

Statistical Analysis Plan

(SAP)

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:

- Statistical Analysis Plan (SAP) VERSION 2.0 (corresponding to the Protocol Version 3.0). Date: 02nd January 2021.

Approved by: Ethical and Biomedical Research Committee (EBRC) from the Fundación Valle del Lili, Cali, Colombia

- Summary of Changes to the SAP

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Statistical Analysis Plan

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(SAP)

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

29

30

31 **The HiFlo-COVID collaborative group**

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45

CALI COLOMBIA

46

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73

74 **1 INTRODUCTION**

75 Arterial hypoxemia is the leading feature of severe cases of Covid-19. In general,
76 management of hypoxemic respiratory failure relies on oxygen supplementation
77 aiming to improve oxygenation and to support respiratory effort.

78 High-flow oxygen therapy through a nasal cannula is a technique whereby a mixture
79 of heated and humidified oxygen and air are delivered to the nose at high flow rates.
80 Data suggest that high flow oxygen through a nasal cannula might decrease the need
81 for tracheal intubation and might reduce the risk of escalation of oxygen therapy in
82 patients with acute respiratory hypoxemic failure, with no apparent impact on
83 mortality rates. Nevertheless, there is no information about if such data are applicable
84 to Covid-19. Accordingly, we conducted a trial to assess the impact of high-flow
85 oxygen therapy through a nasal cannula vs. conventional oxygen therapy on the need
86 for intubation and the time to clinical recovery in patients with severe Covid-19.

87

88 **2 STUDY DESIGN / INTERVENTIONS**

89 Open (non-blind), randomized, controlled, Phase IIb clinical trial including adults with
90 acute respiratory failure and partial pressure of arterial oxygen to fraction of inspired
91 oxygen (PaO_2/FiO_2) ratio < 200 due to suspected or confirmed infection by SARS-CoV-
92 2. Patients will be randomly allocated to high-flow oxygen through a nasal cannula vs.
93 conventional oxygen therapy within the 6 hours of fulfilling acute respiratory failure
94 and prespecified hypoxemia threshold.

95

96 **3 STUDY MAIN OBJECTIVE**

97 To evaluate the impact of using high-flow oxygen through a nasal cannula vs.
98 conventional oxygen therapy on the need for intubation/support with invasive
99 mechanical ventilation and clinical status as assessed by a 7-category ordinal scale in
100 patients with acute hypoxemic respiratory failure secondary to severe Covid-19.

101

102

103 4 OUTCOMES

104 4.1 Co-Primary Outcomes

105 • Need for intubation / invasive mechanical ventilation support (time frame:
106 28 days).

107 • Time to clinical recovery as assessed by a 7-category ordinal scale (time
108 frame: 28 days).

109

110 4.2. Secondary - tertiary outcomes and Prespecified Subgroup Analysis

111

112 Secondary Outcomes

113 Efficiency

114 • Early requirement of intubation / invasive mechanical ventilation support
115 (time frame: 7 days – 14 days).

116 • Mechanical ventilation-free days (time frame: 28 days).

117 • Renal replacement therapy-free days (time frame: 28 days)

118 • Length of ICU stay (time frame: 28 days)

119 • Length of hospital stay (time frame: 28 days)

120 • Hospital mortality – all causes (time frame: 14 and 28 days)

121 Safety

122 • Occurrence / proportion of patients with serious adverse events (time frame:
123 28 days)

124 • Occurrence / proportion of bacterial - fungal infections (time frame: 28 days).

125

126 Tertiary Outcomes

127 • Time-course of oxygen flow and PaO₂/FiO₂ ratio among the groups under
128 study (time frame: 7 days)

- 129 • Time elapsed from randomization to intubation / invasive mechanical
130 ventilation support in patients failing to high-flow oxygen therapy and
131 conventional oxygen therapy (time frame: 28 days).
132 • Clinical condition at day-28 (time frame: 28 days).
133 • Evolvment of multiorgan dysfunction as assessed by SOFA score (time frame:
134 14 days)
135 • Evolvment of extra-pulmonary organ dysfunction as assessed by extra-
136 pulmonary SOFA score (time frame: 14 days).
137 • HACOR and ROX scores at 2- and 4-hours post-randomization and their
138 relation with requirement of intubation (time frame: 28 days)
139 • Differences in time-course of IL-6 and IL-8 between study groups (time frame:
140 7 days)
141 • Differences in time-course of ferritin, LDH, leukocyte count, neutrophil to
142 lymphocyte count relationship, platelet count, and D-dimer among the groups
143 under study (time frame: 7 days)
144 •
145

146 Subgroup Analysis

- 147 • Time to intubation / invasive mechanical ventilation and clinical recovery in
148 subgroups with baseline PaO₂/FiO₂ > and < 100 mmHg (time frame: 28 days)
149 • Time to intubation / invasive mechanical ventilation and clinical recovery in
150 subgroups with baseline IL-6 > and < 100 pg/mL (time frame: 28 days)
151 • Time to intubation / invasive mechanical ventilation and clinical recovery in
152 subgroups aged > and < 60 years (time frame: 28 days)

153

154 **5 Study Population**

155

156 **5.1. Inclusion criteria**

- 157 • Age 18 years or older;
158 • Suspected or confirmed infection by SARS-CoV-2;
159 • Acute respiratory distress with a ratio of the partial pressure of arterial oxygen
160 to the fraction of inspired oxygen (PaO₂/FiO₂) < 200;

- 161 • Clinical signs of respiratory failure: laborious breathing, use of accessory
162 muscles and respiratory rate greater than 25/min;
163 • Less than 6 hours from fulfilling the criteria of acute respiratory failure;
164 • Having a progression < 6 hours since fulfilling definition of moderate or severe
165 acute respiratory failure due to suspected or confirmed SARS-CoV-2 infection.

166

167 **5.2. Exclusion criteria**

- 168 • < 18 years.
169 • Indication for immediate tracheal intubation.
170 • Pregnant woman / positive pregnancy test at the time of potential inclusion.
171 • Chronic liver disease / liver cirrhosis Child-Pugh C.
172 • Confirmation of active bacterial or fungal infection.
173 • Uncontrolled HIV/AIDS disease (defined by presence of viral load > 200
174 copies/mL).
175 • Previous history of COPD Gold C – D.
176 • History of COPD requiring hospitalization or ICU admission during the last
177 year.
178 • History of congestive heart failure NYHA III – IV.
179 • History or actual left ventricular ejection fraction < 45%
180 • Highly suspected or confirmed cardiogenic pulmonary edema.
181 • Hypercapnic respiratory failure (PaCO₂ > 55 mmHg).
182 • History or high suspicion of central or peripheral demyelinating disorders at
183 the time of potential inclusion.
184 • Imminence of death within the next 24 hours (according to investigator's
185 clinical judgment)
186 • Any serious medical condition or clinical laboratory test abnormality that, at
187 the investigator's judgment, prevents safe patient participation and completion
188 of the study.
189 • Participation in another clinical trial (except other related to SARS-CoV-2.
190 These criteria will be always discussed among steering committee members

191

192 6 Sample Size Calculation

193 Sample size was calculated under the assumption of an intubation rate of 60%,
194 according to the data obtained from the first 75 patients with Covid-19-related
195 moderate and severe hypoxemic respiratory failure treated in the coordinating center.
196 Such proportion of intubation events was in agreement with previous data from a
197 randomized controlled trial testing high-flow oxygen through nasal cannula in a mixed
198 population of patients with acute hypoxemic respiratory failure (1). In such a trial, the
199 maximal value of the 95% confidence interval for intubation at day 28 in the groups
200 subjected to standard oxygen therapy and non-invasive mechanical ventilation were
201 57% and 59% independently of basal oxygenation, and 64% and 68% for those with
202 an initial PaO₂/FiO₂ ratio < 200. Consequently, estimating an intubation rate around
203 60% in conventionally-treated patients, we calculated that enrollment of 196 patients
204 would be necessary to demonstrate an absolute reduction of 20% in the proportion of
205 intubation and requirement of invasive mechanical ventilation with an 80% power
206 and two-side alpha level of 0.05. In addition, data obtained from the initial cohort of
207 patients with Covid-19-related severe hypoxemic respiratory failure treated in the
208 coordinating center revealed a time to recovery of 14 (± 4.5) vs. 12 (± 4.0) days for the
209 conventional oxygen and high-flow oxygen therapy groups respectively. Thus, it was
210 estimated that 160 patients (80 by arm) would be necessary to demonstrate such a
211 difference with an 80% power and two-side alpha level of 0.05. Consequently, the
212 sample size of 196 patients was retained as the sample size target.

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

221

222 7 Type of analysis

223 Main analysis will be performed on an intention-to-treat basis with no exclusion after
224 randomization except exclusions for withdrawn consent, according to the local
225 regulations. Baseline characteristics will be displayed as the shown Table 1.

226

227 **7.1. Primary Outcome Analysis**

228 The first primary outcome is to evaluate the effect of high-flow oxygen through a nasal
229 cannula on the requirement of intubation and invasive mechanical ventilation within
230 28-days from randomization. The effect of the allocated treatment (high-flow oxygen
231 vs. conventional oxygen therapy) on the cumulative incidence of intubation / invasive
232 mechanical ventilation will be calculated with a Cox proportional hazard model with
233 stratification by age (< or ≥ 60 years old), initial hypoxemia severity (PaO₂/FiO₂ ratio
234 as continuous variable), and comorbidities (a composite of arterial hypertension,
235 diabetes, obesity [body mass index > 30], chronic obstructive pulmonary disease, end-
236 stage renal failure, heart failure, cirrhosis Child-Pugh A-B). The proportional hazards
237 assumption will be tested with the Grambsch and Therneau method (2). Results will
238 be reported as hazard ratios with 95% confidence intervals and represented in
239 Kaplan-Meier curves.

240 The other primary outcome is the clinical improvement within 28 days from
241 randomization. Time to clinical improvement is defined as the time elapsed from
242 randomization until the first day, during the 28 days after enrollment, on which a
243 patient attained a reduction in two or more points in the modified ordinal 7-category
244 scale. The effect size of the allocated therapy treatment (high-flow oxygen vs.
245 conventional oxygen therapy) on the time to recovery will be assessed by computing
246 the hazard ratio with its 95% confidence interval (CI) as estimated from Cox
247 proportional hazard model adjusted by age (< or ≥ 60 years old), initial hypoxemia
248 severity (PaO₂/FiO₂ ratio as continuous variable), and comorbidities (a composite of
249 arterial hypertension, diabetes, obesity [body mass index > 30], chronic obstructive
250 pulmonary disease, end-stage renal failure, heart failure, cirrhosis Child-Pugh A-B).
251 Such analysis will be constructed for the overall population and also stratified
252 according to baseline 7-category ordinal scale at enrollment (i.e., scores of 4 or 5), and
253 plotted in Kaplan-Meier curves.

254 Hazard ratios calculated for the outcome clinical recovery greater than 1, will indicate
255 benefit with the high-flow oxygen therapy. Meanwhile, hazard ratios calculated for
256 need for intubation less than 1 will indicate benefit with the use of high-flow oxygen
257 therapy.

258

259

260 7.2. Secondary outcomes, tertiary outcomes, and predefined subgroups analysis

261

262 Continuous variables will be described as medians (interquartile ranges) and
263 categorical variables as proportions.

264

265 Secondary Outcomes analysis

266 • Proportion of patients requiring early intubation and mechanical ventilation
267 support: defined as the proportion of patients requiring intubation for mechanical
268 ventilatory support by days 7 and 14. Differences between groups will be
269 compared by using a Mann Whitney test.

270 • Mechanical ventilation free-days within 28 days: defined as the number of days
271 from day 2 up to 28 days after randomization in which the patients remained
272 without mechanical ventilation support. A Proportional odds model adjusted for
273 age (\geq or $<$ 60 years old), PaO₂/FiO₂ ratio at the randomization, and comorbidities
274 (a composite of arterial hypertension, diabetes, obesity [body mass index $>$ 30],
275 chronic obstructive pulmonary disease, end-stage renal failure, heart failure,
276 cirrhosis Child-Pugh A-B) will be used to determine differences between groups.
277 Odds ratios $>$ 1 will indicate benefit with the use of High-Flow Oxygen Therapy and
278 vice versa.

279 • Renal replacement therapy-free days: defined as the number of days from day 2 up
280 to 28 days after randomization in which the patients remained without renal
281 replacement support. A Proportional odds model adjusted for age (\geq or $<$ 60 years
282 old), PaO₂/FiO₂ ratio at the randomization, and comorbidities (a composite of
283 arterial hypertension, diabetes, obesity [body mass index $>$ 30], chronic obstructive
284 pulmonary disease, end-stage renal failure, heart failure, cirrhosis Child-Pugh A-B)
285 will be used to determine differences between groups. Odds ratios $>$ 1 will indicate
286 benefit with the use of High-Flow Oxygen Therapy and vice versa.

287 • Hospital length of stay: number of days in which the patient remained hospitalized.
288 A Proportional odds model adjusted for age (\geq or $<$ 60 years old), PaO₂/FiO₂ ratio at
289 the randomization, and comorbidities (a composite of arterial hypertension,
290 diabetes, obesity [body mass index $>$ 30], chronic obstructive pulmonary disease,
291 end-stage renal failure, heart failure, cirrhosis Child-Pugh A-B) will be used to
292 determine differences between groups. Odds ratios $>$ 1 will indicate benefit with
293 the use of High-Flow Oxygen Therapy and vice versa.

294 • Hospital length of ICU stay: number of days in which the patient remained
295 hospitalized in the Intensive Care Unit. A Proportional odds model adjusted for age

- 296 (\geq or $<$ 60 years old), PaO₂/FiO₂ ratio at the randomization, and comorbidities (a
297 composite of arterial hypertension, diabetes, obesity [body mass index $>$ 30],
298 chronic obstructive pulmonary disease, end-stage renal failure, heart failure,
299 cirrhosis Child-Pugh A-B) will be used to determine differences between groups.
300 Odds ratios $>$ 1 will indicate benefit with the use of High-Flow Oxygen Therapy and
301 vice versa.
- 302 • Mortality at days- 14 and 28: defined as mortality within the 14 and 28 days from
303 randomization. A Proportional odds model adjusted for age (\geq or $<$ 60 years old),
304 PaO₂/FiO₂ ratio at the randomization, and comorbidities (a composite of arterial
305 hypertension, diabetes, obesity [body mass index $>$ 30], chronic obstructive
306 pulmonary disease, end-stage renal failure, heart failure, cirrhosis Child-Pugh A-B)
307 will be used to determine differences between groups. Odds ratios $<$ 1 will indicate
308 benefit with the use of High-Flow Oxygen Therapy and vice versa.
 - 309 • Proportion of major events: defined as the proportion of patients developing some
310 defined major adverse event. Differences between groups will be compared by
311 using a Mann Whitney test

312 Tertiary Outcomes analysis

- 313 • Time-course of oxygen flow and PaO₂/FiO₂ ratio among the groups under study.
314 Differences between groups will be estimated by using a mixed linear regression
315 considering patient as random effect and adjusting for baseline value of the
316 variable.
- 317 • Time elapsed from randomization to intubation / invasive mechanical ventilation
318 support: defined by the number of hours between randomization up to intubation
319 (when required). Differences between groups will be compared by using a Mann
320 Whitney test
- 321 • Clinical condition at day-28 according to 7-category ordinal scale: defined as the
322 patient clinical condition at day-28 after randomization according to such scale.
323 Differences between groups will be compared by using a Mann Whitney test
- 324 • Multiple organ dysfunction during the first 7 and 14-days: time-course of
325 multiorgan dysfunction as assessed by the Sequential Organ Failure Assessment
326 Score (SOFA) score (3). Differences between groups will be estimated by using a
327 mixed linear regression considering patient as random effect and adjusting for
328 baseline value of the variable.
- 329 • Extra-pulmonary organ dysfunction during the first 7 and 14-days: time-course of
330 extra pulmonary organ dysfunction as assessed by the Sequential Organ Failure
331 Assessment Score (SOFA) score (3), but excluding the corresponding pulmonary
332 points. Differences between groups will be estimated by using a mixed linear

- 333 regression considering patient as random effect and adjusting for baseline value of
334 the variable.
- 335 • HACOR and ROX scores at 2- and 4-hours post-randomization and their relation
336 with requirement of intubation (time frame: 28 days)
 - 337 • Time-course of IL-6 and IL-8 between study groups (time frame: 14 days): defined
338 as the evolvment in time of IL-6 and IL-8 levels within the first 14 days from
339 randomization. Differences between groups will be estimated by using a mixed
340 linear regression considering patient as random effect and adjusting for baseline
341 value of each variable.
 - 342 • Time-course of ferritin, LDH, leukocyte count, neutrophil/lymphocyte count
343 relationship, platelet count, and D-dimer among the groups under study (time
344 frame: 14 days): defined as the evolvment in time of such markers within the first
345 14 days from randomization. Differences between groups will be estimated by
346 using a mixed linear regression considering patient as random effect and adjusting
347 for baseline value of each variable.

348

349 Predefined subgroups analysis

- 350 • Requirement of intubation / invasive mechanical ventilation in subgroups with
351 baseline PaO₂/FiO₂ > and < 100 mmHg (time frame: 28 days). Differences between
352 groups will be compared by using a Mann Whitney test
- 353 • Time to intubation / invasive mechanical ventilation in subgroups with baseline
354 PaO₂/FiO₂ > and < 100 mmHg (time frame: 28 days). The effect of the allocated
355 treatment (high-flow oxygen vs. conventional oxygen therapy) on the cumulative
356 incidence of intubation / invasive mechanical ventilation will be calculated with a
357 Cox proportional hazard model according to baseline PaO₂/FiO₂ > and < 100
358 mmHg. Hazard ratios < 1 will indicate benefit with the use of High-Flow Oxygen
359 Therapy and vice versa
- 360 • Requirement for intubation / invasive mechanical ventilation in subgroups with
361 baseline IL-6 > and < 100 pg/mL (time frame: 28 days). Differences between
362 groups will be compared by using a Mann Whitney test
- 363 • Time to intubation / invasive mechanical ventilation in subgroups with baseline IL-
364 6 > and < 100 pg/mL (time frame: 28 days). The effect of the allocated treatment
365 (high-flow oxygen vs. conventional oxygen therapy) on the cumulative incidence of
366 intubation / invasive mechanical ventilation will be calculated with a Cox
367 proportional hazard model according to baseline IL-6 > and < 100 pg/mL. Hazard
368 ratios < 1 will indicate benefit with the use of High-Flow Oxygen Therapy and vice
369 versa

- 370 • Requirement intubation / invasive mechanical ventilation in subgroups aged > and
371 < 60 years (time frame: 28 days). Differences between groups will be compared by
372 using a Mann Whitney test
- 373 • Time to intubation / invasive mechanical ventilation in subgroups aged > and < 60
374 years (time frame: 28 days). The effect of the allocated treatment (high-flow oxygen
375 vs. conventional oxygen therapy) on the cumulative incidence of intubation /
376 invasive mechanical ventilation will be calculated with a Cox proportional hazard
377 model according to aged > and < 60 years. Hazard ratios < 1 will indicate benefit
378 with the use of High-Flow Oxygen Therapy and vice versa.
- 379 • Time to clinical recovery in subgroups with baseline PaO₂/FiO₂ > and < 100 mmHg
380 (time frame: 28 days). The effect of the allocated treatment (high-flow oxygen vs.
381 conventional oxygen therapy) on the time to clinical recovery will be calculated
382 with a Cox proportional hazard model according to baseline PaO₂/FiO₂ > and < 100
383 mmHg. Hazard ratios > 1 will indicate benefit with the use of High-Flow Oxygen
384 Therapy and vice versa.
- 385 • Time to clinical recovery in subgroups with baseline IL-6 > and < 100 pg/mL (time
386 frame: 28 days). The effect of the allocated treatment (high-flow oxygen vs.
387 conventional oxygen therapy) on the time to clinical recovery will be calculated
388 with a Cox proportional hazard model according to baseline IL-6 > and < 100
389 pg/mL. Hazard ratios > 1 will indicate benefit with the use of High-Flow Oxygen
390 Therapy and vice versa.
- 391 • Time to clinical recovery in subgroups aged > and < 60 years (time frame: 28 days).
392 The effect of the allocated treatment (high-flow oxygen vs. conventional oxygen
393 therapy) on the time to clinical recovery will be calculated with a Cox proportional
394 hazard model according to age > and < 60 years. Hazard ratios > 1 will indicate
395 benefit with the use of High-Flow Oxygen Therapy and vice versa.

396
397

398 **7.3. Additional analysis (Post-Hoc Analysis)**

399 Sensitivity analysis

400 We will consider to perform some sensitivity analyses:

- 401 - Including just patients with confirmed SARS-CoV-2 infection by means of RT-
402 PCR test.
- 403 - Including patients receiving the randomly allocated treatment (per-protocol
404 analysis)

405 - Imputation analysis including patients excluded because early transfers to
406 other hospitals because administrative reasons

407

408 **7.4. Handling missing data**

409

410 **For Primary outcomes**

411 The primary outcome is expected to be available in all patients. If death occurs during
412 follow-up, data will be censored until last observation. In the case of lost of follow-up,
413 the last report on the 7-category scale will be considered as the outcome.

414

415 **For Covariates**

416 It is expected to collect information about all covariates for both primary and
417 secondary outcomes. Nevertheless, in the case of missing data of variables needed to
418 analyze effect modification, and this may have an effect the primary outcomes, then
419 simple imputation will be performed using the median of the treatment group to
420 which the observation belongs based on the information collected with complete data.

421 Data will not be imputed for secondary outcomes.

422

423 **8 INTERIM ANALYSIS**

424 A first and only interim analysis was conducted when the 28-day follow-up had been
425 completed for the first 100 randomized patients. Database will be prepared and sent
426 to the members of the Data Safety Monitoring Board (DSMB). An independent
427 statistician will perform the analysis and will discuss it with the DSMB, who later will
428 communicate results to the Steering Committee. Haybittle–Peto stopping boundaries
429 (4) are a priori proposed as rules to continue or stop the trial. Thus, a P-value
430 threshold of less than 0.001 will be considered to interrupt the trial for safety and a P-
431 value threshold of less than 0.0001 to interrupt the trial for efficacy.

432

433

434 9 TABLES

435 9.1 Table 1. Patients characteristics at randomization

436

437

Characteristic	High-Flow Oxygen Therapy (n=xxx)	Conventional Oxygen Therapy (n=xxx)
Demographics		
Age, median (IQR) - years	xx (xx - xx)	xx (xx - xx)
Sex - No. (%)		
Men	xx (xx)	xx (xx)
Women	xx (xx)	xx (xx)
Body Mass Index, median (IQR) †	xx (xx - xx)	xx (xx - xx)
APACHE II	xx (xx - xx)	xx (xx - xx)
Testing for COVID-19, No. (%)		
Positive on RT-PCR	xx (xx)	xx (xx)
Negative on RT-PCR or unavailable	xx (xx)	xx (xx)
Comorbidities, No. (%)		
Hypertension	xx (xx)	xx (xx)
Diabetes	xx (xx)	xx (xx)
Chronic Obstructive Pulmonary Disease	xx (xx)	xx (xx)
Heart Failure	xx (xx)	xx (xx)
Chronic Renal Disease	xx (xx)	xx (xx)
Cancer	xx (xx)	xx (xx)
Cirrhosis Child A-B	xx (xx)	xx (xx)
Previous medications, No. (%)		
Steroids	xx (xx)	xx (xx)
ACE inhibitor	xx (xx)	xx (xx)
Angiotensin II Receptor Antagonist	xx (xx)	xx (xx)
Statins	xx (xx)	xx (xx)
Characteristics at randomization		
Median time from symptom onset to randomization (IQR) - days	xx (xx - xx)	xx (xx - xx)
Median time from admission to	xx (xx - xx)	xx (xx - xx)

randomization (IQR) - days		
SOFA score at randomization	xx (xx - xx)	xx (xx - xx)
Respiratory status just before randomization		
Respiratory Rate, median (IQR), /min	xx (xx - xx)	xx (xx - xx)
PaO ₂ /FiO ₂ ratio, median (IQR)	xx (xx - xx)	xx (xx - xx)
Received standard oxygen therapy before randomization		
Oxygen flow, median (IQR), L/min	xx (xx - xx)	xx (xx - xx)
PaO ₂ with standard oxygen, median (IQR), mmHg	xx (xx - xx)	xx (xx - xx)
PaCO ₂ with standard oxygen, median (IQR), mmHg	xx (xx - xx)	xx (xx - xx)
Score on Seven-Level Ordinal Scale - No. (%) ††		
4. Hospitalized and receiving supplemental oxygen	xx (xx)	xx (xx)
5. Hospitalized in ICU and receiving oxygen supplementation	xx (xx)	xx (xx)

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9.2 Table 1S. Other patient characteristics at randomization

Characteristic	High-Flow Oxygen Therapy (n=xxx)	Conventional Oxygen Therapy (n=xxx)	P
Symptoms			
Fever - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Odynophagia - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Cough - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Vomiting / diarrhea - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Asthenia / adynamia - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Anosmia / dysgeusia - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Odynophagia - no. (%)	XX (XX.X)	XX (XX.X)	.XX
Vital signs at admission, median (IQR)			
Systolic arterial pressure, mmHg	XX (XX – XX)	XX (XX – XX)	.XX
Diastolic arterial pressure, mmHg	XX (XX – XX)	XX (XX – XX)	.XX
Mean arterial pressure, mmHg	XX (XX – XX)	XX (XX – XX)	.XX
Heart rate, beats/min	XX (XX – XX)	XX (XX – XX)	.XX
Respiratory rate, breaths/min	XX (XX – XX)	XX (XX – XX)	.XX
Laboratory, median (IQR)			
pH	X.XX (X.XX – X.XX)	X.XX (X.XX – X.XX)	.XX
PaCO ₂ , mmHg	XX (XX – XX)	XX (XX – XX)	.XX
PaO ₂ , mmHg	XX (XX – XX)	XX (XX – XX)	.XX
HCO ₃ ⁻ , mmol/L	XX.X (XX.X – XX.X)	XX.X (XX.X – XX.X)	.XX

Base excess, mmol/L	X.XX (X.XX – X.XX)	X.XX (X.XX – X.XX)	.XX454
PaO ₂ /FiO ₂ ratio	XX (XX – XX)	XX (XX – XX)	.XX
Lactate, mmol/L	X.XX (X.XX – X.XX)	X.XX (X.XX – X.XX)	.XX455
Hemoglobin, gr/dL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX456
Hematocrit, %	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX457
Platelets, /mm ³	XXX,XXX (XXX,XXX – XXX,XXX)	XXX,XX (XXX,XXX – XXX,XXX)	.XX458
Prothrombin Time – PT, sec	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX459
Activated Partial Thromboplastin Time – aPTT, sec	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX460
Fibrinogen, mg/dL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX462
Leucocytes, /mm ³	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX463
Neutrophils, /mm ³	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX464
Lymphocytes, /mm ³	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX465
Macrophages, /mm ³	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX466
Neutrophil: Lymphocyte Ratio	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX467
Bilirubin, mg/dL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX468
Aspartate Amino Transferase – AST, IU/L	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX469
Alanine Amino Transferase – ALT, IU/L	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX470
C-Reactive Protein – CRP, mg/L	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX471
Lactate dehydrogenase – LDH, U/L	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX472
Ferritin, ng/mL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX473
D-dimer, µg/mL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX474
IL-6	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX475
IL-8	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX476
Creatinine, mg/dL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX477
Blood Nitrogen Urea – BUN, mg/dL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX478
Troponin, ng/mL	XX.XX (XX.XX – XX.XX)	XX.XX (XX.XX – XX.XX)	.XX479

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9.3. Table 2. Primary and Secondary Outcomes

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	Overall		Ordinal Score at Baseline			
		4			5	
	High-Flow Oxygen Therapy (n=XXX)	Conventional Oxygen Therapy (n=XXX)	High-Flow Oxygen Therapy (n=XX)	Conventional Oxygen Therapy (n=XX)	High-Flow Oxygen Therapy (n=XX)	Conventional Oxygen Therapy (n=XX)
Primary Outcomes						
Intubation over first 28 days						
No. of intubations by day 28	XX	XX	XX	XX	XX	XX
Hazard ratio (95%CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{SE}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{SE}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{SE}	
Clinical Recovery §						
No. of recoveries	XX	XX	XX	XX	XX	XX
Median time to recovery (95%CI) - days	XX (XX -XX)	XX (XX -XX)	XX (XX -XX)	XX (XX -XX)	XX (XX -XX)	XX (XX -XX)
Hazard ratio (95%CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{SE}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{SE}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{SE}	

Secondary Outcomes								
Ordinal score at day 28 - no. (%) f f								
1	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
2	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
3	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
4	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
5	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
6	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
7	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
Odds ratio (95%CI)	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	
Mortality								
At day 14								
No. of patients (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	
Hazard Ratio (95%CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}		X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}		X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}		X.XX (X.XX-X.XX) [p=X.XX] ^[T] _{SEp}	
At day 28								

No. of patients (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Hazard Ratio (95%CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]
Intubation						
At day 7						
No. of patients (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Hazard Ratio (95%CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]
Intubation						
At day 14						
No. of patients (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Hazard Ratio (95%CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]
Time elapsed from randomization to Intubation, hours	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)	X.XX (X.XX-X.XX)
Adjusted odds ratio (95% CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]	X.XX (X.XX-X.XX) [p=X.XX] ^[T1] _[SEP]
Ventilation-free days at day-28, days (IQR)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)

Adjusted odds ratio (95% CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}	
Renal replacement therapy-free days, , days (IQR)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)
Adjusted odds ratio (95% CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}	
Length of Stay - Intensive Care Unit, days (IQR)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)
Adjusted odds ratio (95% CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}	
Length of Stay - Hospital, days (IQR)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)	XX (XX - XX)
Adjusted odds ratio (95% CI) for data through day 28	X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}		X.XX (X.XX-X.XX) [p=X.XX] ^[1] _{\$SEP\$}	

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499 **9.4 Table 3. Time from randomization to intubation / invasive mechanical ventilation support / additional**
500 **respiratory support maneuvers**

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	High-Flow Oxygen Therapy (n=XXX)	Conventional Oxygen Therapy (n=XXX)	P value
No. of intubations by day 28, (%)	XX (XX.X)	XX (XX.X)	0.026 †
Time elapsed from randomization to Intubation, hours	XX.X (XX.X - XX.X)	XX.X (XX.X - XX.X)	0.69
Time elapsed with FiO ₂ > 0.70 from randomization to Intubation, hours	XX.X (XX.X - XX.X)	XX.X (XX.X - XX.X)	< 0.001
Awake prone position, n (%)	XX (XX.X)	XX (XX.X)	0.12
Time in awake prone position, hours (interquartile range)	XX.X (XX.X - XX.X)	XX.X (XX.X - XX.X)	0.35
Prone position during mechanical ventilation, n (%)	XX (XX.X)	XX (XX.X)	0.08
Time in prone position during mechanical ventilation, hours (interquartile range)	XX.X (XX.X - XX.X)	XX.X (XX.X - XX.X)	0.90
Neuromuscular paralysis, n (% from total population)	XX (XX.X)	XX (XX.X)	0.04

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Statistical Analysis Plan

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(SAP)

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

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The HiFlo-COVID collaborative group

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SUMMARY OF CHANGES

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573 **Versions and dates**

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575 Statistical Analysis Plan version 1.0

576 Version date: 16th July, 2020

577 Refers to protocol Version 1.0

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579 Statistical Analysis Plan version 2.0

580 Version date: 02nd January, 2021

581 Refers to protocol Version 3.0

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585 **Summary of changes from SAP version 1.0 to version 2.0**

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587 1. Sample Size

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589 Changes: Increasing of sample size

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591 In the Protocol amendment 1.0, sample size had been increased from 196 to 200
592 patients (i.e., 2 more by arm) aiming to compensate a potential 2% of losses.
593 Nevertheless, due to the particular health system conditions during pandemic, an
594 important number of participants (n=18, representing the 9.2% of the total sample
595 size) had been transferred to other hospitals within 72 hours from randomization at
596 the time in which Protocol amendment 3.0 was being constructed. After an extensive
597 discussion with the Ethical Committee and trying to favor the possibility that results
598 of HiFlo-Covid trial keep sufficient power and consequently, more reliable results, the

599 number total of randomized patients was newly adjusted up to complete a total of 220
600 participants.

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602 2. Objectives and Outcomes

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604 Changes: Re-arrangement of Objectives and Outcomes list

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606 Primary and secondary outcomes were preserved as initially conceived in the
607 Protocol version 1.0 and Statistical Plan Analysis version 1.0. Nevertheless, for a
608 better understanding, secondary and tertiary outcomes, and predefined subgroups
609 were listed separately

610 Time-course for labs was shortened to 7 days because median length of stay < 14 days
611 observed during interim analysis.

612