CLINICAL TRIAL PROTOCOL

Trial title: **Randomized controlled trial of methylprednisolone versus dexamethasone in COVID-19 pneumonia (MEDEAS)**

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Abbreviations

AIFA	Agenzia Italiana del Farmaco
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
COVID-19	Coronavirus Disease 19
CTA	Clinical Trial Authorization
DM	Dexamethasone
DSMB	Data safety and monitoring board
ECMO	Extracorporeal Membrane Oxygenation
HFNC	High-Flow nasal cannula
GC	Glucocorticoid
GRα	Glucocorticoid Receptor alpha
ICU	Intensive care unit
IV	Intravenously
LMWH	Low molecular weight heparin
IMV	Invasive mechanical ventilation
MP	Methylprednisolone
MV	Mechanical ventilation (both NPPV and IMV)
NOAC	New oral anticoagulants
NPPV	Noninvasive positive pressure ventilation
PEEP	Positive End-Expiratory Pressure
PO	Per os
RHDU	Respiratory high-dependency unit
RT-qPCR	Real-time quantitative polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization

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2. Introduction

2.1. Background and rationale

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection is associated with an acute respiratory decompensation requiring supplemental oxygen therapy in approximately 60% of the hospitalized cases and with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation in about 20% of cases.(1) The rationale for glucocorticoid treatment in COVID-19 was recently reviewed.(2) Low-dose glucocorticoid (GC) treatment is the only intervention shown to significantly reduce mortality in cases of COVID-19 pneumonia requiring oxygen supplementation or ventilatory support. In particular, a large UK randomized controlled trial (RECOVERY trial) demonstrated the efficacy of dexamethasone at a dosage of 6mg/day for 10 days in reducing mortality by 17% on average compared to usual therapy, with a greater impact on patients requiring mechanical ventilation (36% reduction) or oxygen therapy (18% reduction) than on those who did not need respiratory support.(1)

Several other RCTs have shown similar results, confirming the strong rationale for the use of glucocorticoids in moderate and severe SARS-CoV-2 pneumonia.(3) Nevertheless, generally speaking, there is paucity of information guiding glucocorticoid administration in severe pneumonia and ARDS, which led to a great heterogeneity of treatment protocols and misinterpretation of available findings. Glucocorticoids are a large group of agonist compounds that bind to the glucocorticoid receptor alpha (GRα) producing similar pharmacological response, but their specific anti-inflammatory effect and pharmacological properties are different. Clinical efficacy depends on the magnitude and duration of exposure to GC, including genomic and non-genomic effects. The pharmacological principles guiding prolonged glucocorticoid treatment in ARDS have been recently reviewed.(4,5) Based on RCTs findings, GC plasma concentration-time profiles and pharmacodynamic studies, optimal results are most likely achievable with early intervention and an administration schedule that consists of an initial bolus dose to achieve close-to-maximal GRα saturation, followed by a continuous infusion to maintain high levels of response throughout the treatment period.(6) In addition, patients receiving similar GC doses may experience substantial between-patient variability in plasma concentrations affecting clinical response.(5) GC should be dose-adjusted and administered for a duration targeting clinical and laboratory improvement, followed by dose-tapering to achieve gradual recovery of the suppressed hypothalamic-pituitary-adrenal (HPA) axis. These findings have practical clinical relevance. At present, however, there is no evidence of the superiority of a steroid drug -nor of a therapeutic scheme- compared to the others, due to the lack of comparative studies.

In a recent longitudinal observational study conducted in 14 Italian RHDUs, a protocol with prolonged low-dose methylprednisolone, administered in a subgroup of patients with severe

pneumonia and high levels of systemic inflammation, demonstrated a 71% reduction in mortality and the achievement of other secondary endpoints such as an increase in ventilation-free days by study day 28.(7) The treatment was well tolerated and did not affect viral shedding from the airways.

The main differences between the protocol used in this study and that one used in the RECOVERY trial are: a) the use of a treatment protocol with a strong biochemical and pharmacological rationale, that had already proven effective in reducing mortality in severe pneumonia of both bacterial and viral etiology in previous RCTs; b) the possibility to titrate treatment duration on parameters reflecting clinical severity; c) the slow dosage de-escalation, in order to avoid inflammatory rebound. Furthermore, bioinformatics studies support the greater theoretical efficacy of methylprednisolone over dexamethasone based on their molecular targets during SARS-CoV-2 infection.(8)

In light of these data, the present study aims to compare in hospitalized patients needing noninvasive respiratory support (oxygen supplementation, HFNC, NPPV) the efficacy of methylprednisolone 80 mg in continuous IV infusion over 24 hours for at least 8 days and that of dexamethasone 6 mg IV/PO once daily for 10 days in increasing survival by day 28, as well as in reducing the need and duration for mechanical ventilation.

2.2. Objectives

We hypothesize that in patients hospitalized for COVID-19 pneumonia requiring respiratory support (either oxygen supplementation, HFNC, NPPV), the methylprednisolone protocol is superior to the dexamethasone protocol in improving clinical outcomes.

The primary objective is to assess the efficacy of the methylprednisolone protocol in improving survival by day 28 compared to the dexamethasone protocol.

The secondary objectives are to compare efficacy of the two protocols in achieving:

a) Reduction in the need and duration of mechanical ventilation
b) Reduction in hospital mortality
c) Reduction in the duration of hospitalization
d) Reduction in duration of requirement for oxygen supplementation

Additional end-points include anti-inflammatory potency based on longitudinal reduction in systemic C-reactive protein levels and reduction in disease progression based on the WHO clinical progression scale.(9)

3. Study design

This study is a phase 3 adaptive randomized controlled trial (2 parallel arms, allocation ratio 1:1) implemented during a massive epidemic emergency. Adaptation is a carefully considered

investigational procedure for modifying study parameters while the trial is ongoing, based on a review of the interim data analyses.(10–12)

Our adaptive trial is a sequential random controlled trial, with 2 interim analyses (K=3). We aim to evaluate the safety and efficacy of two different protocol of steroids therapy in adult patients with severe COVID-19.

The trial adaptive framework includes:

a) a 3-stage sequential O'Brien and Fleming design;
b) sample size re-calculation at each stage;
c) binding stopping rule for efficacy according with preplanned critical values;
d) binding stopping rule for futility according with a preplanned critical values.

3.1. Sequential design

Sequential design is a pivotal element of the adaptive strategy that allows for assessing participants data while the trial is ongoing for optimizing trial performance. In this study, we include a 3-stage procedure with two homogeneous interim analyses and one final analysis (K=3). Sequential design is always associated with inflation of statistical error due to multiple comparisons on the same accrued set of data. To control for this bias, we have defined ad hoc statistical plan and define adequate error spending function. When the sample size expected for each interim analysis is reached, patients will continue to be enrolled and randomized until either the results of that interim analysis will be available or the minimum sample size expected for the subsequent stage will be reached.

3.2. Sample size recalculation

The adequacy of sample size is important for clinical trials. However, in the current circumstance there are significant uncertainties about the sizes of parameters that are needed for optimizing study power. To prevent under-powering (i.e. leading to drop of efficacious intervention) and oversizing (leading to expanding time and cost of the study) we will implement a sequential recalculation of the sample size for each one of the three interim analyses.

3.3. Stopping rule for efficacy

Stopping rule for efficacy allows to early terminating the trial if a significant effect of methylprednisolone is already evident in the early analysis. Stopping rule for efficacy implies early rejection of H0 by using accruing data from ongoing trial and thus it is associated with an inflation of type I error. To prevent this issue we have defined a preplanned analysis with predefined critical value and a formal alpha spending function.

3.4. Stopping rule for futility

Stopping rule for futility allows to early terminating the trial if interim analysis does not support the efficacy of methylprednisolone. Stopping rule for efficacy implies early acceptation of H0 by using accruing data form ongoing trial and thus it is associated with an inflation of type II error. To prevent this issue we have defined a preplanned analysis with predefined critical value and a formal beta-spending function.

4. Methods: participants, interventions and outcomes

4.1. Study Setting

This is a multi-center study involving Italian hospitals. The study population will be drawn from any patient admitted to the participating Centers, who tested positive RT-qPCR-positive on at least one upper respiratory swab, bronchial wash or bronchoalveolar lavage. There will be no restrictions on race, gender or ethnicity. Minors (aged <18y) will be excluded in order to simplify the informed consent acquisition procedure.

4.2. Eligibility Criteria

Inclusion criteria are the following:

a) Able to understand and sign the informed consent form
b) SARS-CoV-2 positive on at least one upper respiratory swab or bronchoalveolar lavage
c) PaO2 ≤ 60 mmHg or SpO2 ≤ 90% or on HFNC, CPAP or NPPV at randomization
d) Age ≥ 18 years old at randomization

Exclusion criteria are the following:

a) On invasive mechanical ventilation (either intubated or tracheostomized)
b) Heart failure as the main cause of acute respiratory failure
c) On long-term oxygen or home mechanical ventilation
d) Decompensated liver cirrhosis
e) Immunosuppression (i.e., cancer on treatment, post-organ transplantation, HIV-positive, on immunosuppressant therapy)
f) On chronic steroid therapy or other immunomodulant therapy (e.g., azathioprine, methotrexate, mycophenolate, convalescent/hyperimmune plasma)
g) Chronic renal failure with dialysis dependence
h) Progressive neuro-muscular disorders
i) Cognitively impaired, dementia or decompensated psychiatric disorder
j) Quadriplegia/Hemiplegia or quadriparesis/hemiparesis
k) Do-not-resuscitate order

l) Participating in other clinical trial including experimental compound with proved or expected activity against SARS-CoV-2 infection
m) Any other condition that in the opinion of the investigator may significantly impact with patient's capability to comply with protocol intervention
n) Refuse to participate in the study or absence of signed informed consent form.

4.3. Interventions

All patients who meet the above inclusion and exclusion criteria are randomized to one of the following treatment protocols.

1. Arm 1 (methylprednisolone, MP):
    A. On day 1, loading dose of MP 80 mg IV in 30 minutes, promptly followed by continuous infusion of MP 80 mg/day in 240 mL of normal saline at 10 mL/h.
    B. From day 2 to day 8: infusion of MP 80 mg/day in 240 mL of normal saline at 10 mL/h.
    C. From day 9 and beyond:
        a) If not intubated patient and PaO_2/FiO_2 > 200, taper to MP 20 mg IV in 30 minutes three times a day for 3 days, then MP 20 mg IV twice daily for 3 days, then MP 20 mg IV once daily for 2 days, then switch to MP 16 mg/day PO for 2 days, then MP 8mg/day PO for 2 days, then MP 4mg/day PO for 2 days;
        b) If intubated patient or $PaO_2/FiO_2 \leq 200$ with at least 5 cmH_2O CPAP, continue infusion of MP 80 mg/day in 240 mL of normal saline at 10 mL/h until PaO_2/FiO_2 > 200 then taper as in a)
2. Arm 2 (dexamethasone, DM)
    A. DM 6 mg IV in 30 minutes or PO from day 1 to day 10 or until hospital discharge (if sooner).
    B. After day 10 study treatment is interrupted.

Both methylprednisolone and dexamethasone are licensed in Italy. They have been widely used in clinical practice for many years and have proven efficacy in a variety of syndromes including COVID-19, with limited toxicity or adverse reactions.
Both drugs will be stored and administered in accordance with standard pharmacy procedures; they are both routinely available on the hospital formulary.
Both drugs will be given open label by either intravenous injection diluted to the treating dose in the appropriate diluent or *per os* according to treatment protocol.

4.4. Standard of Care (SoC)

Both groups receive the same SoC. In particular:

- Respiratory support (oxygen therapy, HFNC, NPPV, IMV, ECMO) is granted to all patients and titrated on the failure of the previous line in improving oxygenation (assessed by PaO2/FiO2 ratio) after 24-48 hours.
- Anticoagulation with low molecular weight or unfractionated heparin must be always administered, at either prophylactic or anticoagulant dose according to clinical need (eg, conditions that require guidelines-directed anticoagulation) or pre-existing comorbidities (eg, already on anticoagulants).

Additional therapies are allowed but they must be specified in the appropriate section of the data collection form.

4.5. Outcomes

Primary outcome measure

- Survival proportion at 28 days in both arms

Secondary outcome measures

- Number of days free from mechanical ventilation (either NPPV or IMV) by study day 28 in both arms
- Number of days of hospitalization among survivors in both arms
- Proportion of patients requiring tracheostomy in both arms
- C-reactive protein level (mg/L) at study day 3, 7 and 14 in both arms
- PaO_2/FiO_2 ratio (mmHg) at study day 3, 7 and 14 in both arms
- WHO clinical progression scale at study day 3, 7 and 14 in both arms(9)

4.6. Schedule of assessments

Time-line	Activity/Treatment	Measurements
Day 1	Consent obtained; randomization; study drug administration by randomized group; vital signs monitoring.	SpO2 (%), PaO_2 (mmHg), CRP (mg/L), PaO_2/FiO_2 (mmHg)*, baseline data collection§
Day 3	Treatment continued, as defined above	CRP (mg/L), Worst daily PaO_2/FiO_2 (mmHg)*, WHO clinical progression score
Day 7	Treatment continued, as defined above	CRP (mg/L), Worst daily PaO_2/FiO_2 (mmHg)*, WHO clinical progression score

Day 14	Treatment continued, as defined above	CRP (mg/L), Worst daily PaO_2/FiO_2 (mmHg)*, WHO clinical progression score
Day 28		Patient's outcome determined (mortality, total days of mechanical ventilation, days of invasive mechanical ventilation, days of noninvasive mechanical ventilation) and final data collection°
Hospital discharge		Patient's outcome determined (mortality, days of hospitalization)

* The type of respiratory support (low-flow oxygen therapy, HFNC, NPPV, IMV, ECMO) under which the PaO_2/FiO_2 is obtained must be always specified in the appropriate section of the data collection form.

§ Baseline data should include:

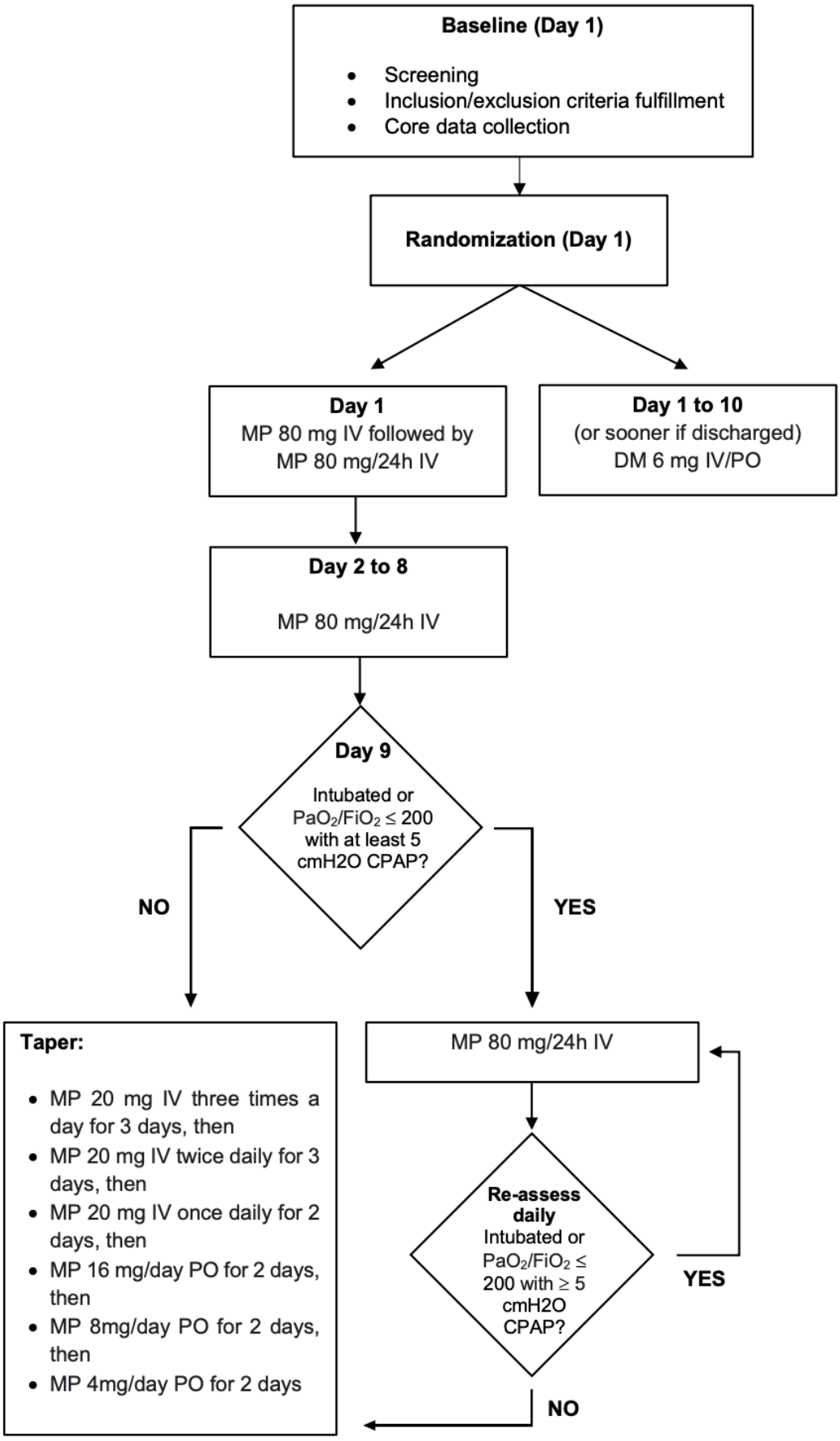
a) Date of birth
b) Sex
c) BMI
d) Smoke (yes/no/former)
e) Date of the onset of symptoms
f) Date of hospitalization
g) Date of randomization
h) Type of respiratory support at randomization (i.e., low-flow oxygen, HFNC, NPPV)
i) Comorbidities (COPD, Bronchiectasis, Asthma, Other respiratory disease, Pre-existing Diabetes, Atrial fibrillation, Coronaropathy, Chronic heart failure, Other relevant disease of the heart and large vessels, Pulmonary embolism/chronic thromboembolism, Other conditions requiring long-term anticoagulation, Systemic hypertension, Autoimmune Disease, OSA/OHS, Chronic Kidney Disease, Minor stroke, History of Cancer)

°Other data to be collected:

a) Date of treatment initiation
b) Date of full-dose treatment completion
c) Date of de-escalation completion
d) Deviation from protocol (yes/no; if yes, date of deviation and reason for deviation)
e) Remdesivir (yes/no)
f) Anticoagulation:
    - LMWH (prophylactic/anticoagulant)
    - Unfractionated heparin
    - Warfarin

- NOAC

g) Relevant in-hospital therapies other than home therapy continuation, prophylactic antibiotics, (specify drug and dosage)
h) NPPV (yes/no; if yes dates of start/end, in case of switch to IMV and then re-initiation of NPPV, enter only the end date of the second NPPV session)
i) IMV (yes/no; if yes dates of start/end)
j) HFNC (yes/no)
k) ECMO (yes/no; if yes specify date of ECMO start and end)
l) Tracheostomy (yes/no; if yes specify date of tracheostomy)
m) Pronation (yes/no)
n) Adverse events related to study treatment (Anaphylaxis, Agitation, Psychosis, Insomnia, Hyperglycemia/diabetes of new onset, Other: specify)
o) In-hospital complications (Bradycardia, Diarrhea, Increased liver enzymes, Hypotension, Hypokalemia, Superinfection – specify microorganism, Shock requiring vasopressors not induced by the study drug, Acute renal failure, Disseminated Intravascular Coagulation, Acute myocardial infarction, Stroke, Atrial fibrillation or other major arrythmias, Cardiorespiratory arrest, Pulmonary embolism, Other: specify).
p) Date of hospital discharge
q) Date of death


Baseline (Day 1)
Screening
Inclusion/exclusion criteria fulfillment
Core data collection
Randomization (Day 1)
Day 1
MP 80 mg IV followed by
MP 80 mg/24h IV
Day 1 to 10
(or sooner if discharged)
DM 6 mg IV/PO
Day 2 to 8
MP 80 mg/24h IV
Day 9
Intubated or
PaO2/FiO2 ≤ 200
with at least 5
cmH2O CPAP?
NO
YES
Taper:
MP 20 mg IV three times a day for 3 days, then
MP 20 mg IV twice daily for 3 days, then
MP 20 mg IV once daily for 2 days, then
MP 16 mg/day PO for 2 days, then
MP 8mg/day PO for 2 days, then
MP 4mg/day PO for 2 days
MP 80 mg/24h IV
Re-assess daily
Intubated or
PaO2/FiO2 ≤ 200 with ≥ 5
cmH2O CPAP?
YES
NO

5. Study procedure

5.1. Assignment of interventions

Randomization will be centralized and coordinated by the University of Trieste. The randomization list will be generated by a study statistician with Stata 14.2 using block randomization. The list will be implemented in the REDCap® randomization module, which allows centralized allocation of patients through the REDCap® web platform and grants allocation concealment. In each participating center the clinician in charge of the randomization will have secure access to the REDCap® web platform and, after checking whether the study inclusion and exclusion criteria are met, will automatically receive the assignment arm for the enrolled patient. This is an open-label trial, therefore, both the clinician and the patient will be aware of the assigned treatment.

5.2. Data collection and management

A clinical database using REDCap® trial data management system will be developed with a web hosting facility. Electronic case report forms (eCRFs) will be developed to collect all clinical and laboratory related information. The trial database will include baseline information, information on demographics (age, gender), underlying illnesses, baseline and follow-up clinical and laboratory data for the purpose of assessment of clinical outcome. All data queries and corrections will be jointly conducted by the study team prior to database lock. The study team at the University of Trieste, Centro di Riferimento Oncologico of Aviano, and the Institute for Infectious Diseases “L. Spallanzani” of Rome will manage the data and will conduct quality control of the data. All analyses performed, the Clinical Study Report(s) and the final data set will be archived together according to the standard operating procedures and the guidelines of the University Hospital of Cattinara.

6. Statistical plan

6.1. Sequential design procedures

This is a sequential open label randomized clinical trial with 2 interim analyses (K=3) with unblinded sample size recalculation (adaptive sample size), stopping rule for early efficacy and stopping rule for futility according to O’Brien and Fleming sequential study design. Stopping rule for either futility or efficacy are bound to specific error spending function according to a Fisher’s exact test calculated on primary outcome.

The experimental hypothesis of the study is that treatment with MP improves 28-day survival from 77% in arm 2 to 87% in arm 1 (i.e. risk difference 10%). If this hypothesis is true, the study has a one tail alpha-error <0.025 and an overall power >90% by using a Fisher’s exact test and critical alpha and beta error value for type I and type II error spending function.

Preplanned critical values and plots are reported in table 1 and figure 1, respectively.

6.2. Sample size

Minimum and maximum sample size will significantly change according to the observed effect within the trial sample (expected **average** sample size is between 200 and 680 participants, figure 2). In particular, we expect to enroll 100 participants per arm at the first stage and then between 15 and 175 per arm for each eventual stage if the stopping rules were not met. The actual number of new participants in each arm will be calculated according to the maximum likelihood estimates on observed efficacy at each interim analysis with an overall conditional power for next stage equal to 90%. This approach allows either to minimize the number of enrolled participants if the experimental hypothesis is too conservative or to have a good power level if the experimental hypothesis is too optimistic. The average sample size with relative power and the overall probability for meeting stopping rules according to different level of efficacy of arm 1 vs. arm 2 are reported in figure 2 and figure 3, respectively.

$$H0: \pi_T - \pi_C = 0$$

Critical values	Stage 1	Stage 2	Stage 3
Reject H0 (Efficacy)	3.421	2.419	1.975
Accept H0 (Futility)	-0.695	1.002	1.975
Information rate	0.333	0.667	1
alpha spent	0.0003	0.0079	0.025

Table 1 Preplanned critical values (Fisher test) for application of early stopping rules

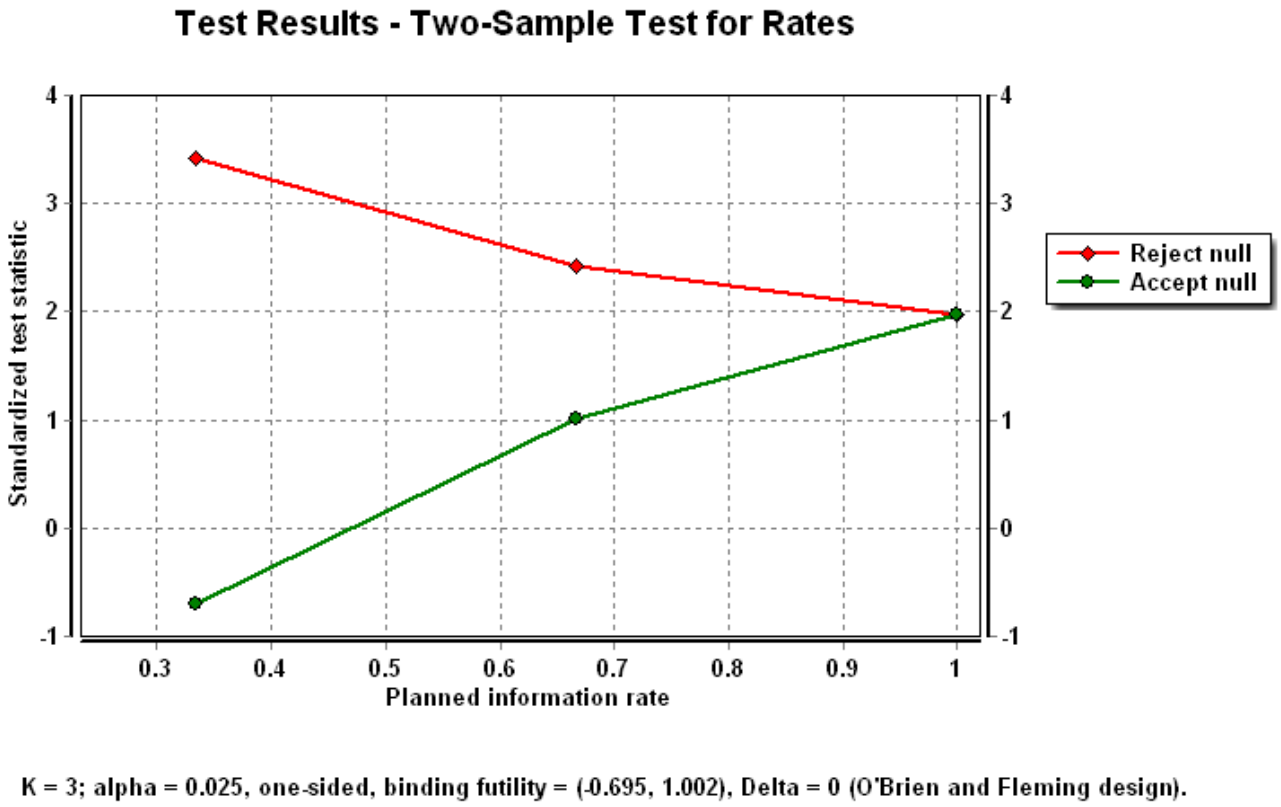


Figure 1 Plot for application of early stopping rule. Uncertainty area (i.e. H0 is neither accepted nor rejected) lies above the green line and below the red lines

6.3. Analysis of efficacy (primary outcome)

Interim analyses and final analysis will be carried out by taking into account the potential effect of each individual component of the adaptive design. The interim analyses will provide:

a) estimate of efficacy as risk difference and relative 95% CI
b) criteria for stopping rules
c) if the stopping rules are not met the analysis will provide the number of participants to be randomized for the subsequent stage in each arm.
d) final analysis will provide efficacy as difference estimate of efficacy as risk difference and relative 95% CI

Subgroup analyses will be carried out if the sample size will allow to. In this case, the following groups will be taken into consideration:

a) Patients requiring only oxygen therapy, either low-flow or high-flow (HFNC) during the study period
b) Patients requiring only low-flow oxygen therapy during the study period;

c) Patients requiring high-flow oxygen therapy (HFNC) but not ventilatory support during the study period
d) Patients requiring mechanical ventilation, either invasive or noninvasive during the study period
e) Patients requiring noninvasive mechanical ventilation but not invasive mechanical ventilation during the study period
f) Patients requiring invasive mechanical ventilation during the study period.

All the analyses will be conducted by the trial statisticians following the intention-to-treat principle. In case of deviations from the study protocol, such as cross-over between arms, sensitivity analysis will be carried out (eg., *per protocol* analysis).

6.4. Analysis of secondary outcomes

Binary variables (i.e., proportion of patients requiring tracheostomy) will be modelled according to separate logistic regression models to assess the potential effect of each different treatment arm. All models will be adjusted for the effect of age and gender in the case of unbalanced groups following randomization.

Continuous variables including the number of days free from mechanical ventilation, number of days of hospitalization, C-reactive protein level (mg/L) at study day 3, 7, 14 and PaO_2/FiO_2 ratio (mmHg) at study day 3, 7 and 14 after randomization will be modelled by linear regression models and the estimates will be given adjusted for age and sex in the case of unbalanced groups following randomization.

6.5. Software for simulation and analysis

Study design, simulations, interim analysis and final analysis of primary outcome will be carried out by ICON ADDPLAN V 6.1. This is a proprietary statistical package that contains approved algorithm for dealing with the adaptive design according to EMA and FDA standards. The analysis of secondary outcomes will be carried out at the end of the trial and will be carried out by STATA V.15.

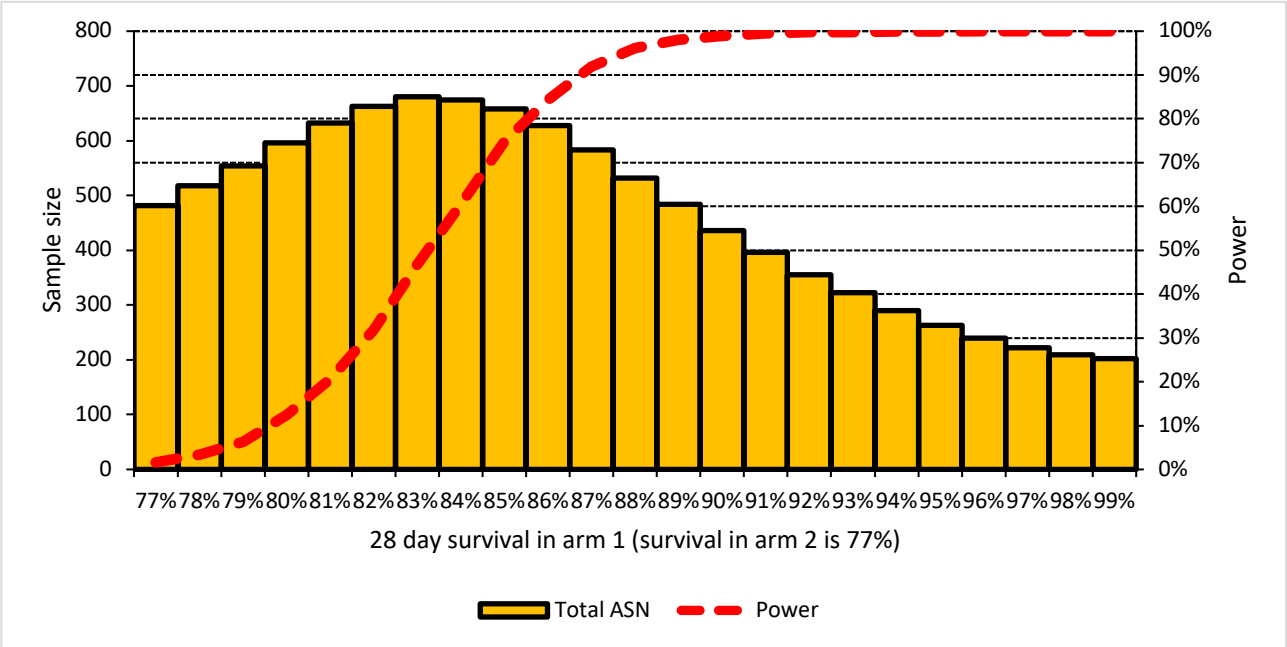


Figure 2 Adaptive sample size and power. *The yellow bars represent the number of patients to be enrolled in the trial. Red dotted line shows the study power (i.e. the probability to detect a real difference between arm 1 and arm 2 if arm 1 is superior to arm2 is). Simulation has been carried out assuming 1:1 ratio between arms; first analysis is carried out at 200 patients; adaptive sample size between 30-350 and p-value calculated according Fisher exact statistics conditional power for next analysis 90%; K=3 (i.e. 2 interim analysis and one final analysis).*

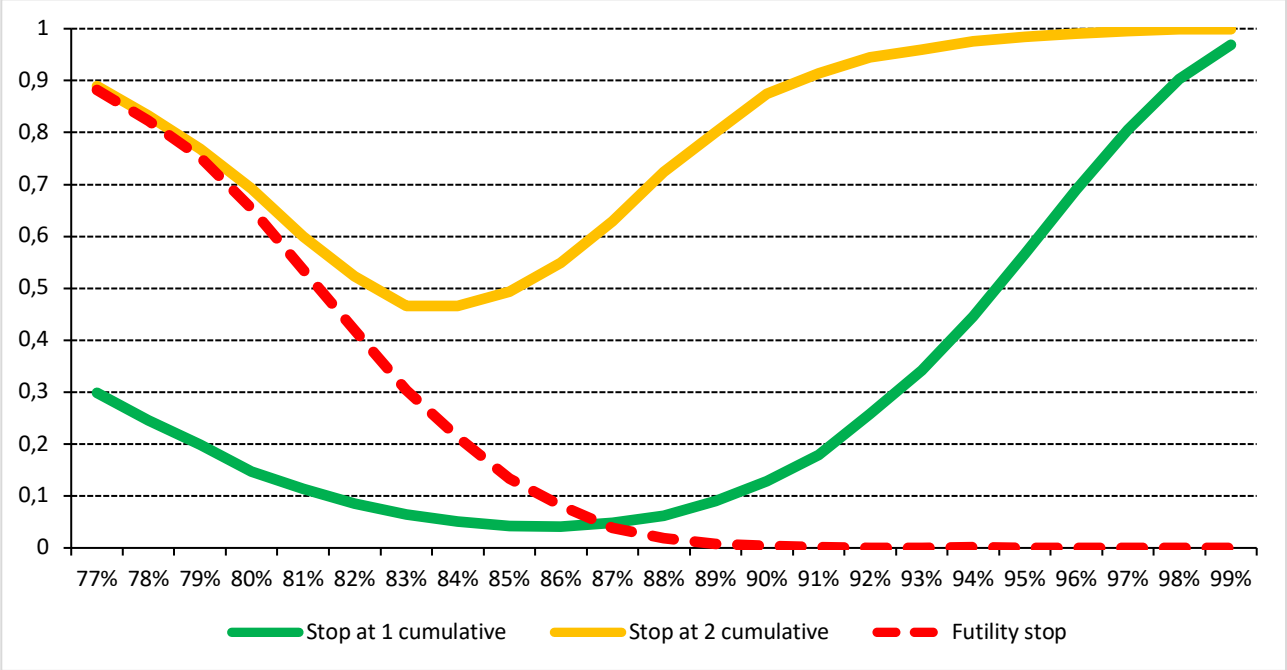


Figure 3 Cumulative probability of trial termination*. Continuous lines show the cumulative probability of* ***early termination*** *either at first (green line) or second (yellow line) interim analysis. Early termination at both stages can be driven either by efficacy (i.e. reject H0) or futility (i.e. accept H0). The red dotted line shows the cumulative probability to* ***termination for futility*** *regardless the stage of analysis (i.e. at first interim, second interim of final analysis).*

7. Safety measurements

7.1. Definitions

An adverse event is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.”

Events will be reviewed and classified by the site PI. The relationship of the event to the study drug and whether the event is an expected event or not will be assessed using the listing of adverse effects contained in the summary of product characteristics for the glucocorticoid drugs used.

The treating team has the primary responsibility for reviewing laboratory test results and determining whether an abnormal value in an individual study participant requires action. In general, abnormal laboratory without clinical significance (based on clinical judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse. The investigators should liaise closely with the treating teams and remain aware of any such adverse events.

Serious adverse event (SAE) are defined as an adverse event that:

- Is fatal
- Is life threatening (places the participant at immediate risk of death
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Causes a congenital anomaly/birth defect
- Other significant medical hazard

However, since both the study drugs have been in wide clinical use for many years, their effects and possible adverse events are well recognized. As such, although adverse events may occur, we would not anticipate that they would be unexpected or widely divergent from established frequencies. Rarely, life threatening adverse reactions can occur with the use of any glucocorticoid. Other serious adverse events might include hyperglycemia, psychosis, depression or other psychic disorder, increased liver enzymes, venous thrombosis, wound healing impairment. However, multiple meta-analyses, involving thousands of critically ill patients with sepsis or ARDS, have demonstrated a relatively low-dose and short treatment courses like the ones proposed in this study are rarely associated with serious complications.(13)

All deaths and SAEs will be notified to the local PI and site research governance, along with the DSMB, who will then notify the Italian Regulatory Agency (AIFA). Unforeseen adverse events will be discussed with collaborating investigators at other Centers; such information will be regularly reviewed. If any member of the trial team becomes aware of an unexpected death or serious adverse

event at any stage of the trial review period, the PI will be alerted. All deaths and adverse events will be recorded and reported in the final analysis.

7.2. Collecting, Recording and Reporting of "Serious Adverse Event (SAE)/Safety/Suspected Unexpected Serious Adverse Reaction (SUSAR)")

Any events that are unexpected (in terms of severity or frequency), that can reasonably be attributed to the drug under study and that may expose other subjects to harm will be reported. SAE/Safety/SUSAR events refers to problems, in general, to include any incident, experience, or outcome (including adverse events) that meets ALL of the following criteria:

1. Unexpected
   In terms of nature, severity or frequency of the problem as described in the study documentation (e.g., protocol, consent documents etc.);
2. Related or possibly related to participation in the research
   Possibly related means there is a reasonable possibility that the problem may have been caused by the procedures involved in the research;
3. Risk of harm
   Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reporting Timeline for SAE/Safety/SUSAR Events:

1. Urgent Reporting: all problems involving local deaths, whether related or not to the study drug, should be reported immediately – within 24 hours after first knowledge by the local investigator.
2. Expedited Reporting: All other problems must be reported as soon as possible but not later than 7 calendar days after first knowledge by the local investigator.

7.3. Safety Monitoring Plan

A DSMB will be established, comprising four independent physicians with statistical support provided to them by the Institute for Infectious Diseases "L. Spallanzani". The trial statisticians will provide details of safety outcomes and any significant differences in primary outcomes according to treatment arm to the DSMB at any scheduled interim analysis. The stopping rule will be a statistically significant difference in primary outcomes between the two arms. The interim analysis results will be communicated to the trial team along with the DSMB recommendations for action. If there is a significant safety concern will be raised, the DSMB may recommend to the Principal Investigator that the trial should be stopped.

8. Ethical considerations

8.1. Research ethics approval

The trial will not commence until a Clinical Trial Authorization (CTA) is obtained from the National Ethics Committee and the local Ethics Committee for the Coordinating Centre (University Hospital of Cattinara). The protocol and trial conduct will comply with the Declaration of Helsinki (last revision, Fortaleza 2013), the Good Clinical Practice (ICH E6 Guideline for Good Clinical Practice, 1996), Italian laws and European Regulations. Ethics Committee sand regulatory authorities will be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements

8.2. Informed Consent

The study team representative will approach the patient at the bedside. All co-investigators will be allowed to obtain informed consent from subjects. Patients will be given adequate time to consider their options. Although patients may still be unwell at the time of recruitment, informed consent will only be obtained if it is judged that the patient has capacity to make an informed choice. It will be made clear to patients that the study team are not in overall control of their clinical care, which will in no way be affected by their refusal to participate. The person taking consent will not exert undue influence or coerce potential recruits - this will be reinforced to team members by the PI and co-investigators. Patients will be given every opportunity to reverse their decision to enrol in the study. For non-Italian speakers, qualified translators will be provided as per local hospital protocols. For non-literate subjects, an impartial witness will be asked to certify in writing that the study has been explained in language that the subject understands and that he/she has agreed to participate in the study. Cognitively-impaired patients are excluded from this trial according to exclusion criteria. Patients should be offered the chance to receive a written summary of the trial after completion and publication should they wish – if so, a record of the contact details will be kept for this purpose.

8.3. Confidentiality of data and patient records

Study data will be collected and treated in accordance with the European Regulation for data protection no. 679/2016 (General Data Protection Regulation - GDPR) and Italian laws (d.lgs. 101/2018 and d.lgs. 196/2003). An anonymous identification code (i.e., progressive number) will be automatically assigned through the REDCap® web platform to any patient at enrollment and will be reported in the case report form (CRF). Encrypted transmission of data will be granted by the use of the REDCap® web platform. All study findings and documents will be regarded as confidential. The investigators and other study personnel must not disclose such information without prior written approval from the Principal Investigator. Subject confidentiality will be strictly maintained to the

extent possible under the law and local hospital policy. Identifiable information will be removed from any published data.

8.4. Publications

The data obtained from all participating sites will be pooled and analyzed together as soon as possible after trail completion. Individual researchers will not publish data from the trial until the main study publication has been released.

8.5. Retention of trial documents

Any electronic data records will be password-protected and stored on a server of the Coordinating Center. The PI will keep any paper-based records, study files or source documentation in a locked cabinet within the department. These records, electronic and physical, will be kept for a minimum of 10 years after the completion of the trial before being destroyed or erased. These documents will be retained for a longer period if required by the applicable regulatory requirements or institutional policy.

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