ERC Advanced Grant
Research Plan
(version 7, January 1, 2024)

A non-inferiority randomized trial testing an advice of moderate drinking pattern versus advice on abstention on major disease and mortality

UNATI

- Name of the Principal Investigator (PI): Miguel A. Martínez-González
- Name of the PI's host institution for the project: University of Navarra

Project number: **101097681**
Project name: **A non-inferiority randomized trial testing an advice of moderate drinking pattern versus advice on abstention on major disease and mortality**
Project acronym: **UNATI (University of Navarra Alumni Trialist Initiative)**
Call: ERC-2022-ADG
Topic: ERC-2022-ADG
Type of action: **HORIZON ERC Grants**
Granting authority: **European Research Council Executive Agency**
Grant managed through EU Funding & Tenders Portal: **Yes (eGrants)**
Project starting date: fixed date: **1 December 2023**
Project end date: **30 November 2028**
Project duration: 60 months
Consortium agreement: No

Web page: **https://medpreventiva.es/AhsYnr**
Inscription for Coordinators and *trialists*: **https://medpreventiva.es/aqjNtR**

ABSTRACT

Policymakers and clinicians are currently perplexed on how to reduce alcohol harms in drinkers, because of **contradictory guidelines**: **abstention** is proposed as the healthiest option by many health advocates, stating that "there is no safe level of alcohol intake"; but most nonrandomized studies found *lower* all-cause mortality and other beneficial outcomes in **moderate** drinkers than in abstainers among subjects >50 years. However, potential biases may compromise these latter studies, particularly when effects are null or moderate. A **large pragmatic randomized controlled trial** (RCT) of realistic advice aimed to change behaviour **addressing clinical endpoints is long overdue**. It will provide **first-level evidence** to confront the harms of one of the most widely used substances by humankind.

The **European Research Council** has funded, through an Advanced Research Grant (2023-2028) to the University of Navarra (Spain), as Host Institution, a **4-year non-inferiority RCT with >10,000 drinkers (men 50-70 years or women 55-75 years consuming >=3 but <40 drinks/wk)**. The name of the trial is UNATI (University of Navarra Alumni Trialist Initiative).

At least ten thousand drinkers will be randomized in a 1:1 ratio to repeatedly (4 contacts/year) receive during 4 years two different advices:

1) **abstention**;

2) **moderation** (**<=7 drinks/wk in women and <=14 drinks/wk in men)**, avoidance of binge drinking, with preference for red wine consumed always with meals, and consumption spread out throughout the week, following the traditional Mediterranean Alcohol Drinking Pattern (MADP). Moderate consumption is hypothesized to be non-inferior. No initiation or increment in alcohol intake will be promoted.

The primary endpoint will be a **global index of all-cause mortality, cardiovascular events, any invasive cancer, liver cirrhosis,** type 2 **diabetes, depression, dementia, injury** requiring hospital admission or **tuberculosis** or other **infections** requiring hospitalization. As a secondary analysis, the most severe outcomes (mortality, invasive cancer, stroke, myocardial infarction) will be considered independently with sufficient priority over less severe outcomes, using *ad hoc* methods.

The UNATI trial will provide for the first time an evidence-based answer to a question of the utmost interest in clinical medicine, given the high prevalence of moderate alcohol intake, and the current situation of equipoise with opposing views in the scientific community on the most sensible advice for moderate drinkers. The starting date for the project is **December 1, 2023**. The randomization of participants will start on **June 2024**.

Web page: **https://medpreventiva.es/AhsYnr**
Inscription for Coordinators and *trialists*: **https://medpreventiva.es/aqjNtR**

SPECIFIC AIMS

Primary aim:

To test in current drinkers (men 50-70 years or women 55-75 years consuming >=3 but ≤40 drinks/wk) the **non-inferiority** of a 4-year harm-reduction intervention versus abstention. One intervention will include **quarterly contacts** promoting **moderation** by upgrading adherence to **a Mediterranean alcohol drinking pattern (MADP).** The MADP consists of moderate alcohol intake, allowing only for **<=7** drinks/wk (**females**) and **<=14** drinks/wk (**males**), avoidance of binge drinking, with preferential consumption of red wine, always consumed with meals, and spread out throughout the week. The **comparator** will be a **4-year intervention** program in these drinkers promoting **abstention** (also with **quarterly contacts).**

The **primary end-point** will be a **global index (primary endpoint)** including all-cause mortality, and the incidence of cardiovascular events (myocardial infarction, stroke, heart failure, atrial fibrillation), all localizations of invasive cancer (except non-melanoma skin cancer), liver cirrhosis, depression, dementia, type 2 diabetes, injury requiring hospital admission, or infections requiring hospitalization.

Secondary aims:

a) To establish a **network of >400** medical doctors (**trialists**) all around Spain, mostly former students from the University of Navarra ("**University of Navarra Alumni Trialist Initiative", UNATI**), to recruit participants for randomized trials testing prevention interventions of diet and lifestyles.

b) To test the **non-inferiority** of a harm-reduction intervention promoting **moderation** (according to the **MADP)** versus another intervention promoting abstention from alcohol on **anthropometric measurements**, liver enzymes, **blood pressure**, blood **lipid/glucose** biomarkers, **depression symptoms**, prevalence of excessive/problematic alcohol intake (**AUDIT questionnaire**), **cognitive** function and **quality of life**.

c) To test the **non-inferiority** of moderation (MADP) vs abstention on **secondary** endpoints (each considered individually): **all-cause mortality, type-2 diabetes, cardiovascular events, severe injury and depression.**

d) To repeatedly assess **the incidence of all locations of invasive cancer** (excluding non-melanoma skin cancer) in both arms of the trial **after 10-year follow-up**.

e) To test the effect of alcohol intake on the primary and secondary endpoints **separately in women and men,** assessing **effect modification by sex**, to ascertain whether differential preventive approaches for alcohol-related harms may be needed for men and women (gender perspective).

From a patient-centered perspective:

a) To compare actually **attained compliance (average alcohol intake)** for the abstention arm and the moderation arm of the trial after up to 4 years of intervention using self-reports in the full cohort and biomarkers in random subsamples.

b) To test the effect of the observed actual compliance with a 4-year period of **abstention** (or substantial reduction, i.e., >60%, in average total alcohol consumption from baseline) versus a 4-year period of drinking in moderation, as measured by **adherence to the operational definition of the MADP**[14], on the primary outcome (**per-protocol analyses**).

c) To describe, from a **personalized medicine** point of view, the causes and **predictors of lack of compliance** with each of the intended interventions (abstention or moderation) among drinkers willing to receive counseling, who were randomized, separately for each arm, and separately for men and women (gender perspective).

A) STATE-OF-THE-ART

Harmful **alcohol** consumption represents an important global health problem and a **priority for public health**, included in the Sustainable Development Goals (target 3.5)[1], and ranked as the seventh global leading risk factor for death and disability[2]. More than 2 million deaths yearly are globally attributed to alcohol, together with social harms that also extend beyond the drinker, including intimate-partner violence (with a heavy burden on women), exacerbation of poverty, traffic injuries and other effects[3].

The burden of disease associated with alcohol consumption is usually assumed to result from an imbalance between beneficial and harmful effects. Nonrandomized, conventional epidemiologic studies have attributed some benefits to moderate alcohol consumption on **ischemic heart disease**, **diabetes** or **ischemic stroke** usually observed in subjects older than 50 years, whereas they found detrimental effects on injury, suicide, several types of **cancer**, **liver** disease, **mental disorders**, and **communicable** diseases[2]. Considering the net balance, simple messages have been issued such as **the safe level of alcohol intake should be zero**[3,4-8] , "**no level of alcohol consumption improves health**"[4] or **"less is better"**[9].

However, the specific **drinking pattern** might act as an **effect modifier**, including heavy episodic intake (binge drinking), beverage preference, consumption with or without meals and distribution throughout the week[10-20]. Large cohorts concluded that **'healthy' patterns of moderate drinking reduce CVD**[10,11,21-30], **diabetes**[31] and also all-cause **mortality**[32-38], particularly in subjects 50 to 75 years[26,29,39,40].

Notwithstanding, many cohorts included highly educated subjects and some evidence suggested that an **upper educational** attainment may **modify** the effect of alcohol with lower mortality rates associated with moderate consumption only among subjects with higher educational levels[41]. Moreover, the repeatedly reported J-shaped association between alcohol intake and all-cause mortality in observational studies **is dependent on the distribution of causes of death and levels of alcohol intake in cohort participants**, with few of them drinking high amounts or indulging in binge drinking[8]. This fact may compromise the strength of their potential **causal** inferences[42-45], particularly given the fact that a more careful degree of **adjustment** for **potential confounding** was shown to attenuate or even eliminate the apparent protection against all-cause mortality associated with small or moderate intakes[46]. However, lack of sufficient control for smoking (because of suboptimal granularity in smoking measurement) in nonrandomized studies may apparently attribute to alcohol some of the well-known adverse health effects of active or passive smoking, given that usually higher levels of exposure to cigarette smoking are found in drinkers[10-14,22,23].

In addition, **Mendelian Randomization (MR) analyses challenged that moderate alcohol consumption may reduce CVD or total mortality**[47-49]. Particularly, for ischemic stroke and cardiovascular risk factors, MR studies showed a direct linear adverse effect of any alcohol intake, in contrast with conventional prospective cohort studies which showed a J-shaped dose-response association[48]. Nevertheless, there is controversy on the assumptions of MR methods[50-52]. Specifically, a systematic review of MR studies on alcohol and CVD concluded that **potential conclusions from these studies were precluded** because of the **heterogeneity in methodological quality** of the included MR studies[49]. Limitations of the MR methods include uncontrolled confounding, pleiotropy of the genetic variants, adaptation, weak instrument bias, and failure of replication[51].

The Global Burden of Disease (GDB) studies[2-4,53,54] were also repeatedly invoked, particularly since 2018, to support that **total abstention** is the healthiest alcohol dose[3,4]. Despite their utmost importance, these studies assume that true causal measures of effect are known for all relevant diseases and in all continents and countries, also in the homeless, the less well-off strata and other underserved sectors of the population. They also assume that all relevant **effect modifiers** have been identified and that accurate **prevalence** estimates of alcohol consumption and related diseases are available for all countries. Their estimates are **highly sensitive to the selection and precision of their inputs**, which are not always explicitly disclosed. Importantly, they **did not consider** the effect of the **drinking pattern**. Even more important was the fact that strong categorical statements claiming zero intake as the universal healthiest alcohol consumption were mainly supported by one report published in 2018 by the Global Burden of Disease Study Group (GBD-2016)[2]. However, in 2022 the same Study Group published a new report[55] (GBD-2020), that, in some way, contradicted the conclusions of their previous report. In 2022, the GBD-2020 concluded that there was "strong evidence to support recommendations on alcohol consumption varying by age and location" and that "**small amounts of alcohol consumption are associated with improved health outcomes** in populations that predominantly face a high burden of cardiovascular diseases, particularly older adults in

many world regions"[55]. A potential protection for light to moderate drinking is likely to be present in older age groups and geographic locations where the burden of cardiovascular disease is higher[55].

In any case the **drinking pattern** -not considered by the MR or GBD studies– is likely to exert an important role as an **effect modifie**r[11-15,17,19,20-21,56-58]. This fact also highlights the importance of conducting interventions on the drinking **pattern**. Effect modification by the drinking pattern may even be present for the well-established relationship of alcohol with liver **cirrhosis**[67].

Specifically, **wine consumption**, particularly in Mediterranean countries, has been postulated as a key feature of the Mediterranean diet with strong cardio-protective properties[11,12,18-21,30], due to the abundance of phenolic compounds (particularly in red wine) with postulated substantial antioxidant and anti-inflammatory beneficial effects[20,68-71].

In fact, a traditional **Mediterranean alcohol drinking pattern** (MADP), i.e. a moderate consumption of preferably red wine during meals, spread out throughout the week, and avoidance of binge-drinking, originally proposed by our group, was found to be associated with **lower all-cause mortality** as compared to **abstention** or to the departure from this MADP within constant levels of alcohol intake in the SUN cohort [12,14,17,21]. Our findings were subsequently **replicated** in large prospective assessments conducted in drinkers within the UK Biobank[15,19] and in Italian cohorts[11]. However, issues related to the nonrandomized design of these studies remain a reason for concern and hesitation on these results.

Methodological problems in nonrandomized studies

The **"sick quitter" effect** and the **"healthy user" effect** (or the "sick nonstarter" bias[72]) are well-known methodological concerns of observational, nonrandomized studies on alcohol. They are explained because the group of non-drinkers may include former drinkers who quitted due to illness or because healthier subjects are more likely to self-select themselves to drink moderately. Whereas those who never initiated alcohol intake might be "sick nonstarters". This may confound the association between moderate alcohol intake and clinical outcomes and might provide a likely non-causal explanation on why, in some nonrandomized studies, abstainers showed a higher risk of chronic disease or all-cause mortality than moderate consumers of alcohol[73].

In addition, **residual confounding** by socioeconomic status, social integration, diet, lifestyles, health consciousness, and self-control cannot be ruled out in nonrandomized studies. A higher level of responsibility and better abilities for self-discipline, including the capability to dominate and overcome primary impulses and appetencies, are likely to be more prevalent in subjects who maintain a lifetime habit of light-to-moderate drinking without trespassing dangerous thresholds. Their drinking characteristics can merely reflect levels of general moderation, character, self-control and virtue, usually associated with better health outcomes. These associations may induce residual confounding in nonrandomized studies[74-75]. In fact, in some meta-analyses, **careful adjustment for potential confounders** and other biases **attenuated the reduction in mortality** observed among moderate consumers[42,45,46,73-75]. However, these speculations on nonrandomized studies are difficult to test. In fact, not all data support the "sick-quitter"/"healthy user" biases[76].

On a wider perspective, in any case, the addictive properties of alcohol deserve special consideration because of the well-known threats that addictions represent for public health.

Diverging recommendations

In this complex situation, there is a continuous unsolved controversy about the best and most practical **and realistic** advice for drinkers aged 50-75 years old. **Two completely opposite points of view are defended, but they have never been tested face-to-face** in a sufficiently large and long-term randomized trial[74]**.**

On one hand, complete **abstention** is proposed as the healthiest option, affirming that "**there is no safe level of alcohol intake**" for all sectors of the population regardless of their age, health conditions, usual drinking patterns and initial consumption levels. On the other hand, a **harm reduction strategy** for adults aged 50 to 75 years can be defended, especially when they exhibit some cardiovascular risk factor, or any disease or condition associated with a higher risk of ischemic CVD, as the last GDB study (GDB2020) established in its 2022 report[55]. This is also a rationale for **recommending** to drinkers **"moderate" alcohol intake** (≤7 drinks/wk in females and ≤14 in males) and avoidance of binge drinking, as supported during decades by wide sectors of the public health community, including the US Dietary Guidelines for Americans.

This open controversy represents a cause of perplexity for most doctors in their clinical practice and it demands for an evidence-based response. But it also provides the needed balance between two alternatives (i.e., *equipoise*) needed to conduct a randomized trial according to ethical principles.

Interestingly, in large US cohorts, intakes of 5-15 g/d for women and 5-30 g/d for men represented one of the 5 elements of a lifestyle score robustly associated with longer life expectancy[37].

Therefore, **both opposite types of advice** are apparently supported by nonrandomized cohorts, modeling studies and meta-analyses. This paradoxical situation is usually addressed only with plausible assumptions and speculations, but not with the needed sound evidence.

Clinicians need sound **evidence-based answers** to clarify this controversy because they need to know what advice they should give to moderate drinkers older than 45-50 years. Before opting for any of the two alternatives of advice, the most sensible approach to overcome inconsistencies and inherent limitations derived from measurement errors, selection biases, reverse causation, residual confounding, and misclassification would be to conduct a **large RCT comparing face-to-face two different and apparently opposed types of advice on alcohol given to drinkers 50-75 years old using hard clinical events as endpoints**. This task will require **interdisciplinary work** and can contribute enormously to the **advancement of science** to address the relevant and long-pending issue of what is the ideal option for given advice on alcohol intake among adults 50-75 years.

This **RCT is long overdue** and has largely been warranted for decades. Given the potential biases inherent to nonrandomized studies[77-79], they may **not be valid** when the expected **effects are likely to be actually null or only moderate,** with relative risks less than twofold[79]. This is most probably the case for the overall effects of light to moderate alcohol intake.

In the **era of evidence based-medicine** and given the abundance of alcohol intake by the general adult population, **it is surprising that no large, long-term, RCT has ever been conducted to appropriately test the effects of advice to drinkers on alcohol.** A previous attempt for conducting a trial on alcohol, the MACH15 study, although nicely-designed and thoroughly planned, was terminated by the NIH under suspicion of conflicting interests and the funding was withdrawn. That unprecedented study demonstrated the feasibility and timeliness of a trial addressing interventions on alcohol intake[80,81]. However, the MACH15 trial was aimed to evaluate the potential risks and benefits of drinking a dose of 11–15 g daily in participants who had consumed at least one drink of alcohol during the past five years, and excluded drinkers of >7 drinks/wk in the past six months. A different practical question for clinicians is the pragmatic type of advice that should be given to moderate **drinkers** with a **wider range (3 to 40 drinks/wk)** of usual alcohol intake and to specifically address the **modification of the drinking pattern**, which is the most relevant question to be answered by the current UNATI project on the basis of a non-inferiority design of the trial.

Unless such a large RCT is conducted, discussions on alcohol issues based upon mere assumptions and speculations on nonrandomized studies seem useless. A clear and definitive answer based on **first-level evidence is of utmost need**. An RCT should assess the effects of recommending **moderation versus abstention** on a **holistic and comprehensive global index outcome**, including cardiovascular disease, invasive cancer, other chronic diseases, severe injuries, major infectious diseases, and all-cause mortality, as previously claimed[80]. Although it may appear heterogeneous, such a **global index endpoint** is needed because alcohol is related to many (>200) individual diseases[4]. The balance between potential benefits and harms needs to be adequately considered if a large RCT is going to be conducted. Unless a large RCT is completed, starting from an *agnostic* perspective and *free of competing interests*, **the needed first-level scientific evidence will remain elusive and futile debates will continue for decades to come**.

The **longest** to date trial of alcohol was the CArdiovaSCulAr Diabetes & Ethanol (CASCADE) trial, that **lasted 2 years** and included **224 participants** with well-controlled type 2 diabetes[82]. All participants were **initially alcohol abstainers**, and they were randomly assigned 1:1:1 to consume 150 mL of mineral water, white wine, or red wine with dinner. Subjects **randomized to initiate red wine increased their HDL-C and Apo A1** and reduced their number of components of the metabolic syndrome as compared to the mineral water group. Within genetically-defined subgroups, beneficial effects on glucose metabolism and blood pressure were also observed for wine[83].

In Italy, another RCT conducted in 131 patients with myocardial infarction and diabetes randomized to Mediterranean-type diet with or without the addition of 4 daily ounces of red wine in a 1:1 ratio, reported for **red wine higher levels of HDL, lower levels of oxidation markers, reductions in several inflammatory biomarkers, lower fasting insulin levels and improved left ventricular function** after 1 year[84].

In 2020, a 6-month RCT with 140 drinkers in six hospitals in Australia concluded that **abstinence** from alcohol **reduced atrial fibrillation** (AF) recurrences among drinkers with previous AF, who were in

sinus rhythm at baseline[85]. The 70 participants in the abstention group successfully reduced their alcohol intake from a mean (±SD) of 16.8±7.7 standard drinks per week to 2.1±3.7 standard drinks per week (87.5% relative reduction), with **complete abstinence achieved by 61%** of patients in that group. AF recurred in 37 of 70 patients (53%) in the abstinence group versus 51 of 70 patients (73%) in the control group. This was **the first RCT of an intervention on alcohol with a clinical endpoint**. Surprisingly, except for these 140 drinkers, to date **there is no other RCT** in a free-living population evaluating the risk of **any other major clinical hard end-point** for two alternative types of advice on alcohol.

A daily glass of wine was one of the recommended 14 goals to be attained in the Mediterranean diet intervention conducted in the successful PREDIMED randomized trial[86]. This is a sound ethical basis, under the **equipoise principle,** for randomizing one arm of the UNATI trial to receive advice on **moderate intake of red wine with meals following the MADP**[11,12], as an alternative to abstention. It is widely admitted that harm reduction strategies can be ethically applied in the context of addictions. Given the **addictive nature of alcohol**, and the inherent practical difficulties to achieve and maintain abstention in drinkers, a **harm-reduction approach** (namely, the MADP) can be ethically appropriate for drinkers insofar it is supported by scientific evidence.

A creative technique to overcome resistance of drinkers to the possibility of being randomized to long-term abstention could be that trialists (medical doctors) should start the invitation by explaining to their patients aged 50-75 years (who usually will present some chronic disease or risk factor) that, according to the most recent recommendations, given their conditions, clinical situation and risk factors, they should receive an absolute advice encouraging total abstention from alcohol. However, patients now are **fortunate as to be able to enter an RCT with 50% chances to be allocated to a seemingly easier harm-reduction alternative (the MADP)**. In addition, drinkers found to have alterations in blood parameters, even if they are only minor, those with a recent chronic disease (e.g., hypertension, diabetes, cardiovascular disease), those admitted to a hospital because of an injury or infection, or those with a past history of pancreatitis, traffic injuries, gastroesophageal reflux, gallstones or other conditions present **an excellent 'teachable moment' for alcohol reduction interventions in their clinical visits**, as it is known to happen with smoking cessation interventions[87].

Rationale

Among current drinkers who consume ≥3 but ≤40 drinks/wk, a behavior change educational program will be conducted. In one randomized arm they will receive advice aimed to attain the goal of total abstinence of alcohol. **The intervention in the abstention arm will repeatedly (4 contacts/year during 4 years) emphasize complete abstention.** The intervention in the other arm with the same frequency and number of contacts will be an advice directed to **improve adherence to the MADP**[11,12,74]. This second intervention will have the following goals:

1) **moderate** consumption (≤7 drinks/wk for women; ≤14/wk for men) of **red wine** (a drink=150 ml),
2) always during **meals**,
3) spread out **throughout the whole week**, and
4) **avoidance of binge-drinking episodes**.

This moderate intervention might be more **pragmatic** and can be as effective (or at least non-inferior) as the abstention advice to avoid the harms and risks of excessive drinking, and it might result (or not) in similar (or at least non-inferior) reductions in alcohol-related harms than an advice promoting abstention (message of zero alcohol). **In any case, no participant will be invited to start or increase his/her alcohol intake. No advice will ever be given to increase alcohol consumption.**

The rationale to use a global index clinical endpoint as the primary outcome is supported by the idea of capturing the **global health impact** of two alternative approaches to provide recommendations on alcohol drinking in the frame of a **non-inferiority pragmatic** trial[88,89], since we will be evaluating the combined multifactorial effects of a single exposure. The benefits or harms induced by alcohol intake on the risk only of a single disease may be irrelevant when viewed in a full clinical context. There is a need to consider all outcomes together in order to capture **the balance of risks and benefits** using a **global index** summarizing the balance of risks and benefits, as it was done in other large randomized field trials[90,91].

B) METHODOLOGY

UNATI is designed as a network of >400 practicing **medical doctors** (**'trialists'**), who will serve as recruiters and investigators for this trial. The acronym for the project, **"University of Navarra Alumni Trialists Initiative" (UNATI)** will emphasize and rely on trialists' sense of belonging to their *alma mater* and their connection with their former classmates, mentors and professors. All trialists recruiting for UNATI trial will work **in Spain**. Their motivation, commitment and bond to their University, are important features, as it has been shown with other alumni in the development and successful continuation of the "Seguimiento Universidad de Navarra" (SUN) cohort[40].

DESIGN

Randomized controlled pragmatic **non-inferiority** trial with two intervention arms. Potential participants will be invited to be randomized to receive advice either towards abstention or moderation. In each of these 2 groups they will receive intensive intervention **by specialized coaches** (psychologists, dietitians, and other health professionals, **not by the trialists**) to promote the respective behavior change in their drinking habits. Free gifts (different according to the arm of the trial, see below) will be given to participants to reinforce their behavior changes.

PARTICIPANTS

Inclusion criteria: Drinkers of any alcoholic beverage initially consuming ≥**3 but ≤40 drinks/wk** (<3 drinks/wk was considered as almost abstainer and not included) aged 50-70 years (males) or 55-75 (females), not institutionalized, with **projected life expectancy >5** years (according to the judgment of their attending physicians) and willing to receive advice during up to 4 years on how to improve their alcohol intake, making it healthier.

- Candidates with prevalent cardiovascular disease, diabetes, cancer, or a history of depression are eligible.
- On the contrary, severe psychiatric conditions, a medical diagnosis of liver cirrhosis, cognitive impairment/dementia, or a previous history (in the last 10 years) of liver cancer, or breast cancer are exclusion criteria.

No participant will be invited to initiate or increase his/her alcohol consumption.

For practical reasons, married couples will be randomized together (as a cluster of 2 participants both assigned to the same arm of the trial), if both spouses are willing to participate. The clustering effect will be appropriately addressed in the statistical analyses.

Participants must have a smartphone and a computer (or tablet) with internet connection at home. They must be internet literate and very familiar with the required technologies. According to our data from a 2014 assessment in the Spanish PREDIMED-Plus trial (with 23 recruitment centers all over Spain) and with participants who were slightly older (55-75 years, 49% women, 48% with only primary studies), 96% of them owned a smartphone and 70% used a computer, as assessed by an *ad hoc* questionnaire (unpublished results). A particularly **innovative** feature of this trial will be **the massive use of remote on-line technologies**. We have acquired ample experience after the success of this remote methodology in the PREDIMAR trial[92] also applied in the PREDIMED-Plus trial during the pandemic lockdown period[93], and in both cases the behavior modification intervention changed the complete dietary pattern. Patients with previous cancer/CVD or other conditions (except liver cancer or recent breast cancer) will be eligible as long as they are stable and their clinical situation allows them to drink within the intended limits of the moderation arm, according to the judgment of their attending physicians.

Exclusion criteria:

1)-Drinkers of less than 30 g of pure alcohol/wk or more than 400 g of pure alcohol/wk.
2)-Illiteracy, inability/unwillingness to give written informed consent or communicate with study staff, or inadequate abilities for the use of on-line technologies (either smart phones, tablets or computers).
3)-Participants with any severe psychiatric condition* or with a diagnosis of cognitive impairment or dementia.

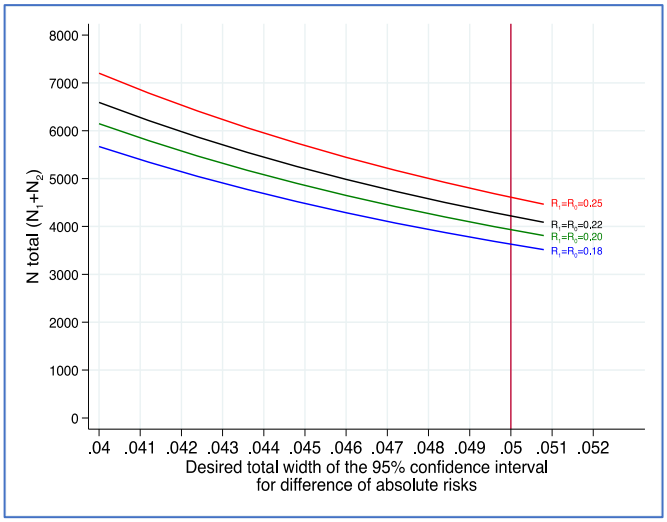
* Despite the fact that the expectation in both arms of the UNATI trial is a **reduction** in average alcohol intake, as shown in the pilot study (see below), there are 2 important reasons for excluding some psychiatric patients: 1) Those patients whose severe condition or

4)-Participants with liver cirrhosis or prior liver cancer.
5)-Patients with a recent diagnosis of breast cancer (diagnosed in the last 10 years).
6)-Patients under habitual use of high-dose medications that completely preclude any use of alcohol. Most of these patients will be already excluded by the first or third exclusion criteria. Exceptional cases will be evaluated individually[#]. In any case, these enrollment criteria regarding the use of medication can be applied with **flexibility** according to the clinical judgment of the attending physician, given that the expectation is always a ***reduction*** in average alcohol intake in ***both*** arms of the trial.

ESTIMATION OF SAMPLE SIZE

The primary end-point will include the ***first*** occurrence of any of the following medically diagnosed diseases, as adjudicated by the Clinical End-Point independent Committee: all-cause mortality, cardiovascular events (myocardial infarction, stroke, heart failure or atrial fibrillation), all invasive cancer of any location (except non-melanoma skin cancer), liver cirrhosis, depression, dementia, or type 2 diabetes, and also first or *repeated* incidence of injury requiring hospital admission or infections requiring hospitalization. The minimum expected **cumulative incidence** of this primary global index endpoint after up to **4-year** follow-up should be higher than **15%,** considering the multiplicity of potentially qualifying events for the primary endpoint. To estimate the required sample size, more realistic assumptions were made.

We assumed a potential range of values for the absolute risk (R_i) of the primary end-point from 18% to 25% (always equal in both groups) and adopted a perspective on precision rather than power for the estimation of sample size[94]. Under assumptions from 0.04 to 0.05 for the total width of the 95% confidence interval of the risk difference (upper/lower bound of the difference between 2% and 2.5%) the needed sample sizes are those shown in the graph at the right (total N, summing up the two arms of the trial). Alternatively, with conventional power calculations, the with sample size for a non-inferiority test are 8038 participants under assumptions of alpha=0.025 (one-sided), and beta=0.2 and a minimal clinically important difference of 2.5% in the primary global index endpoint. Please, check the command *artbin* in Stata, www.mrcctu.ucl.ac.uk/our-research/methodology/software/. An additional 25% was added to account for potential losses to follow-up. Therefore, the recruitment goal is **>5000 per group** (**total >10,000**). For any secondary outcome with a lower cumulative incidence (5%), the non-inferiority test would be sufficiently powered (87%) for a minimal clinically important absolute difference of 1.25%



TRIALISTS AND COACHES

We have recruited 33 medical doctors as **Coordinators** for the rest of trialists. These **Coordinators are mostly former students** (**alumni**) of the Medical School of the University of Navarra (UNAV) and will have a proper role as investigators responsible for the trial. Several Coordinators were actively involved in the PREDIMED, PREDIMED-Plus and PREDIMAR trials[95-100]. Each of these Coordinators will be **supervising between 7 and 28 trialists**, thus totaling **around 500 medical doctors as trialists**. **Most of the trialists are**

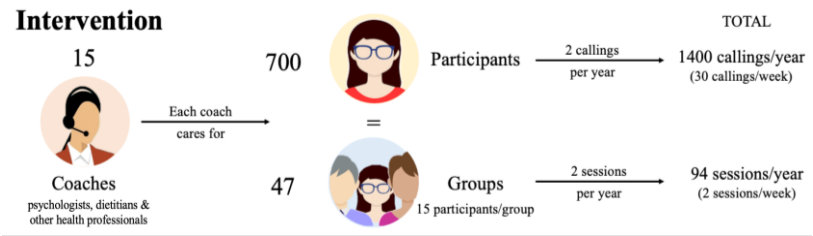
strong medication clearly precludes any use of alcohol, even in minimal amounts; 2) those psychiatric patients who present such symptoms and clinical situation that, according to their attending physician, will be refractory or reluctant to attend and follow the advices given by the coaches or not willing to answer the phone callings or to participate in the conference calls or group sessions. In both cases (1 and 2), the physician will not recruit them for the UNATI trial

[#] Direct acting anticoagulants (Dabigatran; Apixaban; Ribaroxaban and Edoxaban) are not contraindicated for moderate alcohol consumption; in fact, patients who use them usually drink alcohol - Benzodiazepines consumers may even represent a real epidemic in Spain and are not a reason for exclusion unless they are used in very high doses. It is not the same a daily small dose of lorazepam before sleeping than a high dose every 8 hours (in this case it would be prescribed only for a serious psychiatric disease, which is already a cause of exclusion). The proposed alcohol consumption level in the moderation arm of the trial will not produce any harm in those patients who usually take only low doses of benzodiazepines or zolpidem. For those patients who already take some alcohol and are using these drugs, changing the type of alcohol consumption (it will NEVER increase) will not change anything or alter any effect of these drugs (if anything, the moderation will reduce the potential harmful effects, by always consuming alcohol with food, which slows down the psychological effects of alcohol).

former students of the Medical School at the University of Navarra. We have considered as candidates to become trialists or Coordinators only those Medical Doctors who spontaneously sent us their requests for becoming part of our research team. After our initial experience (up to July 7th, 2023) consisting in the fact that >120 physicians, former students of our University of Navarra Medical School, sent us their willingness to participate as trialists or Coordinators, we assumed that we will have a sufficiently large number of applications by Medical Doctors applying for participation without any further need to publicize the study. We have sent invitational letter only to those candidates to be trialists who *motu proprio* contacted us to show their willingness to participate. We will also have conference calls with them and send them periodically short videos with explanations of the study protocol and the role that the trialists will play. We have requested from each of them **a signed agreement** showing his/her voluntary conformity to act as trialist or Coordinator and their commitment to apply all the required methodological tasks and all procedures needed for the success of the trial, including the commitment to meet the high scientific standards of the protocol and to avoid inquiring on the arm allocated to the participants which they recruit[**]. Nevertheless, the trialist, as the clinician caring for the participants, should not be forbidden to talk about excess alcohol consumption with his/her patients.

The research resources generated will be made available to trialists and other researchers so that they can apply to research projects and evaluate hypotheses. These resources will always be fully anonymized.

Fifteen coaches (mainly **psychologists** and **dietitians**) will be hired, **trained and certified** to deliver a **high-quality behavioral intervention** in each arm of the trial. These coaches will be psychologists, dietitians and other health professionals. They will be working together and continually exchanging among themselves their mutual skills and experiences.



We have long expertise in training, certifying and supervising health professionals to deliver complex behavioral interventions aimed to bring about substantial changes in the consumption of foods and beverages among adults of this age. We will take special care to ensure that all coaches will be able to deliver a high-quality intervention equally in both arms of the trial, and that the personal beliefs and perceptions of coaches with respect to alcohol intake (some of them may be personally more favorable to abstention; some of them may preferentially support red wine in moderation) do not interfere with the intended intervention according to the randomized arm. All coaches will deliver both interventions.

Our goal is that each trialist will eventually recruit approximately 25 **participants among his/her patients** to be randomized (after excluding non-willing and non-consenting candidates). With close to 500 trialists, each recruiting an average of 25 participants, the total number of randomized patients will be >10,000. This is realistic, because the 33 Coordinators will play an analogous role as the 11 principal investigators of the 11 recruiting centers in PREDIMED successfully did[95-97] or those of the 23 recruiting centers in PREDIMED-Plus[98-99] or the 4 centers of PREDIMAR[100].

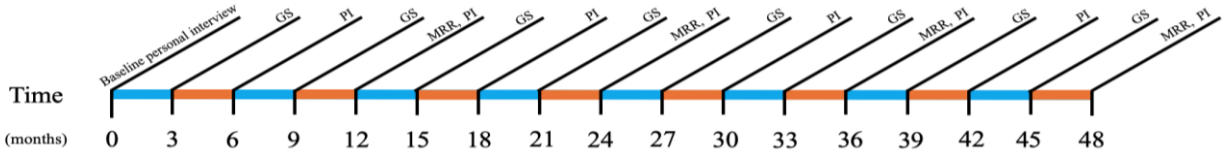
The methods, that have been instrumental in previous trials for these aims, will be now used again. They include **repeated quarterly small group sessions** (<20 participants, with approximately 47 groups per coach), and periodical **personal interviews** (phone calls in this trial). The average duration will be 30 to 40 minutes for both group sessions and personal interviews in the abstention/reduction arm and only 15-20 minutes in the moderation arm. We assume that the needed behavior change will be minimal for many patients in the moderation arm, because a sizable proportion of them may be already meeting the goals of the MADP. Therefore, the time and work load for coaches will be lower in the moderation arm.

[**] If the trialist changes hospital or health center, care should be taken not to interrupt data collection, for example, by transferring the patients to another colleague in the same center, who is already a trialist or who wishes to join as a new trialist. Those who change center will not cease to be trialists. If they remain in the same autonomous community and -as it is established in the protocol- have the permission of their former patients to review their clinical records, they will continue to collaborate by means of the **annual review of clinical records** through the computerized system of records that each Autonomous Community maintains. If recruitment were to remain open when they change centers, they could recruit new patients at the health center to which they move

We plan to perform the intervention **remotely**, mainly using conference calls, and virtual group meetings (via Zoom or similar systems), as we did from 2017 to 2020 in the PREDIMAR trial[92,100] and during the COVID-19 pandemic (due to lockdown) in PREDIMED-Plus[93]. **Educational videos** will be developed by our team, similar to those elaborated in PREDIMAR[92,100].

Each of the **coaches** will be responsible for delivering the intervention to approximately 700 participants (15 x >700= >10,000). During up to 4 years, participants will have **1 contact every 3 months** (**alternating group sessions** in one contact with a **personal conference call** in the next contact). The workload for each coach will thus include 1400 calls/year (700 participants x 2 personal calls/y) and 94 group sessions/y (with an average of 15 participants per session and 2 group sessions per year per participant, i.e. 2 x >700/15=94). Assuming 47 working wk/y, this workload will represent a mean of 30 callings/wk and 2 group sessions/wk per coach. The main allocation of funds in our budget from the ERC is aimed at hiring full time these 15 coaches.

In the **interactive on-line group sessions**, separated for each arm of the trial, coaches will foster participation and will present advantages of 0 alcohol intake (in the abstention arm) or comprehensive explanations of the MADP (moderation arm). Detailed analyses of high-risk situations, clues for overcoming them, suggested coping strategies, displays of actual drinking vessels, and thoughtful accounts of health and social harms of alcohol misuse will be discussed. The method of the "expert patient" and reinforcements by previously trained participants who attained the intended goals will be also used in these group sessions.



GS: Group session. PI: Personal Interview. MRR: Medical Record Review.

RECRUITMENT AND RETENTION STRATEGIES

The above-mentioned network of medical doctors (**'trialists'**) will serve as recruiters for the UNATI trial. All of them should work **in Spain**, either in public or private hospitals, primary care centers or private clinics. The mission of trialists is to **ensure a high recruitment rate** and almost 100% diligence in the annual **review of medical records** and **collection of clinical information on events and other parameters** during follow-up. They will help to minimize losses to follow-up and ensure the **appropriate collection of clinical data during the follow-up** period.

Importantly, trialists will not be responsible for the intervention at all, and they will be **blinded to the randomized** arm of the patient. This requirement is clearly established in the protocol and in the informed consent form to be signed by the patient, and it will be frequently repeated to each trialist during the execution of the trial. Each **trialist** has signed a form with his/her commitment to meet with **high quality all procedures** and duties established in the protocol and also a special commitment **to avoid inquiring the randomized patients about their actual allocated intervention group**.

INFORMED CONSENT/ETHICS COMMITTEE

All aspects of this study protocol were definitively approved by the **Ethics Committee** of the University of Navarra in its session held on September 14th, 2023 ("Comité de Ética de la Investigación de la Universidad de Navarra, Proyecto 2023.083"), Chair, Maria del Carmen Berasain Lasarte (document signed on October 9, 2023).

Eligible candidates will sign informed **written consent forms**. All procedures and anticipated time commitments will be explained in detail to participants (see attachment with the information sheet for the patient). The informed consent form includes a statement **allowing trialists** and researchers to **review the participants' medical records** throughout the trial at both the primary care centers and reference hospitals to ascertain clinical events. All personal research data will be always used anonymously (see below).

The UNATI trial imposes very few time commitments or added time on trialists. The workload of medical doctors acting as trialists in UNATI will be minimal. It comprises routine tasks in clinical care and annual review of medical records. As physicians involved in the recruitment process, **trialists** in the main trial will also be responsible for all aspects of the participants' medical care (as they already routinely do) that are **not** related to education on alcohol. **All behavioral interventions on alcohol will only pertain to the coaches**

during the trial, never to trialists. In fact, this represents a reduction in their workload, because of the assistance provided by the coaches for this health-promotion task.

Contrary to what occurred in PREDIMED or PREDIMED-Plus, there is no need to occupy any room or facility in the clinical centers to perform the UNATI trial, because the intervention will be exclusively remotely delivered meanwhile the patients are usually at their homes. Contrary to PREDIMED or PREDIMED-Plus large trials, no personnel from the hired staff for the trial will need to visit the Primary Health Centers or hospitals.

No potential ethical conflict regarding confidentiality exists when identifying suitable candidates or reviewing medical records because these are tasks assigned exclusively to the trialists, who are the attending physicians for the volunteers.

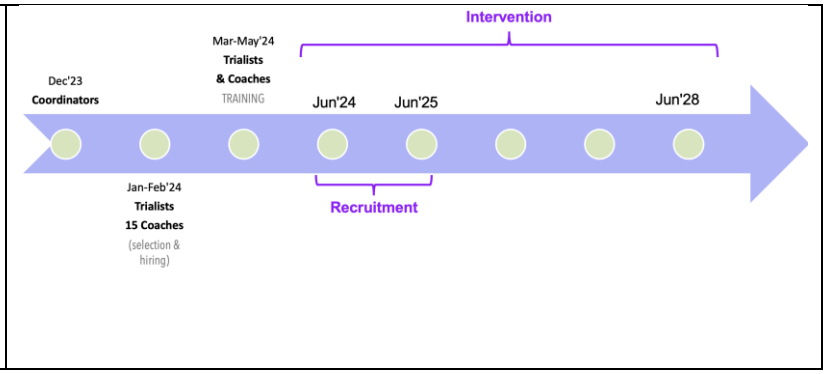
Participants' eligibility criteria and demographic data are collected by the trialists from medical records at the Primary Care Centers or hospitals, which are entirely computer-based. This is done at a pre-screening evaluation stage by the trialist before the potential participant is contacted. Candidates are then interviewed (either in person or by telephone) by the trialist, informed about the study, and invited to complete the brief **eligibility questionnaire assisted by the trialist**. This questionnaire will be completed online and will be immediately available for the coach, once the participant agrees.

Once the coach receives this brief eligibility questionnaire, which includes the phone number of the candidate, he/she will invite the participant to sign the informed consent and to attend the **first visit** via remote contact. After the informed consent is signed by the participant, the coach introduces the data in the internet-based randomization system and the participant is randomized. In this first formal visit with the coach (**time zero**), participants are informed of their allocated group and receive the first instructions and the first motivational counseling via personal telephone interview.

The hired **coaches** –and **not the trialists–** will be responsible for introducing the data in the internet-based system for randomization (with means to ensure a **blinded sequence of randomization,** see below). The coaches will implement the randomization process only once they receive the brief eligibility questionnaire completed by the trialist and confirm that the candidate met the eligibility criteria and **signed the informed consent** form. Only after checking that the informed consent has been signed by the participant, can the trialist introduce the corresponding medical data of that participant in the internet-based system.

WORKING PLAN AND LAUNCHING OF THE TRIAL

The Starting day of the trial was **December 1, 2023**, as signed in the Agreement with the European Research Council. The deadlines and milestones started to count on that day. The end date is November 30, 2028.



EVALUATIONS AND MEASUREMENTS

Prior to randomization, candidates will complete, assisted by their medical doctor (i.e., trialist), a brief **eligibility questionnaire** collecting data about alcohol consumption, exclusion criteria, and willingness to change drinking behaviors. Then, after randomization, participants will complete, assisted by the coach, a **baseline general questionnaire** collecting sociodemographic data, medical history, medication use, and a **validated 143-item food frequency questionnaire (FFQ)**. They will complete by themselves (on-line, at home) a physical activity questionnaire, a questionnaire on sleeping habits, the Beck **Depression** Inventory-II, the **quality of life** questionnaire (SF-36), and the questionnaire of the Human Flourishing Index proposed by Vandeweele. At the baseline visit, the **trialist** (medical doctor, attending physician) will collect anthropometric data, systolic and diastolic blood pressure, and several tests, if they are clinically appropriate for the patient, including an electrocardiogram (ECG), measurements of blood lipids, liver enzymes and fasting glucose. Also, the recruiting medical doctors will conduct a **yearly review of the medical records** to identify new hospital admissions, and diagnoses of any significant clinical event included in the protocol. In person follow-up of participants by the trialists will take place at baseline and at years 1, 2, 3 and 4 (end of the intervention). All questionnaires will also be available **online,** so participants will

always have the opportunity to complete them online. **The following table** shows the main data collection measurements by visit.

		0	Y1	Y2	Y3	Y4
TRIALIST	Brief eligibility questionnaire	X				
	Weight, height, waist and blood pressure	X	X	X	X	X
	ECG*	X				X
	Blood count, lipids, glucose, liver enzymes*	X	X	X	X	X
	Medical Record Review		X	X	X	X
COACH	STICS (MMSE), Clock Drawing test	X				X
	Baseline questionnaire (includes CAGE)	X				
	Follow-up questionnaire (includes CAGE)		X	X	X	X
	143-item FFQ & MEDAS	X		X		X
	Mediterranean Alcohol Drinking Pattern Q.	X	4X	4X	4X	4X
PARTICIPANT	Physical activity/sedentary lifestyles quest.	X		X		X
	7-item Subjective Cognitive Complaints	X				X
	SF-36 & Human Fluorishing questionnaire	X		X		X
	AUDIT	X		X		X
	Beck Depression Inventory-II	X				X
	Sleep, loneliness, social support	X				X

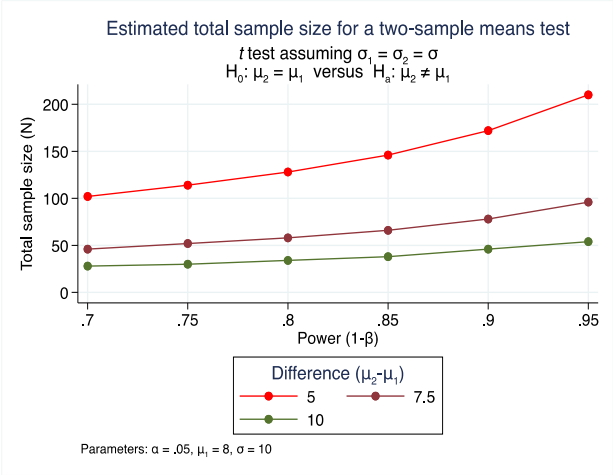
STICS (MMSE): Telephone adaptation of Mini-Mental Status Examination (MMSE).
CAGE alcohol misuse screening test.
AUDIT alcohol abuse screening test.
SF-36: Questionnaire of quality of life Short-Form 36 (SF-36).
FFQ: validated food frequency questionnaire (143 items).
MEDAS: Mediterranean Diet Adherence Screener (14 items).
The Mediterranean Alcohol Drinking Pattern Questionnaire will be repeatedly assessed 4 times/y (4x), every 3 months, and it will provide an excellent opportunity for the coaches to conduct a negotiated agreement with the participants in the moderation in order to upgrade their adherence to the Mediterranean Alcohol Drinking Pattern and to agree goals for the next 3 months.
*ECG and analytical data are only collected by the trialist from the clinical records if they were done according to the clinical situation of the patient.

Several self-reported questionnaires will be used to assess exposures or outcomes related to psychological well-being, always with the option of opting out by the participant.

In addition, discretionally for the attending medical doctor, and according to his/her clinical judgment, other tests can be added if the clinical situation of the participant deserves such testing, including serum sodium, potassium, calcium, uric acid, urea, creatinine, albumin, C-reactive protein, erythrocyte sedimentation rate, hemoglobin A1C, other liver function tests (serum bilirubin, alkaline phosphatase) and coagulation tests (prothrombin time, activated partial thromboplastin time and fibrinogen). These data are expected to be available for a sizable proportion of participants, given that recruitment will be done in clinical settings and the trial includes patients because of the primary and secondary prevention characteristics of the RCT design. Trialists will be responsible for digitizing this analytical information, and for including it in the on-line database for all patients and analyses. **Additional grants are being submitted to the Spanish National Institutes of Health Carlos III (and other agencies) by Coordinators** to assess ancillary hypotheses nested in the overall trial, part of these funds could be allocated to complete the analytical and genetic determinations in a subgroup of participants.

Objective assessment of alcohol intake

Also, we will analyze **hair samples** to detect ethylglucuronide (ETG) in a **random** subgroup of **100 participants self-reporting abstention** during the trial[101,102]. In addition, another subgroup of **200 randomly selected participants (100 in each arm** of the trial) will be asked to send us hair samples at 0, 3-month, 6-month, 2-year and 4-year assessments. Given the integrated nature of this biomarker, the collection of hair can be easily scheduled as to match the usual date of hair-cutting of the patient.



Only in randomly selected subgroups of 100 participants in each of the two arms (total sample size, N=200) we will contact the patients to ask them if they want to send us a sample of **hair** (at time points 0, 3 months, 6 months, 2 years and 4 years) to measure **ethyl glucuronide** (ETG) which is a reliable biomarker of cumulative alcohol intake during the last 3 months, particularly when reference values are standardized according to the underlying clinical conditions[101-104]. Assuming a standard deviation = 10 pg/mg (see Fig. 3 in ref. 168), the statistical power will be sufficiently high (see left panel) as to identify differences as low as 5 pg/mg of ETG between both arms of the trial, assuming 2-tailed alpha=5%, baseline mean= 8 pg/mg and statistical power>90%.

RANDOMIZATION PROCEDURES

Randomization will be done using a **centrally-controlled, computer-generated web-based random-number system** that will be exclusively available online. The coordination trial group sited at the Department of Preventive Medicine and Public Health at the University of Navarra will be responsible for the randomization procedures by which participants will be randomly assigned with **stratification by three dichotomous variables: 1) sex, 2) age** group (<65, >=65 years), and **3) past drinking history** (light-moderate versus heavy (>200 g/wk or binge drinking)), but not by Coordinator. The coaches, once the participant has signed the informed consent, will enter the participant's identification criteria into the internet-based system. The system will then automatically assign participants to their groups without giving the coach any possibility to predict the allocated group or to change allocation once it is adjudicated by the system (to ensure the **blinding of the randomization sequence**). Participants or coaches will be unable to change their group. Variable-size blocks of 4 and 6 participants will be randomly distributed in the allocation system to avoid any possibility of guessing the next allocation.

OUTCOME DEFINITION AND ASCERTAINMENT

Clinical events will be ascertained by an independent **Clinical Event Ascertainment Board**, including cardiologists, neurologists, psychiatrists, endocrinologists, oncologists, specialists in hepatic diseases, internal medicine and other medical specialties. Clinical event ascertainment will be based on the information collected from the participants' **medical records**, which **each year** will be obtained in the review done on an *ad hoc* basis by the trialists. These trialists will send the relevant documentation to the independent Clinical Event Ascertainment Board. Both the trialists and the members of the Clinical Board will be **blinded to the assignment** of participants to the two intervention groups, as they signed in their inscription for participating in the trial. The reports sent to the Clinical Board will contain no personal information about the participants and will be identified only by a code. Therefore, adjudication of clinical events by this Clinical Board will be blinded not only to the allocated intervention but also to the very identity of the participant.

Components of the primary endpoint (global index):

Specific criteria for adjudicating most components of the primary end-point have already been described in the corresponding paper for our previously ERC-funded large trial (PREDIMED-Plus) in a specific publication. They can be found in Supplement 2 of our previous JAMA publication[99].

All-cause mortality: All deaths should be confirmed by reviewing every year the National Death Index (which, thanks to a specific agreement also provides the cause of death).

Myocardial infarction: New (incident) cases of acute myocardial infarction (MI) will be defined according to the third universal definition of MI on behalf of the Joint ESC/ACCF/AHA/WHF Task Force[99].

Stroke: will be defined following the updated definition of stroke for the 21st Century[99].

The global index for the primary end-point will also include any incident case of **atrial fibrillation**, **heart failure, cancer** (all cancers except non-melanoma skin cancer), **type 2-diabetes**, **depression**, **dementia**, **or liver cirrhosis**. All these specific components will be individually adjudicated by the Clinical Event Ascertainment Committee only if they were not present at baseline (they need to be new-onset, incident cases, without any previous history of that disease). However, a particular prevalent condition does not preclude the adjudication of a new primary end-point due to another incident disease; for example, if a patient with prevalent atrial failure at baseline develops prostate cancer, he will be included as a new primary event because of his new incident cancer diagnosed during the trial. For the adjudication of **cancer** cases, biopsy confirmation will be required, and they will be coded according to the International Classification of the World Health Organization.

For two components of the primary end-point, namely, **infection** with hospitalization and hospital admission for any **injury**, **recurrent** hospital admissions will be also included as primary end-points, regardless of the previous history of another infection or another injury.

In any case, a participant can contribute only once to the accrual of the primary end-point.

Ensuring trialist blinding concerning the allocated arm may be challenging. It is crucial to guarantee that they always send all clinical information related to the participants to the Clinical Event Ascertainment Committee when they find any suspicion of any incident event.

INTERVENTIONS

Intervention in the abstention arm

The intervention in the **abstention** arm will consist of repeated advices (4 contacts/y) recommending participants to **completely stop their alcohol** intake by means of group sessions (on-line meetings) and personal interviews over the phone. The average duration will be 30 to 45 minutes for each. This advice needs to be given often in clinical practice and it should be duly tested, not only for assessing its ideal efficacy, but also for appraising practical effectiveness in real life.

A Cochrane meta-analysis assessing 34 trials with 15,197 participants found moderate-quality evidence that only a brief intervention was able to bring down alcohol consumption as compared to a minimal or no intervention after one year (mean difference -20 g/wk, 95% confidence interval: -28 to -12)[105]. More intensive and repeated interventions, as proposed in our trial, are likely to obtain greater differences, though excessive frequency or intensity may lead to fatigue. Our experience in PREDIMED and other trials supports that 4 contacts per year could represent an ideal balance. A reduction in alcohol intake from baseline of **at least 60%** will be considered as enough **compliance** with the intervention for the abstention arm. Days abstinent from alcohol will also be recorded and included in ancillary analyses. Through personal interviews over the phone and group sessions, coaches will deliver repeated advice, motivational strategies, and periodical education on social-, family- and health-related alcohol harms. They will use the following resources to help participants and persuade them **to attain abstention**: negotiated goal setting, psychological support, cognitive behavior therapy[106], tools for self-assessment/self-reward/self-efficacy and techniques for the prevention of relapses, with a specific **adaptation to the particular clinical situation of each participant**. This last point is especially relevant according to our previous experience in behavior modification techniques used in PREDIMED, PREDIMED-Plus, PREDIMAR and LIFEbreast. Coaches should connect abstention with the stage of change of the participant (precontemplation, contemplation, decision, action) regarding alcohol abstention and with the **expected health benefits for the particular condition or risk factor of the patient**. The coach will approach the patients as somebody who can help them to leave alcohol with large expected benefits for their health. There is evidence of the effectiveness of behavioral interventions **remotely delivered**[106-110]. Abundant written material will be also shipped to participants.

A **contingency plan** will be applied to those participants allocated to the abstention arm who after 1-year intervention do not reduce their alcohol intake: we will suspend gifts and will develop a special plan with longer contacts and motivational interviews, deeper exploration of their underlying psychological conditions, more abundance of shipped written material and a higher frequency of contacts.

In our experience, the most important aspect for a high compliance is the degree of commitment and involvement of the coach, his/her continuous show of availability and the personal human relationship

established between the coach and each participant. We will provide **gift foods and beverages (without alcohol, for participants allocated to the abstention arm) at no cost (or at reduced cost)**. To avoid potential conflicts of interest we have not requested these gifts from the alcohol industry, but from a large supermarket chain in Spain. Gifts will consist in 0%-alcohol beer, and extra-virgin olive oil to foster adherence to the Mediterranean diet in the **abstention** arm.

In the **moderation** arm we will **provide red wine (1.5 l/mo)** and the same amount of extra-virgin olive oil to foster adherence to the Mediterranean diet as in the other group. The amount to be provided is possible thanks to the free provision that we got from the supermarket chain. Given that the prices of dealcoholized beverages (eg., 0%-alcohol beers, "tinto de verano sin azúcar y sin alcohol", i.e., red wine for summer without sugar or alcohol) and regular red wine are not very different, the **differential free provision of beverages** in each arm **will not introduce disparities in costs between both arms of the trial**.

Very importantly, to avoid the threat that free provision of red wine may lead to increased consumption in the moderation arm, we will put our best efforts into selecting highly skilled coaches and in their meticulous training and motivation for delivering a high-quality motivational and behavioral intervention lasting up to 4 years, emphasizing always the need to *reduce* the total amount of ethanol intake if it was above 70 g/wk in women or 140 g/wk in men and, in any case, never to increase it above the baseline levels even if they are very low.

The intervention in the **moderation arm** will require shorter contacts (15-20 minutes). It will include:

a) **Moderate** consumption of alcohol: participants will *never* be encouraged to increase their alcohol intake and they will be advised to never exceed the limits of ≤**7 drinks/wk** (women) or ≤**14 drinks/wk** (men). If alcohol intake does not exceed those limits, the intervention will be focused in improving the adherence to the MADP but never in increasing the total amount of ethanol intake.
b) They will be advised to **spread their consumption over the week**: alcohol intake should not be concentrated in weekends. Participants will be encouraged to increase their days of drinking during the week without increasing the total weekly quantity consumed.
c) Drink **with meals**: drink alcohol only with meals and never with an empty stomach.
d) Drink wine, only **red wine**. They will be specially encouraged to stop the consumption of distilled drinks.
e) Completely **avoid binge-drinking** episodes: even during special days of parties, participants will be encouraged to never drink >4 drinks for women or >5 drinks for men during a single occasion.

STATISTICAL ANALYSIS

Data analysis will be performed with multivariable linear regression or Cox regression depending on the outcome (continuous or time to event). **The intention to treat** approach **will be used for the primary analysis.** Given the non-inferiority design and the potential issues related to suboptimal compliance, a **per protocol approach** will be added as sensitivity analysis. All analyses will be based on a **non-inferiority** design, defining a minimal clinically important difference of 2.5% in the cumulative incidence for the global index and 1.25% for the component outcomes studied individually. We will use the most up-to-date techniques in causal inference for pragmatic trials, including techniques of inverse probability weighting. In these models we will adjust for relevant covariates related to the outcomes and which can confound the association according to previous scientific knowledge using **causal diagrams (directed acyclic graphs)** for identifying covariates[111-113]. In these models we will check: 1) hazards proportionality, with a flexible approach for this assumption as appropriately suggested[114]; 2) the linearity of continuous variables by smoothing restricted cubic splines, checking the statistical significance of the non-linear part; 3) The influence of observations on a parameter estimate, assessed by delta-betas. Further approaches will depend upon the results obtained above (i.e. log transformations, stratified analyses, etc.).

The data from the UNATI trial will be analyzed at **3 intervals (2 interim analyses and the final analysis) after 2-, 3-year median follow-up, and 48 months after recruitment started**. An adequate follow-up of a trial must include at least one interim analysis, not only for methodological aspects but especially for ethical reasons[115]. This principle needs to be applied also in non-inferiority trials, provided that their data may also show superiority of one of the two options, with strong clinical and ethical implications. To preserve an overall alpha error at 0.05, interim analyses have to be penalized. The boundaries proposed by O'Brien and Fleming will be used considering the potential eventuality of finding superiority for anyone of the 2 trial arms, with a priori 2-tailed p values to stop the trial of **p=0.0005 at 2 years (first interim**

analysis), p=0.014 at 3 years (second interim analysis) and p=0.045 for the final analysis at 4 years[116]. These p values should not be considered as mandatory, particularly because an early benefit for cardiovascular disease could be later off-set by an increased cancer risk. They represent guidance for the External Data Safety and Monitoring Board (DSMB, see below), who will also ponder the attained proportion of abstainers in the abstention arm, the actual contrast in ethanol intake between both arms, the effect size, effect heterogeneity, evidence from other ongoing trials and observational studies, among other elements of judgment, and thus decide on the recommendation on the trial continuation or interruption. Reasons for interrupting this trial will include: 1) early evidence for beneficial effect of one of the interventions (the trial will only be stopped if the relative effect of one of the two interventions on the primary endpoint is very large); 2) extremely low compliance with the intervention (<10% of abstention in the abstention arm after 1 year) or tiny differences (<5 g/d) in average alcohol intake between both arms of the trial.

As frequent outcomes with a **shorter latency time** (and probably less severe, particularly type 2 diabetes) may drive the results, ancillary secondary analyses will be conducted by analyzing in first place the subset of more severe events (mortality, invasive cancer, stroke, myocardial infarction) and only in second place including the rest of events. After considering the rates observed in similar trials and cohorts conducted in subjects 50-75 years in Spain, the expected number of events to be accrued during the expected duration (median= 48 months) of the UNATI trial will be:

	Expected number of events
Type 2 diabetes	662
All invasive cancer (except NMSC*)	533
Atrial fibrillation	363
All-cause mortality	196
Depression	111
Heart failure	107
Non-fatal myocardial infarction	85
Non-fatal stroke	81
Liver cirrhosis	40
Infection with hospital admission	40
Injury with hospital admission	37
Dementia	34
Total	**2289**

*NMSC: non-melanoma skin cancer

The approach known as the "win ratio" initially proposed by Pocock et al. for cardiovascular trials using composite outcomes as primary end-points[117] will be applied to UNATI in this ancillary sensitivity analysis. The hierarchy for classifying events in the win ratio approach will include only 2 groups: 1) mortality, invasive cancer, stroke, myocardial infarction; 2) all other events.

SUPERVISION AND MONITORING PROCEDURES

Monitoring the recruitment of participants and compliance rates with the intervention strategies are crucial to the success of a trial of this nature. For this reason, a 5-member **Steering Committee** composed of the PI (chair), Maira Bes-Rastrollo, Miguel Ruiz-Canela, Miguel Alvarez-Mon and Diego Martínez-Urbistondo will be established with **weekly meetings** to keep track of all recruitment, training and compliance procedures and achievements. The independent **DSMB is composed of well-known and highly-reputed Academic Members, namely,** Meir J Stampfer (chair), Agustin Albillos, Roberto Elosua, Almudena Sánchez-Villegas and Ramon Estruch. They are not otherwise involved in the trial. They will be responsible for monitoring and supervising the trial. They will be convened to review the implementation of the protocol, and to monitor the trial's progress on an **annual** basis. The trial will be registered in ClinicalTrials.gov before starting the recruitment. We will adhere to CONSORT guidelines for reporting results.

POTENTIAL HEALTH RISKS FOR PARTICIPANTS

No participant will be invited by coaches to start drinking alcohol. No advice will ever be given to increase alcohol consumption. Nevertheless, it might be possible that the free provision or red wine in the moderation arm of the trial may unwantedly foster an increased alcohol intake over the baseline levels. The coaches will be specifically trained to completely avoid this unwanted effect of increased levels of consumption. There is a minimal risk that participants who stop drinking might become more susceptible to the effects of alcohol. This can entail risks associated with drinking and driving. Coaches will include in their intervention the caution that participants who were drinking and now abstain need to be even more careful not to drive if on some special occasion they end up drinking alcohol.

STUDY LIMITATIONS AND STRENGTHS

A limitation is that we will **not be able to test the effect of initiating** moderate drinking or increasing it versus remaining in abstention, using the advantages of randomization. Alcohol intake may be a risk for health, so, for ethical reasons, we discarded those interventions. Moreover, we will not be able to assess the effect of **different levels of alcohol intake**. However, "as treated" analyses[118] will be done to overcome this limitation. Repeated measurements of actual alcohol intake will be used to assess which level is optimal for reducing the risk of the primary outcome, following the paradigm of emulating a randomized trial[119-121]. Of course, given the randomized design of UNATI, there is no need to use an emulation of a randomized trial, but some of these methods could be implemented in case of potential residual confounding related to randomization, or other issues.

As in any other longitudinal study, **losses to follow-up** may represent a threat for validity. We will try to maximize retention in the trial thanks to the **commitment** of highly selected trialists and coaches. This could occur mainly in the abstention group and this is likely to represent an important problem. Additional strategies for this group would be established, including particular efforts to tailoring the intervention to their specific clinical situation, thorough evaluation by coaches of their propensity to behavior change according to the stages of change paradigm, adapting the intervention to the specific stage of change of each participant, reinforcing always the emotional bonding of participants with their individual coaches, focusing on drinking refusal self-efficacy, and promoting resilience. This is one of the reasons why each contact with participants in the abstention group needs to be longer. In addition, the free provision of extravirgin olive oil and zero-alcohol beer is conditioned to the attendance to the interviews and group sessions and, in our experience in PREDIMED and other large trials, this procedure increases the long-term retention of participants.

In any case, we will collect **predictors of censoring** to be able to analyze data with the most up-to-date causal inferences techniques. Another potential limitation is that participants may **under-report their alcohol intake**. To try to reduce this possibility, we will measure biomarkers of alcohol intake (**HDL-cholesterol**) in all participants and hair **ethyl glucuronide** in random subsamples. In addition, both the abstention arm and the moderation arm will be informed that objective biomarkers will be used to verify their self-reports.

Participants will be 50-75 years old. This criterion precludes generalization to younger or older age groups. Participants must own a smartphone and a computer/tablet to enter the study. We will exclude participants older than 75 years because they are less likely to have expertise with on-line tools and because it may be too late for changing their drinking habits[74]. During follow-up, some participants may lose their abilities to use on-line material. If so, they will receive printed material, and online contacts will be replaced by telephone calls. We will request at baseline contacts of younger relatives of all participants in allow online contact if the participant eventually loses these abilities.

An anticipated difficulty relies on finding sufficient participants **willing to be randomized** to either one of the two alternative interventions, particularly to the abstention arm, given the addictive nature of alcohol. If the recruitment pace were low, more Coordinators and Trialists will be recruited. The trial may not be long enough to observe effects on some outcomes, such as cancer endpoints. We admit this possibility and assume that expanded follow-up after 10 years will be needed. This is the reason why we have included an ancillary analysis of cancer endpoints after 10-year follow-up. Funding will be requested from other sources for this purpose. However, cases of cancer occurring during the 4 first years of the trial will be assessed, and the expected number of cases of invasive cancer of any location during the active trial period of the trial is sufficiently large to observe an effect (only for type 2 diabetes the expected number is

higher). For most endpoints 4 years will be enough, given that the AF trial[85] observed effects **only after 6 months**.

Importantly, if compliance is low, a high risk exists that the **between-group contrast in average alcohol intake will not eventually be sufficiently large**. This represents a threat for this RCT, particularly given the non-inferiority design. This is the reason why we include a per-protocol analysis. More importantly, to avoid this threat, we will put our best efforts in selecting highly skilled coaches and in their meticulous **training** and **motivation** for delivering a high-quality motivational and behavioural intervention lasting up to 4 years. Monitoring of these goals represents a high priority for the validity of the trial. The assessment of objective alcohol intake biomarkers in a random sample at 3 and 6 months will allow us to obtain a confirmation that the contrast in alcohol intake between the two arms of the trial is sufficiently high.

Our goals of **at least 50% abstention** proportion in the abstention arm (or 60% reduction in average alcohol intake) seem feasible and will provide enough contrast for the per-protocol analysis. Also, a contingency plan will be applied for participants who repeatedly remain far from abstention, with special attention to those who increase their alcohol intake.

Our study will not be able to assess the differential effect of each type of alcoholic beverage. Wine was selected because it may be superior to other beverages, in particular within a MADP[11,12,14,16,19]. Moreover, moderation is strongly associated with the preference for wine[11,12,20]. It is well known that wine drinkers have a lower risk of becoming heavy drinkers and are less exposed to binge drinking[11,122].

One the potential "unwanted" effects of the intervention is a possible decrease in total energy intake (less calories from alcohol) or an increase in sugar intake or in the consumption of artificial sweeteners (replacing the pleasure given by alcohol with increased intake of sweets). These are important reasons for monitoring diet so we will detect these changes and will address them in the statistical analyses. Conceptually, a reduction in energy intake could be a mechanism by which abstention from alcohol is beneficial. Of course, weight changes will be compared between both arms of the trial as one of the ancillary end-points[123].

Conversely, an increased intake of artificial sweeteners, sugar or sugary desserts could be considered as a mechanism of potential harm. There may be other unexpected changes in lifestyles associated with abstinence (e.g. some participants may stop smoking, or abstinence may have negative impact on social life, or contribute to change their use of medication, such as sleep-inducing pills or anxiolytic use). These are important reasons to collect and analyze this information.

The UNATI randomized trial for the first time will provide **first-level evidence** to answer the important question of what option is the healthiest **when giving an advice on alcohol intake to drinkers in clinical settings**. Alcohol is one of the substances most familiar to mankind for millennia but there is an important gap in this knowledge. The present trial will be also very informative on how to provide a practical advice to change alcohol drinking behaviours. The wide behavioural approach adopted by this RCT is framed into the most appropriate pathway to reverse the ominous losses in health gains of the last decades, as Narayan *et al* wisely suggested in 2019[124]. Targeting drinkers aged 50-75 years (a sizable fraction of the population at risk for premature mortality and chronic disease) confers a great potential for **practicality** and clinical **translation** and represents an outstanding goal and a strong **priority for public health**. The research plan of the trial is highly **innovative** because no such a trial has ever been conducted and because we will include a massive use of new technologies for remotely delivering a behaviour change intervention. The protocol for this intervention is conveniently structured as to avoid the overloading of medical doctors, and the study is **appropriately powered** to ascertain the effect of the intervention on **a relevant outcome**.

The UNATI trial indeed represents a notable **challenge**. But this pragmatic non-inferiority trial is very likely to provide a **novel and groundbreaking** approach to address the accruing problems of alcohol harms. It will go **beyond the state of the art** by using all the advantages of an RCT design. This design prevents misclassification, confounding and selection biases usually compromising previous nonrandomized studies. It will answer a decisive question of utmost importance in **clinical medicine** and **public health**, with strong **economic** implications. A top journal in Clinical Nutrition already mentioned the UNATI trial in an article written by the Principal Investigator[74].

Indeed, the results of the UNATI trial will attract great interest and will achieve a huge potential for dissemination to the media and the general population because of their intrinsic interest. Our previous experience with the substantial translational potential of the scientific results published from the SUN

cohort, and from the two large trials, PREDIMED and PREDIMED-Plus, all of them conducted by the same Principal Investigator as the UNATI trial, attests that this would be feasible and the population at large will benefit from the results of this trial.

The generated dataset (completely anonymized) will be made available to every proficient researcher who may present a relevant research proposal to the Steering Committee for further exploitation of the data. All the usual legal precautions for the protection of individual data will be respected. There will be a small off-line database that will be kept by each coach with the personal identification data of each of his/her patients (name and surname, address, telephone, email, name of relatives and alternative telephone numbers to recover the contact, birthday, name of the trialist who recruited him, hospital or health center) and with the informed consent signed by each of the patients that each coach will attend.

In addition, each patient will be given a correlative identification number that will constitute the exclusive unique identifier of the general anonymized database where all other data (questionnaires, analyses and clinical events of the participants, but not the aforementioned data) will be stored. neither the zip code nor the exact date of birth will be included in this general anonymized database. To replace the date of birth, the general anonymized database will round all days of the month of birth to the 1st or 15th of that month, so that there is no way to identify participants by their birthday. The database for statistical analyses used by the researchers will be the general anonymized database. Only those biomedical researchers, duly qualified, who submit a scientifically rigorous and relevant analysis proposal for consideration by the Steering Committee, once it is approved by the Steering Committee, will be provided with variables (only those that are really essential) from this general anonymized database. They will be asked to destroy the data, once the article is published, and to send the syntax and codes used to the Steering Committee.

REFERENCES

1) United Nations. Sustainable Development Goals. Goal 3 targets. Available at: https://www.un.org/sustainabledevelopment/health/ (accessed August 17th, 2023).
2) GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015-35. Erratum in: Lancet. 2018;392:1116. Erratum in: Lancet. 2019;393:e44.
3) Casswell S. Will alcohol harm get the global response it deserves? Lancet 2019;394:1396-7.
4) Burton R, Sheron N. No level of alcohol consumption improves health. Lancet. 2018;392:987-8.
5) Goiana-da-Silva F, Cruz-E-Silva D, Lindeman M, et al. Implementing the European Action Plan on Alcohol. Lancet Public Health. 2019;4:e493.
6) Rehm J, Baliunas D, Borges GL, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction. 2010;105:817-43.
7) Stockwell T, Naimi T. Study raises new doubts regarding the hypothesised health benefits of 'moderate' alcohol use. Evid Based Med. 2016;21:156.
8) Naimi TS. Comment on Rehm: Alcohol, cohort studies and all-cause mortality: Where to from here?. Drug Alcohol Rev. 2019;38:9-10.
9) Rani S, Lapaucis A. "Less is better" is the best message when talking to patients about alcohol. CMAJ 2023;195:E1232-3.
10) Mukamal KJ, Conigrave KM, Mittleman MA, et al. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med. 2003;348:109-18.
11) Campanella A, Bonfiglio C, Cuccaro F, Donghia R, Tatoli R, Giannelli G. High Adherence to a Mediterranean Alcohol-Drinking Pattern and Mediterranean Diet Can Mitigate the Harmful Effect of Alcohol on Mortality Risk. Nutrients 2024;16:59.
12) Gea A, Bes-Rastrollo M, Toledo E, Garcia-Lopez M, Beunza JJ, Estruch R, Martinez-Gonzalez MA. Mediterranean alcohol-drinking pattern and mortality in the SUN (Seguimiento Universidad de Navarra) Project: a prospective cohort study. Br J Nutr. 2014;111:1871-80.
13) Roerecke M, Rehm J. Alcohol consumption, drinking patterns, and ischemic heart disease: a narrative review of meta-analyses and a systematic review and meta-analysis of the impact of heavy drinking occasions on risk for moderate drinkers. BMC Med. 2014;12:182.
14) Hernandez-Hernandez A, Gea A, Ruiz-Canela M, Toledo E, Beunza JJ, Bes-Rastrollo M, Martinez-Gonzalez MA. Mediterranean Alcohol-Drinking Pattern and the Incidence of Cardiovascular Disease and Cardiovascular Mortality: The SUN Project. Nutrients. 2015;7:9116-26.

15) Ma H, Li X, Zhou T, Sun D, Shai I, Heianza Y, Rimm EB, Manson JE, Qi L. Alcohol Consumption Levels as Compared With Drinking Habits in Predicting All-Cause Mortality and Cause-Specific Mortality in Current Drinkers. Mayo Clin Proc. 2021;96:1758-69.
16) Rehm J, Hasan OSM. Is burden of disease differentially linked to spirits? A systematic scoping review and implications for alcohol policy. Alcohol. 2020;82:1-10.
17) Morales G, Martínez-González MA, Barbería-Latasa M, Bes-Rastrollo M, Gea A. Mediterranean diet, alcohol-drinking pattern and their combined effect on all-cause mortality: the Seguimiento Universidad de Navarra (SUN) cohort. Eur J Nutr. 2020;60:1489-98.
18) Giacosa A, Barale R, Bavaresco L, et al. Mediterranean Way of Drinking and Longevity. Crit Rev Food Sci Nutr. 2016;56:635-40.
19) Jani BD, McQueenie R, Nicholl BI, Field R, Hanlon P, Gallacher KI, Mair FS, Lewsey J. Association between patterns of alcohol consumption (beverage type, frequency and consumption with food) and risk of adverse health outcomes: a prospective cohort study. BMC Med. 2021;19:8.
20) Li X, Hur J, Cao Y, Song M, Smith-Warner SA, Liang L, Mukamal KJ, Rimm EB, Giovannucci EL. Moderate alcohol consumption, types of beverages and drinking pattern with cardiometabolic biomarkers in three cohorts of US men and women. Eur J Epidemiol. 2023;38:1185-1196.
21) Barbería-Latasa M, Gea A, Martínez-González MA. Alcohol, Drinking Pattern, and Chronic Disease. Nutrients. 2022;14:1954.
22) Bell S, Daskalopoulou M, Rapsomaniki E, et al. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. BMJ 2017;356:j909.
23) Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011;342:d671.
24) Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med. 2004;38:613-19.
25) De Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. Arch Intern Med. 2006;166:2437-45.
26) Yoon SJ, Jung JG, Lee S, et al. The protective effect of alcohol consumption on the incidence of cardiovascular diseases: is it real? A systematic review and meta-analysis of studies conducted in community settings. BMC Public Health. 2020;20:90.
27) Britton KA, Gaziano JM, Sesso HD, Djousse L. Relation of alcohol consumption and coronary heart disease in hypertensive male physicians (from the Physicians' Health Study). Am J Cardiol. 2009;104:932-35.
28) Mukamal KJ, Chiuve SE, Rimm EB. Alcohol consumption and risk for coronary heart disease in men with healthy lifestyles. Arch Intern Med. 2006;166:2145-50.
29) Hvidtfeldt UA, Tolstrup JS, Jakobsen MU, et al. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. Circulation. 2010;121:1589-97.
30) Lucerón-Lucas-Torres M, Saz-Lara A, et al. Association between Wine Consumption with Cardiovascular Disease and Cardiovascular Mortality: A Systematic Review and Meta-Analysis. Nutrients. 2023;15:2785.
31) Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. Ann Intern Med. 2004;140:211.
32) Tian Y, Liu J, Zhao Y, Jiang N, Liu X, Zhao G, Wang X. Alcohol consumption and all-cause and cause-specific mortality among US adults: prospective cohort study. BMC Med. 2023;21:208.
33) Gmel G, Gutjahr E, Rehm J. How stable is the risk curve between alcohol and all-cause mortality and what factors influence the shape? A precision-weighted hierarchical meta-analysis. Eur J Epidemiol. 2003;18:631-42.
34) Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to alcohol consumption: a prospective study among male British doctors. Int J Epidemiol. 2005;34:199-204.
35) Bellavia A, Bottai M, Wolk A, Orsini N. Alcohol consumption and mortality: a dose-response analysis in terms of time. Ann Epidemiol. 2014;24:291-6.
36) Mostofsky E, Mukamal KJ, Giovannucci EL, Stampfer MJ, Rimm EB. Key findings on alcohol consumption and a variety of health outcomes from the Nurses' Health Study. Am J Public Health. 2016;106:1586-91.

37) Li Y, Pan A, Wang DD, et al. Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. Circulation. 2018;138:345-55. [correction in Circulation. 2018;138:e75]
38) Keyes KM, Calvo E, Ornstein KA, et al. Alcohol Consumption in Later Life and Mortality in the United States: Results from 9 Waves of the Health and Retirement Study. Alcohol Clin Exp Res. 2019;43:1734-46.
39) Zhao J, Stockwell T, Roemer A, Naimi T, Chikritzhs T. Alcohol Consumption and Mortality From Coronary Heart Disease: An Updated Meta-Analysis of Cohort Studies. J Stud Alcohol Drugs. 2017;78:375-86.
40) Martínez-González MA, Barbería-Latasa M, Pérez de Rojas J, Domínguez Rodriguez LJ, Gea Sánchez A. Alcohol and early mortality (before 65 years) in the 'Seguimiento Universidad de Navarra' (SUN) cohort: does any level reduce mortality? Br J Nutr. 2022;127:1415-25.
41) Di Castelnuovo A, Bonaccio M, Costanzo S, et al. Drinking alcohol in moderation is associated with lower rate of all-cause mortality in individuals with higher rather than lower educational level: findings from the MORGAM project. Eur J Epidemiol 2023;38:869-81.
42) Rehm J. Why the relationship between level of alcohol-use and all-cause mortality cannot be addressed with meta-analyses of cohort studies. Drug Alcohol Rev. 2019;38:3-4.
43) Stockwell T. Greater precision at the price of greater uncertainty? A response to Rehm. Drug Alcohol Rev. 2019;38:5-6.
44) Angus C, Holmes J. The allure, and challenges, of complexity in epidemiological modelling of alcohol harm: Commentary on Rehm. Drug Alcohol Rev. 2019;38:11-2.
45) Naimi TS, Stockwell T, Zhao J, et al. Selection biases in observational studies affect associations between 'moderate' alcohol consumption and mortality. Addiction. 2017;112:207–14.
46) Zhao J, Stockwell T, Naimi T, Churchill S, Clay J, Sherk A. Association Between Daily Alcohol Intake and Risk of All-Cause Mortality: A Systematic Review and Meta-analyses. JAMA Netw Open. 2023;6:e236185. Erratum in: JAMA Netw Open. 2023;6:e2315283.
47) Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 2014:349:g4164.
48) Millwood I, Walters RG, Mei XW, et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500.000 men and women in China. Lancet. 2019;393:1831-42.
49) van de Luitgaarden IAT, van Oort S, Bouman EJ, et al. Alcohol consumption in relation to cardiovascular diseases and mortality: a systematic review of Mendelian randomization studies. Eur J Epidemiol. 2022;37:655-69.
50) Swanson SA, Tiemeier H, Ikram MA, Hernan MA. Nature as a Trialist?: Deconstructing the Analogy Between Mendelian Randomization and Randomized Trials. Epidemiology. 2017;28:653-9.
51) Mukamal KJ, Stampfer MJ, Rimm EB. Genetic instrumental variable analysis: time to call mendelian randomization what it is. The example of alcohol and cardiovascular disease. Eur J Epidemiol. 2020;35:93-7.
52) Shi J, Swanson SA, Kraft P, Rosner B, De Vivo I, Hernán MA. Mendelian Randomization With Repeated Measures of a Time-varying Exposure: An Application of Structural Mean Models. Epidemiology. 2022;33:84-94.
53) GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1223-1249.
54) GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5:987-1012 [correction in Lancet Psychiatry. 2019;6:e2].
55) GBD 2020 Alcohol Collaborators. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. Lancet. 2022;400:185-235. Erratum in: Lancet. 2022;400:358.
56) Koo HY, Han K, Shin DW, Yoo JE, Cho MH, Jeon KH, Kim D, Hong S, Jun JK. Alcohol Drinking Pattern and Risk of Head and Neck Cancer: A Nationwide Cohort Study. Int J Environ Res Public Health. 2021;18:11204.

57) Boban M, Stockley C, Teissedre PL, Restani P, Fradera U, Stein-Hammer C, Ruf JC. Drinking pattern of wine and effects on human health: why should we drink moderately and with meals? Food Funct. 2016;7:2937-42.
58) Ma H, Wang X, Li X, Heianza Y, Qi L. Moderate alcohol drinking with meals is related to lower incidence of type 2 diabetes. Am J Clin Nutr. 2022;116:1507-14.
66) Klein WMP, Jacobsen PB, Helzlsouer KJ. Alcohol and cancer risk. Clinical and research Implications. JAMA. 2020;323:23-4.
67) Simpson RF, Hermon C, Liu B, et al. Million Women Study Collaborators. Alcohol drinking patterns and liver cirrhosis risk: analysis of the prospective UK Million Women Study. Lancet Public Health. 2019;4:e41-8.
68) Klatsky AL. Alcohol and cardiovascular mortality: common sense and scientific truth. J Am Coll Cardiol. 2010;55:1336-8.
69) Haseeb S, Alexander B, Baranchuk A. Wine and Cardiovascular Health: A Comprehensive Review. Circulation. 2017;136:1434-48.
70) Pavlidou E, Mantzorou M, Fasoulas A, et al. Wine: An Aspiring Agent in Promoting Longevity and Preventing Chronic Diseases. Diseases. 2018;6:73.
71) Ditano-Vazquez P, Torres-Peña JD, Galeano-Valle F, et al. The Fluid Aspect of the Mediterranean Diet in the Prevention and Management of Cardiovascular Disease and Diabetes: The Role of Polyphenol Content in Moderate Consumption of Wine and Olive Oil. Nutrients. 2019;11:2833.
72) Ng Fat L, Cable N, Marmot MG, Shelton N. Persistent long-standing illness and non-drinking over time, implications for the use of lifetime abstainers as a control group. J Epidemiol Community Health. 2014;68:71-7. Erratum in: J Epidemiol Community Health. 2014;68:191.
73) Tsai MK, Gao W, Wen CP. The relationship between alcohol consumption and health: J-shaped or less is more? BMC Med. 2023;21:228.
74) Martinez-Gonzalez MA. Should we remove wine from the Mediterranean diet?: a narrative review. Am J Clin Nutr 2024. https://doi.org/10.1016/j.ajcnut.2023.12.020
75) Logan DE, Kilmer JR, Marlatt GA. The virtuous drinker: character virtues as correlates and moderators of college student drinking and consequences. J Am Coll Health. 2010;58:317-24.
76) Sterling SA, Palzes VA, Lu Y, et al. Associations Between Medical Conditions and Alcohol Consumption Levels in an Adult Primary Care Population. JAMA Netw Open. 2020;3:e204687.
77) Hoek AG, van Oort S, Mukamal KJ, Beulens JWJ. Alcohol Consumption and Cardiovascular Disease Risk: Placing New Data in Context. Curr Atheroscler Rep. 2022;24:51-59.
78) Califf RM, Hernandez AF, Landray M. Weighing the Benefits and Risks of Proliferating Observational Treatment Assessments: Observational Cacophony, Randomized Harmony. JAMA. 2020;324:625-6.
79) Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. N Engl J Med. 2020;382:674-8.
80) Spiegelman D, Lovato LC, Khudyakov P, et al. The Moderate Alcohol and Cardiovascular Health Trial (MACH15): Design and methods for a randomized trial of moderate alcohol consumption and cardiometabolic risk. Eur J Prev Cardiol. 2020;27:1967-82.
81) Miller LM, Anderson CA, Ix JH. Editorial: From MACH15 to MACH0 – a missed opportunity to understand the health effects of moderate alcohol intake. Eur J Prev Cardiol. 2021;28:e23-e24..
82) Gepner Y, Golan R, Harman-Boehm I, et al. Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: a 2-year randomized, controlled trial. Ann Intern Med. 2015;163:569-79.
83) Shai I, Wainstein J, Harman-Boehm I, et al. Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multicenter, randomized, clinical intervention trial. Diabetes Care. 2007;30:3011-6.
84) Marfella R, Cacciapuoti F, Siniscalchi M, et al. Effect of moderate red wine intake on cardiac prognosis after recent acute myocardial infarction of subjects with Type 2 diabetes mellitus. Diabet Med. 2006;23:974-81.
85) Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol abstinence in drinkers with atrial fibrillation. N Engl J Med. 2020;382:20-8.
86) Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018;378:e34
87) Li WHC, Wang MP, Ho KY, et al. Helping cancer patients quit smoking using brief advice based on risk communication: A randomized controlled trial. Sci Rep. 2018;8:2712.

88) Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011;13:217-24.
89) Hernan MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med. 2017;377:1391-8.
90) Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-33.
91) Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended post-stopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310:1353-68.
92) Goñi L, de la O V, Barrio-López MT, et al. A remote nutritional intervention to change the dietary habits of patients undergoing ablation of atrial fibrillation: Randomized Controlled Trial. J Med Internet Res. 2020;22:e21436.
93) Paz-Graniel I, Fitó M, Ros E, et al. Impact of COVID-19 pandemic on the PREDIMED-Plus randomized clinical trial: Effects on the interventions, participants follow-up, and adiposity. Front Nutr. 2023;9:1098269.
94) Rothman KJ, Greenland S. Planning Study Size Based on Precision Rather Than Power. Epidemiology. 2018;29:599-603.
95) Zazpe I, Sanchez-Tainta A, Estruch R, et al. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. J Am Diet Assoc. 2008;108:1134-45.
96) Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E. Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. Prog Cardiovasc Dis. 2015;58:50-60.
97) Hu EA, Toledo E, Diez-Espino J, et al. Lifestyles and risk factors associated with adherence to the Mediterranean diet: a baseline assessment of the PREDIMED trial. PLoS One. 2013;8:e60166.
98) Downer MK, Gea A, Stampfer M, et al. Predictors of short- and long-term adherence with a Mediterranean-type diet intervention: the PREDIMED randomized trial. Int J Behav Nutr Phys Act. 2016;13:67.
99) Sayón-Orea C, Razquin C, Bulló M, et al. Effect of a Nutritional and Behavioral Intervention on Energy-Reduced Mediterranean Diet Adherence Among Patients With Metabolic Syndrome: Interim Analysis of the PREDIMED-Plus Randomized Clinical Trial. JAMA. 2019;322:1486-99.
100) Barrio-Lopez MT, Ruiz-Canela M, Ramos P, et al. PREvention of recurrent arrhythmias with Mediterranean diet (PREDIMAR) study in patients with atrial fibrillation: Rationale, design and methods. Am Heart J. 2020;220:127-36.
101) Mattia A, Moschella C, David MC, Fiore M, Gariglio S, Salomone A, Vincenti M. Development and Validation of a GC-EI-MS/MS Method for Ethyl Glucuronide Quantification in Human Hair. Front Chem. 2022;10:858205.
102) Marchei E, Gomez-Ruiz LM, Acosta-López A, et al. Assessment of alcohol consumption in mexican pregnant women by hair testing of ethyl glucuronide. Alcohol. 2023;111:59-65.
103) Triolo V, Spanò M, Buscemi R, Gioè S, Malta G, Čaplinskiene M, Vaiano F, Bertol E, Zerbo S, Albano GD, Argo A. EtG Quantification in Hair and Different Reference Cut-Offs in Relation to Various Pathologies: A Scoping Review. Toxics. 2022;10:682.
104) Ghosh S, Jain R, Rao R, Mishra AK, Jhanjee S. Does ethyl glucuronide in hair correlate with alcohol consumption? A comparative study with other traditional biomarkers among individuals with alcohol dependence syndrome. Alcohol. 2023;106:55-60.
105) Kaner EF, Beyer FR, Muirhead C, et al. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database Syst Rev. 2018;2:CD004148.
106) Hadjistavropoulos HD, Mehta S, Wilhelms A, Keough MT, Sundström C. A systematic review of internet-delivered cognitive behavior therapy for alcohol misuse: study characteristics, program content and outcomes. Cogn Behav Ther. 2020;49:327-46.
107) Willis EA, Szabo-Reed AN, Ptomey LT, et al. Do weight management interventions delivered by online social networks effectively improve body weight, body composition, and chronic disease risk factors? A systematic review. J Telemed Telecare. 2016;23:263-72.
108) Afshin A, Babalola D, Mclean M, Yu Z, et al. Information technology and lifestyle: A systematic evaluation of internet and mobile interventions for improving diet, physical activity, obesity, tobacco, and alcohol use. J Am Heart Assoc 2016;5:e003058.

109) Teasdale N, Elhussein A, Butcher F, et al. Systematic review and meta-analysis of remotely delivered interventions using self-monitoring or tailored feedback to change dietary behavior. Am J Clin Nutr. 2018;107:247-56.
110) Dedert EA, McDuffie JR, Stein R, et al. Electronic Interventions for Alcohol Misuse and Alcohol Use Disorders: A Systematic Review. Ann Intern Med. 2015;163:205-14.
111) Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10:37-48.
112) Howards PP, Schisterman EF, Poole C, Kaufman JS, Weinberg CR. "Toward a clearer definition of confounding" revisited with directed acyclic graphs. Am J Epidemiol. 2012;176:506-11.
113) McQuire C, de Vocht F. Methodological advances to mitigate some of the challenges of research on alcohol and all-cause mortality: Commentary on Rehm. Drug Alcohol Rev. 2019;38:7-8.
114) Stensrud MJ, Hernán MA. Why Test for Proportional Hazards? JAMA. 2020;323:1401-2.
115) Schulz KF, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. Lancet. 2005;365:1657-61.
116) O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-56.
117) Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012;33:176-82.
118) Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. Clin Trials. 2012;9:48-55.
119) Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183:758-64.
120) Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. BMJ. 2022;378:e071108.
121) Chiu YH, Chavarro JE, Dickerman BA, et al. Estimating the effect of nutritional interventions using observational data: the American Heart Association's 2020 Dietary Goals and mortality. Am J Clin Nutr. 2021;114:690-703.
122) Jensen MK, Andersen AT, Sørensen TI, Becker U, Thorsen T, Grønbaek M. Alcoholic beverage preference and risk of becoming a heavy drinker. Epidemiology. 2002;13:127-32.
123) Sayon-Orea C, Martinez-Gonzalez MA, Bes-Rastrollo M. Alcohol consumption and body weight: a systematic review. Nutr Rev. 2011;69:419-31.
124) Narayan KMV, Patel SA, Cunningham SA, Curran J. Ominous Reversal of Health Gains in the United States: Time to rethink research priorities? Ann Intern Med. 2019;170:330-1.

SUPPLEMENT 1

PATIENT INFORMATION SHEET

MODELO HOJA DE INFORMACIÓN AL PACIENTE: ESTUDIO UNATI DE INTERVENCIÓN CON CONSEJOS SOBRE CONSUMO DE ALCOHOL

TÍTULO DEL ESTUDIO: "Ensayo aleatorizado de no inferioridad para evaluar un consejo de consumo moderado de alcohol frente a un consejo de abstención"

Investigador Principal: MIGUEL ANGEL MARTÍNEZ GONZÁLEZ

Servicio Promotor del estudio: DEPARTAMENTO DE MEDICINA PREVENTIVA Y SALUD PÚBLICA

Centro: UNIVERSIDAD DE NAVARRA

Teléfono: 948 42 56 00

Le invitamos a participar en una investigación acerca de los efectos de nuestros consejos sobre el consumo de alcohol para mejorar su salud.

Antes de decidir si desea participar en este estudio, es importante que entienda por qué es necesaria esta investigación, lo que va a implicar su participación, cómo se va a utilizar su información y sus posibles beneficios, riesgos y molestias. Por favor, tómese el tiempo necesario para leer atentamente la información proporcionada a continuación.

RESUMEN DEL ESTUDIO

Se propone desarrollar un estudio clínico dirigido a la mejora de los hábitos de consumo de alcohol y cuyo objetivo es estudiar la prevención de los principales riesgos cardiovasculares, metabólicos, hepáticos, de cáncer, de enfermedad mental y de accidentes relacionados con el consumo de alcohol, así como de la mortalidad prematura que se puede evitar al reducir o moderar el consumo de alcohol. Para esto, se compararán dos tipos de consejos sanitarios.

PARTICIPACIÓN VOLUNTARIA Y RETIRADA DEL ESTUDIO

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

En caso de que Vd. decidiera abandonar el estudio puede hacerlo permitiendo el uso de los datos obtenidos hasta el momento y de las muestras biológicas para la finalidad del estudio o, si fuera su voluntad, sus muestras biológicas serían destruidas y sus datos borrados de los ficheros informáticos.

También se le podrá retirar del estudio si en cualquier momento se le diagnosticase una enfermedad de importante magnitud que no le permita el consumo moderado de alcohol.

Todo esto se realizará en todo momento de manera coordinada y bajo la supervisión de su médico y el equipo investigador.

¿Quién puede participar?

El estudio se realizará en voluntarios de ambos sexos, mayores de edad, que acostumbren a consumir alcohol, al menos 3 bebidas a la semana. No podrá participar en el estudio quien tenga enfermedades crónicas que desaconsejen el consumo de alcohol, intolerancia al alcohol, tiene historia personal o familiar de adicción al alcohol, ni quien no esté dispuesto a escuchar consejos que le ayuden a cambiar su consumo de alcohol durante el periodo de estudio.

Si acepta participar, usted va a formar parte de un estudio en el que se incluirán a unos 10000 pacientes.

Tras comprobar que se cumplen los criterios de inclusión para poder empezar el estudio, usted será contactado telefónicamente por la coordinación del estudio para citarle a una primera entrevista telefónica de recogida de datos.

¿En qué consiste este estudio?

El estudio consiste en comparar dos tipos de consejos sobre el consumo de alcohol. En concreto se pretende ver cuál de ellos es más efectivo para reducir los riesgos de las enfermedades que se pueden relacionar con el consumo de alcohol.

En la primera consulta se recogerán a través de un cuestionario administrado por medio de internet (y que podrá usted rellenar desde su ordenador o teléfono móvil) sus datos socio-demográficos, personales y clínicos (edad, sexo, escolarización), estilo de vida, dieta, actividad física, antecedentes personales, antecedentes patológicos y toma de medicaciones, así como variables relacionadas con el consumo de alcohol (consumo habitual, tipo de bebida), y con la dieta. Además, se recogerá información sobre sintomatología depresiva, función cognitiva y calidad de vida. En la consulta del médico que les ha invitado, a todos los pacientes se les pesará, tallará, medirá la circunferencia de la cintura y la presión arterial. Anualmente su médico accederá a su Historia Clínica y enviará a los investigadores del proyecto los resultados que haya de análisis de sangre rutinarios que le hayan hecho para valorar glucosa, lípidos o enzimas hepáticas en sangre y si se le hubiera hecho un Electrocardiograma durante el primer y cuarto año.

Durante 4 años, cada año de seguimiento, se le volverán a realizar las mismas mediciones que al inicio del estudio, salvo el electrocardiograma, que solo se recogerá, si está disponible, al final de los 4 años (en caso de que sea una prueba indicada por su médico).

A un pequeño porcentaje de pacientes, solo a un 3 por ciento elegido al azar, se les pedirá que, cuando vayan a la peluquería a cortarse el pelo, proporcionen a los investigadores una muestra de pelo (de medio centímetro cada una) para enviarlas a Italia (universidad de Turín) para medir en ese pelo unos compuestos químicos derivados del alcohol. Se pedirá una

muestra de pelo en dos ocasiones durante el tiempo de duración del estudio. En caso de ser elegido, nos pondremos en contacto para explicarle el procedimiento de recogida de la muestra de pelo. Los gastos de estos envíos se cubrirán desde el estudio. Las muestras de pelo enviadas tendrán un código de modo que no se podrá conocer la identidad del donante por parte de los investigadores de la Universidad de Turín. Una vez realizados los análisis necesarios las muestras de pelo serán destruidas.

¿Cuánto tiempo supondrá mi participación en este estudio?

La duración del estudio es de 4 años. Después de la visita inicial, se realizará una visita de revisión cada 12 meses con su médico. En el transcurso del seguimiento, se le preguntará dos veces al año por el consumo de alcohol mediante entrevista individual telefónica-teleconferencia y otras dos veces se le invitará a una sesión en grupo también mantenida a través de internet por teleconferencia.

Los pacientes de cada grupo de intervención serán contactados de este modo (4 veces al año en total, dos entrevistas individuales y dos sesiones de grupo) para recibir información sobre cómo actuar sobre su consumo de alcohol y recibir consejo y ayuda al respecto.

Al inicio del estudio, así como en una de las visitas de cada año, deberá rellenar una serie de cuestionarios que, junto con las preguntas de la dietista o psicólogo, supondrán aproximadamente 45 minutos.

Es importante resaltar que no va a recibir ningún fármaco ni se le modificará el tratamiento que usted toma habitualmente. Si a lo largo del estudio fueran necesarias modificaciones en su tratamiento habitual, éstas serán realizadas por el personal médico y de enfermería que le atienden actualmente.

¿Cómo se asigna la intervención?

El tipo de intervención que va a recibir se asigna al azar, es decir, ni usted ni el investigador deciden el grupo al que van a pertenecer. La asignación al azar es aceptable porque los consejos que se recibirán en ambos grupos son igualmente recomendables y no existe ningún ensayo que haya evaluado qué recomendación con respecto al consumo de alcohol es la más adecuada. Este procedimiento es muy necesario para que los resultados del estudio sean válidos.

¿En qué consiste mi participación?

En primer lugar, usted habrá contestado a unas preguntas para determinar si cumple los requisitos de entrada en el estudio. Una vez que haya sido seleccionado, su participación consistirá en:

Contestar encuestas sobre su estado de salud, consumo de alimentos, actividad física, consumo de tabaco y alcohol, y calidad de vida, así como facilitar muestras de pelo, si le correspondiese por azar hacerlo.

Recibir periódicamente consejos, material educativo sobre el consumo de alcohol que usted deberá seguir tal como se le asigne desde el principio del estudio, teniendo en cuenta que bajo ningún concepto se le pedirá que incremente su ingesta de alcohol.

Como se le ha explicado previamente usted será asignado al azar a participar en uno de los dos posibles grupos de intervención. La participación descrita más arriba no es igual en los dos grupos. La diferencia es que cada uno de ellos recibirá una recomendación diferente en cuanto a la manera de mejorar su consumo de alcohol. Usted no debe desvelar a su médico a qué tipo de consejo sobre el alcohol se le ha asignado. Su médico ya es consciente de que usted no le revelará esta información.

¿Cuáles son los posibles beneficios y riesgos derivados de mi participación en el estudio?

Su participación en el estudio le facilitará un programa para cambiar su consumo de alcohol a un consumo más saludable.

También es posible que usted no obtenga ningún beneficio directo por participar en el estudio. No obstante, se prevé que la información que se recogerá pueda beneficiar en un futuro a otros pacientes para prevenir la aparición de enfermedades crónicas.

Al finalizar la investigación podrá ser informado, si lo desea, sobre los principales resultados y las conclusiones generales del estudio.

¿Quién tiene acceso a mis datos personales y cómo se protegen?

Todos los datos personales incluidos los clínicos serán tratados conforme a las leyes actuales de protección de datos, especialmente conforme al RGPD.

Los médicos del estudio (si no surgiese ningún inconveniente, solo será su médico, quien le ha invitado a participar) podrán acceder anualmente a su historia clínica para verificar si le ha sido diagnosticada alguna enfermedad durante los 10 años siguientes al inicio del estudio.

Los informes y datos sobre posible ocurrencia de nuevas enfermedades obtenidos de su historia clínica que tenga que enviar su médico al comité independiente de médicos que juzgará si se han producido o no algunos eventos clínicos nunca contendrá información personal sobre su identidad, y sólo se identificarán los datos mediante un código numérico, que no permitirá identificarle. Por lo tanto, la adjudicación de eventos clínicos por este comité será ciega a la identidad del participante.

El conjunto de datos que se genere (completamente anonimizado) se pondrá a disposición de cualquier investigador competente, que podrá presentar una propuesta de investigación pertinente al Comité Directivo para su posterior explotación. Se respetarán todas las precauciones legales habituales para la protección de datos individuales. Existirá una pequeña base de datos (no conectada nunca a internet) que será custodiada solo por la persona del estudio que mantenga contacto con usted y contendrá sus datos de identificación personal (nombre y apellidos, dirección, teléfono, correo electrónico, nombre de familiares y teléfonos alternativos para recuperar el contacto, fecha de nacimiento, nombre del médico que le invitó, hospital o centro de salud) y con su hoja de consentimiento informado firmado.

Si el médico que le ha invitado cambiase de Centro sanitario en la misma Comunidad Autónoma, se le solicitará a usted la autorización para que continúen entrando en su historia clínica otros médicos del estudio, siempre que usted los autorice y sigan trabajando en el sistema nacional de salud.

Además, a cada participante se le asignará un número de identificación correlativo que constituirá el identificador único exclusivo de la base de datos general anonimizada en la que se almacenarán todos los demás datos (cuestionarios, análisis y eventos clínicos de los participantes, pero no los datos antes mencionados). En esa base de datos general anonimizada no se incluirán ni el código postal ni la fecha exacta de nacimiento. Para sustituir la fecha de nacimiento, la base de datos anonimizada general redondeará todos los días del mes de nacimiento al 1 o al 15 de ese mes, de modo que no haya forma de identificar a los participantes por su fecha de cumpleaños. La base de datos utilizada por los investigadores para los análisis estadísticos será la base de datos general anonimizada. Sólo aquellos investigadores biomédicos, debidamente cualificados, que presenten una propuesta de análisis científicamente rigurosa y relevante para su consideración por el Comité de Dirección, una vez aprobada por éste, dispondrán de variables (sólo las realmente imprescindibles) de esta base de datos general anonimizada. Se les pedirá que destruyan los datos, una vez publicado el artículo, y que envíen la sintaxis y los códigos utilizados al Comité Directivo.

El Responsable del Tratamiento de los datos de la Universidad de Navarra, en cumplimiento del Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de éstos, en adelante RGPD, le informa que si participa en este estudio, sus datos clínicos serán tratados por el equipo investigador para extraer concusiones del Proyecto. También podrán acceder a los datos las autoridades sanitarias y los miembros del comité ético si lo considerasen necesario.

No será posible identificarle a usted a través de las comunicaciones que pudiera generar este estudio.

Usted es el responsable de la veracidad y corrección de los datos que nos entrega y tiene la facultad de ejercer los derechos de acceso, rectificación, supresión, limitación del tratamiento, portabilidad y de oposición de sus datos de acuerdo con lo dispuesto en la normativa de protección de datos. Para ejercerlos, deberá dirigirse por escrito al Delegado de Protección de

Datos de la Universidad de Navarra a la siguiente dirección postal: Oficina del DPO, Edificio Amigos, Campus Universitario, 31080 Pamplona (Navarra, España) o a la dirección de correo electrónico dpo@unav.es , en cualquier caso, para ejercer estos derechos deberá adjuntar una fotocopia de su documento nacional de identidad o equivalente.

En caso de no estar de acuerdo con el tratamiento realizado por nuestra Entidad o considerar vulnerados sus derechos, tiene derecho a presentar una reclamación ante la Agencia Española de Protección de datos.

Si usted lo autoriza, los datos clínicos encontrados durante el estudio y que sean relevantes para su salud le serán comunicados a través del equipo investigador. Estos datos clínicos pueden ser resultados previstos en los objetivos del estudio o pueden ser hallazgos inesperados pero relevantes para su salud.

¿Recibiré algún tipo de compensación económica?

No se prevé ningún tipo de compensación económica durante el estudio.

¿Quién financia esta investigación?

Los resultados previos a este estudio son financiados por fondos públicos procedentes del Consejo Europeo de Investigación (*European Research Council*) perteneciente a la Unión Europea. Está previsto presentar el proyecto a otras convocatorias regionales, nacionales e internacionales.

OTRA INFORMACIÓN RELEVANTE

Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.

CALIDAD CIENTÍFICA Y REQUERIMIENTOS ÉTICOS DEL ESTUDIO

Este estudio ha sido sometido a aprobación por el Comité de ética de investigación de la UNIVERSIDAD DE NAVARRA que vela por la calidad científica y ética de los proyectos de investigación que se llevan a cabo en el centro. Este comité vigila para que la investigación que se hace con personas se realice de acuerdo con la declaración de Helsinki y se aplique la normativa legal vigente sobre investigación biomédica (ley 14/2007, de 3 de Junio de investigación biomédica).

PREGUNTAS

Llegado este momento le damos la oportunidad de que, si no lo ha hecho antes, formule las preguntas que considere oportunas. El equipo investigador le responderá lo mejor que le sea posible.

INVESTIGADORES DEL ESTUDIO

Si tiene alguna duda sobre algún aspecto del estudio o le gustaría comentar algún aspecto de esta información, por favor no deje de preguntar a los miembros del equipo investigador. Si así lo desea puede ponerse en contacto con los médicos que le han atendido y que participan en esta investigación o con el investigador principal del proyecto, el Dr. Miguel A. Martínez-González (Telf. 948 42 56 00 EXT. 806463). Si el médico que le ha invitado cambiase de centro sanitario se procurará no interrumpir la recogida de sus datos, por ejemplo, transfiriendo la responsabilidad a otro colega del mismo centro que ya sea investigador en este proyecto o que quiera incorporarse como nuevo investigador. Si el médico que le invitó y cambia de centro sanitario permaneciese en su misma comunidad autónoma, seguirá colaborando mediante la revisión anual de su historia clínica a través del sistema informatizado de historias que tiene cada comunidad autónoma. En caso de que una vez leída esta información y aclaradas las dudas decida participar en el estudio, deberá firmar su consentimiento informado.

CONSENTIMIENTO INFORMADO

Nombre y Apellidos:.....

DNI:.....

Dirección Postal.....

Quién ha informado:.....

Médico del participante:.....

	SI	NO
Acepto participar de forma voluntaria en el estudio:		
He leído la Hoja de Información al Paciente, comprendo los riesgos y los beneficios que comporta, que mi participación es voluntaria y que me puedo retirar o solicitar que retiren mis datos y/o muestras siempre que quiera.	□	
Comprendo que mi participación en el estudio consiste en: entrevistas telefónicas o por teleconferencia programadas para sesiones individuales y/o grupales informativas, seguir con las pautas indicadas por los dietistas, psicólogos y médicos del estudio.	□	
Comprendo que no recibiré un beneficio directo por mi participación en este estudio y que no recibiré ningún beneficio económico en el futuro en el caso en que se desarrolle un nuevo tratamiento o test médico.	□	
Comprendo que la información del estudio será confidencial y que ninguna persona no autorizada tendrá acceso a los datos o a las muestras.	□	
Sé cómo ponerme en contacto con los investigadores si lo necesito.	□	
Doy mi permiso para que los investigadores contacten conmigo nuevamente si soy apto para el estudio UNATI a través de los teléfonos que también indico: ……	□	□
Autorizo que los datos clínicos encontrados durante el estudio y que sean relevantes para mi salud, me sean comunicados a través del equipo investigador.	□	□
Autorizo donar dos muestra de pelo si formo parte del 3% de todos los participantes a los que se les van a solicitar estas muestras	□	□
Autorizo a que los médicos del estudio (si no surgiese ningún inconveniente, será mi médico, quien me invitó a participar) podrán acceder anualmente a mi historia clínica durante los 10 años siguientes al inicio del estudio.	□	□

Firmas

Participante:	Quién ha informado:

Fecha (Día/mes/año):

SUPPLEMENT 2
INFORMATION AND CONSENT FOR TRIALISTS

Estimado compañero,

Hemos recibido tu amable solicitud para recibir información sobre el proyecto UNATI. Ante el interés que has manifestado, es un placer para nosotros invitarte formalmente mediante esta carta a formar parte de pleno derecho del equipo investigador del proyecto "**University of Navarra Alumni Trialists Initiative (UNATI)",** financiado por el Consejo Europeo de Investigación (***European Research Council*****, ERC**) para el periodo **2023-2028**.

UNATI es un ensayo aleatorizado, de no inferioridad, pragmático y con amplios criterios de inclusión, que no usa medicamentos, pues es de estilo de vida. Se trata del **mayor ensayo sobre alcohol y salud** que se ha realizado hasta ahora. Comparará dos consejos distintos sobre el consumo de **alcohol** en pacientes bebedores de 50 a 75 años (que consuman entre 3 y 40 bebidas alcohólicas estándar por semana). Aproximadamente, el 50% de los pacientes reclutados serán asignados al azar a aconsejarles que reduzcan su consumo con la meta final de dejar de beber alcohol y al otro 50% se les asignará a recomendarles un consumo moderado, preferentemente de vino tinto, solo con las comidas, repartido a lo largo de toda la semana y a evitar el consumo en atracón (*binge drinking*).

El propio nombre del estudio incluye el término **'trialists'** *(ensayistas)* para referirse a los médicos investigadores del proyecto que reclutarán y seguirán clínicamente pacientes para **UNATI**. Este será tu papel en el ensayo si aceptas nuestra invitación. A partir de tu incorporación, pondremos a tu disposición los recursos de investigación y bases de datos que se generen. Esto también permitirá que puedas solicitar proyectos de investigación y valorar las hipótesis que creas pertinentes, como investigador de este equipo. Los recursos de investigación que se generen y se os facilitarán a los investigadores para que podáis solicitar proyectos de investigación y valorar hipótesis estarán siempre totalmente anonimizados y respetarán todas las normas legales sobre protección de datos de carácter personal.

Para que un médico pueda participar como investigador-ensayista (*trialist*) se requiere que desarrolle su actividad clínica sobre adultos **en España**, ya sea en un centro sanitario público o privado. La misión de los ensayistas es **asegurar inicialmente un ritmo ágil y eficiente de reclutamiento y, después, una gran** diligencia en la **revisión anual de las historias** clínicas de los pacientes participantes **para recoger los datos necesarios cada año, durante 4 años consecutivos.** Los datos concretos que debe recoger el médico son: **a)** basalmente: datos básicos sociodemográficos y verificar criterios de **inclusión**; **b)** basalmente y luego cada año durante 4 años consecutivos: **peso, talla, circunferencia de la cintura y presiones arteriales** sistólica y diastólica; **c)** basalmente y a los 4 años: **ECG** si está disponible en la historia o se ha tenido que realizar por estar clínicamente indicado en el paciente; **d)** analíticas rutinarias basalmente y cada año si constan en la historia o se realizaron por estar clínicamente indicadas en el paciente (incluyen **lípidos, glucemia y enzimas hepáticas**); **e)** cada año, **solo a partir del primer año**, la información clínica sobre los **eventos nuevos** si es que se han producido (casos incidentes, es decir nuevos diagnósticos de enfermedad cardiovascular, cáncer, diabetes, depresión, demencia, lesiones o infecciones que requieran hospitalización así como los nuevos diagnósticos confirmados de tuberculosis).

Se ha *minimizado* en el protocolo la *carga de trabajo* que debe recaer sobre cada *trialist*. La meta es reclutar **como mínimo 25 pacientes** por *trialist*. El *trialist* deberá contactar inicialmente con cada uno de esos 25 (o más) pacientes para invitarles a que *participen en un ensayo que valora consejos sobre el consumo de alcohol y la salud*.

La participación del paciente consistirá en que recibirá llamadas para entrevistas y sesiones grupales (en total, 4 contactos al año) y mensajes por pantallas y teléfonos móviles. También se debe informar al paciente de que *posiblemente el proyecto regale o promueva regalos de bebidas o bonos para reducir el precio de la compra de bebidas con o sin alcohol, dependiendo del grupo al que se aleatorice al paciente*. El *trialist* también deberá rellenar *on-line* inicialmente un breve cuestionario con los datos básicos sociodemográficos de cada paciente que acepte participar (**anexo 1**).

Es importante recalcar que los médicos *trialists* **no** serán responsables de realizar la intervención y que deben quedar enmascarados respecto al grupo al que será asignado el paciente. Nunca deben preguntarle por los consejos que recibe sobre alcohol desde el personal contratado por **UNATI**. Este aspecto es metodológicamente clave y debe quedar claro. Por eso el *trialist* **debe firmar su compromiso en el documento adjunto que incluye también su compromiso con la aplicación continuada de la metodología y procedimientos que deberán utilizarse (anexo 2)**[1].

Otras personas, los profesionales sanitarios contratados por UNATI (*coaches*), serán quienes hagan la intervención, empezando por verificar con detalle que el paciente cumple los criterios de elegibilidad una vez que reciban el breve cuestionario que habrá completado *on-line* el médico *trialist* (datos básicos sociodemográficos del paciente). Estos *coaches* también explicarán y recogerán el consentimiento informado, realizarán el proceso de aleatorización y mantendrán las entrevistas personales y las sesiones grupales periódicas por vía remota (teléfono, tableta u ordenador) con cada paciente para ayudarle a que cambie su patrón de consumo de alcohol y para recoger los cuestionarios. Nada de esto recaerá sobre el *trialist*.

Los **criterios de inclusión** son muy amplios, son elegibles todos los pacientes, con cualquier patología (excepto **enfermedad psiquiátrica activa severa, cáncer de mama reciente, enfermedades hepáticas graves o demencia diagnosticada)**, de 50-70 años (varones) o 55-75 años (mujeres), no institucionalizados, con una esperanza de vida proyectada >5 años (según el criterio del médico que les atiende). Deben estar dispuestos a recibir asesoramiento (por vía remota, sin tener que desplazarse) durante 4 años sobre cómo mejorar su consumo de alcohol, haciéndolo más saludable.

Los **criterios de exclusión** son:

1) Abstemios y bebedores de menos de 30 g de alcohol puro/semana o de más de 400 g de alcohol puro/semana. O paciente en tratamiento con naltrexona.
2) Analfabetismo, incapacidad/no disposición para dar el consentimiento informado por escrito o para comunicarse con el personal del estudio, o capacidades subóptimas para el uso de tecnologías en línea (basta con que puedan usar con cierta solvencia o bien teléfonos inteligentes o bien tabletas o bien ordenadores).
3) Alguna afección psiquiátrica grave o diagnóstico de demencia.
4) Cualquier enfermedad hepática crónica grave, excepto hígado graso no alcohólico.
5)-Pacientes con diagnóstico reciente (últimos 10 años) de cáncer de mama.
6)-Pacientes con cualquier tratamiento crónico en dosis tan altas que impidan el consumo de alcohol. La mayoría de estos pacientes ya estarán excluidos por el primer o tercer criterio de exclusión. Los casos excepcionales se pueden evaluar individualmente tras comprobar las interacciones farmacológicas con el alcohol y su relevancia clínica o práctica.
7)- Paciente para el que el médico tenga evidencia fuerte de que el consumo de alcohol es una contraindicación por el grave perjuicio que puede tener para su salud, dada su condición clínica particular o por constar episodios recientes de agravamiento de su situación al consumir alcohol.

Por favor, si deseas integrarte en el equipo investigador de **UNATI**, no olvides enviarnos tu **compromiso de participación y de confidencialidad/enmascaramiento para no indagar nunca el brazo del** ensayo al que sea aleatorizado cada paciente. Puedes hacerlo en **https://medpreventiva.es/AhsYnr**.

Un cordial saludo,

Miguel A. Martínez-González
Investigador Principal del Proyecto UNATI
mamartinez@unav.es

[1] Si el médico cambia de centro sanitario se procurará no interrumpir la recogida de datos, por ejemplo, transfiriendo los pacientes a otro colega del mismo centro que ya sea trialist o que quiera incorporarse como nuevo trialist. Los que cambien de centro no dejarán de ser trialists. Si permanecen en la misma comunidad autónoma y -como es de esperar- cuentan con el permiso de sus antiguos pacientes para revisar las historias clínicas, seguirán colaborando mediante la revisión anual de historias clínicas a través del sistema informatizado de historias que tiene cada comunidad autónoma. Si siguiese abierto el reclutamiento cuando cambien de centro, podrían reclutan nuevos pacientes en el centro sanitario al que se trasladen.

Anexo I

DATOS DEL PACIENTE (a rellenar *on-line* por el médico-investigador o *trialist*)

Nombre:	
Apellido 1:	
Apellido 2:	

Sexo		
Edad		

Domicilio (calle, nº, piso):	
Código postal:	
Ciudad (provincia):	
Correo electrónico:	
Teléfono móvil:	
Segundo teléfono de contacto:	

¿Usa habitualmente teléfono móvil?	□ Sí	□ No
¿Sabe usar internet?	□ Sí	□ No
¿Posee una tableta con internet?	□ Sí	□ No
¿Posee ordenador con internet?	□ Sí	□ No

¿Padece actualmente alguna enfermedad hepática grave?	□ Sí	□ No
¿Tuvo cáncer de mama hace <10 años?	□ Sí	□ No
¿Ha sido diagnosticado de demencia?	□ Sí	□ No
¿Padece actualmente enfermedad psiquiátrica grave?	□ Sí	□ No
¿Está en tratamiento con naltrexona?	□ Sí	□ No
¿Está en tratamiento habitualmente con algún fármaco en dosis suficientemente altas como para que impidan todo consumo (aun minimo) de alcohol	□ Sí	□ No
¿Cuántas bebidas con alcohol consume aproximadamente a la semana?		

Anexo 2

MODELO DE COMPROMISO DE PARTICIPACIÓN EN EL PROYECTO, CONFIDENCIALIDAD Y ENMASCARAMIENTO: ESTUDIO UNATI DE INTERVENCIÓN CON CONSEJOS SOBRE CONSUMO DE ALCOHOL

Para garantizar el enmascaramiento del médico respecto al brazo del ensayo al que aleatoriamente se haya asignado al participante, resulta imprescindible que el médico que ha reclutado a cada paciente y le visitará anualmente NUNCA le interrogue sobre el grupo asignado. Tampoco debe interrogarle sobre los consejos que está recibiendo por vía remota de las personas que ejercen de *coaches* (dietistas o psicólogos), ya que conocer esa asignación podría consciente o inconscientemente sesgar la recogida de información clínica que hará el médico reclutador.

COMPROMISO DE ENMASCARAMIENTO Y PARTICIPACION

Nombre y Apellidos del médico:.....
DNI:.....
Dirección Postal.....
Centro Sanitario:.....

	SI	NO
Acepto participar como reclutador de forma voluntaria en el estudio.	□	
He leído las condiciones de compromiso de confidencialidad, comprendo los riesgos y los beneficios que comporta, y me comprometo a que, mientras dure el ensayo, nunca preguntaré al paciente sobre el brazo de aleatorización al que fue asignado o los consejos que recibe del ensayo	□	
Comprendo que mi participación en el estudio consiste en: valorar sus requisitos de elegibilidad, invitar a los pacientes elegibles a que reciban una llamada para que les expliquen el estudio y les propongan participar y revisar anualmente sus historias clínicas para remitir al investigador principal los nuevos diagnósticos que son considerados eventos primarios o secundarios.	□	
Comprendo que no recibiré un beneficio económico por mi participación como reclutador en este estudio.	□	
Me comprometo a cumplir con continuidad y esmero todos los aspectos metodológicos detallados en el Plan de Investigación (Research Plan) del ensayo UNATI, a reclutar al menos 25 pacientes y a seguirlos 4 años	□	

Firmas

Médico:	Quién le ha informado:

Fecha (Día/mes/año):

SUPPLEMENT 3
INFORMATION AND CONSENT FOR COORDINATORS

Estimado compañero,

Hemos recibido tu amable solicitud para recibir información sobre el proyecto UNATI en el que nos has pedido asumir la responsabilidad de actuar como Coordinador-Investigador. Ante el interés que has manifestado, es un placer para nosotros invitarte formalmente mediante esta carta a ser uno de los Coordinadores-Investigadores que dirigirán el equipo investigador del proyecto "**University of Navarra Alumni Trialists Initiative (UNATI)",** financiado por el Consejo Europeo de Investigación (***European Research Council*, ERC**) para el periodo **2023-2028**.

UNATI es un ensayo aleatorizado, de no inferioridad, pragmático y con amplios criterios de inclusión, que no usa medicamentos, pues es de estilo de vida. Se trata del **mayor ensayo sobre alcohol y salud** que se ha realizado hasta ahora. Comparará dos consejos distintos sobre el consumo de **alcohol** en pacientes bebedores de 50 a 75 años (que consuman entre 3 y 40 bebidas alcohólicas estándar por semana). Aproximadamente, el 50% de los pacientes reclutados serán asignados al azar a aconsejarles que reduzcan su consumo con la meta final de dejar de beber alcohol y al otro 50% se les asignará a recomendarles un consumo moderado, preferentemente de vino tinto, solo con las comidas, repartido a lo largo de toda la semana y a evitar el consumo en atracón (*binge drinking*).

El propio nombre del estudio incluye el término **'trialists'** *(ensayistas)* para referirse a los médicos investigadores del proyecto que reclutarán y seguirán clínicamente pacientes para **UNATI**. Coordinar a estos trialists será tu papel en el ensayo si aceptas nuestra invitación. A partir de tu incorporación, pondremos a tu disposición los recursos de investigación y bases de datos que se generen. Esto también permitirá que puedas solicitar proyectos de investigación y valorar las hipótesis que creas pertinentes, como uno de los investigadores que dirige este equipo. Los recursos de investigación que se generen y se os facilitarán a los investigadores para que podáis solicitar proyectos de investigación y valorar hipótesis estarán siempre totalmente anonimizados y respetarán todas las normas legales sobre protección de datos de carácter personal.

Para que un médico pueda participar como investigador-ensayista (*trialist*) se requiere que desarrolle su actividad clínica sobre adultos **en España**, ya sea en un centro sanitario público o privado. La misión de los Coordinadores es mantener un contacto permanente con los médicos ensayistas de su equipo (unos 10). Estos contactos deben ser ágiles y pueden hacerse frecuentemente por correo electrónico o whatsapp, pero al menos una vez el mes deben ser por teléfono, teleconferencia o cuando sea posible, personalmente, cara a cara. En tales contactos el Coordinador debe asegurar que los ensayistas están cumpliendo los plazos y están desarrollando con exactitud y fidelidad cada una de las tareas que tienen asignadas en el protocolo del proyecto.

Las tareas de los ensayistas son **asegurar inicialmente un ritmo ágil y eficiente de reclutamiento y, después, una gran** diligencia en la **revisión anual de las historias** clínicas de los pacientes participantes **para recoger los datos necesarios cada año, durante 4 años consecutivos.** Los datos concretos que debe recoger cada ensayista son: **a)** basalmente: datos básicos sociodemográficos y verificar criterios de **inclusión**; **b)** basalmente y luego cada año durante 4 años consecutivos: **peso, talla, circunferencia de la cintura y presiones arteriales** sistólica y diastólica; **c)** basalmente y a los 4 años: **ECG** si está disponible en la historia o se ha tenido que realizar por estar clínicamente indicado en el paciente; **d)** analíticas rutinarias basalmente y cada año si constan en la historia o se realizaron por estar clínicamente indicadas en el paciente (incluyen **lípidos, glucemia y enzimas hepáticas**); **e)** cada año, **solo a partir del primer año**, la información clínica sobre los **eventos nuevos** si es que se han producido (casos incidentes, es decir nuevos diagnósticos de enfermedad cardiovascular, cáncer, diabetes, depresión, demencia, lesiones o infecciones que requieran hospitalización así como los nuevos diagnósticos confirmados de tuberculosis).

Se ha *minimizado* en el protocolo la *carga de trabajo* que debe recaer sobre cada *trialist*. La meta es reclutar **como mínimo 25 pacientes** por *trialist*. El *trialist* deberá contactar inicialmente con cada uno de esos 25 (o más) pacientes para invitarles a que *participen en un ensayo que valora consejos sobre el consumo de alcohol y la salud*. Así, cada Coordinador, junto con su equipo de unos 20 trialists,

será responsable de que unos 400 a 500 pacientes sean aleatorizados y seguidos con fidelidad a lo establecido en el protocolo.

La participación del paciente consistirá en que recibirá llamadas para entrevistas y sesiones grupales (en total, 4 contactos al año) y mensajes por pantallas y teléfonos móviles. También se debe informar al paciente de que *posiblemente el proyecto regale o promueva regalos de bebidas o bonos para reducir el precio de la compra de bebidas con o sin alcohol, dependiendo del grupo al que se aleatorice al paciente*. El *trialist* también deberá rellenar *on-line* inicialmente un breve cuestionario con los datos básicos sociodemográficos de cada paciente que acepte participar (**anexo 1**).

Es importante recalcar que ni los Coordinadores, ni los médicos *trialists* serán responsables de realizar la intervención y que deben quedar enmascarados respecto al grupo al que será asignado el paciente. Nunca deben preguntarle por los consejos que recibe sobre alcohol desde el personal contratado por **UNATI**. Este aspecto es metodológicamente clave y debe quedar claro. Por eso, tanto el Coordinador como el *trialist* **debe firmar su compromiso en el documento adjunto que incluye también su compromiso con la aplicación continuada de la metodología y procedimientos que deberán utilizarse (anexo 2)**[2].

Otras personas, los profesionales sanitarios contratados por UNATI (*coaches*), serán quienes hagan la intervención, empezando por verificar con detalle que el paciente cumple los criterios de elegibilidad una vez que reciban el breve cuestionario que habrá completado *on-line* el médico *trialist* (datos básicos sociodemográficos del paciente). Estos *coaches* también explicarán y recogerán el consentimiento informado, realizarán el proceso de aleatorización y mantendrán las entrevistas personales y las sesiones grupales periódicas por vía remota (teléfono, tableta u ordenador) con cada paciente para ayudarle a que cambie su patrón de consumo de alcohol y para recoger los cuestionarios. Nada de esto recaerá sobre el *trialist*.

Los **criterios de inclusión** son muy amplios, son elegibles todos los pacientes, con cualquier patología (excepto **enfermedad psiquiátrica activa severa, cáncer de mama reciente, enfermedades hepáticas graves o demencia diagnosticada)**, de 50-70 años (varones) o 55-75 años (mujeres), no institucionalizados, con una esperanza de vida proyectada >5 años (según el criterio del médico que les atiende). Deben estar dispuestos a recibir asesoramiento (por vía remota, sin tener que desplazarse) durante 4 años sobre cómo mejorar su consumo de alcohol, haciéndolo más saludable.

Los **criterios de exclusión** son:

1) Abstemios y bebedores de menos de 30 g de alcohol puro/semana o de más de 400 g de alcohol puro/semana. O paciente en tratamiento con naltrexona.

2) Analfabetismo, incapacidad/no disposición para dar el consentimiento informado por escrito o para comunicarse con el personal del estudio, o capacidades subóptimas para el uso de tecnologías en línea (basta con que puedan usar con cierta solvencia o bien teléfonos inteligentes o bien tabletas o bien ordenadores).

3) Alguna afección psiquiátrica grave o diagnóstico de demencia.

4) Cualquier enfermedad hepática crónica grave, excepto hígado graso no alcohólico.

5)-Pacientes con diagnóstico reciente (últimos 10 años) de cáncer de mama.

6)- Pacientes con cualquier tratamiento crónico en dosis tan altas que impidan el consumo de alcohol. La mayoría de estos pacientes ya estarán excluidos por el primer o tercer criterio de exclusión. Los casos excepcionales se pueden evaluar individualmente tras comprobar las interacciones farmacológicas con el alcohol y su relevancia clínica o práctica.

7)- Paciente para el que el médico tenga evidencia fuerte de que el consumo de alcohol es una contraindicación por el grave perjuicio que puede tener para su salud, dada su condición clínica particular o por constar episodios recientes de agravamiento de su situación al consumir alcohol.

[2] Si el médico cambia de centro sanitario se procurará no interrumpir la recogida de datos, por ejemplo, transfiriendo los pacientes a otro colega del mismo centro que ya sea trialist o que quiera incorporarse como nuevo trialist. Los que cambien de centro no dejarán de ser trialists. Si permanecen en la misma comunidad autónoma y -como es de esperar- cuentan con el permiso de sus antiguos pacientes para revisar las historias clínicas, seguirán colaborando mediante la revisión anual de historias clínicas a través del sistema informatizado de historias que tiene cada comunidad autónoma. Si siguiese abierto el reclutamiento cuando cambien de centro, podrían reclutan nuevos pacientes en el centro sanitario al que se trasladen.

Por favor, si deseas integrarte como Coordinador-Investigador en el equipo investigador de **UNATI**, no olvides enviarnos tu **compromiso de participación y de confidencialidad/enmascaramiento para no indagar nunca el brazo del** ensayo al que sea aleatorizado cada paciente. Puedes hacerlo en **https://medpreventiva.es/AhsYnr**.

Un cordial saludo,

Miguel A. Martínez-González
Investigador Principal del Proyecto UNATI
mamartinez@unav.es

Anexo 2

MODELO DE COMPROMISO DE PARTICIPACIÓN COMO COORDINADOR EN EL PROYECTO, CONFIDENCIALIDAD Y ENMASCARAMIENTO: ESTUDIO UNATI DE INTERVENCIÓN CON CONSEJOS SOBRE CONSUMO DE ALCOHOL

Para garantizar el enmascaramiento del médico respecto al brazo del ensayo al que aleatoriamente se haya asignado al participante, resulta imprescindible que el médico que ha reclutado a cada paciente y le visitará anualmente NUNCA le interrogue sobre el grupo asignado. Tampoco debe interrogarle sobre los consejos que está recibiendo por vía remota de las personas que ejercen de *coaches* (dietistas o psicólogos), ya que conocer esa asignación podría consciente o inconscientemente sesgar la recogida de información clínica que hará el médico reclutador. El Coordinador deberá asegurar esta confidencialidad.

COMPROMISO DE ENMASCARAMIENTO Y PARTICIPACION

Nombre y Apellidos del Coordinador:.....
DNI:.....
Dirección Postal.....
Centro Sanitario:.....

	SI	NO
Acepto participar como Coordinador de forma voluntaria en el estudio.	□	
He leído las condiciones de compromiso de confidencialidad, comprendo los riesgos y los beneficios que comporta, y me comprometo a que, mientras dure el ensayo, nunca preguntaré al paciente sobre el brazo de aleatorización al que fue asignado o los consejos que recibe del ensayo	□	
Comprendo que mi participación en el estudio como Coordinador consiste en asegurar que todos los trialistas en mi equipo, para cada paciente: valoren sus requisitos de elegibilidad, inviten a los pacientes elegibles a que reciban una llamada para que les expliquen el estudio y les propongan participar y revisar anualmente sus historias clínicas para remitir al investigador principal los nuevos diagnósticos que son considerados eventos primarios o secundarios.	□	
Comprendo que no recibiré un beneficio económico por mi participación como Coordinador en este estudio.	□	
Me comprometo a cumplir con continuidad y esmero todos los aspectos metodológicos detallados en el Plan de Investigación (Research Plan) del ensayo UNATI, para ser Coordinador y dirigir un equipo de aproximadamente 20 trialistas y que cada uno de ellos reclute unos 25 pacientes y los siga 4 años	□	

Firmas

Coordinador:	Quién le ha informado:

Fecha (Día/mes/año):