Study Protocol

Practice of adjunctive treatments in critically ill COVID–19 patients—rational for the multicenter observational PRoAcT-COVID study in The Netherlands

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Background: Patients with coronavirus disease 2019 (COVID-19) may need hospitalization for supplemental oxygen, and some need intensive care unit (ICU) admission for escalation of care. Practice of adjunctive and supportive treatments remain uncertain and may vary widely between countries, within countries between hospitals, and possibly even within ICUs. We aim to investigate practice of adjunctive and supportive treatments, and their associations with outcome, in critically ill COVID-19 patients.

Methods: The 'PRactice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019' (PRoAcT-COVID) study is a national, observational study to be undertaken in a large set of ICUs in The Netherlands. The PRoAcT-COVID includes consecutive ICU patients, admitted because of COVID-19 to one of the participating ICUs during a 3-month period. Daily follow-up lasts 28 days. The primary endpoint is a combination of adjunctive treatments, including types of oxygen support, ventilation, rescue therapies for hypoxemia refractory to supplementary oxygen or during invasive ventilation, other

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adjunctive and supportive treatments, and experimental therapies. We will also collect tracheostomy rate, duration of invasive ventilation and ventilator-free days and alive at day 28 (VFD-28), ICU and hospital length of stay, and the mortality rates in the ICU, hospital and at day 90.

Discussion: The PRoAcT-COVID study is an observational study combining high density treatment data with relevant clinical outcomes. Information on treatment practices, and their associations with outcomes in COVID-19 patients in highly and urgently needed. The results of the PRoAcT-COVID study will be rapidly available, and circulated through online presentations, such as webinars and electronic conferences, and publications in peer-reviewed journals—findings will also be presented at a dedicated website. At request, and after agreement of the PRoAcT-COVID steering committee, source data will be made available through local, regional and national anonymized datasets.

Trial registration: The PRoAcT-COVID study is registered at clinicaltrials.gov (study identifier NCT04719182).

Keywords: Coronavirus disease 2019 (COVID-19); intensive care; ventilatory support; adjunctive treatments; mortality

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Introduction

The Netherlands is currently facing a new surge of coronavirus disease 2019 (COVID-19) patients. COVID-19 patients frequently need hospitalization and a substantial number of them end up in an intensive care unit (ICU) for escalation of care (1).

Many patients with COVID-19 develop hypoxemia. Hypoxemia may respond well to simple oxygen support, like supplementary oxygen through interfaces like a nasal prong or cannula, and non-rebreather or Venturi masks—this type of support is usually provided on a normal ward. Patients with severe COVID-19 may develop hypoxemia that is refractory to simple supplementary oxygen, for which more intense oxygen support is needed, like continuous positive airway pressure (CPAP) or high-flow nasal oxygen (HFNO)—these types of support usually mandate admission to an ICU. If oxygenation does not improve, so-called 'awake proning' has been suggested as a rescue therapy, but non-invasive ventilation (NIV) and eventually invasive ventilation may become necessary. Even with invasive ventilation hypoxemia may persist (2-5). Rescue therapies for persistent hypoxemia may include higher airway pressures and prone positioning, at times in combination with continuous or intermitted muscle paralysis. In certain cases, extracorporeal membrane oxygenation (ECMO) may even be necessary. Other adjunctive treatments in patients with COVID-19 can include intensified thromboprophylaxis, and in cases of suspected or proven deep venous thrombosis (DVT) or pulmonary embolism (PE), full anticoagulation. Also, various antiviral and immunomodulating strategies have been advocated (6). Experimental supportive care may consist of various types of minerals or vitamins, and other pharmacological interventions (6-9).

Care for patients with COVID-19 varies widely between countries and regions, and probably also within The Netherlands. It is very well possible that differences in care are amplified by a lack of consensus on best care for COVID-19. They all could affect outcome, though. We aim to investigate practice of adjunctive and supportive treatments in critically ill COVID-19 patients in The Netherlands, in a study named 'PRactice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019' (PRoAcT-COVID). We also wish to determine associations with patient-centered outcomes. This study may form an important step towards creating a guideline for standard care in patients with COVID-19. Standardization and implementation of guidelines has the potential to improve care and outcome of critically ill COVID-19 patients. We present the following article in accordance with the SPIRIT reporting checklist (available at http://dx.doi.org/10.21037/atm-21-764).

Methods

Design and settings

The PRoAcT-COVID study is an investigator-initiated observational study in critically ill patients admitted because of COVID-19 in one of the participating ICUs in The Netherlands. The PRoAcT-COVID study will capture treatment data with high granularity in up to 20 hospitals. The study is registered at www.clinicaltrials.gov (trial identifier NCT04719182). The study protocol (version 1.0; November 30, 2020) is approved by local Institutional Review Boards of all participating hospitals; central approval was obtained in the Amsterdam UMD, location 'AMC' (W20_526 # 20.583).

Study population

More than 1,000 critically ill patients admitted because of COVID-19 to one of the participating ICUs in The Netherlands, from October 2020 through December 2020—this is the first 3 months of the second surge of COVID-19 patients in The Netherlands.

Since it is possible that patients receive accelerated care by intensivists at other locations within a hospital during the pandemic, the study will not be restricted to 'physical' ICUs—whether a patient outside an ICU will count as an 'ICU patient' is to be decided by the local physicians. Since it is possible that patients receive care at different ICUs, in different hospitals, due to local surges of patients, we may have partially incomplete sets of treatment data for some patients. Outcome data, however, will be captured for all patients.

Patients aged ≥18 years of age are eligible for participation in the PRoAcT-COVID study in case COVID-19 was the reason for ICU admission, and if COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR). ICU patients who are infected with SARS-Corona Virus-2, but do not have COVID-19 are excluded. The study has no other exclusion criteria.

Study conduct

The steering committee members of the PRoAcT-COVID study will directly contact study sites. Then, after approval, the study coordinators will contact local doctors, and if needed trained data collectors will assist them in collecting the data. The study coordinators will take care of integrity, and ascertain that the International Conference on Harmonization Good Clinical Practice-guidelines are followed and timely completion of data collection. Data collection will start as of end-February 2021 and will continue until the mid May.

Data to be collected

From the first day of stay in ICU, baseline and demographic variables will be captured—sex, age, weight and height, medication and comorbidities, day of start of complaints, day of definite diagnosis, day of hospital admission and day of ICU admission. In addition, disease severity score, including the Simplified Acute Physiology Score (SAPS) II and the Sequential Organ Failure Scores (SOFA) are collected.

The following treatment variables will be collected daily:

- Types of oxygen support [including oxygen supplementation via nasal prong or nasal canula, non-rebreather masks, Venturi masks, continuous positive airway pressure (CPAP), high-flow nasal oxygen (HFNO), NIV and invasive ventilation]; practice of awake proning; characteristics of invasive ventilation; rescue therapies for hypoxemia refractory to supplementary oxygen or during invasive ventilation [including prone positioning, higher positive-end expiratory pressure (PEEP)], continuous or intermitted muscle paralysis, and extracorporeal membrane oxygenation (ECMO);
- Practice of thromboprophylaxis, antiplatelet therapy, and practice of full anticoagulation in patients with suspected or confirmed DVT or PE; practice of stress ulcer prophylaxis; practice of sedatives and muscle paralysis;
- Practice of antiviral treatments (including, but not restricted to remdesivir, lopinavir-ritonavir, baloxavir marboxil, darunavir-cobicistat, favipiravir, sofosbuvir-daclatasvir, triazavirin, umifenovir and practice of immunomodulating treatments (including, but not restricted to corticosteroids, chloroquine or hydroxychloroquine, interferon, aprepitant, colchicine, immunoglobulin, ivermectin, ruxolitinib, telmisartan, tocilizumab and convalescence plasma);
- Practice of aerosolized medication (including, but not restricted to salbutamol, ipratropium and acetylcysteine);
- Practice of experimental supportive care (including, but not restricted to minerals or vitamins, and other

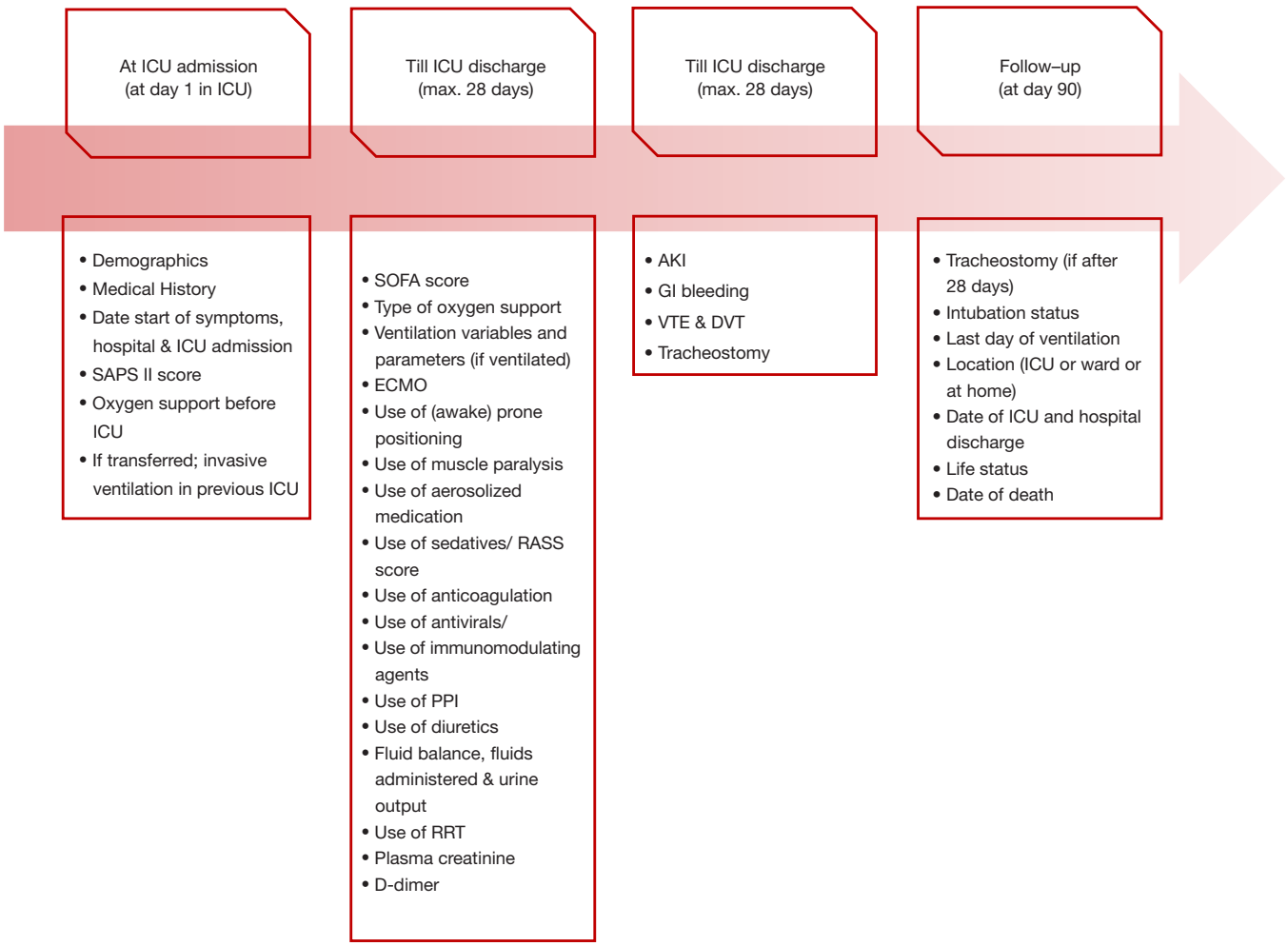

Figure 1 Sequence of data collection. ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA score, Sequential Organ Failure Assessment score; ECMO, extracorporeal membrane oxygenation; RASS score, Richmond Agitation-Sedation score; PPI, proton pump inhibitors; AKI, acute kidney injury; RRT, renal replacement therapy; GI, gastrointestinal; VTE, venous thromboembolism; DVT, deep venous thrombosis.

pharmacologic agents, like zinc, N-acetylcysteine, and vitamins);

- ❖ Daily cumulative fluid balances and cumulative urine production;
- ❖ Incidence of acute kidney injury (AKI) and renal replacement therapy (RRT);
- ❖ Proven DVT or PE, incidence of gastrointestinal (GI) bleeding;
- ❖ Place where care was provided (i.e., in an ICU or at other locations within a hospital during the pandemic).

Final follow-up data will be collected at days 28 and 90:

- ❖ Duration of ventilation in survivors, number of ventilator-free days and alive at day 28 (VFD-28), and tracheostomy incidence;
- ❖ ICU and hospital length of stay, and mortality rates in ICU, hospital and at day 90.

In addition, on ICU level, data on standard ventilator care including, but not restricted to active or passive humidification, tracheal suctioning procedures and manual hyperinflation will be collected.

Workflow of data collection is represented in *Figure 1*.

Study endpoints

Study endpoints are a combination of adjunctive treatments, including types of oxygen support, ventilation, and rescue

therapies for hypoxemia refractory to supplementary oxygen or during invasive ventilation during invasive ventilation (primary), adjunctive and supportive treatments and experimental therapies. Other endpoints include duration of ventilation and VFD-28 and tracheostomy rate, complication rates, including DVT and PE, GI bleeding, AKI and use of RRT, and duration of ICU and hospital stay, and ICU, hospital and 90-day mortality.

Definitions

VFD-28 is defined as the number of days without invasive ventilation and alive during the first 28 days from start of invasive ventilation. DVT and PE are defined as a proven DVT with a duplex ultrasound and/or proven PE with computerized tomography pulmonary angiography. GI bleeding is defined as observed blood from the gastric tube or melena, eventual confirmed by gastroscopy or coloscopy. AKI is defined using the KDIGO definition (10), and RRT is defined by the usage of continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis without filtration (CVVHD), hemodialysis or peritoneal dialysis. ICU and hospital length of stay is calculated from the first day of admission to the ICU or hospital and ICU discharge from ICU or hospital. All-cause mortality in ICU, hospital or at day 90 is defined as any death in the ICU, in the hospital or within 90 days of admission.

Data management

For data collection, we will use the locally used electronic patient data management systems. Data will be transcribed into a pseudo-anonymized online electronic case report form (eCRF) (Castor Electronic Data Capture; https://castoredc.com). The eCRF is protected by a personalized username and password.

Study sites

The following hospitals are invited to participate in the PRoAcT-COVID study: Department of Intensive Care, University Medical Center Groningen, Groningen [1]; Medical Center Leeuwarden, Leeuwarden, The Netherlands [2]; Department of Intensive Care, ISALA hospital, Zwolle, The Netherlands [3]; Department of Intensive Care, Rijnstate Hospital, Arnhem, The Netherlands [4]; Department of Intensive Care, Gelderse Vallei, Ede, The Netherlands [5]; Department of Intensive Care, Gelre hospitals, Apeldoorn [6]; Department of Intensive Care, University Medical Centers Utrecht, Utrecht, The Netherlands [7]; Department of Intensive Care, Antonius hospital, Nieuwegein, The Netherlands [8]; Department of Intensive Care, Amsterdam University medical centers [AMC], Amsterdam, The Netherlands [9]; Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands [10]; Department of Intensive Care, Spaarne hospital, Hoofddorp, The Netherlands [11]; Department of Intensive Care, Dijklander hospital, Hoorn, The Netherlands [12]; Department of Intensive Care, HAGA hospital, Den Haag, The Netherlands [13]; Department of Intensive Care, Haaglanden Medical Centers, Den Haag, The Netherlands [14]; Department of Intensive Care, Reinier de Graaf hospital, Delft, The Netherlands [15]; Department of Intensive Care, Catharina hospital, Eindhoven, The Netherlands [16]; Department of Intensive Care, Amphia hospital, Breda, The Netherlands [17]; Department of Intensive Care, Zuyderland Hospital, Heerlen, The Netherlands [18]; Department of Intensive Care, Maastricht University Medical Center, Maastricht, The Netherlands [19]; Department of Intensive Care, Flevo Hospital, Almere, The Netherlands [20].

With these hospitals participating, we expect to include over 40% of critically ill patients with COVID-19 in The Netherlands.

Preliminary statistical analysis plan

Descriptive data are reported as numbers and relative proportions for categorical variables or as medians (quartile 25%–quartile 75%) for continuous variables. In case subgroups are compared, baseline characteristics are compared using Fisher exact tests for categorical variables or Wilcoxon rank-sum test for continuous variables. The impact of adjunctive therapies on outcomes will be assessed through regression modelling according to the distribution of each outcome. Time-to-event outcomes will be reported in Kaplan-Meier curves and compared using appropriate statistical tests. For each analysis of impact on outcomes, there will be an updated analysis plan before assessing the data, in which it is explained how to control the confounders.

A P value <0.05 is considered statistically significant. All analyses are planned to be conducted in R v.4.0.2. An updated and finalized statistical analysis plan will be published online on the PRoAcT-COVID website (11).

Study organization

Selected members of the PRoAcT-COVID collaborative group will serve as Steering Committee members—these are involved in study design of the analysis of the data. Trained data collectors from the Amsterdam UMC, location AMC, and local doctors will collect data onsite and import them into the eCRF. Incomplete or incorrect eCRFs will be signaled in the online eCRF for completion or correction by the data collectors before closing the database.

Patient and public involvement

There is no involvement from patients or public in the study.

Ethics and dissemination

The PRoAcT-COVID study will be conducted in accordance with the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013). The Institutional Review Board of the Amsterdam UMC, location 'AMC', rated this study as a service review. The need for informed consent was waived. In all other centers the study protocol will be rated by the local Institutional Review Boards for local feasibility.

The results of the PRoAcT-COVID study will be rapidly available, and circulated through online presentations, such as webinars and electronic conferences, and publications in peer-reviewed journals—findings will also be presented at a dedicated website. At request, and after agreement of the PRoAcT-COVID steering committee, source data will be made available through local, regional and national anonymized datasets.

Discussion

The PRoAcT-COVID study will allow us to compare practices regarding adjunctive treatments in critically ill COVID-19 patients, and to determine whether certain adjunctive treatments have an independent association with relevant clinical outcomes. The findings of PRoAcT-COVID will serve as a basis for national, and maybe also international guidelines for care in critically ill COVID-19 patients.

The results of the PRoAcT-COVID study will be available shortly after completion of data-capturing, thus allowing fast optimization of adjunctive treatment practices in The Netherlands. Both academic and non-academic, and teaching and non-teaching hospitals will participate, covering all provinces in The Netherlands, and we expect to collect data of approximately 40% of patients with COVID-19 in The Netherlands—thus allowing a thorough national insight in care for critically ill COVID-19 patients.

Practice of care for COVID-19 patients remains based on evidence from a small set of randomized clinical trials performed over the last 12 months, e.g., for thromboprophylaxis (12), use of remdesivir (13-17), lopinavir-ritonavir (15,18-20), hydroxychloroquine (15,21,22), hydrocortisone, methylprednisolone and dexamethasone (23-28), interleukin 6 receptor antagonists (29-33), vitamin D (7,34) and convalescent plasma (35-37). Some of these trials lack statistical power. To our best knowledge there have been no published trials of other treatments yet. Our study will be the first that combines patient demographics with granular data on adjunctive treatment practices and clinical outcomes in critically ill COVID-19 patients.

Strengths of this study include its size (PRoAcT-COVID will be one of the largest studies of adjunctive treatment practices and outcomes in COVID-19) and its high granularity (PRoAcT-COVID will collect daily data through the first 28 days after ICU admission, and have a final follow-up at day 90). Its retrospective design, however, could be seen as a limitation. Also, because of its observational character, we can only speak of associations, and never causal relations between practices and outcomes. Associations, therefore, should be interpreted with caution.

The results of PRoAcT-COVID are highly relevant for care in critically ill COVID-19 patients. Prompt generation and fast implementation of recommendations for adjunctive treatments have the potential to improve outcomes of COVID-19 patients, and may increase ICU capacity if such treatments lead to a more rapid ICU discharge.

The PRoAcT-COVID study is the successor of the PRoVENT-COVID study, a service review of care processes in the first 3 months of COVID-19 pandemic in The Netherlands (38). In the first 3 months of the pandemic, nearly all patients who needed ICU admission did so because of the need for invasive ventilation—consequently, the PRoVENT-COVID study focused on ventilation management and clinical outcomes. In the first 3 months of the second and current surge, many more ICU patients do not need invasive ventilation—thus, ventilatory support could be different, but also other aspects of care may differ. Together, the PRoVENT-COVID and PRoAcT-COVID

studies will provide insights into demographics, care management and clinical outcome in critically ill patients with COVID-19. The two studies could also find changes in care from the first to the second surge. Therefore, the databases of the PRoVENT-COVID and PRoAcT-COVID studies can and will be merged for additional analyses.

Strengths and limitations of this study

- ❖ The database of the PRoAcT-COVID study will contain granular information on adjunctive treatments and clinical outcomes in critically ill COVID-19 patients;
- ❖ The PRoAcT-COVID study will allows for a robust analysis of adjunctive therapies, and associations between these therapies and patient-centered clinical outcomes, because of its large sample size;
- ❖ In absence of randomized clinical trials, the data generated by the PRoAcT-COVID study will provide guidance to practice in critically ill COVID-19 patients;
- ❖ The PRoAcT-COVID study is limited by its observational nature and national character;
- ❖ The PRoAcT-COVID and PRoVENT-COVID studies, will help to understand whether, and how patient demographics, management, and outcomes in critically ill COVID-19 patients has evolved in The Netherlands.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-764

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-764). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The PRoAcT-COVID study is registered at www.clinicaltrials.gov (trial identification number NCT04719182). The study protocol (version 1.0 30-11-2020) is approved by the local Institutional Review Board of the Amsterdam UMC, location 'AMC' (W20_526 # 20.583). The PRoAcT-COVID study will be conducted in accordance with the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013). The Institutional Review Board of the Amsterdam UMC, location 'AMC' sees this study as a service review. Since no research-related interventions will take place, and because the study collects pseudo-anonymous data, which can no longer be attributed to a specific data subject, there were no ethical concerns and there is no concern for informed consent.

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