|---|---|
| Monzino Cardiology Center | Giulio Pompilio, Damiano Baldassarre |
| IRCCS Italian Institute for Auxology | Gianfranco Parati |
| Humanitas Research Hospital | Gianluigi Condorelli |
| Institute of Pharmacological Research Mario Negri IRCCS | Giuseppe Remuzzi |
| IRCCS MultiMedica | Gianfranco Gensini |
| Neuromed Mediterranean Neurological Institute | Luigi Frati |
| Policlinico San Donato Research Hospital | Lorenzo Menicanti |
| Clinical Scientific Institutes Maugeri (ICS Maugeri) | Walter Ricciardi |
| Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) | Pier Giulio Conaldi |
| San Martino Polyclinic Hospital | Antonio Uccelli |
| IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico | Fabio Blandini |
| Agostino Gemelli IRCCS University Hospital Foundation | Giovanni Scambia |
| Foundation IRCCS Polyclinic San Matteo | Eloisa Arbustini |
| IRCCS San Raffaele Rome | Massimo Fini |
| Consorzio Sanità (Co.S.) | Antonio Di Malta |
| Romeo and Enrica Invernizzi Foundation | Emilio Trabucchi |

**Supplemental Table 2. List of operative units and enrolled cohorts**

| OPERATIVE UNITS | ENROLLED COHORTS |
|---|---|
| Consorzio Sanità (Co.S.) | 50,000 subjects attending the ambulatory of the participanting GPs |
| Monzino Cardiology Center | 5,000 subjects attending pharmacies of the Lombardy territory |
| IRCCS Italian Institute for Auxology | 5,000 subjects attending the institute (including 1,500 subjects referred to the Sleep Medicine Center) |
| Humanitas Research Hospital | 2,000 subjects attending the institution |
| IRCCS MultiMedica | 1,000 subjects with diabetes and 2,000 subjects from the general population |
| Neuromed Mediterranean Neurological Institute | 10,000 subjects from the Neuromed clinical research centre |
| Policlinico San Donato Research Hospital | 1,000 subjects selected among their own employees |
| Clinical Scientific Institutes Maugeri (ICS Maugeri) | 1,000 subjects selected among their own employees |
| Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) | 150 subjects included in a program of physical training and lifestyle modifications |
| San Martino Polyclinic Hospital | 2,000 male subjects from the Municipality of Genoa |
| IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico | 2,000 blood donors afferent to its own Department of Transfusion Medicine and Hematology |
| Agostino Gemelli IRCCS University Hospital Foundation | 1,000 subjects attending to the outpatient clinics of the Non-Invasive Cardiology Diagnostic Unit, of the Centre for Hypertension, and of the Centre for Endocrine and Metabolic Diseases |
| Foundation IRCCS Polyclinic San Matteo | 500 subjects selected among asymptomatic relatives of patients attending to the Policlinico San Matteo for cardiology reasons |
| IRCCS San Raffaele Rome | 150 subjects selected among its own employees |
| Institute of Pharmacological Research Mario Negri IRCCS | Non-recruiting unit. Role: Monitoring center for the cohort of subjects recruited by GPs |

GPs: general practitioners

## STAFF TRAINING, STANDARD OPERATING PROCEDURES (SOPs) AND QUALITY CONTROL

CV-PREVITAL uses several training models for study staff, including web-based and on-site training. Operators involved in recruitment are also required to read a manual for data management, before receiving the ID and the password to access the CV-PREVITAL digital platform. Standard operating procedures (SOPs; available upon request) have also been implemented to ensure that all the research activities are performed according to predetermined standards, definitions, and schedules.
The quality control activities include (a) the dissemination of SOPs developed to ensure data integrity, (b) the implementation in the electronic "Case Report Form" (eCRF) of warning messages appearing when data imputed fall in an implausible range, and (c) the implementation in the eCRF of warning or halting messages appearing when specific variables and/or questionnaires (or part of them) are left unfilled. For quality control of the 7-year outcome assessment, a random sample of outcomes is reviewed and adjudicated by a centrally appointed panel of cardiologists. At year seven of the trial, if at least 10 composite specific outcomes (including at least 2 myocardial infarctions, 2 hospitalizations for angina, 2 strokes, 2 revascularizations, 2 deaths) adjudicated locally in each recruiting center are validated with the full agreement of the central panel of cardiologists, then local classification and adjudication does not require further central review. Otherwise, the procedure continues until local adjudication reaches the full agreement with the central one. In the event that a specific recruitment center records a total of less than 10 events, all events are adjudicated centrally. The quality control for the collection of data on 7-year vascular events, needed to avoid the "lost at follow up bias", is warranted by an active recalling of participants or of their relatives in case of death. The quality control regarding the use of the app during the follow up, including the participants' adherence to the proposed activities, is accomplished and verified by the App itself. Indeed, as already described in the paragraph "Intervention", in addition to sending reminders, personalized motivational feedback, and messages based on task evaluation and periodic goal achievement (also exploiting the logic of gaming), the app also provides for logging of non-use or sub-optimal use of the app itself.



## WEB BASED TRIAL MANAGEMENT

The hub for CV-PREVITAL data collection and storage is the IT platform of the Italian Cardiology Network (ICN), developed in collaboration with the Consortium of Bioengineering and Medical Informatics (Italian acronym: CBIM) of the Italian Ministry of Health and hosted in REDCap. This platform is integrated with the IT platform of Consorzio Sanità (Co.S.), i.e. the interface used by primary care physicians participating in the study, and with the CV-PREVITAL app database. All data collected by general practitioners (GPs) are entered directly into web-based forms and saved to a structured database of each local GPs cooperative. Data are then harmonized and transferred to the dataset of Co.S.. Data included in such dataset are then transfer to the REDCap dataset of the ICN managed by CBIM. All data collected from research hospitals (Italian acronym: IRCCS) and pharmacies, instead, are directly entered into web-based forms and saved into the structured database at CBIM. All the quoted web-based systems incorporate real-time data entry quality control, as well as informatics tools verification of eligibility to recruitment prior to randomization. The web access to each portion of the various digital platforms hosting the various datasets is protected with passwords and restricted to individuals with specific access privilege by virtue of their role in the study. Person-identifiable information are kept separate from all other information and linked only by a pseudo-anonymous study-ID for each participant.

## DETAILS ON RANDOMIZATION PROCEDURES

### Modalities of randomization for GPs cohort

In the randomization modality for GPs cohort, sampling involves three hierarchical levels:

**level 1**: 50 CSPs (acronym of the Italian term: Centri Sanitari Polifunzionali) i.e. fifty GPs health centers coordinated by Co.S. each including at least 3 practitioners
**level 2**: Approximately 250 GPs, with an average of 5 GPs for each CSP
**level 3**: 50,000 individuals to be enrolled (200 for each GP)

In order to reduce the risk of unbalance, randomization is performed by GP, stratifying by CSP. In each CSP, GPs assigned to the control group and GPs assigned to the intervention group are balanced. The randomization of GPs is centralized and managed by CBIM.

**Modalities of randomization for IRCCSs Cohorts**

In the case of the IRCCSs cohorts, individuals are randomized directly, with the exception of the one recruited in community pharmacies, where the procedure randomizes pharmacies and not individuals. For IRCCSs that randomize individuals, the randomization takes place without stratification by age and sex, to avoid unnecessarily lengthening of time required for participant enrollment. Potential discrepancies between IRCCSs cohorts (and/or sub-studies), in terms of distribution of age, sex and any other important covariates (geography, socio-economic status, etc.), are handled by adopting a meta-analytic approach with individual participant data, with random effects, in global analyses, and by stratifying for the appropriate subgroups in specific analyses. Randomization of the different cohorts enrolled in the various IRCCSs is also centralized, using the ICN IT platform to create specific randomization lists for each sub-study. The assignment of patients to the appropriate treatment arm is managed remotely and automatically at the time of patient inclusion in the study. This approach also allows a centralized real-time monitoring of enrollment progression. In case of specific design (for instance, a 2x2 factorial), the randomization procedure ensures a balance of individuals in the two main treatment arms (mHealth vs. Usual care) and in the two specific secondary arms.

## RISK SCORE USED AS PRIMARY OUTCOME

The score was constructed by analysing the combined impact of different modifiable factors on the risk of developing cardiovascular diseases (CVD) in the follow up of the MOLI-SANI study.[1,2] The analysis was conducted on n=21,806 MOLI-SANI participants free of personal history of CVD. The event considered was a combined outcome of cardiovascular death and nonfatal cardiovascular events. The number of events observed was n=816, with 8.1 years of median follow-up. The analysis model included the following covariates: age, sex, history of cancer at baseline, drug therapy for diabetes, hypertension, or dyslipidemia, BMI (4 categories), income (4 categories), and schooling (2 categories). The modifiable risk factor score included the following variables (all on a continuous scale): (1) number of cigarettes (per day); (2) adherence to the Mediterranean diet (score from 0 to 9 points, calculated as in Trichopoulou et al.[3]); (3) mean arterial pressure (MAP) = (2*diastolic+systolic)/3; (4) relative fat mass (RFM) (proxy for percentage of adipose fat as in Woolcott et al.[4]); (5) blood glucose; (6) LDL cholesterol; (7) HDL cholesterol; (8) triglycerides; and (9) leisure-time physical activity. The above variables have been standardized to mean zero and standard deviation one, separately for men and women (with the exception of number of cigarettes and Mediterranean diet adherence index, left in their original scales).

For each individual, a score of modifiable cardiovascular (CV) risk factors was obtained as a weighted sum of the following variables: number of cigarettes, score of adhesion to Mediterranean diet and z-values of LDL, HDL, triglycerides, mean arterial pressure, glucose, leisure time physical activity and relative fat mass. Weights were natural logarithms of hazard ratio of each variable, as calculated in the full-adjusted model. Risk factors positively associated with the endpoint showed hazard ratio >1 and consequently they were summed up with positive weights. On the contrary, variables negatively associated with endpoint entered in the score with negative weights as consequence of their hazard ratio in the range 0-1. By construction, the higher the score, the higher the magnitude of its association with the endpoint. To improve interpretability of the score, we divided it by 0.06859, which is the natural logarithm of the hazard ratio for one year more of age as measured in the derivation cohort. In this way, one unit of the re-scaled score resulted associated with the outcome as one year of age more at baseline was. Practically, 1-point increase in the score is equivalent (in terms of cardiovascular risk) to an increase of 1 year of age.

Smoke_score = (number of cigarettes per day) * 0.029
Diet_med_score = (Mediterranean diet adherence score) * 0.061
LDL_score = (z-score of LDL) * 0.198

HDL_score = (z-score of HDL) * 0.154
Triglycerides_score = (triglycerides z-score) * 0.015
MAP_score = (z-score of MAP) * 0.186
Glucose_score = (z-score of glucose) * 0.135
Physical_activity_score = (z-score of leisure-time physical activity index) * 0.045
RFM_score = (z-score of relative fat mass index) * 0.036

SCORE_TOT =
(Smoke_score + LDL_score + Triglycerides_score + MAP_score + Glucose_score + RFM_score - Diet_med_score - HDL_score - Physical_activity_score) / 0.06859

For the calculation of z-scores (z-score=(value-average) / standard deviation) it is possible to refer to the following values observed in the MOLI-SANI project (population aged ≥45 years):

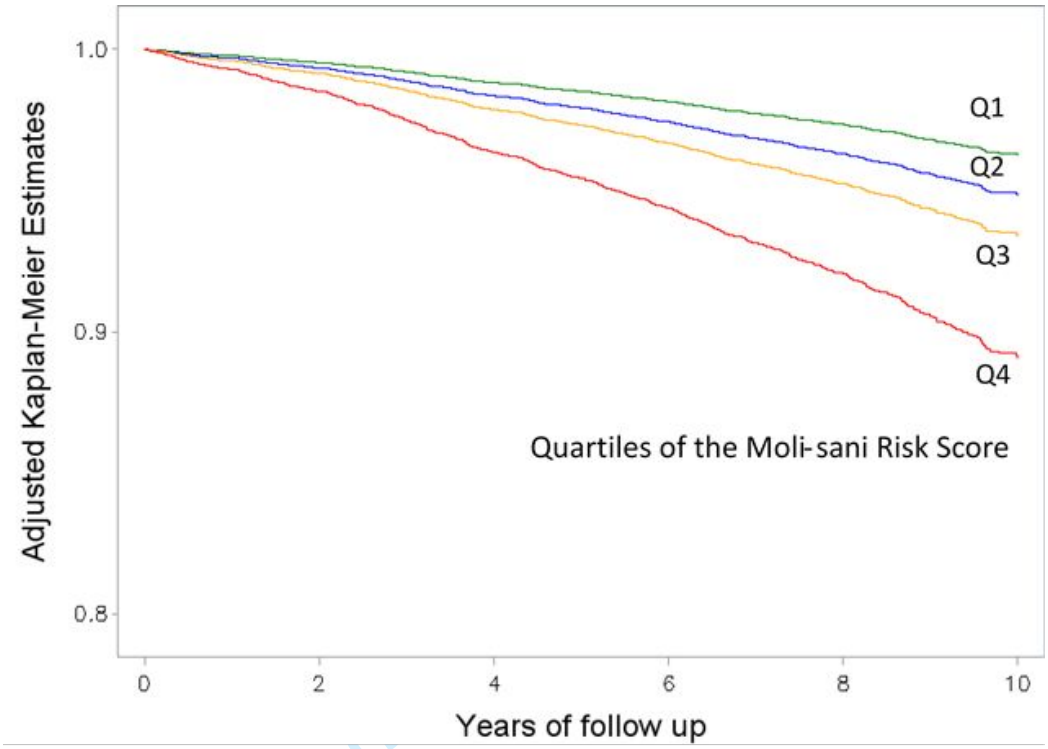
| Variable | Mean | Standard deviation | Mean | Standard deviation |
|---|---|---|---|---|
| | MEN | | WOMEN | |
| LDL (mg/dL) | 130 | 35 | 136 | 36 |
| HDL (mg/dL) | 52 | 13 | 63 | 15 |
| Triglycerides (mg/dL) | 150 | 99 | 118 | 66 |
| MAP (mmHg) | 105 | 11 | 102 | 12 |
| Blood Glucose (mg/dL) | 107 | 28 | 98 | 23 |
| Physical_activity (MET-hours/day) | 4.6 | 4.7 | 2.7 | 3.2 |
| RFM (%) (males) | 29 | 3.6 | 42 | 5 |

MAP=(2*diastolic+systolic)/3
RFM=64 - (20 × height (cm)/waist circumference (cm)) for men and
RFM=76 - (20 × height (cm)/waist circumference (cm)) for women

Assessing physical activity (in leisure time) in terms of met-h/day can be challenging. Consider replacing this measure with a proxy based on a multi-level qualitative classification of such physical activity. For example, a 3-level classification: 'sedentary', 'moderately active', 'active' can be transformed into corresponding (approximate) z-scores = -1, 0, 1.

In the MOLI-SANI project, the score has median -5.0 and interquartile range 8.3 (min=-26.9, low risk and max=41.5, high risk). Each score point was associated (in the MOLI-SANI study) with a risk of MACE approximately equal to that of one additional year at baseline (HR for one score point: 1.071, 95%CI: 1.062 to 1.080).

Survival curves by score categories, as observed in the MOLI-SANI project, are shown below:




| Quartiles | Median | Min-max | N | No. events | % events | HR* | 95% CI |
|---|---|---|---|---|---|---|---|
| Q1 | -9.8 | -26.9 to -7.0 | 4164 | 114 | 2.74 | 1 | (reference) |
| Q2 | -5.0 | -7.1 to -3.0 | 4164 | 164 | 3.94 | 1.40 | 1.10 to 1.79 |
| Q3 | -1.1 | -3.1 to 1.2 | 4164 | 205 | 4.92 | 1.83 | 1.44 to 2.31 |
| Q4 | 4.5 | 1.3 to 41.5 | 4164 | 333 | 8.00 | 3.18 | 2.54 to 3.97 |

## ANCILLARY STUDIES

The CV-PREVITAL study includes a number of ancillary studies. Each ancillary study has its own protocol and objectives. The objectives and outcome information of the ancillary studies are given below.

**Ancillary study of Monzino Cardiology Center**

The ancillary study of the IRCCS Monzino Cardiology Center (acronym: Monzino) evaluates the hypothesis that the same mHealth intervention of the parent study can, in the short term, improve metabolic balance and, in the long term, reduce the onset of type 2 diabetes in individuals considered at high risk of developing this disease because carriers of a clinical condition defined “pre-diabetes”. To this end, 1,000 individuals already enrolled at the outpatient clinics of GPs or at Monzino or at pharmacies, including 200 with a diagnosis of type 2 diabetes mellitus (T2DM), 400 with a diagnosis of pre-diabetes and 400 normoglycaemic equally divided in control and intervention group, are invited to undergo an in-depth diabetological evaluation at Monzino. The diabetological evaluation consists of a clinical visit, non-invasive diagnostic tests for the assessment of carotid subclinical atherosclerosis [i.e. atherosclerotic plaque size, total plaque area, total plaque volume, intima-media thickness (IMT), interadventitia common carotid artery diameter (ICCAD), and wall echolucency], endothelial function (i.e. reactive hyperemia index), peripheral atherosclerosis [i.e. Ankle Brachial Index (ABI)], diabetic retinopathy (i.e. fundus retinography), and collection of blood and urine samples for biochemical analysis. These include: OGTT [oral glucose tolerance test of fasting blood glucose (FPG) and 120 minutes after ingestion of 75 grams of glucose (2h

PG)]; HbA1c (by standardized HPLC method); insulinemia. Additional haematological tests include: fasting apolipoprotein B and lipoprotein(a); hs-CRP; microalbuminuria (Albumin/Creatinine ratio); creatinine and eGFR. Total cholesterol, HDL cholesterol, triglycerides and LDL cholesterol (calculated), already measured by point-of-care test within the parent study are re-measured with standard laboratory methods. After 12 months of follow-up, each individual entered into the Monzino sub-study is invited to attend to the same facility for repeating all the evaluations performed at baseline, except for the evaluations of carotid subclinical atherosclerosis, endothelial function, peripheral atherosclerosis and diabetic retinopathy. The proportion of subjects who changed from a diagnosis of T2DM to a diagnosis of pre-diabetes or from a diagnosis of pre-diabetes to a diagnosis of normoglycemia, compared to the baseline examination is thus evaluated. After 7 years of follow-up, occurrence of cardiovascular events and overt diabetes, depending on the length of time in pre-diabetes and the interaction of pre-diabetes with other risk factors (e.g. obesity, hypertension, hypertriglyceridemia, etc.), is also assessed.

**Ancillary study of IRCCS Italian Institute for Auxology**

The ancillary study of the IRCCS Italian Institute for Auxology (acronym: Auxologico) enrols 5,000 individuals, divided into sub-cohorts based on the presence/absence of hypertension, obesity, or sleep problems. In these individuals, besides the conventional cardiovascular risk factors foreseen by the parent study, several supplementary variables are investigated. In particular, in subjects with sleep problems attending the Center for Sleep Medicine, detailed information on the qualitative and quantitative characteristics of night sleep is recorded by the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Other sleep complaint-related evaluations include the Epworth Sleepness Scale (ESS) questionnaire[5,6] to assess the improvement in daytime sleepiness and the diagnosis of obstructive sleep apnea (OSA) by polysomnographic indices like the apnea-hypopnea index (AHI) (<5/hour = normal OSA; 5–14.9/hour = mild OSA; 15–29.9/hour = moderate OSA; ≥30/hour = severe OSA). In subjects with OSA, difference in the usage of positive airway pressure (PAP) devices and in the PAP treatment daily usage at 1 year after randomization between control and intervention groups are also evaluated. In the hypertensive subjects sub-cohort the following parameters are evaluated: 24-h systolic blood pressure (SBP); ambulatory blood pressure variables [i.e. 24-h SBP, 24-h diastolic blood pressure (DBP), day-time SBP, day-time DBP, night-time SBP, night-time DBP, SD 24-h SBP, SD 24-h DBP, SD day-time SBP, SD day-time DBP, SD night-time SBP, SD night-time DBP]; dipping status (i.e. the difference between the mean SBP in the day and mean SBP during the night, expressed as a percentage of the day time mean); 24h-sodium urinary secretion; microalbuminuria; creatinine; eGFR; left ventricular hypertrophy (evaluated with Sokolow index and Cornell product). In obese/overweight subjects sub-cohort the following parameters are evaluated: BMI; waist circumference; waist/hips ratio; fasting insulinemia and fasting blood glucose levels. Additional evaluation in subjects classified as both hypertensive and obese/overweight include cardiovascular risk estimate according to clinical variables and biomarkers (Troponin I, cut off of 0.008 ng/mL; hs-CRP, cut off of 6.81 mg/L; N terminal pro-BNP, cut off of 187 pg/mL) and measurement of uric acid levels.
After 12 months of follow-up, each individual entered into the Auxologico sub-study is invited to attend to the same facility for repeating all the evaluations performed at baseline.

**Ancillary study of Humanitas Research Hospital**

As ancillary study, the IRCCS Humanitas Research Hospital (acronym: Humanitas) performs a quantitative evaluation of coronary artery calcium (CAC) score by CT imaging, in 1,000 individuals. CAC score is calculated by the Agatston method and by the determination of the volume of calcium.[7] The study has 2x2 factorial design: subjects are first randomized 1:1 to app or usual care; each subject is then randomized 1:1 to CT scanning on top of traditional risk factor assessment or traditional risk factor assessment alone. In both groups, the cardiovascular risk is calculated. Other evaluations include the rate of statin and aspirin therapy initiation and lipid biomarkers. After 12 months of follow-up, each individual is invited to attend to the IRCCS Humanitas again for repeating the aforementioned evaluations. Comparison of the mean change from baseline between the 2 groups is performed.
At 12-month, the ability of SNPs identified in previous genome wide association studies or newly identified in this study of predicting severe coronary artery calcification is also assessed.

At 7-year, the incremental effectiveness [i.e. healthy quality-adjusted life years (QALYs)], and the incremental cost effectiveness ratios (ICERs) of screening by CT scanning for CAC score are assessed. Finally, major adverse cardiovascular and cerebrovascular events between subjects randomized to screening by CT scanning or traditional risk factor assessment alone are assessed.

**Ancillary study of IRCCS MultiMedica**

In its ancillary study, the IRCCS Multimedica (acronym: Multimedica) performs additional investigations in 1,000 diabetic patients and in 2,000 individuals recruited from the general population. These investigations include: organ damage assessment (indexed by common carotid IMT), ABI, and endothelial function as assessed through ICAM and VCAM; quality of life, as assessed by the WHOQOL-Measuring Quality of Life questionnaire; psychological conditions, measured with Mini Mental Status Test; cardiovascular risk, measured by the "SCORE" (Systematic COronary Risk Evaluation) algorithm;[8] and hematochemical investigations, useful to define the condition of diabetes or dyslipidemia. Hematochemical investigations carried out in diabetic subjects includes: blood glucose, Brain Natriuretic Peptide (BNP), creatinine (eGFR), hs-CRP, interleukin 6 (IL-6), interleukin 1 beta (IL-1 beta), microalbuminuria. Besides total cholesterol, HDL cholesterol, triglycerides and LDL cholesterol (calculated) measured within the procedures adopted for the parent study, additional hematochemical variables measured in dyslipidemic individuals includes: apolipoprotein AI, apolipoprotein B, lipoprotein(a), creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine transaminase (ALT) and gamma-glutamyltransferase (GGT). After 12 months of follow-up, each individual is invited to attend again the IRCCS Multimedica for repeating all the aforementioned evaluations. Comparison of the mean change from baseline between the 2 groups is performed.

The ancillary study also includes: multivariable analyses of baseline data for identification of determinants and factors predisposing to diabetes status, dyslipidemia and hypertension; the detection of causative mutations in the case of suspected genetic disorders; the 12-month evaluation of CAC score in patients with suspected familial hypercholesterolemia; and the assessment of occurrence of cardiovascular events, and new diagnosis of diabetes and hypertension over 7-year follow-up period.

**Ancillary study of Neuromed Mediterranean Neurological Institute**

Besides the biochemical variables measured within the parent study, in its ancillary study the IRCCS Neuromed Mediterranean Neurological Institute (acronym: Neuromed) assesses hs-CRP and creatinine (eGFR). Moreover, Neuromed ancillary study also includes the administration of supplementary questionnaires about dietary habits (to assess the proportion of subjects who changed the consumption of ultraprocessed foods, according to the NOVA classification[9] and the evaluation of cognitive status by the Montreal cognitive assessment (MOCA) test.[10] Finally, the IRCCS Neuromed analyses with multivariable approaches determinants of dietary changes. After 12 months of follow-up, each individual is invited to attend to IRCCS Neuromed again for repeating the aforementioned evaluations. Comparison of the mean change from baseline between the 2 groups is performed.

**Ancillary study of Policlinico San Donato Research Hospital**

In its ancillary study, the IRCCS Policlinico San Donato Research Hospital (acronym: San Donato) performs additional investigations on 1,000 individuals, including subjects. At baseline, participants undergo: 1) a vascular investigation (carotid Doppler ultrasonography) to assess IMT, plaques size, presence/absence of atherosclerotic plaques, and total plaque area; 2) a trans-thoracic echocardiographic examination (TT-Echo) to assess relative wall thickness, E/A ratio, E/e' ratio, heart mass, end-diastolic and end-systolic volume, left atrial volume, Ejection Fraction (EF; %), maximal tricuspid regurgitation velocity (TRV max), and epicardial adipose tissue (EAT). Moreover, additional hematochemical analyses are performed, including NT-proBNP, since this biomarker has been inserted in the algorithm for the diagnosis of heart failure with preserved ejection fraction,[11] and TSH, to investigate the relationship between disthyroidism and cardiovascular disease. Finally, in order to refine the cardiovascular risk, the ancillary study of San Donato evaluates other additional serum biomarkers in individuals with comorbidities, such as diabetes mellitus, overweight, obesity, abdominal obesity (number estimated=400 individuals). In particular, insulinemia, homocysteine, hs-CRP, $Na^+$, $K^+$, IL-6, and sRAGE are analysed.

After 12 months of follow-up, participants are invited to attend to IRCCS San Donato for assessing the mean change from baseline in NT-proBNP and TSH values. The value of ultrasound and transthoracic-echocardiographic parameters as predictor of cardiovascular events is assessed at the end of the 7-years follow-up.

**Ancillary study of Clinical Scientific Institutes Maugeri**

In the ancillary study of the IRCCS Clinical Scientific Institutes Maugeri (acronym: Maugeri), 1,000 individuals are categorized according to their cardiovascular risk. Subjects at intermediate/high risk undergo additional hematochemical analyses including blood glucose, uricemia, and microalbuminuria. In participants who need further risk stratification, additional tests to assess atherosclerotic organ damage are performed, including ABI, the CT CAC score and carotid artery ultrasound.

In all individuals, in addition to the usual care or mHealth intervention planned for the entire study, a personalized program of physical activity is also prescribed. In particular, in individuals classified at high-risk, an exercise test for silent ischemia screening is performed, in order to obtain the prescriptive drivers needed to personalize the physical training intervention. Finally, in all participants at intermediate/high risk a blood sample for genetic and epigenetic tests and for the evaluation of possible additional hematochemical factors predisposing to atherosclerotic diseases is collected.

Change from baseline in cardiovascular events, silent ischemia, ABI, CAC score and carotid imaging markers, over 7-year follow-up period depending on the length of time in physical activities programs, are evaluated. For the relationship with carotid imaging markers, the interaction of physical activity with other risk factors (e.g. obesity, hypertension, hypertriglyceridemia, etc.) is also performed.

**Ancillary study of Mediterranean Institute for Transplantation and Advanced Specialized Therapies**

In its ancillary study, the IRCCS Mediterranean Institute for Transplantation and Advanced Specialized Therapies (acronym: ISMETT) envisages, at baseline and at 12 months, the execution of: 1) a CT scan for the assessment of CAC score; 2) a cardiac magnetic resonance for the assessment of myocardial fibrosis 3) the evaluation of a series of circulating biomarkers indicating cardiac stress and/or heart failure and kidney dysfunction (i.e. creatinine, blood urea, nitrogen (Blood Urea Nitrogen, BUN), and hs-CRP). Other biomarkers tested are: NT-proBNP, $Na^+$, $K^+$, homocysteine, iron, ferritin, transferrin, and complete blood count. The effect of specific cardiovascular risk factors (e.g. obesity, hypertension, diabetes etc) on outcomes 1, 2 and 3 is also evaluated. Comparison of the mean change from baseline between the 2 groups is performed.

**Ancillary study of San Martino Polyclinic Hospital**

In the ancillary study of the IRCCS San Martino Polyclinic Hospital (acronym: San Martino), 1,500 male individuals, recruited in the city of Genoa, undergo an ecocolor Doppler examination for early detection of abdominal aortic and iliac aneurysm. In an additional group of 500 male individuals, a color Doppler ultrasound of external carotid arteries is performed for the evaluation of the average IMT and for early diagnosis of carotid plaques and any carotid stenosis. In such individuals, the risk stratification for cardiovascular disease is also evaluated.

**Ancillary study of IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico**

In the ancillary study of the IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico (acronym: Ca' Granda), individuals with cardiovascular risk >7.5% or with at least 3 metabolic risk factors selected among the 2,000 participants enrolled in their structure undergo: 1) an ultrasonographic scan for the assessment of carotid subclinical atherosclerosis (indexed by plaques size, presence/absence of plaques and IMT); 2) a non-invasive fibroscan analysis to assess the amount of hepatic fat/lipotoxicity (indexed by CAP Score) and the hepatic fibrosis stage (indexed by FIB-4 Index); 3) a series of blood chemistry tests, including microalbuminuria, AST, ALT, GGT, HbA1c, insulinemia, coagulation balance (i.e. von Willebrand Factor Antigen, Protein C and Factor VIII), D-Dimer levels, and interleukin-32 (as a circulating biomarker of lipotoxicity).

After 12 months of follow-up, each individual is invited to attend to IRCSS Ca' Granda again for the follow up visit. Comparison of the mean change from baseline between control and intervention group is

performed for all the variable mentioned above, with the exception of coagulation balance and D-Dimer levels that are measured only at baseline.
In addition, in a subgroup of 200 individuals characterization of the intestinal microbiome is performed at baseline and after 7 years by 1) a metagenomic analysis (taxonomic and functional), including the evaluation of serum levels of trimethylamine oxide (TMAO) and other metabolites of bacterial origin [branched-chain amino acid (BCAAs), aromatic amino acid (AAAs)], and 2) the interaction of the microbiome with classical and inherited risk factors. Finally, a genetic characterization is performed in the whole Ca' Granda cohort by Whole Exome Sequencing (WES) and genotyping (GWAS) for *PNPLA3 I148M, TM6SF2 E167K, GCKR P446L, MBOAT7* influencing intracellular lipid handling.

**Ancillary study of Agostino Gemelli IRCCS University Hospital Foundation**
The additional investigations performed in the 1,000 individuals enrolled by the Agostino Gemelli IRCCS University Hospital Foundation (acronym: Gemelli) include ultrasonographic scan of carotid arteries for evaluation of IMT, measurement of additional variables of lipid metabolism (Lp(a) and serum oxidized LDL levels), and inflammation (hs-CRP, IL1beta, IL-18, IL-6, IL-10, and TNF-alpha), and measurement of serum additional biochemical variables including human lipopolysaccharides (LPS), metabolite of bacterial origin and TMAO. Finally, this ancillary study also envisages the assessment of the intestinal microbiome composition with Next Generation Sequencing (NGS) technology and of a serum marker of intestinal permeability (zonulin).
After 12 months of follow-up, each individual is invited to attend to IRCSS Gemelli for repeating the aforementioned evaluations. Comparison of the mean change from baseline between control and intervention group is performed. The assessment of cardiovascular events incidence over the 7-year follow-up period, depending on the significant biomarkers variation and microbiome composition detected, is also evaluated.

**Ancillary study of Foundation IRCCS Polyclinic San Matteo**
In its ancillary study, the Foundation IRCCS Polyclinic San Matteo (acronym: San Matteo) develops a multigene analysis panel that allows the identification of a genotype at risk of diabetes before the appearance of the clinical phenotype. To this end, 200 diabetic patients and 400 pre-diabetic patients (enrolled at IRCCS Monzino) and 500 healthy individuals (enrolled at the Genetics Unit of IRCCS San Matteo) are subjected to genetic testing using a multigene NGS panel. DNA is collected from WBC. The gene prevalence is calculated as the ratio between patients carrying pathogenic variants and all patients of the studied cohort. In addition, IRCCS San Matteo ancillary study also aims at investigating the prevalence of likely pathogenic and pathogenic variants in genes related with familial hypercholesterolemia in subjects with diagnosis of hypercholesterolemia. Finally, the ancillary study envisages the development of new monogenic/polygenic scores and the validation of existing scores for the assessment of the risk of developing diabetes, hypertension and hypercholesterolemia not present at baseline.

**Ancillary study of San Raffaele Roma**
In its ancillary study, the IRCCS San Raffaele Roma (acronym: San Raffaele Roma) enrols a cohort of 150 individuals aged ≥ 45 years selected among its employees. These individuals are included in a program of physical activity monitored and combined with nutrition education provided in the workplace, aimed at reducing the incidence of hyperlipidemia and overweight/obesity and related risks such as the onset of T2DM and hypertension. In addition to the evaluations already planned in the parent study, the study forsees to assess the amount of daily physical activity through an accelerometer app, adherence to Mediterranean diet by Mediterranean diet Scale (MDS) questionnaire[12] in addition to PREDIMED[13] and Moli-sani questionnaires (an adaptation of the MEDAS questionnaire[14]), and complete blood count. All measurements are performed at 6 and 12 moths from baseline, except the assessment of daily physical activity which is also performed at month 3. Comparison of the mean change from baseline between the 2 groups at the different time points is performed.

**Supplemental Table 3. Name of approving body and approval number/ID of CV-PREVITAL studies**

| | Approval Number | Board Name |
|---|---|---|
| **Parent study** | R1256/20-CCM 1319 | Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino |
| **Ancillary studies of Monzino** | R1579/21-CCM 1677; R1617/22-CCM 1723 | Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino |
| **Ancillary study of Istituto Auxologico Italiano** | 2022_03_08_06 | Comitato Etico dell'IRCCS Istituto Auxologico Italiano |
| **Ancillary study of Humanitas** | 2860 | Comitato Etico Indipendente dell'Istituto Clinico Humanitas |
| **Ancillary study of Multimedica** | MM: 472.2021 | Comitato Etico IRCCS Multimedica - Sezione del Comitato Etico Centrale IRCCS Lombardia |
| **Ancillary study of Neuromed** | Session of 28/09/2020 | Comitato Etico dell'Istituto Neurologico Mediterraneo Neuromed |
| **Ancillary study of San Donato** | 197/INT/2021 | Comitato Etico IRCCS Ospedale San Raffaele |
| **Ancillary study of Maugeri** | 2575 CE | Comitato Etico degli Istituti Clinici Scientifici Maugeri |
| **Ancillary study of ISMETT** | IRRB/16/22 | Comitato Etico IRCCS Sicilia Sezione ISMETT IRCCS srl |
| **Ancillary study of San Martino** | 173/2021 | Comitato Etico Regionale della Liguria |
| **Ancillary study of Ca' Granda** | 887_2020 | Comitato Etico Milano Area 2 |
| **Ancillary study of Gemelli** | 3614 | Comitato Etico della Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore |
| **Ancillary studies of San Matteo** | 2022-3.11/91; 2022-3.11/493 | Comitato Etico Pavia |
| **Ancillary study of San Raffaele Roma** | 21/21 | Comitato Etico IRCCS San Raffaele Roma |

## CV-PREVITAL Study Group

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***Consorzio Sanità (Co.S.)***
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***Federfarma Lombardia***
*Annarosa Racca, Manuela Bandi, Giulia Protti.*

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**Online Supplemental file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents**

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3, 4 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Online Supplemental file 2 |
| Protocol version | 3 | Date and version identifier | N/A |
| Funding | 4 | Sources and types of financial, material, and other support | 4, 12 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 2, 11, 12 |
| | 5b | Name and contact information for the trial sponsor | 12 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 12 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 4, Online Supplemental Material |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4 |

| | | | |
|---|---|---|---|
| | 6b | Explanation for choice of comparators | N/A |
| Objectives | 7 | Specific objectives or hypotheses | 6, 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5, 9 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5, 6 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | N/A |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | N/A |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 6-8, Online Supplemental Material |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Online Supplemental file 4 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5, Online Supplemental Material |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5, Online Supplemental Material |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 6-9 |

| | | | |
|---|---|---|---|
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 8 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 9, Online Supplemental Material |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 9 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 8 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 8 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | N/A |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |

| | | | |
|---|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 9, 10, Online Supplemental Material |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 11 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 9 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 10 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 11 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | N/A |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | N/A |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |

**Appendices**

| | | | |
|---|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Online Supplemental file 3* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | Online Supplemental file 5 |

*Online Supplemental file 3 is the informed consent form (written in Italian language) in use within the parent study. Each ancillary study has its own informed consent form (available on request)

**Online Supplemental file 2. SPIRIT Item 2b: All items from the World Health Organization Trial Registration Data Set**

| Data category | Information |
|---|---|
| Primary registry and trial identifying number | ClinicalTrials.gov NCT05339841 |
| Date of registration in primary registry | 21 April, 2022 |
| Secondary identifying numbers | R1256/20-CCM 1319; RCR-2019-23669116_001 |
| Source(s) of monetary or material support | Italian Ministry of Health |
| Primary sponsor | Monzino Cardiology Center IRCCS |
| Secondary sponsor(s) | none |
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| Contact for scientific queries | Principal Investigators:<br>Giulio Pompilio, Centro Cardiologico Monzino IRCCS (giulio.pompilio@cardiologicomonzino.it);<br>Gianfranco Parati, Istituto Auxologico Italiano IRCCS (parati@auxologico.it)<br>Scientific contact: studiocvprevital@retecardiologica.it |
| Public title | Italian Digital Primary Cardiovascular Prevention Study (CV-PREVITAL) |
| Scientific title | Digital Strategies in Primary Cardiovascular Prevention in the Italian Population |
| Countries of recruitment | Italy |
| Health condition(s) or problem(s) studied | Subjects in primary cardiovascular prevention |
| Intervention(s) | Intervention group: subjects assigned to a mobile health application (mHealth) app that delivers a personalized digital health support program based on periodic messages with advice, motivational reminders and support to improve lifestyle habits and risk factor control |
| | Control group: subjects assigned to usual care |
| Key inclusion and exclusion criteria | Ages eligible for study: ≥45 years; Sexes eligible for study: both;<br>Accepts healthy volunteers: yes |
| | Inclusion criteria: adult subjects (≥45 years) consenting to participate in the study and using a smartphone |
| | Exclusion criteria: current or previous cardiovascular disease (personal history of myocardial infarction, angina pectoris, arterial revascularization procedures, stroke, transient ischemic attack, peripheral artery disease); Psychiatric disorders; Participation in other clinical trials |
| Study type | Interventional (mobile health application vs usual care) |
| | Allocation: randomized;<br>Intervention model: parallel assignment;<br>Masking: none (Open Label); |

| | |
|---|---|
| | Primary purpose: cardiovascular disease prevention |
| | Phase: not applicable |
| Date of first enrolment | June 10, 2022 |
| Target sample size | 82,800 |
| Recruitment status | Recruiting |
| Primary outcome(s) | • Short term (month 12): change in cardiovascular risk<br>• Long term (year 7): between groups difference in the incidence of vascular events |
| Key secondary outcomes | • Change of a combined endpoint including hypertension, diabetes, hypercholesterolemia [month 12]<br>• Systolic and diastolic blood pressure (mmHg) [month 12]<br>• HDL-C, LDL-C, and triglycerides (mg/dL) [month 12]<br>• HbA1c (%) [month 12]<br>• Body weight (kg) [month 12]<br>• Physical activity (IPAQ questionnaire) [month 12]<br>• Mediterranean diet adherence (PREDIMED questionnaire) [month 12]<br>• Mediterranean diet adherence (Moli-Sani questionnaire) [month 12]<br>• Smoking status [month 12]<br>• Alcohol intake [month 12]<br>• Salt intake (MiniSal questionnaire) [month 12]<br>• Stress (Perceived Stress Scale; PSS) [month 12]<br>• Psychological distress (PHQ 4 questionnaire) [month 12]<br>• Anxiety (PHQ 4 questionnaire) [month 12]<br>• Depression (PHQ 4 questionnaire) [month 12]<br>• Multidimensional Health Locus of Control Scale (MHLCS) - Internality [month 12]<br>• Multidimensional Health Locus of Control Scale (MHLCS) - Powerful Others Externality [month 12]<br>• Multidimensional Health Locus of Control Scale (MHLCS) - Chance Externality [month 12]<br>• General Self Efficacy (GSE Scale) [month 12]<br>• Risk propensity (RPS Scale) [month 12]<br>• Sleep quality (Pittsburgh Sleep Quality Index) [month 12]<br>• Subjects' adherence to data recording [month 12]<br>• Interruptions in the use of the mHealth App [month 12]<br>• Adherence to recommended therapies [month 12]<br>• Cost/effectiveness of intervention [year 7]<br>• House ownership as socioeconomic status indicator [year 7] |

| | |
|---|---|
| | • Type of residence as socioeconomic status indicator [year 7]<br>• Education as socioeconomic status indicator [year 7]<br>• Employment status as socioeconomic status indicator [year 7]<br>• Type of profession as socioeconomic status indicator [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of hospitalization (questionnaire) [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of symptoms (questionnaire) [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of asymptomatic disease (questionnaire) [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of vaccination (questionnaire) [year 7] |

**Online supplemental file 3 - Informed consent materials**

Studio CV PREVITAL Versione 2.0 del 31.05.2021

**MODULO DI INFORMAZIONE PER IL PAZIENTE**

# Studio CV PREVITAL

## Strategie di Prevenzione primaria cardiovascolare nella popolazione italiana

### Invito a partecipare allo studio CV PREVITAL

Gentile Signora/e la invitiamo a partecipare alla Ricerca CV PREVITAL.

### Cos'è lo studio CV PREVITAL?

Lo studio CV PREVITAL è una ricerca collaborativa condotta da Medici di Famiglia, che si svolge a livello nazionale con l'obiettivo di migliorare la prevenzione primaria cardiovascolare in Italia.
Lo studio CV PREVITAL è promosso dal Ministero della Salute che riconosce nella prevenzione l'arma più efficace per ridurre l'insorgenza delle malattie cardiovascolari.

### Perché è importante lo studio CV PREVITAL?

Attualmente, la prevenzione rappresenta la strategia più importante di intervento per diminuire l'incidenza di malattie cardiovascolari quali l'infarto del miocardio e l'ictus cerebrale. Identificare precocemente i soggetti a rischio di sviluppare queste malattie, e informare adeguatamente le persone interessate su come adottare stili di vita "sani" si sono dimostrate strategie molto efficaci per contrastare l'insorgenza di ipertensione, di diabete e di ipercolesterolemia che insieme al fumo e all'obesità rappresentano i principali fattori di rischio per l'insorgenza delle malattie cardiovascolari.
In questo contesto le tecnologie digitali stanno dimostrando un grande potenziale nel miglioramento della salute pubblica ed individuale, in quanto possono essere utilizzati come strumenti di supporto al medico per la gestione dei fattori di rischio.
Infatti negli ultimi anni si sta diffondendo sempre di più l'espressione "mobile-health" o "m-health", con cui si indica l'insieme di tecnologie (cellulari e smartphone, tablet, dispositivi digitali) applicate in ambito medico-sanitario, che stanno dimostrando un grande potenziale nel miglioramento della salute pubblica ed individuale.

### Obiettivo dello studio

L'obiettivo dello studio è quello di valutare l'efficacia di un intervento di m-health nella riduzione dei principali fattori di rischio cardiovascolari e nell'insorgenza a lungo termine delle principali malattie cardiovascolari. L'intervento consiste nell'uso di un'applicazione, scaricabile sul proprio smartphone, che invierà dei messaggi educativi e formativi personalizzati, e permetterà il monitoraggio e l'auto-controllo dei principali fattori di rischio cardiovascolari e degli stili di vita.

### In che cosa consiste lo studio

Lo studio coinvolgerà circa 250 Medici di Famiglia, distribuiti in diverse regioni di Italia e in totale verranno inclusi 50.000 soggetti.

Il suo medico verificherà che lei abbia i requisiti per partecipare allo studio e in caso positivo la inviterà ad aderire allo stesso firmando il consenso allegato.

Lo studio CV PREVITAL è uno studio clinico randomizzato non farmacologico, dove i medici partecipanti saranno divisi casualmente in due gruppi:

1. gruppo di controllo
2. gruppo di intervento

I medici del "gruppo di controllo" gestiranno i propri pazienti secondo la normale pratica clinica (usal care), al meglio delle conoscenze attualmente disponibili.

I medici del "gruppo di intervento", in aggiunta a quanto previsto dalla normale pratica clinica, seguiranno i pazienti anche avvalendosi del supporto di una App che i partecipanti potranno scaricare sul proprio smartphone attraverso un link dedicato.

Lo studio clinico randomizzato è il metodo più appropriato, scientificamente riconosciuto, per poter valutare l'efficacia di interventi volti a modificare una condizione clinica. Nel caso del presente studio, l'uso della App per migliorare il controllo dei fattori di rischio cardiovascolare.

**Che cosa comporta l'adesione allo studio CV PREVITAL?**

Se dovesse decidere di partecipare a questo studio, il suo medico Le proporrà una serie di domande volte a valutare lo stato della sua salute cardiovascolare. In particolare sarà invitato a compilare, con l'aiuto di personale infermieristico e/o di tutorial digitali, alcuni questionari riguardanti le abitudini alimentari, l'attività fisica, l'abitudine al fumo e fattori psico-sociali e comportamentali. Le saranno inoltre misurati i livelli di colesterolo totale, LDL, HDL e l'emoglobina glicata mediante una goccia di sangue ottenuta grazie ad un prelievo capillare (piccola puntura sul dito). Infine, saranno effettuate le misurazioni di pressione arteriosa, peso, altezza e circonferenza vita. Il tutto sarà ripetuto dopo 12 mesi.

Il suo medico e il personale infermieristico La seguiranno mettendo in atto tutte le conoscenze disponibili per migliorare il suo profilo di rischio cardiovascolare. Se il suo medico fa parte del gruppo di intervento, Le verrà anche spiegato come utilizzare una specifica App. Questa servirà a raccogliere ulteriori dati nel periodo intercorrente fra l'incontro iniziale e quello a 12 mesi. Durante questo periodo, Le saranno inviati dei promemoria al fine di ricordarle di rispondere a delle semplici domande riguardanti le sue abitudini. Le sue risposte permetteranno sia di personalizzare i messaggi educativi che riceverà per aiutarla a migliorare il suo stile di vita, sia di valutare l'efficacia di questi interventi educazionali. Inoltre, se durante l'incontro basale si fosse riscontrata la presenza di uno o più fattori di rischio cardiovascolari, quali ad esempio ipertensione, diabete o ipercolesterolemia, le sarà chiesto di inserire, ad intervalli regolari, alcuni dati numerici (esempio: pressione arteriosa, emoglobina glicata, ecc.) che saranno utili per valutare l'andamento di questi fattori di rischio nel tempo e l'efficacia delle strategie educazionali messe in atto.

Dopo 7 anni Lei sarà ricontattato dal suo medico per verificare se nell'arco di questo tempo siano comparsi eventi vascolari maggiori (es infarto miocardico e ictus), o nuove diagnosi di angina e di arteriopatie periferiche, e/o se sia stato ospedalizzato per malattie cardiovascolari.

**Quali sono i rischi e i benefici per chi partecipa allo studio?**
Lo studio non La espone ad alcun tipo di rischio in quanto prevede soltanto l'utilizzo di una semplice App e non implica interventi di carattere invasivo. Anche i prelievi di sangue ai quali sarà sottoposto in occasione dell'incontro iniziale e di quello a 12 mesi, essendo effettuati attraverso una puntura sul dito (prelievo capillare) non la esporranno a rischi aggiuntivi. La partecipazione allo studio potrebbe invece comportare dei benefici. Ad esempio, conoscere meglio i propri fattori di rischio ed avere la possibilità di tenerli sotto controllo in modo più efficiente dovrebbe ridurre la velocità di insorgenza o di progressione delle malattie cardiovascolari in generale, e la probabilità di sviluppare eventi clinici acuti (ad es. un infarto) in particolare.

**Il rifiuto a partecipare allo studio compromette in qualche modo il rapporto con il medico?**
Assolutamente no, la partecipazione allo studio è volontaria e Lei è libero di ritirare il consenso in qualsiasi momento senza che Le sia richiesta alcuna motivazione. Il rapporto con il suo medico non sarà in alcun modo compromesso.

**La partecipazione è gratuita o è remunerata?**
La partecipazione allo studio è totalmente gratuita e non è previsto alcun compenso.

**Uso dei dati**
I Suoi dati verranno usati in ottemperanza alla normativa vigente in materia di tutela del trattamento dei dati personali. A tal fine, è prevista una specifica informativa che Le sarà fornita contestualmente alla proposta di adesione allo studio.

**Approvazione dello studio**
Lo studio è stato approvato dal Ministero della Salute, dal Comitato Etico Coordinatore e dai Comitati Etici locali di riferimento per i Medici che partecipano allo studio.

# DICHIARAZIONE DI CONSENSO

## Studio CV PREVITAL
## Strategie di Prevenzione primaria cardiovascolare nella popolazione italiana

Ho letto e compreso il modulo informativo per il paziente e il mio medico curante ha risposto a tutte le mie domande relative allo studio.

Ho avuto tempo per decidere se partecipare allo studio e sono consapevole che la mia partecipazione è completamente volontaria.

Sono consapevole che posso ritirarmi dallo studio in qualsiasi momento e senza l'obbligo di motivare la mia decisione.

Do, pertanto, il mio consenso a partecipare allo studio CV PREVITAL

| **Nome/Cognome del paziente** | **Firma** | **Data** |
|---|---|---|
| | | |

| **Nome/Cognome dello sperimentatore responsabile** | **Firma** | **Data** |
|---|---|---|
| | | |

| **Nome/Cognome del testimone** | **Firma** | **Data** |
|---|---|---|
| | | |

# INFORMATIVA PER IL TRATTAMENTO DEI DATI PERSONALI

**Titolo dello studio:**
Strategie di prevenzione primaria cardiovascolare nella popolazione italiana – CV PREVITAL

**Promotore:** IRCCS Centro Cardiologico Monzino

**Categorie di dati oggetto del trattamento**
Lo studio comporta l'acquisizione e l'utilizzo di informazioni considerate "dati personali" (quali: età, sesso, etnia, stato civile, stato socio-economico), incluse informazioni inerenti lo stato di salute, lo stile di vita, la storia familiare, considerate "dati particolari", e come tali sottoposte alla normativa vigente in materia di protezione dei dati personali:

- Regolamento Generale sulla Protezione dei Dati - UE 679/2016
- Codice in Materia di Protezione dei Dati Personali - D.lgs. n° 101/2018
- Regole deontologiche per trattamenti a fini statistici o di ricerca scientifica – 2018
- Provvedimento - 2018, che individua:
  Prescrizioni relative al trattamento dei dati personali effettuato per scopi di ricerca scientifica
  Prescrizioni relative al trattamento dei dati genetici per clinica e ricerca scientifica

**Finalità del trattamento**
I dati sopra descritti saranno trattati per consentire lo svolgimento dello studio CV PREVITAL e di tutte le relative operazioni ed attività connesse

**Base giuridica del trattamento**
Il consenso informato costituisce la base giuridica per il trattamento dei Suoi dati per gli scopi descritti nel modulo informativo. In assenza di consenso firmato non potremo utilizzare i Suoi dati per la conduzione e le analisi dello Studio.
Potrà interrompere la Sua partecipazione in qualsiasi momento e senza fornire alcuna motivazione; in tal caso, i Suoi dati saranno trattati come descritto nel modulo informativo dello Studio. Non saranno raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

**Natura del conferimento dei dati**
La partecipazione alla sperimentazione avviene su base volontaria, pertanto, il conferimento dei dati personali è assolutamente volontario, nel senso che Lei potrà decidere di non conferire i Suoi dati personali e, quindi, di non partecipare allo Studio.

**Modalità di Trattamento dei dati**
Le finalità sopra indicate prevedono lo svolgimento del trattamento dei dati personali mediante strumenti manuali ed informatici con logiche strettamente correlate alle finalità stesse e, comunque, in modo da garantire la sicurezza e la riservatezza dei dati stessi.
I dati raccolti per i fini dello studio CV PREVITAL saranno gestiti in forma codificata.

Il medico che La seguirà nello studio, La identificherà con un codice che non permetterà di risalire direttamente alla Sua identità, se non presso lo studio medico partecipante.
I dati che La riguardano, raccolti nel corso dello studio, ad eccezione del Suo nominativo e il suo telefono, saranno trasmessi al Promotore in qualità di Titolare dei dati e ai Responsabili del trattamento dei dati prima elencati, e dagli stessi registrati, elaborati e conservati. I dati che Lei inserirà tramite la stazione intermodale multifunzione (totem multimediale presente nell'ambulatorio del suo medico) o da remoto (via internet) e i dati che inserirà tramite la App (se il suo medico fa parte del gruppo di intervento), saranno memorizzati in un database cloud e resi disponibili, in forma pseudonimizzata, alla piattaforma informatica della Rete Cardiologica.
Soltanto il medico, il personale responsabile del monitoraggio dello Studio *(Istituto di Ricerche Farmacologiche Mario Negri IRCCS)* e il personale delegato dalle Autorità Competenti per attività di verifica, potranno collegare questo codice al Suo nominativo quando necessario.

**Ambito di comunicazione dei dati**
La Sua partecipazione allo studio CV PREVITAL implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, soltanto il personale incaricato delle attività di monitoraggio, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.
La diffusione dei dati scientifici risultanti dalle analisi dei dati dello studio CV PREVITAL, potrà avvenire solo in forma anonima e per sole finalità scientifiche. In pratica, i risultati delle ricerche scientifiche, potranno essere presentati in forma aggregata nell'ambito di Convegni o pubblicati su riviste specializzate senza mai permettere la precisa identificazione dei pazienti.
Se previsto dal protocollo, i Suoi dati personali potranno essere trasferiti a Centri esterni per le finalità previste dal protocollo, designati dai Titolari quali "Responsabili del trattamento".
Potrà conoscere l'elenco aggiornato dei Responsabili del Trattamento, inviando una comunicazione al Responsabile della protezione dei dati (DPO) del Promotore.

In linea generale, la informiamo che ai sensi della normativa vigente, le informazioni, potranno essere condivise con altri enti e istituti di ricerca, con associazioni e altri organismi pubblici e privati aventi finalità di ricerca.
Nello specifico, lo studio CV PREVITAL è parte integrante di un più vasto progetto sviluppato con il Ministero della Salute, su indicazione del Parlamento per migliorare le strategie di prevenzione primaria cardiovascolare nella popolazione italiana, che coinvolge, Medici di Medicina Generale (MMG), Farmacie, IRCCS della Rete Cardiovascolare, la Società Italiana per la Salute Digitale e la Telemedicina e la Fondazione Romeo e Enrica Invernizzi.
Pertanto le informazioni dello studio CV PREVITAL potranno essere condivise con altri Istituti o Enti che partecipano al più vasto progetto di ricerca, fatte salve le garanzie dei sui diritti in materia di protezione dei dati personali.
Qualora dalle indagini effettuate per fini di ricerca in ambito scientifico conseguano informazioni, anche inattese, in grado di arrecare un beneficio concreto e diretto in termini di terapia o di prevenzione o in funzione di consapevoli scelte riproduttive, tali informazioni potranno essere comunicate a terzi su Sua autorizzazione, tranne eccezioni previste dalla normativa vigente.

**Politica in materia di conservazione dei dati personali**
I dati personali raccolti nell'ambito dello studio CV PREVITAL saranno conservati presso lo studio medico del Suo MMG, il Promotore e le strutture coinvolte nello Studio, per un periodo minimo di 7 anni dopo la conclusione dello Studio o per un periodo più lungo, se necessario, in base ad ulteriori requisiti di legge. Il periodo massimo di conservazione dei dati è di 25 anni dopo la conclusione dello studio.

**Titolare e Responsabile della Protezione dei dati:** Il Promotore che ha commissionato lo studio CV PREVITAL e il suo MMG, in qualità di Titolari del Trattamento, e l'Istituto di Ricerche Farmacologiche Mario Negri IRCCS e il Consorzio Sanità (Co.S.), in qualità di Responsabili del Trattamento, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme di Buona Pratica Clinica (D.L. 211/2003), dal Regolamento UE 2016/679 del Parlamento e del Consiglio Europeo relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati (di seguito GDPR), dal D.lgs. 196/03 integrato dal dall'Autorizzazione generale n.9/2016 al trattamento dei dati personali effettuato a scopi di ricerca scientifica del 15 dicembre 2016 e dalla Delibera del Garante per le "Linee guida per i trattamenti di dati personali nell'ambito delle sperimentazioni cliniche di medicinali" del 24 luglio 2008 e successive modifiche, tratteranno i suoi dati personali, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello Studio e per le finalità di seguito indicate.

La informiamo che i Titolari, ai sensi dell'articolo 37 del GDPR EU 2016/679, hanno proceduto ad individuare e nominare il Responsabile della Protezione dei dati (anche "*Data Protection Officer*" o "DPO":

Dati di contatto DPO del MMG:
*[...]*

Dati di contatto DPO del Promotore:
*[...]*

**Diritti dell'Interessato**

*Diritto di accesso ai dati*
Può chiedere di consultare le informazioni che sono state raccolte su di Lei. Tuttavia, per salvaguardare l'integrità scientifica dello studio, potrebbe non essere possibile accedere ad alcuni dati prima della conclusione dello studio stesso.

*Diritto di rettifica ai dati*
Può richiedere la modifica dei dati che La riguardano, qualora fossero errati o incompleti. Durante la valutazione di tale richiesta, ha il diritto di limitare il trattamento dei dati che La riguardano.

*Diritto di portabilità dei dati*
Può richiedere il trasferimento dei dati che La riguardano a Lei stesso o a qualcun altro in un formato comunemente utilizzato (cartaceo o elettronico).

*Diritto di cancellazione dei dati*
Può ritirare il consenso in qualsiasi momento senza darne motivazione alcuna. Può ritirare il consenso per la partecipazione allo studio e/o ai follow up successivi, anche senza ritirare il consenso per il trattamento dei dati. Qualora cambiasse idea sul trattamento dei Suoi dati, non sarà possibile rimuovere le informazioni personali già elaborate per lo studio prima del Suo ritiro (coperte dal consenso originale). In seguito, al ritiro del consenso al trattamento dei Suoi dati non verrebbero acquisite ulteriori informazioni che La riguardano.

*Diritto di reclamo*
Può presentare un reclamo presso l'autorità incaricata della protezione dei dati:
Garante della privacy, E-mail: garante@garanteprivacy.it Sito web: http://www.garanteprivacy.it

**In merito all'esercizio di tali diritti, potrà rivolgersi direttamente al suo medico di medicina generale o, per il suo tramite, al Responsabile della protezione dei dati (DPO) del Promotore.**

Definizioni

- Dato personale: qualsiasi informazione riguardante una persona fisica identificata o identificabile («interessato»); si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo online o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale.

- Dati particolari: dati personali che rivelino l'origine razziale o etnica, le opinioni politiche, le convinzioni religiose o filosofiche, o l'appartenenza sindacale; i dati genetici, i dati biometrici intesi a identificare in modo univoco una persona fisica, i dati relativi alla salute o alla vita sessuale o all'orientamento sessuale della persona.

- Dati relativi alla salute: i dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute; quali ad esempio i dati relativi ad attività di ricovero, visite specialistiche ambulatoriali, consumo di farmaci e prestazioni di tipo socio-sanitario

**Consenso al trattamento dei dati personali**
ai sensi del GDPR UE 2016/679

Preso atto dell'informativa di cui all'art. 13 del GDPR UE 2016/679, il sottoscritto_____,
nato a_____, il_____,
in qualità di interessato

☐ dà il proprio consenso ☐ nega il proprio consenso
al trattamento dei dati per finalità relative allo studio clinico "Strategie di prevenzione primaria cardiovascolare nella popolazione italiana – CV PREVITAL"

☐ dà il proprio consenso ☐ nega il proprio consenso
affinché i risultati delle analisi e di eventuali scoperte inattese che emergano durante le attività di sperimentazione siano comunicate a:

☐ me medesimo

☐ familiare (Cognome e nome _____)

☐ convivente /coniuge (Cognome e nome _____)

☐ medico di famiglia (Cognome e nome _____)

| **Nome/Cognome del paziente** | **Firma** | **Data** |
|---|---|---|
| | | |

| **Nome/Cognome del Medico di Medicina Generale responsabile** | **Firma** | **Data** |
|---|---|---|
| | | |

**Online Supplemental file 4. SPIRIT Item 13: Participant timeline**

| TIMEPOINT | T0 baseline | T1 month 12 | T2 year 7 |
|---|---|---|---|
| Eligibility screen<br>Informed consent<br>Allocation | √ | | |
| Administration of self-report questionnaires covering the following areas:<br>1. family and personal history of diseases (cardio- and cerebrovascular disease; metabolic disease)<br>2. ethnicity, socio-economic status and marital status<br>3. smoking habits<br>4. alcohol consumption (PREDIMED questionnaire[8])<br>5. adherence to Mediterranean diet (PREDIMED questionnaire[8] and Moli-Sani questionnaire–an adaptation of the MEDAS questionnaire[9])<br>6. salt consumption (MiniSal questionnaire[10])<br>7. physical activity (IPAQ–International Physical Activity Questionnaire[11])<br>8. personal history of sleep disorder and sleep quality (PSQI–Pittsburgh Sleep Quality Index[12])<br>9. psycho-behavioral factors:<br>9.1 perceived stress (PSS–Perceived Stress Scale)<br>9.2 anxiety and depression (PHQ 4–Patient Health Questionnaire 4)<br>9.3 self-efficacy (GSE–General Self-Efficacy Scale)<br>9.4 locus of control (Multidimensional Health Locus of Control Scale)<br>9.5 risk propensity (RPS–Risk Propensity Scale)<br>10. personal history of COVID-19 disease | √ | √ | |
| Measurement of systolic and diastolic blood pressure | √ | √ | |
| Measurement of weight, height, waist circumference | √ | √ | |
| Assessment of total cholesterol, HDL-C, triglycerides, calculated LDL-C, glycated hemoglobin | √ | √ | |
| Cardiovascular risk score calculation | √ | √ | |
| App delivery (intervention group only) | √ | | |
| Collection of data on occurrence of cardiovascular events | | √ | √ |

**Online Supplemental file 5: Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies**

In the CV-PREVITAL Study, each IRCCS recruits a number of participants to whom, in addition to the questionnaires, samples of biological material (blood, saliva or feces) are taken. The biological material collected is stored in the cryospaces dedicated by each IRCCS to the Widespread Biobank of the Italian Cardiology Network. In order to harmonize the collection and storage of samples, Standard Operating Procedures (SOPs) has been created for the Widespread Biobank and shared among the participating centers for the management of the sample from the patient recruitment and signing phase of the informed consent, to the collection and storage of biological samples and possible redistribution of the aliquots. The harmonization of sample collection also includes the use of the same container for sample collection, the same cryovials for storage, and the same codes for pseudonymization of samples. All aliquots are stored in cryotubes with QR Code to facilitate the distribution and sharing of samples among the recruiting centers of the CV-PREVITAL study or with other national or international institutes.

**SOPs for blood derivates**

All Cell Pellet (ACP) and plasma EDTA

In order to optimize the blood collection, ACP and plasma EDTA are obtained from the same collection tube. The venous sampling is carried out using K3EDTA tubes. Blood is processed within 2 hours from collection. Tubes are centrifuged without brake at 3000rpm at RT (18–22 °C) for 15 minutes to separate the plasma from the cells. Using a micropipette, plasma is divided into at least 3x300 microliter aliquots in cryotubes and then transferred to -80 °C for storage as soon as possible. After removing the residual plasma, the tube is inverted two or three times to homogenize the sample. ACP is divided in 3x300-microliter aliquots in cryotubes and transferred to a -80 °C for storage as soon as possible.

Serum

The venous sampling is carried out using tubes with coagulation activator and gel separator. Blood is processed within 2 hours from collection and allowed to clot for a minimum of 15-20 minutes at RT (18-22°C) or until the clot is completely formed. Tubes are centrifuged at 3000rpm at RT (18–22 °C) for 15 minutes to separate serum from the cells. Using a micropipette, serum is collected without touching the separator gel with the pipette tip and divided into at least 3x300-microliter aliquots in cryotubes. Aliquots are transfer red to a -80 °C freezer for storage as soon as possible.

Whole blood for total RNA extraction

The venous sampling is carried out using Tempus Blood RNA Tube (Applied Biosystems). Immediately after filling the Tempus tube, the blood is stabilized by vigorously shaking or vertexing the tube for 10-12 seconds. Samples are maintained at +4 °C for a maximum of 24 hours and then stored at -80 °C.

**Saliva Samples**

Saliva is collected using Salivette Cortisol tube (Sardstedt) and the collection is carried out by the subject participant to the project according to the manufacturer's instructions.

Harvesting must be done in the morning and it is recommended:

- for at least 2 hours before harvesting:
  - not to eat
  - not to drink
  - not to smoke
  - not to take chewing gum

- to brush teeth at least 2 hours before the start of the harvest
- to avoid the use of cosmetic products for lips.

Samples are maintained at +4 °C and centrifuged within 1 hour from collection without brake at 3000rpm at RT for 15 minutes. Using a micropipette, the sample is divided into at least 3x300 microliter aliquots in cryotubes and stored at -80 °C within 2 hours from collection.

**Stool Samples**

Stool sample is collected using DANASTOOL Sample Collection MICROBIOME Kit (DANAGEN) and the collection was carried out by the subject participant to the project according to the manufacturer's instructions.

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# RATIONALE AND DESIGN OF THE CV-PREVITAL STUDY: AN ITALIAN MULTIPLE COHORT RANDOMISED CONTROLLED TRIAL INVESTIGATING INNOVATIVE DIGITAL STRATEGIES IN PRIMARY CARDIOVASCULAR PREVENTION



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# RATIONALE AND DESIGN OF THE CV-PREVITAL STUDY: AN ITALIAN MULTIPLE COHORT RANDOMISED CONTROLLED TRIAL INVESTIGATING INNOVATIVE DIGITAL STRATEGIES IN PRIMARY CARDIOVASCULAR PREVENTION

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**Short running head:** mHealth in primary CV prevention: the CV-PREVITAL study

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No new data were generated or analysed in support of this research.

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**Abstract**

**Introduction:** Prevention of cardiovascular disease (CVD) is of key importance in reducing morbidity, disability and mortality worldwide. Observational studies suggest that digital health interventions can be an effective strategy to reduce cardiovascular (CV) risk. However, evidence from large randomized clinical trials is lacking.

**Methods and analysis:** The CV-PREVITAL study is a multicenter, prospective, randomized, controlled, open-label interventional trial designed to compare the effectiveness of an educational and motivational mobile health (mHealth) intervention versus usual care in reducing CV risk. The intervention aims at improving diet, physical activity, sleep quality, psycho-behavioral aspects, as well as promoting smoking cessation and adherence to pharmacological treatment for CV risk factors. The trial enrolls approximately 80,000 subjects without overt CVDs referring to general practitioners' offices, community pharmacies or clinics of Scientific Institute for Research, Hospitalization and Health Care (Italian acronym IRCCS) affiliated with the Italian Cardiology Network. All participants are evaluated at baseline and after 12 months to assess the effectiveness of the intervention on short-term endpoints, namely improvement in CV risk score and reduction of major CV risk factors. Beyond the funded life of the study, a long-term (7 years) follow-up is also planned to assess the effectiveness of the intervention on the incidence of major adverse CV events. A series of ancillary studies designed to evaluate the effect of the mHealth intervention on additional risk biomarkers are also performed.

**Ethics and dissemination:** This study received ethics approval from the ethics committee of the coordinating center (Monzino Cardiology Center; R1256/20-CCM 1319) and from all other relevant IRBs and ethics committees. Findings are disseminated through scientific meetings and peer-reviewed journals and via social media. Partners are informed about the study's course and findings through regular meetings.

**ClinicalTrials.gov: NCT05339841**

**Key Words**:
Randomized controlled trial; Digital health; cardiometabolic diseases; study design; gamified mobile app.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- ⇒ The randomized controlled design of the study and the enrollment of a large population of participants (N~80,000) recruited in different real-world settings, including general medicine, community pharmacies and Scientific Institute for Research, Hospitalization and Health Care (IRCCS)
- ⇒ The adoption of a coordinated network strategy that also envisages the creation of an IT infrastructure for communication among health operators
- ⇒ The collection of biological samples for the multisite biobank of the Italian Cardiology Network, according to specific Standard Operating Procedures for sample collection, storage and transfer
- ⇒ The lack of standardization of the equipment used for hematological testing and blood pressure measurement, due to the real-world nature of the study, is a possible limitation of the trial
- ⇒ Due to the nature of the intervention, the trial personnel and participants are not blinded to the treatment allocation

## INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death in developed countries.[1] In Italy, there are 136,353 deaths annually attributed to atherosclerotic CVD, with acute coronary syndromes and ischemic strokes accounting for about 22% of total deaths.[2] CVDs are also among the major causes of chronic disability, affecting millions of people worldwide.

CVDs are, to a large extent, preventable. Prevention of CVD is of key importance, not only to reduce morbidity, disability and mortality, but also to increase the years of healthy living among the growing elderly population, thus contributing to alleviate the socioeconomic burden associated with cardiovascular (CV) events. However, according to European data,[3] only a small percentage of the healthcare budget is allocated to preventive measures. In this context, there is an urgent need for exploring innovative approaches to better address the challenge of CVD prevention. Internet-based tools and smartphone applications have the potential to play a significant role in CVD prevention by enabling remote lifestyle monitoring, diagnosis, self-management of CV risk factors, medication adherence, education and psychological support. Preliminary evidence suggests that digital health interventions can be an easy-to-implement and cost-effective strategy to reduce CV risk in primary prevention.[4] However, more robust evidence is still required, which can only be provided by large controlled trials.

In response to this need, and driven by a specific mandate from the Italian Parliament (Law No. 136, Dec. 17, 2018, and Law No. 145, Dec. 30, 2018), the Italian Cardiology Network (ICN), a network of Scientific Institute for Research, Hospitalization and Health Care (Italian acronym IRCCS) engaged in the CV field promoted by the Ministry of Health, launched the "Digital Strategies in Primary Cardiovascular Prevention in the Italian Population (CV-PREVITAL)" study in 2020.

CV-PREVITAL is a multicenter, prospective, randomized, controlled, open-label interventional trial that aims to compare the effectiveness of an educational and motivational mobile health (mHealth) intervention with that of usual care in primary CV prevention. The main hypothesis of the study is that digital technologies can be used efficiently for improving the control of CV risk factors and detrimental lifestyles, thereby reducing CVD incidence and mortality, compared to usual care. The trial also includes several ancillary studies. The purpose of this report is to provide a comprehensive description of the project background and of the study protocol, which is also publicly available at www.clinicaltrials.gov with the identifier NCT05339841.

## METHODS AND ANALYSIS

The study protocol adhere to "The Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013 statement"[5] (**Online Supplemental File 1**).

### Trial organization

CV-PREVITAL consists of a large clinical trial (the parent study) and of a series of ancillary studies. The organizational structure of CV-PREVITAL is presented in **Figure 1**. The organizational structure includes several integrated committees: the Steering Committee (see also **Online Supplemental Material - Supplemental Table 1**); the Central Management Committee (based at the Monzino Cardiology Center) responsible for organizing and coordinating the entire study; the Scientific Coordination Committee, and nine Technical Committees (TCs). The TCs are tasked with coordinating specific activities in various areas, including clinics, hematological analysis, socio-economic status assessment, non-invasive diagnostic techniques, genetic analysis, statistics, artificial intelligence, mHealth, eHealth, and technology platforms, and technology transfer.

The list of operative units and their role in the study are shown in **Online Supplemental Material - Supplemental Table 2**. A part from the Institute of Pharmacological Research Mario Negri IRCCS, which acts as the monitoring center for the cohort of subjects recruited by general practitioners (GPs), all other IRCCSs participate as recruiting centers. The working group also includes Consorzio Sanità (Co.S.), a consortium of cooperatives of GPs working in the National Health Service.

Study data are collected and managed using REDCap electronic data capture tools hosted at the Consortium of Bioengineering and Medical Informatics (CBIM).[6 7]

**Trial design**

CV-PREVITAL is a multicenter, prospective, parallel-arm, randomized, open-label interventional study. It aims to recruit approximately 80,000 participants (aged ≥45 years) nationwide. Of these, 50,000 subjects are selected among those who daily access the participanting GPs offices. Additionally, to evaluate the effectiveness of the mHealth intervention in settings other than primary care, several specific cohorts are enrolled by IRCCSs (**Online Supplemental Material - Supplemental Table 2**). These cohorts consist of approximately 34,000 subjects from outpatient clinics, diagnostic centers, blood donor centers, company cohorts, the general population, and pharmacies. The actual study start date (first participant enrolled) is June 10, 2022; the estimated completion date is June 2029.

The full list of study sites is available on ClinicalTrials.gov (NCT05339841). A structured summary of the trial based on the WHO Trial Registration Data Set is provided in **Online Supplemental File 2**. The data flow of CV-PREVITAL is illustrated in **Figure 2**.

**Eligibility**

Participants of both sexes are eligible to participate in the study if they meet the following criteria: (a) they are in primary CV prevention, (b) they are ≥ 45 years old, (c) they possess a smartphone and (d) they have provided their informed consent by signing the relevant documents. Individuals who meet any of the following conditions are not eligible for the study: (a) informed consent not signed, (b) age lower than 45 years, (c) history of overt CVD [myocardial infarction (MI), angina pectoris, stroke, transient ischemic attack (TIA), aortic aneurysm or arteriopathy obliterating lower limb pathologies, or congestive heart failure (NYHA Class III-IV)]. Prior to randomization, eligible participants are asked by the study investigators to sign the informed consent forms (**Online Supplemental File 3**). To promote participation across all recruitment settings, leaflets and posters promoting the study and explanatory videos emphasizing the importance of proper management of CV risk factors have been realized. The number of screened individuals who are deemed ineligible is centrally recorded in the ICN database.

**Randomization**

To assess the effectiveness of the intervention, the participants are allocated randomly in a 1:1 fashion into two groups: 1) the control group, receiving conventional care (usual care); and 2) the intervention group, receiving mHealth intervention in addition to usual care. Randomization is carried out in three different ways depending on whether the participants are enrolled by GPs, by community pharmacies, or IRCCSs. For participants enrolled by GPs, the randomization procedure ensures that the number of physicians assigned to the control group is balanced with the number assigned to the intervention group within each group practice (referred to as Centro Sanitario Polifunzionale or CSP). For participants enrolled by community pharmacies, the randomization procedure ensures that the number of pharmacies assigned to the control group is balanced with the number assigned to the intervention group in each geographic area. For participants enrolled by IRCCSs, the procedure directly randomises the participants themselves. The randomization process is carried out by means of a central randomisation service developed in-house. Allocation concealment is ensured, as the randomization code is not revealed until the participant is recruited and baseline measurements are completed. Additional details are provided in the **Online Supplemental Material**.

**Intervention**

At baseline, participants allocated to the intervention group (mHealth group) receive, in addition to usual care, a smartphone application (CV-PREVITAL app) designed for managing a personalized primary CV prevention program. The app serves the following purposes: (a) education on CV risk, remote monitoring and self-management of CV risk factors, (b) education on and remote monitoring and self-management of psycho-behavioral variables, and (c) detection and/or modification of harmful lifestyles. The CV risk factors monitored by the app include high blood pressure, dyslipidemia, diabetes mellitus, obesity, abdominal

obesity, and sleep disorders. Psycho-behavioral variables include stress, depression, anxiety and factors related to aspects of the human sphere relevant for patients' empowerment, such as risk propensity, self-efficacy and locus of control. Harmful lifestyles include unhealthy diet, excessive alcohol intake, smoking habits and a sedentary lifestyle. The app is organized in several educational sections and tools for monitoring the variables under consideration, allowing participants to track their progress over time. It delivers personalized educational contents and provides guided access to different sections based on the participant's profile (e.g. subjects with hypertension or hypercholesterolemia or diabetes, etc.). Profiling is performed through specific algorithms according to data collected at baseline (see below), which are recorded in a pseudonymized form on the ICN platform database. Lifestyle monitoring is carried out through active participation, where participants periodically provide information relevant to their health, such as dietary habits, assumption of medications, specific anthropometric parameters, sleep quality, and level of physical activity practiced. The app may integrate with native wellness apps to automatically track step counts and sleep duration with the user's permission. The app also provides reminders, personalized motivational feedback and evaluation of tasks and goal achievements on a periodic basis. These elements are implemented using a gamification logic,[8] i.e. an approach that seeks to create experiences reminiscent of gaming and that implies not only a combination of concepts such as rewards (e.g. points, achievement badges, and challenges), but also the use of narrative storylines, avatar-based self-representation, and onboarding tutorials. Gamification logic has been proposed for a twofold purpose: to make study participation and data compilation tasks more enjoyable, and to encourage long-term commitment to tasks that may be perceived as boring or demotivating over time. The ultimate goal is to help users complete the required tasks, improve health literacy, and adhesion to healthy behaviors and/or maintaining healthy habits. Data collected through the app during the follow-up period are transmitted to the ICN database. This allows the treating doctor to access the information and personalize further prevention activities based on the collected data.

**Control group**

Participants allocated to the control group are followed by the conventional approach (usual care) based on regular visits respecting the usual schedule dictated by the rules of general practice. As a part of the baseline assessment, they receive counselling and are encouraged to maintain or improve their current physical activity level, dietary habits, medical adherence, etc., depending on their individual goals and needs.

**Hypotheses and outcomes**

The primary hypothesis of the trial is that a personalized intervention of CV primary prevention based on mHealth technology can be more effective than usual care in controlling conventional risk factors and harmful lifestyles in the short term and in reducing vascular events in the long term. The primary outcome used to measure the efficacy of the mHealth intervention at short term (12 months) is the change in a risk score developed specifically for the Italian population. The score, referred to as the "modified Moli-Sani score" (details in **Online Supplemental Material**), was created by analysing the combined impact of different modifiable risk factors on the risk of developing CVD during the follow-up of the Moli-Sani study, which collects data from the general population of Molise, a region in south-central Italy.[9 10] An improvement of one unit (approximately 33% reduction) in the modified Moli-Sani score between the baseline and final assessment in the intervention group (App), compared to the score change observed in the control group (Usual care), is indicative of a clinically meaningful intervention effectiveness in the short term. This is because, according to the construction of the Moli-Sani risk score, a one-point improvement in the Moli-Sani risk score is equivalent (in terms of CV risk) to an increase of one year of age. The primary outcome used to measure the efficacy of the mHealth intervention in the long term (7 years) includes major adverse cardiovascular events (MACE), i.e. CV death, MI, stroke, TIA, peripheral artery disease, new diagnoses of angina, hospitalizations for CVD, and need for revascularization.

Several short-term secondary outcomes are also pre-specified. These include: (a) a combined endpoint including the simultaneous change in hypertension, diabetes and hypercholesterolemia; (b) the change in

at least one of the risk factors considered in the score; (c) the percentage of subjects who agree to complete questionnaires; (d) the percentage of subjects who interrupts the use of the app during the follow-up; and (e) adherence to recommended therapies.
Besides these clinical outcomes, other outputs of the project include the development and validation of a new algorithm for estimating CV risk, the estimation of the costs and effectiveness of the intervention, and the identification of new socio-economic and behavioral risk factors.

**Measurements performed at baseline and follow-up**

At baseline, subjects identified as potentially eligible for recruitment receive information material and consent forms for study participation. Those who agree to participate are invited to complete a series of questionnaires. Questionnaires can be completed in two ways: (a) on-site by a direct access to an electronic "Case Report Form" (eCRF), with the assistance of a healthcare professional; or (b) remotely via web access to the eCRF, with the help of computer tutorials or phone assistance, after having provided a digital informed consent and using a secure access. The remote option was provided to cope with the limitations due to the COVID-19 pandemic, which required social distancing to limit the spread of SARS-CoV-2.
Self-report questionnaires administered at baseline cover the following areas:

1. family and personal history of diseases (cardio- and cerebrovascular disease; metabolic disease)
2. ethnicity, socioeconomic status and marital status
3. smoking habits
4. alcohol consumption (PREDIMED questionnaire[11])
5. adherence to Mediterranean diet (PREDIMED questionnaire[11] and Moli-Sani questionnaire–an adaptation of the MEDAS questionnaire[12])
6. salt consumption (MiniSal questionnaire[13])
7. physical activity (IPAQ–International Physical Activity Questionnaire[14])
8. personal history of sleep disorder and sleep quality (PSQI–Pittsburgh Sleep Quality Index[15])
9. psycho-behavioral factors:
   - 9.1 perceived stress (PSS–Perceived Stress Scale[16])
   - 9.2 anxiety and depression (PHQ 4 questionnaire[17])
   - 9.3 self-efficacy (GSE–General Self-Efficacy Scale[18])
   - 9.4 locus of control (Multidimensional Health Locus of Control Scale[19])
   - 9.5 risk propensity (RPS–Risk Propensity Scale[20])
10. personal history of coronavirus disease (COVID-19)

Baseline evaluation is completed by healthcare professionals (nurses or physicians) with the collection of the following data: (a) ongoing pharmacological treatments (chronic therapies); (b) personal history of organ damage from diabetes and hypertension; (c) measurements of anthropometric parameters (weight, height, body mass index, waist circumference,[21] blood pressure and heart rate); and (d) biochemical variables (total, LDL and HDL cholesterol, triglycerides and glycated hemoglobin) assessed by point-of-care testing or by standard laboratory methods. Based on these data, by using validated algorithms a series of risk scores are estimated, including scores assessing the risk of developing metabolic diseases such as diabetes (Findrisc),[22] and hypertension,[23] and a score assessing the risk of developing vascular events (the modified Moli-Sani score). Other risk algorithms, such as those developed within the "Progetto Cuore" framework,[24] the European and the American risk algorithms (i.e. SCORE-Risk[25] and Framingham Risk Score,[26] respectively), and the ASCVD (i.e. the score proposed within the American College of Cardiology/American Heart Association Task Force on Practice guidelines[27]), are also calculated for comparison.
At the 12-month follow-up, participants are invited to return to the recruitment center to complete the baseline questionnaires again and to repeat the anthropometric and biochemical measurements made during the first assessment. At the 7 year follow-up, participants are contacted to monitor the occurrence of new MACE. In the case of fatal events, information is obtained by contacting the participant's family.
All follow-up visits adhere to routine clinical practice for CV prevention. Reasons for discontinuation are documented using a dedicated eCRF form.

A schematic diagram illustrating the data collected at the three time points of the study protocol (baseline, 12 months, and 7 years) is shown in **Online Supplemental File 4.**

**Sample size**

The sample size has been calculated based on the long-term endpoint (i.e. incidence of CV events). Using data from the IMPROVE study, which included approximately 1,000 Italians (around 50% men and 50% women) aged 55 to 79 years with a 7-year follow-up (Italian groups of the IMPROVE study[28]), the annual incidence of MACE was estimated. With an assumed incidence rate of 0.0116/year, it was projected that with a sample size of 50,000 participants, with an approximately equal distribution of men and women, a total of 3,921 events would occur over 7 years. This sample size was determined to be sufficient to detect as statistically significant (alpha=0.05) and with a power of 80% an 8.5% reduction in MACE incidence in the intervention group compared to the usual care group, with an Hazard Ratio of 0.915. Additionally, on the basis of the data of the Moli-Sani study, which included 21,806 subjects with a median follow-up of 8.2 years and 862 events, the incidence rate is 0.0048 and the expected number of events in the CV-PREVITAL population is 1,687. This sample size provides a power of 80% to detect as significant (alpha=0.05) a 12.8% reduction in MACE incidence in the intervention group compared to the usual care group, with an Hazard Ratio of 0.872. Based on past experience of prevention studies with very long follow-ups (≥5 years), e.g. IMPROVE, the number of lost at follow-up is particularly high (even >50%). In order to take account of such a potentially high rate of loss to follow-up, the calculated sample size (n=50,000) was increased by approximately 60% to a final number of ~80,000. It's worth noting that being calculated on the vascular events at 7 years, this sample size yields a very high power (>95%) to detect even very small differences in short-term end-points, in both risk scores and single risk factors (e.g. < 1 mg/dL for total cholesterol and blood glucose, and <1 mmHg for systolic blood pressure). So, all the results obtained derived from a sample sufficiently powered (1-β=80%) to perform also sex stratified analyses. Results obtained from different cohorts, such as those enrolled by GPs and various IRCCSs, are combined using a meta-analytic approach to ensure a comprehensive analysis.

**Statistical analysis**

Continuous data will be presented as means and standard deviations (SDs) and as medians and interquartiles, categorical data as frequencies and percentage.

Three classes of pre-specified statistical analyses have been planned. The first class involves analysing variables collected at enrollment to estimate the baseline prevalence of different risk factors and conditions among the recruited cohorts. The second class focuses on variables collected at the end of the short-term follow-up (12 months) to assess the effectiveness of the intervention (App vs. Usual care) on CV risk. The third class of analyses pertains to variables collected at the end of the long-term follow-up (7 years) to assess the effectiveness of the intervention on the incidence of fatal and non-fatal CV events.

Cross-sectional analyses on data collected at baseline will be carried out using logistic regression and general linear models (GLMs). The short-term primary endpoint, i.e. the change in CV risk score in the two treatment arms, will be analyzed with GLMs adjusting for potential confounders possibly unbalanced between the two groups. Secondary endpoints, i.e. changes in the level of individual risk factors, will be analyzed with GLMs and Bonferroni correction will be applied to account for the number of tests performed. The long-term primary end-point, i.e. the incidence of fatal and nonfatal CV events, will be analyzed by Cox regression models adjusting for potential confounders. As long-term secondary end-points, new risk algorithms will be developed using Cox models and validated using ROC curve analysis and reclassification techniques. Results generalizability will be tested with cross-validation approaches. Subgroup analyses stratified by gender are also planned.

Missing outcomes for the primary endpoint will be imputed using multiple imputation, and a sensitivity analysis on the imputed data will be performed. Drop-outs will not be replaced.

The efficacy analyses will be performed according to the intention to treat (ITT) principle on the full analysis set. A sensitivity analysis will also be performed in the population with adherence to protocol (PP analysis).

**Cost-effectiveness assessment**

In the assessment of cost-effectiveness for different screening scenarios, the economic aspects of digital-health interventions are recognized as complex due to their nature as "complex interventions in a complex system". Instead, in the intervention involving health professionals the costs are relatively limited and include: (a) cost of implementing and mainteining the IT platform required for the intervention; (b) cost for developing the smartphone application that, once implemented, has virtually negligible installation costs; and (c) cost of the time spent by health professionals for training, utilizing the IT platform, and engaging and educating the participants. For an analytical evaluation of the economic aspects of the intervention, two approaches are applied: cost/efficacy analysis (CEA) and cost/utility analysis (CUA). CEA is the simplest and most frequently used form of evaluation in health economics. It aims to estimate the relationship between the costs of the resources used and the effectiveness achieved through their use. Effectiveness is estimated using a single indicator in two ways: first, as the number of participants who achieve the target in the main risk factors (hypertension, diabetes and hypercholesterolemia); and second, as the number of CV events (both fatal and non-fatal) avoided during the 7-year follow-up, relative to the incurred costs. CUA, on the other hand, considers not only the duration, but also the quality of life that participants experience as a result of the intervention. Quality-adjusted life years (QALYs) are used as summary measures to comprehensively assess the overall health and well-being of the individuals. To estimate QALYs, validated instruments such as World Health Organization Quality Of Life (WHOQOL) or similar tools will be used and administered during the follow-up period.

**Web based trial management**

To establish an effective communication network between GPs and physicians from the IRCCSs, all the data collected are stored in the IT platform of the ICN, as shown in **Figure 2**. This platform is integrated with the Co.S. IT platform, which is the interface used by GPs participating in the study (**Figure 2**). Additionally, the ICN database communicates with the mHealth interface (App for smartphones) dedicated to the population, which serves for both educational purposes and additional data collection (**Figure 2**).

To ensure data protection and comply with security recommendations specified by the National Institute of Standards and Technology[29] and European data protection regulations,[30] various measures have been implemented. These measures are designed to safeguard the confidentiality, integrity, and availability of the collected data. A detailed description of the web-based system for data management and the specific data protection measures implemented is provided in the **Online Supplemental Material**.

**Staff training, standard operating procedures (SOPs) and quality control**

A detailed description of models for staff training, standard operating procedures (SOPs; available upon request), and quality control activities is reported in the **Online Supplemental Material**.

**Ancillary studies (CV-PREVITAL sub-studies)**

CV PREVITAL also includes a series of ancillary studies that are conducted by the various IRCCSs already participating in the parent study. Ancillary studies were designed to evaluate a series of additional risk biomarkers in groups or selected sub-groups included in the parent study. A detailed description of the specific variables evaluated in each ancillary study is reported in the **Online Supplemental Material**.

The steering committee reviewed all the ancillary study protocols to ensure that the specific objectives did not duplicate or interfere with those of the parent study and that all the adopted procedures were consistent with those established in the main protocol. Beyond the specific aims of single sub-studies, a particularly relevant goal, common to all the sub-studies, is the collection of biological samples (e.g. serum, plasma, DNA or RNA) for the multisite biobank of the ICN. For this purpose, the research consortium developed specific SOPs for collection, storage and samples transfer e.g. towards centers acting as core lab. A brief description of the plan for collection, processing, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies is provided in the **Online Supplemental File 5**. A biobank informed consent is obtained to specifically address the collection of these samples.

**Patient and public involvement**

Patients and/or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**ETHICS AND DISSEMINATION**

The CV-PREVITAL study has been approved by all relevant IRBs and ethics committees. Their list and the study approval number-IDs are provided in the supplemental material (**Online Supplemental Material - Supplemental Table 3**). Any protocol amendment is promptly reported to all relevant parties (namely, investigators, ethical committees/IRBs, ClinicalTrials.gov). Personal data are processed in compliance with the provisions set out in Regulation (UE) 2016/679 (the "GDPR") and in Legislative Decree. 196/2003 (Personal Data Protection Code, added by the Legislative Decree 101/2018). Personal information is available to researchers using password-protected files. In addition, all data for presentations are anonymized and aggregated, so the participants' identity is not revealed in any way. CV-PREVITAL results will be disseminated at conferences, through publication in peer-reviewed journals, and through other channels (e.g. web sites of the ICN and of all the hospital involved, social media) in order to reach a diverse community of researchers, GPs, pharmacists and other stakeholders, including citizen and policymakers.

**DISCUSSION**

To the best of our knowledge, this is the first randomized, controlled trial designed to evaluate the effects of an individualized digital intervention delivered through an app containing tools for education on CV risk, remote monitoring and self-management of CV risk factors, detection and/or modification of harmful lifestyles, and patient empowerment.

Preliminary data show that smartphone applications might actually have a great potential in the remote monitoring and self-management of CV risk factors and in improving therapy adherence in hypertensive, diabetic, and dyslipidemic patients.[31 32] However, more evidence is needed to confirm their effectiveness in primary CV prevention programs. CV-PREVITAL, by collecting information in a prospective, randomized and controlled way on a large-scale, has the potential to provide strong evidence to support policy makers in making informed decisions about strategic planning and resources allocation in primary CV prevention.

If the proposed intervention proves to be workable and successful, the study will provide robust evidence that digital medicine can be a useful strategy to engage, motivate and empower people towards primary prevention of CVD. In addition, due to the large sample size and the different types of cohorts involved, the study has also the potential to generate reliable evidence for implementing digital technology-based CV primary prevention programs not only in general or specialist medicine, but also in other settings such as occupational medicine, blood donors centers, and community pharmacies.

A significant strength of the CV-PREVITAL study design is the adoption of a coordinated network strategy involving IRCCSs with proven experience in primary prevention programs, epidemiology and biomedical statistics, along with a large number of GPs spread throughout the national territory. We expect that such strategy, which also envisages the creation of an IT infrastructure for communication among GPs and IRCCSs, may provide the basis for their permanent collaboration, increase the opportunity for future real-world research and enhances knowledge transfer among healthcare professionals.

The participation of a large number of pharmacies is another significant strength, considering their wide distribution and frequent access by citizens, which makes them capable of taking an active role as an outpost of the national health systems for the delivery of health services and the implementation of primary prevention programs. In this regard, it is worth mentioning that it is estimated that approximately 4,000,000 people enter the ~20,000 pharmacies existing in Italy every day.[33]

Another important strength of the study is that it allows to make inference on (a) the level of adherence to the digital prevention programs, (b) the rate of drop-outs associated with this programs in different cohorts and in different age and sex classes, and (c) the barriers to participation based on participants' feedbacks. These insights are crucial for decision makers to understand and address barriers that can hinder the

successful implementation of digital health in primary prevention of CVD, including digital literacy, internet access, concerns about privacy and data security, and perceptions of digital approaches' usefulness.
A last important aspect of the CV-PREVITAL study is that it was designed in the pre-COVID-19 era, but is in fact being carried out during the pandemic. While this presented challenges, it also provided new opportunities to highlight the usefulness of digital tools and accelerate their adoption in remote monitoring and CVD management worldwide.[34]
A possible limitation of the study is the lack of standardized equipment for hematological testing and blood pressure measurement. However, blood pressure measurement devices validated according to internationally acknowledged validation protocols are used.[35] Although aware of the inevitable increase in variability of measurements associated to this type of choice, the decision was made to obtain data better reflecting what happens in real-world prevention programs.
Overall, the CV-PREVITAL study holds promise to contribute significant evidence and insights into the effectiveness and implementation of digital interventions in primary CV prevention.

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**Authors contribution**

**Substantial contributions to the conception of the work and final approval of the version to be published:**
GPo, DB, RB, MA, JPW, SG, GCol, CV, MLB, BF, ARa, DSa, DC, ARo, MGir, MGiu, ABono, MR, CTr, CCi, MMon, FCo, GPa, CI, GB, MPen, FGo, LA, AFa, CL, ADiB, DR, CTo, LGi, DSo, AZ, EP, LZ, LB, LCov, DG, LGr, GCon, GF, LPa, VS, FI, IR, GR, MCR, MBav, LO, AFo, FCler, APa, GFG, GA, ACa, RM, EL, LL, LGM, FMad, LF, LI, ADiC, AGi, ADeC, MBo, FGi, AGh, SMag, FN, SCo, SE, SO, MPer, FBr, TP, ER, RPar, SFr, MMor, FD, CCe, GDeG, MBD, LM, SCa, AEM, MMCR, RCard, ACe, CD, MBT, LVR, VMi, SBov, PG, LR, IB, GDeA, WR, MTL, SS, APi, AGo, FO, MBu, CGae, PB, TB, MBal, LCom, ML, AO, ET, CGar, RS, PGC, VA, FClem, GG, GCar, NC, GDiG, AGr, IL, FT, AUc, BP, DPa, GSp, GM, PA, GZ, AFi, IP, GPra, FBl, DPr, LV, LS, MC, SP, CB, RCarp, GPe, SMar, GSc, GL, GAL, ASe, DPe, DD, AD'Ai, RV, ABona, MBr, SFi, RPas, SBoc, AUr, MS, ASa, LPr, DT, MCG, EA, CK, SL, AE, ACu, MU, ADiT, LG, MF, MVo, GCam, FMar, BS, FGu, VMo, AM, ADiM, MVi, ARac, MBan, GPro, ETre, FV, SBos

**Design of the work:**
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**Acquisition of data:**
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**Statistical advice:**
DB, MA, ABono, DSo, GF, FI, LGM, ADiC, VMi, SBov, PB, FT, RPas, SBoc, CK, FV

**Drafting the work:**
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**Revising the work critically for important intellectual content:**
GPo, DB, RB, MA, JPW, DC, ABono, GPa, MPen, FGo, GCon, GF, MCR, MBav, LO, AFo, ACa, LI, ADiC, SCa, MTL, AGo, VA, AUc, BP, GM, DPr, LV, GL, EA, CK, MVo, FV

**Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:**
DB, RB, MA

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**Declaration of conflicting interests**
Authors and collaborators disclosed the relationships/activities/interests reported below.
Grants or contracts from any entity: GSc, ACa, DPr, JPW, ADiC, LV, LB, FCler, APa, LGM; Consulting fees: GSc, GL, SG, LV, LL, LGM, SL, IP; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: GSc, GA, ACa, DPr, GL, JPW, SG, LV, LL, GPa, LB, LGi, EP, PA; Support for attending meetings and/or travel: DPr, LV, LL, EP, PA; Patents planned, issued or pending: LL, CGae; Participation on a Data Safety Monitoring Board or Advisory Board: GA, DPr, SG, LV, LL, LB, PA; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: GA, LV; Receipt of equipment, materials, drugs, medical writing, gifts or other services: LB, PA.
Details are available in the individual ICMJE online disclosure forms (available upon request).

**Trial Sponsor**
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**Legends to the figure**

**Figure 1: CV-PREVITAL organizational structure**

Abbreviations: SC: Steering Committee; CMC: Central Management Committee; SCC: Scientific Coordination Committee; TCs: Technical Committees; DMC: Data Management Committee.

**Figure 2: CV-PREVITAL data flow**

Abbreviations: IRCCS: Scientific Institute for Research, Hospitalization and Health Care (Istituto di Ricovero e Cura a Carattere Scientifico in Italian language); GP: General practitioner; UPI: Unique Partecipant Identifier; GARR: Gruppo per l'Armonizzazione della Rete della Ricerca; Co.S: Consorzio Sanità; VPN: Virtual Private Network.

**Figure 1**

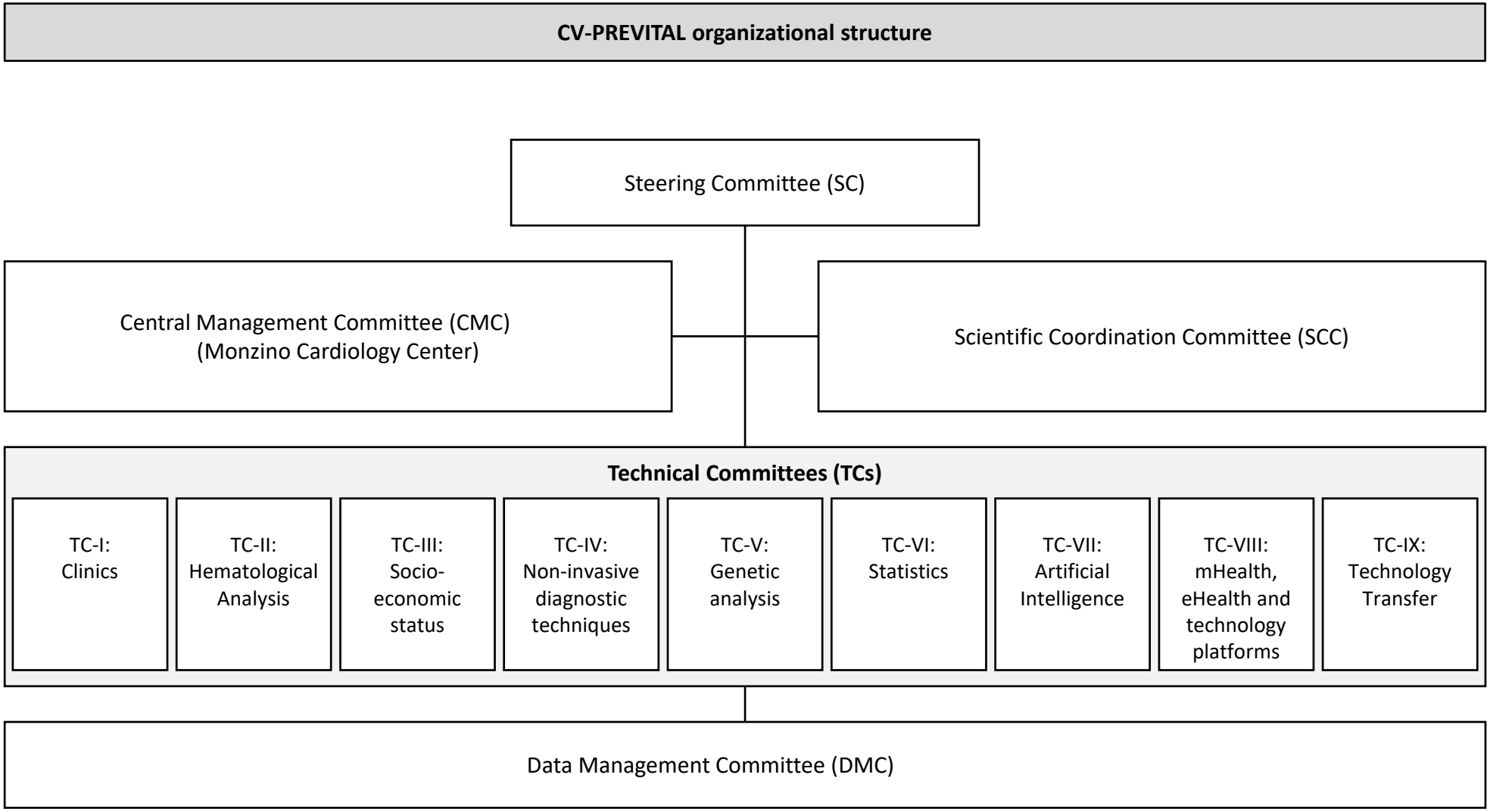
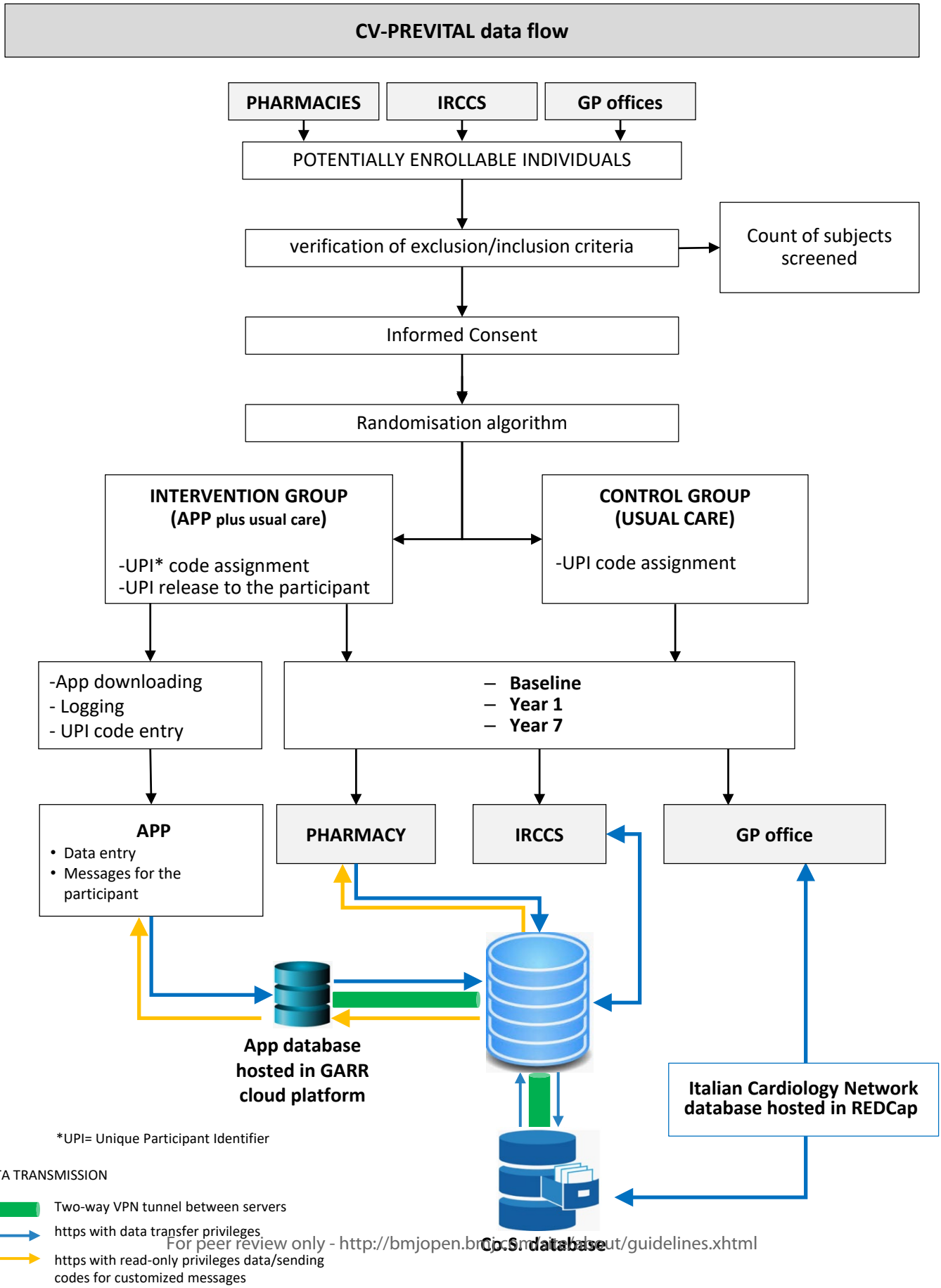

CV-PREVITAL organizational structure
Steering Committee (SC)
Central Management Committee (CMC)
(Monzino Cardiology Center)
Scientific Coordination Committee (SCC)
Technical Committees (TCs)
TC-I: Clinics
TC-II: Hematological Analysis
TC-III: Socio-economic status
TC-IV: Non-invasive diagnostic techniques
TC-V: Genetic analysis
TC-VI: Statistics
TC-VII: Artificial Intelligence
TC-VIII: mHealth, eHealth and technology platforms
TC-IX: Technology Transfer
Data Management Committee (DMC)

**Figure 2**



**ONLINE SUPPLEMENTAL MATERIAL**

**Supplemental Table 1. Members of the Steering Committee of the CV-PREVITAL study**

| Institution | Member of the Steering Committee |
|---|---|
| Monzino Cardiology Center | Giulio Pompilio, Damiano Baldassarre |
| IRCCS Italian Institute for Auxology | Gianfranco Parati |
| Humanitas Research Hospital | Gianluigi Condorelli |
| Institute of Pharmacological Research Mario Negri IRCCS | Giuseppe Remuzzi |
| IRCCS MultiMedica | Gianfranco Gensini |
| Neuromed Mediterranean Neurological Institute | Luigi Frati |
| Policlinico San Donato Research Hospital | Lorenzo Menicanti |
| Clinical Scientific Institutes Maugeri (ICS Maugeri) | Walter Ricciardi |
| Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) | Pier Giulio Conaldi |
| San Martino Polyclinic Hospital | Antonio Uccelli |
| IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico | Fabio Blandini |
| Agostino Gemelli IRCCS University Hospital Foundation | Giovanni Scambia |
| Foundation IRCCS Polyclinic San Matteo | Eloisa Arbustini |
| IRCCS San Raffaele Rome | Massimo Fini |
| Consorzio Sanità (Co.S.) | Antonio Di Malta |
| Romeo and Enrica Invernizzi Foundation | Emilio Trabucchi |

**Supplemental Table 2. List of operative units and enrolled cohorts**

| OPERATIVE UNITS | ENROLLED COHORTS |
|---|---|
| Consorzio Sanità (Co.S.) | 50,000 subjects attending the ambulatory of the participating GPs |
| Monzino Cardiology Center | 5,000 subjects attending pharmacies of the Lombardy territory |
| IRCCS Italian Institute for Auxology | 5,000 subjects attending the institute (including 1,500 subjects referred to the Sleep Medicine Center) |
| Humanitas Research Hospital | 2,000 subjects attending the institution |
| IRCCS MultiMedica | 1,000 subjects with diabetes and 2,000 subjects from the general population |
| Neuromed Mediterranean Neurological Institute | 10,000 subjects from the Neuromed clinical research centre |
| Policlinico San Donato Research Hospital | 1,000 subjects selected among its own employees |
| Clinical Scientific Institutes Maugeri (ICS Maugeri) | 1,000 subjects selected among their own employees |
| Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT) | 150 subjects included in a program of physical training and lifestyle modifications |
| San Martino Polyclinic Hospital | 2,000 male subjects from the Municipality of Genoa |
| IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico | 2,000 blood donors afferent to the Department of Transfusion Medicine and Hematology |
| Agostino Gemelli IRCCS University Hospital Foundation | 1,000 subjects attending to the outpatient clinics of the Non-Invasive Cardiology Diagnostic Unit, of the Centre for Hypertension, and of the Centre for Endocrine and Metabolic Diseases |
| Foundation IRCCS Polyclinic San Matteo | 500 subjects selected among asymptomatic relatives of patients attending to the Polyclinic San Matteo for cardiology reasons plus 100 healthy individuals attending to the Genetics Unit of IRCCS San Matteo |
| IRCCS San Raffaele Rome | 150 subjects selected among its own employees |
| Institute of Pharmacological Research Mario Negri IRCCS | Non-recruiting unit. Role: Monitoring center for the cohort of subjects recruited by GPs |

GPs: general practitioners

## STAFF TRAINING, STANDARD OPERATING PROCEDURES (SOPs) AND QUALITY CONTROL

CV-PREVITAL uses several training models for study staff, including web-based and on-site training. Operators involved in recruitment are also required to read a manual for data management before receiving the ID and password to access the CV-PREVITAL digital platform. Standard operating procedures (SOPs), which are available upon request, have also been implemented to ensure that all research activities are performed according to predetermined standards, definitions, and schedules.

Quality control activities include (a) disseminating SOPs developed to ensure data integrity, (b) implementing warning messages in the electronic "Case Report Form" (eCRF) when data input falls within an implausible range, and (c) implementing warning or halting messages when specific variables and/or questionnaires (or parts of them) are left unfilled in the eCRF. For quality control of the 7-year outcome assessment, a random sample of outcomes is reviewed and adjudicated by a centrally appointed panel of cardiologists. At year seven of the trial, if at least 10 composite specific outcomes (including at least 2 myocardial infarctions, 2 hospitalizations for angina, 2 strokes, 2 revascularizations, and 2 deaths) adjudicated locally in each recruiting center are validated with full agreement from the central panel of cardiologists, then local classification and adjudication does not require further central review. Otherwise, the procedure continues until local adjudication reaches full agreement with the central panel. In the event that a specific recruitment center records a total of less than 10 events, all events are adjudicated centrally. The quality control for the collection of data on 7-year vascular events, needed to avoid the "lost at follow-up bias", is warranted by active recalling of participants or their relatives in case of death. The quality control regarding the use of the app during follow up, including the participants' adherence to the proposed activities, is accomplished and verified by the app itself. Indeed, as described in the paragraph "Intervention", in addition to sending reminders, personalized motivational feedback, and messages based on task evaluation and periodic goal achievement (also exploiting the logic of gaming), the app also provides for logging of non-use or sub-optimal use of the app itself.

## WEB BASED TRIAL MANAGEMENT

The hub for CV-PREVITAL data collection and storage is the IT platform of the Italian Cardiology Network (ICN), developed in collaboration with the Consortium of Bioengineering and Medical Informatics (Italian acronym: CBIM) of the Italian Ministry of Health and hosted in REDCap. This platform is integrated with the IT platform of Consorzio Sanità (Co.S.), which is the interface used by primary care physicians participating in the study, as well as with the CV-PREVITAL app database. All data collected by general practitioners (GPs) are entered directly into web-based forms and saved to a structured database of each local GPs cooperative. The data are then harmonized and transferred to the dataset of Co.S.. Data included in this dataset are then transferred to the REDCap dataset of the ICN managed by CBIM. Instead, all data collected from research hospitals (Italian acronym: IRCCS) and pharmacies are directly entered into web-based forms and saved into the structured database at CBIM. All of the web-based systems mentioned incorporate real-time data entry quality control, as well as informatics tools to verify eligibility for recruitment prior to randomization. Access to each portion of the various digital platforms that host the various datasets is protected with passwords and restricted to individuals with specific access privileges. Person identifying information is kept separate from all other information and linked only by a pseudo-anonymous study ID for each participant.

## DETAILS ON RANDOMIZATION PROCEDURES

### Modalities of randomization for GPs cohort

In the randomization modality for GPs cohort, sampling involves three hierarchical levels:

**level 1**: 50 CSPs (acronym of the Italian term Centri Sanitari Polifunzionali) i.e., fifty GPs health centers coordinated by Co.S., each including at least 3 practitioners.
**level 2**: Approximately 250 GPs, with an average of 5 GPs for each CSP.
**level 3**: 50,000 individuals to be enrolled (200 for each GP).

To reduce the risk of imbalance, randomization is performed by GP, stratifying by CSP. In each CSP, GPs assigned to the control group and GPs assigned to the intervention group are balanced. The randomization of GPs is centralized and managed by CBIM.

**Modalities of randomization for IRCCSs Cohorts**

In the case of the IRCCSs cohorts, individuals are randomized directly, with the exception of the one recruited in community pharmacies, where the procedure randomizes pharmacies and not individuals. For IRCCSs that randomize individuals, the randomization takes place without stratification by age and sex, to avoid unnecessarily lengthening the time required for participant enrollment. Potential discrepancies between IRCCSs cohorts (and/or sub-studies), in terms of distribution of age, sex and any other important covariates (geography, socioeconomic status, etc.), are handled by adopting a meta-analytic approach with individual participant data, with random effects in global analyses, and by stratifying for the appropriate subgroups in specific analyses. Randomization of the different cohorts enrolled in the various IRCCSs is also centralized, using the ICN IT platform to create specific randomization lists for each sub-study. The assignment of patients to the appropriate treatment arm is managed remotely and automatically at the time of patient inclusion in the study. This approach also allows for centralized real-time monitoring of enrollment progression. In case of a specific design (for instance, a 2x2 factorial), the randomization procedure ensures a balance of individuals in the two main treatment arms (mHealth vs. Usual care) and in the two specific secondary arms.

## RISK SCORE USED AS PRIMARY OUTCOME

The score was constructed by analysing the combined impact of different modifiable factors on the risk of developing cardiovascular diseases (CVD) during the follow up of the MOLI-SANI study.[1 2] The analysis was conducted on n=21,806 MOLI-SANI participants free of personal history of CVD. The event considered was a combined outcome of cardiovascular death and nonfatal cardiovascular events. The number of observed events was n=816, with a median follow-up of 8.1 years of. The analysis model included the following covariates: age, sex, history of cancer at baseline, drug therapy for diabetes, hypertension, or dyslipidemia, BMI (4 categories), income (4 categories), and schooling (2 categories). The modifiable risk factor score included the following variables (all on a continuous scale): (1) the number of cigarettes (per day); (2) adherence to the Mediterranean diet (score from 0 to 9 points, calculated as in Trichopoulou et al.[3]); (3) mean arterial pressure (MAP) = (2*diastolic+systolic)/3; (4) relative fat mass (RFM) (proxy for percentage of adipose fat as in Woolcott et al.[4]); (5) blood glucose; (6) LDL cholesterol; (7) HDL cholesterol; (8) triglycerides; and (9) leisure-time physical activity. The above variables have been standardized to mean zero and standard deviation one, separately for men and women (with the exception of the number of cigarettes and Mediterranean diet adherence index, left in their original scales).

For each individual, a score of modifiable cardiovascular (CV) risk factors was obtained as a weighted sum of the following variables: number of cigarettes, score of adhesion to Mediterranean diet and z-values of LDL, HDL, triglycerides, mean arterial pressure, glucose, leisure time physical activity and relative fat mass. Weights were natural logarithms of the hazard ratio of each variable, as calculated in the fully adjusted model. Risk factors positively associated with the endpoint showed hazard ratio >1 and consequently they were summed up with positive weights. On the contrary, variables negatively associated with the endpoint entered the score with negative weights as a consequence of their hazard ratio in the range 0-1. By construction, the higher the score, the higher the magnitude of its association with the endpoint. To improve the interpretability of the score, we divided it by 0.06859, which is the natural logarithm of the hazard ratio for one year more of age as measured in the derivation cohort. In this way, one unit of the rescaled score resulted in being associated with the outcome as one year of age more at baseline. Practically, a 1-point increase in the score is equivalent (in terms of cardiovascular risk) to an increase of 1 year of age.

Smoke_score = (number of cigarettes per day) * 0.029
Diet_med_score = (Mediterranean diet adherence score) * 0.061

LDL_score = (z-score of LDL) * 0.198
HDL_score = (z-score of HDL) * 0.154
Triglycerides_score = (triglycerides z-score) * 0.015
MAP_score = (z-score of MAP) * 0.186
Glucose_score = (z-score of glucose) * 0.135
Physical_activity_score = (z-score of leisure-time physical activity index) * 0.045
RFM_score = (z-score of relative fat mass index) * 0.036

SCORE_TOT =
(Smoke_score + LDL_score + Triglycerides_score + MAP_score + Glucose_score + RFM_score - Diet_med_score - HDL_score - Physical_activity_score) / 0.06859

For the calculation of z-scores (z-score=(value-average) / standard deviation) it is possible to refer to the following values observed in the MOLI-SANI project (population aged ≥45 years):

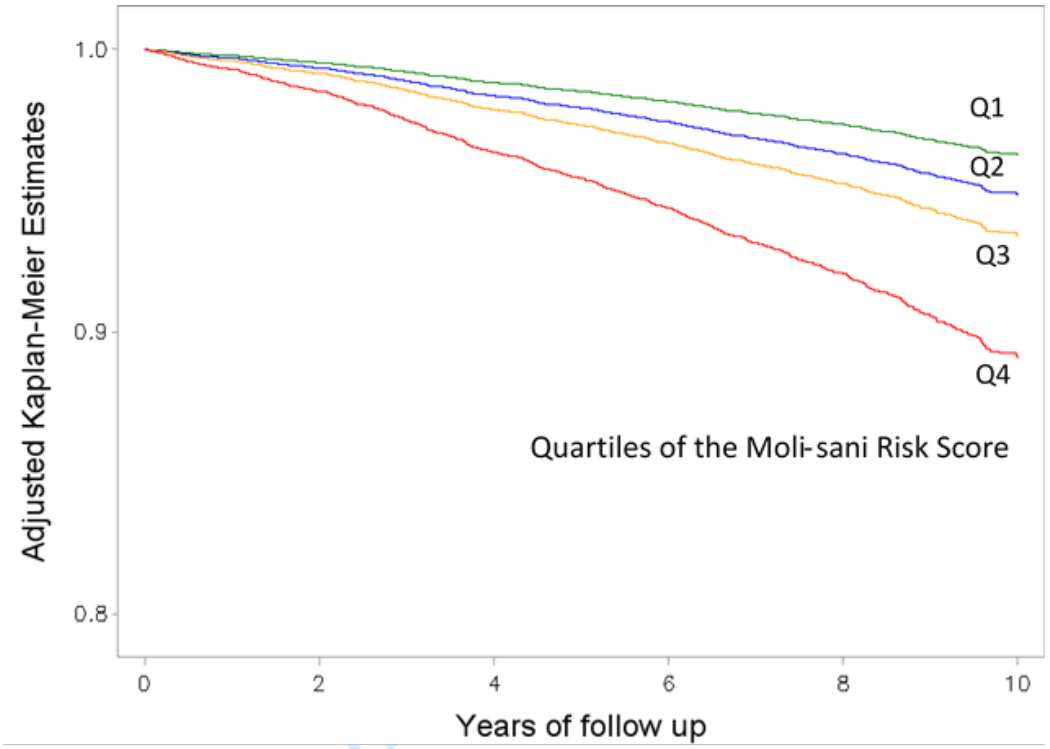
| Variable | Mean | Standard deviation | Mean | Standard deviation |
|---|---|---|---|---|
| | | MEN | | WOMEN |
| LDL (mg/dL) | 130 | 35 | 136 | 36 |
| HDL (mg/dL) | 52 | 13 | 63 | 15 |
| Triglycerides (mg/dL) | 150 | 99 | 118 | 66 |
| MAP (mmHg) | 105 | 11 | 102 | 12 |
| Blood Glucose (mg/dL) | 107 | 28 | 98 | 23 |
| Physical_activity (MET-hours/day) | 4.6 | 4.7 | 2.7 | 3.2 |
| RFM (%) (males) | 29 | 3.6 | 42 | 5 |

MAP=(2*diastolic+systolic)/3
RFM=64 - (20 × height (cm)/waist circumference (cm)) for men and
RFM=76 - (20 × height (cm)/waist circumference (cm)) for women

Assessing physical activity (in leisure time) in terms of met-h/day can be challenging. Consider replacing this measure with a proxy based on a multi-level qualitative classification of such physical activity. For example, a 3-level classification: 'sedentary', 'moderately active', 'active' can be transformed into corresponding (approximate) z-scores = -1, 0, 1.

In the MOLI-SANI project, the score has median -5.0 and interquartile range 8.3 (min=-26.9, low risk and max=41.5, high risk). Each score point was associated (in the MOLI-SANI study) with a risk of MACE approximately equal to that of one additional year at baseline (HR for one score point: 1.071, 95%CI: 1.062 to 1.080).

Survival curves by score categories, as observed in the MOLI-SANI project, are shown below:




| Quartiles | Median | Min-max | N | No. events | % events | HR* | 95% CI |
|---|---|---|---|---|---|---|---|
| Q1 | -9.8 | -26.9 to -7.0 | 4164 | 114 | 2.74 | 1 | (reference) |
| Q2 | -5.0 | -7.1 to -3.0 | 4164 | 164 | 3.94 | 1.40 | 1.10 to 1.79 |
| Q3 | -1.1 | -3.1 to 1.2 | 4164 | 205 | 4.92 | 1.83 | 1.44 to 2.31 |
| Q4 | 4.5 | 1.3 to 41.5 | 4164 | 333 | 8.00 | 3.18 | 2.54 to 3.97 |

## ANCILLARY STUDIES

The CV-PREVITAL study includes several ancillary studies, each with its own protocol. The objectives and outcomes of the ancillary studies are described below.

**Ancillary study of Monzino Cardiology Center**

The ancillary study of the IRCCS Monzino Cardiology Center (abbreviated as Monzino) aims to evaluate the hypothesis that the same mHealth intervention investigated in the parent study can improve metabolic balance in the short term and reduce the onset of type 2 diabetes in the long term in individuals at high risk of developing this disease due to pre-diabetes. To this end, 1,000 participants already enrolled in the parent study at the outpatient clinics of GPs or at pharmacies (including 200 subjects with a diagnosis of type 2 diabetes mellitus (T2DM), 400 subjects with a diagnosis of pre-diabetes and 400 normoglycemic individuals) equally divided into control and intervention groups, are invited to undergo an in-depth diabetological evaluation at Monzino. This evaluation includes a clinical visit, non-invasive diagnostic tests to assess carotid subclinical atherosclerosis (i.e., atherosclerotic plaque size, total plaque area, total plaque volume, intima-media thickness (IMT), interadventitia common carotid artery diameter (ICCAD), and wall echolucency), endothelial function (i.e., reactive hyperemia index), peripheral atherosclerosis (i.e., Ankle Brachial Index (ABI)), diabetic retinopathy (i.e., fundus retinography), and collection of blood and urine samples for biochemical analysis. These include OGTT (oral glucose tolerance test of fasting blood glucose (FPG) and 120 minutes after ingestion of 75 grams of glucose (2h PG)), HbA1c (by standardized HPLC

method), insulinemia, fasting apolipoprotein B and lipoprotein(a), hs-CRP, microalbuminuria (Albumin/Creatinine ratio), creatinine and eGFR. Total cholesterol, HDL cholesterol, triglycerides, and calculated LDL cholesterol, which were already measured by point-of-care tests within the parent study, are re-measured with standard laboratory methods. After 12 months of follow-up, each individual in the Monzino sub-study is invited to attend to the same facility for repeating all the evaluations performed at baseline, except for the evaluations of carotid subclinical atherosclerosis, endothelial function, peripheral atherosclerosis and diabetic retinopathy. The proportion of subjects who change from a diagnosis of T2DM to a diagnosis of pre-diabetes or from a diagnosis of pre-diabetes to a diagnosis of normoglycemia, compared to the baseline examination is thus evaluated. After 7 years of follow-up, the occurrence of cardiovascular events and overt diabetes, depending on the length of time in pre-diabetes and the interaction of pre-diabetes with other risk factors (e.g. obesity, hypertension, hypertriglyceridemia, etc.), is also assessed. The sample size of this ancillary study was calculated based on the difference between groups in glucose response during OGTT. In the subsamples of normal (n=400) and prediabetic (n=400) subjects, a comparison of two groups of 200 subjects (App Vs. Usual care) ensures a significant evaluation ($p<0.017$, applying Bonferroni correction for 3 independent tests) of a between-group difference of approximately 32% of a standard deviation of blood glucose at two hours after the start of the test, with a statistical power of 80%. In the subsample of diabetic subjects (n=200), the comparison of two groups of 100 subjects (App Vs. Usual care) ensures the detection of a minimal difference of approximately 46% of a standard deviation of blood glucose at two hours after the start of the test, again with 80% power and a $p<0.017$.

**Ancillary study of IRCCS Italian Institute for Auxology**

The ancillary study of the IRCCS Italian Institute for Auxology (abbreviated as Auxologico) enrols 5,000 individuals, divided into three sub-cohorts based on the presence or absence of hypertension, obesity, or sleep problems. In these individuals, in addition to the conventional cardiovascular risk factors included in the parent study, several supplementary variables are investigated. In the hypertensive subjects sub-cohort, the following parameters are evaluated: 24-hour systolic blood pressure (SBP); ambulatory blood pressure variables (i.e., 24-hour SBP, 24-hour diastolic blood pressure (DBP), day-time SBP, day-time DBP, night-time SBP, night-time DBP, SD 24-hour SBP, SD 24-hour DBP, SD day-time SBP, SD day-time DBP, SD night-time SBP, SD night-time DBP); dipping status (i.e., the difference between the mean SBP during the day and mean SBP during the night, expressed as a percentage of the daytime mean); 24-hour urinary sodium secretion; microalbuminuria; creatinine; eGFR; left ventricular hypertrophy (evaluated with the Sokolow index and Cornell product). In the obese/overweight subjects sub-cohort, the following parameters are evaluated: BMI; waist circumference; waist/hip ratio; fasting insulinemia and fasting blood glucose levels. Additional evaluation in subjects classified as both hypertensive and obese/overweight includes cardiovascular risk estimate based on clinical variables and biomarkers (Troponin I, cut-off of 0.008 ng/mL; hs-CRP, cut-off of 6.81 mg/L; N-terminal pro-BNP, cut-off of 187 pg/mL) and measurement of uric acid levels. In subjects with sleep problems attending the Center for Sleep Medicine, detailed information on the qualitative and quantitative characteristics of night sleep is recorded using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Other evaluations related to sleep complaint include the Epworth Sleepiness Scale (ESS) questionnaire [5 6] to assess the improvement in daytime sleepiness and the diagnosis of obstructive sleep apnea (OSA) by polysomnographic indices such as the apnea-hypopnea index (AHI) (<5/hour = normal OSA; 5–14.9/hour = mild OSA; 15–29.9/hour = moderate OSA; ≥30/hour = severe OSA). In subjects with OSA, differences in the usage of positive airway pressure (PAP) devices and in the daily usage of PAP treatment at 1 year after randomization between control and intervention groups are also evaluated.

After 12 months of follow-up, each individual enrolled in the Auxologico sub-study is invited to return to the same facility to repeat all the evaluations performed at baseline.

The primary outcome measures in the three sub-cohorts of the Auxologico ancillary study are as follows: 1) the difference in mean systolic 24-hour blood pressure at 12 months between the two study arms (App-based intervention vs. usual care); 2) the difference in mean BMI at 12 months between the two study arms; 3) the difference in sleep quality (mean score on the Pittsburgh questionnaire - PSQI) at 12 months

between the two study arms.
A sample size of 506 hypertensive subjects (253 in each group) will allow detection of a 3 mmHg mean systolic 24-hour blood pressure difference between the intervention (APP) and control groups, assuming a first-type error rate of 5%, a power of 80%, and a standard deviation of 12 mmHg.[7] This sample size was calculated using a two-tailed t-test under the assumption of equal variances between groups. Assuming a dropout probability of 25%, the final sample size will consist of 676 subjects (338 in each group).
A sample size of 426 overweight or obese subjects (213 in each group) will allow detection of a 1.5 Kg/m$^2$ BMI difference between the intervention (APP) and control groups, assuming a first-type error rate of 5%, a power of 80%, and a standard deviation of 5.5 Kg/m$^2$.[8] This sample size was calculated using a two-tailed t-test under the assumption of equal variances between groups. Assuming a dropout probability of 25%, the final sample size will consist of 578 subjects (284 in each group). A sample size of 1,132 subjects with impaired sleep quality as per PSQI>5 (566 in each group) will allow detection of a 0.7 difference in PSQI score between the intervention (APP) and control groups, assuming a first-type error rate of 5%, a power of 80%, and a standard deviation of 4.2 points.[9] This sample size was calculated using a two-tailed t-test under the assumption of equal variances between groups. Assuming a dropout probability of 25%, the final sample size will consist of 1,510 subjects (775 in each group).

**Ancillary study of Humanitas Research Hospital**
As an ancillary study, the IRCCS-Humanitas Research Hospital (abbreviated as Humanitas) performs a quantitative evaluation of the coronary artery calcium (CAC) score through CT imaging in half of the participants. CAC score is calculated using the Agatston method and by determining the volume of calcium.[10] The study has a 2x2 factorial design: subjects are randomized 1:1 to receive either an app or usual care as in the parent study. Each subject is then further randomized 1:1 to receive either CT scanning on top of usual care or usual care alone.
After 12 months of follow-up, each individual is invited to attend the IRCCS Humanitas again, as in the parent study. A comparison of the mean change in lipid biomarkers from baseline to follow-up between the two groups (CT scan or usual care alone) is performed.
It is expected that patients randomized to CT scanning compared to usual care will experience a larger reduction in LDL-C levels from baseline; i.e., a difference in the mean reduction in LDL-C of 0.25 mmol/L (9.65 mg/dL), with an SD of 1 mmol/L (38.6 mg/dL). The rationale for this hypothesis is that the presence of a calcium score > zero will increase the likelihood of statin prescription and subject adherence.
To detect this difference, a total of 506 participants (253 in each group) will be required with 80% power, and a two-sided α of 0.05. However, based on a previous study on primary prevention performed at the same institution, considering that the prevalence of patients with a zero calcium score would be approximately 60%, the total number of participants will increase to 1,265. Considering an overall 5% dropout, the final total number of participants will be 1,328 (664 in each group).
Furthermore, at 12 months, the ability of SNPs identified in previous genome-wide association studies or newly identified in this study to predict severe coronary artery calcification is also assessed.
At 7 years, the incremental effectiveness (i.e., healthy quality-adjusted life years (QALYs)), and the incremental cost-effectiveness ratios (ICERs) of screening by CT scanning for CAC score are assessed.
Finally, major adverse cardiovascular and cerebrovascular events between subjects randomized to screening by CT scanning or traditional risk factor assessment alone are assessed.

**Ancillary study of IRCCS MultiMedica**
In its ancillary study, IRCCS MultiMedica (abbreviated as MultiMedica) performs additional investigations in 1,000 diabetic patients and in 2,000 individuals recruited from the general population. These investigations include: evaluation of organ damage (indexed by common carotid IMT), ABI, and endothelial function as assessed through ICAM and VCAM; quality of life, assessed by using the WHOQOL-Measuring Quality of Life questionnaire; psychological conditions, measured using the Mini Mental Status test; cardiovascular risk, measured by the "SCORE" (Systematic COronary Risk Evaluation) algorithm;[11] and hematochemical investigations, useful to define the condition of diabetes or dyslipidemia. Hematochemical and biochemical investigations carried out in diabetic subjects include: blood glucose, Brain Natriuretic Peptide (BNP),

creatinine (eGFR), hs-CRP, interleukin 6 (IL-6), interleukin 1 beta (IL-1 beta), microalbuminuria. In addition to total cholesterol, HDL cholesterol, triglycerides and calculated LDL cholesterol measured within the procedures adopted for the parent study, additional variables measured in dyslipidemic individuals include: apolipoprotein AI, apolipoprotein B, lipoprotein(a), creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT). After 12 months of follow-up, each individual is invited to return to IRCCS MultiMedica to repeat all the aforementioned evaluations. The mean change from baseline between the 2 groups is compared. The ancillary study also includes: multivariate analysis of baseline data for the identification of determinants and predisposing factors to the diabetes status, dyslipidemia and hypertension; the detection of causative mutations in case of suspected genetic disorders; the 12-month evaluation of CAC score in patients with suspected familial hypercholesterolemia; and the assessment of the onset of cardiovascular events, and new diagnosis of diabetes and hypertension in the 7-year follow-up period.
1,782 subjects will be needed to identify a significant reduction (alpha=0.01) in scores after one year of intervention, assuming a standard deviation of 5 and a statistical power of 95%. Assuming a dropout rate of about 10%, 2,000 patients will be recruited.

**Ancillary study of Neuromed Mediterranean Neurological Institute**

In addition to the biochemical variables measured in the parent study, in the ancillary study of the IRCCS Neuromed Mediterranean Neurological Institute (abbreviated as Neuromed) hs-CRP and creatinine (eGFR) are evaluated. Moreover, Neuromed ancillary study includes the administration of supplementary questionnaires on dietary habits (to assess the proportion of subjects who change their consumption of ultra-processed foods, according to the NOVA classification[12]) and the evaluation of cognitive status by using the Montreal Cognitive Assessment (MOCA) test.[13] Finally, IRCCS Neuromed analyses the determinants of dietary changes using multivariable approaches. After 12 months of follow-up, each individual is invited to return to IRCCS Neuromed to repeat the aforementioned evaluations. The mean change from baseline between the 2 groups is compared. This ancillary study will be conducted in a subset (N=1,000) of the recruited population. This sample size is large enough to guarantee large power (power>90%; $\alpha$=0.01) for testing the hypotheses of this ancillary study (assessment of determinants of dietary changes concerning the consumption of ultra-processed foods, and evaluation of cognitive status by the Montreal cognitive assessment test).

**Ancillary study of Policlinico San Donato Research Hospital**

In the ancillary study, the IRCCS Policlinico San Donato Research Hospital (abbreviated as San Donato) performs additional investigations on 1,000 subjects selected among its own employees. At baseline, participants undergo: 1) a vascular investigation (carotid B-mode ultrasonography) to assess IMT, plaques size, presence/absence of atherosclerotic plaques, and total plaque area; 2) a trans-thoracic echocardiographic examination (TT-Echo) to assess relative wall thickness, E/A ratio, E/e' ratio, heart mass, end-diastolic and end-systolic volume, left atrial volume, Ejection Fraction (EF; %), maximal tricuspid regurgitation velocity (TRV max), and epicardial adipose tissue (EAT). Moreover, additional hematochemical analyses are performed, including NT-proBNP, as this biomarker has been inserted in the algorithm for the diagnosis of heart failure with preserved ejection fraction,[14] and TSH, to investigate the relationship between disthyroidism and cardiovascular disease. Finally, in order to refine the cardiovascular risk estimation, the ancillary study of San Donato evaluates other additional serum biomarkers in individuals with comorbidities, such as diabetes mellitus, overweight, obesity, abdominal obesity (number estimated=400 individuals). In particular, insulinemia, homocysteine, hs-CRP, $Na^+$, $K^+$, IL-6, and sRAGE are analysed.
After 12 months of follow-up, participants are invited to attend to IRCCS San Donato for assessing the mean change from baseline in NT-proBNP and TSH values. The value of ultrasound and transthoracic-echocardiographic variables as predictor of cardiovascular events is assessed at the end of the 7-years follow-up.
1,000 patients will be sufficient to estimate as significant a correlation coefficient (alpha=0.001, adjusted for Bonferroni to account for multiple comparisons) of 0.15, with a statistical power of 80%. Moreover, the

same sample size will allow to assess as significant (alpha(two-sided)=0.05) a difference mean after 12 months from baseline of 0.10 standard deviations of the parameters considered, with a power of 80%. Finally, in the analyses to refine the cardiovascular risk, 400 patients will provide a significant correlation coefficient (alpha(two-sided)=0.01) of 0.20, with a statistical power of 80%.

**Ancillary study of Clinical Scientific Institutes Maugeri (ICS Maugeri)**

In the ancillary study of the IRCCS Clinical Scientific Institutes Maugeri (abbreviated as Maugeri), 1,000 individuals are categorized according to their cardiovascular risk. Subjects at intermediate/high risk undergo additional hematochemical analyses including blood glucose, uricemia, and microalbuminuria. In participants who need further risk stratification, additional tests to assess atherosclerotic organ damage are performed, including ABI, the CT CAC score and carotid artery ultrasound.

In all individuals, in addition to the usual care or mHealth intervention planned for the parent study, a personalized program of physical activity is also prescribed. In particular, for individuals classified at high-risk, an exercise test for silent ischemia screening is performed to obtain the prescriptive drivers needed to personalize the physical training intervention. Finally, in all participants at intermediate/high risk, a blood sample for genetic and epigenetic tests and for the evaluation of possible additional hematochemical factors predisposing to atherosclerotic diseases is collected.

Cardiovascular events, silent ischemia and change from baseline in ABI, CAC score and carotid imaging markers over a 7-year follow-up period, depending on the length of time in physical activities programs, are evaluated. The interaction of physical activity with other risk factors (e.g. obesity, hypertension, hypertriglyceridemia, etc.) is also performed to assess the relationship with carotid imaging markers. Assuming a prevalence of subjects at intermediate/high cardiovascular risk of about 15%, 150 patients will guarantee a significant correlation coefficient (alpha=0.01) of 0.30, with a statistical power of 80%. The other analysis will only be exploratory descriptive analysis for which the sample calculation was not done.

**Ancillary study of Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT)**

In its ancillary study, the IRCCS Mediterranean Institute for Transplantation and Advanced Specialized Therapies (abbreviated as ISMETT) plans to conduct baseline and 12-month assessments, including: 1) a CT scan to assess CAC score; 2) a cardiac magnetic resonance to evaluate myocardial fibrosis; 3) an evaluation of a series of circulating biomarkers indicating cardiac stress and/or heart failure and kidney dysfunction, including creatinine, blood urea, nitrogen (Blood Urea Nitrogen, BUN), and hs-CRP. Other biomarkers tested include NT-proBNP, $Na^+$, $K^+$, homocysteine, iron, ferritin, transferrin, and complete blood count. The effect of specific cardiovascular risk factors (e.g. obesity, hypertension, diabetes etc.) on outcomes 1, 2 and 3 is also evaluated. The mean change from baseline between the 2 groups is compared.

To assess as significant a difference (alpha(two-sided)=0.05) in mean change after 12 months from baseline of 0.22 standard deviations of the parameters considered with a power of 80%, 150 subjects are needed.

**Ancillary study of San Martino Polyclinic Hospital**

In the ancillary study of the IRCCS San Martino Polyclinic Hospital (abbreviated as San Martino), 1,500 male individuals, recruited in the city of Genoa, undergo an echocolor Doppler examination for the early detection of abdominal aortic and iliac aneurysm. In an additional group of 500 male individuals, a color Doppler ultrasound of external carotid arteries is performed to evaluate the average IMT for the early diagnosis of carotid plaques and carotid stenosis. In such individuals, the risk stratification for cardiovascular disease is also evaluated. To ensure a 95% confidence interval of 18.8, 29.3, assuming a mean aortic diameter equal to 19.43 mm, 1500 subjects are needed[15].

**Ancillary study of IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico**

In the ancillary study of the IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico (abbreviated as Ca' Granda), individuals with a cardiovascular risk >7.5% or with at least 3 metabolic risk factors selected among the 2,000 participants enrolled in their structure undergo: 1) an ultrasonographic scan to assess carotid subclinical atherosclerosis (indexed by plaque size, presence/absence of plaques, and IMT); 2) a non-invasive fibroscan analysis to assess the amount of hepatic fat/lipotoxicity (indexed by the CAP Score)

and the hepatic fibrosis stage (indexed by the FIB-4 Index); 3) a series of blood chemistry tests, including microalbuminuria, AST, ALT, GGT, HbA1c, insulinemia, coagulation balance (i.e., von Willebrand Factor Antigen, Protein C, and Factor VIII), D-Dimer levels, and interleukin-32 (as a circulating biomarker of lipotoxicity). After 12 months of follow-up, each individual is invited to attend to IRCSS Ca' Granda again for the follow up visit. The mean change from baseline between the control and intervention groups is compared for all the variables mentioned above, except for coagulation balance and D-Dimer levels, which are measured only at baseline.

In addition, the characterization of the intestinal microbiome is performed in a subgroup of 200 individuals at baseline and after 7 years by: 1) a metagenomic analysis (taxonomic and functional), including the evaluation of serum levels of trimethylamine oxide (TMAO) and other metabolites of bacterial origin (branched-chain amino acid (BCAAs), aromatic amino acid (AAAs)), and 2) the interaction of the microbiome with classical and inherited risk factors. Finally, a genetic characterization is performed in the whole Ca' Granda cohort by Whole Exome Sequencing (WES) and genotyping (GWAS) for *PNPLA3 I148M, TM6SF2 E167K, GCKR P446L* and *MBOAT7* genetic variants influencing hepatic fat content (HFC).

A genetic risk score based on these variants (hepatic fat content-genetic risk score, HFC-GRS) is calculated, and the association of HFC-GRS with early cardiovascular damage (estimated by IMT) is evaluated. As we have preliminary data indicating that high HFC-GRS (above the median) is associated with a >3-fold higher risk of developing NASH and clinically significant fibrosis, the power of the study to detect an impact of genetic scores on the risk of liver disease (NASH or clinically significant fibrosis) is >95% ($p<0.05$, two-tailed). Regarding the possibility of prospectively evaluating extra-hepatic outcomes, given the age range and the presence of metabolic risk factors, the cumulative incidence of major cardiovascular thrombotic events (death, myocardial infarction or cerebrovascular events, venous thromboembolism) is expected to be 3-4% in the cohort. The sample size has a >80% power to detect a hazard ratio of 1.8 of non-hepatic events, which is consistent with literature data, associated with genetically determined hepatic fat accumulation.

**Ancillary study of Agostino Gemelli IRCCS University Hospital Foundation**

The additional investigations performed in the 1,000 individuals enrolled by the Agostino Gemelli IRCCS University Hospital Foundation (abbreviated as Gemelli) include ultrasonographic scan of carotid arteries for evaluation of IMT, measurement of additional variables of lipid metabolism (Lp(a) and serum oxidized LDL levels), and inflammation (hs-CRP, IL1beta, IL-18, IL-6, IL-10, and TNF-alpha), and measurement of serum additional biochemical variables including human lipopolysaccharides (LPS), metabolite of bacterial origin and TMAO. Finally, this ancillary study also envisages the assessment of the intestinal microbiome composition with Next Generation Sequencing (NGS) technology and of a serum marker of intestinal permeability (zonulin).

After 12 months of follow-up, each individual is invited to attend the IRCSS Gemelli for repeating the aforementioned evaluations. The mean change from baseline between the control and intervention groups is compared. The assessment of cardiovascular events incidence over the 7-year follow-up period, depending on the significant biomarkers variation and microbiome composition detected, is also evaluated.

The primary endpoint in this ancillary study is the mean change in compositional microbiome after treatment between the two subgroups, measured in terms of microbiome entropy, i.e., Shannon's alpha diversity index. Given the paucity of evidence on this topic and the already available sample size, a post-hoc power calculation is proposed, assuming 500 subjects per group, a two-sided 95% confidence interval with a significance level (type I error) of 0.05. Based on these assumptions, 1000 subjects, i.e., 500/group, are able to detect a small Cohen's d effect size equal to 0.2, with an estimated power of 0.8847885. The power estimate was computed with the "pwr" R package (https://CRAN.R-project.org/package=pwr), which was installed in the R environment v4.2.3 (CRAN ®, R Core 2022, Wien, Austria) (https://www.R-project.org/), by applying a two-sided, two-sample t test with effect size. The script is provided accordingly (https://github.com/piaclarapafundi/Italian-Cardiologic-Network-Ancillary-Study).

**Ancillary study of Foundation IRCCS Polyclinic San Matteo**

In its ancillary study, the Foundation IRCCS Polyclinic San Matteo (abbreviated as San Matteo) develops a multigene analysis panel that allows the identification of a genotype at risk of diabetes before the appearance of the clinical phenotype. To this end, 200 diabetic patients, 400 pre-diabetic subjects, and 400 normoglycaemic subjects (enrolled at IRCCS Monzino) and 100 healthy individuals (enrolled at the Genetics Unit of IRCCS San Matteo) are subjected to genetic testing using a multigene NGS panel. DNA is collected from white blood cells. The gene prevalence is calculated as the ratio between patients carrying pathogenic variants and all patients of the studied cohort. In addition, San Matteo ancillary study also aims to investigate the prevalence of likely pathogenic and pathogenic variants in genes related to familial hypercholesterolemia in subjects with a diagnosis of hypercholesterolemia. Finally, the ancillary study envisages the development of new monogenic/polygenic scores and the validation of existing scores for the assessment of the risk of developing diabetes, hypertension and hypercholesterolemia not present at baseline.

The sample size of 100 subjects enrolled at San Matteo is based on feasibility. The precision of the prevalence estimates given the sample size of 100 subjects is summarized in the table and calculated as half of the 95% confidence interval for different scenarios. No correction for multiple tests is applied (exploratory study). Assuming we analyse the 100 patients at San Matteo with the patients enrolled at IRCCS Monzino, a sample size of 1,000 patients estimates the confidence intervals as shown in the table.

| Proportion | Binomial exact (95% confidence interval), n=100 | | Binomial exact (95% confidence interval), n=1000 | |
|---|---|---|---|---|
| 0.5 | 0.39832 | 0.60168 | 0.46855 | 0.53145 |
| 0.05 | 0.16432 | 0.11283 | 0.03733 | 0.06539 |
| 0.02 | 0.00243 | 0.07038 | 0.01226 | 0.03072 |
| 0.01 | 0.00025 | 0.05446 | 0.00480 | 0.01813 |

**Ancillary study of IRCCS San Raffaele Roma**

In its ancillary study, the IRCCS San Raffaele Roma (abbreviated as San Raffaele Roma) recruits a cohort of 150 individuals aged ≥ 45 years selected among its employees. These individuals are included in a program of physical activity monitored and combined with nutrition education provided in the workplace, aimed at reducing the incidence of hyperlipidemia, overweight/obesity, and related risks such as the onset of T2DM and hypertension. In addition to the evaluations already planned in the parent study, the study foresees assessing the amount of daily physical activity through an accelerometer app, adherence to the Mediterranean diet by the Mediterranean Diet Scale (MDS) questionnaire[16] and complete blood count. All measurements are performed at 6 and 12 months from baseline, except the assessment of daily physical activity which is also performed at month 3. Comparison of the mean change from baseline between the 2 groups at the different time points is performed.

Assuming a CVD event incidence of 747.6/100,000 population, 125 subjects are needed to ensure 80% power and a maximum 95% confidence interval width of 3%, with an alpha of 0.05. Considering an estimated 20% dropout during the study, we will enroll a sample size of 150 total subjects (thus 75 per group).

**Supplemental Table 3. Name of approving body and approval number/ID of CV-PREVITAL studies**

| | Approval Number | Board Name |
|---|---|---|
| **Parent study** | R1256/20-CCM 1319 | Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino |
| **Ancillary studies of Monzino** | R1579/21-CCM 1677; R1617/22-CCM 1723 | Comitato Etico degli IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino |
| **Ancillary study of Istituto Auxologico Italiano** | 2022_03_08_06 | Comitato Etico dell'IRCCS Istituto Auxologico Italiano |
| **Ancillary study of Humanitas** | 2860 | Comitato Etico Indipendente dell'Istituto Clinico Humanitas |
| **Ancillary study of MultiMedica** | MM: 472.2021 | Comitato Etico IRCCS MultiMedica - Sezione del Comitato Etico Centrale IRCCS Lombardia |
| **Ancillary study of Neuromed** | Session of 28/09/2020 | Comitato Etico dell'Istituto Neurologico Mediterraneo Neuromed |
| **Ancillary study of San Donato** | 197/INT/2021 | Comitato Etico IRCCS Ospedale San Raffaele |
| **Ancillary study of Maugeri** | 2575 CE | Comitato Etico degli Istituti Clinici Scientifici Maugeri |
| **Ancillary study of ISMETT** | IRRB/16/22 | Comitato Etico IRCCS Sicilia Sezione ISMETT IRCCS srl |
| **Ancillary study of San Martino** | 173/2021 | Comitato Etico Regionale della Liguria |
| **Ancillary study of Ca' Granda** | 887_2020 | Comitato Etico Milano Area 2 |
| **Ancillary study of Gemelli** | 3614 | Comitato Etico della Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore |
| **Ancillary studies of San Matteo** | 2022-3.11/91; 2022-3.11/493 | Comitato Etico Pavia |
| **Ancillary study of San Raffaele Roma** | 21/21 | Comitato Etico IRCCS San Raffaele Roma |

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**Online Supplemental file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents**

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3, 4 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Online Supplemental file 2 |
| Protocol version | 3 | Date and version identifier | N/A |
| Funding | 4 | Sources and types of financial, material, and other support | 4, 11 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 2, 11 |
| | 5b | Name and contact information for the trial sponsor | 12 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 11 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 4, Online Supplemental Material |
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4 |

| | | | |
|---|---|---|---|
| | 6b | Explanation for choice of comparators | N/A |
| Objectives | 7 | Specific objectives or hypotheses | 6, 7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5, Online Supplemental Material |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5, 6 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | N/A |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | N/A |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 6-8, Online Supplemental Material |

| | | | |
|---|---|---|---|
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Online Supplemental file 4 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8, Online Supplemental Material |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5, Online Supplemental Material |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6, Online Supplemental Material |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5, 6, Online Supplemental Material |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 6-9 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 6 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 9, Online Supplemental Material |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 8, 9 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 8, 9 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 9 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | N/A |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |

**Ethics and dissemination**

| | | | |
|---|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 10, Online Supplemental Material |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 10 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 10 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 10 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 12 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | N/A |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | N/A |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | N/A |

| | | | |
|---|---|---|---|
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | N/A |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Online Supplemental file 3a and 3b* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | Online Supplemental file 5 |

*Online Supplemental file 3a is the informed consent form (written in Italian language) in use within the parent study. Online Supplemental file 3b is the English version of Online Supplemental file 3a. Each ancillary study has its own informed consent form (available on request).

**Online Supplemental file 2. SPIRIT Item 2b: All items from the World Health Organization Trial Registration Data Set**

| Data category | Information |
|---|---|
| Primary registry and trial identifying number | ClinicalTrials.gov NCT05339841 |
| Date of registration in primary registry | 21 April, 2022 |
| Secondary identifying numbers | R1256/20-CCM 1319; RCR-2019-23669116_001 |
| Source(s) of monetary or material support | Italian Ministry of Health |
| Primary sponsor | Monzino Cardiology Center IRCCS |
| Secondary sponsor(s) | none |
| Contact for public queries | Damiano Baldassarre (damiano.baldassarre@cardiologicomonzino.it);<br>Roberta Baetta (roberta.baetta@cardiologicomonzino.it) |
| Contact for scientific queries | Principal Investigators:<br>Giulio Pompilio, Centro Cardiologico Monzino IRCCS (giulio.pompilio@cardiologicomonzino.it);<br>Gianfranco Parati, Istituto Auxologico Italiano IRCCS (parati@auxologico.it)<br>Scientific contact: studiocvprevital@retecardiologica.it |
| Public title | Italian Digital Primary Cardiovascular Prevention Study (CV-PREVITAL) |
| Scientific title | Digital Strategies in Primary Cardiovascular Prevention in the Italian Population |
| Countries of recruitment | Italy |
| Health condition(s) or problem(s) studied | Subjects in primary cardiovascular prevention |
| Intervention(s) | Intervention group: subjects assigned to a mobile health application (mHealth) app that delivers a personalized digital health support program based on periodic messages with advice, motivational reminders and support to improve lifestyle habits and risk factor control |
| | Control group: subjects assigned to usual care |
| Key inclusion and exclusion criteria | Ages eligible for study: ≥45 years; Sexes eligible for study: both;<br>Accepts healthy volunteers: yes |
| | Inclusion criteria: adult subjects (≥45 years) consenting to participate in the study and using a smartphone |
| | Exclusion criteria: current or previous cardiovascular disease (personal history of myocardial infarction, angina pectoris, arterial revascularization procedures, stroke, transient ischemic attack, peripheral artery disease); Psychiatric disorders; Participation in other clinical trials |
| Study type | Interventional (mobile health application vs usual care) |
| | Allocation: randomized;<br>Intervention model: parallel assignment;<br>Masking: none (Open Label); |

| | |
|---|---|
| | Primary purpose: cardiovascular disease prevention |
| | Phase: not applicable |
| Date of first enrolment | June 10, 2022 |
| Target sample size | 82,800 |
| Recruitment status | Recruiting |
| Primary outcome(s) | • Short term (month 12): change in cardiovascular risk<br>• Long term (year 7): between groups difference in the incidence of vascular events |
| Key secondary outcomes | • Change of a combined endpoint including hypertension, diabetes, hypercholesterolemia [month 12]<br>• Systolic and diastolic blood pressure (mmHg) [month 12]<br>• HDL-C, LDL-C, and triglycerides (mg/dL) [month 12]<br>• HbA1c (%) [month 12]<br>• Body weight (kg) [month 12]<br>• Physical activity (IPAQ questionnaire) [month 12]<br>• Mediterranean diet adherence (PREDIMED questionnaire) [month 12]<br>• Mediterranean diet adherence (Moli-Sani questionnaire) [month 12]<br>• Smoking status [month 12]<br>• Alcohol intake [month 12]<br>• Salt intake (MiniSal questionnaire) [month 12]<br>• Stress (Perceived Stress Scale; PSS) [month 12]<br>• Psychological distress (PHQ 4 questionnaire) [month 12]<br>• Anxiety (PHQ 4 questionnaire) [month 12]<br>• Depression (PHQ 4 questionnaire) [month 12]<br>• Multidimensional Health Locus of Control Scale (MHLCS) - Internality [month 12]<br>• Multidimensional Health Locus of Control Scale (MHLCS) - Powerful Others Externality [month 12]<br>• Multidimensional Health Locus of Control Scale (MHLCS) - Chance Externality [month 12]<br>• General Self Efficacy (GSE Scale) [month 12]<br>• Risk propensity (RPS Scale) [month 12]<br>• Sleep quality (Pittsburgh Sleep Quality Index) [month 12]<br>• Subjects' adherence to data recording [month 12]<br>• Interruptions in the use of the mHealth App [month 12]<br>• Adherence to recommended therapies [month 12]<br>• Cost/effectiveness of intervention [year 7]<br>• House ownership as socioeconomic status indicator [year 7] |

| | |
|---|---|
| | • Type of residence as socioeconomic status indicator [year 7]<br>• Education as socioeconomic status indicator [year 7]<br>• Employment status as socioeconomic status indicator [year 7]<br>• Type of profession as socioeconomic status indicator [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of hospitalization (questionnaire) [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of symptoms (questionnaire) [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of asymptomatic disease (questionnaire) [year 7]<br>• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - history of vaccination (questionnaire) [year 7] |

**Online Supplemental file 3a - Informed consent materials**

Studio CV PREVITAL Versione 2.0 del 31.05.2021

**MODULO DI INFORMAZIONE PER IL PAZIENTE**

# Studio CV PREVITAL

## Strategie di Prevenzione primaria cardiovascolare nella popolazione italiana

### Invito a partecipare allo studio CV PREVITAL

Gentile Signora/e la invitiamo a partecipare alla Ricerca CV PREVITAL.

### Cos'è lo studio CV PREVITAL?

Lo studio CV PREVITAL è una ricerca collaborativa condotta da Medici di Famiglia, che si svolge a livello nazionale con l'obiettivo di migliorare la prevenzione primaria cardiovascolare in Italia.
Lo studio CV PREVITAL è promosso dal Ministero della Salute che riconosce nella prevenzione l'arma più efficace per ridurre l'insorgenza delle malattie cardiovascolari.

### Perché è importante lo studio CV PREVITAL?

Attualmente, la prevenzione rappresenta la strategia più importante di intervento per diminuire l'incidenza di malattie cardiovascolari quali l'infarto del miocardio e l'ictus cerebrale. Identificare precocemente i soggetti a rischio di sviluppare queste malattie, e informare adeguatamente le persone interessate su come adottare stili di vita "sani" si sono dimostrate strategie molto efficaci per contrastare l'insorgenza di ipertensione, di diabete e di ipercolesterolemia che insieme al fumo e all'obesità rappresentano i principali fattori di rischio per l'insorgenza delle malattie cardiovascolari.
In questo contesto le tecnologie digitali stanno dimostrando un grande potenziale nel miglioramento della salute pubblica ed individuale, in quanto possono essere utilizzati come strumenti di supporto al medico per la gestione dei fattori di rischio.
Infatti negli ultimi anni si sta diffondendo sempre di più l'espressione "mobile-health" o "m-health", con cui si indica l'insieme di tecnologie (cellulari e smartphone, tablet, dispositivi digitali) applicate in ambito medico-sanitario, che stanno dimostrando un grande potenziale nel miglioramento della salute pubblica ed individuale.

### Obiettivo dello studio

L'obiettivo dello studio è quello di valutare l'efficacia di un intervento di m-health nella riduzione dei principali fattori di rischio cardiovascolari e nell'insorgenza a lungo termine delle principali malattie cardiovascolari. L'intervento consiste nell'uso di un'applicazione, scaricabile sul proprio smartphone, che invierà dei messaggi educativi e formativi personalizzati, e permetterà il monitoraggio e l'auto-controllo dei principali fattori di rischio cardiovascolari e degli stili di vita.

### In che cosa consiste lo studio

Lo studio coinvolgerà circa 250 Medici di Famiglia, distribuiti in diverse regioni di Italia e in totale verranno inclusi 50.000 soggetti.

Il suo medico verificherà che lei abbia i requisiti per partecipare allo studio e in caso positivo la inviterà ad aderire allo stesso firmando il consenso allegato.

Lo studio CV PREVITAL è uno studio clinico randomizzato non farmacologico, dove i medici partecipanti saranno divisi casualmente in due gruppi:

1. gruppo di controllo
2. gruppo di intervento

I medici del "gruppo di controllo" gestiranno i propri pazienti secondo la normale pratica clinica (usal care), al meglio delle conoscenze attualmente disponibili.

I medici del "gruppo di intervento", in aggiunta a quanto previsto dalla normale pratica clinica, seguiranno i pazienti anche avvalendosi del supporto di una App che i partecipanti potranno scaricare sul proprio smartphone attraverso un link dedicato.

Lo studio clinico randomizzato è il metodo più appropriato, scientificamente riconosciuto, per poter valutare l'efficacia di interventi volti a modificare una condizione clinica. Nel caso del presente studio, l'uso della App per migliorare il controllo dei fattori di rischio cardiovascolare.

**Che cosa comporta l'adesione allo studio CV PREVITAL?**

Se dovesse decidere di partecipare a questo studio, il suo medico Le proporrà una serie di domande volte a valutare lo stato della sua salute cardiovascolare. In particolare sarà invitato a compilare, con l'aiuto di personale infermieristico e/o di tutorial digitali, alcuni questionari riguardanti le abitudini alimentari, l'attività fisica, l'abitudine al fumo e fattori psico-sociali e comportamentali. Le saranno inoltre misurati i livelli di colesterolo totale, LDL, HDL e l'emoglobina glicata mediante una goccia di sangue ottenuta grazie ad un prelievo capillare (piccola puntura sul dito). Infine, saranno effettuate le misurazioni di pressione arteriosa, peso, altezza e circonferenza vita. Il tutto sarà ripetuto dopo 12 mesi.

Il suo medico e il personale infermieristico La seguiranno mettendo in atto tutte le conoscenze disponibili per migliorare il suo profilo di rischio cardiovascolare. Se il suo medico fa parte del gruppo di intervento, Le verrà anche spiegato come utilizzare una specifica App. Questa servirà a raccogliere ulteriori dati nel periodo intercorrente fra l'incontro iniziale e quello a 12 mesi. Durante questo periodo, Le saranno inviati dei promemoria al fine di ricordarle di rispondere a delle semplici domande riguardanti le sue abitudini. Le sue risposte permetteranno sia di personalizzare i messaggi educativi che riceverà per aiutarla a migliorare il suo stile di vita, sia di valutare l'efficacia di questi interventi educazionali. Inoltre, se durante l'incontro basale si fosse riscontrata la presenza di uno o più fattori di rischio cardiovascolari, quali ad esempio ipertensione, diabete o ipercolesterolemia, le sarà chiesto di inserire, ad intervalli regolari, alcuni dati numerici (esempio: pressione arteriosa, emoglobina glicata, ecc.) che saranno utili per valutare l'andamento di questi fattori di rischio nel tempo e l'efficacia delle strategie educazionali messe in atto.

Dopo 7 anni Lei sarà ricontattato dal suo medico per verificare se nell'arco di questo tempo siano comparsi eventi vascolari maggiori (es infarto miocardico e ictus), o nuove diagnosi di angina e di arteriopatie periferiche, e/o se sia stato ospedalizzato per malattie cardiovascolari.

**Quali sono i rischi e i benefici per chi partecipa allo studio?**
Lo studio non La espone ad alcun tipo di rischio in quanto prevede soltanto l'utilizzo di una semplice App e non implica interventi di carattere invasivo. Anche i prelievi di sangue ai quali sarà sottoposto in occasione dell'incontro iniziale e di quello a 12 mesi, essendo effettuati attraverso una puntura sul dito (prelievo capillare) non la esporranno a rischi aggiuntivi. La partecipazione allo studio potrebbe invece comportare dei benefici. Ad esempio, conoscere meglio i propri fattori di rischio ed avere la possibilità di tenerli sotto controllo in modo più efficiente dovrebbe ridurre la velocità di insorgenza o di progressione delle malattie cardiovascolari in generale, e la probabilità di sviluppare eventi clinici acuti (ad es. un infarto) in particolare.

**Il rifiuto a partecipare allo studio compromette in qualche modo il rapporto con il medico?**
Assolutamente no, la partecipazione allo studio è volontaria e Lei è libero di ritirare il consenso in qualsiasi momento senza che Le sia richiesta alcuna motivazione. Il rapporto con il suo medico non sarà in alcun modo compromesso.

**La partecipazione è gratuita o è remunerata?**
La partecipazione allo studio è totalmente gratuita e non è previsto alcun compenso.

**Uso dei dati**
I Suoi dati verranno usati in ottemperanza alla normativa vigente in materia di tutela del trattamento dei dati personali. A tal fine, è prevista una specifica informativa che Le sarà fornita contestualmente alla proposta di adesione allo studio.

**Approvazione dello studio**
Lo studio è stato approvato dal Ministero della Salute, dal Comitato Etico Coordinatore e dai Comitati Etici locali di riferimento per i Medici che partecipano allo studio.

Studio CV PREVITAL
Versione 2.0 del 31.05.2021

# DICHIARAZIONE DI CONSENSO

## Studio CV PREVITAL
## Strategie di Prevenzione primaria cardiovascolare nella popolazione italiana

Ho letto e compreso il modulo informativo per il paziente e il mio medico curante ha risposto a tutte le mie domande relative allo studio.

Ho avuto tempo per decidere se partecipare allo studio e sono consapevole che la mia partecipazione è completamente volontaria.

Sono consapevole che posso ritirarmi dallo studio in qualsiasi momento e senza l'obbligo di motivare la mia decisione.

Do, pertanto, il mio consenso a partecipare allo studio CV PREVITAL

| **Nome/Cognome del paziente** | **Firma** | **Data** |
|---|---|---|
| | | |

| **Nome/Cognome dello sperimentatore responsabile** | **Firma** | **Data** |
|---|---|---|
| | | |

| **Nome/Cognome del testimone** | **Firma** | **Data** |
|---|---|---|
| | | |

# INFORMATIVA PER IL TRATTAMENTO DEI DATI PERSONALI

**Titolo dello studio:**
Strategie di prevenzione primaria cardiovascolare nella popolazione italiana – CV PREVITAL

**Promotore:** IRCCS Centro Cardiologico Monzino

**Categorie di dati oggetto del trattamento**
Lo studio comporta l'acquisizione e l'utilizzo di informazioni considerate "dati personali" (quali: età, sesso, etnia, stato civile, stato socio-economico), incluse informazioni inerenti lo stato di salute, lo stile di vita, la storia familiare, considerate "dati particolari", e come tali sottoposte alla normativa vigente in materia di protezione dei dati personali:

- Regolamento Generale sulla Protezione dei Dati - UE 679/2016
- Codice in Materia di Protezione dei Dati Personali - D.lgs. n° 101/2018
- Regole deontologiche per trattamenti a fini statistici o di ricerca scientifica – 2018
- Provvedimento - 2018, che individua:
  Prescrizioni relative al trattamento dei dati personali effettuato per scopi di ricerca scientifica
  Prescrizioni relative al trattamento dei dati genetici per clinica e ricerca scientifica

**Finalità del trattamento**
I dati sopra descritti saranno trattati per consentire lo svolgimento dello studio CV PREVITAL e di tutte le relative operazioni ed attività connesse

**Base giuridica del trattamento**
Il consenso informato costituisce la base giuridica per il trattamento dei Suoi dati per gli scopi descritti nel modulo informativo. In assenza di consenso firmato non potremo utilizzare i Suoi dati per la conduzione e le analisi dello Studio.
Potrà interrompere la Sua partecipazione in qualsiasi momento e senza fornire alcuna motivazione; in tal caso, i Suoi dati saranno trattati come descritto nel modulo informativo dello Studio. Non saranno raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

**Natura del conferimento dei dati**
La partecipazione alla sperimentazione avviene su base volontaria, pertanto, il conferimento dei dati personali è assolutamente volontario, nel senso che Lei potrà decidere di non conferire i Suoi dati personali e, quindi, di non partecipare allo Studio.

**Modalità di Trattamento dei dati**
Le finalità sopra indicate prevedono lo svolgimento del trattamento dei dati personali mediante strumenti manuali ed informatici con logiche strettamente correlate alle finalità stesse e, comunque, in modo da garantire la sicurezza e la riservatezza dei dati stessi.
I dati raccolti per i fini dello studio CV PREVITAL saranno gestiti in forma codificata.

Il medico che La seguirà nello studio, La identificherà con un codice che non permetterà di risalire direttamente alla Sua identità, se non presso lo studio medico partecipante.
I dati che La riguardano, raccolti nel corso dello studio, ad eccezione del Suo nominativo e il suo telefono, saranno trasmessi al Promotore in qualità di Titolare dei dati e ai Responsabili del trattamento dei dati prima elencati, e dagli stessi registrati, elaborati e conservati. I dati che Lei inserirà tramite la stazione intermodale multifunzione (totem multimediale presente nell'ambulatorio del suo medico) o da remoto (via internet) e i dati che inserirà tramite la App (se il suo medico fa parte del gruppo di intervento), saranno memorizzati in un database cloud e resi disponibili, in forma pseudonimizzata, alla piattaforma informatica della Rete Cardiologica.
Soltanto il medico, il personale responsabile del monitoraggio dello Studio *(Istituto di Ricerche Farmacologiche Mario Negri IRCCS)* e il personale delegato dalle Autorità Competenti per attività di verifica, potranno collegare questo codice al Suo nominativo quando necessario.

**Ambito di comunicazione dei dati**
La Sua partecipazione allo studio CV PREVITAL implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, soltanto il personale incaricato delle attività di monitoraggio, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.
La diffusione dei dati scientifici risultanti dalle analisi dei dati dello studio CV PREVITAL, potrà avvenire solo in forma anonima e per sole finalità scientifiche. In pratica, i risultati delle ricerche scientifiche, potranno essere presentati in forma aggregata nell'ambito di Convegni o pubblicati su riviste specializzate senza mai permettere la precisa identificazione dei pazienti.
Se previsto dal protocollo, i Suoi dati personali potranno essere trasferiti a Centri esterni per le finalità previste dal protocollo, designati dai Titolari quali "Responsabili del trattamento".
Potrà conoscere l'elenco aggiornato dei Responsabili del Trattamento, inviando una comunicazione al Responsabile della protezione dei dati (DPO) del Promotore.

In linea generale, la informiamo che ai sensi della normativa vigente, le informazioni, potranno essere condivise con altri enti e istituti di ricerca, con associazioni e altri organismi pubblici e privati aventi finalità di ricerca.
Nello specifico, lo studio CV PREVITAL è parte integrante di un più vasto progetto sviluppato con il Ministero della Salute, su indicazione del Parlamento per migliorare le strategie di prevenzione primaria cardiovascolare nella popolazione italiana, che coinvolge, Medici di Medicina Generale (MMG), Farmacie, IRCCS della Rete Cardiovascolare, la Società Italiana per la Salute Digitale e la Telemedicina e la Fondazione Romeo e Enrica Invernizzi.
Pertanto le informazioni dello studio CV PREVITAL potranno essere condivise con altri Istituti o Enti che partecipano al più vasto progetto di ricerca, fatte salve le garanzie dei sui diritti in materia di protezione dei dati personali.
Qualora dalle indagini effettuate per fini di ricerca in ambito scientifico conseguano informazioni, anche inattese, in grado di arrecare un beneficio concreto e diretto in termini di terapia o di prevenzione o in funzione di consapevoli scelte riproduttive, tali informazioni potranno essere comunicate a terzi su Sua autorizzazione, tranne eccezioni previste dalla normativa vigente.

**Politica in materia di conservazione dei dati personali**
I dati personali raccolti nell'ambito dello studio CV PREVITAL saranno conservati presso lo studio medico del Suo MMG, il Promotore e le strutture coinvolte nello Studio, per un periodo minimo di 7 anni dopo la conclusione dello Studio o per un periodo più lungo, se necessario, in base ad ulteriori requisiti di legge. Il periodo massimo di conservazione dei dati è di 25 anni dopo la conclusione dello studio.

**Titolare e Responsabile della Protezione dei dati:** Il Promotore che ha commissionato lo studio CV PREVITAL e il suo MMG, in qualità di Titolari del Trattamento, e l'Istituto di Ricerche Farmacologiche Mario Negri IRCCS e il Consorzio Sanità (Co.S.), in qualità di Responsabili del Trattamento, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme di Buona Pratica Clinica (D.L. 211/2003), dal Regolamento UE 2016/679 del Parlamento e del Consiglio Europeo relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati (di seguito GDPR), dal D.lgs. 196/03 integrato dal dall'Autorizzazione generale n.9/2016 al trattamento dei dati personali effettuato a scopi di ricerca scientifica del 15 dicembre 2016 e dalla Delibera del Garante per le "Linee guida per i trattamenti di dati personali nell'ambito delle sperimentazioni cliniche di medicinali" del 24 luglio 2008 e successive modifiche, tratteranno i suoi dati personali, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello Studio e per le finalità di seguito indicate.

La informiamo che i Titolari, ai sensi dell'articolo 37 del GDPR EU 2016/679, hanno proceduto ad individuare e nominare il Responsabile della Protezione dei dati (anche "*Data Protection Officer*" o "DPO":

Dati di contatto DPO del MMG:
*[...]*

Dati di contatto DPO del Promotore:
*[...]*

**Diritti dell'Interessato**

*Diritto di accesso ai dati*
Può chiedere di consultare le informazioni che sono state raccolte su di Lei. Tuttavia, per salvaguardare l'integrità scientifica dello studio, potrebbe non essere possibile accedere ad alcuni dati prima della conclusione dello studio stesso.

*Diritto di rettifica ai dati*
Può richiedere la modifica dei dati che La riguardano, qualora fossero errati o incompleti. Durante la valutazione di tale richiesta, ha il diritto di limitare il trattamento dei dati che La riguardano.

*Diritto di portabilità dei dati*
Può richiedere il trasferimento dei dati che La riguardano a Lei stesso o a qualcun altro in un formato comunemente utilizzato (cartaceo o elettronico).

*Diritto di cancellazione dei dati*
Può ritirare il consenso in qualsiasi momento senza darne motivazione alcuna. Può ritirare il consenso per la partecipazione allo studio e/o ai follow up successivi, anche senza ritirare il consenso per il trattamento dei dati. Qualora cambiasse idea sul trattamento dei Suoi dati, non sarà possibile rimuovere le informazioni personali già elaborate per lo studio prima del Suo ritiro (coperte dal consenso originale). In seguito, al ritiro del consenso al trattamento dei Suoi dati non verrebbero acquisite ulteriori informazioni che La riguardano.

*Diritto di reclamo*
Può presentare un reclamo presso l'autorità incaricata della protezione dei dati:
Garante della privacy, E-mail: garante@garanteprivacy.it Sito web: http://www.garanteprivacy.it

**In merito all'esercizio di tali diritti, potrà rivolgersi direttamente al suo medico di medicina generale o, per il suo tramite, al Responsabile della protezione dei dati (DPO) del Promotore.**

Definizioni

- Dato personale: qualsiasi informazione riguardante una persona fisica identificata o identificabile («interessato»); si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo online o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale.

- Dati particolari: dati personali che rivelino l'origine razziale o etnica, le opinioni politiche, le convinzioni religiose o filosofiche, o l'appartenenza sindacale; i dati genetici, i dati biometrici intesi a identificare in modo univoco una persona fisica, i dati relativi alla salute o alla vita sessuale o all'orientamento sessuale della persona.

- Dati relativi alla salute: i dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute; quali ad esempio i dati relativi ad attività di ricovero, visite specialistiche ambulatoriali, consumo di farmaci e prestazioni di tipo socio-sanitario

**Consenso al trattamento dei dati personali**
ai sensi del GDPR UE 2016/679

Preso atto dell'informativa di cui all'art. 13 del GDPR UE 2016/679, il sottoscritto_____,
nato a_____, il_____,
in qualità di interessato

☐ dà il proprio consenso ☐ nega il proprio consenso
al trattamento dei dati per finalità relative allo studio clinico "Strategie di prevenzione primaria cardiovascolare nella popolazione italiana – CV PREVITAL"

☐ dà il proprio consenso ☐ nega il proprio consenso
affinché i risultati delle analisi e di eventuali scoperte inattese che emergano durante le attività di sperimentazione siano comunicate a:

☐ me medesimo

☐ familiare (Cognome e nome _____)

☐ convivente /coniuge (Cognome e nome _____)

☐ medico di famiglia (Cognome e nome _____)

| **Nome/Cognome del paziente** | **Firma** | **Data** |
|---|---|---|
| | | |

| **Nome/Cognome del Medico di Medicina Generale responsabile** | **Firma** | **Data** |
|---|---|---|
| | | |

**Online Supplemental file 4. SPIRIT Item 13: Participant timeline**

| TIMEPOINT | T0 baseline | T1 month 12 | T2 year 7 |
|---|---|---|---|
| Eligibility screen<br>Informed consent<br>Allocation | √ | | |
| Administration of self-report questionnaires covering the following areas:<br>1. family and personal history of diseases (cardio- and cerebrovascular disease; metabolic disease)<br>2. ethnicity, socio-economic status and marital status<br>3. smoking habits<br>4. alcohol consumption (PREDIMED questionnaire[8])<br>5. adherence to Mediterranean diet (PREDIMED questionnaire[8] and Moli-Sani questionnaire–an adaptation of the MEDAS questionnaire[9])<br>6. salt consumption (MiniSal questionnaire[10])<br>7. physical activity (IPAQ–International Physical Activity Questionnaire[11])<br>8. personal history of sleep disorder and sleep quality (PSQI–Pittsburgh Sleep Quality Index[12])<br>9. psycho-behavioral factors:<br>9.1 perceived stress (PSS–Perceived Stress Scale)<br>9.2 anxiety and depression (PHQ 4–Patient Health Questionnaire 4)<br>9.3 self-efficacy (GSE–General Self-Efficacy Scale)<br>9.4 locus of control (Multidimensional Health Locus of Control Scale)<br>9.5 risk propensity (RPS–Risk Propensity Scale)<br>10. personal history of COVID-19 disease | √ | √ | |
| Measurement of systolic and diastolic blood pressure | √ | √ | |
| Measurement of weight, height, waist circumference | √ | √ | |
| Assessment of total cholesterol, HDL-C, triglycerides, calculated LDL-C, glycated hemoglobin | √ | √ | |
| Cardiovascular risk score calculation | √ | √ | |
| App delivery (intervention group only) | √ | | |
| Collection of data on occurrence of cardiovascular events | | √ | √ |

**Online Supplemental file 5: Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies**

In the CV-PREVITAL Study, each IRCCS recruits a number of participants to whom, in addition to the questionnaires, samples of biological material (blood, saliva or feces) are taken. The biological material collected is stored in the cryospaces dedicated by each IRCCS to the Widespread Biobank of the Italian Cardiology Network. In order to harmonize the collection and storage of samples, Standard Operating Procedures (SOPs) has been created for the Widespread Biobank and shared among the participating centers for the management of the sample from the patient recruitment and signing phase of the informed consent, to the collection and storage of biological samples and possible redistribution of the aliquots. The harmonization of sample collection also includes the use of the same container for sample collection, the same cryovials for storage, and the same codes for pseudonymization of samples. All aliquots are stored in cryotubes with QR Code to facilitate the distribution and sharing of samples among the recruiting centers of the CV-PREVITAL study or with other national or international institutes.

**SOPs for blood derivates**

All Cell Pellet (ACP) and plasma EDTA

In order to optimize the blood collection, ACP and plasma EDTA are obtained from the same collection tube. The venous sampling is carried out using K3EDTA tubes. Blood is processed within 2 hours from collection. Tubes are centrifuged without brake at 3000rpm at RT (18–22 °C) for 15 minutes to separate the plasma from the cells. Using a micropipette, plasma is divided into at least 3x300 microliter aliquots in cryotubes and then transferred to -80 °C for storage as soon as possible. After removing the residual plasma, the tube is inverted two or three times to homogenize the sample. ACP is divided in 3x300-microliter aliquots in cryotubes and transferred to a -80 °C for storage as soon as possible.

Serum

The venous sampling is carried out using tubes with coagulation activator and gel separator. Blood is processed within 2 hours from collection and allowed to clot for a minimum of 15-20 minutes at RT (18-22°C) or until the clot is completely formed. Tubes are centrifuged at 3000rpm at RT (18–22 °C) for 15 minutes to separate serum from the cells. Using a micropipette, serum is collected without touching the separator gel with the pipette tip and divided into at least 3x300-microliter aliquots in cryotubes. Aliquots are transfer red to a -80 °C freezer for storage as soon as possible.

Whole blood for total RNA extraction

The venous sampling is carried out using Tempus Blood RNA Tube (Applied Biosystems). Immediately after filling the Tempus tube, the blood is stabilized by vigorously shaking or vertexing the tube for 10-12 seconds. Samples are maintained at +4 °C for a maximum of 24 hours and then stored at -80 °C.

**Saliva Samples**

Saliva is collected using Salivette Cortisol tube (Sardstedt) and the collection is carried out by the subject participant to the project according to the manufacturer's instructions.

Harvesting must be done in the morning and it is recommended:

- for at least 2 hours before harvesting:
  - not to eat
  - not to drink
  - not to smoke
  - not to take chewing gum

- to brush teeth at least 2 hours before the start of the harvest
- to avoid the use of cosmetic products for lips.

Samples are maintained at +4 °C and centrifuged within 1 hour from collection without brake at 3000rpm at RT for 15 minutes. Using a micropipette, the sample is divided into at least 3x300 microliter aliquots in cryotubes and stored at -80 °C within 2 hours from collection.

**Stool Samples**

Stool sample is collected using DANASTOOL Sample Collection MICROBIOME Kit (DANAGEN) and the collection was carried out by the subject participant to the project according to the manufacturer's instructions.