HIGH-FLOW vs. CONVENTIONAL OXYGEN THERAPY IN PATIENTS WITH ACUTE RESPIRATORY FAILURE DUE TO SARS-CoV-2: The HiFLo-COVID RANDOMIZED CLINICAL TRIAL

The HiFLo-COVID collaborative group

This document includes:

- HiFLo-COVID Protocol Version 3.0. Date: 02nd January 2.021.

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- Summary of Changes to the protocol (from VERSION 1.0 to VERSION 3.0)

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SYNOPSIS

HIGH-FLOW vs. CONVENTIONAL OXYGEN THERAPY FOR PATIENTS WITH ACUTE RESPIRATORY FAILURE DUE TO SARS-CoV-2: The HiFLo-COVID RANDOMIZED CLINICAL TRIAL

Data category:	Information:
Registration - Study Identification Number:	Fundación Valle del Lili EBRC; protocol number: 1635; approval number: 259 - 2020
Date of Registration:	July 2020.
ClinicalTrials.gov Identifier:	NCT04609462
Main Sponsor:	Centro de Investigaciones Clínicas – Fundación Valle del Lili. Cali, Colombia.
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Scientific title:	HIGH-FLOW vs. CONVENTIONAL OXYGEN THERAPY FOR PATIENTS WITH ACUTE RESPIRATORY FAILURE DUE TO SARS-CoV-2: The HiFLo-COVID RANDOMIZED CLINICAL TRIAL
Coordinator Center:	Fundación Valle del Lili. Cali, Colombia .
Recruitment centers:	3 (Colombia)
Health Condition or Problem:	Severe SARS-CoV-2 infection.
Type of Study:	Open (non-blind), randomized, controlled, Phase II clinical trial.
Primary Objective:	To evaluate the impact of using high-flow oxygen through a nasal cannula vs. conventional oxygen therapy on the need for intubation/support with invasive mechanical ventilation and clinical status as assessed by a 7-category ordinal scale in patients with acute hypoxemic respiratory failure secondary to severe Covid-19
Specific Objectives:	*Secondary Objectives* Efficiency • To evaluate the impact of high-flow oxygen therapy through a nasal cannula (HFNC) vs. conventional oxygen therapy (COT) on the requirement of early intubation and invasive mechanical ventilation support. • To assess the impact of HFNC vs. COT on mechanical ventilation-free days. • Assess the impact of HFNC vs. COT on renal replacement therapy-free days. • To assess differences in length of hospital/ICU stay between study groups. • To assess differences in all-cause mortality at days 14 and

Data category:	Information:
	28 post-randomization, between study groups Safety • To assess the occurrence / proportion of patients with severe adverse events within 28 days from randomization. • To assess the occurrence / proportion of bacterial / fungal infections within 28 days from randomization. *Tertiary Objectives* • To evaluate the differences in the evolvement of oxygen flow requirement and PaO_2/FiO_2 ratio between groups • To evaluate the differences for the time elapsed from randomization to intubation / invasive mechanical ventilation support in patients failing to high-flow oxygen therapy and conventional oxygen therapy • To evaluate the impact of HFNC vs. COT on the clinical condition at day 28 • To evaluate the impact of HFNC vs. COT on the development and evolution of multiorgan dysfunction as assessed by the SOFA score. • To evaluate the impact of HFNC vs. COT on the development and evolution of extra-pulmonary organ dysfunction as assessed by extra-pulmonary SOFA score • To evaluate the differences in HACOR and ROX scores at 2 and 4 hours post-randomization between the groups and their relationship with requiring intubation and mechanical ventilation-free days • To assess differences in IL-6 and IL-8 kinetics within 7 days from randomization, between study groups • To assess differences in ferritin kinetics, LDH, leukocyte count, neutrophil/lymphocyte count relationship, platelet count and D-dimer during the 7 days following randomization, between study groups *For Predefined Subgroups* • To assess the impact of high-flow oxygen vs. conventional oxygen therapy on the need for intubation / invasive ventilation support and the time to clinical recovery (as assessed by a 7-category ordinal scale) in patients with initial PaO_2/FiO_2 ratio > and < 100 mmHg. • To assess the impact of high-flow oxygen vs. conventional oxygen therapy on the need for intubation / invasive ventilation support and the time to clinical recovery (as assessed by a 7-category ordinal scale) in patients with baseline IL-6 levels > and < 100 pg/mL. • To assess the impact of high-flow oxygen vs. conventional oxygen therapy on the need for intubation / invasive ventilation support and the time to clinical recovery (as assessed by a 7-category ordinal scale) in patients aged >

Data category:	Information:
	and < 60 years.
Study design:	Multicenter, randomized, open-label, controlled study on the use of high-flow oxygen therapy through a nasal cannula vs. conventional oxygen therapy in patients with moderate / severe hypoxemic respiratory failure due to SARS-CoV-2 infection.
Intervention group:	High-Flow oxygen therapy through a nasal cannula (HFNC).
Control:	Conventional oxygen therapy (COT).
Co-Interventions:	Usual care (hemodynamic / respiratory / metabolic / hematological / general).
Population:	Adult patients (>18 years) admitted to the emergency room or Intensive Care Unit (ICU) with moderate / severe acute hypoxemic respiratory failure secondary to SARS-CoV-2 infection.
Inclusion Criteria:	• Adults > 18 years old. • Emergency or ICU admission under suspected / confirmed SARS-CoV-2 infection. • Moderate/severe acute respiratory failure: - PaO2/FiO2 < 200. - Use of accessory muscles. - Breathing rate > 25 per minute. • Having a progression < 6 hours since fulfilling definition of moderate or severe acute respiratory failure due to suspected or confirmed SARS-CoV-2 infection.
Exclusion Criteria	• < 18 years. • Indication for immediate tracheal intubation. • Pregnant woman / positive pregnancy test at the time of potential inclusion. • Chronic liver disease / liver cirrhosis Child-Pugh C. • Confirmation of active bacterial or fungal infection. • Uncontrolled HIV/AIDS disease (defined by presence of viral load > 200 copies/mL). • Previous history of COPD Gold C – D. • History of COPD requiring hospitalization or ICU admission during the last year. • History of congestive heart failure NYHA III – IV. • History or actual left ventricular ejection fraction < 45% • Highly suspected or confirmed cardiogenic pulmonary edema. • Hypercapnic respiratory failure ($PaCO_2$ > 55 mmHg). • History or high suspicion of central or peripheral demyelinating disorders at the time of potential inclusion. • Imminence of death within the next 24 hours (according to investigator´s clinical judgment) • Any serious medical condition or clinical laboratory test abnormality that, at the investigator's judgment, prevents safe patient participation and completion of the study. • Participation in another clinical trial (except other related to SARS-CoV-2. These criteria will be always discussed among steering committee members
Sample Size	220 patients (110 by arm).

Data category:	Information:
Randomization method	Permuted blocks of size 4 and 6, stratified by center.
Primary outcomes	• Need for intubation / invasive mechanical ventilation support (time frame: 28 days). • Clinical recovery as assessed by a 7-category ordinal scale (time frame: 28 days).
Secondary – tertiary outcomes / subgroup analysis	*Secondary Outcomes* Efficiency • Early requirement of intubation / invasive mechanical ventilation support (time frame: 7 days – 14 days). • Mechanical ventilation-free days (time frame: 28 days). • Renal replacement therapy-free days (time frame: 28 days) • Length of ICU stay (time frame: 28 days) • Length of hospital stay (time frame: 28 days) • Hospital mortality – all causes (time frame: 14 and 28 days) Safety • Occurrence / proportion of patients with serious adverse events (time frame: 28 days) • Occurrence / proportion of bacterial - fungal infections (time frame: 28 days). *Tertiary Outcomes* • Evolvement of oxygen flow requirement and PaO_2/FiO_2 ratio (time frame: 7 days) • Time elapsed from randomization to intubation / invasive mechanical ventilation support in patients failing to high-flow oxygen therapy and conventional oxygen therapy (time frame: 28 days). • Clinical condition at day-28 (time frame: 28 days). • Evolvement of multiorgan dysfunction as assessed by SOFA score (time frame: 14 days) • Evolvement of extra-pulmonary organ dysfunction as assessed by extra-pulmonary SOFA score (time frame: 14 days). • HACOR and ROX scores at 2- and 4-hours post-randomization and their relation with requirement of intubation (time frame: 28 days) • Differences in time-course of IL-6 and IL-8 between study groups (time frame: 7 days) • Differences in time-course of ferritin, LDH, leukocyte count, neutrophil to lymphocyte count relationship, platelet count, and D-dimer among the groups under study (time frame: 7 days)

Data category:	Information:
	Subgroup Analysis • Time to intubation / invasive mechanical ventilation and clinical recovery in subgroups with baseline PaO_2/FiO_2 > and < 100 mmHg (time frame: 28 days) • Time to intubation / invasive mechanical ventilation and clinical recovery in subgroups with baseline IL-6 > and < 100 pg/mL (time frame: 28 days) • Time to intubation / invasive mechanical ventilation and clinical recovery in subgroups aged > and < 60 years (time frame: 28 days)
Statistical analysis	The effect of the treatment on the primary outcome requirement of intubation / invasive mechanical ventilation support will be calculated by using a Cox proportional hazard model adjusted by age, initial PaO_2/FiO_2 and comorbidities (diabetes, hypertension, obesity BMI ≥ 30). The results will be reported as hazard ratios with 95% confidence intervals and represented in Kaplan-Meier curves. This same analysis will be performed separately on those individuals who meet the definition of moderate and severe confirmed cases. Time to clinical improvement was defined as time elapsed from randomization until the first day, during the 28 days after enrollment, on which a patient attained a reduction in two or more points in the modified ordinal 7-category scale. The effect size of the allocated therapy on the time to recovery was assessed by computing the hazard ratio with its 95% confidence interval (CI) as estimated from Cox proportional hazard model stratified by age, hypoxemia severity, and comorbidities. Such analysis will be constructed for the overall population and also stratified according to baseline 7-category ordinal scale at enrollment (i.e., scores of 4 or 5), and plotted in Kaplan-Meier curves. All the analysis will be performed on an intention-to-treat basis with no exclusion after randomization except exclusions for withdrawn consent, according to the local regulations. In addition, some predefined subgroups will be analyzed: - Age group: <60 years and ≥60 years. - IL-6 at randomization: <100 and ≥100 pg/mL. - PaO_2/FiO_2 initial <150 and ≥150. Significance level will be 5%.
Keywords	High-flow nasal cannula, high-flow oxygen therapy, conventional oxygen therapy, oxygen therapy, acute hypoxemic respiratory failure, severe hypoxemia, SARS-CoV-2 infection, Covid-19.

INTRODUCTION

In early December 2010, a new coronavirus designated as SARS-CoV-2 caused a local outbreak in Hubei Province (China) that ultimately spread to more than 190 countries causing a new pandemic situation, officially designated as such by the World Health Organization on 11 March 2020 (1). Although mortality associated with SAR-CoV-2 disease was initially estimated at 0.1% in mild cases and 8.1% in severe cases (2), this number has been substantially variable among different regions and countries, being unclear whether this represents the effect of insufficient sampling (unreliable denominators) or clinical susceptibility inherent to some population groups (3). Factors such as age (4) and the presence of co-morbidities (5) would appear to be determinants in developing more severe forms of disease and unfavorable outcomes. Meanwhile, using some cardiovascular drugs such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers would not appear to play a significant role in both the severity and survival probabilities (6, 7). Other data suggest that severity of inflammation determined by interleukin-6 (IL-6) levels and the activation of the coagulation system reflected by elevated D-dimer levels appear to be determinants in developing more severe forms of disease leading to worse clinical outcomes (8, 9).

Data from 72,314 cases of SARS-CoV-2 disease from China revealed that 14% of patients were classified to have a severe disease (i.e., dyspnea, respiratory rate > 30/min, SpO_2 <93%, PaO_2/FiO_2 < 300 and/or pulmonary infiltrates >50% within 24-48 hours), while 5% were classified as critical (i.e., respiratory failure, septic shock and/or multiorgan dysfunction) (10). In this series, mortality was 2.3% among all confirmed cases and 49% among those classified as critical (10). Data from 12 hospitals in the New York area showed that 14.2% of patients required intensive care unit management, while 12.2% required invasive mechanical ventilation (11). Remarkably, 88.1% of patients subjected to invasive ventilatory support had died at the time of the study report (11), which raised serious concerns about the ventilation strategies in patients with severe SARS-CoV-2 infection.

Up to the time this research protocol was prepared, no therapeutic or supportive intervention had demonstrated to modify clinical outcomes in severe SARS-CoV-2 infection. In fact, management of moderate and severe forms of SARS-CoV-2 infection currently relies on expert recommendations, mostly without a high level of evidence

supporting them (12, 13). Until now, use of antiviral drug has led to disappointing results in predominantly mild- and moderate forms of disease (14). A study on the use of remdesivir in 1063 patients with SARS-CoV-2 infection led to a highly questionable decrease in symptom duration, without impacting the recovery of those patients with a higher requirement for oxygen support, non-invasive mechanical ventilation and invasive mechanical ventilation (15). Finally, observational results about the use of hydroxychloroquine alone or in combination with azithromycin suggested its lack of efficacy to control SARS-CoV-2 infection (16, 17), while another observational study suggested potential harm related to ST segment prolongation when high doses of hydroxychloroquine are used (18). Importantly, chloroquine-related cardiovascular risk would be confirmed in a randomized trial in hospitalized patients with SARS-CoV-2 infection when those receiving high doses of the drug showed an excess of major adverse cardiovascular events (19).

Beyond general supportive measures, there are as yet no specific medications or interventions able to modify the course of severe SARS-CoV-2 disease. However, given the respiratory nature of the infection, respiratory support is a key component in its management. Throughout the development of the pandemic, the need for invasive mechanical ventilation has been emphasized and, in fact, government agencies around the world have responded almost unanimously by trying to increase the capacity and number of mechanical ventilation devices in their hospital networks. However, other non-invasive respiratory support devices such as high-flow nasal cannula could be useful in the management of hypoxemic respiratory failure secondary to SARS-CoV-2 infection. Nevertheless, the role of high-flow oxygen therapy has not been widely studied in Covid-19. Thus, the present study aims to evaluate the role of high flow oxygen through a nasal cannula vs. conventional oxygen therapy in patients with moderate and severe acute hypoxemic respiratory failure in patients with severe Covid-19.

3. BACKGROUND

Coronaviruses (CoV) are a large family of respiratory viruses able to cause respiratory manifestations in a wide range of severity: from a syndrome similar to the common cold

up to severe manifestations such as the Middle East Respiratory Syndrome (MERS) (20) and Severe Acute Respiratory Syndrome (SARS) (21-23). These latter are considered as zoonotic diseases able to induce fatal infections at the lower respiratory tract as well as severe extra pulmonary manifestations. The new coronavirus, designated SARS-CoV-2, is a member of the Beta-CoV line B that was identified in Hubei Province in China by local health agencies (24). SARS-CoV-2 has a genome sequence 75-80% identical to its predecessor, SARS-CoV (25). SARS-CoV was responsible for an outbreak of severe respiratory infection that began in Guandong Province, China in 2002, causing more than 8,000 cases and about 774 deaths in 26 countries on 5 continents (21-23); meanwhile, other outbreak of coronavirus caused the MERS epidemic (20), resulting in 1879 cases and 659 deaths in 27 countries. Although an apparent initial zoonotic contamination was identified in the current SARS-CoV-2 outbreak, transmission among humans from the same family, hospitals and special care environments have also been reported (26-28). The virus spread globally during the following weeks after its first report in China and subsequently, World Health Organization declared a pandemic alert by the 11 March 2020 (1). The number of cases of SARS-CoV-2 infection increased rapidly, reaching a total of 10,145,791 cases and 501,898 deaths worldwide by June 29, 2020.

3.1. Spectrum of disease

According to data from 72,314 cases of SARS-CoV-2 disease in China, 44,672 (62%) were confirmed through genomic screening tests (10). Meanwhile, 16,186 (22%) were declared as suspected cases based on the presence of symptoms and exposure (absence of genomic detection due to logistical problems); other 10,567 (15%) were classified clinically (based on symptoms, exposure and presence of images compatible with SARS-CoV-2 infection) and 889 (1%) were considered as asymptomatic patients (positive genomic detection in the absence of symptoms such as fever, dry cough and fatigue). SARS-CoV-2 induces a wide range of severity, with mild disease representing most of the cases (81%). Meanwhile, 14% induce a severe disease (i.e., dyspnea, respiratory rate > 30/min, SpO2 <93%, PaO2/FiO2 < 300 and/or pulmonary infiltrates >50% within 24-48 hours), while 5% led to critical disease (i.e., respiratory failure, septic shock and/or multiorgan dysfunction) (10).

In general terms, disease induced by SARS-CoV-2 shows a time-course that could be summarized in three phases:

1. Phase 1 (or early phase): characterized by the immune response to the virus, usually within the first 5 to 8 days. Typical symptoms include fever 80%, dry cough 50%, mild dyspnea 60%, fatigue 60%, diarrhea and other gastrointestinal symptoms 50%. Laboratory abnormalities include lymphopenia, increased D-dimer, LDH and ferritin levels. Viral load increases during this phase in some individuals. Nevertheless, most patients experience a significant drop in viral load at the end of this phase, although this may vary among patients. Potential antiviral therapies (i.e., remdesivir, favipiravir), hydroxychloroquine, azithromycin, and others, have been reported to be most useful in this early phase (although with not successful clinical results).

2. Phase 2 (or pulmonary phase): characterized by moderate symptoms from day 10 to day 14. Laboratory abnormalities include mild increase in aminotransferases and procalcitonina levels. Lymphopenia may be pronounced. During this phase oxygen might be needed and sometimes, clinical deterioration occurs. This phase represents a breaking point for development of severe complications in some individuals. Most of them persist with detectable viral loads during this phase.

3. Phase 3 (or hyper-inflammation phase): A minority of COVID-19 patients will transition into the third and most severe stage of the illness, which manifests as an extrapulmonary systemic hyperinflammation syndrome. Usually appearing after day 14. Main feature is severe hypoxemia. Bacterial superinfections may occur in some cases. Interleukin-6 (IL-6), ferritin and LDH can increase. Cardiac involvement and prothrombotic phenomena may also occur. Mortality in patients attaining this phase is high. Using immunomodulatory drugs could be promising.

Initial phases are characterized by large viral replication, presence of mild symptoms, lymphopenia, increased inflammatory markers and activation of coagulation system (29). Over time, the immune response of the host takes on progressive importance, since it is actually the inflammatory response that determines the appearance of progressively more

severe manifestations of the disease. Thus, it seems logical that during phase 1 and initial part of phase 2, therapies aimed to control viral replication could have a great impact; meanwhile, in the transition from phase 2 to phase 3, and during this latter, therapy should aim to modulate the immune response by the host.

3.2 Acute respiratory failure

Acute hypoxemic respiratory failure is a pathological condition characterized by altered oxygenation demonstrated by a decrease in oxygen blood pressure (PaO2) < 60 mmHg, oxygen saturation (SaO2) < 90% or PaO2/FiO2 index < 300. This syndrome has different etiologies and pathophysiological mechanisms; however, regardless of its origin, therapy of hypoxemia is primarily based on the administration of supplemental oxygen as supportive therapy while the triggering cause is resolved.

3.2.1. General line of management: invasive mechanical ventilation and other non-invasive modalities

In most cases, initial oxygen therapy can be provided through devices delivering oxygen at low flow rates (conventional nasal cannula, simple face mask, Venturi mask and reservoir mask). Nevertheless, unresponsive cases to these initial support strategies will require other support modalities as non-invasive and invasive mechanical ventilation. Nonetheless, although invasive mechanical ventilation (IMV) provides oxygen and relieves respiratory load, IMV may be associated with complications widely described in the literature, including those related to intubation, immobility due to the use of sedatives and neuromuscular blockers, and lung injury induced by mechanical ventilation itself (30). In fact, other authors have recognized their effects on mortality (31). Accordingly, a metanalysis including several studies investigating the role of non-invasive mechanical ventilation (NIMV) in patients with acute hypoxemic respiratory failure suggested some potential effect on decrease the need for intubation but not in other clinical outcomes (32, 33). Nevertheless, up to 50% of NIV treatment failure has been described in the subgroup of hypoxemic respiratory failure (5) and high mortality associated with such treatment failure (6).

High-Flow oxygen therapy through a Nasal Cannula (HFNC) is another therapeutic modality to provide respiratory support. HFNC delivers a mixture of heated and humidified air and oxygen at concentrations between 21 and 100%, and flows between 60 - 80 liters/minute. HFNC allows better coupling with inspiratory demands of patients in respiratory failure by avoiding dilution of the delivered oxygen and ensuring a programmed oxygen concentration. It has other physiological effects such as maintenance of mucociliary function and clearance of secretions, decreases energy consumption due to heat loss, and produces a CO2 washout at the level of the upper airway, which has the effect of reducing dead space (34). Although it has historically been used in the pediatric population, its use has increased in critically ill adults in the last decade.

HFNC is other non-invasive support strategy that can overcome limitations offer by conventional oxygen therapy and NIMV. A meta-analysis on the use of HFNC during hypoxemic respiratory failure included the 9 best quality clinical trials performed to date, with a total of 2093 patients (35). Five of such studies were conducted in the ICU (36-40) and four in the emergency department (41-44) (see Table 1). Criteria used to define hypoxemia were different: some used a single parameter (SO2, PaO2, or PaO2/FiO2), while others used a combination of these three parameters. Duration of intervention and outcomes proposed were different in all of these studies, being the need for IMV or escalation of therapy the most common. Comfort and relief of dyspnea were also evaluated, and only five reported complications, which did not allow inferring data for meta-analyses of this aspect. The sample size was also highly variable, ranging from 14 to 778 patients, and causes leading to hypoxemic respiratory failure were also diverse, being chronic obstructive pulmonary disease (COPD), pneumonia and pulmonary edema, the most common. As a result, this meta-analysis found that HFNC might decrease the need for intubation with an absolute reduction of 4.4%, with no impact on mortality. Finally, authors concluded that future research should be focused on special subgroups potentially benefiting from using HFNC.

3.2.2 Use of HFNC in SARS-CoV-2 infection

Evidence on the use of HFNC in patients with acute hypoxemic respiratory failure due to SARS-CoV-2 infection is limited, as only some case reports have been reported suggesting

its potential benefit. Nevertheless, some scientific societies worldwide have recommended using HFNC in patients not responding to conventional oxygen therapy based on evidence from hypoxemic respiratory failure from other etiologies (12, 45, 46) and recognizing that reducing the need for intubation could be an important objective during a pandemic context (47).

A case series of 17 patients in Chongqing, China using HFNC in patients with hypoxemic respiratory failure due to SARS-CoV-2 infection (48) showed a failure rate of HFNC of 41% (0% in those with PaO2/FiO2 > 200 and 63% in those with PaO2/FiO2 < 200), thus suggesting that HFNC may be an alternative respiratory support in mild cases.

Despite of potential advantages provide by HFNC, serious concerns about aerosolization and increased risk of infection for health care workers were raised because the possible aerosol spreading generated by high-flow therapy. In this regard, a systematic review including 7 studies assessing the risk of aerosolization, dispersion and infection (24) (six of which were conducted in healthy volunteers or were electronic simulations and one clinical study with crossover between conventional oxygen therapy and HFNC), found a substantial risk of error in study designs, limitations regarding to small sample sizes and lack of information about studies conducted in patients with SARS-CoV-2 infection or similar germs that could be extrapolated to the Covid-19. That systematic review suggested that increasing oxygen flow during HFNC therapy effectively increases the distance at which aerosol particles are dispersed, but such dispersion occurs at lower distances that those caused by application of nasal CPAP (49) or conventional oxygen therapy devices (50). In addition, wearing a surgical mask on the patient's face during HFNC application can effectively reduce the dispersion of aerosol particles [Leonard S. Chest 2020; DOI: https://doi.org/10.1016/j.chest.2020.03.043.]. Similarly, in the case series reported, no cases of infection occurred in health care personnel (48, 51, 52).

In conclusion, HFNC is a reliable modality to support acute hypoxemic respiratory failure. Nevertheless, the effect of HFNC in patients with moderate and severe respiratory failure due to COVID-19 has not been elucidated. Interestingly, clinical practice during early Covid-19 pandemics reveals a quite similar number of patients under HFNC and NIMV (22). Although high-quality evidence on the use of HFNC in Covid-19 is still lacking, results from studies in hypoxemic failure signal that HFNC may reduce the need for intubation,

while the risk of aerosol spreading is probably not higher than that observed with other non-invasive devices. Nevertheless, patient should be carefully selected for its use and closely monitored to avoid delays in intubation.

Table 1. Clinical studies on the use of High-Flow Oxygen therapy in acute hypoxemic respiratory failure

Study	Number of randomized patients	Population	Intervention	Controls	Outcomes
Azoulay, 2018	778	Inclusion: ICU patients, PaO_2 < 60mmHg or SpO_2 <90% at FiO_2 0.21 (ambient air), immunosuppression Exclusion: increased CO_2	Initial parameters: Flow 50 L/min FiO_2: 1.0 Duration: not specified.	Conventional Nasal Cannula or face mask Initial parameters: Flow: to reach SpO2 ≥ 95%	Mortality (Primary); Need for IMV, ICU-LOS, hospital-LOS, comfort and dyspnea.
Bell, 2015	100	Inclusion: Urgent patients, RR ≥ 25 breaths /min, SpO_2 ≤ 93%. Exclusion: Patients requiring immediate NIMV or IMV	parameters: Flow rate: 50 L/min FiO_2: 0.3 Duration: 2 hours.	Conventional Nasal Cannula or face mask Initial parameters: O_2 in both groups was titrated during a period of 2hours	Need for IMV, comfort.
Frat, 2015	313	Inclusion: ICU patients, acute respiratory failure with RR > 25 breaths / min, PaO_2/FiO_2 ≤ 300, at O2 ≥ 10 L/min by ≥ 15 min. Exclusion: asthma, chronic lung disease, increased CO_2, Cardiovascular instability, need for IMV.	Initial parameters Flow rate: 50 L/min FiO2: 1.0 Duration: not specified.	Non-Rebreathing Mask Initial parameters: Flow: ≥ 10 L/min	Mortality (primary), Need for IMV need, ICU-LOS, comfort.
Jones, 2016	322	Inclusion: Emergency patients, SpO_2 ≤ 92% to ambient air, RR ≥ 22 breaths/min. Exclusion: urgent NIMV or IMV.	Initial parameters: Flow rate: 40 L/min FiO_2: 0.28 Duration: not specified.	Nasal mask or cannula Initial parameters: N/A.	Mortality need for IMV, escalation (primary). LOS hospitals.
Lemiale, 2015	102	Inclusion: ICU patients, immunocompromised, O_2 at > 6 L/min to maintain SpO_2 > 95% or respiratory distress Exclusion: increased CO_2, IMV requirement or urgent intubation.	Initial parameters: Flow rate: 40-50 L/min FiO_2: 1.0 Duration: 2 hours.	Venturi mask Initial parameters: Flow rate: 15 L/min FiO_2: 0.6.	IMV requirement (primary). Dyspnea, comfort.
Makdee, 2017	136	Inclusion: Emergency patients, Pulmonary	Initial parameters:	Nasal cannula or	Mortality, need for IMV,

		edema, SpO_2 < 95% to ambient air, RR >24 breaths /min Exclusion: Urgent NIV or IMV requirement, CV instability, RR >35 breaths /min, SpO_2 < 90%, End-stage renal disease.	Flow rate: 35 L/min FiO2: N/A Duration: 1 hour.	non-rebreathing mask Initial parameters: N/A.	escalation, LOS-hospital, dyspnea, comfort.
Parke, 2011	60	Inclusion: ICU patients, O2 ≥ 4 L/min per CN for > 4 h or ≥ 6 L/min per face mask > 2 h and/or RR ≥ 25 breaths /min and/or WOB Exclusion: NIMV or IMV requirement urgent	Initial parameters: Flow rate: 35 L/min FiO2: N/A Duration: not specified.	Face mask Initial parameters: N/A.	Escalation in therapy
Rittayamai, 2015	40	Inclusion: Emergency patients, RR > 24 resp/min, SpO_2 < 94% to ambient air Exclusion: Need for IMV, Cardiovascular instability, chronic respiratory failure.	Initial parameters: Flow rate: 35 L/min FiO_2: N/A Duration: 1 hour.	NC or non-rebreathing mask Initial parameters: N/A	Need for IMV scaling, dyspnea (primary), comfort.
Schwabbauer, 2014 (Crossover)	14	Inclusion: ICU patients, PaO_2 < 55mmHg on R/A Exclusion: CPE, CV instability.	Initial Settings: Flow rate: 55 L/min Duration: 30 min FiO_2: 0.6	Venturi Mask Initial parameters: Flow rate: 15 L/min FiO_2: 0.6	Dyspnea and Comfort.

4. JUSTIFICATION

Until the preparation of this protocol, there were no high quality studies testing specific medications or interventions modifying the time course or clinical outcomes in severe forms of SARS-CoV-2 infection. Nevertheless, it should be expected that advanced life support measures and a high quality critical care should contribute to greater survival probabilities and functional recovery in more severe cases.

Arterial hypoxemia is the leading feature of severe cases of Covid-19. In general, management of hypoxemic respiratory failure relies on oxygen supplementation aiming to improve oxygenation and to support respiratory effort. At the beginning of the SARS-CoV-2 pandemic, many patients were immediately intubated and placed on mechanical ventilation perhaps due to the perception of severity in terms of hypoxemia, and also because the concerns about the safety of non-invasive respiratory support systems for health care professionals. Remarkably, some authors related the need of mechanical ventilation with high mortality rates in general populations with acute hypoxemic respiratory failure. Nevertheless, this contrasts with the view stating that spontaneously breathing non-intubated patients may auto-injure lungs when breathing large tidal volumes because high respiratory drive and potentially injurious transpulmonary pressure swings.

High-flow oxygen therapy through a nasal cannula is a technique whereby a mixture of heated and humidified oxygen and air are delivered to the nose at high flow rates. Data suggest that high flow oxygen through a nasal cannula might decrease the need for tracheal intubation and might reduce the risk of escalation of oxygen therapy in patients with acute respiratory hypoxemic failure, with no apparent impact on mortality rates. There is not clear if such data are applicable to Covid-19. Nonetheless, some international guidelines proposed the use high-flow nasal cannula to initially treat patients with Covid-19-related acute respiratory hypoxemic failure and observational studies published after the starting of the current trial suggested this respiratory modality as feasible and at least, as safe as standard oxygen therapy. As evidence supporting the use of this respiratory support modality is limited, we conducted a trial to assess the impact of high-flow oxygen therapy through a nasal cannula vs. conventional oxygen therapy on the need for intubation and the time to clinical recovery in patients with severe Covid-19.

5. RESEARCH QUESTION

Does the use of a high-flow oxygen therapy through a nasal cannula, compared with conventional oxygen therapy, reduce requirement of intubation and time to clinical improvement among patients with severe Covid-19?

6. OBJECTIVES

6.1. Primary objective

To evaluate the impact of the use of high-flow oxygen through a nasal cannula vs. conventional oxygen therapy on the need for intubation/support with invasive mechanical ventilation and clinical status as assessed by a 7-category ordinal scale in patients with moderate/severe hypoxemic respiratory failure secondary to SARS-CoV-2 infection.

6.2. Specific objectives

For secondary Outcomes

Efficiency

- To evaluate the impact of high-flow oxygen therapy through a nasal cannula (HFNC) vs. conventional oxygen therapy (COT) on the requirement of early intubation and invasive mechanical ventilation support.
- To assess the impact of HFNC vs. COT on mechanical ventilation-free days.
- Assess the impact of HFNC vs. COT on renal replacement therapy-free days.
- To assess differences in length of hospital/ICU stay between study groups.
- To assess differences in all-cause mortality at days 14 and 28 post-randomization, between study groups

Safety

- To assess the occurrence / proportion of patients with severe adverse events within 28 days from randomization.
- To assess the occurrence / proportion of bacterial / fungal infections within 28 days from randomization.

For Tertiary Outcomes

- To evaluate the differences in the evolvement of oxygen flow requirement and PaO_2/FiO_2 ratio between groups
- To evaluate the differences for the time elapsed from randomization to intubation / invasive mechanical ventilation support in patients failing to high-flow oxygen therapy and conventional oxygen therapy
- To evaluate the impact of HFNC vs. COT on the clinical condition at day 28
- To evaluate the impact of HFNC vs. COT on the development and evolution of multiorgan dysfunction as assessed by the SOFA score.
- To evaluate the impact of HFNC vs. COT on the development and evolution of extra-pulmonary organ dysfunction as assessed by extra-pulmonary SOFA score
- To evaluate the differences in HACOR and ROX scores at 2 and 4 hours post-randomization between the groups and their relationship with requiring intubation and mechanical ventilation-free days
- To assess differences in IL-6 and IL-8 kinetics within 7 days from randomization, between study groups
- To assess differences in ferritin kinetics, LDH, leukocyte count, neutrophil/lymphocyte count relationship, platelet count and D-dimer during the 7 days following randomization, between study groups

For Predefined Subgroups

- To assess the impact of high-flow oxygen vs. conventional oxygen therapy on the need for intubation / invasive ventilation support and the time to clinical recovery (as assessed by a 7-category ordinal scale) in patients with initial PaO_2/FiO_2 ratio > and < 100 mmHg.
- To assess the impact of high-flow oxygen vs. conventional oxygen therapy on the need for intubation / invasive ventilation support and the time to clinical recovery (as assessed by a 7-category ordinal scale) in patients with baseline IL-6 levels > and < 100 pg/mL.

- To assess the impact of high-flow oxygen vs. conventional oxygen therapy on the need for intubation / invasive ventilation support and the time to clinical recovery (as assessed by a 7-category ordinal scale) in patients aged > and < 60 years.

7. HYPOTHESIS

7.1. Primary hypothesis

- The use of high-flow nasal cannula support will lead to lower intubation rates and lesser requirement for invasive mechanical ventilation within 28 days of randomization
- The use of high-flow nasal cannula support will decrease the time to clinical recovery as assessed by a 7-point ordinal scale.

7.2. Secondary /terciary hypotheses

- The use of high-flow oxygen through a nasal cannula will decrease early requirement of tracheal intubation
- The use of high-flow oxygen through a nasal cannula will increase the number of mechanical ventilation-free days.
- Patients undergoing support with HFNC will have more renal replacement therapy-free days than those undergoing COT.
- Patients subjected to HFNC support will show shorter hospital/ICU lengths of stay
- The use of high-flow oxygen through a nasal cannula will lead to better clinical condition at day-28
- Patients subjected to HFNC support will show no difference in all-cause mortality at days 7, 14 and 28 post-randomization compared to those subjected to conventional oxygen therapy.
- Proportion of serious adverse effects will be similar between groups
- Time elapsed from randomization to intubation / invasive mechanical ventilation support will be no different between groups
- The use of high-flow oxygen through a nasal cannula will show less severe multiorgan dysfunction
- High-flow oxygen therapy will be related with lesser extra-pulmonary organ dysfunction

- HACOR and ROX scores will allow to early identify patients failing to high-flow oxygen therapy
- Patients successfully supported by HFNC will show similar kinetics of IL-6 and IL-8, during the 7 days following randomization
- Patients successfully supported by HFNC will show similar kinetics of ferritin, LDH, leukocyte count, neutrophil/lymphocyte count ratio, platelet count, and D-dimer during the 7 days after randomization
- Benefit of high flow nasal cannula support on requirement for intubation / invasive mechanical ventilation and time to clinical recovery will be greater in patients with initial PaO2/FiO2 > 100 mmHg.
- Benefit of high flow nasal cannula support on requirement for intubation / invasive mechanical ventilation and time to clinical recovery will be greater in patients with initial IL-6 levels < 100 pg/mL.
- Benefit of high flow nasal cannula support on requirement for intubation / invasive mechanical ventilation and time to clinical recovery will be greater in patients < 60 years.

8. OUTCOMES

8.1. Primary outcomes

- Need for intubation / invasive mechanical ventilation support (time frame: 28 days).
- Clinical recovery as assessed by a 7-category ordinal scale (time frame: 28 days).

8.2. Secondary and tertiary outcomes / subgroup analysis

Secondary Outcomes

Efficiency

- Early requirement of intubation / invasive mechanical ventilation support (time frame: 7 days – 14 days).
- Mechanical ventilation-free days (time frame: 28 days).
- Renal replacement therapy-free days (time frame: 28 days)
- Length of ICU stay (time frame: 28 days)
- Length of hospital stay (time frame: 28 days)
- Hospital mortality – all causes (time frame: 14 and 28 days)

Safety

- Occurrence / proportion of patients with serious adverse events (time frame: 28 days)
- Occurrence / proportion of bacterial - fungal infections (time frame: 28 days).

Tertiary Outcomes

- Evolvement of oxygen flow requirement and PaO_2/FiO_2 ratio (time frame: 7 days)
- Time elapsed from randomization to intubation / invasive mechanical ventilation support in patients failing to high-flow oxygen therapy and conventional oxygen therapy (time frame: 28 days).
- Clinical condition at day 28 (time frame: 28 days)
- Evolvement of multiorgan dysfunction as assessed by SOFA score (time frame: 14 days)
- Evolvement of extra-pulmonary organ dysfunction as assessed by extra-pulmonary SOFA score (time frame: 14 days).
- HACOR and ROX scores at 2- and 4-hours post-randomization and their relation with requirement of intubation (time frame: 28 days)
- Differences in time-course of IL-6 and IL-8 between study groups (time frame: 7 days)
- Differences in time-course of ferritin, LDH, leukocyte count, neutrophil to lymphocyte count relationship, platelet count, and D-dimer among the groups under study (time frame: 7 days)

Subgroup Analysis

- Time to intubation / invasive mechanical ventilation and clinical recovery in subgroups with baseline PaO_2/FiO_2 > and < 100 mmHg (time frame: 28 days)
- Time to intubation / invasive mechanical ventilation and clinical recovery in subgroups with baseline IL-6 > and < 100 pg/mL (time frame: 28 days)

Time to intubation / invasive mechanical ventilation and clinical recovery in subgroups aged > and < 60 years (time frame: 28 days)

9. METHODS

9.1. Design

Phase IIb, multicenter, randomized, open-label, controlled study of the use of high- flow oxygen therapy through a nasal cannula vs. conventional oxygen therapy in patients with severe Covid-19.

9.2. Study population

Adult patients (>18 years) admitted to the emergency room or Intensive Care Unit with acute hypoxemic respiratory failure due to Covid-19

9.3. Groups under study

- High-Flow oxygen therapy through a Nasal Cannula (HFNC).
- Conventional oxygen therapy (COT).

All patients will receive standard care (hemodynamic / respiratory / metabolic / hematological / general).

9.4. Inclusion criteria

- Adults > 18 years old.
- Emergency or ICU admission under suspected / confirmed SARS-CoV-2 infection.
- Acute respiratory distress with:
  - $PaO_2/FiO_2 < 200$.

- Use of accessory muscles.
- Breathing rate > 25 per minute.

- Having a progression < 6 hours since fulfilling definition of moderate or severe acute respiratory failure due to suspected or confirmed SARS-CoV-2 infection.

9.5. Exclusion Criteria

- < 18 years.
- Indication for immediate tracheal intubation.
- Pregnant woman / positive pregnancy test at the time of potential inclusion.
- Chronic liver disease / liver cirrhosis Child-Pugh C.
- Confirmation of active bacterial or fungal infection.
- Uncontrolled HIV/AIDS disease (defined by presence of viral load > 200 copies/mL).
- Previous history of COPD Gold C – D.
- History of COPD requiring hospitalization or ICU admission during the last year.
- History of congestive heart failure NYHA III – IV.
- History or actual left ventricular ejection fraction < 45%
- Highly suspected or confirmed cardiogenic pulmonary edema.
- Hypercapnic respiratory failure ($PaCO_2$ > 55 mmHg).
- History or high suspicion of central or peripheral demyelinating disorders at the time of potential inclusion.
- Imminence of death within the next 24 hours (according to investigator´s clinical judgment)
- Any serious medical condition or clinical laboratory test abnormality that, at the investigator's judgment, prevents safe patient participation and completion of the study.
- Participation in another clinical trial (except other related to SARS-CoV-2. These criteria will be always discussed among steering committee members

9.6. Sample size

Sample size was calculated under the assumption of an intubation rate of 60%, according to the data obtained from 75 patients with Covid-19-related moderate and severe hypoxemic respiratory failure treated in the coordinating center between March and June 2020. Such proportion of intubation events was in agreement with previous data from a randomized controlled trial testing high-flow oxygen through nasal cannula in mixed populations of patients with acute hypoxemic respiratory failure.

Estimating an intubation rate around 60% in conventionally-treated patients, we calculated that enrollment of 196 patients would be necessary to demonstrate an absolute reduction of 20% in the proportion of intubation and requirement of invasive mechanical ventilation with an 80% power and two-side alpha level of 0.05. In addition, it was estimated that 160 patients (80 by arm) would be necessary to demonstrate a difference in time to recovery from 14 (± 4.5) to 12 (± 4.0) days for the conventional oxygen and high-flow oxygen therapy groups respectively, with an 80% power and two-side alpha level of 0.05. Consequently, the sample size of 196 patients was retained as the sample size target.

Nevertheless, due to the particular situation during pandemic, an important number of participants (n=18, representing the 9.2% of the total sample size) were transferred to other hospitals within 72 hours from randomization at the time in which the HiFLo-Covid protocol amendment 2.0 was constructed. After an extensive discussion with the Ethical Committee and trying to favor the possibility that results of this trial keep sufficient power and consequently, more reliable results, the number total of randomized patients is newly adjusted up to complete a total of 220 participants.

9.7. Recruitment strategy

9.7.1. Screening

All adult patients >18 years old admitted to the emergency department, or Intensive Care Unit with suspected SARS-CoV-2 infection will be considered as potential candidates for

the study. Due to the nature of the disease, it is expected that potential patients to be placed on a conventional oxygen system previous to inclusion. Research teams at each center will follow up patients fulfilling initial criteria for suspected or confirmed SARS-CoV-2 and acute respiratory failure. Arterial blood gas analysis will be essential for making decisions on admission to the study. Those patients fulfilling all inclusion criteria and discarding all exclusion will be selected for the study (See Annex 1: Inclusion / Exclusion Forms) will be requested for informed consent and potential inclusion. Each center will be responsible for completing information about all suspected and confirmed cases of acute respiratory failure due to SARS-CoV-2 being selected or not for the study, recording reasons for non-inclusion for these last (See Annex 2: Summary Screening).

9.7.2. Randomization

Randomization will be centrally performed by using an electronic case-report form system (RedCap®) and stratified by study site in permuted block of 4 and 6, to ensure allocation concealment. An independent statistician from the Clinical Research Center (Cento de Investigaciones Clínicas, Fundación Valle del Lili, Cali - Colombia) will monitor this process. He/she will use a public access package: Random Allocation Software (http://www.msaghaei.com/Softwares/dnld/RA.zip) for this purpose. Randomization sequence will rest in the REDCap® system and will be revealed once the screening process and informed consent from each patient is completed.

9.7.3. Masking and concealment

Assignment to the therapeutic group will be disclosed only after confirmation of patient inclusion and informed consent has been obtained. Due to the characteristics of the interventions, masking will not be possible. Information from each patient will be recorded in an electronic format. Therapeutic modality will not be expressly identified, so that independent statistician will not know the allocated therapy that each patient was assigned.

9.8. Statistical analysis plan

All the analysis will be performed on an intention-to-treat basis with no exclusion after randomization except exclusions for withdrawn consent, according to the local regulations. In addition, the following predefined subgroups will be analyzed:

- Age group: <60 years and ≥60 years.
- IL-6 at randomization: <100 and ≥100 pg/mL.
- PaO2/FiO2 initial <100 and ≥100.

Data distribution will be evaluated by the Shapiro-Wilk test. Then, comparisons between groups will be performed according to type of variable (continuous / discrete) and whether or not assumptions of normality are met. The t of student or Wilcoxon Mann Whitney will be used for continuous variables (according to the type of distribution), while X^2 or Fisher's exact test will be used for discrete ones.

No participants will be excluded from analysis because of missing or incomplete data.

9.8.1. Analysis Plan for Primary Outcomes

Proportion of patients requiring intubation within 28 days of inclusion will be compared using the X^2 test. The effect of treatment on the primary outcome (requirement for intubation / invasive mechanical ventilation) will be calculated with a proportional Cox model of risk adjusted according to 3 pre-specified variables: age (≥ or < 60 years old), baseline PaO_2/FiO_2 and comorbidities (a composite of arterial hypertension, diabetes, obesity [body mass index > 30], chronic obstructive pulmonary disease, end-stage renal failure, heart failure, cirrhosis Child-Pugh A-B). The results will be reported as hazard ratios with 95% confidence intervals and represented in Kaplan-Meier curves. Same analysis will be performed separately according to initial 7-point category ordinal scale.

Time to clinical improvement will be defined as time elapsed from randomization until the first day, during the 28 days after enrollment, on which a patient attained a reduction in two or more points in the modified ordinal 7-category scale. Primary efficacy analysis of this objective will be evaluated during the first 28 days after randomization, taking into

account failure to improve clinically (< 2 points on the scale) or death as "censures". Time to clinical improvement will be represented by a Kaplan-Meier curve and compared with a log-rank test. Hazard ratios and 95% confidence intervals will be calculated using a proportional model of Cox risk adjusted according to 3 pre-specified variables: age (> or < 60 years old), baseline PaO_2/FiO_2 and comorbidities (diabetes, hypertension, obesity BMI ≥ 30). Same analysis will be performed separately according to initial 7-point category ordinal scale.

9.8.1. Analysis Plan for Secondary Outcomes

Evaluation of secondary outcomes will be performed by comparing proportions by the X^2 test or the Fisher Exact test, as appropriate. Continuous variables will be compared with the T-test or the Wilcoxon-Mann-Whitney test according to distribution depicted by the variables. Categorical variables will be compared with the Wilcoxon-Mann-Whitney test. Time to outcome variables will be analyzed as previously described. A $p<0.05$ will be considered as significant.

A complete description for secondary and tertiary outcomes along with subgroup analysis can be consulted in the Statistical Analysis Plan Supplement V2.0.

9.8.2. Interim analysis plan

A single interim analysis is planned when the 28-day follow-up had been completed for the first 100 randomized patients. Database will be prepared and sent to the Members of the Safety Monitoring Board (MSMB). An independent statistician will perform the analysis and will discuss it with the MSMB, who later will communicate the results to the Steering Committee. The Haybittle–Peto stopping boundaries ill be used, with a P-value threshold of less than 0.001 to interrupt the trial for safety and a P-value thresh- old of less than 0.0001 to interrupt the trial for efficacy. The data will be analyzed in a blind manner but data about group allocation would be revealed in the event that security issues or unexpected events are detected. Safety monitoring board will recommend to continue or to stop with the enrollment accordingly.

10. GENERAL MANAGEMENT PROTOCOL

10.1. Initial approach

All adult patients >18 years old admitted to the emergency department or Intensive Care Unit under suspicion of SARS-CoV-2 infection will be considered as potential candidates for study (see 10.3: Operational case definitions). The attending physician will guide initial management according to SpO_2, respiratory rate, and the presence / absence of respiratory distress. Thus, three possible initial scenarios are proposed:

- Scenario 1: patient with SARS-CoV-2 disease compatible symptoms, but without hypoxemia (SpO_2 >95% at FiO_2 0.21).
  - Action: not a candidate for study. Management according to individual institutional protocol.

- Scenario 2: patient with SARS-CoV-2 disease compatible symptoms, and initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate 25 - 40 /min, with no signs of immediate indication for intubation.
  - Action: potential candidate for admission. Start oxygen supply by using a low flow system (conventional nasal cannula, venturi system, mask with reservoir), arterial blood sampling for gas analysis, monitoring and general management according to local protocol (monitoring, venous access, paraclinical testing, etc.).

- Scenario 3: patient with SARS-CoV-2 disease compatible symptoms, WITH signs of immediate indication for intubation.
  - Action: Immediate intubation. Not candidate for study. General management according to local protocol

Patients in "scenario 1" will be follow-up ONLY if requiring hospitalization and might become candidates for study admission if the event that their clinical condition vary to "scenario 2" at any time.

Patients in "scenario 2" will be considered potential study candidates. Arterial blood gas analysis will be performed once a conventional oxygen system has been installed according to decision of the attending physician. Patients with clinical symptoms and signs compatible with SARS-CoV-2 infection and having a PaO_2/FiO_2 < 200 ratio will be classified as moderate or severe hypoxemia (100 < PaO_2/FiO_2 < 200 or PaO_2/FiO_2 < 100, respectively) and might be randomly allocated to receive either high-flow oxygen therapy through a nasal cannula (HFNC) or conventional oxygen therapy (COT) once all inclusion criteria are met and all exclusion criteria are discarded. “Suspect status” will change to "confirmed case" once a positive genomic test for SARS-CoV-2 is obtained from a sample from upper or lower airway.

Patients in "scenario 3" will undergo immediate tracheal intubation and will NOT be included in the study at any time but they will be recorded on the study screening form.

10.2. Criteria for IMMEDIATE INTUBATION (NOT Randomized patients)

These pre-determined criteria will be applied for patients with acute respiratory failure and need for immediate intubation (i.e., not candidate patients to study because need for immediate intubation before any attempt of randomization). These criteria are a guide aimed to avoid delayed intubation, and include:

- Signs of respiratory failure despite initial oxygen supplementation.
- Signs of respiratory muscle fatigue suggesting imminent cardio-respiratory arrest.
- Breathing rate > 40 / minute or < 8 / minute.
- Abundant bronchial secretions/mismanagement of secretions/mechanical airway obstruction.
- Acidosis - pH < 7.20.
- SpO2 < 90% for more than 5 minutes (ruling out signal problems in its measurement) having maximized conventional oxygen supply (mask with reservoir / FiO2 0.80).
- Hemodynamic signs.

- PAS < 90 mmHg or MAP < 60 mmHg persistent, with vasopressor support requirement (Noradrenaline > 0.10 µgr/kg/min) despite initial volume input (at least 8 cc/kg).
- Deterioration of consciousness (Glasgow Coma Scale ≤ 12 points).

10.3. Internal operational case definitions

10.3.1. Suspected Moderate Case

A patient will be considered in this category when meet ALL the following parameters:

- **Signs and symptoms consistent with SARS-CoV-2 infection not explained by any other previously known or current clinical condition** (bacterial or viral infectious; autoimmune; neoplastic): fever, cough, odynophagia/anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- Confirmed **100 < PaO_2/FiO_2 < 200** (according to arterial gas analysis), **WITHOUT evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

10.3.2. Suspected Severe Case

A patient will be considered in this category when meet ALL the following parameters:

- **Signs and symptoms consistent with SARS-CoV-2 infection not explained by any other previously known or current clinical condition** (bacterial or viral infectious; autoimmune; neoplastic): fever, cough, odynophagia/anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- Confirmed **PaO_2/FiO_2 < 100** (according to arterial gas analysis), **AND / OR evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

10.2.3. Confirmed Moderate Case

A patient will be considered in this category when meet ALL the following parameters:

- **Confirmed SARS-CoV-2 infection by genomic detection** from an upper or lower airway sample in presence of compatible symptoms: fever, cough, odynophagia / anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- Confirmed **100 < PaO_2/FiO_2 < 200** (according to arterial gas analysis), **WITHOUT evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

10.3.4. Confirmed Severe Case

A patient will be considered in this category when they meet ALL of the following parameters:

- **Confirmed SARS-CoV-2 infection by genomic detection** from an upper or lower airway sample in presence of compatible symptoms: fever, cough, odynophagia / anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- **Confirmation of PaO2/FiO2 < 100** (according to arterial gas analysis), **AND / OR evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

10.4. General protocol for respiratory support

10.4.1. High-flow nasal cannula (HFNC)

Starting parameters: flow between 60 liters – 80 / minute (according to available device). FiO_2 0.6 to 1.0 aiming SpO_2 ≥ 92%. Adequate wetting of system should be ensured according to recommendations from each HFNC device manufacturer. FiO_2 may be decreased gradually according to individual condition, trying to maintain SpO_2 ≥ 92%. Flow gas will be adjusted according to the following parameters:

FiO_2 %	.21- .30	.30 - .40	.40 - .60	.60 – 1.0
Flow rate L/minute	30	30-40	40 -50	50-70

10.4.2. Conventional oxygen therapy (OCT)

Oxygen by conventional nasal cannula / prongs, venturi mask, or mask with reservoir, at flows between 3 and 15 liters / minute, to attain $SpO_2 \geq 92\%$. The FiO_2 may be decreased gradually according to individual conditions, trying to maintain $SpO_2 \geq 92\%$.

10.5. Monitoring of respiratory support therapy (HFNC vs. COT)

Once the participants have been randomly assigned to their respective respiratory support therapy, clinical and paraclinical evaluations will be performed at 2- and 4-hours from starting the respective respiratory support modality. Such evaluation will include arterial gas analysis and clinical condition. Signs of failure to the allocated respiratory support therapy will be looked for at these points and daily up to hospital discharge. If failure to respiratory support therapy is declared, tracheal intubation and invasive mechanical ventilation support will be performed.

10.6. Failure to respiratory support therapy (HFNC or COT)

Failure to respiratory support (high-flow or conventional oxygen therapy) was considered if at least one of the following was present:

- $PaO_2 < 55$ mmHg
- Fail to improve signs of respiratory distress
- Development of copious bronchial secretions
- $SpO_2 < 92\%$ for more then five minutes (discarding signal problems or other technical issues) while receiving the maximal support according to the group allocation
- Acidosis (metabolic / respiratory): pH < 7.25
- Development of shock state (any type)
- $PaCO_2 > 55$ mmHg (accompanied by acidosis)
- Neurological deterioration

10.6.1. Intubation Criteria (for Patients included in the study)

Predefined intubation criteria were followed in order to avoid delayed invasive mechanical ventilation support. Such intubation criteria were applied under the assumption that patient was under the maximum possible respiratory support provided by the therapy assigned (high-flow oxygen or conventional oxygen therapy). Such criteria were as follows:

- Signs of persistent respiratory distress
  - Respiratory rate > 40 / min
  - No improvement of laborious breathing - use of accessory muscles
  - Development of copious bronchial secretions / impossibility to manage bronchial secretions
  - Acidosis (metabolic / respiratory): pH < 7.25
  - PaO_2 < 55 mmHg
  - $PaCO_2$ > 55 mmHg (accompanied by acidosis)
  - SpO_2 < 92% for more then five minutes (discarding signal problems or other technical issues)

- Signs of hemodynamic derangement
  - Persistent systolic arterial pressure < 90 or mean arterial pressure < 60 mmHg, with vasopressor support requirement (norepinephrine > 0.10 μgr.kg.min^{-1}) in presence of an adequate intravascular volume
  - Clinical signs of severe tissue hypoperfusion: capillary refill time > 10 seconds; Mottling score ≥ 4
  - Arterial lactate ≥ 4.0 mmol/L in presence of any clinical sign of tissue hypoperfusion (capillary refill time > 3 seconds; Mottling score ≥ 2)

- Signs of neurological derangement
  - Neurological impairment (Glasgow coma scale ≤ 12)

10.7. Additional management

10.7.1. Hemodynamic

Each center will adjust general management according to their local guidelines. However, we strongly recommend:

- A resuscitation strategy with low fluid intake. For this, we recommend IMMEDIATE initiation of vasopressor in patients with a diastolic blood pressure < 40 mmHg or a heart rate/diastolic blood pressure ratio > 2.30 (diastolic shock index – DSI > 2.30) (53).
- Administration of fluid resuscitation boluses according to dynamic predictors of fluid responsiveness. Because some patients will be ventilated with tidal volumes < 8 ml/kg and/or FR > 25 / minute, we recommend the use of tests in which cardiac output variation is directly estimated (e.g.: VTI variation x echocardiography in response to passive leg raising; cardiac index variation by pulse contour analysis in response to end-expiratory occlusion maneuver for 20 seconds).
- A combined strategy of clinical signs resuscitation-guided / arterial lactate-guided resuscitation (54).
- Use of norepinephrine as first vasopressor.
- Use of vasopressin/epinephrine according to each institution's protocol.
- Use of low-dose steroids in case of persistent hypotension/vasopressor requirement after adequate volumetric resuscitation.
- Use of albumin/crystalloids according to local protocol.
- NO use of gelatin / dextrose as resuscitation fluids

10.7.2. Renal

Each center will adjust local protocols for the use of renal replacement therapy. However, we strongly recommend:

- Provide renal replacement therapy according to conventional parameters of pH, electrolytes, BUN / creatinine
- Maintain neutral/negative fluid balance according to individual clinical condition.

10.7.3. Hematological

Each center will adjust management according to their local guidelines. However, we strongly recommend:

- NOT using systematic anticoagulation in patients with SARS-CoV-2 infection, unless there is a clear indication to do so.
- Note that elevated D-dimer does NOT represent a sufficient reason for formal anticoagulation.

10.7.4. Steroid use

Each center will adjust management according to their local guidelines. However, we strongly recommend:

- Using low-dose steroids in patients with moderate/severe SARS-CoV-2 infection, unless there is a clear contraindication.

10.7.5. Use of sedation / neuromuscular paralysis

Each center will adjust management according to their local guidelines. However, we strongly recommend:

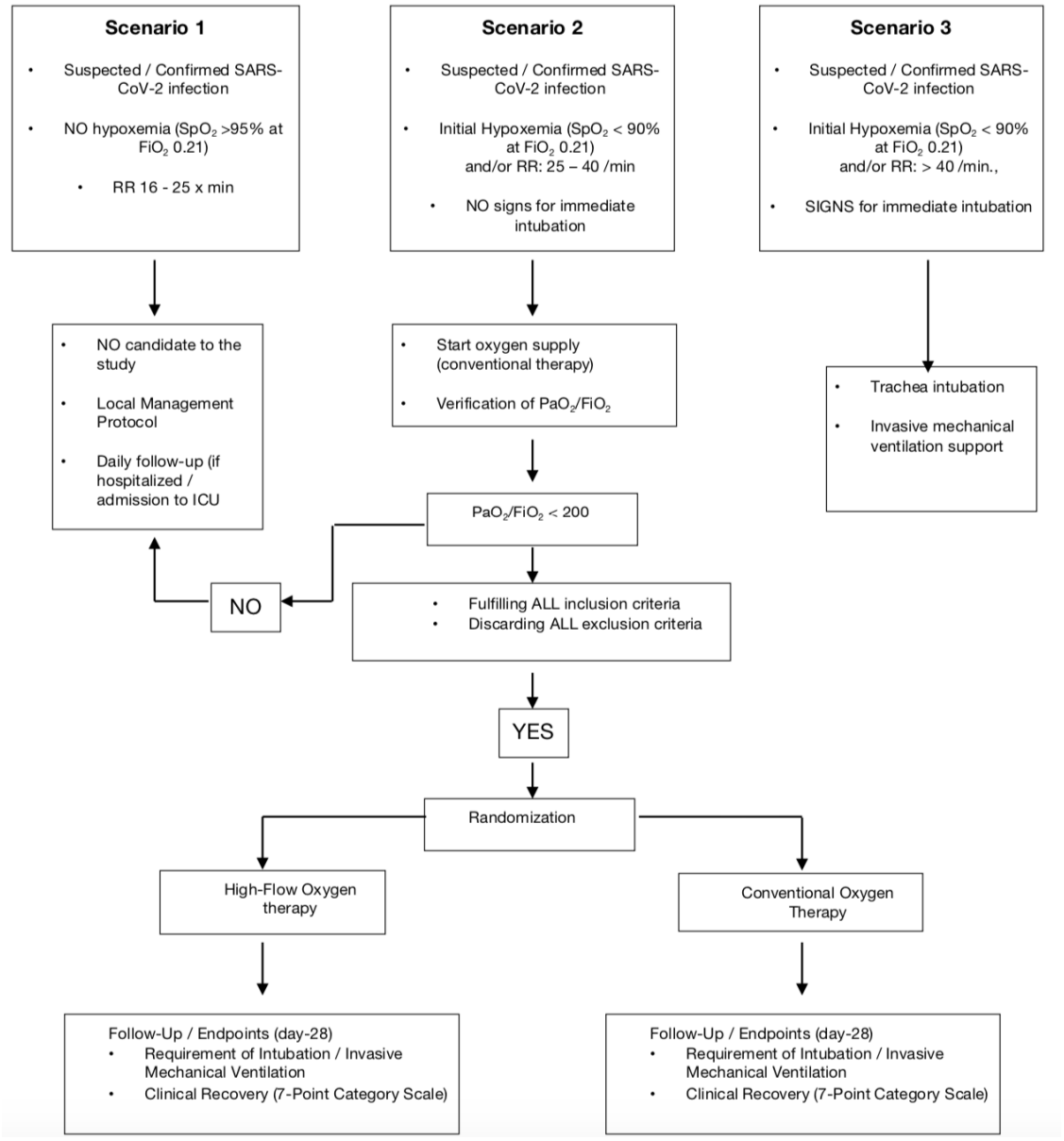
- Use of adjusted doses of sedatives (benzodiazepines, opiates, propofol, central alpha-2 agonists) according to standard scales to guide depth of sedation.
- Use of relaxation monitoring devices to guide neuromuscular blockade (and for the shortest time clinically possible).

10.7.6. Glycemic control

Each center will adjust management according to their local guidelines. However, we strongly recommend:

- Maintain glycemia < 180 mg / dL (use of infusion or mobile insulin plans, according to local protocol).

10.8 General Study Flow



11. DATA COLLECTION, PATIENT FOLLOW-UP, STUDY MONITORING AND CLINICAL OUTCOMES.

11.1 Coordination, Registration and Data Management

The Centro de Investigaciones Clínicas (CIC) of the Fundación Valle del Lili (FVL) will be in charge of creating and safeguarding all the screening, inclusion and follow-up records of the study. Additionally, an independent statistician adscript to the CIC will be in charge to monitor the random allocation of patients during the study. Screening, inclusion, record files, CRF and follow-up formats will be managed by coordinators assigned by the CIC-FVL.

The former research committee will be made up of the following participants:

Intensive Care Unit: Dr. Gustavo A. Ospina-Tascón; Dr. Diego F. Bautista Rincón, Dr. Mónica P. Vargas Ordóñez, Dr. Alberto F. García (Fundación Valle del Lili Researchers) and at least one co-investigator/representative from each of the participating centers.

Research Assistants: CIC-assigned Research Assistants (at the Fundación Valle del Lili, Cali - Colombia) and at least one research assistant from each participating center.

Independent data quality surveillance committee (DQSC): CIC-assigned persons not linked to the study.

Methodology Committee: CIC Statistics Group – Fundación Valle del Lili, Cali. Colombia.

Technical support: CIC-assigned engineer.

11.2. Patient monitoring / Electronic data capture

Electronic data collection format will be based on the CRF provided in this protocol version (See Annex 3: Data Collection Format; Annex 4: Variable Description).

Study coordinators at each site will be responsible for collecting all information required by the protocol. Each coordinator will have a digital user profile to upload all information.

Coordinators at each center will also be in charge to evaluate possible serious and non-serious adverse events together with the attending physician and the local main investigator designed (see Annex 5: Serious Adverse Event Reporting). Occurrence of major adverse events should be reported to the local Ethic Committee within 24 hours of its detection.

11.3 Blood Sampling and Cytokine Measurement

Blood samples will be collected and stored for later measurement of IL-6, IL-8, IL-10. These samples will be stored and secured by the Centro de Investigaciones Clínicas - Fundación Valle del Lili (Cali, Colombia) until completing the sample size of 220 patients. The Fundación Valle del Lili will maintain such blood samples under strict supervision in a restricted-access area to guarantee their security and integrity. Once the planned measurement of inflammation markers is completed, remaining aliquots will be destroyed according to the institutional procedure.

11.4. Study Completion

Study completion will be declared when the last subject completes 28 days of follow-up from randomization and investigators have completed the last visit evaluation, including the follow-up and closure of adverse events. Two additional points will be taken in account:

- Withdraw from study due to voluntary or administrative reasons: under such circumstances, the participant will be excluded from analysis and his/her data will not be analyzed for primary and secondary outcomes, unless the participant had completed criteria to stop oxygen supply

- Hospital discharge because satisfactory condition. In such case, a structured telephone call will be performed at day 28 to confirm his/her clinical condition between hospital discharge and day 28

11.5. Withdrawal of Informed Consent

The participant or his/her legal representative may voluntarily withdraw consent to participate in the study for any reason at any time. In the event of withdrawal of consent, study procedures should be suspended, and every effort made to continue follow-up until the 28th day. If the participant or his legal representative does not wish to continue follow-up either, information from visits after the time of withdrawal of consent should be considered missing. If any important safety findings are identified for the subject who has withdrawn consent, every effort should be made to communicate this to the participant and inform him/her of the actions to be taken. Information collected from individuals withdrawing consent will NOT be used in the analyses.

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1160 11.6 Follow-Up Schedule

Visit name	Selection	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16 – D27	D28	Discharge ICU	Discharge Hospital
Activity																				
Informed consent	X																			
Randomization	X																			
Demographic characteristics	X																			
Inclusion and exclusion criteria	X																			
Medical history chart	X																			
Clinical Antecedents	X																			
Verification of clinical status (follow-up)																				
Respiratory symptoms	X																			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests																				
Blood Count		X	X	X	X	X	X	X			X				X					
Inflammatory markers (IL-6 - IL-8)		X		X				X												
C-reactive Protein		X		X				X			X				X					
D-Dimer		X		X				X			X				X					
LDH		X		X				X			X				X					

Ferritin		X		X				X			X				X				
Liver function		X		X				X			X				X				
pH		X	X	X	X	X	X	X			X				X				
pO_2		X	X	X	X	X	X	X			X				X				
pCO_2		X	X	X	X	X	X	X			X				X				
BE_{ecf}		X	X	X	X	X	X	X			X				X				
Monitoring data																			
7-Category Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intubation (Y/N)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SOFA		X	X	X	X	X	X	X			X				X				
Renal replacement therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genomic test for SARS-CoV-2		X						X							X			X	
Serious Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

12. ETHICAL CONSIDERATIONS

12.1. Risk Level (According to Resolution 8430, Colombian Health Ministry)

The risk implicit in this study is considered to be "greater than the minimum" according to Res.008430 of 1993 of the Colombian Ministry of Health, since interventions received by the participants will be randomly assigned. However, such interventions are part of conventional and accepted therapeutic options for the management of acute hypoxemic respiratory failure: conventional oxygen therapy (COT) and high-flow oxygen through a nasal cannula (HFNC). It should be clarified and emphasized that requirement for tracheal intubation and invasive mechanical ventilation support will be standardized in order to avoid its delay.

This study is designed to adhere to Resolution 2378 of 2008 and the ethical principles of the Declaration of Helsinki, highlighting that:

- Maintaining confidentiality of the participants included will protect life, health and privacy.

- An extensive review and discussion among local experts was conducted to support the need for this study.

- The results will allow determining if the use of high-flow oxygen therapy through a nasal cannula (HFNC) might decrease the need for orotracheal intubation / support with invasive mechanical ventilation and promote clinical improvement in patients with acute hypoxemic respiratory failure secondary to SARS-CoV-2 infection (severe Covid-19).

12.2. Informed consent

12.2.1. Procedure for taking informed consent: legal considerations

Justification of the modality of informed consent not initially given by the participant in written form, or given by a family member as legal representative in written or verbal form (or combination of the two options) and sometimes with the authorization of an

independent physician in the absence of the participant's family member and/or legal representative.

Situations leading us to define an alternative procedure for obtaining informed consent different from the traditional form, in which speaking directly to the patient/legal representative signature of a document is obtained in physical form, along with two witnesses and the investigator, are the following:

1. Critically ill patients (with variable degree of hypoxemia) with potential physical and mental incapacity to sign the informed consent.

2. Current situation of SARS-CoV-2 pandemic where admission to hospital facilities is restricted to reduce risk of infection or virus spreading from symptomatic or asymptomatic infected persons, will limit an easy access to family members from potential study participants.

3. Contact among family members and health care workers / researchers would potentially increase risk of SARS-CoV-2 infection in both ways. Close contact during explanation of the study procedures and signing physical legal documents and custody in other places different from hospitalization, emergency room, ICU or non-respiratory care areas might also increase risk of infection transmission.

4. Severe infection due to SARS Cov-2 might lead to clinical conditions in which therapies should be rapidly instituted. In such conditions, patient might not be able to consent and contacting his/her legal representative can be complicated.

Once explained such situations, following normative precepts (according to Colombian law) are observed:

According to resolution 8430 of 1993 in title II article 14, for research on human beings there will be written Informed Consent, by which the research subject or his/her legal representative understands and accepts his/her consent, with the exceptions set out in this resolution.

According to resolution 8430 of 1993 in Chapter II. On pharmacological research, Article 59, paragraph b) "Informed Consent will be obtained from the research subject, or in its absence, from the legal representative or the closest family member, except when: the subject's condition renders him/her incapable or prevents him/her from giving it, the legal representative or family member is unavailable or when discontinuing the use of the investigational drug represents an absolute risk of death".

According to the WHO GCP informed consent guidelines, in emergency situations, if it is not possible to obtain the subject's informed consent, the consent of the legally acceptable representative, if any, should be sought shall. If prior consent of the individual or his/her representative is not possible, the inclusion of the individual will be carried out with the documented approval of the Ethics Committee to protect the rights, safety and well-being of the individual and in accordance with applicable regulatory requirements. The individual or his/her legally acceptable representative will be informed of the study as soon as possible and will be asked for consent to continue or other consent as appropriate. (https://apps.who.int/medicinedocs/documents/s18627es/s18627es.pdf)

Guideline 16 of the "International Ethical Guidelines for Research Involving Human Subjects" developed by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) describes the following:

"The researcher and the Research Ethics Committee should agree on a maximum time period for a person's participation without obtaining the person's informed consent or consent given by an authorized third party if the person is still unable to give consent. If individual or surrogate consent has not been obtained after this time, the participant should be withdrawn from the study provided that the withdrawal does not worsen the participant's situation. The participant or his/her representative should have the opportunity to object to the use of data derived from the patient's participation without his/her consent or permission. If there is no advance directive allowing participation in the research for the period of disability, permission must be sought from a legally authorized representative. This permission should take into account the participant's preferences and values expressed above, if any. In all cases in which research has been approved to begin without the prior consent of persons who are incapacitated due to sudden onset conditions, they should be given all relevant information as soon as they regain their capacity, and their consent to continue in the study should be

obtained as soon as reasonably possible. In addition, they must be given the opportunity to opt out of the study.

A therapeutic window is defined in which the investigator will make every effort to obtain consent rather than start without it. A summary of all efforts made will be documented and provided to the ethics committee during the continuing review of the study (by the IRB) (https://apps.who.int/medicinedocs/documents/s18627es/s18627es.pdf).

According to Decree 1377 of 2013, Chapter II, Article 7, Ways to obtain authorization "those responsible for the processing of personal data shall establish mechanisms to obtain the authorization of the holders or of those who are entitled to it in accordance with the provisions of Article 20 of this decree, which guarantee its consultation. These mechanisms may be pre-determined through technical means that facilitate the Holder's automated manifestation. It shall be understood that the authorization complies with these requirements when it is manifested (I) in writing, (II) orally or (III) by means of unequivocal conduct on the part of the holder that allows a reasonable conclusion to be drawn that the authorization was granted. In no case may silence be assimilated to unequivocal conduct". http://www.suin-juriscol.gov.co/viewDocument.asp?ruta=Decretos/1276081

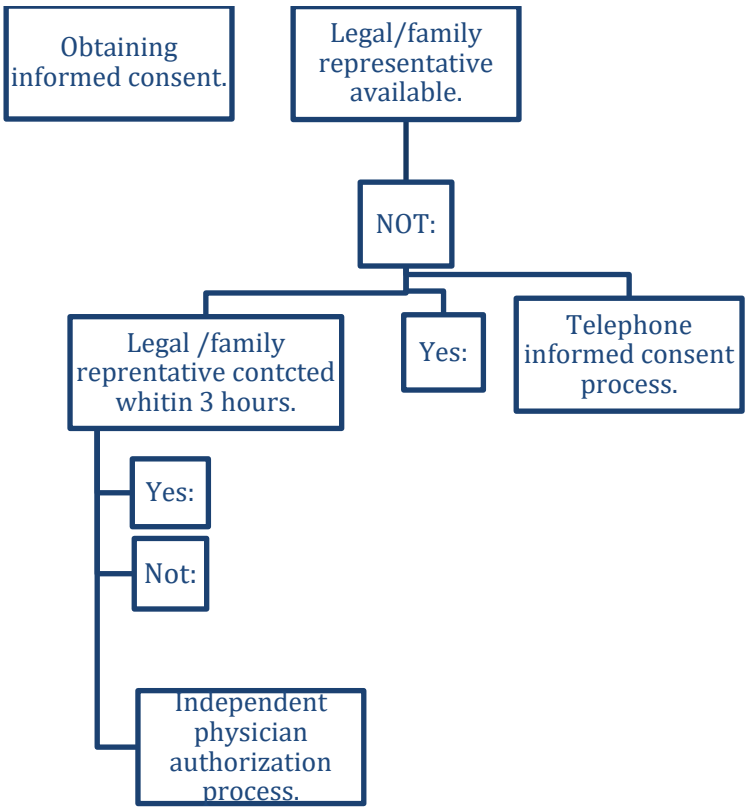
According to the guidance of the Council for International Organizations of Medical Sciences (CIOMS), it states in guideline 9 that consent can be indicated in several ways. The participant may express consent verbally or sign a consent form. When consent has been obtained verbally, researchers should provide documentation of consent to the Research Ethics committee certified by the person obtaining consent or by a witness present at the time of obtaining consent.

According to the Council for International Organizations of Medical Sciences (CIOMS) guidelines, in Guideline 10, Modifications and Waivers of Informed Consent, "A Research Ethics Committee may approve a modification or waiver of informed consent for research if: it would not be feasible or practicable to conduct the research without such a waiver or modification; the research has significant social value; and the research involves only minimal risk to participants. Other provisions may come into play when waivers or modifications of informed consent are approved in specific research settings. This allows the Research Ethics Committee to even allow for a minor increase in risk above the minimum, and to approve

informed consent (guideline 16). https://cioms.ch/wp-content/uploads/2017/12/CIOMS-EthicalGuideline_SP_INTERIOR-FINAL.pdf

And finally, according to the GUIDE FOR RESEARCH ETHICS COMMITTEES of the INVIMA, it is stipulated that the Committee of Ethics is the maximum authority within the Research Center in what concerns the maintenance of the integrity of the research participant. https://www.invima.gov.co/documents/20143/453029/ASS-RSA-GU040.pdf/96ea752d-2639-3024-4287-4527589fb26b

Under such national and international regulations, the following flow to obtain informed consent for the current study is considered:



Therapeutic window considered to locate the legal representative in case he/she is not available at the time the patient is considered to meet the criteria to enter the study will be 3 hours, after that time without locating him, the authorization will be used by an independent physician.

The following information will be provided to the legal representative in order to obtain consent:

- Purpose of the trial and procedures.
- Study inclusion criteria and duration of interventions and follow-up.
- Risks and benefits.
- Confidentiality of information.
- Payments and compensation.

An electronic informed consent will be obtained by direct interview with the participant or legal representative. A phone call for a legal representative might be accepted (if no possible to have direct contact –according to the particular situation during pandemic). If consent would be obtained by a phone call, it will be recorded and then sent it to the local ethics committee as evidence of the process. In any case, a copy form of the consent will be given to the patient and to a family member/legal representative. Once the patient or representative agree with participate, their full identification data and acceptance should be recorded. The participant and/or representative should sign the document and an electronic copy should be sent back to his/her address if requested.

If no legal representative is able to authorize participation in the trial, a meeting between two physicians (one of whom is an independent physician not participating in the trial) will be contemplated, considering all eligibility and exclusion criteria and also considering some known opinion about trial participation previously issued by the patient. After such meeting, the two physicians will decide about to enroll or not the patient into the trial. In all cases, this process SHOULD be followed by a representative authorization to participate within the next

72 hours; otherwise, the patient would be removed from the trial. Document to be used for this process will have prior approval by the Biomedical Research Ethics Committee.

In the event that participants regain physical and mental capacity to give consent, they will receive complete information about the study (informed consent form) and will be requested to continue the trial. Patients and representatives can withdraw consent at any time.

13. ADVERSE EVENTS REPORTING

Serious adverse event reporting will encompass all possible events that might be related with the application of high-flow or conventional oxygen therapies and the potential effects of hypoxemia because possible delays in tracheal intubation or escalation to other advanced life support modalities. Principal investigator at each site will be committed to manage compliance and adherence to the protocol and also to identify adverse events potentially related or not with the study interventions.

Adverse events should be recorded along with:

- Identification of the study participant.
- Time from randomization to occurrence of the event.
- Identification of possible causality between the event and the study intervention (high-flow oxygen or conventional oxygen therapies)
- Resolution or improvement of such adverse event.

13.1. Monitoring of adverse events (AE)

All adverse events (AEs) occurring within 28 days from randomization should be reported to their respective ethics committee following the Serious Adverse Event (SAE) reporting guidelines, maintaining confidentiality principles. It is recommended performing such report within 24 hours from the event when SAE is death. In all cases, AEs will be reported to the study's coordinating center (CIC – Fundación Valle del Lili), which will collect data for analysis during programmed meetings of the Steering Committee and Safety Monitoring Board.

13.3. Data Safety Monitoring Board

As previously mentioned, the Data Safety Monitoring Board (DSMB) will be made up of two highly reputed international experts in critical care medicine and an international statistician, all independent from the HiFLo-Covid Investigators. DSMB will be responsible to conduct the interim analysis when 50% of the sample has completed the 28-day follow-up. Such analysis will include the occurrence of serious adverse events recorded during this period (see 9.8.2. Interim analysis plan).

ANNEX 1. INCLUSION / EXCLUSION FORMAT

INCLUSION/EXCLUSION FORMAT:

Institution: _____ Medical History # : _____

First name: _____ Surname: _____

Initials for registration: ___ ___ ___

Inclusion / Exclusion Criteria:

	INCLUSION CRITERIA		
1	Adult > 18 years old.	YES	NO
2	Suspected / confirmed case of SARS-CoV-2 infection (according to internal definitions).	YES	NO
3	Moderate / severe acute hypoxemic respiratory failure: PaO_2/FiO_2 ratio < 200.	YES	NO
4	Signs of acute respiratory distress; at least 1 of the following: - Increased accessory muscle contraction. - Tonic contraction of the sternocleidomastoid muscle - Supra-sternal retraction. - Intercostal retraction. - Tracheal "tapping" to the neck. - Thoraco-abdominal imbalance.	YES	NO
5	Respiratory rate > 25 x minute.	YES	NO
6	Less than 6 hours since the definition of moderate/severe acute respiratory failure secondary to suspected/confirmed SARS-CoV-2 infection.	YES	NO
	EXCLUSION CRITERIA		
1	< 18 years.	YES	NO
2	Indication for immediate tracheal intubation.	YES	NO
3	Pregnant woman / positive pregnancy test at potential study entry.	YES	NO
4	Chronic liver disease / liver cirrhosis Child-Pugh C.	YES	NO
5	Confirmation of active bacterial or fungal infection.	YES	NO
5	Uncontrolled HIV/AIDS disease (defined by presence of viral load > 200 copies/mL).	YES	NO
6	Previous history of COPD Gold C – D.	YES	NO
7	History of COPD with hospitalization / ICU in the last year.	YES	NO
8	Known history of congestive heart failure NYHA III – IV.	YES	NO

9	Left ventricular ejection fraction < 45% previously known (or actual)	YES	NO
10	Clinically suspected or confirmed cardiogenic pulmonary edema.	YES	NO
11	Hypercapnic respiratory failure ($PaCO_2$ > 55 mmHg).	YES	NO
12	Central/peripheral demyelinating disorders due to medical history or high suspicion of these at the time of eligibility for the study.	YES	NO
13	Dying / NO Resuscitation Order.	YES	NO
14	Any serious medical condition or clinical laboratory test abnormality that, in the investigator's judgment, prevents safe patient participation and completion of the study.	YES	NO
15	Participation in another clinical trial (except one related to SARS-CoV-2 - CRITERIA TO BE DISCUSSED BETWEEN MAIN GROUP OF RESEARCHERS).	YES	NO
	INCLUSION IN THE STUDY IF NOT	YES	NO
	Date:		

Suspected Moderate Case

A patient will be considered in this category when meet ALL the following parameters:

- **Signs and symptoms consistent with SARS-CoV-2 infection not explained by any other previously known or current clinical condition** (bacterial or viral infectious; autoimmune; neoplastic): fever, cough, odynophagia/anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- Confirmed **100 < PaO_2/FiO_2 < 200** (according to arterial gas analysis), **WITHOUT evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

Suspected Severe Case

A patient will be considered in this category when meet ALL the following parameters:

- **Signs and symptoms consistent with SARS-CoV-2 infection not explained by any other previously known or current clinical condition** (bacterial or viral infectious; autoimmune; neoplastic): fever, cough, odynophagia/anosmia and dyspnea.

- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- Confirmed **PaO_2/FiO_2 < 100** (according to arterial gas analysis), **AND / OR evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

Confirmed Moderate Case

A patient will be considered in this category when meet ALL the following parameters:

- **Confirmed SARS-CoV-2 infection by genomic detection** from an upper or lower airway sample in presence of compatible symptoms: fever, cough, odynophagia / anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- Confirmed **100 < PaO_2/FiO_2 < 200** (according to arterial gas analysis), **WITHOUT evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

Confirmed Severe Case

A patient will be considered in this category when they meet ALL of the following parameters:

- **Confirmed SARS-CoV-2 infection by genomic detection** from an upper or lower airway sample in presence of compatible symptoms: fever, cough, odynophagia / anosmia and dyspnea.
- Radiological signs compatible with pneumonia consisting of interstitial / alveolar infiltrates in the chest X-ray and/or frosted glass infiltrates in chest CT scan (suggestive of viral infection).
- Initial hypoxemia (SpO_2 < 90% at FiO_2 0.21) and/or respiratory rate > 25/min, requiring oxygen supplementation at 0.28 < FiO_2 < 0.60 to achieve SpO_2 > 92% (at least 5 minutes after SpO_2 signal stabilization).
- **Confirmation of PaO2/FiO2 < 100** (according to arterial gas analysis), **AND / OR evidence of extra-pulmonary organ dysfunction** (extra-pulmonary SOFA score > 2 points).

ANNEX 2. SCREENING FORMAT

Screening summary

Hospital: _____

		Randomization		Cause of NON-randomization
	ID	**YES**	**NO**	(enter hit number to list)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				

Causes of non-inclusion:

1. Incomplete inclusion criteria
2. Presence of some exclusion criteria.
3. Immediate intubation criteria.
4. NO high-flow nasal cannula available (at time of randomization).
5. > 6 hours from compliance with moderate/severe hypoxemic respiratory failure criteria.
6. 6.Refusal of Treating Physician to Participate or Use Assigned Device.
7. 7.Denial of informed consent.

ANNEX 3. CASE REPORT FORMAT (CRF)

1. GENERAL DATA AND MEDICAL HISTORY

Record ID: _____

Hospital:

_____

Name: _____ **c.c. / ID:** _____

Age: _____ yo **Gender: M** ____ **F** _____ **Height:** _____ cm **weight:** _____ kg **BMI:** _____

Clinical Antecedents							
Chronic heart failure		CKD stage III - IV		Hydroxychloroquine use		Atorvastatin use	
Coronary artery disease		CKD stage V		Azithromycin use		Antidepressants use	
Connective tissue disease		Cirrhosis Child A - B		Steroids use			
Diabetes		COPD Gold A - C		iECA use			
Arterial hypertension		History of AIS		Inh. ARA-II use			

2. SIGNS AND SYMPTOMS

Symptoms onset date: DD / MM / YYYY
Days after symptoms onset to randomization: _____ **days**

Symptoms					
Fever		Dyspnea		Cough	
Odynophagia		Anosmia and dysgeusia		Vomiting / Diarrhea	
Asthenia / Adynamia		Muscular pain			

3. HOSPITAL ADMISSION DATA

Date of hospital admission : DD / MM / YYYY **Hour:** _____

SAP		MAP		Temp		Capillary refill time (CRT)	
DAP		HR		SpO_2			

4. RANDOMIZATION

Randomization date: DD / MM / YYYY **Hour:** _____

SOFA (admission): _____ **APACHE II:** _____ **NEWS II:** _____

BASELINE LABS

STUDY ENTRY LABORATORIES					
pH		PTT		PCR	
pCO_2		Fibrinogen		LDH	
pO_2		Leucocyte		Ferritin	
HCO_3		Neutrophils		D-dimer	
BE ecf/std		Lynphocytes		IL-6	
Lactate		Macrophage		IL-8	
Hemoglobin		NLR		Creat	
Hematocrit		Bilirrubin		BUN	
Platelet		AST		Troponin	
PT		ALT			

RESPIRATORY SUPPORT PRE AND POST IMMEDIATE RANDOMIZATION

PRE RANDOMIZATION					
Respiratory support		**Arterial blood gas**		**Clinical signs**	
Conventional nasal cannula		pH		Respiratory rate	
Venturi mask		pO_2		Heart rate	
Mask with reservoir		FiO_2 (%)		SpO_2	
L/min		PaO_2/FiO_2		BORG Scale	
		SaO_2		Glasgow Coma Score	

POST RANDOMIZATION (2 Hours)					
Respiratory support		**Arterial blood gas**		**Clinical signs**	
HFNC		pH		Respiratory rate	
Conventional nasal cannula		pO_2		Heart rate	
Venturi mask		FiO_2 (%)		SpO_2	
Mask with reservoir		PaO_2/FiO_2		Signs of acute respiratory distress (Yes/Not)	
L/min		SaO_2		En. Intubation. (Yes/Not)	
				BORG Scale	
				Glasgow Coma Score	

POST RANDOMIZATION (4 Hours)					
Respiratory support		**Arterial blood gas**		**Clinical signs**	
HFNC		pH		Respiratory rate	
Conventional nasal cannula		pO_2		Heart rate	
Venturi mask		FiO_2 (%)		SpO_2	
Mask with reservoir		PaO_2/FiO_2		Signs of acute respiratory distress (Yes/Not)	

L/min		SaO_2		En. Intubation. (Yes/Not)	
				BORG Scale	
				Glasgow Coma Score	

5. FOLLOW-UP

RESPIRATORY								
Variable		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
HFNC Group								
HFNC start (date)	DD / MM / YYYY							
HFNC end (date)	DD / MM / YYYY							
Intubation (1. Yes / 0. No)								
FiO_2 (higher)								
L/Min (higher)								
Awake Prone (1. Yes / 0. No)								
Hours on Awake Prone								
COT Group								
COT start (date)	DD / MM / YYYY							
COT end (date)	DD / MM / YYYY							
Intubation (1. Yes / 0. No)								
FiO_2 (higher)								
L/Min (higher)								
Awake Prone (1. Yes / 0. No)								
Hours on Awake Prone								
Endotracheal Intubation Requirement	1. Yes / 0. No							
INTUBATION CRITERIA	**Persistent signs of respiratory failure despite oxygen supplementation**							
	• Respiratory rate > 40 / minute.							
	• Lack of improvement in signs of respiratory muscle fatigue.							
	• Increased and mismanaged bronchial secretions.							
	• Acidosis – pH < 7.25							
	• PaO_2 < 55 mmHg							
	• $PaCO_2$ > 55 mmHg (accompanied by acidosis)							

	• SpO2 < 92% for more than 5 minutes (ruling out signal problems in its measurement) receiving the maximum possible substitution with its respective respiratory support strategy (HFNC vs. COT).	
	Hemodynamic signs	
	• Persistent SBP < 90 mmHg or MAP < 60 mmHg, with requirement for vasopressor support (Noradrenaline > 0.10 µgr/kg/min) in the presence of adequate intravascular volume.	
	• Progression of clinical signs of tissue hypoperfusion: capillary filling > 10 seconds; Mottling score ≥ 4.	
	• Arterial lactate ≥ 4 mmol/L in the presence of any clinical signs of hypoperfusion (capillary filling > 3 seconds; Mottling score ≥ 2).	
	Neurological signs.	
	• Deterioration of consciousness (Glasgow Coma Scale ≤ 12 points).	
	Other criteria	

Invasive mechanical ventilation

Start (date)	DD / MM / YYYY								
End (date)	DD / MM / YYYY								
Mode									
Tidal volume									
Tidal volume (mL/Kg)									
RR									
PEEP									
Ppeak									
Pplat									
Cest									
Cdin									
Driving pressure									

1521
1522
1523

LABORATORIES									
Variable	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**Day 14**
pH									
$PaCO_2$									
PaO_2									
HCO_3									

BE ecf / std									
Lactate									
Hemoglobin									
Hematocrit									
Leucocyte									
Neutrophils									
Lynphocytes									
Macrophage									
NLR									
Platelet									
PCR									
Bilirrubin									
AST									
ALT									
PCR									
Ferritin									
LDH									
D-dimer									
Interleukin 6									
Interleukin 8									
Interleukin 10									

1524

HEMODYNAMICS / PERFUSION									
Variable	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**Day 14**
SAP									
DAP									
PAM									
Heart Rate									
Temperature									
SpO_2									
Capillary Refill Time (sec.)									

1525

MULTIPLE ORGAN DYSFUNCTION - SOFA										
SOFA		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**Day 14**
SOFA Respiratory	PaO_2									
	FiO_2									
	PaO_2 / FiO_2									
	Score									
SOFA Cardiovascular	MAP									

	Vasopressor									
	Inodilator									
	Score									
SOFA Renal	Creatinine									
	Urine output									
	Score									
SOFA Liver	Bilirubin									
	Score									
SOFA Coagulation	Platelet									
	Score									
SOFA CNS	Glasgow Coma Scale									
	Score									
SOFA (total score)										

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7-point Clinical Scale									
7-point Clinical Scale	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**
	Day 10	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 16**	**Day 17**	**Day 18**
	Day 19	**Day 20**	**Day 21**	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**
	Day 28								

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1529
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6. ADJUVANT THERAPIES

Adjuvant therapies				
Treatment	1. Yes / 0. Not	**Start date**	**End date**	**Dose**
Hydroxychloroquine		DD / MM / YYYY	DD / MM / YYYY	
Azithromycin		DD / MM / YYYY	DD / MM / YYYY	
Ivermectin		DD / MM / YYYY	DD / MM / YYYY	
Dexamethasone		DD / MM / YYYY	DD / MM / YYYY	
Methylprednisolone		DD / MM / YYYY	DD / MM / YYYY	
Tocilizumab		DD / MM / YYYY	DD / MM / YYYY	

1531
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7. RESUSCITATION FLUIDS

Resuscitation and fluid balance							
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Total resuscitation fluids (mL)							
Crystalloids (mL)							
Colloids (mL)							
Trasfusion (mL)							
Total balance (24h)							

8. ADJUNCTIVE HYPOXEMIA MANAGEMENT

MANAGEMENT OF REFRACTORY HYPOXEMIA					
Prone position (IMV)	(1. Yes / 0. Not)	Cycle #1		Time	hours
		Cycle #2		Time	hours
		Cycle #3		Time	hours
		Cycle #4		Time	hours
				Total	hours
Neuromuscular blockers	(1. Yes / 0. Not)	Start date	DD / MM / YYYY	End date	DD / MM / YYYY
		Total Days			
Lung recruitment maneuvers	(1. Yes / 0. Not)				
ECMO	(1. Yes / 0. Not)	Start date	DD / MM / YYYY	End date	DD / MM / YYYY
		Total Days			

9. ADVERSE EVENTS

ADVERSE EVENTS			
Event	**(1. Yes / 0. Not)**	.	
Cardiac arrest (pre / Post EI)		Date	DD / MM / YYYY
Supra / ventricular Arrhythmia (pre / post EI)		Date	DD / MM / YYYY
Refractory shock (post EI)		Date	DD / MM / YYYY
Atelectasis		Date	DD / MM / YYYY
Death		Date	DD / MM / YYYY

10. OUTCOMES

OUTCOMES					
Mechanical ventilation	(1. Yes / 0. Not)	RRT	(1. Yes / 0. Not)	Tracheostomy	(1. Yes / 0. Not)
Days free of MV		Days free of RRT			
ICU length of stay		Hospital length of stay			
Hospital survival		(1. Yes / 0. Not)	28-Day survival		(1. Yes / 0. Not)
Date of positive rtPCR SARS-CoV-2			DD / MM / YYYY		
Probable mechanism of death	1. Refractory hypoxemia			2. Sudden arrhythmia	
	3. Shock			4. Multiple organ dysfunction	

7-CATEGORY ORDINAL SCALE: (*)

1. Discharged from the hospital, resuming complete day-life activities
2. Discharged from the hospital, but limitation of activities, home oxygen requirement, or both
3. Hospitalized in general ward (not intensive care unit), not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)
4. Hospitalized in general ward (not intensive care unit), requiring supplemental oxygen / requiring ongoing medical care (Covid-19–related or other medical conditions);
5. Hospitalized in the intensive care unit, requiring any supplemental oxygen;
6. Hospitalized in the intensive care unit, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
7. Death

* Wang Y, Fan G, Horby P, et al.
Comparative Outcomes of Adults Hospitalized With Seasonal Influenza A or B Virus Infection: Application of the 7-Category Ordinal Scale.
Open Forum Infect Dis. 2019 Feb 15;6(3):ofz053. doi: 10.1093/ofid/ofz053.

ANNEX 4. ADVERSE EVENT REPORTING

ADVERSE EVENT REPORT

1. **Adverse Event definition (AE)**

Adverse event will be defined as an untoward medical occurrence in a patient or clinical investigation subject who received a drug or clinical intervention that does not necessarily translates in a causal relationship between such drug or intervention and the outcome. It can be either an unfavorable non-intentional sign (including abnormal laboratory results), a symptom or a disease presented at the same time the drug o investigation intervention is administered.

Events fulfilling AE definition

- Laboratory test results: Hematology, biochemistry, urine analysis, EKG, radiological images, vital signs (including deterioration since admission) among others considered of clinical and investigatory relevance by the investigator.
- Exacerbation of a pre-existent chronic or intermittent disease. Either increases in frequency or increases in affection.
- Detection or diagnosis of new medical conditions present prior or subsequent to investigation intervention.
- Signs, symptoms or clinical sequels, which may be due to drug interaction.
- Signs, symptoms or clinical sequels, which may be due to intervention drug overdose, or the patient's medication.
- In case of AE related drug overdose, both clinical symptoms and abnormal laboratory test results must be present. When one of the above is not present, the event is defined as "accidental overdose or intentional overdose without adverse event".
- Newly diagnosed cancer or a progression in pre-existent cancer.

Events do not fulfilling AE definition

- Medical or surgical procedure: the event that leads to the procedure is the AE.

- Situations where no medical condition is present. Such as hospital admissions for social reasons or comfort.
- Pre-existent medical conditions detected at admission that do not deteriorate. Or expected daily fluctuations in specific diseases.
- Ambulatory surgery before the patient's admission to the study, to treat a pre-existent medical condition.

2. Serious Adverse Event Definition (SAE)

A Serious Adverse Event (SAE) is defined as any unfavorable occurrence independent to dosage and leading / related with one of the following:

a. Death
b. Risk for life
c. Requiring either hospital admission or enlarging hospital stay.
d. Causing persistent or significant disability or inability. Events of minor clinical relevance such as headache, nausea, vomiting, diarrhea, common cold or accidental traumatism are not included.
e. Congenital abnormalities or birth defects in the patient's offspring
f. Significant life threatening or endangering medical events defined by the principal investigator

3. SAE and AE registry

- The investigator must review all documentation related to the adverse event and information must be recorded in data collection format.
- The investigator must define the diagnosis according to signs, symptoms and clinical information. The diagnosis is the adverse event.

4. SAE and AE intensity evaluation

- Grade 1, mild event: mild symptoms that cause minimal or no interference in social and functional activities, with no intervention needed
- Grade 2, moderate event: moderate symptoms causing more than a minimal interference in social and functional activities with intervention requirement.
- Grade 3, severe event: severe event causing inability to perform social and functional activities with intervention or hospital admission requirement.

- Grade 4, Possible life threatening event: clinical manifestations that can be life threatening or that can cause inability to perform basic functional activities. With requirement of intervention to prevent permanent failure, disability or death.
- Grade 5, adverse event-related death

5. Causality evaluation:

- The investigator must determine the probability of causality between AE and the product. Nevertheless, during AE follow-up the investigator can re-evaluate the causality.
- The criterion above describes a guideline for causality evaluation:
    i. Exposition: a confirmation of exposure of the patient to the product
    ii. Temporal evaluation: An existent relation between the AE onset, product administration and the effect.
    iii. Reasonable and probable. Cause
    iv. Withdrawal effect: a resolution or improvement of the AE manifestation when withdrawing o reducing dose, exposition or frequency of the product.

Non-Serious Adverse Events / Serious Adverse Events (NSAE / SAE)

Adverse Event	Description	NSAE*	SAE**	Security Objective
Cardiorespiratory arrest	Cardiorespiratory arrest previous or subsequent to intubation. Involving ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity and asystole.		**X**	**X**
Severe supra o ventricular arrythmias	Supra or ventricular arrythmia with pulse. Defined as severe by the induction of deterioration or acute hemodynamic or respiratory decompensation		**X**	
Non severe supra ventricular arrythmias	Defined as non-severe if supraventricular arrythmia is present with no deterioration or acute or respiratory decompensation	**X**		**X**
Refractory Shock	Vasodilatory or cardiogenic shock onset or both, with vasopressor requirement (norepinephrine >0.2 mgr/kg/min and/or vasopressin and/or methylene blue		**X**	**X**
Atelectasis	Atelectasis confirmed by X-ray.	**X**		

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HIGH-FLOW vs. CONVENTIONAL OXYGEN THERAPY IN PATIENTS WITH ACUTE RESPIRATORY FAILURE DUE TO SARS-CoV-2: The HiFLo-COVID RANDOMIZED CLINICAL TRIAL

The HiFLo-COVID collaborative group

SUMMARY OF CHANGES

Versions and dates

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Protocol version 1.0

Version date: 16th July, 2020

Refers to Statistical Analysis Plan (SAP) Version 1.0

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Protocol version 2.0 (amendment 2.0)

Version date: 16th September, 2020

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Protocol version 3.0 (amendment 2.0)

Version date: 02nd January, 2021

Refers to Statistical Analysis Plan (SAP) Version 3.0

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Amendment 1.0	**Version 2.0; 16th September, 2.020**
9.6 Sample Size	Actual sample size has been estimated in 196 participants (98 by arm) aiming to demonstrate a reduction in the need for intubation from 60 to 40%, assuming an alpha error of 0.05 and power of 0.80. Nevertheless, anticipating some follow-up losses, the new proposed sample size will be 200 patients (i.e., 2 more by arm).
11.3 Blood Sampling and Cytokine Measurement	Blood sampling will be performed in selected centers until the final sample size is completed. Each center will be committed to storage and safeguard such blood samples. Once the size sample is completed, blood samples will be sent to the Fundación Valle del Lili, Cali - Colombia in order to proceed to the prespecified

	cytokine measurement.
11.4. Study Completion	Some clarifying paragraphs on the follow-up until day-28: • Withdraw from study due to voluntary or administrative reasons. Under such circumstances, the participant will be excluded from analysis and his/her data will not be analyzed for primary and secondary outcomes, unless the participant had completed criteria to stop oxygen supply • Hospital discharge because satisfactory condition. In such case, a structured telephone call will be performed at day 28 to confirm his/her clinical condition between hospital discharge and day 28
11.6 Follow-Up Schedule	A structured telephone call performed at day 28 is added
Serious and Non-Serious Adverse Events	• The adverse events: bacterial pneumonia, bacteremia and fungal bloodstream dissemination, primarily defined as security outcomes, will be henceforth reported to the Ethical Committee as serious adverse events • All serious and non-serious adverse events related with intubation (pre and post procedure) will be henceforth reported to the Ethical Committee as serious adverse events

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Amendment 2.0	**Version 3.0; 02nd January, 2.021**
9.6 Sample Size	In the amendment 1.0, sample size had been increased to 200 patients (i.e., 2 more by arm) aiming to compensate a potential 2% of losses. Nevertheless, due to the particular situation during pandemic, an important number of participants (n=18, representing the 9.2% of the total sample size) had been transferred to other hospitals within 72 hours from randomization at the time in which this amendment was constructed. After an extensive discussion with the Ethical Committee and trying to favor the possibility that results of this trial keep sufficient power and consequently, more reliable results, the number total of randomized patients is newly adjusted up to complete a total of

	220 participants.
6. Objectives	Primary and secondary objectives were preserved as initially conceived. Nevertheless, for a better understanding, objectives for secondary and tertiary outcomes, and for predefined subgroup analysis were listed separately
7. Hypotheses	Hypotheses for primary and secondary outcomes and for subgroups analysis were listed accordingly
8. Outcomes	Primary and secondary outcomes were preserved as initially conceived. Nevertheless, for a better understanding, secondary and tertiary outcomes were listed separately as well as the predefined subgroup analysis.

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