Original Article

Clinical Effectiveness and Safety of Sofosbuvir–Velpatasvir as Add-on Treatment for COVID-19 Patients: Study Protocol and Preliminary Data for the Randomized Controlled Trial

Abstract

Objectives: COVID-19 is a worldwide health problem. Although the most infected patients experience a mild-to-moderate disease, some patients (especially older people) develop pulmonary distress with fatal lung failure and multi-organ damage. There is currently no known effective treatment for this disease. Sofosbuvir, an FDA-approved drug for the treatment of hepatitis C virus, is also able to inhibit other members of positive strand RNA viruses with conserved polymerase and may be helpful for the treatment of SARS-CoV-2. The goal of the current trial is to determine the usefulness of "standard of care (SOC) plus hydroxychloroquine and lopinavir/ritonavir" vs. "SOC plus a combination of lopinavir/ritonavir hydroxychloroquine and *sofosbuvir*/*velpatasvir*" in patients hospitalized with COVID-19. **The Design of Clinical Trial:** In this randomized controlled trial, patients over 18 years who have been diagnosed with COVID-19 by the positive SARS-CoV-2 reverse transcriptase–polymerase chain reaction (RT–PCR) test or compatible chest computed tomography (CT) scan were candidates for the study. Eighty patients from Kermanshah province, West of Iran were allocated to treatment with SOC plus hydroxychloroquine and lopinavir/ritonavir (dual therapy) or SOC plus a combination of hydroxychloroquine and lopinavir/ritonavir and sofosbuvir/velpatasvir (triple therapy) for 10 days. Allocation was conducted using simple randomization. The primary outcomes were reducing mortality up to 28 days after hospitalization. Adverse events were handled and reported in accordance with the Good Clinical Practice guidelines. **Participants:** Patients who were hospitalized with COVID-19 (with positive SARS-CoV-2 RT–PCR test and/or compatible chest CT scan) were screened for eligibility at Farabi Hospital, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran. **Intervention and Comparator:** Both arms received active treatment and none was given placebo. The intervention arm received hydroxychloroquine 400 mg single dose and lopinavir–ritonavir (400 and 100 mg) twice daily plus sofosbuvir–velpatasvir (400 and 100 mg) once daily orally, plus SOC for 10 days. The comparator arm received hydroxychloroquine 400 mg single dose and lopinavir–ritonavir (400 and 100 mg) twice daily orally, plus SOC for 10 days. SOC includes oxygen therapy, non-invasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and corticosteroids. **Primary Outcomes:** The main outcomes are reducing mortality until 28 days after hospitalization. Other outcomes can be found in full protocol file. **Randomization:** For the purpose of allocation sequence generation, using an Excel file (random-numbers table) and simple random allocation, 80 included patients entered to the study, 40 patients in each group (1:1 ratio). In order to maintain the allocation sequence concealment, the details of treatment for each patient were contained in a sealed envelope, labeled by the numbers from 1 to 80. In fact, our study was a randomized open label clinical trial in which all the physicians and nurses plus all patients were aware of the type of treatment. **Blinding:** Our study was a randomized open label clinical trial in which all the physicians and nurses plus all patients were aware of the type of treatment. **Numbers to be Randomized (Sample Size):** Eighty included patients entered to the study, 40 patients in each group using simple random allocation. **Trial Status:** The finalized protocol version 1.5 was used in the trial study and the recruitment/intervention process started on April 11, 2020, finished on May 11, and the related follow-up finished on June 8, 2020. **Registry of Clinical Trial:** This clinical trial has been registered on March 30, 2020 under IRCT number 46790, in the Iranian Registry of Clinical Trials (https://www.irct.ir/trial/46790) and by KUMS under Grant No. 990097. **Full Protocol:** The full protocol and other details are attached as a Supplementary File (full protocol), accessible from the journal website. **Preliminary Data:** The sofosbuvir/velpatasvir regimen does not improve survival, clinical improvement, and duration of hospitalization in hospitalized COVID-19 patients.

Keywords: *COVID-19, protocol, randomized controlled trial, sofosbuvir/velpatasvir, treatment*

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Introduction

Since December 2019, COVID-19 (an international health problem around the world), developed by SARS-CoV-2, has caused a global outbreak of pulmonary disease.[1,2] In contrast to this fact that the most infected patients appear mild, some patients have pulmonary complications with lethal lung injury.[3] More than 52 million individuals worldwide have been affected by COVID-19 and 1,284,690 have died as of November 11, 2020 (https://www.worldometers.info/coronavirus/). Although the most of participants experience a mild-to-moderate disease, some patients develop pulmonary distress with lung damage and multi-organ failure. To date, there are no known available effective antiviral drug for the treatment of severe COVID-19 patients.[4,5] Hydroxychloroquine administration did not decrease the risk of mortality.[6] Remdesivir has not shown any statistically meaningful clinical advantages.[2] In hospitalized individuals with severe COVID-19, lopinavir–ritonavir treatment had no benefit over the existing standard of care (SOC).[7] Tocilizumab, mavrilimumab, anakinra, and interferon beta-1b may be effective, but confirmation of effectiveness requires more controlled trials; therefore, referring patients to clinical trials is very important.[8-12] Sofosbuvir, the FDA-approved drug for the treatment of hepatitis C virus (HCV), also is able to inhibit other members of positive-sense RNA viruses (Togaviridae and Flaviviridae). The available data reported the theoretical efficacy of ribavirin and sofosbuvir in the treatment of COVID-19 patients.[13-16] Coronaviruses are a family of RNA viruses with conserved RNA-dependent polymerase (RdRp), so that SARS-CoV-2 RdRp is most probably to be successfully inhibited by this safe and well-tolerated antiviral drug and it is suggested that sofosbuvir could be used as treatment against SARS-CoV-2 infection.[15] Also, velpatasvir is a potent inhibitor of the NS5A protein of HCV. According to the recent studies, velpatasvir can inhibit the biological activity of 3C-like protease (3CLpro) of coronavirus.[14] Therefore, sofosbuvir in combination with velpatasvir may be good candidates as inhibitor of two coronavirus enzymes, and this combined therapy may reduce the emergence of virus resistance. Direct-acting antiviral agents have fewer associated side effects and also they are simply administered orally.[17] The goal of the current trial is to determine the usefulness of "SOC plus hydroxychloroquine and lopinavir/ritonavir" vs. "SOC plus a combination of hydroxychloroquine and lopinavir/ritonavir and sofosbuvir/velpatasvir" in hospitalized individuals with laboratory-confirmed COVID-19 disease.

Methods/design

In this randomized controlled trial, individuals over 18 years of age who have been diagnosed with COVID-19 by positive reverse transcriptase–polymerase chain reaction (RT–PCR) for SARS-CoV-2 or compatible chest computed tomography (CT) scan were candidates for the study. Eighty patients from Kermanshah province, West of Iran were allocated to treatment with SOC plus hydroxychloroquine and lopinavir/ritonavir (dual therapy) or SOC plus a combination of hydroxychloroquine and lopinavir/ritonavir and sofosbuvir/velpatasvir (triple therapy) for 10 days.

Allocation was conducted using simple randomization. The primary outcomes were reducing mortality up to 28 days after hospitalization and reducing hospital stays. Adverse events were handled and reported in accordance with the Good Clinical Practice (GCP) guidelines.

Perspective

If COVID-19 treatment with sofosbuvir/velpatasvir-containing regimen can reduce mortality, reduce time to clinical improvement, or reduce hospital stay, it may be introduced as one of the effective treatments for this disease.

Trial registration

This clinical trial has been registered on March 30, 2020 under IRCT number 46790, in the Iranian Registry of Clinical Trials (https://www.irct.ir/trial/46790).

Objectives

The goal of this survey is to determine the safety and efficacy of "SOC plus hydroxychloroquine and lopinavir/ritonavir" vs. "SOC plus a combination of hydroxychloroquine and lopinavir/ritonavir and *sofosbuvir*/*velpatasvir*" in hospitalized individuals with SARS-CoV-2-related disease, i.e., COVID-19. In other words, the primary goal of this clinical trial is to assess (1) all-cause mortality in hospital and up to 28 days after randomization and (2) the efficacy of the employed regimens with respect to clinical status (clinical improvement, time to clinical improvement, duration of hospitalization). Clinical improvement was assessed by a six-stage saturation status on days 3, 5, and 7. Clinical improvement was defined as follows: reduce the two points (from the status at randomization) on a six-stage saturation status or live discharge from the hospital, whichever comes first, i.e., the point at which the individual/recovered patient was deemed eligible for discharge from hospital as per the study-specific criteria. Also we set out to determine whether the employed sofosbuvir–velpatasvir-based regimen could shorten the duration of hospitalization and modify ICU admissions and/or requirement for invasive mechanical ventilation.

Materials and Methods

Design

This project was a single center, prospective, randomized controlled trial, with two arms (ratio 1:1) parallel groups design. One arm of the patients received treatment with SOC plus hydroxychloroquine and lopinavir/ritonavir (dual therapy) and the other arm received treatment with SOC plus a combination of hydroxychloroquine and lopinavir/ritonavir and sofosbuvir/velpatasvir (triple therapy). The study followed the principles of GCP. SOVECOD stands for sofosbuvir/velpatasvir for possible COVID-19 treatment.

Patients

Patients who were hospitalized with COVID-19 (according to positive RT–PCR and/or compatible chest CT scan) were

screened for eligibility at Farabi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Inclusion and exclusion criteria

Patients showing signs and symptoms of COVID-19 were screened for eligibility using a flowchart. This flowchart is already in use at Farabi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran (see Supplementary File). The screening was carried out by an infectious diseases' resident or a trained General Practitioner. The individuals who meet eligibility criteria were adequately given information about the SOVECOD study. If they wanted to participate, they would be given a consent form which should be signed by the participant and the principle investigator. The Kermanshah University of Medical Sciences (KUMS) and the National Research Ethics Committee in Iran confirmed the consent form.

Inclusion criteria

Inclusion criteria are as follows:

- Confirmed COVID-19 diagnosis (positive RT–PCR and/or compatible chest CT scan);
- Patients over 18 years;
- Absolute lymphocyte count <1100/μL or $SaO_2 \leq 93$.

Exclusion criteria

Exclusion criteria are selected according to the doctor's decision, and patients who have any of the following criteria will be excluded to participate in the survey:

- Pregnancy and breast-feeding;
- The doctor's decision that enrollment in the study was not a good option for patients;
- Presence of conditions that do not allow the protocol to be completed;
- Known hypersensitivity or allergy to hydroxychloroquine, sofosbuvir–velpatasvir, or lopinavir–ritonavir;
- Known severe liver disease (e.g., cirrhosis, with an alanine aminotransferase or an aspartate aminotransferase level >5× the upper limit of the normal range);
- Use of drugs that are contraindicated include hydroxychloroquine, sofosbuvir–velpatasvir, or lopinavir–ritonavir;
- Known human immunodeficiency virus (HIV) or HCV infection.

If the patient is having difficulty swallowing, oral drugs are administered through NG tube.

Data collection and management

Nasopharyngeal swab

Nasopharyngeal swab specimens were collected on day 1 (before drug administration) and at the time of discharge for qualitative SARS-CoV-2 RT–PCR.

Six-stage saturation status, drugs safety, and laboratory findings

Patients were visited every day by trained nurses using daily record cards and flow-sheets that captured data on a six-stage saturation status and on safety from day 1 to hospital discharge or death. Safety was checked in accordance with the GCP guidelines (see Supplementary File).

Outcomes

Primary outcome measures

- All-cause mortality in hospital and up to 28 days after randomization.

Secondary outcome measures

- *Clinical improvement*: Reduce the two points (from the status at randomization) on a six-stage saturation status (see Supplementary File) or live discharge from the hospital, whichever comes first;
- *Clinical recovery time*: The time from randomization to clinical recovery;
- Length of hospital stay;
- Need for mechanical ventilation;
- Duration for mechanical ventilation;
- The number of days from randomization to death;
- PCR conversion from positive to negative at the time of randomization to discharge from hospital.

The size of sample

Although there were several outcomes that the investigators were interested in, as previous studies have not compared these two types of treatment regimens, we decided to determine the size of sample according to the "duration of stay in hospital." By consulting with the infectious disease specialists who were all involved in the management of COVID-19 cases, we assumed that the significant difference between the two groups is only 1 day with a standard deviation of 1.5 days. Therefore, such study needs 36 experimental individuals and 36 control individuals to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 0.8. The Type I error probability associated with this test of null hypothesis is 0.05.

Blinding and randomization

For the purpose of allocation sequence generation, using a random-numbers table (as Excel file) and simple random allocation, 80 included patients entered to the study, 40 patients in each group. In order to maintain the allocation sequence concealment, the details of treatment for each patient were contained in a sealed envelope, labeled by the numbers from 1 to 80. In fact, our study was an open label, randomized trial in which all the physicians and nurses plus all patients were aware of the type of treatment.

Intervention

Day 1

After the consent form was signed by the patient and physician, the epidemiological and clinical information questionnaire was completed by an infectious diseases' resident. Also, the status of the patients on a six-stage saturation status and laboratory findings upon enrollment records were registered in cards and flow-sheets. Specimens of nasopharyngeal swab were collected on day 1 (before drug administration). The patients were randomized into two arms: both arms received active treatment and none was given placebo. The intervention arm received hydroxychloroquine 400 mg single dose and lopinavir–ritonavir (400 and 100 mg) twice daily plus sofosbuvir–velpatasvir (400 and 100 mg) once daily orally, plus SOC for 10 days. The comparator arm received hydroxychloroquine 400 mg single dose and lopinavir–ritonavir (400 and 100 mg) twice daily orally, plus SOC for 10 days. SOC includes non-invasive and invasive ventilation, supplemental oxygen, vasopressor support, antibiotic agents, renal-replacement therapy, and corticosteroids.

Days 1–10 or day of hospital discharge or death

Patients were regularly visited every day by an infectious disease doctor and their treatment process was thoroughly checked. Also, they were assessed daily by trained nurses using daily record cards and flow-sheets that captured data on a six-stage saturation status and on safety from day 1 to hospital discharge, or death. Safety was monitored according to the GCP guidelines. Specimens of nasopharyngeal swab were collected on day 1 (before drug administration) and at the time of discharge (see Supplementary File).

Day 28

The health status of patients who have been discharged from the hospital prior to 28 days after enrollment to the study was questioned/followed over the phone and recorded in their respective files.

Safety

Criteria for termination of the study

For the individual patient:

- Serious adverse effect to the study drugs;
- Decided to leave the survey.

For the study itself:

- When an enough number of individual cases are included in the study;
- If more than 10% of cases in each study arm stop taking the drugs for any reason.

Adverse effects

We expected gastrointestinal intolerance for both study arms. During the daily visit of patients, the occurrence of drug side effects was considered by the infectious disease specialist and patients were asked about them and are openly recorded in the patients' files. In case of severe adverse effects, it was reported according to the principles of GCP and treatment was stopped.

Potential drug interactions

Sofosbuvir/velpatasvir has no interaction with hydroxychloroquine. In contrast, sofosbuvir/velpatasvir has interaction with ritonavir and their interactions can lead to an increase in the amount of sofosbuvir/velpatasvir in the patient's body, but as the amount of ritonavir in lopinavir/ritonavir is very low (its amount in our daily regimen is 100 mg), it is not used therapeutically, so this combination therapy has shown good safety with minimal drug interactions. In other words, ritonavir is a protease inhibitor, an anti-HIV drug, that decreases the amount of virus in the body and its effective dose for the treatment of HIV infection is 300 mg twice daily which is a very high dose. However, ritonavir is currently exclusively used as a pharmacokinetic enhancer of other protease inhibitors with the standard adult dose of 100 mg twice daily which is a very low dose compared with 300 mg twice daily (for the treatment of HIV infection). So in this trial, combination of ritonavir with sofosbuvir/velpatasvir has demonstrated minimal drug interactions. More importantly, sofosbuvir is safe and well tolerated at 400 mg (and even 1200 mg) daily in a 24-week therapeutic regimen; therefore, its interaction was not serious.

Registering and handling of data

Data registration was done during the study. For this purpose, a file had been prepared for each patient and data handling followed the principles of GCP. Subject requests for access to the trial database will be considered in discussion with the local Research Ethics Committee.

Statistical analyses

Data analyses were conducted according to the intention-to-treat basis and employed to cover all the patients included in the randomization process. The median [inter-quartile range (IQR)] and number (percent) were considered for the quantitative and qualitative variables, respectively. The independent sample *T*-test and the Mann–Whitney test were used to compare the groups in terms of quantitative variables. Also, using the χ^2 test, qualitative variables in the groups were compared. In addition, Fisher's exact test was applied in case of data sparsity. Employing version 14 of Stata software, the statistical analysis was performed. In the course of analysis, impossible range data and outlier were taken into consideration and finally, $P < 0.05$ was considered significant.

Monitoring

A person has been appointed by the University Ethics Committee to oversee all stages of the project. This trial was managed in consistent with the rules of the GCP, ethical principles of the Helsinki Declaration, and national laws and regulations.

Ethical considerations

Unfortunately, there is not any effective antiviral treatment for COVID-19 patients[5,6]; therefore, referring patients to clinical trials is crucial.[11,12] In the current trial, half of the cases received hydroxychloroquine 400 mg single dose and lopinavir–ritonavir (400 and 100 mg) twice daily orally, plus SOC for 10 days, and the other half was administered with hydroxychloroquine 400 mg single dose and lopinavir–ritonavir (400 and 100 mg) twice daily plus sofosbuvir–velpatasvir (400 and 100 mg) once daily. Developing serious adverse effect was low because of acceptable safety profile of sofosbuvir/velpatasvir in the intervention arm. If the patient was diagnosed as eligible to enter the study, he/she would be provided by the required information orally and in writing. It is noteworthy that participation was entirely voluntary and leaving the study had no effect on the type/quality of assistance or treatment. It was clear that a participant can leave the research study at any moment. If the participants had any questions about the clinical trial, they could call a research nurse or a research physician at the study site. It is emphasized that if the participants worsened during the survey or experienced serious side effects, they informed the infectious disease specialist or the nurses of the hospital, and the trial was discontinued if anyone displayed an unusual or unknown reaction.

Ethical approval for this study was received from the Research Ethics Committee at Kermanshah University of Medical Sciences, Kermanshah, Iran on March 3, 2020 (this trial is sponsored by the Kermanshah University of Medical Sciences, reference IR.KUMS.REC.1399.044). All the information about intervention details plus SOC for 10 days were in the informed consent. All of the research participants were given the SOC as well as the drugs recommended in the international guidelines for the treatment of COVID-19.

Preliminary Results and Discussion

There is no known established treatment recommended for SARS-CoV-2 infection. Patients who had moderate-to-acute illness are usually admitted at the hospital. Although some medications have been suggested to treat COVID-19, their results are not sufficient to apply these experimental treatments outside of clinical research. Well-organized randomized controlled studies are essential for the treatment of Covid-19. Sofosbuvir, the clinically approved drug against HCV, is also able to inhibit other members of positive-sense RNA viruses (Togaviridae and Flaviviridae) and may have inhibitory activity against SARS-CoV-2 RdRp. Notably, sofosbuvir is safe and well tolerated at 400 mg (and even 1200 mg) a day in a 24-week therapeutic regimen.[15] Sofosbuvir active metabolite, however, indicates very high intracellular stability; therefore, it is predicted that SARS-CoV-2 infection *in vivo* could also be susceptible to sofosbuvir,[15] whereas velpatasvir can inhibit the biological activity of 3C-like protease (3CLpro) of coronavirus, so we conducted an open label randomized controlled trial to assess safety, efficacy, and effectiveness of sofosbuvir–velpatasvir as add-on treatment to national SOC in hospitalized adults with Covid-19. If we demonstrate that all-cause mortality in hospital and up to 28 days after randomization is significantly lower in the sofosbuvir–velpatasvir arm, we can suggest the use of this drug in future "large-scale trials" in patients with severe illness to determine the benefits of treatment. Shortening clinical improvement time, reducing hospital stay, the need for mechanical ventilation, duration for mechanical ventilation, the number of days from randomization to death, and also PCR conversion from positive to negative at the time of randomization to discharge from hospital in the intervention arm can be due to the possible effectiveness of sofosbuvir/velpatasvir.

As a primary outcome, the 28-day mortality rate was numerically greater in the sofosbuvir/velpatasvir arm (n = 3, 13%) in comparison to the control arm (n = 1, 3.7%); but the difference was statistically non-significant. In addition, it is to be noted that after randomization, one patient in the sofosbuvir/velpatasvir arm died within the first 24 h of admission and did not administer sofosbuvir/velpatasvir.

As a secondary outcome, the median time to clinical recovery within 28 days in the sofosbuvir/velpatasvir [6 days (IQR 5–8)] and control arms [6 days (IQR 4–12)] was the same. Other secondary outcome was the length of stay in hospital. The median length of hospitalization in the control group and intervention group was also the same (6 days). Moreover, conversion of RT–PCR result was statistically non-significant between the two arms; P=0.17 [Table 1].

In addition, need for mechanical ventilation and duration of mechanical ventilation were not significantly different between arms (data not shown). More common adverse reactions in both arms (the intervention and control arms) were nausea, vomiting, diarrhea, and headache, respectively. Diarrhea incidence in the intervention arm was significantly higher than that in the control group. No significant difference existed in the incidence of other adverse events between the arms. Furthermore, there were no apparent differences in biochemistry laboratory abnormalities between the arms (data not shown).

As a summary, the antiviral drug, sofosbuvir, displayed encouraging results for the inhibition of SARS-CoV-2 RdRp activity *in vitro* (see citing references of Sayad *et al.*[15]). But, interestingly, clinical recovery within specified days of trial, duration of hospital stays, and the pooled risk of all-cause mortality in the sofosbuvir/velpatasvir arm (in the clinical trial) showed no statistically significant change when compared with those of the control arm [Table 1]. So, it can be inspired from the evidence that the sofosbuvir/velpatasvir regimen does not improve recovery and the dead rate in hospitalized COVID-19 patients with moderate-to-severe illness. However, we should wait for the final results of the research and re-analyze the whole data. The preliminary result of this well-designed trial is of great importance because Simmons *et al.*[18] in a recently published report have concluded that sofosbuvir/daclatasvir improves recovery and survival in hospitalized COVID-19 patients with moderate-to-severe illness. However,

Table 1: Interim analysis on the 13th day of the study

Characteristics	Total (*n*=50)	Sofosbuvir/ velpatasvir (*n*=23)	Standard of care (*n*=27)	*P*-value
Age, mean±SD (years)	52.5 ±18.4	54.8±17.0	50.7±19.6	0.43
Male sex, *n* (%)	28 (56.0)	12 (52.0)	16 (59.0)	0.61
Have contact history, *n* (%)	9 (18.0	5 (22.0)	4 (15.0)	0.96
Comorbidities, *n* (%)				
Hypertension	15 (30.0)	5 (21.8)	10 (37.0)	0.23
Diabetes	11(22.0)	6 (26.0)	5 (18.5)	0.52
Cardiovascular diseases	9 (18.0)	3 (13.0)	6 (22.2)	0.42
Pulmonary disorders	8 (16.0)	4 (17.4)	4 (14.8)	0.80
Other	11 (22.0)	6 (26.0)	5 (18.5)	0.52
Time from starting symptoms to randomization, median (IQR) (days)	7 (4–10)	7 (4–10)	6 (4–10)	0.67
Mortality, *n* (%)	4 (8.0)	3 (13.0)*	1 (3.7)	0.22
Clinical recovery time, median no. of days (IQR)	6 (4–9)	6 (5–8)	6 (4–12)	0.99
Length of stay in hospital, median no. of days (IQR)	6 (5–12)	6 (5–12)	6 (5–14)	0.79
PCR conversion (positive to negative), *n* (%)	9 (18.0)	6 (26.0)	3 (11.1)	0.17

*One patient died within the first 24 h of admission and *did not administer* sofosbuvir/velpatasvir

it is noteworthy that (contrary to our well-designed clinical trial) in the mentioned study: (a) the size of the sample for clinical trial was approximately small, (b) one of the analyses was not randomized, and (c) the designs were not standardized and the results should be confirmed in greater randomized clinical trials. Change in the drug administration (for instance, sofosbuvir as rectal formulation), increase of duration of the intervention, or increase of drug dosage (e.g., 800 mg daily of sofosbuvir) should be considered in upcoming clinical trials.

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Conflicts of interest

The authors declare that they have no competing interests. Ethics approval and consent to participate were given.

Authors' contributions

BS and RK conceived and designed the study, FN and FKS contributed to randomization and statistical analysis, RM, ZMA, FM, MSH, and MS contributed to study design. RK led the drafting of the manuscript and BS and MM edited the manuscript. The authors wrote, read, and approved the final manuscript.

Ethical approval and consent form to participate

This trial has received ethical approval from the Research Ethics Committee at Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran on March 3, 2020 (reference IR.KUMS.REC.1399.044). We also certify that this trial has received ethical approval from the appropriate ethical committee as described above. *Written informed consent* was obtained from all patients or their legal representative if they were unable to provide consent.

Consent for publication

Not applicable.

Data and materials availability

The data (in details) will be available from the corresponding author (on reasonable request). This needs agreement of KUMS Research Council.

Trial registration

This clinical trial has been registered on March 30, 2020 under IRCT number 46790, as: "Comparative assessment of the efficacy and safety of add-on treatment with 'sofosbuvir plus velpatasvir' to 'standard of care therapeutic regimen' in patients with COVID-19" in Iranian Registry of Clinical Trials (https://www.irct.ir/trial/46790).

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Clinical Effectiveness and Safety of Sofosbuvir-Velpatasvir as add-on treatment for COVID-19 patients: Study Protocol and Preliminary Data for the Randomized Controlled Trial

Protocol Date: 20th April 2020

Protocol Version: 1.5

Sponsor: Kermanshah University of Medical Sciences (KUMS Grant No. 990097)

Principal Investigator 1:

Dr. Babak Sayad

[1]*Professor of infectious diseases, Infectious Diseases Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran*

Principal Investigator 2:

Dr. Reza Khodarahmi

[2]Professor of Biochemistry, Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; [3]Department of Pharmacognosy and Biotechnology, Faculty of Pharmacy, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran

Co-investigators: Please see http://research.kums.ac.ir/webdocument/load.action?webdocument_code=1000&masterCode=3013296

Protocol Title:

Efficacy and Safety of Sofosbuvir-Velpatasvir as add-on treatment for hospitalized patients with COVID-19: Study Protocol for a Randomized Controlled Trial

KUMS Protocol Number: 990097

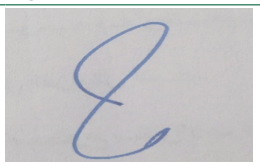
Iranian Registry of Clinical Trials (IRCT) protocol link/number: 46790

https://www.irct.ir/trial/46790

I, the undersigned, am responsible for the conduct of the trial at this site and agree to the following:

- I understand and will conduct the trial according to the protocol, any approved protocol amendments,and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior reviewand written approval from National Ethics Committee, except where necessary to prevent anyimmediate danger to the subject.
- I have read and understand fully the *Summaries of Product Characteristics* (SmPCs) for the investigational medicinal products; and I am familiarwith the Investigational Medicinal Product(s) (IMP) and its use according to this protocol.
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I haveavailable an adequate number of qualified staff and adequate facilities for the foreseen duration of thetrial to conduct the trial properly and safely.
- I will ensure that any staff at my site(s) who are involved in the trial conduct areadequately trainedregarding the Investigational Medicinal Products, the protocol and their responsibilities.

In the case ofdelegating any of my trial responsibilities I will provide the Sponsor with a Delegation of Activitiescertificate.

	Name	Signature	Date
Principal Investigator 1	Dr. Babak Sayad		30-March-2020

Document	Date of Issue	Summary of Changes
Version 1.0 – Original protocol	21-Feb-2020	Not applicable
Version 1.2 – Amended protocol	28-Feb-2020	Changes made to Protocol following feedback from the Reviewers: - Modification to Exclusion Criteria/ Inclusion Criteria- Sample size calculation - Revision of Statistical Analyses
Version 1.3 – Amended protocol	03-March-2020	Changes made following feedback from theEthics Committee Review of the protocol: -Revision of Outcome Measures -Revision of Written Informed Consent
Version 1.4 – Amended protocol	10-March-2020	Changes made following feedback from theFunding Committee Review of the protocol: -Revision of Personnel costs
Version 1.5 – Amendedprotocol	20-April-2020	Changes made to the protocol by PIs following additional Literature Review: -Revision of "Clinical and Laboratory Monitoring" based on WHO-ISARIC

The enrollment process started on 11 April, 2020 and finished on 11 May and the related follow-up finished on 8 June, 2020.

Kermanshah University of medical Sciences

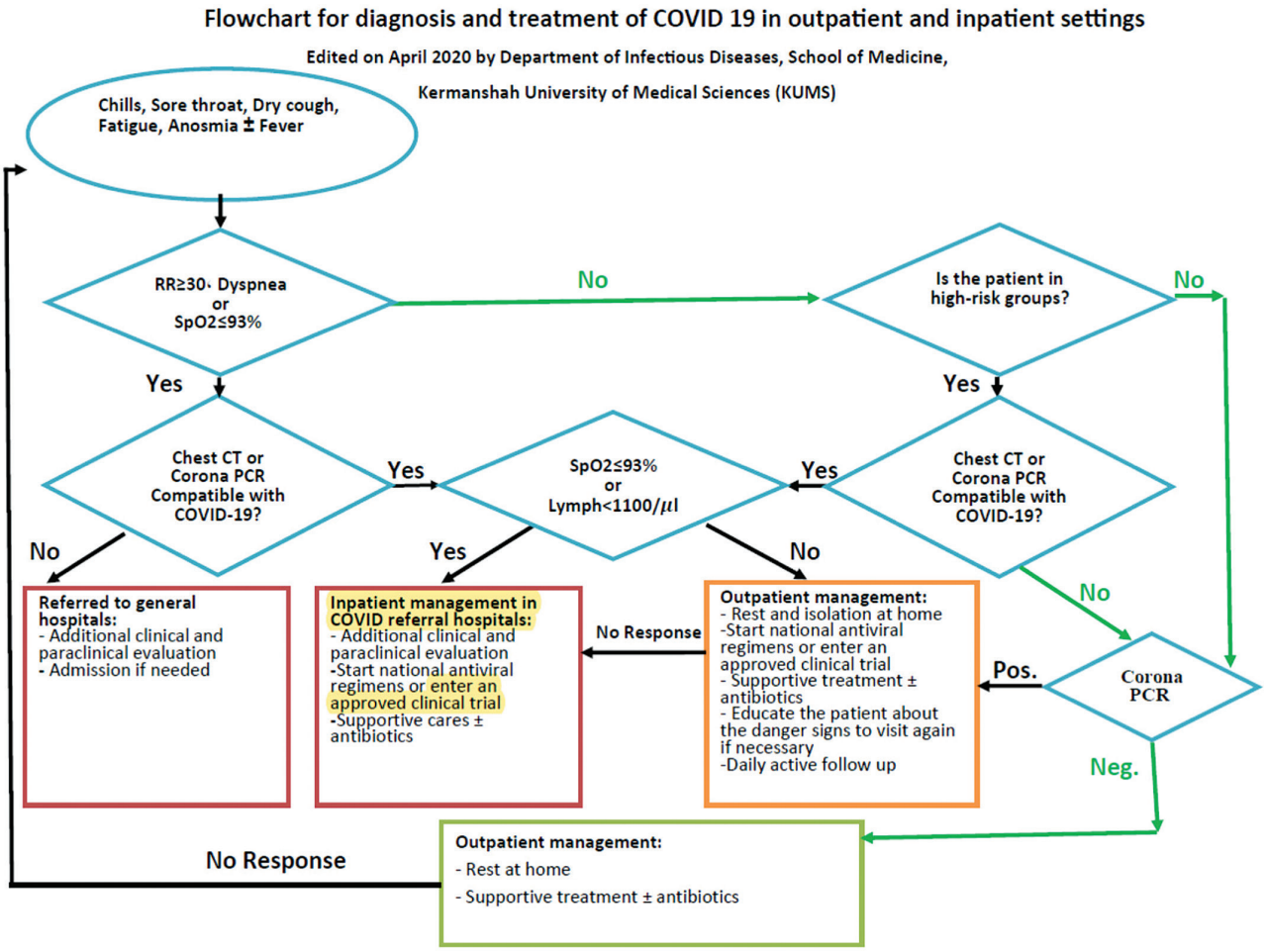
Research Ethics Certificate

Approval ID:	IR.KUMS.REC.1399.044	Approval Date:	2020-03-03
Evaluated by:	Kermanshah University of medical Sciences		
Status:	Approved		
Approval Statement:	The project was found to be in accordance to the ethical principles and the national norms and standards for conducting Medical Research in Iran. Notice: • Although the proposal has been approved by the research ethics committee, meeting the professional and legal requirements is the sole responsibility of the PI and other project collaborators. • This certificate is reliant on the proposal/documents received by this committee on **2020-03-03**. The committee must be notified by the PI as soon as the proposal/documents are modified.		
Proposal Title:	Comparative assessment of the efficacy and safety of add on treatment with "Sofosbuvir/Velpatasvir" to "standard of care therapeutic regimen" in patients with COVID-19		
Principal Investigator:	**Name:** babak sayad **Email:** babak sayad@yahoo.com		

Dr. mahmoodreza moradi
Director of University/Regional Research Ethics Committee
Kermanshah University of medical Sciences

Dr. Farid Najafi
Secretary of University/Regional Research Ethics Committee
Kermanshah University of medical Sciences

KUMS Ethical Approval of the *SOVECOD*



Flowchart for diagnosis and treatment of COVID 19 in outpatient and inpatient settingsis already in use at Farabi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran(snapshot of the main page).

دانشگاه علوم پزشکی و خدمات
بهداشتی درمانی کرمانشاه
معاونت تحقیقات و فناوری

شماره ثبت این طرح مصوب کشوری در مرکز ملی کارآزمایی بالینی:
IRCTID: IRCT20130812014333N145

فرم اخذ رضایت آگاهانه از بیمار

جهت شرکت در پژوهش مطابق با موازین و مقررات جهانی و ملی، مجریان طرح خود را ملزم به رعایت موازین اخلاقی و حقوقی جهت حفاظت از بیمار میدانند. فرم حاضر در ۳ برگ طراحی گردیده که هر ۳ برگ آن باید توسط افراد شرکت کننده در طرح پژوهشی (افراد بیمار) و یا قیم قانونی آنان و نیز مجری اول طرح پژوهشی امضاء گردد.

شرح و بیان اهداف و شیوه های پژوهش:

بیمار محترم: تاکنون برای درمان بیماری نوظهور کووید-۱۹ (یا همان بیماری کرونای جدید) حتی در پیشرفته ترین کشورهای دنیا هیچ دارو یا واکسنی به شکل اختصاصی پیشنهاد، تصویب و ساخته نشده است. محققین و پزشکان سرتاسر جهان (از جمله اینجانبان و همکاران) در تلاش شبانه روزی هستند تا با بهره گیری از مطالعات عمیق علمی و همفکری مستمر، موثر ترین داروها را جهت کاستن درد و رنج و در نهایت نجات بیماران تجویز و نتیجه را به جامعه تحقیقاتی-پزشکی جهان منعکس نمایند. در حال حاضر در ایران دو دارو با اسامی کلترا (با اثر درمانی کم) و هیدروکسی کلروکین (با اثر درمانی بهتر) برای بیماران مبتلا به بیماری فوق تجویز میگردد. این داروها اثر مهاری نسبی بر بیماری داشته، لذا جهت کاستن هر چه بیشتر از رنج و نیز دوره بیماری شما، مجریان طرح حاضر با مطالعه دقیق متون علمی معتقدند که داروی داروی سوفوسبوویر/ ولپاتاسویر که در مهار (ویروس) هپاتیت C بسیار موفق عمل کرده است، در ریشه کنی هر چه سریعتر ویروس کرونای جدید نیز قوی و موثر عمل می کند.

بیمار و یا قیم قانونی ایشان مطمئن باشد که در صورت تشخیص پزشک متخصص/ مسئول مبنی بر تجویز این دارو برای بیمار:

۱- ما هرگز هیچ یک از بیماران را از درمان دارویی استاندارد محروم نمی کنیم. یک دسته از بیماران داروی استاندارد را بطور کامل دریافت میکنند و دسته دیگر از بیماران بنا به تشخیص مجریان (و به عنوان درمان اضافه) علاوه بر داروی استاندارد، داروی انتخاب شده را دریافت میکنند.
۲- هیچ هزینه اضافی مرتبط با خرید درمان اضافه و نیز خدمات درمانی مربوطه از بیمار اخذ نخواهد شد و تمام هزینه های مذکور بر عهده دانشگاه علوم پزشکی کرمانشاه میباشد.
۳- داروی سوفوسبوویر/ ولپاتاسویر کم ضرر بوده و عوارض جانبی کمی دارد. بنابراین مصرف آن به هدف رفع بیماری دارای ارزش است.

امضاء
مجری اول طرح پژوهشی
دکتر بابک صیاد– متخصص عفونی و استاد دانشگاه

امضاء و اثر انگشت
بیمار یا قیم قانونی ایشان

Persian Edition of Informed Consent (snapshot of the 1st page)

گزارش وضعیت بیمار در روز ..... درمان تاریخ: .....

الف) جایگاه بیمار در پلکان

کمک تنفسی / (بدون اکسیژن) o2 Sat	Stage (پله)	
>93	۱	
88-93	۲	
85-87	۳	
80-84	۴	
< 80 / NIV	۵	
< 80 / Intubation	۶	

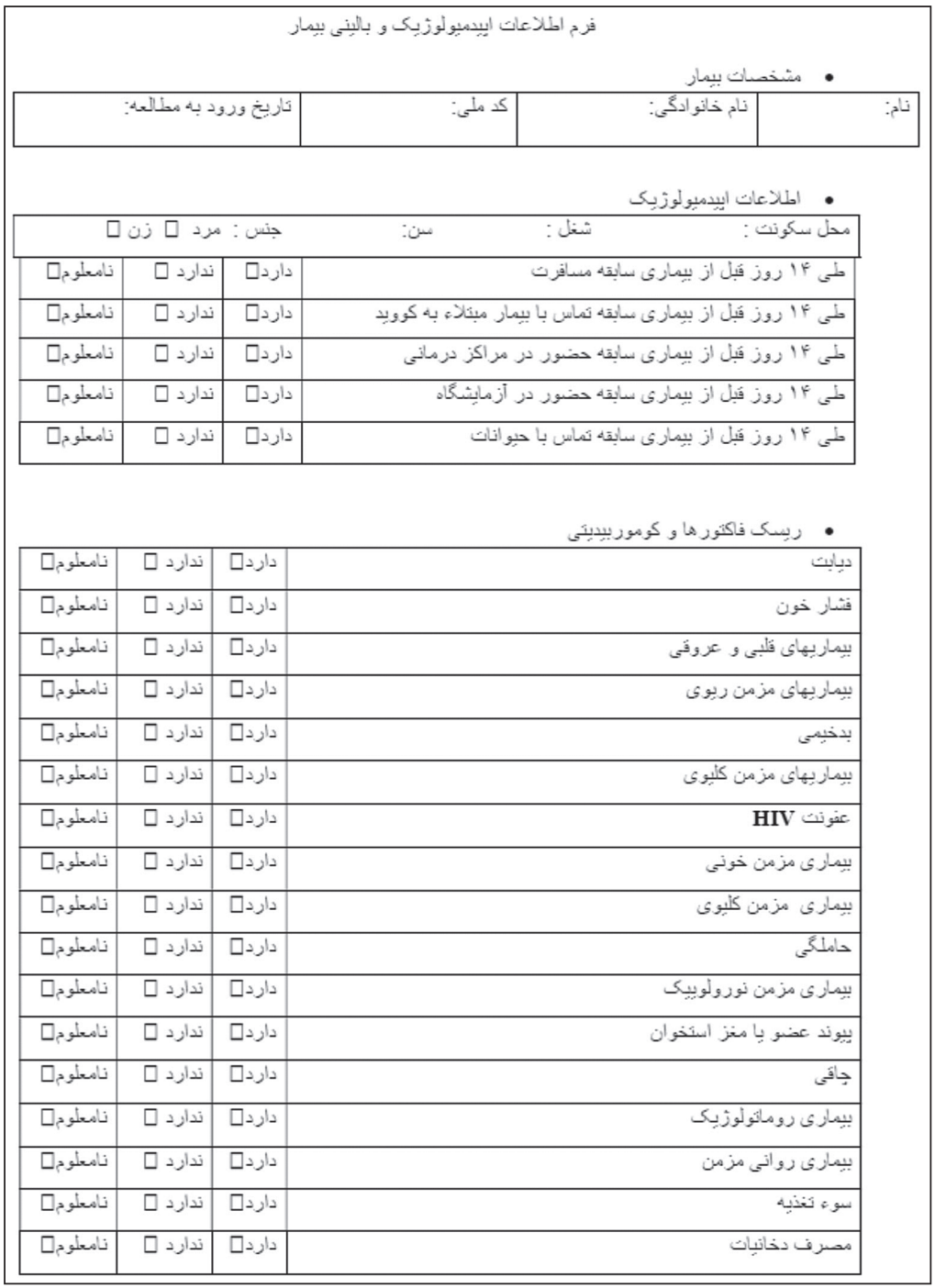
ب) عارضه دارویی ندارد ☐ عارضه دارویی دارد ☐ دارو بعلت عارضه قطع شد ☐

نوع عارضه :

ج) بیمار ترخیص شد ☐ وضعیت PCR در زمان ترخیص:

د) بیمار فوت کرد ☐ وضعیت PCR در زمان فوت:

Persian Edition of six-stage saturation status and safety from (snapshot from the patients file)



فرم اطلاعات اپیدمیولوژیک و بالینی بیمار

- مشخصات بیمار

نام:	نام خانوادگی:	کد ملی:	تاریخ ورود به مطالعه:

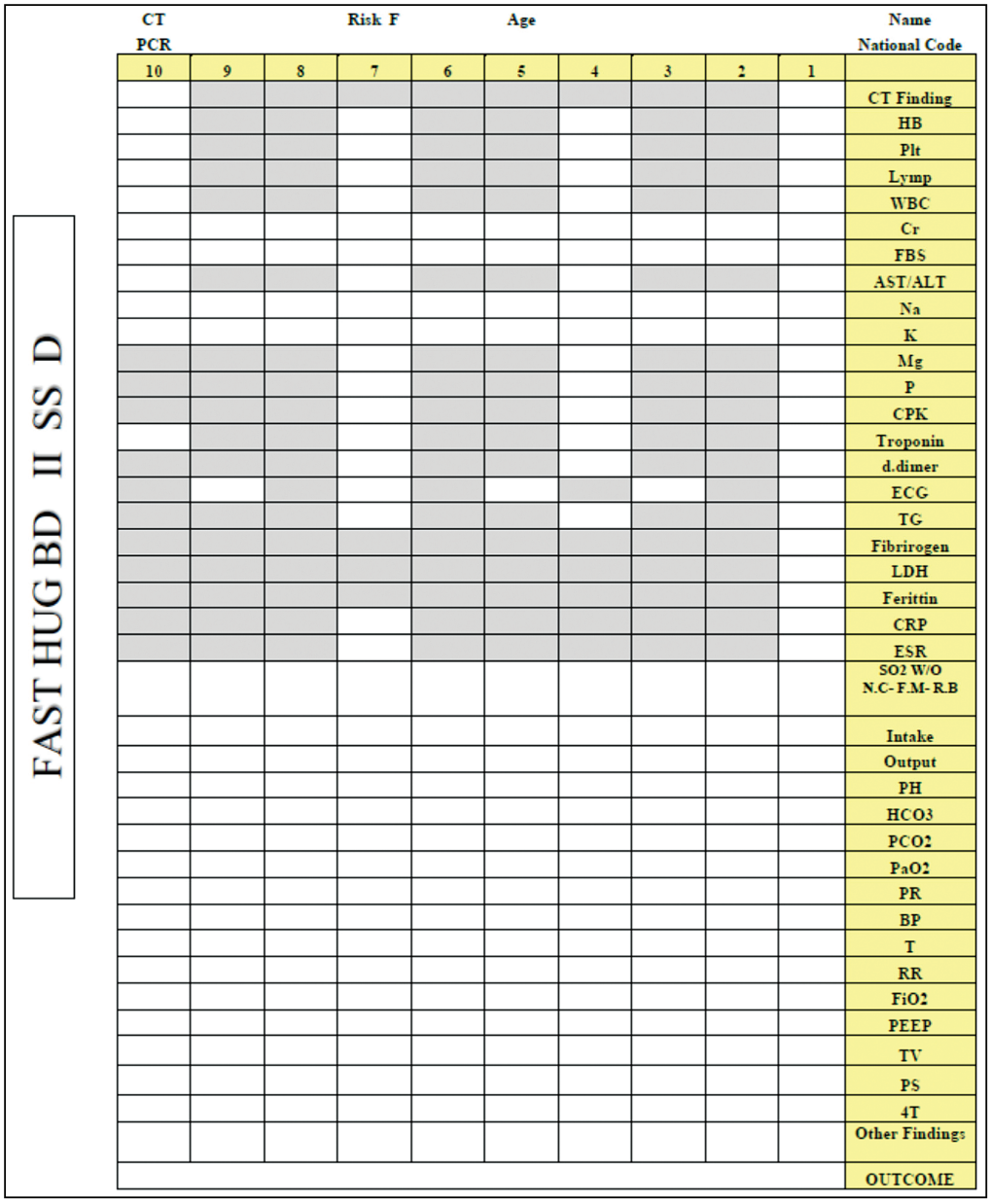
- اطلاعات اپیدمیولوژیک

محل سکونت : شغل : سن: جنس : مرد ☐ زن ☐			
طی ۱۴ روز قبل از بیماری سابقه مسافرت	دارد☐	ندارد ☐	نامعلوم☐
طی ۱۴ روز قبل از بیماری سابقه تماس با بیمار مبتلاء به کووید	دارد☐	ندارد ☐	نامعلوم☐
طی ۱۴ روز قبل از بیماری سابقه حضور در مراکز درمانی	دارد☐	ندارد ☐	نامعلوم☐
طی ۱۴ روز قبل از بیماری سابقه حضور در آزمایشگاه	دارد☐	ندارد ☐	نامعلوم☐
طی ۱۴ روز قبل از بیماری سابقه تماس با حیوانات	دارد☐	ندارد ☐	نامعلوم☐

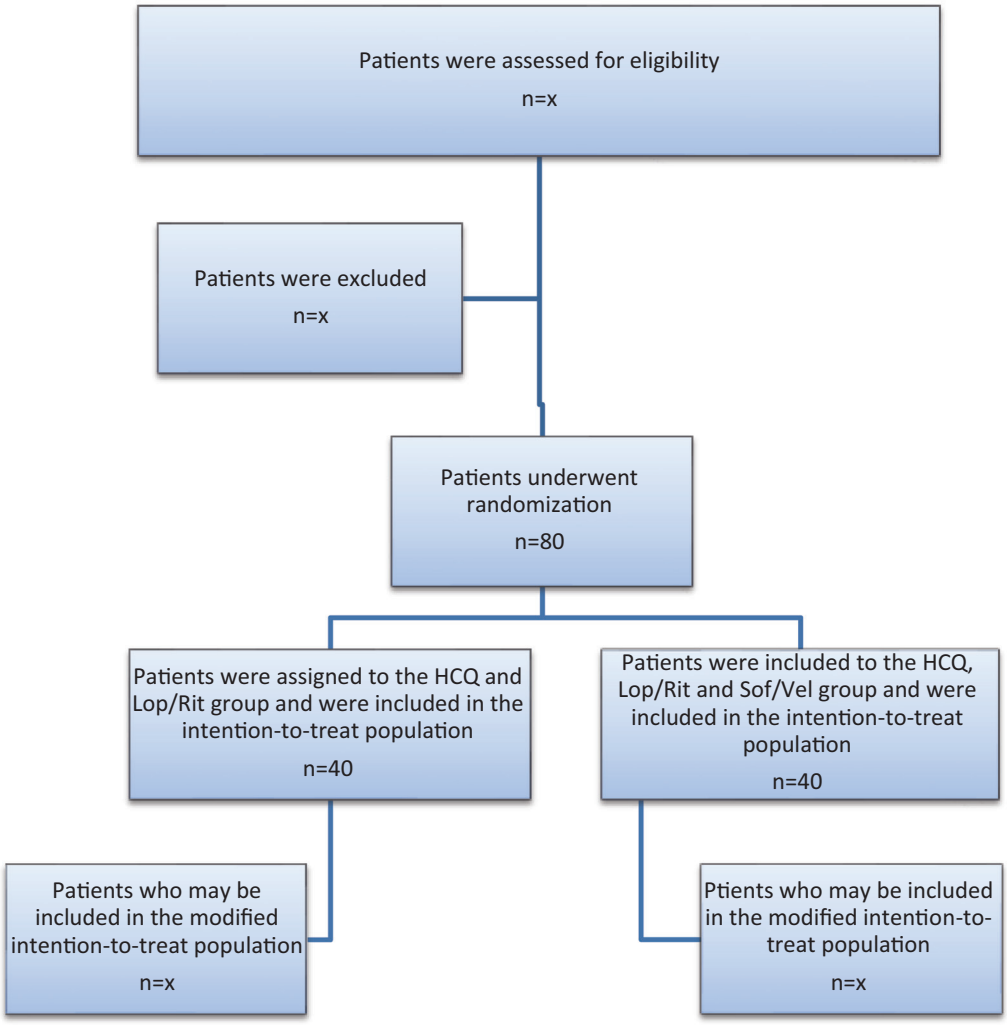
- ریسک فاکتورها و کوموربیدیتی

دیابت	دارد☐	ندارد ☐	نامعلوم☐
فشار خون	دارد☐	ندارد ☐	نامعلوم☐
بیماریهای قلبی و عروقی	دارد☐	ندارد ☐	نامعلوم☐
بیماریهای مزمن ریوی	دارد☐	ندارد ☐	نامعلوم☐
بدخیمی	دارد☐	ندارد ☐	نامعلوم☐
بیماریهای مزمن کلیوی	دارد☐	ندارد ☐	نامعلوم☐
عفونت **HIV**	دارد☐	ندارد ☐	نامعلوم☐
بیماری مزمن خونی	دارد☐	ندارد ☐	نامعلوم☐
بیماری مزمن کلیوی	دارد☐	ندارد ☐	نامعلوم☐
حاملگی	دارد☐	ندارد ☐	نامعلوم☐
بیماری مزمن نورولوبیک	دارد☐	ندارد ☐	نامعلوم☐
پیوند عضو یا مغز استخوان	دارد☐	ندارد ☐	نامعلوم☐
چاقی	دارد☐	ندارد ☐	نامعلوم☐
بیماری رومانولوژیک	دارد☐	ندارد ☐	نامعلوم☐
بیماری روانی مزمن	دارد☐	ندارد ☐	نامعلوم☐
سوء تغذیه	دارد☐	ندارد ☐	نامعلوم☐
مصرف دخانیات	دارد☐	ندارد ☐	نامعلوم☐

Persian Edition ofthe epidemiological and clinical information questionnaire (snapshot of the 1st page)

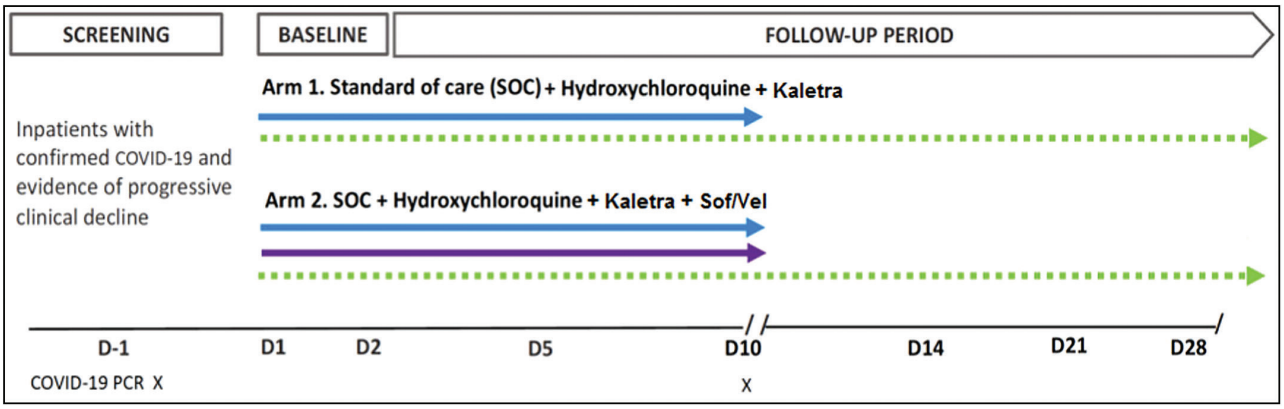


Daily record flowsheet that captured clinical and laboratory data



Randomization and Treatment Assignment

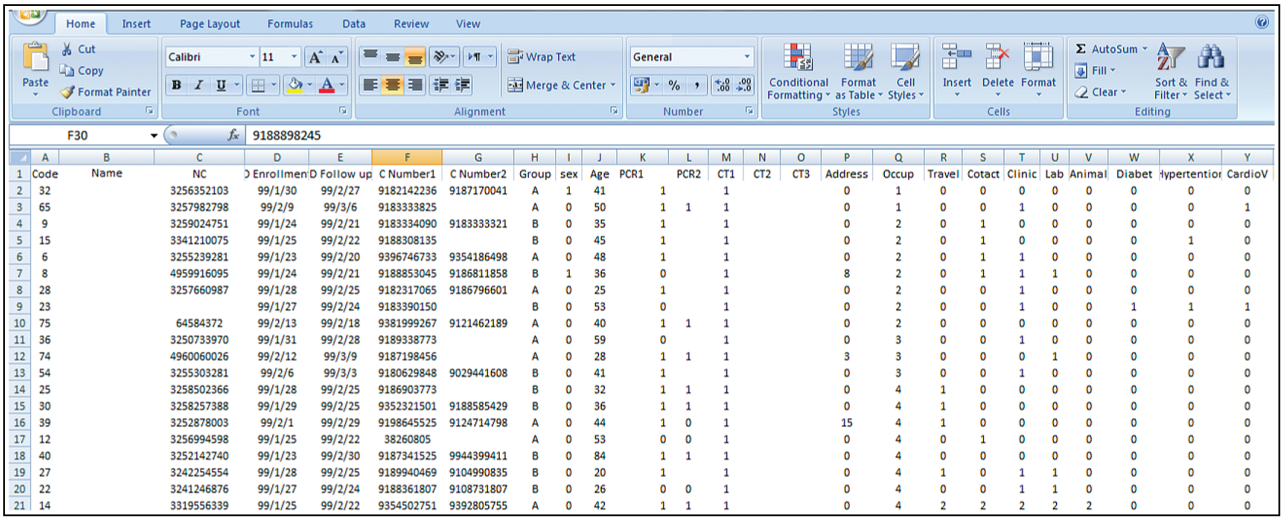
Treatment and follow up of patients



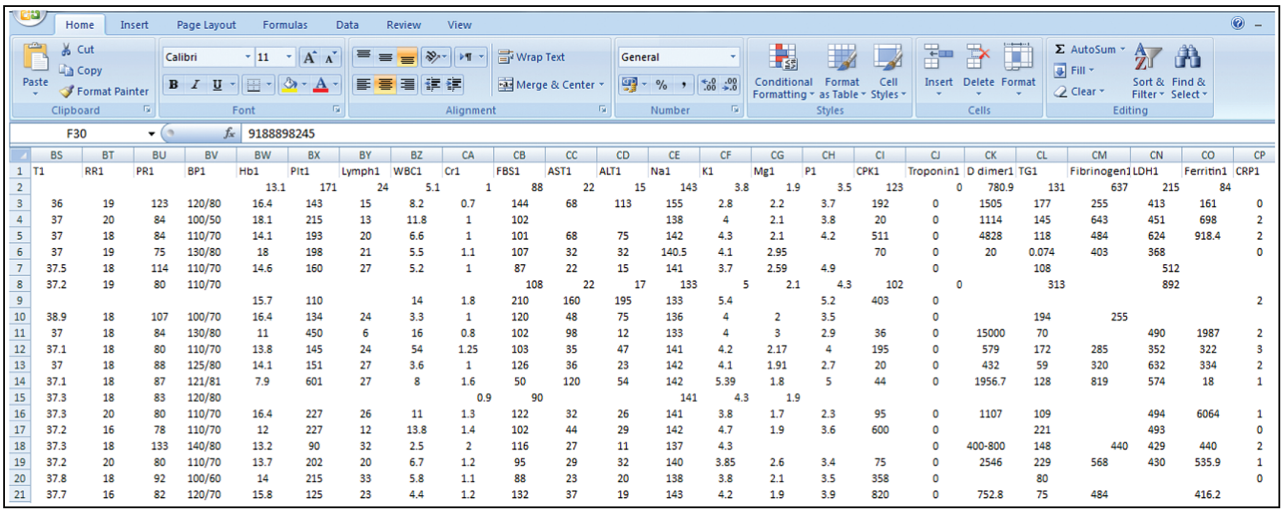
Drug administration

Study Drug	Hydroxychloroquine	(Lopinavir/Ritonavir)	Sofosbuvir/Velpatasvir
Dose Strength	400 mg	400/100 mg	400/100 mg
Dose Regimen	Single Dose	Towice Daily	Once Daily
Rout of Administration	Oral	Oral	Oral
Duration of treatment	Day 1	Day 1-10	Day 1-10

Data collection (This screenshot, as a representative, represents the accurate recording of clinical parameters as well as details during this well-designed clinical trial. Secondly, it will be appeared in the supplementary information (S.I. as additional file)



Code	Name	NC	Enrollmen	Follow up	C Number1	C Number2	Group	sex	Age	PCR1	PCR2	CT1	CT2	CT3	Address	Occup	Travel	Cotact	Clinic	Lab	Animal	Diabet	Hypertentio	CardioV
32		3256352103	99/1/30	99/2/27	9182142236	9187170041	A	1	41		1	1			0	1	0	0	0	0	0	0	0	0
65		3257982798	99/2/9	99/3/6	9183333825		A	0	50		1	1			0	1	0	0	1	0	0	0	0	1
9		3259024751	99/1/24	99/2/21	9183334090	9183333321	B	0	35		1	1			0	2	0	1	0	0	0	0	0	0
15		3341210075	99/1/25	99/2/22	9188308135		B	0	45		1	1			0	2	0	1	0	0	0	0	1	0
6		3255239281	99/1/23	99/2/20	9396746733	9354186498	A	0	48		1	1			0	2	0	1	1	0	0	0	0	0
8		4959916095	99/1/24	99/2/21	9188853045	9186811858	B	1	36		0	1			8	2	0	1	1	1	0	0	0	0
28		3257660987	99/1/28	99/2/25	9182317065	9186796601	A	0	25		1	1			0	2	0	0	1	0	0	0	0	0
23			99/1/27	99/2/24	9183390150		B	0	53		0	1			0	2	0	0	1	0	0	1	1	1
75		64584372	99/2/13	99/2/18	9381999267	9121462189	A	0	40		1	1			0	2	0	0	0	0	0	0	0	0
36		3250733970	99/1/31	99/2/28	9189338773		A	0	59		0	1			0	3	0	0	1	0	0	0	0	0
74		4960060026	99/2/12	99/3/9	9187198456		A	0	28		1	1			3	3	0	0	0	1	0	0	0	0
54		3255303281	99/2/6	99/3/3	9180629848	9029441608	B	0	41		1	1			0	3	0	0	1	0	0	0	0	0
25		3258502366	99/1/28	99/2/25	9186903773		B	0	32		1	1			0	4	1	0	0	0	0	0	0	0
30		3258257388	99/1/29	99/2/25	9352321501	9188585429	B	0	36		1	1			0	4	1	0	0	0	0	0	0	0
39		3252878003	99/2/1	99/2/29	9198645525	9124714798	A	0	44		1	0	1		15	4	1	0	0	0	0	0	0	0
12		3256994598	99/1/25	99/2/22	38260805		A	0	53		0	0	1		0	4	0	1	0	0	0	0	0	0
40		3252142740	99/1/23	99/2/30	9187341525	9944399411	B	0	84		1	1	1		0	4	0	0	0	0	0	0	0	0
27		3242254554	99/1/28	99/2/25	9189940469	9104990835	B	0	20		1		1		0	4	1	0	1	1	0	0	0	0
22		3241246876	99/1/27	99/2/24	9188361807	9108731807	B	0	26		0	0	1		0	4	0	0	1	1	0	0	0	0
14		3319556339	99/1/25	99/2/22	9354502751	9392805755	A	0	42		1	1	1		0	4	2	2	2	2	2	0	0	0



T1	RR1	PR1	BP1	Hb1	Plt1	Lymph1	WBC1	Cr1	FBS1	AST1	ALT1	Na1	K1	Mg1	P1	CPK1	Troponin1	D dimer1	TG1	Fibrinogen1	LDH1	Ferritin1	CRP1
				13.1	171	24	5.1	1	88	22	15	143	3.8	1.9	3.5	123	0	780.9	131	637	215	84		
36	19	123	120/80	16.4	143	15	8.2	0.7	144	68	113	155	2.8	2.2	3.7	192	0	1505	177	255	413	161	0	
37	20	84	100/50	18.1	215	13	11.8	1	102			138	4	2.1	3.8	20	0	1114	145	643	451	698	2	
37	18	84	110/70	14.1	193	20	6.6	1	101	68	75	142	4.3	2.1	4.2	511	0	4828	118	484	624	918.4	2	
37	19	75	130/80	18	198	21	5.5	1.1	107	32	32	140.5	4.1	2.95		70	0	20	0.074	403	368		0	
37.5	18	114	110/70	14.6	160	27	5.2	1	87	22	15	141	3.7	2.59	4.9		0		108		512			
37.2	19	80	110/70						108	22	17	133	5	2.1	4.3	102	0		313		892			
				15.7	110		14	1.8	210	160	195	133	5.4		5.2	403	0						2	
38.9	18	107	100/70	16.4	134	24	3.3	1	120	48	75	136	4	2	3.5		0		194	255				
37	18	84	130/80	11	450	6	16	0.8	102	98	12	133	4	3	2.9	36	0	15000	70		490	1987	2	
37.1	18	80	110/70	13.8	145	24	54	1.25	103	35	47	141	4.2	2.17	4	195	0	579	172	285	352	322	3	
37	18	88	125/80	14.1	151	27	3.6	1	126	36	23	142	4.1	1.91	2.7	20	0	432	59	320	632	334	2	
37.1	18	87	121/81	7.9	601	27	8	1.6	50	120	54	142	5.39	1.8	5	44	0	1956.7	128	819	574	18	1	
37.3	18	83	120/80					0.9	90			141	4.3	1.9										
37.3	20	80	110/70	16.4	227	26	11	1.3	122	32	26	141	3.8	1.7	2.3	95	0	1107	109		494	6064	1	
37.2	16	78	110/70	12	227	12	13.8	1.4	102	44	29	142	4.7	1.9	3.6	600	0		221		493		0	
37.3	18	133	140/80	13.2	90	32	2.5	2	116	27	11	137	4.3				0	400-800	148	440	429	440	2	
37.2	20	80	110/70	13.7	202	20	6.7	1.2	95	29	32	140	3.85	2.6	3.4	75	0	2546	229	568	430	535.9	1	
37.8	18	92	100/60	14	215	33	5.8	1.1	88	23	20	138	3.8	2.1	3.5	358	0		80				0	
37.7	16	82	120/70	15.8	125	23	4.4	1.2	132	37	19	143	4.2	1.9	3.9	820	0	752.8	75	484		416.2		

Medicinal Products: See Main File

Laboratory Reference Ranges: According to text books/guidelines

Declaration of Helsinki

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Ethical Principles for Medical Research Involving Human Subjects

In 1964, the World Medical Association drew up a code of ethics on human experimentation. This code, known as the Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added), 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added), 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 and the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 reads:

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving

subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.