

University of Groningen

Optimal Dosing and Timing of High-Dose Corticosteroid Therapy in Hospitalized Patients With COVID-19

PRoVENT- and PRoAcT-COVID Collaborative Group; Daenen, Katrijn; Huijben, Jilske A; Boyd, Anders; Bos, Lieuwe D J; Stoof, Sara C M; van Willigen, Hugo; Gommers, Diederik A M P J; Moeniralam, Hazra S; den Uil, Corstiaan A

Published in:
JMIR research protocols

DOI:
[10.2196/48183](https://doi.org/10.2196/48183)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

PRoVENT- and PRoAcT-COVID Collaborative Group, Daenen, K., Huijben, J. A., Boyd, A., Bos, L. D. J., Stoof, S. C. M., van Willigen, H., Gommers, D. A. M. P. J., Moeniralam, H. S., den Uil, C. A., Juffermans, N. P., Kant, M., Valkenburg, A. J., Pillay, J., van Meenen, D. M. P., Paulus, F., Schultz, M. J., Dalm, V. A. S. H., van Gorp, E. C. M., ... Endeman, H. (2023). Optimal Dosing and Timing of High-Dose Corticosteroid Therapy in Hospitalized Patients With COVID-19: Study Protocol for a Retrospective Observational Multicenter Study (SELECT). *JMIR research protocols*, 12, Article e48183. <https://doi.org/10.2196/48183>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Protocol

Optimal Dosing and Timing of High-Dose Corticosteroid Therapy in Hospitalized Patients With COVID-19: Study Protocol for a Retrospective Observational Multicenter Study (SELECT)

Katrijn Daenen^{1,2}, MD; Jilske A Huijben¹, MD, PhD; Anders Boyd^{3,4,5}, PhD; Lieuwe D J Bos^{6,7}, MD, PhD; Sara C M Stoof¹, MD, PhD; Hugo van Willigen⁸, MD; Diederik A M P J Gommers¹, MD, PhD; Hazra S Moeniralam⁹, MD, PhD; Corstiaan A den Uil¹⁰, MD, PhD; Nicole P Juffermans^{11,12}, MD, PhD; Merijn Kant^{13,14}, MD; Abraham J Valkenburg¹⁵, MD, PhD; Janesh Pillay^{16,17}, MD, PhD; David M P van Meenen^{6,18}, MD, PhD; Frederique Paulus^{6,19}, PhD; Marcus J Schultz^{6,7}, MD, PhD; Virgil A S H Dalm^{20,21}, MD, PhD; Eric C M van Gorp^{2,22}, MD, PhD; Janke Schinkel⁸, MD, PhD; Henrik Endeman¹, MD, PhD; PRoVENT- and PRoAcT-COVID Collaborative Group²³

¹Department of Intensive Care, Erasmus University Medical Center, Rotterdam, Netherlands

²Department of Viroscience, Erasmus University Medical Center, Rotterdam, Netherlands

³Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands

⁴HIV Monitoring Foundation, Amsterdam, Netherlands

⁵Infectious Diseases, Amsterdam University Medical Centers, location University of Amsterdam, Amsterdam, Netherlands

⁶Department of Intensive Care, Amsterdam University Medical Centers, location Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

⁷Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Centers, location Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

⁸Department of Medical Microbiology & Infection Prevention, Amsterdam University Medical Centers, location University of Amsterdam, Amsterdam, Netherlands

⁹Department of Internal Medicine and Intensive Care, St Antonius Hospital, Nieuwegein, Netherlands

¹⁰Department of Intensive Care, Maastrad Ziekenhuis, Rotterdam, Netherlands

¹¹Department of Intensive Care, Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, Netherlands

¹²Laboratory of Translational Intensive Care, Erasmus University Medical Center, Rotterdam, Netherlands

¹³Department of Pulmonology, Amphia Hospital, Breda, Netherlands

¹⁴Department of Intensive Care, Amphia Hospital, Breda, Netherlands

¹⁵Department of Anesthesiology and Intensive Care, Isala Clinics, Zwolle, Netherlands

¹⁶Department of Intensive Care, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

¹⁷Department of Pathology and Medical Biology, Groningen Research Institute for Asthma and Chronic Obstructive Pulmonary Disease, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

¹⁸Department of Anesthesiology, Amsterdam University Medical Centers, location Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

¹⁹Center of Expertise Urban Vitality, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, Netherlands

²⁰Department of Immunology, Erasmus University Medical Center, Rotterdam, Netherlands

²¹Division of Allergy & Clinical Immunology, Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands

²²Department of Internal Medicine, Erasmus University Medical Center, Erasmus, Netherlands

²³See Acknowledgements

Corresponding Author:

Katrijn Daenen, MD

Department of Intensive Care

Erasmus University Medical Center

Dr. Molewaterplein 40

Rotterdam, 3015 GD

Netherlands

Phone: 31 107038737

Email: k.daenen@erasmusmc.nl

Abstract

Background: In hospitalized patients with COVID-19, the dosing and timing of corticosteroids vary widely. Low-dose dexamethasone therapy reduces mortality in patients requiring respiratory support, but it remains unclear how to treat patients when this therapy fails. In critically ill patients, high-dose corticosteroids are often administered as salvage late in the disease course, whereas earlier administration may be more beneficial in preventing disease progression. Previous research has revealed that increased levels of various biomarkers are associated with mortality, and whole blood transcriptome sequencing has the ability to identify host factors predisposing to critical illness in patients with COVID-19.

Objective: Our goal is to determine the most optimal dosing and timing of corticosteroid therapy and to provide a basis for personalized corticosteroid treatment regimens to reduce morbidity and mortality in hospitalized patients with COVID-19.

Methods: This is a retrospective, observational, multicenter study that includes adult patients who were hospitalized due to COVID-19 in the Netherlands. We will use the differences in therapeutic strategies between hospitals (per protocol high-dose corticosteroids or not) over time to determine whether high-dose corticosteroids have an effect on the following outcome measures: mechanical ventilation or high-flow nasal cannula therapy, in-hospital mortality, and 28-day survival. We will also explore biomarker profiles in serum and bronchoalveolar lavage fluid and use whole blood transcriptome analysis to determine factors that influence the relationship between high-dose corticosteroids and outcome. Existing databases that contain routinely collected electronic data during ward and intensive care admissions, as well as existing biobanks, will be used. We will apply longitudinal modeling appropriate for each data structure to answer the research questions at hand.

Results: As of April 2023, data have been collected for a total of 1500 patients, with data collection anticipated to be completed by December 2023. We expect the first results to be available in early 2024.

Conclusions: This study protocol presents a strategy to investigate the effect of high-dose corticosteroids throughout the entire clinical course of hospitalized patients with COVID-19, from hospital admission to the ward or intensive care unit until hospital discharge. Moreover, our exploration of biomarker and gene expression profiles for targeted corticosteroid therapy represents a first step towards personalized COVID-19 corticosteroid treatment.

Trial Registration: ClinicalTrials.gov NCT05403359; <https://clinicaltrials.gov/ct2/show/NCT05403359>

International Registered Report Identifier (IRRID): DERR1-10.2196/48183

(*JMIR Res Protoc* 2023;12:e48183) doi: [10.2196/48183](https://doi.org/10.2196/48183)

KEYWORDS

COVID-19; corticosteroid; infectious diseases; virology

Introduction

Background

The emergence of SARS-CoV-2 in Wuhan caused a global COVID-19 pandemic, with a high mortality and morbidity rate worldwide [1]. Over the past years, many efforts have been made to unravel the underlying complex pathophysiological mechanisms and explore various treatment options. Substantial variation exists in systemic and alveolar levels of inflammation between patients, contributing to the heterogeneous clinical course of the disease. This ranges from asymptomatic infection to life-threatening hypoxemic pneumonia. Corticosteroid therapy has the potential to inhibit disease progression and decrease the severity of clinical symptoms and is first-line immunosuppressive therapy in patients with COVID-19 with hypoxia [2].

The main reason for hospitalization of patients with COVID-19 is the requirement of supplemental oxygen therapy because of hypoxemia. In some patients, ground glass opacification and the beginning of consolidations on pulmonary CT scan are observed [3], accompanied by increased parameters of inflammation and coagulation in bronchoalveolar lavage fluid (BALF) and the systemic compartment [4,5]. In case of progressive respiratory failure, patients with COVID-19 will

be admitted to the intensive care unit (ICU). These patients have a significantly decreased partial pressure of oxygen in arterial blood—fraction of inspiratory oxygen concentration ratio and frequently fulfill the Berlin criteria of moderate and severe acute respiratory distress syndrome (ARDS) [6]. Analysis of their inflammatory profiles shows a further elevation of proinflammatory cytokines, which is associated with increased mortality [7,8].

For decades, corticosteroids are given to treat patients with non-COVID-19 ARDS because of their strong anti-inflammatory effects [9]. Among patients with COVID-19, the Randomized Evaluation of Covid-19 Therapy (ie, RECOVERY) study showed that low-dose dexamethasone reduces mortality in patients requiring supplemental oxygen therapy or invasive mechanical ventilation but not in patients without respiratory support [10]. Current COVID-19 guidelines recommend a dose of 6 mg of dexamethasone per day for 10 days when oxygen therapy is required, regardless of the level of inflammation or severity of the disease [2]. Unfortunately, a proportion of patients still show progressive deterioration despite this treatment.

In these dexamethasone-unresponsive patients with COVID-19, corticosteroid therapy is sometimes escalated to a much higher dose. However, large heterogeneity in the type, timing, and

dosing of escalated corticosteroid therapy exists [11]. High-dose corticosteroids are mainly administered during the late phase of the clinical course and in patients with the most severe disease, while earlier administration could be beneficial in preventing disease progression. However, the results of the studies on high-dose corticosteroid treatment for critically ill patients with COVID-19 are contradicting [12-15]. A recent meta-analysis compared high-dose corticosteroids versus low-dose corticosteroids in hospitalized patients with COVID-19 and reported no difference in mortality. Given the low level of evidence, inconclusive trial sequential analysis, and substantial heterogeneity, the authors stress the importance of future research to improve the certainty of evidence [16].

Treatment with high-dose corticosteroids may come at the cost of complications, such as secondary infections due to the immunosuppressive effects. To better predict the response to high-dose corticosteroids prior to therapy, additional diagnostic tools such as serum and BALF biomarker determination and whole blood transcriptome analysis could be helpful [17]. Implementation of these tools may result in a more precise and individualized approach to corticosteroid dosing in clinical practice.

Overall, the optimal dosing and timing of high-dose corticosteroids in hospitalized patients with COVID-19 remains uncertain. Here, we present the study design and methodological

considerations of the SELECT (Steroids in Hospitalized Patients with COVID-19 in The Netherlands) study, a multicenter study that aims to study the most optimal dosing and timing of corticosteroid therapy to reduce the morbidity and mortality of hospitalized patients with COVID-19. In addition, we aim to provide a basis for personalized corticosteroid treatment regimens by exploring the predictive value of biomarkers and whole blood transcriptome analysis. We hypothesize that the effect of corticosteroid therapy on outcome is determined by the dosage and timing of administration, as well as the patient's underlying inflammatory state.

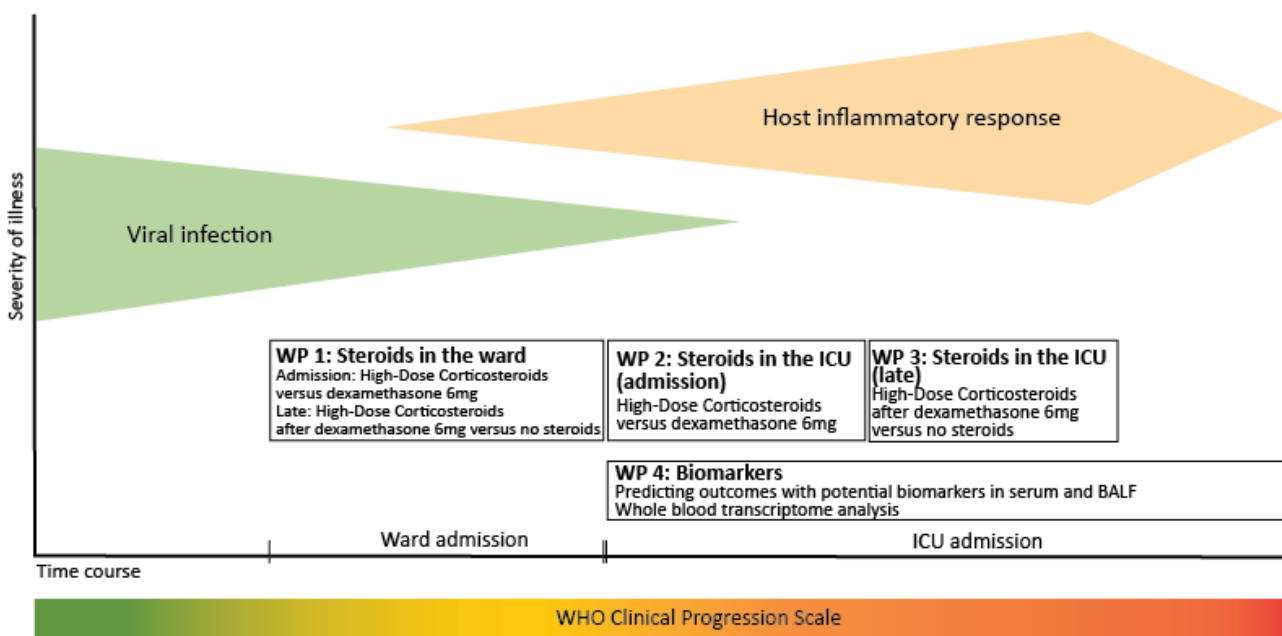
Study Aims

Work Package 1: High-Dose Corticosteroid Treatment in the Ward

Work package 1A (WP1A) is used to investigate whether initial treatment with high-dose corticosteroids compared to treatment with 6 mg dexamethasone per day for 10 days, or an equivalent corticosteroid, improves patient outcomes in the ward (Figure 1).

WP1B is used to investigate whether treatment with high-dose corticosteroids compared to no corticosteroids, after treatment with 6 mg dexamethasone per day for 10 days, improves patient outcomes in the ward.

Figure 1. Integration of work packages in the Steroids in Hospitalized Patients with COVID-19 in The Netherlands (SELECT) study. On the y-axis, the viral and host inflammatory response are depicted. On the x-axis, the admission to the ward or intensive care unit (ICU) is shown, and below that, the World Health Organization (WHO) clinical progression scale is displayed as a measure of supplemental oxygen therapy. steroids: corticosteroids; HDS: high-dose corticosteroids; WP: work package.



Work Package 2: High-Dose Corticosteroid Treatment in the ICU

Work package 2 (WP2) is used to investigate whether initial treatment with high-dose corticosteroids compared to treatment

with 6 mg dexamethasone per day for 10 days, or an equivalent corticosteroid, improves patient outcomes in the ICU.

Work Package 3: High-Dose Corticosteroid Treatment After Standard Corticosteroid Treatment in the ICU

Work package 3 (WP3) is used to investigate whether treatment with high-dose corticosteroids compared to no corticosteroids, after treatment with 6 mg dexamethasone per day for 10 days, improves patient outcomes in the ICU.

Work Package 4: Biomarker Profiles and Whole Blood Genome Transcriptomes in High-Dose Corticosteroid Treatment

Work package 4a (WP4a) is used to investigate whether biomarker profiles in serum and BALF act as response predictors for high-dose corticosteroids on the outcome.

WP4b is used to investigate whether whole blood transcriptome analysis acts as a response predictor for high-dose corticosteroids on the outcome.

Methods

Definition High-Dose Corticosteroids

High-dose corticosteroids are defined as every treatment with dexamethasone >6 mg daily or an equivalent corticosteroid (Table 1). Regarding prior and continuing use of corticosteroids for other conditions, corticosteroids are considered as part of the COVID-19-related intervention when the high-dose threshold is passed.

Table 1. Equivalent corticosteroids and dosages (total daily dosing)^a.

Drug	Equivalent dose (mg)	Low-dose (mg)	High-dose (mg)
Dexamethasone	0.75	≤6	>6
Cortisone	25	≤200	>200
Hydrocortisone	20	≤160	>160
Prednis(ol)one	5	≤40	>40
Methylprednisolone	4	≤32	>32
Bethamethasone	0.75	≤6	>6

^aThis table shows the equivalent corticosteroids and dosages. The equivalent dose is derived from Farmacotherapeutisch Kompas [18].

Study Design and Setting

The SELECT study is a retrospective cohort study with data from 22 hospitals in the Netherlands, including 4 academic and 18 nonacademic hospitals (Figure 2). Other hospitals may be included as the study progresses and we will use routinely collected electronic data from the participating hospitals. The data sets will contain data on hospitalized patients with COVID-19 from the date the first patient was admitted to the hospital in the Netherlands (March 1, 2020) until data transfer (expected May-December 2023). We will use the heterogeneity

in therapeutic regimens in time (ie, first, second, and third epidemiological wave), centers (per protocol high-dose corticosteroids or not), and individual patients in the initial databases to address our aims. In a subpopulation of patients, we will use biobank material collected within the Collaboration on Identification, Understanding and Improved Management of patients with infectious diseases study of the Erasmus MC or collected at the Amsterdam University Medical Center (UMC) within the MERMAIDS-ARI, VIS cohort study or the Amsterdam UMC COVID-19 biobank.

Figure 2. Participating hospitals of the Steroids in Hospitalized Patients with COVID-19 in The Netherlands (SELECT) study. UMC: University Medical Center. MC: Medical Center; OLVG: Onze Lieve Vrouwe Gasthuis.

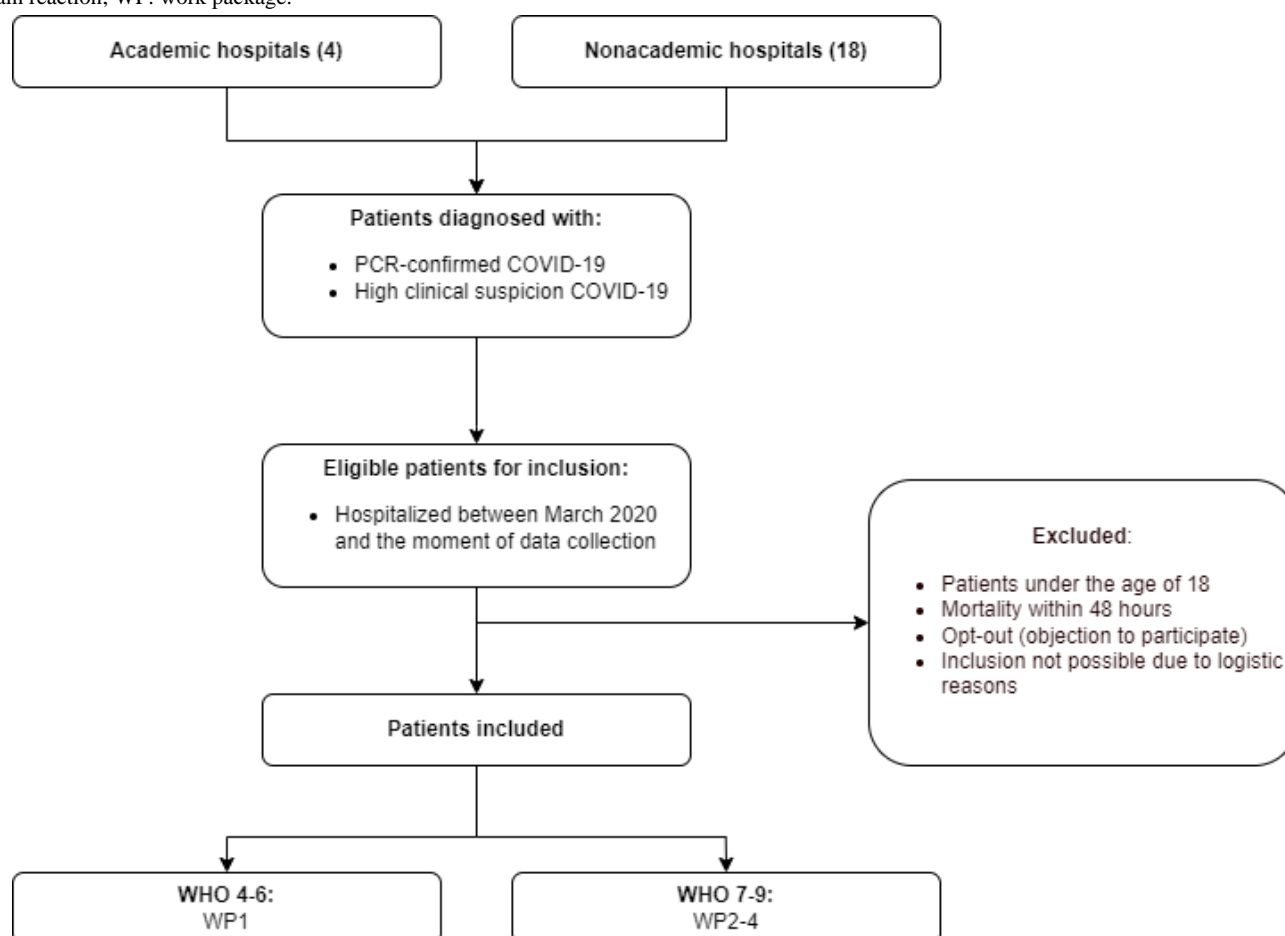


Patient Selection and Inclusion Criteria

Adult patients (≥ 18 years) hospitalized with polymerase chain reaction–confirmed COVID-19 or high clinical suspicion of COVID-19 will be included (Figure 3). Pregnant patients and patients receiving corticosteroids for other conditions during or prior to hospital admission are eligible, although a prespecified sensitivity analysis excluding these patients will be performed. Patients who die within 48 hours after admission or patients who object to participate will be excluded from the study. In WP1 and WP4, we will include patients from all SARS-CoV-2 epidemic waves, and in WP2-3, we will include patients from the first and second waves only. Specific inclusion and exclusion criteria for each work package will be applied. In WP1A, patients will be included who are admitted to the ward with a

World Health Organization clinical progression scale class of 4-5 [19] (ie, no oxygen or oxygen therapy via a cannula or [non-rebreather] mask). WP1B includes patients who have progressed to the World Health Organization clinical progression scale class of 5-6 (ie, noninvasive oxygen therapy, including conventional oxygen via cannula [non-rebreather] mask, high-flow nasal cannula, noninvasive continuous positive airway pressure, and noninvasive bilevel positive airway pressure) after in-hospital treatment with 10 days of 6 mg per day dexamethasone. The study population for WP2-4 consists of patients admitted to the ICU for a period exceeding 48 hours, who received invasive mechanical ventilation via an endotracheal tube, a tracheostomy, or extracorporeal membrane oxygenation during their ICU stay.

Figure 3. Patient inclusion. World Health Organization (WHO) classification: 0=uninfected, 1=asymptomatic; viral RNA detected, 2=symptomatic; independent, 3=symptomatic; assistance needed, 4=hospitalized; oxygen by mask or nasal prongs, 5=hospitalized; oxygen by mask or nasal prongs, 6=hospitalized; oxygen by noninvasive ventilation or high flow, 7=intubation and mechanical ventilation partial pressure of oxygen in arterial blood–fraction of inspiratory oxygen concentration (PaO₂/FiO₂) ratio of ≥ 150 , 8=mechanical ventilation PaO₂/FiO₂ ratio of <150 or vasopressors, 9=mechanical ventilation PaO₂/FiO₂ ratio of <150 and vasopressors, dialysis or extracorporeal membrane oxygenation, 10=dead. PCR: polymerase chain reaction; WP: work package.



Ethics Approval and Consent to Participate

The study will be conducted according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and in accordance with Erasmus MC Research code, Netherlands Code of Conduct for Research Integrity, General Data Protection Regulation, Code of Conduct for Health Research (not subjected to the Medical Research Involving Human Subjects Act [non-WMO]), Code of Conduct for Responsible Use of Human Tissue (Non-WMO), and Medical Treatment Contracts Act. The study was approved by the Medical Research Ethics Committee from Erasmus University Medical Center (MEC-2022-0297) and the local review boards of all other participating centers. Regarding informed consent procedure: within the Erasmus MC, a consent waiver was provided by the Medical Research Ethics Committee for research including patients with COVID-19 due to the pandemic (exception due to emergency situation). Therefore, an opt-out informed consent procedure will be used in the participating centers, and subjects with registered objections to participate will be excluded from the study. This opt-out registration method was approved by the Medical Research Ethics Committee from Erasmus University Medical Center (MEC-2022-0297). Each center is

responsible for appropriate informed consent procedures, which are covered in the data transfer agreements. Regarding the biobank data, only biobank material collected within the Collaboration on Identification, Understanding and Improved Management of patients with infectious diseases study of the Erasmus MC (METC number primary application: 2017-0417 and amendment 2020-0222) and samples collected at the Amsterdam UMC within the MERMAIDS-ARI (NL54834.018.15), VIS cohort study (NL73759.018.20), and the Amsterdam UMC COVID-19 biobank will be used.

Data Collection

In WP1, variation in corticosteroid treatment protocols on the ward between centers is evaluated via questionnaires and extraction of data from the electronic patient record. The focus lies on collecting data from centers that use high-dose corticosteroids on the ward directly after admission and subsequently collecting data from centers with low-dose regimens as a comparison. For the data collection of ICU patients (WP2-3), a collaboration with 2 large COVID-19 study groups is started: the Practice of Ventilation in COVID-19 study (ie, PROVENT-COVID) study and the “Practice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019” (PROACT-COVID) study [20,21]. The data of

interest will be collected in Castor EDC [22], and it will be imported from each center via a secured data transfer system. Corticosteroid data will be collected on a daily basis including type, dose, and administration route. Regarding biobank WP4, a number of serum biomarker levels were already determined during standard COVID-19 care. In case of missing measurements, the stored samples (Tempus tubes) in the biobank can be used. The BALF was collected during routine COVID-19 care in the Amsterdam University Medical Centers and saved in aliquots at -80°C for further analysis. SARS-CoV-2 viral load will be measured in BALF by using an in-house reverse transcription polymerase chain reaction. Subsequently, other commercially and generally available biomarkers might be determined in serum and BALF later by using a multiplex assay, such as Luminex. For the whole genome transcriptomes analysis, material was collected and saved in blood RNA Tempus tubes.

Interventions

Patients were administered with >6 mg dexamethasone or an equivalent corticosteroid for a minimum of 3 consecutive days (Table 1). Our study permits the use of other general concurrent interventions, such as venous thromboembolism prophylaxis, fever and glucose control, fluid management, antibiotics, and antiviral drugs. The use of other immunomodulatory agents such as baricitinib, JAK inhibitors, and interleukin 6 pathway inhibitors, as well as antiviral drugs such as remdesivir, is allowed as part of a clinical trial or hospital policy. However, a sensitivity analysis will be performed excluding these patients.

Outcomes

Primary Outcomes

Several outcome parameters will be studied for the different work packages based on the available data. In WP1A, the primary outcome of interest is hospital mortality in patients who do not receive high-flow nasal canule or invasive mechanical ventilation due to restrictions in care, either on medical grounds or advance directives of the patient. In patients who do not have restrictions in care, the need for high-flow nasal canule or invasive mechanical ventilation will be the primary outcome of interest (WHO severity 6-9). In WP1B, WP2, and WP3, 28-day survival and 28-day need for invasive mechanical ventilation will be studied as primary outcomes. In WP4, we will study the response to corticosteroids using the same outcomes.

Secondary Outcomes

Secondary outcomes for the ICU work packages include ICU mortality; in-hospital mortality; hospital length of stay (the number of days from the date of ICU admission to date of ICU discharge or death); mechanical ventilation duration (total duration of mechanical ventilation in days); and ventilator-free days, and alive at day 28. In all 4 work packages, we will evaluate the incidence of general systemic complications during the hospital stay as a secondary outcome, including myocardial infarction, deep venous thrombosis, pulmonary embolus, hyperglycemia, acute kidney injury, and sepsis. The definition of the various general systemic complications is shown in Table S1 in [Multimedia Appendix 1](#).

Statistical Analysis

Data will be analyzed on a convenience sample. No sample size calculations are considered for the study nor will they be provided post hoc [23]. The use of high-dose corticosteroids will be defined as a dichotomous variable (yes or no) in primary analysis and as a continuous variable in secondary analysis.

To study between-center variation in corticosteroid dosing strategy, the proportion of individuals who received high-dose corticosteroids will be compared across hospitals. Determinants of receiving high-dose corticosteroids will be evaluated using a multivariable logistic regression model with study center forced in the model. Whether the effects of significant determinants are different across centers will be tested through a determinant \times center interaction term added for each determinant, separately.

In WP1, WP2, and WP3, several statistical analysis approaches will be considered to determine the association between high-dose corticosteroids and outcome, and statistical analyses will depend on the structure of the available data. A multivariable logistic regression model will be used with high-dose corticosteroids as exposure and survival at day 28 as an outcome. Covariates used for adjustment will include age, gender, BMI, smoking status, prior administration of corticosteroids during admission, comorbidity, sequential organ failure assessment score, oxygen saturation, partial pressure of oxygen in arterial blood–fraction of inspiratory oxygen concentration ratio, C-reactive protein, procalcitonin, ferritin, interleukin 6, D-dimer, lactate dehydrogenase, platelet count, lymphopenia, and level of respiratory support. Covariates can be added or removed based on insights from the data set or from the literature. A model might be constructed in which patients are matched on a propensity score based on their probability to receive high-dose corticosteroid treatment. Propensity scores will be determined using a logistic regression model with high-dose corticosteroids as a dependent variable and determinants of high-dose corticosteroids as independent variables. After matching, survival and mortality at day 28 and other outcome parameters will be compared between matched groups using logistic regression. A Cox proportional hazards model might be performed to determine the effect of high-dose corticosteroids on time to death while taking into account the days of administration using time-dependent covariates. Other approaches involving censoring weights for differential loss to follow-up (eg, marginal structural models) or competing risks (eg, joint models) might be explored.

Furthermore, we will use clinical and biological data to perform latent class analysis to search for subphenotypes, which respond more favorably to corticosteroid treatment. This heterogeneity of treatment effect will be evaluated by including the latent class analysis-derived subphenotype, corticosteroid exposure, and an interaction term of the 2 as c-variate in the above-described survival models. Heterogeneity of treatment effect is considered to be present if the interaction term has a P value of $<.05$.

Regarding WP4, patients are randomly selected and cases will be patients treated with high-dose corticosteroids, whereas controls will be patients who were not treated with high-dose

corticosteroids. In WP4a, inverse probability treatment weighting and inverse probability of censoring weights will be used together in a marginal structural model. After we have analyzed the effect of high-dose corticosteroids on mortality and the other outcome measures, we will use this model to determine if the listed biomarkers modify the effect of high-dose corticosteroids on mortality.

In WP4b, we will identify transcriptome features that are differentially altered between cases and controls. Mean transcriptome levels will be compared using an unpaired *t*-test and *P* values will be adjusted for false-discovery rate using the Benjamini-Hochberg procedure. The \log_2 mean fold change of levels between cases and controls will also be calculated for each transcriptome. We will define transcriptome features as those with an adjusted *P* value of $<.05$ and a >2.0 or <-2.0 \log_2 mean fold change in level.

Results

The study was funded in December 2021. As of April 2023, data have been collected for a total of 1500 patients, with data collection anticipated to be completed by December 2023. We expect the first results to be available in early 2024.

Discussion

The SELECT study is a retrospective multicenter observational cohort study that aims to determine the most optimal dosing and timing of high-dose corticosteroid therapy in hospitalized patients with COVID-19 and to provide a basis for personalized treatment regimens using biomarkers and whole transcriptome analyses. Increasing insight in the pathophysiological pathways that underlie SARS-CoV-2 infection and the efficacy of high-dose corticosteroid therapy could lead to more precise targeting of high-dose corticosteroid therapy, and as a result, could improve patient outcomes.

The necessity of exploring this matter is underlined by the fact that there is currently no consensus regarding the administration of high-dose corticosteroid therapy in patients with COVID-19.

This study design has several strengths. First, no studies have been performed that evaluate the effect of high-dose corticosteroids throughout the entire clinical course of

hospitalized patients with COVID-19. Our study will evaluate the effect of high-dose corticosteroids from hospital admission to the ward or ICU, until hospital discharge. Furthermore, our exploration of biomarker and gene expression profiles for targeted corticosteroid therapy represents a first step toward personalized corticosteroid therapy in COVID-19. By using existing research databases and biobanks, successful data collection is assured, and we will be able to include a large number of patients, which increases the generalizability of the results.

Due to the retrospective study design, some methodological considerations require further discussion. A major issue for any observational study is the fact that treatment modalities are not randomly assigned, but rather likely given based on specific patient characteristics or within-center protocols. This nonrandomized assignment is prone to bias by indication. To correct this bias, our initial analysis step will be the identification of factors that contribute to the allocation of corticosteroid treatment. Subsequently, we will examine several statistical approaches, such as the use of propensity scores at the patient level to minimize treatment indication bias.

The findings of this study could support COVID-19 guidelines and hospital protocols regarding the management of hospitalized patients with COVID-19. Thus far, the translation of predictive biomarkers and whole transcriptome analysis into an applicable bedside tool is highly challenging. We expect to provide valuable tools to guide the dosing and timing of high-dose corticosteroid therapy. Furthermore, the answers to our research questions might be extrapolated to patients with non-COVID-19 ARDS, as the use of high-dose corticosteroids is still a matter of debate in this group of patients. The mortality rate of non-COVID-19 ARDS is even higher than that of COVID-19 ARDS [24], emphasizing the need for improved treatment strategies. Nonetheless, more efforts are required to determine similarities and differences between patients with COVID-19 ARDS and those with non-COVID-19 ARDS to determine whether extrapolation from one group to the other is possible.

In conclusion, our study protocol presents a strategy to gain a better understanding of the optimal dosing and timing of high-dose corticosteroid therapy in hospitalized patients with COVID-19 and thereby improve patient outcomes.

Acknowledgments

We gratefully acknowledge all site investigators of the participating centers. PROVENT-COVID Collaborators (in alphabetic order): S Ahuja; JP van Akkeren; AG Algera; CK Algae; RB van Amstel; P van de Berg; DC Bergmans; DI van den Bersselaar; FA Bertens; AJ Bindels; JS Breel; CL Bruna; MM de Boer; S den Boer; LS Boers; M Bogerd; LD Bos; M Botta; OL Baur; H de Bruin; LA Buiteman-Kruizinga; O Cremer; RM Determann; W Dieperink; Jv Dijk; DA Dongelmans; MJ de Graaff; MS Galekaldridge; LA Hagens; JJ Haringman; ST van der Heide; PL van der Heiden; LL Hoeijmakers; L Hol; MW Hollmann; J Horn; R van der Horst; EL Ie; D Ivanov; NP Juffermans; E Kho; ES de Klerk; AW Koopman; M Koopmans; S Kucukcelebi; MA Kuiper; DW de Lange; I Martin-Loeches; G Mazzinari; DM van Meenen; N van Mourik; SG Nijbroek; EA Oostdijk; F Paulus; CJ Pennartz; J Pillay; IM Purmer; TC Rettig; O Roca; JP Roozeman; MJ Schultz; A Serpa Neto; C Sivakorn; GS Shrestha; ME Sleswijk; PE Spronk; AC Strang; W Stilma; P Swart; A Tri; AM Tsonas; CMA Valk; AP Vlaar; LI Veldhuis; WH van der Ven; P van Velzen; P van Vliet; P van der Voort; L van Welie; B van Wijk; T Winters; WY Wong; AR van Zanten. PROACT-COVID Collaborators (in alphabetic order): E Aydeniz; P van de Berg; DC Bergmans; M Bevers; S den Boer; LS Boers; LD Bos; M Botta; LA Buiteman-Kruizinga; W Coene; M Delmte; Vincenzo Di Leo; DA Dongelmans; TP Dormans; LM Elting; AA Esmeijer; M Gama de Abreu; AR Girbes; MJ de Graaff; DM Go; RL Goossen; HJ Hansen; JJ Haringman; L Hol;

MW Hollmann; PL van der Heiden; J Horn; LE van Ingen; NP Juffermans; MA Kuiper; LJ Kuipers; E Koornstra; A Lokhorst; SG Nijbroek; I Martin-Loeches; G Mazzinari; S Myatra; F Paulus; M Offermans; T Pisters; A Prins; P van Oosten; J Pillay; IM Purmer; AS Rezaee; TCD Rettig; O Roca; NM Rosenberg; N Schavemaker; AA Sciascera; MJ Schultz; A Serpa Neto; G Shrestha; ME Sleswijk; W Stilma; AC Strang; PE Spronk; PR Tuinman; AM Tsonas; CMA Valk; M Verboom; AP Vlaar; FL van der Ven; WH van der Ven; P van Velzen; EJ Verhoef; TD Vermeulen; P van Vliet; JJ Voorham; PH van der Voort; M van der Woude; Weiner; N Yaali; JM Zandvliet; AR van Zanten; TZ van Zijl; and SA Zonneveld. The SELECT study received an unrestricted research grant from ZonMw (grant number 0430102110010). The funders of this study did not play any role in the design of the study, nor in the writing of this manuscript or the decision to publish.

Data Availability

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

HE, JS, LDJB, and AB designed the study and arranged funding. AB outlined the statistical analysis. KD, JAH, and VASHD drafted the manuscript. All authors critically revised and approved this final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Definition of general systemic complications.

[[XLSX File \(Microsoft Excel File\), 12 KB-Multimedia Appendix 1](#)]

Multimedia Appendix 2

Peer-review report by the COVID-19 Program - The Netherlands Organisation for Health Research and Development / ZorgOnderzoek Nederland (ZON) and the area Medical Sciences (MW) (ZonMw, Netherlands).

[[PDF File \(Adobe PDF File\), 1304 KB-Multimedia Appendix 2](#)]

References

1. WHO coronavirus (COVID-19) dashboard. World Health Organization. URL: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> [accessed 2023-03-16]
2. Lamontagne F, Agarwal A, Rochweg B, Siemieniuk RA, Agoritsas T, Askie L, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379 [doi: [10.1136/bmj.m3379](https://doi.org/10.1136/bmj.m3379)] [Medline: [32887691](https://pubmed.ncbi.nlm.nih.gov/32887691/)]
3. De Vries HJ, Endeman H, van der Hoeven JG, Heunks LMA. Lung-protective mechanical ventilation in patients with COVID-19. *Neth J Crit Care* 2020;28(3):120-124 [[FREE Full text](#)]
4. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020;8(12):1233-1244 [[FREE Full text](#)] [doi: [10.1016/S2213-2600\(20\)30404-5](https://doi.org/10.1016/S2213-2600(20)30404-5)] [Medline: [33075298](https://pubmed.ncbi.nlm.nih.gov/33075298/)]
5. Nossent EJ, Schuurman AR, Reijnders TDY, Saris A, Jongerius I, Blok SG, et al. Pulmonary procoagulant and innate immune responses in critically ill COVID-19 patients. *Front Immunol* 2021;12:664209 [[FREE Full text](#)] [doi: [10.3389/fimmu.2021.664209](https://doi.org/10.3389/fimmu.2021.664209)] [Medline: [34054832](https://pubmed.ncbi.nlm.nih.gov/34054832/)]
6. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307(23):2526-2533 [doi: [10.1001/jama.2012.5669](https://doi.org/10.1001/jama.2012.5669)] [Medline: [22797452](https://pubmed.ncbi.nlm.nih.gov/22797452/)]
7. Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of adverse prognosis in COVID-19: a systematic review and meta-analysis. *Eur J Clin Invest* 2020;50(10):e13362 [doi: [10.1111/eci.13362](https://doi.org/10.1111/eci.13362)] [Medline: [32726868](https://pubmed.ncbi.nlm.nih.gov/32726868/)]
8. Tong-Minh K, van der Does Y, Engelen S, de Jong E, Ramakers C, Gommers D, et al. High procalcitonin levels associated with increased intensive care unit admission and mortality in patients with a COVID-19 infection in the emergency department. *BMC Infect Dis* 2022;22(1):165 [[FREE Full text](#)] [doi: [10.1186/s12879-022-07144-5](https://doi.org/10.1186/s12879-022-07144-5)] [Medline: [35189826](https://pubmed.ncbi.nlm.nih.gov/35189826/)]
9. Annane D, Pastores SM, Rochweg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2017;43(12):1751-1763 [doi: [10.1007/s00134-017-4919-5](https://doi.org/10.1007/s00134-017-4919-5)] [Medline: [28940011](https://pubmed.ncbi.nlm.nih.gov/28940011/)]
10. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021;384(8):693-704 [[FREE Full text](#)] [doi: [10.1056/NEJMoa2021436](https://doi.org/10.1056/NEJMoa2021436)] [Medline: [32678530](https://pubmed.ncbi.nlm.nih.gov/32678530/)]

11. Azoulay E, de Waele J, Ferrer R, Staudinger T, Borkowska M, Povoia P, et al. International variation in the management of severe COVID-19 patients. *Crit Care* 2020;24(1):486 [FREE Full text] [doi: [10.1186/s13054-020-03194-w](https://doi.org/10.1186/s13054-020-03194-w)] [Medline: [32758266](https://pubmed.ncbi.nlm.nih.gov/32758266/)]
12. Granholm A, Munch MW, Myatra SN, Vijayaraghavan BKT, Cronhjort M, Wahlin RR, et al. Dexamethasone 12 mg versus 6 mg for patients with COVID-19 and severe hypoxaemia: a pre-planned, secondary Bayesian analysis of the COVID STEROID 2 trial. *Intensive Care Med* 2022;48(1):45-55 [FREE Full text] [doi: [10.1007/s00134-021-06573-1](https://doi.org/10.1007/s00134-021-06573-1)] [Medline: [34757439](https://pubmed.ncbi.nlm.nih.gov/34757439/)]
13. Bouadma L, Mekontso-Dessap A, Burdet C, Merdji H, Poissy J, Dupuis C, COVIDICUS Study Group. High-dose dexamethasone and oxygen support strategies in intensive care unit patients with severe COVID-19 acute hypoxemic respiratory failure: the COVIDICUS randomized clinical trial. *JAMA Intern Med* 2022;182(9):906-916 [doi: [10.1001/jamainternmed.2022.2168](https://doi.org/10.1001/jamainternmed.2022.2168)] [Medline: [35788622](https://pubmed.ncbi.nlm.nih.gov/35788622/)]
14. Pinzón MA, Ortiz S, Holguín H, Betancur JF, Cardona Arango D, Laniado H, et al. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. *PLoS One* 2021;16(5):e0252057 [FREE Full text] [doi: [10.1371/journal.pone.0252057](https://doi.org/10.1371/journal.pone.0252057)] [Medline: [34033648](https://pubmed.ncbi.nlm.nih.gov/34033648/)]
15. COVID STEROID 2 Trial Group, Munch MW, Myatra SN, Vijayaraghavan BKT, Saseedharan S, Benfield T, et al. Effect of 12 mg vs 6 mg of Dexamethasone on the number of days alive without life support in adults With COVID-19 and severe hypoxemia: the COVID STEROID 2 randomized trial. *JAMA* 2021;326(18):1807-1817 [FREE Full text] [doi: [10.1001/jama.2021.18295](https://doi.org/10.1001/jama.2021.18295)] [Medline: [34673895](https://pubmed.ncbi.nlm.nih.gov/34673895/)]
16. Tan RSJ, Ng KT, Xin CE, Atan R, Yunos NM, Hasan MS. High-dose versus low-dose corticosteroids in COVID-19 patients: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2022;36(9):3576-3586 [FREE Full text] [doi: [10.1053/j.jvca.2022.05.011](https://doi.org/10.1053/j.jvca.2022.05.011)] [Medline: [35715291](https://pubmed.ncbi.nlm.nih.gov/35715291/)]
17. Meduri GU, Headley S, Tolley E, Shelby M, Stentz F, Postlethwaite A. Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS. *Chest* 1995;108(5):1315-1325 [doi: [10.1378/chest.108.5.1315](https://doi.org/10.1378/chest.108.5.1315)] [Medline: [7587435](https://pubmed.ncbi.nlm.nih.gov/7587435/)]
18. Farmacotherapeutisch Kompas. Zorginstituut Nederland. URL: https://www.farmacotherapeutischkompas.nl/bladeren/groepsteksten/corticosteroiden_systemisch [accessed 2023-05-11]
19. WHO Working Group on the Clinical Characterisation Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020;20(8):e192-e197 [FREE Full text] [doi: [10.1016/S1473-3099\(20\)30483-7](https://doi.org/10.1016/S1473-3099(20)30483-7)] [Medline: [32539990](https://pubmed.ncbi.nlm.nih.gov/32539990/)]
20. Botta M, Tsonas AM, Pillay J, Boers LS, Algera AG, Bos LDJ, PRoVENT-COVID Collaborative Group. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. *Lancet Respir Med* 2021;9(2):139-148 [FREE Full text] [doi: [10.1016/S2213-2600\(20\)30459-8](https://doi.org/10.1016/S2213-2600(20)30459-8)] [Medline: [33169671](https://pubmed.ncbi.nlm.nih.gov/33169671/)]
21. Valk CMA, Swart P, Boers LS, Botta M, Bos LDJ, Gama de Abreu M, et al. Practice of adjunctive treatments in critically ill COVID-19 patients-rational for the multicenter observational PRoAcT-COVID study in The Netherlands. *Ann Transl Med* 2021;9(9):813 [FREE Full text] [doi: [10.21037/atm-21-764](https://doi.org/10.21037/atm-21-764)] [Medline: [34268426](https://pubmed.ncbi.nlm.nih.gov/34268426/)]
22. Castor electronic data capture. Castor EDC. 2019. URL: <https://castoredc.com> [accessed 2023-04-28]
23. Levine M, Ensom MH. Post hoc power analysis: an idea whose time has passed? *Pharmacotherapy* 2001;21(4):405-409 [doi: [10.1592/phco.21.5.405.34503](https://doi.org/10.1592/phco.21.5.405.34503)] [Medline: [11310512](https://pubmed.ncbi.nlm.nih.gov/11310512/)]
24. Villar J, Blanco J, Añón JM, Santos-Bouza A, Blanch L, Ambrós A, ALIEN Network. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med* 2011;37(12):1932-1941 [doi: [10.1007/s00134-011-2380-4](https://doi.org/10.1007/s00134-011-2380-4)] [Medline: [21997128](https://pubmed.ncbi.nlm.nih.gov/21997128/)]

Abbreviations

ARDS: acute respiratory distress syndrome

BALF: bronchoalveolar lavage fluid

ICU: intensive care unit

SELECT: Steroids in Hospitalized Patients with COVID-19 in The Netherlands

UMC: University Medical Center

WP: work package

Edited by T Leung; The proposal for this study was peer reviewed by the COVID-19 Program - The Netherlands Organisation for Health Research and Development / ZorgOnderzoek Nederland (ZON) and the area Medical Sciences (MW) (ZonMw, Netherlands). See the Multimedia Appendix for the peer-review report; Submitted 14.04.23; accepted 24.04.23; published 02.06.23.

Please cite as:

Daenen K, Huijben JA, Boyd A, Bos LDJ, Stoof SCM, van Willigen H, Gommers DAMPJ, Moeniralam HS, den Uil CA, Juffermans NP, Kant M, Valkenburg AJ, Pillay J, van Meenen DMP, Paulus F, Schultz MJ, Dalm VASH, van Gorp ECM, Schinkel J, Endeman H, PRoVENT- and PRoAcT-COVID Collaborative Group

Optimal Dosing and Timing of High-Dose Corticosteroid Therapy in Hospitalized Patients With COVID-19: Study Protocol for a Retrospective Observational Multicenter Study (SELECT)

JMIR Res Protoc 2023;12:e48183

URL: <https://www.researchprotocols.org/2023/1/e48183>

doi: [10.2196/48183](https://doi.org/10.2196/48183)

PMID: [37266993](https://pubmed.ncbi.nlm.nih.gov/37266993/)

©Katrijn Daenen, Jilske A Huijben, Anders Boyd, Lieuwe D J Bos, Sara C M Stoof, Hugo van Willigen, Diederik A M P J Gommers, Hazra S Moeniralam, Corstiaan A den Uil, Nicole P Juffermans, Merijn Kant, Abraham J Valkenburg, Janesh Pillay, David M P van Meenen, Frederique Paulus, Marcus J Schultz, Virgil A S H Dalm, Eric C M van Gorp, Janke Schinkel, Henrik Endeman, PRoVENT- and PRoAcT-COVID Collaborative Group. Originally published in JMIR Research Protocols (<https://www.researchprotocols.org>), 02.06.2023. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on <https://www.researchprotocols.org>, as well as this copyright and license information must be included.