# آسپیرین روکش دار یا آسپیرین جویدنی در بیماران مبتلا به بیماری قلبی-عروقی آترواسکلروتیک و برنامه ای چندجانبه جهت تعدیل عوارض ناشی آلودگی هوا: کارآزمایی بالینی تصادفی COATED-AIR

## شناسنامه طرح

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| عنوان لاتین طرح | Coated Or Chewable Aspirin in Patients with Established AThErosclerotic Disease and a Hybrid Strategy to Mitigate the Adverse Effects of AIR Pollution: The COATED-AIR Randomized Clinical Trial |
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## مجری همکاران

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| مجید ملکی | همکار طرح | مشاور | |
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## دانشده/مرکز مربوطه

| رده | نوع ارتباط با مرکز |
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## اطلاعات تفصیلی

| آیتم ها | متن |
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| **بیان مسئله** | Aspirin is the most widely used antiplatelet agent in patients with atherosclerotic cardiovascular disease (ASCVD)1,2. Since aspirin is an organic acid, it can cause gastrointestinal (GI) discomfort while being absorbed through the gastric mucosa (mainly the stomach). GI discomfort, ulceration, and gastrointestinal (GI) bleeding are among the most notable adverse effects associated with aspirin3. The risk of these adverse events is cumulative over time and may be exacerbated by other gastrotoxic chemicals, such as non-steroidal anti-inflammatory drugs.<br><br>Enteric coating, the application of a polymer barrier to permit transit through the stomach to the small intestine will reduce the exposure of aspirin to gastric mucosa and is one of the strategies to mitigate aspirin-associated GI adverse effects4. It is thought that enteric coating may alleviate dyspepsia. Despite the plausible mechanism, it is unknown whether enteric coating truly reduces |

the risk of gastrointestinal ulcers, GI bleeding, or hemorrhagic risk at large. With respect to the systemic risk of bleeding, it should be considered that besides being toxic to the gastric mucosa, aspirin may predispose to bleeding due to its systemic antiplatelet effects via inhibiting the synthesis of prostaglandins. The existing clinical trials have not been sufficiently large, or of long-term clinical follow-up to prove –or exclude– clinically meaningful benefits for patient-important outcomes5,6. Furthermore, coating delays the absorption of aspirin by changing the main site of absorption from the stomach to the duodenum. Although some have hypothesized that these changes in the pharmacokinetic/ pharmacodynamic properties may impair the antithrombotic properties of aspirin and impact its efficacy7,8, there are no high-quality comparisons with respect to efficacy outcomes such as ischemic stroke, myocardial infarction, .and acute limb events

Air pollution is the fourth leading cause of mortality globally, annually responsible for 6.67 million deaths worldwide 9. Approximately half of the air pollution-related mortality is attributable to cardiovascular diseases 10. Air pollution can similarly increase the risk of nonfatal cardiovascular events such as myocardial infarction, ischemic stroke, and acute limb events 11,12. Several pollutants, including particulate matter, carbon monoxide, ground-level ozone, lead, nitrogen dioxide, and sulfur dioxide have been linked to a wide range of adverse cardiovascular effects 12–15. Depending on the pollutants' size, they can pass through the airways and enter the bloodstream, causing inflammation and oxidative stress 11, and negatively impacting the cardiovascular system 16,17. Short- and long-term exposure to particulate matter air pollution has been associated with an increased risk of hospitalization, morbidity, and mortality related to cardiovascular diseases 18–20. Air pollution with particulate matter has been linked to an .increased risk of stroke, acute myocardial infarction, heart failure, and atrial fibrillation 21–27

Various approaches have been proposed to mitigate the health-related effects of air pollution at societal and individual levels. Regulations that aim to control pollution emissions by targeting fossil fuels, or factories with the likelihood of emitting pollutants in urban or suburban areas, and car traffic control strategies are resource-intensive and a subject of discussion in the medical .academic community and elsewhere 28–30

Individual-level interventions to mitigate the adverse effects of air pollution have recently received increasing attention 31,32. Various interventions have been proposed, including text messaging via mobile phones to alert individuals about unhealthy air quality levels 31,33–35, facemasks, and the use of air filtration systems. Furthermore, a number of studies have evaluated dietary interventions and demonstrated that some nutrients, especially vitamins C and E, may have the potential to mitigate the adverse effects of air pollutants on the cardiovascular system 36–39. However, little is known about the effect of these interventions in reducing the incidence of .clinically relevant outcomes such as myocardial infarction, stroke, and acute limb events

**ضرورت اجرا**

The purpose of the current randomized clinical trial is to compare the efficacy and safety of enteric-coated versus plain low-dose (81 mg) aspirin formulations in a double-blind fashion, and a multifaceted intervention including a one-page informational flashcard, cell phone message alerting on days with poor air quality to encourage patients not to spend time outdoors or to wear KN-95 facemasks outdoors in those days, and encouraging patients to consume citrus fruits on highly polluted days (hereafter referred to as hybrid strategy), versus usual care, in a randomized .controlled trial (RCT) with a 2x2 factorial design

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| بررسی متون | Araban et al. study provided a framework to modify some psychosocial determinants of air pollution preventive behavior other than knowledge using constructs of the Transtheoretical model(TTM) of behavior change and suggests the importance of education. This study was a Randomized controlled trial performed on 104 pregnant women (53 in the intervention and 51 in the control group). The intervention included motivational interviewing, a booklet, and daily SMS messages for pregnant women. The TTM-based intervention was effective in increasing air pollution preventive behaviors among pregnant women. The intervention group showed significant improvements in stages of change, self-efficacy, perceived benefits, and practice regarding air .[pollution preventive behaviors<br><br>Ren et al. evaluated whether dietary vitamin C supplementation can improve vascular health linked to particulate matter (PM) exposure in healthy young adults in Shijiazhuang, China. The study design was a Randomized double-blind crossover trial involving 58 healthy young adults and a Linear mixed-effect model was used to evaluate the effect of vitamin C supplementation. The result showed that - Vitamin C supplementation decreased inflammatory biomarkers and .blood pressure and increased glutathione peroxidase levels<br><br>Guan et al. designed a double-blind, randomized, controlled crossover study to evaluate the effects of facemasks on airway inflammation and endothelial dysfunction in healthy young adults. The result of this study shows that N95 facemasks partially reduced acute particle-associated airway inflammation in healthy young adults. The exhaled nitric oxide level and the levels of interleukin-1α, interleukin-1β, and interleukin-6 in exhaled breath condensate increased significantly in all subjects; however, the increases in those wearing authentic facemasks were statistically significantly lower than in the placebo group |
| منابع | Jacobsen AP, Raber I, McCarthy CP, et al. Lifelong Aspirin for All in the Secondary Prevention .1 of Chronic Coronary Syndrome: Still Sacrosanct or Is Reappraisal Warranted? Circulation. .2020;142(16):1579-1590<br><br>Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular .2 Events and Bleeding Events: A Systematic Review and Meta-analysis. Jama. .2019;321(3):277-287<br><br>Sostres C, Lanas A. Gastrointestinal effects of aspirin. Nat Rev Gastroenterol Hepatol. .3 .2011;8(7):385-394<br><br>Baron JA, Senn S, Voelker M, et al. Gastrointestinal adverse effects of short-term aspirin use: .4 .a meta-analysis of published randomized controlled trials. Drugs R D. 2013;13(1):9-16<br><br>Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular .5 events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, .double-blind, placebo-controlled trial. Lancet. 2018;392(10152):1036-1046<br><br>Sleem A, Effron MB, Stebbins A, et al. Effectiveness and Safety of Enteric-Coated vs Uncoated .6 Aspirin in Patients With Cardiovascular Disease: A Secondary Analysis of the ADAPTABLE .Randomized Clinical Trial. JAMA cardiology. 2023;8(11):1061-1069 |

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**اهداف: هدف اصلی، اهداف اختصاصی، هدف کاربردی**

OBJECTIVES .1

Aspirin randomization .1

:Main objective .1

- To compare the effect of low-dose (81mg) enteric-coated versus plain aspirin once daily on a composite of fatal or non-fatal ischemic stroke (not deemed to be related to systematic hypotension), type I myocardial infarction, acute limb events, or acute or subacute stent thrombosis

:Other objectives .1

- To compare the effect of enteric-coated versus plain low-dose (81 mg) aspirin once daily in reducing a composite of major gastrointestinal bleeding, or new upper gastrointestinal bleeding not meeting criteria for major bleeding but leading to urgent endoscopy (severity according to the International Society on Thrombosis and Haemostasis criteria 40), or new endoscopically-confirmed gastroduodenal ulcer
- To determine the effect of enteric-coated versus plain low-dose (81mg) aspirin once daily on all-cause death
- To explore the robustness of the findings in key subgroups, such as female vs male individuals, patients aged 65 years and older vs those who are younger, patients with versus those without diabetes, patients with ASCVD based on the involved vascular bed (cerebrovascular, coronary, peripheral, or >1 vascular bed[1]), those receiving concomitant

antithrombotic therapy with other agents, and others

Hybrid strategy randomization .2
Main objective .1

- To compare the effect of hybrid strategy versus usual care to mitigate the cardiovascular hazards of air pollution as assessed by a composite of non-fatal ischemic stroke (not deemed to be related to systolic hypotension), type I myocardial infarction, acute limb events, or cardiovascular death in patients with documented ASCVD

:Other objectives .1

- To compare the effect of hybrid strategy versus usual care to mitigate the cardiovascular hazards of air pollution on individual components of the primary composite outcome, including non-fatal ischemic stroke (not deemed to be related to systolic hypotension), type I myocardial infarction, acute limb events, and cardiovascular death in patients with documented ASCVD
- To explore the robustness of the findings in key subgroups, such as female vs male individuals, patients aged 65 years and older vs those who are younger, patients with versus those without diabetes, patients with ASCVD based on the involved vascular bed (cerebrovascular, coronary, peripheral, or >1 vascular bed), those receiving concomitant antithrombotic therapy with other agents, and others
- To compare the effect of hybrid strategy versus usual care to mitigate the respiratory hazards of air pollution as assessed by a composite of hospitalizations for COPD .exacerbation, asthmatic attacks, or pneumonia
- To compare the change in the health-related quality of life in participants randomized to the hybrid strategy versus usual care
- To compare the change in the level of anxiety in participants randomized to the hybrid strategy versus usual care
- To compare the effect of hybrid strategy versus usual care on non-elective cardiovascular hospitalization
- To assess patients' adherence to the individual components of the hybrid strategy in participants randomized to the hybrid strategy
- To assess patients' satisfaction with the hybrid strategy in participants randomized to the hybrid strategy
- To record potential adverse effects (e.g., adverse cardiovascular and respiratory events, bleeding events, anxiety, and severe mask-related skin reactions) in patients randomized to the hybrid strategy versus usual care

**فرضیات یا سوالات پژوهشی**

Aspirin Randomization: ###
1. **Main Objective:**
- *Question:* How does the effect of low-dose (81mg) enteric-coated aspirin compare to plain aspirin once daily in terms of a composite of fatal or non-fatal ischemic stroke (not deemed related to systematic hypotension), type I myocardial infarction, acute limb events, or acute or ?subacute stent thrombosis

Other Objectives:**** .2
- *Question:* What is the comparative effect of enteric-coated versus plain low-dose (81 mg)

aspirin once daily in reducing a composite of major gastrointestinal bleeding or new upper gastrointestinal bleeding not meeting criteria for major bleeding but leading to urgent endoscopy?
– *Question:* How does enteric-coated versus plain low-dose (81mg) aspirin once daily impact all-cause death?
– *Question:* In key subgroups (e.g., female vs male, patients aged 65 years and older vs younger, patients with vs without diabetes), what is the robustness of the findings concerning the ?effect of enteric-coated versus plain aspirin

Hybrid Strategy Randomization: ###
1. **Main Objective:**
– *Question:* What is the comparative effect of the hybrid strategy versus usual care in mitigating the cardiovascular hazards of air pollution, as assessed by a composite of non-fatal ischemic stroke, type I myocardial infarction, acute limb events, or cardiovascular death in patients with ?documented ASCVD

Other Objectives:**** .2
– *Question:* How does the hybrid strategy versus usual care impact individual components of the primary composite outcome, including non-fatal ischemic stroke, type I myocardial infarction, acute limb events, and cardiovascular death in patients with documented ASCVD?
– *Question:* In key subgroups, such as female vs male, patients aged 65 years and older vs younger, and patients with vs without diabetes, what is the robustness of the findings concerning the effect of the hybrid strategy on cardiovascular hazards of air pollution?
– *Question:* What is the effect of the hybrid strategy versus usual care in mitigating the respiratory hazards of air pollution, as assessed by a composite of hospitalizations for COPD exacerbation, asthmatic attacks, or pneumonia?
– *Question:* How do changes in health-related quality of life and anxiety compare in participants randomized to the hybrid strategy versus usual care?
– *Question:* What is the impact of the hybrid strategy versus usual care on non-elective cardiovascular hospitalization?
– *Question:* How do patients' adherence to the individual components of the hybrid strategy and their satisfaction with the strategy compare in participants randomized to the hybrid strategy?
– *Question:* What potential adverse effects (e.g., adverse cardiovascular and respiratory events, bleeding events, anxiety, and severe mask-related skin reactions) are recorded in patients ?randomized to the hybrid strategy versus usual care

**مشخصات ابزار جمع آوری اطلاعات و نحوه جمع آوری آن**

a structured questionnaire will be utilized for the initial data collection of patient information. Subsequently, during follow-up assessments, the questionnaire will be employed to evaluate and .document the temporal progression of outcomes and changes aligned with the study's objectives

**روش اجرا**

DESIGN .1

- Multicenter randomized controlled trial with a 2x2 factorial design with double-blind randomization with 1:1 allocation ratio to low-dose enteric-coated vs plain aspirin, and open-label randomization with 1:1 allocation ratio to hybrid strategy to reduce the cardiovascular effects of air pollution vs usual care. Randomization will be performed via an electronic web-based system with a concealed allocation sequence. All outcomes will .be adjudicated by a Clinical Events Committee blinded to the assigned treatments

SETTING .1

:Teaching hospitals in Tehran province, Iran will be involved, including the following •

Rajaie Cardiovascular Medical and Research Center, Tehran, Iran .1
Tehran Heart Center, Tehran, Iran .2
Firoozgar General Hospital, Tehran, Iran .3
Imam Khomeini Hospital, Tehran, Iran .4
Rasoul-e-Akram Hospital, Tehran, Iran .5

Additional centers may be involved for patient recruitment, at the discretion of the Steering .Committee

PARTICIPANTS .1

Patients with documented ASCVD who meet the eligibility criteria will be considered for enrollment in the first (enteric-coated vs plain low-dose aspirin) and the second randomization (air pollution .reduction hybrid strategy). Each randomization will be powered for its primary outcome

:Documented ASCVD will be categorized as follows

:(**Coronary artery disease (CAD** •
Previous or recent documented type I myocardial infarction *(if not specified, will be • (assumed as type I
History of coronary revascularization (percutaneous coronary intervention or coronary • (artery bypass graft surgery
History of obstructive CAD (>50% stenosis) documented by coronary computed • tomography (CT) or conventional angiography
:(**Peripheral arterial disease (PAD** •
(Previous or recent acute ischemic limb event (>7 days prior •
History of previous endovascular/surgical lower or upper extremities revascularization for • an atherosclerotic cause
.History of ulcer or lower extremities amputation due to ASCVD •
:**Carotid arterial diseases** •
History of previous endovascular/surgical carotid artery revascularization for • atherosclerotic cause
History of > 50% carotid artery stenosis based on documented imaging tests (Duplex US, • (CT angiography, magnetic resonance angiography, or conventional angiography
:**Ischemic stroke** •
History of recent or previous documented ischemic stroke not due to atrial fibrillation, • endocarditis, or systemic hypoperfusion/hypotension being treated with low-dose aspirin

**روش محاسبه حجم نمونه و تعدادآن**

STATISTICAL CONSIDERATIONS AND SAMPLE SIZE CALCULATION .1
Determining the control arm event rate for efficacy analysis (assumed event rate .1 (for the primary efficacy outcome with coated low-dose aspirin

For sample size estimates for the aspirin formulation randomization, there were no prior randomized comparisons in a similar (secondary prevention) patient population with at least one year of follow-up information or longer. We were similarly unable to find prior large prospective

high-quality observational studies in the secondary prevention population that reported the event rates for patients receiving exclusively plain aspirin, or exclusively enteric-coated aspirin. In this context, we approximated the control arm event rate for the composite thrombotic cardiovascular outcomes using data from prior prospective studies in Europe/North America.71-75 In addition, it was considered that the event rates are likely different (higher) in the enrolling sites in Iran, as a result of issues such as limited availability to certain therapies, or air pollution being a major contributor to excess event rates. Therefore, we obtained data about durable event rates in a secondary prevention population who received low-dose aspirin from prospective studies in Iran, .as well

Estimates for event rates in the Europe/North American studies were based on published event rates, with some approximation to accommodate the primary outcome considered for aspirin randomization in COATED (Table 5). For cardiovascular outcomes, the RCTs provided the composite of cardiovascular death, non-fatal MI, and stroke with the pooled estimated incidence at 24 months of 12.14% (95% CI 6.38% - 17.90%) (Figure 2). In contrast, the RCTs did not report acute limb events, which needs to be factored in. Based on the COMPASS trial 56, the addition of acute limb events can increase the number of events by approximately 5% (4% - 6%). Therefore, based on approximation from the RCTs, the estimated incidence of composite cardiovascular death, non-fatal MI, stroke, and acute limb events at 24 months will be 12.75% (95% CI 6.70% - .(18.80%

In order to obtain estimates for event rates from Iran, the published literature was reviewed carefully, and only a single study was deemed to include a prospective design, rigorous quality for outcomes reporting, and a sufficient number of patients to be considered for inclusion.76 The IPACE2 study from Iran 76 reported the composite of stroke/transient ischemic attack (TIA), acute coronary syndrome (ACS), and all-cause mortality with an estimated 24-month incidence of 30.00% (95% CI 27.78% - 32.22%) (Figure 2). Non-cardiac death contributed to 20 out of 246 (8.1%) total events. Moreover, prior studies have shown that nearly one-third of ACS events are related to unstable angina 77-79. Therefore, it was inferred that roughly 52 out of 156 ACS events (52/246 total events: 21.1%) in this study were related to unstable angina and not MI. In addition, prior studies have demonstrated that nearly 23% of acute cerebrovascular events are due to TIA, not stroke 80. Thus, it can be assumed that 5 out of 20 stroke/TIA events (5/246 total events: 2.0%) in this study were due to TIA, and not stroke. In contrast, the study did not report on acute limb events. Therefore, based on these assumptions, to provide an estimated incidence of composite cardiovascular death, non-fatal MI, stroke, and acute ischemic limb events based on this Iranian prospective cohort study, we subtracted 31.2% of the accrued events (related to non-cardiac death, unstable angina, and TIA) and then add 5% for acute limb events. Therefore, the estimated incidence of composite cardiovascular death, non-fatal MI, stroke, and acute limb events in 24 months based on this Iranian prospective cohort study will be 21.59% (95% CI .(18.52% - 25.01%

**ملاحظات اخلاقی**

ETHICAL CONSIDERATIONS .1

The study protocol along with patient informed consent will be approved by the Rajaie

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| Cardiovascular Medical and Research Center (RHC) Ethics Committee, which is valid across all other participating hospitals. Each site PI will discuss the study goals, explain each investigational therapeutic strategy, and the potential risk and benefits of participating in the trial with the patient or their next of kin, in case patients are not conscious or able to make decisions. For those agreeing to participate, a written informed consent will be signed by the patients/their next of kin. During and after the trial, the researchers ensure that adequate medical care is provided to participants whenever any adverse event or complication associated with the trial occurs. In addition, any investigation-related complication related to the research will be communicated with .the participants followed up, and treated for free | |
| Patients may be reluctant to participate in this study; however, by elucidating the benefits that this .program aims to achieve, it is possible to persuade them to engage | **محدودیتهای اجرایی طرح وروش کاهش آنها** |
| ELIGIBILITY CRITERIA .1<br><br>:(Inclusion Criteria (applies similarly for both randomizations<br><br>(Adult patients (≥18 years) with documented ASCVD (defined as mentioned in section VII .1<br>Inhabitant of Tehran province .2<br>Willing to participate and able to provide written informed consent .3 | **معیارهای ورود (فقط مربوط به طرحهای کارآزمایی بالینی)** |
| :Exclusion Criteria<br><br>Being within 72 days of acute/unstable ASCVD events (acute myocardial infarction, acute .1 limb event, and acute ischemic stroke), post-elective revascularization, or receiving triple antithrombotic therapy<br>Active bleeding .2<br>History of upper gastrointestinal bleeding within the past 30 days .3<br>History of intracranial hemorrhage within the past 30 days .4<br>End-stage kidney disease with estimated creatinine clearance < 15 mL/min, or undergoing .5 hemodialysis or peritoneal dialysis<br>Known aspirin sensitivity without prior successful desensitization .6<br>Known comorbidities associated with poor prognosis (e.g., metastatic cancer) in .7 conjunction with an estimated life expectancy of less than one year according to the treating clinician<br>Vascular disease known exclusively to be from causes other than atherosclerosis .8 (spontaneous coronary or peripheral dissection (fibromuscular dysplasia, segmental arterial mediolysis) or vasculitis such as Takayasu arteritis, Buerger's disease (i.e., thromboangiitis obliterans), and Churg-Strauss syndrome<br>Inherited or acquired severe coagulopathies including hemophilia and decompensated .9 liver cirrhosis<br>Any other conditions that make the participants unsuitable for recruitment or follow-up, .10 e.g., illiteracy<br>Not having aspirin as part of the planned durable treatment regimen .11<br>Known allergy to KN-95 or other masks, or citrus fruits .12 | **معیارهای خروج (فقط مربوط به طرحهای کارآزمایی بالینی)** |

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| Any facial dysmorphia that makes the patient unable or unwilling to wear a face mask .13<br>Any medical condition necessitating unblinded facemask use for outdoor activities at the .14 discretion of the treating clinician, or based on patient preference<br>Inability to receive/read text messages/phone calls by personal mobile phone .15<br>Unwillingness to participate, such as hesitation to wear a mask, claustrophobia, or anxiety .16 disorder that makes the patient unable to wear a mask, if randomized | |
| RANDOMIZATION .1<br><br>Permuted block randomization with block sizes of 4, 8, and 12 chosen randomly via an electronic web-based system will be used for the study. The first randomization will occur for aspirin formulation (enteric-coated versus plain). Patients who meet the criteria and agree to be randomized for the first randomization will be randomized for the second randomization (hybrid strategy to reduce the cardiovascular adverse effects of air pollution vs usual care) stratified by the aspirin randomization groups (see Trial Schema, below). The specifications for the generation of the randomization schedule will be prepared by the study biostatistician and the Steering .Committee<br><br>An independent biostatistician, not otherwise part of the study team, will generate the randomization schedule. For this study, the randomization schedule refers to a list that includes the subject identification number, randomization block number, randomization code, and the .allocated treatment | **چگونگی تصادفی سازی و Concealment (فقط مربوط به طرحهای کارآزمایی بالینی)** |
| INTERVENTIONS AND COMPARATORS .1<br><br>In the present RCT with a 2x2 factorial design, two separate interventions will be tested, and each .(will have a separate comparator (see Trial Schema for details<br><br>First randomization: Aspirin formulation .1<br><br>**INTERVENTION.** Enteric-coated aspirin tablets 81 mg once daily<br><br>Second randomization: Mitigation hybrid strategy to reduce the cardiovascular adverse .1 effects of air pollution<br><br>:**INTERVENTION.** A hybrid strategy inclusive of<br><br>A one-page flashcard briefly describing the adverse cardiovascular effects of air pollution .1 (and the AIR individual-level strategies to potentially mitigate these effects (Figure 1A<br>Alerting patients on polluted days (defined as air quality index (AQI) ≥ 131 41) (Table 1) by .2 sending cell phone text messages and recommending to not go outdoors or minimize outdoor activities (especially exercising) on those days. This will also be accompanied by periodic phone calls to ascertain that the patients receive the messages and are attentive .to them<br>Wearing KN-95 facemasks (provided by the investigators of this study) as a physical .3 barrier against air pollution on highly polluted days (defined as AQI ≥ 131) in case the patient cannot avoid going outdoors<br>Dietary intervention by encouraging patients to consume citrus fruits (as quantified in .4 | **تعریف گروه مداخله (فقط مربوط به طرحهای کارآزمایی بالینی)** |

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| .Table 2, such as one medium orange) during days with AQI ≥ 131 | |
| First randomization: Aspirin formulation .1<br><br>**COMPARATOR.** Plain aspirin 81 mg tablets once daily<br><br>Second randomization: Mitigation hybrid strategy to reduce the cardiovascular adverse .1 effects of air pollution<br><br>**COMPARATOR.** No active strategy (usual care) related to air pollution. A control card will be shared with the patients randomized to the control group, which will only include a logo of the .(enrolling center (Figure 1B | **تعریف گروه شاهدیامقایسه (فقط مربوط به طرحهای کارآزمایی بالینی)** |
| PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY .1<br><br>Both enteric-coated and plain aspirin formulations will be manufactured as prepared tablets with identical appearance and shape by, the Actover Pharmaceutical Company, Tehran, Iran, and stored in similar bottles. The company will donate the study drugs in kind, but will have no other role in the design or conduct of the study. Each bottle contains one hundred tablets of either enteric-coated or plain aspirin formulations and has a label indicating the blinded drug name (aspirin 81 mg without referring to coating or lack thereof), number of tablets per bottle, bottle number, storage condition, instruction and route of administration, protocol number, and blinded .batch number<br><br>Aspirin bottles will initially be transported to the Rajaie Cardiovascular Medical and Research Center (RCMRC) by an industry-authorized courier, and delivered to the product storage manager at RCMRC. Furthermore, all study KN-95 facemasks and educational flashcards will be provided by the RCMRC. To be dispensed between other study sites, study materials (i.e., aspirin bottles, KN-95 facemasks, and educational flashcards) will be distributed by the assigned product storage manager, and a specified courier, authorized by the RCMRC, transferred to each site. A site-specific dispenser authorized by their site will receive the distributed products at each site and will be trained to secure and maintain the study drugs and other material and to avoid intentional or unintentional attempts at breaking the blind. A drug accountability record, containing the information about the date and amount of received materials, identification (name, surname, and cell phone number) of the product storage manager, couriers, and site-specific dispensers, will be completed and signed by each party in every single drug delivery session. All drug accountability records will be returned to the distributing party and faxed to both the receiving .party and the sponsor<br><br>All study materials will be stored in a secure and access-limited place at each study center adhering to environmental conditions (temperature, light, and humidity) recommended for storage .of the study drugs<br><br>After being recruited and randomized for both randomizations, each participant will be given 2 bottles of the aspirin tablets (based on the allocated group, although patients and staff will remain blinded), and if in the hybrid strategy arm, NN numbers of KN-95 facemasks and an educational flashcard (only at the end of the initial visit). The process will be repeated during every on-site follow-up visits by the site-specific dispenser. For this purpose, the site-specific dispenser, who | **چگونگی کورسازی (Blinding) (فقط مربوط به طرحهای کارآزمایی بالینی)** |

has unblinded access to the randomization group and allocated treatments, will be notified by the enrolling/visiting study physician, and subsequently provide the study materials based on the randomization group of the patient. The dispenser will label each bottle of aspirin with the trial order of the patient (starts at 10001 as the first patient) and the number order of bottles delivered to the patient. After delivering the study materials to the patient, a receipt, containing the information about the date and quantity of the materials being delivered, and the identification (name and surname, relationship with the patient, and signature) of the person receiving the study materials will be given by the dispenser. Moreover, at every onsite follow-up visit, unused aspirin tablets and their bottles will be collected by the dispenser, before delivering the new study .materials

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| STUDY OUTCOMES .1<br><br>**First randomization: Aspirin formulation**<br><br>**:Efficacy Outcomes** .1<br>**Primary:** Composite of fatal or nonfatal ischemic stroke (not deemed to be related .1 to systemic hypotension), type I myocardial infarction, acute limb events, and acute or subacute stent thrombosis<br>**:Secondary** .2<br>,(Ischemic stroke (not deemed to be related to systematic hypotension .1<br>Type I myocardial infarction .2<br>Acute limb event .3<br>All-cause death .4<br>Cardiovascular death .5<br>Unplanned vascular hospitalization .6<br>**:Exploratory** .3<br>Stent thrombosis .1<br>Unplanned revascularization .2<br>Major amputation .3<br>HF hospitalization .4<br>**:Safety Outcomes** .2<br>**Primary:** Composite of ISTH major or clinically-relevant non-major GI bleeding .1 and new symptomatic diagnosed gastroduodenal ulcer<br>**:Secondary** .2<br>Upper GI bleeding .1<br>Clinically relevant non-major GI bleeding (any non-major GI bleeding .2 (needing medical attention or intervention<br>Any Major bleeding, as defined by the International Society on Thrombosis .3 and Haemostasis<br>Intracranial hemorrhage .4<br>Any clinically-relevant non-major bleeding .5<br>New symptomatic diagnosed gastroduodenal ulcer .6<br>Dyspepsia leading to drug discontinuation or switch to open-label .7 enteric-coated aspirin<br><br>**Second randomization: Mitigation hybrid strategy to reduce the cardiovascular adverse effects of air pollution** | **پیامدها اولیه (primary) ثانویه (secondary) ایمنی (Safety) (فقط مربوط به طرحهای کارآزمایی بالینی)** |

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| :**Efficacy Outcomes** .1<br>**Primary**: Composite of non-fatal ischemic stroke (not deemed to be related to .1 systolic hypotension), type I myocardial infarction, acute limb events, or cardiovascular death<br>:**Secondary** .2<br>(Ischemic stroke (not deemed to be related to systemic hypotension .1<br>Type I myocardial infarction .2<br>Acute limb events .3<br>Cardiovascular death .4<br>All-cause death .5<br>HF hospitalization .6<br>:**Exploratory** .3<br>Adherence to all components of the hybrid strategy (i.e., avoidance from .1 going outdoors on polluted days as stated by text messaging, or wearing KN-95 facemasks if going outdoors on those days, and the dietary recommendations regarding the daily consumption of citrus fruits on highly (polluted days<br>Patient satisfaction with the hybrid strategy .2<br>Change in the health-related quality of life: The health-related quality of life .3 of all participants (i.e., in the intervention and control groups) will be assessed at baseline and the end of the follow-up using the EQ-5D-5L questionnaire 46,47. The change in health-related quality of life from baseline until the end of follow-up will be compared between intervention .and control groups for exploratory purposes<br>:**Safety Outcomes** .2<br>Severe mask-related skin reaction requiring treatment with systemic or topical .1 immunosuppressive agents or a visit by a dermatologist<br>Change in the level of anxiety: The anxiety level of all participants (i.e., in the .2 intervention and control groups) will be screened at baseline and every 6 months until the end of the follow-up using the Generalized Anxiety Disorder-7 (GAD-7) questionnaire 48. The change in anxiety level from baseline until the end of the follow-up will be compared between intervention and control groups for exploratory .(purposes and for deliberations by the Data and Safety Monitoring Board (DSMB | |
| :**Follow up**<br><br>:Patients will receive two types of follow-ups in the COATED-AIR trial<br><br>**A. Phone call follow-up**, which will proceed on month 3,9,15 and 21during which an experienced :research assistant will interrogate the patients regarding the following issues<br><br>**The occurrence of predefined outcomes**: In case of a positive response, the interview will be **.1** continued by the study physician to record correctly the event and facilitate the process of .providing accurate evidence for event adjudication<br><br>**Adherence to the hybrid strategy**: In a subpopulation randomized into the hybrid strategy, the **.2** .participant will be asked about the adherence to different components of the hybrid strategy | **پیگیری (follow up) (فقط مربوط به طرحهای کارآزمایی بالینی)** |

**New complaint:** In case of a positive response, and after the confirmation of the study **.3** .physician, the treating physician will be alerted to schedule a visit for the patient

**B. On-site follow-up:** which will be proceeded by the study physician on months 6, 12, 18, and :24, and the patients will be interviewed about the following issues

**The occurrence of predefined outcomes:** In the case of a positive response, the study **.1** .physician will record the event and collect accurate evidence for event adjudication

**Adherence to the hybrid strategy:** In a subpopulation randomized into the hybrid strategy, the **.2** .participant will be asked about the adherence to different components of the hybrid strategy

**New complaint:** In case of a positive response, and after the confirmation of the study **.3** .physician, the treating physician will be alerted to schedule a visit for the patient

**Patient satisfaction:** Patient satisfaction with the hybrid strategy using a custom-made **.4** .questionnaire in only the intervention group

.**Quality of Life:** Patient quality of life will be assessed based on the EQ-5D-5L questionnaire **.5**

.**Anxiety:** Patient anxiety will be assessed based on the GAD-7 questionnaire **.6**

## جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی - پیوسته است؟ | نوع متغیر کمی - گسسته است؟ | نوع متغیر کیفی - رتبه ای است؟ | نوع متغیر کیفی - اسمی است؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Age | مستقل | ☒ | ☐ | ☐ | ☐ | year | Number of years person lived, recorded at the time of enrollment | Questionner |
| Sex | مستقل | ☐ | ☐ | ☐ | ☒ | Male Female | Patient's sex at birth, recorded at the time of enrollment | Questionner |
| Height | مستقل | ☒ | ☐ | ☐ | ☐ | cm | Patient's height, recorded at the time of enrollment | Questionner |
| Weight | مستقل | ☒ | ☐ | ☐ | ☐ | kg | Patient's weight, recorded at the time of enrollment | Questionner |

# جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی – پیوسته است؟ | نوع متغیر کمی – گسسته است؟ | نوع متغیر کیفی – رتبه ای است؟ | نوع متغیر کیفی – اسمی است؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Highest level of education | مستقل | ☐ | ☐ | ☒ | ☐ | High school or lower<br>Bachelor's or equivalent<br>Master's or equivalent<br>Doctorate degree or equivalent | Highest level of formal education completed by the enrollee at the time of enrollment | Questionner |
| Chest pain grading | مستقل | ☐ | ☐ | ☒ | ☐ | Class 0<br>Class I<br>Class II<br>Class III<br>Class IV | Grade of symptoms or signs in patients with suspected or presumed stable angina (or angina equivalent) according to the Canadian Cardiovascular Society grading scale. | Questionner |
| Past Medical History | مستقل | ☐ | ☐ | ☐ | ☒ | have/doesn't have | comprehensive record of a person's health conditions, illnesses, treatments, and medical events that have occurred prior to the present moment | Questionner |
| Prior myocardial infarction | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of myocardial infarction | Questionner |
| Atrial fibrillation | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of atrial fibrillation/flutter before the enrollment | Questionner |
| Peripheral artery disease ((PAD | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented PAD before the enrollment confirmed by: Previous or recent acute ischemic limb event History of previous endovascular/surgical lower or upper extremities revascularization for an atherosclerotic cause History of ulcer or lower extremities amputation due to | Questionner |
| Coronary artery disease ((CAD | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented CAD before the enrollment confirmed by: Previous documented type I MI History of coronary revascularization (PCI, CABG, or both) History of obstructive CAD (>50% stenosis) documented by CT or conventional angiography in any of the epicardial coronary arteries | Questionner |

# جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی – پیوسته اسات؟ | نوع متغیر کمی – گسسته اسات؟ | نوع متغیر کیفی – رتبه ای اسات؟ | نوع متغیر کیفی – اسمی اسات؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Previous PCI | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Previous percutaneous coronary intervention PCI before enrollment | Questionner |
| Previous CABG surgery | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Coronary artery bypass graft (CABG) surgery before enrollment | Questionner |
| Carotid artery stenosis | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented carotid arterial disease before enrollment confirmed by: ▯ History of previous endovascular/surgical carotid artery ▯ revascularization for atherosclerotic cause ▯ ≥50% stenosis of carotid artery shown in carotid Doppler ultrasound and contrast angiography | Questionner |
| Ischemic stroke and/or Transient ischemic attack ((TIA | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of ischemic stroke or TIA before enrollment | Questionner |
| Hemorrhagic stroke | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of hemorrhagic stroke before the enrollment defined as rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma, ventricular system, or bleeding into the subarachnoid space, that is not caused by trauma | Questionner |
| Venous thromboembolism | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of pulmonary embolism (PE) or deep vein thrombosis (DVT) before the enrollment | Questionner |
| Cigarette smoking | مستقل | ☐ | ☐ | ☐ | ☒ | No ▯ ▯ Former smoker ▯ Current smoker | Former smoker is an adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of the interview according to the CDC. Current smoker is an adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes according to CDC. | Questionner |
| Acute limb ischemia | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of limb-threatening ischemia before the enrollment which is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention | Questionner |
| Peptic ulcer disease ((PUD | مستقل | ☐ | ☐ | ☐ | ☒ | Yes/No | Documented history of gastroduodenal ulcer before the enrollment manifested by gastrointestinal symptoms that persist for > 3 days, with confirmation of ulcer by endoscopy or radiography. An ulcer is defined as any mucosal break at least 3 mm in greatest diameter that has unequivocal depth. | Questionner |

# جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی – پیوسته است؟ | نوع متغیر کمی – گسسته است؟ | نوع متغیر کیفی – رتبه ای است؟ | نوع متغیر کیفی – اسمی است؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Left ventricular ejection fraction | مستقل | ☒ | ☐ | ☐ | ☐ | Percentage | Previous documented left ventricular ejection fraction– within the last year– measured by echocardiography, as provided by the patient upon enrollment. The document will only be validated if was reported by a site attending physician | Questionner |
| Drug History at the time of randomization | مستقل | ☐ | ☐ | ☐ | ☒ | Drug name and Dosage | a comprehensive record of an individual's usage of pharmaceutical substances | Questionner |
| Laboratory data (most recent within 3 months prior to randomization) | مستقل | ☐ | ☐ | ☐ | ☒ | Different for each parameters | Hemoglobin, Platelet count, WBC, Neutrophil count, Lymphocyte count, Plasma creatinine | Laboratory tests |
| Adherence to aspirin therapy | مستقل | ☐ | ☐ | ☒ | ☐ | Questionnaire | Adherence to drug therapy which is consistent and regular consumption of aspirin as prescribed, evaluated at six–month intervals during on–site visits | Questionnaire |
| Adherence to the hybrid strategy | مستقل | ☐ | ☐ | ☒ | ☐ | Questionnaire | Adherence to the individual components of the hybrid strategy | Questionnaire |
| Satisfaction | مستقل | ☐ | ☐ | ☒ | ☐ | Questionnaire | Patient satisfaction with the hybrid strategy using a custom–made questionnaire in only the intervention group for the second randomization. | Questionnaire |
| All–cause death | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Death due to any causes (cardiovascular, non–cardiovascular, or undetermined) within the follow–up period. | Questionner |
| Cardiovascular death | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Cardiovascular death is defined as death resulting from cardiovascular causes. | Questionner |
| Non–cardiovascular death | وابسته | ☐ | ☐ | ☐ | ☒ | Questionner | Non–cardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause | Questionner |

# جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی – پیوسته است؟ | نوع متغیر کمی – گسسته است؟ | نوع متغیر کیفی – رتبه ای است؟ | نوع متغیر کیفی – اسمی است؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Undetermined cause of death | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Undetermined cause of death is defined as a death not attributable to any other category by the clinical event committee because of the absence of any relevant source documents. | Questionner |
| Hospitalization | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Hospitalization due to all the below predefined cardiovascular or respiratory acute events/procedures: | Questionner |
| Hospitalization due to heart failure | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Admission for ≥24 h (or change of calendar date if admission and discharge time are lacking) with a primary diagnosis of heart failure, and the subject has objective evidence of a new or aggravated pre-existing right or left-sided heart failure meeting the criteria for heart failure hospitalization at the clinician's discretion | Questionner |
| Unplanned vascular Hospitalization | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Inpatient admission to a hospital specifically due to acute events involving the vascular system. | Questionner |
| Acute myocardial infarction | وابسته | ☐ | ☐ | ☐ | ☒ | Type I , Type III , Type IV a , Type IV b , Type IV c , Type V , | when blood flow decreases or stops in one of the coronary arteries of the heart | Questionner |
| Cardiac arrest | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Cardiac arrest is the sudden cessation of cardiac activity. The victim becomes unresponsive with no normal breathing and no signs of circulation | Questionner |
| Incident Atrial fibrillation | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | New diagnosis of atrial fibrillation/flutter as confirmed by a 30-second 12-lead ECG, telemetry tracing, or similar | Questionner |
| Pulmonary embolism | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Any pulmonary embolism diagnosed on CT angiography, V/Q scan, invasive pulmonary angiography, echocardiography (thrombus visualized in the main pulmonary artery), based on signs and symptoms of PE plus imaging-confirmed proximal DVT, or at autopsy. | Questionner |

# جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی – پیوسته است؟ | نوع متغیر کمی – گسسته است؟ | نوع متغیر کیفی – رتبه ای است؟ | نوع متغیر کیفی – اسمی است؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Deep vein thrombosis | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Any deep vein thrombosis diagnosed in the upper (internal jugular, brachiocephalic, subclavian, axillary/brachial), or lower extremity (iliac, femoral/popliteal, gastrocnemius, peroneal, posterior tibial) or the inferior vena cava or deep splanchnic veins | Questionner |
| Ischemic stroke | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction | Questionner |
| Acute limb event | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Major adverse limb event (MALE) is defined as ALI or CLI. | Questionner |
| Major amputation | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Any ankle disarticulation, transtibial/below knee amputation, or transfemoral/above knee amputation | Questionner |
| Unplanned revascularization | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/nNo | Any urgent or emergent percutaneous intervention or surgical bypass due to acute vascular events such as acute limb ischemia or acute coronary syndrome to restore blood flow to affected areas and prevent further ischemic damage | Questionner |
| Stent thrombosis | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Angiographic confirmation of stent/scaffold thrombosis: | Questionner |
| Dyspepsia | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Predominant epigastric pain lasting at least 1 month which can be associated with any other upper gastrointestinal symptom such as epigastric fullness, nausea, vomiting, or heartburn | Questionner |
| Newly symptomatic gastroduodenal ulcer | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Gastroduodenal ulcer manifested by gastrointestinal symptoms that persist for > 3 days, with confirmation of ulcer by endoscopy. An ulcer is defined as any mucosal break at least 3 mm in greatest diameter | Questionner |
| Clinically –relevant GI bleeding | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Bleeding from the upper or lower gastrointestinal tract. | Questionner |

# جدول متغیرها

| نام متغیر | نقش متغیر | نوع متغیر کمی – پیوسته است؟ | نوع متغیر کمی – گسسته است؟ | نوع متغیر کیفی – رتبه ای است؟ | نوع متغیر کیفی – اسمی است؟ | واحد اندازه گیری | تعریف کاربردی | نحوه اندازه گیری |
|---|---|---|---|---|---|---|---|---|
| Major bleeding | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | ISTH major bleeding in non-surgical patients defined as having a symptomatic presentation and 40: ▯ Fatal bleeding, and/or ▯ Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. | Questionner |
| Clinically-relevant non-major bleeding | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria 68: ▯ Requiring medical intervention by a healthcare professional ▯ Leading to hospitalization or increased level of care Prompting a face-to-face (i.e., not just a telephone or electronic communication) evaluation | Questionner |
| GAD-7 | وابسته | ☐ | ☒ | ☐ | ☐ | total 7 score for the seven items ranges from 0 to 21: 0–4: minimal anxiety 5–9: mild anxiety 10–14: moderate anxiety 15–21: severe anxiety. | A seven-item instrument that is used to measure or assess the severity of generalized anxiety disorder (GAD)). | Questionner |
| Quality of Life (EQ-5D-5L) | وابسته | ☐ | ☒ | ☐ | ☐ | 5-component scale | A self-assessed, health-related, quality of life questionnaire. The scale measures the quality of life on a 5-component scale | Questionnaire |
| Severe mask-related skin reactions | وابسته | ☐ | ☐ | ☐ | ☒ | Yes/No | Adverse skin reactions occurring due to the use of facial masks which mandate dermatological consultation or the use of topical/systemic corticosteroids or other immunosuppressives | Questionner |

## زمانبندی و اجرا

| شرح مختصر مرحله | درصد مرحله | مدت زمان اجرا ـ ماه | از تاریخ | تا تاریخ |
|---|---|---|---|---|
| نوشتن پروپوزال | | 1 | 1402/10/25 | 1402/12/06 |
| بررسی بیماران و جمع آوری دیتا | | 24 | 1402/12/07 | 1404/12/07 |
| فالوآپ بیماران | | 48 | 1402/12/14 | 1406/12/07 |
| نگارش مقاله | | 2 | 1406/12/07 | 1407/02/07 |
| سابمیت مقاله | | 1 | 1407/02/08 | 1408/04/31 |

## هزینه پرسنلی

| نام و نام خانوادگی | توصیف دقیق فعالیتی که فرد باید در این تحقیق انجام دهد | کل حق الزحمه ـ ریال |
|---|---|---|
| سپهر جمال خانی | Patient Recruitment | 150,000,000 |

## جمع کل هزینه های طرح

| هزینه پرسنلی (هیات علمی و غیر هیات علمی) | هزینه مواد مصرفی | هزینه مواد غیر مصرفی | هزینه تجهیزات،موادوخدمات موجوددر مرکز | هزینه مسافرت | هزینه چاپ و تکثیر | سایر هزینه ها | جمع کل هزینه ـ ریال |
|---|---|---|---|---|---|---|---|
| 150,000,000 | 0 | 0 | 0 | 0 | 0 | 0 | 150,000,000 |