**Universidade de Brasília** **Diretoria de Apoio a Projetos Acadêmicos - DPA**

# Resumo de Convênio

Referência
**21/11/2022**

**Registro =>** **12421**
**Entidade =>** **37.116.704/0001-34**
**FUNDAÇÃO DE EMPREENDIMENTOS CIENTIFICOS E TECNOLÓGICOS - FINATEC**

**Objetivo :** Execução do projeto "Anticorpos no diagnóstico e terapia da Covid-19: estudo clínico e translacional com pacientes convalescentes". Partícipes: NYU Grossman School of Medicine (NYUGSoM), unidade administrativa da New York University, Faculdade de Medicina da Universidade de Brasília (UnB/FM) e Fundação de Empreendimentos Científicos e Tecnológicos (FINATEC).

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**Órgão Gestor :** 570 - FMD - Faculdade de Medicina
**Gestor :** 1097504 - HUGO COSTA PAES
**Gestor Subst.:** 1097733 - CIRO MARTINS GOMES
**Ato:** 241/2022 - 18/11/2022

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**Instrumento :** 1 - Convênio
**Natureza :** 6 - Cooperação Técnica, Intercâmbio
**Esfera Admin. :** 4 - Iniciativa Privada

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**Data Assinatura:** 16/11/2022 **Data Início :** 01/01/2022 **Data Término :** 31/12/2025

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**Valor :** 576.250,00
**Nro Processo :** 23106.066377/2022-62
**Nro Processo Origem :**
**Código SIAFI :**

**----------1ª Publicação DOU----------**

**Responsável:** FUB
**Data :** 21/11/2022 **Número :** 105 **Página :** 218

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**Contato :** FINATEC
**Endereço :** Av. L3 Norte - Edifício Finatec - Asa Norte
Asa Norte Brasília DF
**Telefone :** 3348-0400

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**COMPILE Consortium Agreement**
**2nd Amendment**

This 2nd Amendment ("Amendment #2") is entered into on this 18th day of November, 2022 by and between:

NYU Grossman School of Medicine, an administrative unit of New York University, with a primary place of business at 550 First Avenue, New York, New York 10016 ("NYUGSoM") and The University of Brasilia Faculty of Medicine (the "Consortium Investigator") and Fundacao de Empreendimentos Cientificos e Tecnologicos ("Finatec");

WHEREAS, NYUGSoM and Consortium Investigator entered into the COMPILE Consortium Agreement, fully executed on November 9, 2020 (the "Agreement"), whereby Consortium Investigator agreed to participate in an international pooling project designed to combine patient level data from multiple randomized controlled trials of convalescent plasma in hospitalized patients with COVID-19 ("COMPILE"); and

WHEREAS, the parties thereafter modified such Agreement subsequent to NYUGSoM receiving funding from the National Institutes of Health, National Center for Advancing Translational Sciences, CFDA 93.350, to support COMPILE's assemblage of Qualifying Trial Data from Consortium Investigator and other COMPILE collaborators into an aggregation of COMPILE Consortium Data Set, to continue to be managed at NYUGSoM (the "Grant") (Amendment #1, dated October 5, 2021); and

WHEREAS, NYUGSoM and Consortium Investigator wish to modify the Agreement in order for Consortium Investigator to continue to participate in COMPILE under COMPILE Expand and COMPILE Follow Up, as described herein.

NOW THEREFORE, the parties agree as follows:

1. Consortium Investigator will be participating in COMPILE Expand and the Agreement is therefore modified as follows:

   a. Consortium Investigator shall send to NYUGSoM the Data described in Exhibit A-1 (the "COMPILE Expand Dataset") consistent with the COMPILE Expand Protocol, attached hereto as Exhibit C-1. COMPILE Expand data must be sent by December 31, 2022 (the, "Current Period").

   b. Upon delivery by Consortium Investigator and acceptance by NYUSOM of the COMPILE Expand Dataset, NYUGSoM will be charged, and Consortium Investigator will be paid consistent with the budget and milestones, attached herein at Exhibit B. All payments specified in Exhibit B are consistent with fair market value in an arms-length transaction for work provided.

2. Consortium Investigator will be participating in COMPILE Follow Up and the Agreement is therefore modified as follows:

   a. Consortium Investigator shall send to NYUGSoM the Data described in Exhibit A-2 (the "COMPILE Follow Up Dataset"), consistent with the COMPILE Follow Up Protocol, attached hereto as Exhibit C-2. COMPILE Follow Up data must be sent by the Current Period.

b. Upon delivery by Consortium Investigator and acceptance by NYUSOM of the COMPILE Follow Up Dataset, NYUGSoM will be charged, and Consortium Investigator will be paid consistent with the budget and milestones, attached herein at Exhibit B. All payments specified in Exhibit B are consistent with fair market value in an arms-length transaction for work provided.

3. With respect to the method or means by which Finatec and Consortium Investigator are permitted by NYUGSoM under the Grant to continue after the Current Period to spend the funds hereunder, NYUGSoM defers to the institutional policies and procedures of Finatec and Consortium Investigator should they permit internal spending of the financial balance for the period **January 1, 2022 through December 31, 2025** (the "Residual Term"). Until December 31, Consortium Investigator shall send the data described in Exhibit A-1 (the "COMPILE Expand Dataset") and Exhibit A-2 (the "COMPILE Follow Up Dataset"). Between January 1, 2023 and December 31, 2025, Consortium Investigator can perform research activities as programmed in a specific Work Plan with Finatec. The funds available for this Amendment #2 are only obligated for the Term specified and shall not be carried over into any other period of performance, unless the Term is extended by the parties via a dually executed amendment.

4. All capitalized terms, abbreviations used herein shall, unless otherwise indicated, have the meanings given to them in the Agreement, including its Attachments and Amendments.

5. Except for the changes expressly mentioned herein, all other terms and conditions of the Agreement, and its Attachments and Amendments, shall remain unchanged and continue to be in full force and effect and shall be applicable to this Amendment #2.

In Witness Whereof, the parties have caused this Amendment #2 to be executed by the respective and duly authorized officers as of the Amendment #2's effective date.

By and behalf: **NYU Grossman School of Medicine**

BY: _____

PRINT NAME: Samantha Ebel, JD, MPH

TITLE: Associate Director, OSR

Contracts DATE: 11/18/2022

By and behalf: **The University of Brasilia**

Documento assinado digitalmente
gov.br DIEGO DE TASSIO SILVA
Data: 16/11/2022 16:23:01-0300
Verifique em https://verificador.iti.br

BY: _____

PRINT NAME: DIEGO DE TÁSSIO SILVA

TITLE: INTERNATIONAL AFFAIRS SECRETARY (IN-OFFICE)

DATE: 11/16/2022

By and behalf: **Fundacao de Empreendimentos Cientificos e Tecnologicos**

AUGUSTO CESAR DE MENDONCA BRASIL:18741258215

Assinado de forma digital por AUGUSTO CESAR DE MENDONCA BRASIL:18741258215
Dados: 2022.11.17 11:59:28 -03'00'

BY: _____

PRINT NAME: AUGUSTO CÉSAR DE Mendonça BRASIL

TITLE: DIRECTOR PRESIDENT

DATE: 11/16/2022

**EXHIBIT A-1**

[redacted]

COMPILE-Expand asks for data that might have been obtained at the time patients were randomized in the COMPILE randomized clinical trial. No new data from patients need to be collected.

| Data | Type |
|---|---|
| **Vital Signs** | |
| Systolic Blood Pressure | #; NA = not available |
| Weight (in kg) | #; NA = not available |
| **Medical history** | |
| History of asthma | 0 = no; 1 = yes; NA = not available |
| History of renal replacement therapy | 0 = no; 1 = yes; NA = not available |
| **Medications at randomization** | |
| Any antiplatelet agent | 0 = no; 1 = yes; NA = not available |
| Any intravenous anticoagulant | 0 = no; 1 = yes; NA = not available |
| Any oral anticoagulant | 0 = no; 1 = yes; NA = not available |
| **Pre-treatment antibodies measurements** | |
| IgG | 0 = below cutoff[1]; 1 = above cutoff; NA = not available |
| IgM | 0 = below cutoff[2]; 1 = above cutoff; NA = not available |
| IgA | 0 = below cutoff[3]; 1 = above cutoff; NA = not available |
| **Pre-treatment antigen measurements** | |
| Spike protein | 0 = below cutoff[4]; 1 = above cutoff; NA = not available |
| Nucleocapsid | 0 = below cutoff[5]; 1 = above cutoff; NA = not available |

2This is an assay - and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgM

3This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgA

4This is an assay- and RCT-specific value above which spike protein is considered present

5This is an assay- and RCT-specific value above which nucleocapsid is considered present

**EXHIBIT A-2**

**Definition of terms for the purposes of this form:**

Index episode: COVID-19 illness when the patient participated in the convalescent plasma RCT
Hospital discharge: discharge from hospital stay during the index episode

Information to be obtained from clinical records, patient report, or family member report

Complete this form with information regarding events, treatments, symptoms and vital status **AFTER hospital discharge from index episode during which the patient was enrolled in the original randomized controlled trial (RCT) and was randomized to convalescent plasma or control**

COMPILE RCT ID #_____ COMPILE Site ID #_____ COMPILE Patient ID #_____
Date of randomization in the convalescent plasma randomized controlled trial (RCT): Month___ Year___
Date this form is completed: Month____ Year_____

| Events (Check all that apply) | | | |
|---|---|---|---|
| **Has the patient experienced any of the following events?** | **Yes** | **No** | **Unsure** |
| Recurrent SARS – CoV 2 Infection | | | |
| Myocardial Infarction | | | |
| Stroke | | | |
| Deep Venous Thrombosis | | | |
| Pulmonary Embolus | | | |
| Hospitalization for Heart Failure | | | |
| Hospitalization for respiratory compromise, exacerbation of asthma or COPD | | | |

| Treatments (Check all that apply) | | | |
|---|---|---|---|
| **Has the patient received any of the following treatments?** | **Yes** | **No** | **Unsure** |
| Vaccine for SARS-CoV 2 (any dose, any vaccine) | | | |
| Initiation of renal replacement therapy (even temporarily) | | | |
| Transplant: | | | |
| Heart | | | |
| Lung | | | |
| Kidney | | | |

| Symptoms (Check all that apply) | | | | |
|---|---|---|---|---|
| | **Yes** | | | |
| **Has the patient experienced any of the following symptoms?** | **Still present** | **Resolved** | **No** | **Unsure** |
| Fatigue | | | | |
| If yes, did the fatigue limit everyday functioning | | | | |
| Shortness of breath | | | | |
| Cognitive dysfunction/brain fog/memory loss | | | | |
| Anxiety | | | | |
| Depression | | | | |
| Chest pain | | | | |
| Joint pain | | | | |
| Change in hearing | | | | |
| Change in smell | | | | |
| Change in taste | | | | |

| Vital Status | | | |
|---|---|---|---|
| **Indicate the patient status** | **Yes** | **No** | **Unknown** |
| Alive | | | |
| If dead: Month of Death..... Year of Death..... | | | |

Exhibit B
Budget

| Milestone | Cost per Milestone | Maximum Total Cost |
|---|---|---|
| ***COMPILE Expand dataset*** As set forth in Exhibits A-1 and C-1 | $30,000 USD | $30,000 USD |
| ***COMPILE Follow Up dataset*** As set forth in Exhibits A-2 and C-2 | $2,750 USD per patient<br><br>Maximum # of patients: 31 | $85,250 USD |

Invoices memorialized in the form of the Sample Invoice attached hereto, shall be generated by NYUGSoM and sent to Consortium Institution for certification, prior to authorization of payment. Payments shall be made quarterly.

NYUGSoM's financial contract shall be:
Norka Rappoport, Office of Science and Research
One Park Ave., 6th floor
New York, NY 10016
929-455-2408(Office)
Norka.Rappoport@nyulangone.org

Consortium Investigator's financial contact shall be:

Name: _____

Email: _____

Phone: _____

Exhibit B Sample Invoice

TO: Dr. Eva Petkova
COMPILE COVID Project PI

FROM: [INSERT RCT LEAD HERE]
[INSERT RCT COUNTRY HERE]

DATE: [INSERT DATE HERE]

RE: Data Transfer for COMPILE COVID Study

Where applicable for our RCT Country, we have completed the below task(s) for the COMPILE COVID Data Transfer during the project period beginning 1/1/2022:

The breakdown by task is as follows:

| | | | |
|---|---|---|---|
| | | | Total |
| Task 1 | COMPILE Expand | $30,000 USD | |
| Task 2 | COMPILE Follow Up | # subjects: _____ ($2,750 each) | |

Please remit your payment for the total ***$*** _____ to:

[INSERT RCT INFO HERE]
[ADDRESS]
[CITY, COUNTRY]
ATTN: [INSERT RCT LEAD HERE]

If you have any questions, please email [INSERT RCT PI EMAIL].

# COMPILE Expand

Title: COMPILE Expand – Additional baseline data prior to treatment in a COMPILE CCP RCT

Short title: COMPILE Expand

Protocol version: 1.0

Date: 5/6/2022

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Authors: The COMPILE Consortium

Principal Investigator: Andrea B. Troxel, ScD, NYU Grossman School of Medicine

Steering Committee:

Andrea B. Troxel, ScD, New York University Grossman School of Medicine, NY, USA
(Chair) Liise-Anne Pirofski, MD, Albert Einstein College of Medicine, NY, USA
Mila Ortigoza, MD, New York University Grossman School of Medicine, NY,
USA Cristina Ave˜ndano Sol´a, MD, Universidad Aut´onoma de Madrid, Spain
Rafael F. Duarte Palomino, MD, Universidad Aut´onoma de Madrid,
Spain Priscilla Hsue, MD, University of California San Francisco, CA,
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CA, USA Katharine Bar, MD, University of Pennsylvania, PA, USA Andre
Moraes Nicola, MD, University of Bras´ılia, Brazil
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USA Yi Li, MS, New York University Grossman School of Medicine, NY, USA
Eva Petkova, PhD, New York University Grossman School of Medicine, NY, USA

Advisors:

Elliott Antman, MD (cardiovascular medicine), Harvard School of Medicine, Boston, MA, USA

# PROTOCOL SYNOPSIS

## Title: COMPILE Expand – Additional baseline data prior to treatment in a COMPILE CCP RCT

## Short title: COMPILE Expand

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Background: COMPILE is a consortium of randomized controlled trials (RCTs) of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19 who were not on mechanical ventilation at the time of randomization. The primary objective was to pool individual patient data (IPD) from the different RCTs in order to obtain conclusive results regarding the efficacy of CCP faster than the individual trials would have allowed. Patients in the COMPILE study were enrolled from early 2020 to March 2021 and were observed until day 28(±2) after treatment initiation. The COMPILE database was locked in April 2021. Ultimately, 8 RCTs from 6 countries and 4 continents provided data on 2341 patients. The main results from the study were published [1]. The study also developed a treatment benefit index (TBI) that uses patients' pre-treatment characteristics to predict the specific benefit of acute treatment with CCP compared to treatment without CCP with respect to short-term outcomes at days 14(±1) and 28(±2) post-treatment [2]. An online calculator is available to facilitate the use of this tool in practice http://covid-convalescentplasma-tbi-calc.org.

This current COMPILE Expand study seeks to pool additional baseline data that has been collected as part of the COMPILE RCTs. This additional baseline patient information will be used in an attempt to refine the TBI developed in [2].

Research hypothesis: We hypothesize that combined with the COMPILE pooled dataset, the additional baseline data from COMPILE Expand will improve the initially developed TBI in [2], which would allow more precise guidance of treatment recommendations.

Primary objective: Our primary objective is to enrich the COMPILE dataset with additional baseline patient information. The COMPILE-Expand data will enrich the MDS pooled by COMPILE with additional baseline patient information. From the existing databases of the RCTs participating in COMPILE Expand will pool data on patients' pre-treatment antibodies as well as concomitant medication, and pre-existing health conditions that were not collected as part of the COMPILE MDS.

Secondary Objectives: A secondary objective is to examine whether different patients benefit from different amount of titers in the donors' plasma. One can think of this question as whether different doses of treatment are beneficial for different patients. COMPILE has assembled titers data from the donor's plasma transfused to 50% of the CCP treated patients and those data will be used to investigate the question about optimal "dose" of titers depending on patient characteristics.

Study design: De-identified additional baseline IPD from the COMPILE RCTs will be pooled and merged with the existing COMPILE dataset.

Statistical methods: The COMPILE TBI described in [3] was developed using a specific precision medicine approach described in [4], but several other approaches were tested also to ensure that optimal treatment recommendations can be made based on the TBI. We will use the same approach [4] in the attempt to refine the TBI with the additional baseline information. As in [3], we will also test alternative precision medicine techniques to compare and select the optimal approach.

The methods derived in [4] also allow the selection of optimal dose depending on patients' baseline characteristics and will be used for selecting optimal amount of titers in the donor's plasma for individual patients.

Data sharing: The pooled COMPILE-Expand data will be merged with the existing COMPILE data dataset and will be shared under the same rules.

Governance: The COMPILE-Expand study will be conducted under the governing documents for the COMPILE study.

Abbreviations

| | |
|---|---|
| COMPILE | Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients |
| CCP | COVID-19 Convalescent Plasma |
| FTP | File Transfer Protocol |
| GDPR | General Data Protection Regulations |
| HIPAA | Health Insurance Privacy and Accountability Act |
| IPD | Individual Patient Data |
| MCIT | Medical Center Information Technology |
| MDS | Minimal Data Set |
| MFT | Managed File Transfer |
| NYU | New York University |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| RCT | Randomized Clinical Trial |
| SAP | Statistical Analysis Plan |
| SC | Steering Committee |
| TBI | Treatment benefit index |
| VDI | Virtual Device Infrastructure |

# Contents

# 1 Introduction

## 1.1 Study hypotheses

We hypothesize that additional baseline variables will enable us to refine the treatment benefit index (TBI) [2] that we developed using the original COMPILE minimal data set (MDS). The additional baseline information will include patients' pre-treatment levels of antibodies, concomitant medications and pre-existing health conditions not assessed in the MDS. We also hypothesize that different patients have optimal response when transfused with convalescent plasma containing different amounts of titers and we will study how patient baseline characteristics and titers in donors' plasma jointly determine the benefit from treatment with CCP for individual patients.

## 1.2 Background

COMPILE is a consortium of randomized controlled trials (RCTs) of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19 who were not on mechanical ventilation at the time of randomization. The primary COMPILE objective was to pool individual patient data (IPD) from different RCTs in order to obtain conclusive results regarding the efficacy of CCP faster than the individual trials would have allowed. Patients in the COMPILE study were enrolled from early 2020 to March 2021 and were observed until day 28 (±2) after treatment initiation. The COMPILE database was locked in April 2021. Ultimately, 8 RCTs from 6 countries and 4 continents provided data on 2341 patients.

The main results from the study were published in [1]. The study also developed a treatment benefit index (TBI) that uses patients' pre- treatment characteristics to predict the specific benefit of acute treatment with CCP compared to treatment without CCP with respect to short -term outcomes at days 14(±1) and 28(±2) post-treatment [2]. An online calculator is available to facilitate the use of this tool in practice http://covid-convalescentplasma-tbi-calc.org.

The COMPILE study was conceived early on in the COVID-19 pandemic and collected only a minimal data set (MDS) of patients characteristics at baseline in order to reduce the burden on the RCTs' research teams extracting the information. The MDS was designed based on the existing knowledge at the time (Summer of 2020). Almost two years since the start of the COMPILE study has passed, and the knowledge about the COVID-19 and the accumulating information about the mechanisms of action of CCP, as well as other treatments for COVID-19, suggests that additional baseline patient information might be able to address remaining important questions regarding the efficacy of CCP and specifically, help identify patients who are expected to benefit most from CCP treatment.

Thus, the current COMPILE Expand study seeks to pool additional baseline data that has been collected as part of the COMPILE RCTs. This additional baseline patient information will be used in an attempt to refine the TBI developed in [2].

# 2 Study objectives

## 2.1 Primary objective

The primary objective of this expanded study is to refine the TBI developed using the original COMPILE dataset [2]. This therapeutic index predicts the expected relative treatment benefit from CCP compared with treatment without CCP for patients hospitalized for COVID-19 using patients' baseline characteristics. From the COMPILE RCTs, we will pool the following existing pre-treatment patient data that were not collected under the MDS used in the COMPILE study: concomitant medications (any antiplatelet agents, any intravenous anticoagulant agents, and any oral anticoagulant agents), vital signs (weight and systolic blood pressure (SBP)), pre-existing health conditions (receiving renal replacement therapy and asthma), and antibody and antigen measurements in the COMPILE patients pre-treatment.

#### 2.1.1 Primary outcome

All outcomes in the COMPILE-Expand study (including the primary ones) will be the same as the outcomes in the COMPILE study

## 2.2 Secondary objective

The secondary objective of this extended study is to generate an expanded COMPILE dataset of de-identified IPD from the COMPILE Consortium RCTs, to enable analyses to address additional related questions.

#### 2.2.1 Differential effect of CP

Another secondary objective is to assess the effect of specific patient characteristics on the efficacy of CP compared to control treatment. For this expanded study, these characteristics include the additional baseline variables: concomitant medications (any antiplatelet agents, any intravenous anticoagulant agents, and any oral anticoagulant agents), vital signs (weight, SBP), whether receiving renal replacement therapy, history of asthma, antibody and antigen measurements in recipients. A specific focus of COMPILE-Expand is to assess the effect of patients' pre-treatment antibody and antigen measurements. We will investigate whether and how these antibody and antigen measurements are related to the efficacy of CP compared to control treatment.

#### 2.2.2 Joint effect of patient characteristics and donors' plasma characteristics on CCP efficacy

Another objective is to examine whether different patients benefit from different amount of titers in the donors' plasma. One can think of this question as whether different doses of treatment are beneficial for different patients. COMPILE has assembled titers data from the donor's plasma transfused to 50% of the CCP treated patients and those data will be used to investigate the question about optimal "dose" of titers depending on patient characteristics. This is an enhanced precision medicine question that acknowledges that the best dose of a given treatment might be different between patients.

Usually, the question of dose comes in the context of adverse events, which have not been reported with transfusion of plasma. Recent literature [5, 6] indicates that the concentrations of titers in the donor's plasma is related to the efficacy of this treatment, which has led to the FDA recommendation that only CCP with high titers is used for treatment [7]. We will investigate the evidence that optimal titers' concentrations are different for patients with different characteristics.

# 3 Ethical considerations

## 3.1 Informed consent

All subjects or their legally authorized representatives have given informed consent for the RCT in which they are participating. All patient data will be de-identified (de-identification process described below in Section 4.4) and no additional patient data, that is not part of the data obtained for the qualifying trial in which the patient is participating, will be requested. Therefore, no additional informed consent is necessary.

## 3.2 Protected health information

No protected health information (PHI), as defined by the Health Insurance Portability and Accountability Act (HIPAA) or the General Data Protection Regulations (GDPR), will be contained in the pooled datasets. COMPILE-Expand uses the same procedures to protect patient health information as the original COMPILE protocol.

## 3.3 Risk to subjects

As COMPILE, the protocol for the COMPILE-Expand study will use de-identified, pre-existing data. Patients or their legally authorized representatives have already signed informed consent. No study subject

contact will take place, no additional data will be obtained outside of already collected data for the trial in which the subject is participating, and no PHI will be obtained. Therefore, risk to subjects is minimal.

### 3.4 Data storage

As in the original COMPILE study, the accumulating dataset and the final merged dataset will be hosted at NYU DataCore and stored in a secure location at NYU.

## 4 Investigational plan

### 4.1 Study population and sample

The study population for COMPILE-Expand is the population for the COMPILE study. The study sample consists of all 2341 COMPILE patients on whom data was reported in [1].

### 4.2 Data sources

Individual RCTs will transfer IPD to NYU's MCIT Research DataCore by secure file transfer protocol (FTP) using the GlobalScape managed file transfer (MFT) solution, using the same process as the COMPILE study.

The COMPILE RCTs, site and patient IDs assigned in the COMPILE study will be used in COMPILE-Expand.

### 4.3 Data merger

NYU maintains the COMPILE Consortium data in a secure environment. The data collected in COMPILE-Extpand will pooled across RCTs and merged with the COMPILE dataset in that secure environment.

### 4.4 Ensuring complete data de-identification

To ensure complete data deidentification in compliance with HIPPA and GDPR, the same processes used in COMPILE will be used in COMPILE-Expand

### 4.5 Variables collected in COMPILE-Expand

The COMPILE-Expand will collect the following baseline information on the COMPILE patients:

| Data | Type |
|---|---|
| Vital Signs | |
| Systolic blood pressure | # ; NA = not available |
| Weight (in kg) | # ; NA = not available |
| Disease history | |
| History of asthma | 0 = no; 1 = yes; NA = not available |
| History of receiving renal replacement therapy | 0 = no; 1 = yes; NA = not available |
| Pre-treatment antibodies measurements | |
| IgG | 0= below cutoff[1]; 1= above cutoff; NA = not available |
| IgM | 0= below cutoff[2]; 1= above cutoff; NA = not available |
| IgA | 0= below cutoff[3]; 1= above cutoff; NA = not available |
| Pre-treatment antigen measurements | |
| Spike protein | 0= below cutoff[4]; 1= above cutoff; NA = not available |
| Nuclocapsid | 0= below cutoff[5]; 1= above cutoff; NA = not available |
| Medications at randomization | |
| Any antiplatelet agent | 0 = no; 1 = yes; NA = not available |
| Any intravenous anticoagulant | 0 = no; 1 = yes; NA = not available |
| Any oral anticoagulant | 0 = no; 1 = yes; NA = not available |

# 5 Statistical considerations

## 5.1 Analysis data set

In the COMPILE-Expand study, the following baseline variables: concomitant medications (any antiplatelet agents, any intravenous anticoagulant agents, and any oral anticoagulant agents), vital signs (weight, SBP), whether receiving renal replacement therapy, history of asthma, antibody and antigen measurements in recipients, will be requested from the RCT teams. These variables combined with the original COMPILE MDS forms the analysis data set.

A separate document that defines these variables is attached as an appendix to this protocol.

## 5.2 Statistical analysis plan

The statistical analysis plan (SAP) of the original COMPILE study will be followed in the COMPILE-Expand study, as described in [3].

The strategy for refining the TBI will follow the derivations of the expanded TBI from the basic TBI in [2].

To explore the benefit from CCP as a function of both patient characteristics and titers concentrations in the donors' plasma, we will follow the approach described in [4].

[1] This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgG

[2] This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgM

[3] This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgA

[4] This is an assay- and RCT -specific value above which spike protein is considered present [5] This is an assay- and RCT-specific value above which nucleocapsid is considered present

# 6 Administrative considerations

## 6.1 Compliance

This study will be conducted in accordance with all applicable laws and regulations related to human subjects' research, institutional research policies and procedures, and data privacy and security standards. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Ethics Committee, as applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed any required Human Subjects Protection Training.

## 6.2 Data sharing

The data from the COMPILE study have been stored in a secure platform (sandbox ), where the dataset can be analysed with a provided set of analytic software. Access to the sandbox is provided after submission of a summary of the proposed research question and analytic approach and subsequent approval by the COMPILE Publications Committee (contact Chang.Yu@nyulangone.org and cc Renata.Schwartz@nyulangone.org). NYU provides to the approved requestor a snapshot or data dump of the COMPILE database, which will be cre - ated and stored within a virtual device infrastructure (VDI), or virtual machine, residing within NYU's DataCore. Designated analysts/programmers working with the approved requestor are provided with an NYU Kerberos ID and password, enabling remote access to the VDI; all analyses will be performed within the VDI. All statistical applications, analysis datasets, and programming will remain within the secure VDI.

At the completion of COMPILE Follow Up data collection and transfer, the updated COMPILE dataset hosted by NYU DataCore will be finalized, harmonized, curated, and made available for additional analyses under the same rules at those currently used for access to the COMPILE data.

## 6.3 Governance

See the governance document.

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# COMPILE Follow Up

Title: COMPILE - A Follow Up of Patients 13 to 33 Months After Enrolment in the Convalescent Plasma Trials

Short title: COMPILE Follow Up

Protocol version: 1.0

Date: 5/6/2022

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# PROTOCOL SYNOPSIS

## Title: COMPILE - A Follow Up of Patients 13 to 33 Months After Enrolment in the Convalescent Plasma Trials

## Short title: COMPILE Follow Up

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Background: COMPILE is a consortium of randomized controlled trials (RCTs) of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19 who were not on mechanical ventilation at the time of randomization. The primary goal objective was to pool individual patient data (IPD) from the different RCTs in order to obtain conclusive results regarding the efficacy of CCP faster than the individual trials would have allowed. Patients in the COMPILE study were enrolled from early 2020 to March 2021 and were observed until day 28(±2) after treatment initiation. The COMPILE database was locked in April 2021. Ultimately, 8 RCTs from 6 countries and 4 continents provided data on 2341 patients. The main results from the study were published [1]. The study also developed a therapeutic benefit index that uses patients' pre-treatment characteristics to predict the specific benefit of acute treatment with CCP compared to treatment without CCP with respect to short-term outcomes at days 14(±1) and 28(±2) post-treatment. [2]. An online calculator is available to facilitate the use of this tool in practice http://covid-convalescentplasma-tbi-calc.org.

This current COMPILE Follow Up study seeks to collect data on the COMPILE patients 13 to 33 months after their participation in the RCTs with the goal of assessing the long-term efficacy of CCP.

Research hypothesis: We hypothesize that pooling systematic uniform follow-up information across COM-PILE patients 13 - 33 months after their participation in the CCP RCTs that were part of the COMPILE consortium, would allow the evaluation of the efficacy of CCP with respect to long-term outcomes, including long-COVID symptoms.

Primary objective: Our primary objective is to collect individual patient data (IPD) at follow up from the original COMPILE patients, a sample that is very well characterized at the time of patients' participation in the COMPILE CCP RCTs. Obtaining 13 to 33 month follow up data on a sample of patients who have detailed information prior to treatment with CCC for COVID-19, will allow us to evaluate whether CCP has effects in a long term. Patients will be contacted and assessed for specific clinical characteristics and events that occurred since they participated in the COMPILE RCTs. The follow-up data collected from COM-PILE patients will include information about vaccination, COVID-19 reinfection and symptoms, currently considered to be associated with long-COVID syndrome and major health events. The collected data will be de-identified employing the previously used COMPILE IDs, which would allow us to link the COMPILE data records with the follow-up patient information. We acknowledge that the follow-up intervals will differ between subjects which makes accurate assessment of the effects of CCP on the clinical characteristics com- plicated. Appropriate analytic methods will be employed to draw valid inferences regarding the long-term effects of CCP treatment.

Secondary objectives: A secondary objective is to study the potentially heterogeneous effects of CCP on long-term clinical status of patients infected with COVID-19 who survived. The analysis of the the COMPILE study identified wide heterogeneity of the acute treatment effect of CCP. Similar investigation is planned to identify patients that in a long-term might benefit from CCP more than other individuals infected with COVID-19. We will also investigate the effects of intermittent treatments, such as vaccination, on the CCP long-term efficacy.

Study design: COMPILE patients will be contacted and assessed for a set of clinical characteristics relevant to long-term health status after COVID-19 illness. The de-identified data will be pooled to construct and continuously update a COMPILE follow-up dataset. The follow-up dataset will be merged with the existing COMPILE dataset, containing baseline patient characteristics and 14 and 28 days outcomes.

Statistical methods: The analytic methods developed for and used in the main analysis of the COMPILE study [3] will be adapted for analysis of COMPILE-FollowUp data to accommodate the unequal follow-up

intervals for COMPILE patients (13 to 33 months) as well as the different treatments that patients might have received in the intermittent period.

Data sharing: The data from the COMPILE study have been stored in a secure platform (sandbox ) and access to the platform is provided upon approval by the COMPILE Consortium. The data from COMPILE FollowUp will be merged with the COMPILE dataset and made available in the same sandbox with the approval process for access.

Governance: The COMPILE-FollowUp study will be governed by the COMPILE governing bodies, including the Steering Committee (SC) and the Publications Committee (PC).

Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| COMPILE | Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients |
| CCP | COVID-19 Therapeutic Convalescent Plasma |
| FDA | Food and Drug Administration |
| FTP | File Transfer Protocol |
| GDPR | General Data Protection Regulations |
| HIPAA | Health Insurance Privacy and Accountability Act |
| IPD | Individual Patient Data |
| MCIT | Medical Center Information Technology |
| MFT | Managed File Transfer |
| NYU | New York University |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| RCT | Randomized Clinical Trial |
| SAP | Statistical Analysis Plan |
| SC | Steering Committee |
| VDI | Virtual Device Infrastructure |

# Contents

# 1 Introduction

## 1.1 Definitions

COMPILE CCP RCTs denotes the eight RCTs from Belgium, Brazil, India, the Netherlands, Spain and the USA (at UPenn, at UCSF and the multisite CONTAIN study at NYU).

COMPILE patients refers to the 2341 patients, data from whom was used in the COMPILE study and reported in [1].

A patient's index hospitalization refers to the hospitalization during which the patient participated in a COMPILE CCP RCT.

A patient's index COVID-19 illness refers to the illness episode during which the patient participated in a COMPILE CCP RCT.

Long COVID or what doctors refer to as post-acute sequelae of COVID-19 (PASC), is a condition marked by the continuation of COVID -19 symptoms—or the emergence of new ones—after recovery from acute (or the initial phase of illness of) COVID-19. While there is not yet a formal definition of long COVID, it generally refers to the persistence of symptoms four weeks or longer after the onset of COVID-19.

## 1.2 Study hypothesis

We hypothesize that data on the health status of COMPILE patients 13 to 33 months after the index COVID-19 illness will allow us to evaluate the long-term efficacy of CCP and to assess whether CCP treatment has effect on long COVID symptoms. The compilation of a pooled dataset of de-identified individual patient data (IPD) from COMPILE patients assessed at 13 - 33 months post their index illness will provide evidence regarding the long-term efficacy (or harm) of CCP as a treatment for COVID-19.

## 1.3 Background and rationale

Since the onset of the COVID-19 pandemic, there have been reports of people experiencing persistent symp-toms weeks to months after initial infection. Early studies in Europe reported persistence of symptoms in 87% of patients discharged from the hospital, although it is becoming evident that persistent symptoms after COVID-19 are not restricted to those who were critically ill or hospitalized but can occur in patients who had mild disease and never needed to be hospitalized. The Centers for Disease Control and Prevention (CDC) calls such cases "post-COVID conditions," an umbrella term that refers to a range of "new, returning, or ongoing health problems" experienced by people four or more weeks after initial coronavirus infection. Post-COVID conditions also go by several other names, including long COVID, long-haul COVID, chronic COVID, and post-acute COVID-19.

Given that, theoretically, treatment with polyclonal antibody could help retaining activity against evolving mutant strains, there is a reason to expect that treatment with CCP might be protective against new variants and/or against long COVID, see [4].

COMPILE- FollowUp protocol builds on the success of the COMPILE study, which has assembled systematic baseline characterization of 2341 patients, participants in the CCP trials mostly early on in the pandemic, likely infected with Alpha and Delta variants, and who received CCP from donors with those SARS-CoV-2 variants (the last participants in the COMPILE study was randomized in March 2021). This protocol calls for assessing COMPILE patients in 2022, which will constitute an interval of 13 to 33 months after each patient's index COVID-19 illness and treatment with CCP.

Data collected on the COMPILE patients will be transferred to the COMPILE data team at NYU in the same manner as in the COMPILE study.

COMPILE-FollowUp will be conducted under the same governing rules as COMPILE.

We recognize that the unequal time interval for follow-up for patients as well as the events patients experienced from their index COVID-19 illness to the follow-up assessment (e.g., vaccination and new infections)

will make the evaluation of the long-term efficacy of CCP statistically challenging. However, this problem is not insurmountable and the potential gains from finding answers regarding the long-term efficacy of CCP for COVID-19 treatment using the COMPILE sample, which is very well-characterized at baseline, makes this effort worth.

# 2 Study objectives

## 2.1 Primary objective

The primary objective of this study is to conduct follow-up assessments on COMPILE patients 13-33 months after their index COVID-19 illness when they participated in randomized RCTs evaluating the acute treat-ment efficacy of CCP for COVID- 19; to assemble those data and merge them with the existing COMPILE dataset, which contains baseline patient information and outcomes at days 14 (±1) and 28 (±2,); and to evaluate the long-term efficacy of CCP.

The follow up patient data will be transferred to the COMPILE-FollowUp data team on a regular bi-weekly basis. The data will be de-identified and patients will be assigned the same COMPILE ID number as in the COMPILE study.

### 2.1.1 Clinical assessment at follow-up

The clinical assessment will cover the period since hospital discharge from the index COVID-19 illness when the patient participated in the CCP RCT to the day of the assessment. The information can be obtained from the patients in person, or over the phone, from informers (e.g., spouse, parent, child, partner) of from medical records.

Information about the following health events will be obtained: Recurrent SARS-CoV- 2 Infection; Myocardial Infarction; Stroke; Deep Venous Thrombosis; Pulmonary Embolus; Hospitalization for Heart Failure; and Hospitalization for respiratory compromise, exacerbation of asthma or COPD;

The following symptoms, that are currently most frequently associated with long-COVID will be assessed: Fatigue; Shortness of breath; Cognitive dysfunction/brain fog/memory loss; Anxiety; Depression; Chest pain; Joint pain; Change in hearing; Change in smell; and Change in taste;

The following intermittent treatments will be assessed: Vaccine for SARS-CoV 2 (any dose, any vaccine); Initiation of renal replacement therapy (even temporarily); Transplant of Hearth; Transplant of Lung; and Transplant of Kidney.

### 2.1.2 Outcomes of interest

Outcome of interest are each of the major clinical events and the potential long-COVID symptoms assessed at follow-up, listed in Section 2.1.1.

## 2.2 Secondary objective

The secondary objective of this study is to investigate factors possibly related to the long- term efficacy of CCP and to assess if the CCP effects are heterogenious. Another secondary question is to evaluate the effects of intermittent treatments on the long-term CCP efficacy.

### 2.2.1 Differential effect of CP

One secondary goal is to assess the effect of specific patient baseline characteristics on the long-term efficacy of CP compared to control treatment. Such heterogeneous treatment effect was detected with respect to the efficacy of CCC with respect to acute COVID-19 treatment, [2 ], and we will employ similar approach to study the heterogeneity of the long-term CCP effects. The analysis of the COMPILE study identified wide heterogeneity of the treatment effect of CCP on the 14 and 28 days outcomes and we developed an index that was associated with this heterogeneity. Those investigations suggested that the larges benefit was experienced

by patients with pre-existing health conditions, such as diabetes, cardiovascular and pulmonary disease and who were treated at early stage of the COVID-19 disease. We plan to perform similar investigation to identify patients that in a long-term might benefit from CCP more than other individuals infected with COVID-19.

#### 2.2.2 Effect of intermittent treatments on the long-term effects of CCP

Patients could have received various treatments during the time interval from discharge from the index hospitalization to the follow up assessment time. Such treatments will be outside the COMPILE RCTs protocol and are likely to be imbalanced between the randomized treatment conditions in the COMPILE RCTs. We will assess the potential effect of those treatments on the long-term CCP efficacy. To address the lack of randomization in the receipt of those treatments, approached from causal inference for observational studies will be employed [5], including sensitivity analyses.

#### 2.2.3 Effect of antibodies in the donors' CCP

Information on the titers in the donor's plasma from half of the COMPILE patients treated with CCP is available. We will assess the evidence that the amount of titers in the donors' plasma is related to the long-term efficacy of CCP.

# 3 Ethical considerations

## 3.1 Informed consent

As required by local regulations, subjects or their legally authorized representatives will provide the necessary consent for collection of follow- up assessments. All patient data will be de-identified (the same de-identification process as the one used in the COMPILE study will be followed).

## 3.2 Protected health information

No protected health information (PHI), as defined by the Health Insurance Portability and Accountability Act (HIPAA) or the General Data Protection Regulations (GDPR), will be contained in the pooled datasets. No PHI from the RCT data will be transferred for this protocol. It will not be possible to identify patients from the pooled datasets. Key codes used to identify subjects will be retained only by participating RCT institutions and will not be available to members of this protocol as was done in the COMPILE study.

## 3.3 Risk to subjects

This protocol will re-assess the COMPILE patients. Data will be used only from patients who have signed informed consent. Follow-up data will be obtained through an interview with the patients, or an informant, or from medical records. No procedures other than an interview will be performed. Only de-identified data will be transferred to the COMPILE-FollowUp study. Therefore, risk to subjects is minimal.

## 3.4 Data storage

The accumulating dataset and the final dataset will be hosted at NYU DataCore and stored in a secure location at NYU.

# 4 Investigational plan

## 4.1 Study population

The COMPILE-FollowUp study will collect 12-33 months follow-up information of the COMPILE patients. The goal is to evaluate the long-term efficacy of CCP 13 - 33 months after the index COVID-19 illness.

In general, we will be analyzing the data on an intent- to-treat basis. However, the COMPILE patients might have received different treatments in the intermittent period between the end of the COMPILE CCP RCTs and the follow- up assessment. Therefore, special causal inference approaches, including sensitivity analysis, will be employed to obtain valid inferences regarding the long-term effects of CCP [5].

### 4.2 Data sources

Individual RCTs will transfer IPD to NYU's MCIT Research DataCore by secure file transfer protocol (FTP) using the GlobalScape managed file transfer (MFT) solution. The same process employed in the COMPILE data transfer protocol will be used in the COMPILE-FollowUp study.

### 4.3 Data merger

NYU maintains the COMPILE dataset in a secure environment. Follow-up data on COMPILE patients will be merged with the COMPILE dataset, which will be maintained by NYU as a common database within a secure Hadoop or MCIT-managed network drive.

### 4.4 Ensuring complete data de-identification

To ensure complete data de-identification in compliance with HIPPA and GDPR, the same process of de-identifying as the one used in COMPILE will be employed. Compile patients will be assigned the same COMPILE IDs as in the COMPILE study.

## 5 Statistical considerations

### 5.1 Follow-up data collection

Figure 1 shows the clinical research form (CRF) that will be used for follow-up assessments of COMPILE patients. Where required, the RCTs will translate this CRF in the local language. The researchers will be instructed to carefully communicate to the patients or their informers the time interval for which the reporting is required, as specified in the header of the CRF.

### 5.2 Data transfer

The information for formatting the data transferred to the COMPILE data repository is presented in the instructions for data transfer document.

### 5.3 Statistical analysis plan

See the most current version of the statistical analysis plan (SAP).

## 6 Administrative considerations

### 6.1 Compliance

This study will be conducted in accordance with all applicable laws and regulations related to human subjects' research, institutional research policies and procedures, and data privacy and security standards. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Ethics Committee, as applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed any required Human Subjects Protection Training.

**Definition of terms for the purposes of this form:**

Index COVID illness: COVID-19 illness when the patient participated in the convalescent plasma RCT
Hospital discharge: discharge from hospital stay during the index COVID illness

Information to be obtained from clinical records, patient report, or family member report

Complete this form with information regarding events, treatments, symptoms and vital status **AFTER hospital discharge from index episode during which the patient was enrolled in the original randomized controlled trial (RCT) and was randomized to convalescent plasma or control**

COMPILE RCT ID #_____ COMPILE Site ID #_____ COMPILE Patient ID #_____
Date of randomization in the convalescent plasma randomized controlled trial (RCT): Month___ Year___
Date this form is completed: Month____ Year_____

| **Events (Check all that apply)** | | | |
|---|---|---|---|
| **Has the patient experienced any of the following events?** | **Yes** | **No** | **Unsure** |
| Recurrent SARS – CoV 2 Infection | | | |
| Myocardial Infarction | | | |
| Stroke | | | |
| Deep Venous Thrombosis | | | |
| Pulmonary Embolus | | | |
| Hospitalization for Heart Failure | | | |
| Hospitalization for respiratory compromise, exacerbation of asthma or COPD | | | |

| **Treatments (Check all that apply)** | | | |
|---|---|---|---|
| **Has the patient received any of the following treatments?** | **Yes** | **No** | **Unsure** |
| Vaccine for SARS-CoV 2 (any dose, any vaccine) | | | |
| Initiation of renal replacement therapy (even temporarily) | | | |
| Transplant: | | | |
| Heart | | | |
| Lung | | | |
| Kidney | | | |

| **Symptoms (Check all that apply)** | | | | |
|---|---|---|---|---|
| **Has the patient experienced any of the following symptoms?** | **Yes** | | **No** | **Unsure** |
| | **Still present** | **Resolved** | | |
| Fatigue | | | | |
| If yes, did the fatigue limit everyday functioning | | | | |
| Shortness of breath | | | | |
| Cognitive dysfunction/brain fog/memory loss | | | | |
| Anxiety | | | | |
| Depression | | | | |
| Chest pain | | | | |
| Joint pain | | | | |
| Change in hearing | | | | |
| Change in smell | | | | |
| Change in taste | | | | |

| **Vital Status** | | | |
|---|---|---|---|
| **Indicate the patient status** | **Yes** | **No** | **Unknown** |
| Alive | | | |
| If dead: Month of Death……__ Year of Death……__ | | | |

Figure 1: Clinical research form for follow-up data collection

## 6.2 Data sharing

The data from the COMPILE study have been stored in a secure platform (sandbox ), where the dataset can be analysed with a provided set of analytic software. Access to the sandbox is provided after submission of a summary of the proposed research question and analytic approach and subsequent approval by the COMPILE Publications Committee (contact Chang.Yu@nyulangone.org and cc Renata.Schwartz@nyulangone.org). NYU provides to the approved requestor a snapshot or data dump of the COMPILE database, which will be cre - ated and stored within a virtual device infrastructure (VDI), or virtual machine, residing within NYU's DataCore. Designated analysts/programmers working with the approved requestor are provided with an NYU Kerberos ID and password, enabling remote access to the VDI; all analyses will be performed within the VDI. All statistical applications, analysis datasets, and programming will remain within the secure VDI.

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# References

[1] Andrea B. Troxel, Eva Petkova, Keith Goldfeld, Mengling Liu, Thaddeus Tarpey, Yinxiang Wu, Danni Wu, Anup Agarwal, Cristina Avenda˜no-Sol´a, Emma Bainbridge, Katherine J. Bar, Timothy Devos, Rafael F. Duarte, Arvind Gharbharan, Priscilla Y. Hsue, Gunjan Kumar, Annie F. Luetkemeyer, Geert Meyfroidt, Andr´e M. Nicola, Aparna Mukherjee, Mila B. Ortigoza, Liise-anne Pirofski, Bart J. A. Rijnders, Casper Rokx, Arantxa Sancho-Lopez, Pamela Shaw, Pablo Tebas, Hyun-Ah Yoon, Corita Grudzen, Judith Hochman, and Elliott M. Antman. Association of Convalescent Plasma Treatment With Clinical Status in Patients Hospitalized With COVID-19: A Meta-analysis. JAMA Network Open, 5(1):e2147331– e2147331, 01 2022.

[2] Hyung Park, Thaddeus Tarpey, Mengling Liu, Keith Goldfeld, Yinxiang Wu, Danni Wu, Yi Li, Jinchun Zhang, Dipyaman Ganguly, Yogiraj Ray, Shekhar Ranjan Paul, Prasun Bhattacharya, Artur Belov, Yin Huang, Carlos Villa, Richard Forshee, Nicole C. Verdun, Hyun ah Yoon, Anup Agarwal, Ven-tura Alejandro Simonovich, Paula Scibona, Leandro Burgos Pratx, Waldo Belloso, Cristina Avenda˜no-Sol´a, Katharine J Bar, Rafael F. Duarte, Priscilla Y. Hsue, Anne F. Luetkemeyer, Geert Meyfroidt, Andr´e M. Nicola, Aparna Mukherjee, Mila B. Ortigoza, Liise-anne Pirofski, Bart J. A. Rijnders, Andrea Troxel, Elliott M. Antman, and Eva Petkova. Development and Validation of a Treatment Benefit Index to Identify Hospitalized Patients With COVID-19 Who May Benefit From Convalescent Plasma. JAMA Network Open, 5(1):e2147375–e2147375, 01 2022.

[3] Keith S. Goldfeld, Danni Wu, Thaddeus Tarpey, Mengling Liu, Yinxiang Wu, Andrea B. Troxel, and Eva Petkova. Prospective individual patient data meta-analysis: evaluating convalescent plasma for COVID-19. Statistics in Medicine, 40(24):5131–5151, 2021.

[4] Lise Estcourt and Jeannie Callum. Convalescent Plasma for COVID-19 — Making Sense of the Inconsistencies. New England Journal of Medicine, 386(18):1753–1754, 2022.

[5] Hern´an MA and Robins JM. Causal Inference: What If. Chapman & Hall/CRC, 2020.

**Acordo do Consórcio COMPILE**
**2ª Emenda**

Esta 2ª Emenda ("Emenda n. 2") é firmada no dia 18 de Novembro de 2022 entre:

A NYU Grossman School of Medicine, unidade administrativa da New York University, com sede em 550 First Avenue, Nova York, Nova York 10016 (a "NYUGSoM"), e a Faculdade de Medicina da Universidade de Brasília (a "Pesquisadora do Consórcio") e a Fundação de Empreendimentos Científicos e Tecnológicos ("Finatec");

CONSIDERANDO que a NYUGSoM e a Pesquisadora do Consórcio celebraram o Acordo do Consórcio COMPILE, totalmente executado em 9 de novembro de 2020, (o "Acordo"), pelo qual a Pesquisadora do Consórcio concordou em participar de um projeto conjunto internacional, designado para combinar dados de pacientes de múltiplos testes controlados randomizados com plasma de pacientes convalescente hospitalizados com COVID-19 ("COMPILE"); e

CONSIDERANDO que as partes posteriormente alteraram o Acordo após a NYUGSoM receber financiamento dos Institutos Nacionais de Saúde, Centro Nacional de Promoção de Ciências Translacionais, CFDA 93.350, para apoiar a montagem do projeto COMPILE de Dados de Testes Qualificados, entre a Pesquisadora do Consórcio e outros colaboradores do projeto COMPILE, em um conjunto de Dados do Consórcio COMPILE, de forma a continuarem a ser geridos pela NYUGSoM (a "Concessora") (Emenda n. 1, datada de 5 de outubro de 2021); e

CONSIDERANDO que a NYUGSoM e a Pesquisadora do Consórcio desejam modificar o Acordo para que a Pesquisadora do Consórcio continue a participar do COMPILE sob a Expansão COMPILE e o Seguimento COMPILE, conforme descrito nesta emenda.

ASSIM, as partes concordam com o seguinte:

1. A Pesquisadora do Consórcio participará da Expansão do COMPILE e o Acordo é, portanto, alterado como segue:

   a. A Pesquisadora do Consórcio enviará à NYUGSoM os Dados descritos no Anexo A1 (o "Conjunto de Dados da Expansão COMPILE") conforme Protocolo da Expansão COMPILE, apensado a esta como Anexo C-1. Os dados da Expansão do COMPILE deverão ser enviados até 31 de dezembro de 2022 (o "Período Corrente").

   b. Após a entrega pela Pesquisadora do Consórcio e aceitação da NYUGSoM do Conjunto de Dados da Expansão do COMPILE, a NYUGSoM receberá a cobrança e a Pesquisadora do Consórcio será paga conforme o orçamento e metas, apensadas a esta no Anexo B. Todos os pagamentos especificados no Anexo B são consistentes com o valor de mercado e com uma transação comercial justa em relação ao trabalho fornecido.

2. A Pesquisadora do Consórcio participará no Seguimento COMPILE e o Acordo é, portanto, alterado como segue:

   a. A Pesquisadora do Consórcio enviará à NYUGSoM os Dados descritos no Anexo A-2 (o "Conjunto de Dados de Seguimento COMPILE"), conforme o Protocolo de Seguimento COMPILE, apensado a esta como Anexo C-2. Os dados do Seguimento COMPILE deverão ser enviados até o Período Corrente.

b. Após envio pela Pesquisadora do Consórcio e aceitação pela NYUSoM do Conjunto de Dados de Seguimento COMPILE, a NYUGSoM receberá a cobrança e a Pesquisadora do Consórcio será paga será paga conforme o orçamento e metas, apensadas a esta no Anexo B. Todos os pagamentos especificados no Anexo B são consistentes com o valor de mercado e com uma transação comercial justa em relação ao trabalho fornecido.

3. Com respeito aos métodos ou meios pelos quais a Finatec e a Pesquisadora do Consórcio são permitidas pela NYUGSoM como a Concessora a continuar usando os recursos após o Período Corrente, NYUGSoM defere às políticas e procedimentos da Finatec e da Pesquisadora do Consórcio caso elas permitam uso interno do recurso restante no período de **1 de janeiro de 2022 a 31 de dezembro de 2025** (o Período Residual). Até 31 de dezembro de 2022, a Pesquisadora do Consórcio deverá entregar os dados descritos nos Anexos A1 (o "Conjunto de Dados da Expansão COMPILE") e A-2 (o "Conjunto de Dados do Seguimento COMPILE"). No período de 01 de janeiro de 2023 a 31 de dezembro de 2025, a Pesquisadora do Consórcio poderá executar as atividades de pesquisa programadas em Plano de Trabalho específico estabelecido com a Finatec. Os fundos disponíveis para esta Emenda n. 2 estão comprometidos apenas para a Vigência especificada e não serão transferidos para qualquer outro período de atuação, salvo se a Vigência for estendida pelas partes por meio de uma emenda assinada por ambas.

4. Todos os termos em maiúsculas e abreviações utilizadas nesta, salvo indicação do contrário, possuem os significados definidos no Acordo, incluindo seus Anexos e Emendas.

5. Salvo pelas alterações expressamente aqui mencionadas, todos os outros termos e condições do Acordo e seus Anexos e Emendas permanecerão sem alterações, continuarão em pleno vigor e serão aplicáveis a esta Emenda n. 2.

Em testemunho, as partes fizeram com que esta Emenda n. 2 fosse assinada pelos seus respectivos representantes devidamente autorizados na data efetiva da Emenda n. 2.

Em nome da: **NYU Grossman School of Medicine**

ASSINATURA: _____

NOME EM LETRA DE FORMA: Samantha Ebel, JD, MPH

FUNÇÃO: Associate Director, O0053R

DATA CONTRATADA: 11/18/2022

Em nome da: **Universidade de Brasília**

Documento assinado digitalmente
gov.br DIEGO DE TASSIO SILVA
Data: 16/11/2022 16:24:59-0300
Verifique em https://verificador.iti.br

ASSINATURA: _____

NOME EM LETRA DE FORMA: DIEGO DE TÁSSIO SILVA

FUNÇÃO: SECRETÁRIO DE ASSUNTOS INTERNACIONAIS (SUBSTITUTO)

DATA: 16/11/2022

Em nome da: **Fundação de Empreendimentos Científicos e Tecnológicos**

ASSINATURA: AUGUSTO CESAR DE MENDONCA BRASIL:18741258215 Assinado de forma digital por AUGUSTO CESAR DE MENDONCA BRASIL:18741258215 Dados: 2022.11.17 12:04:53 -03'00'

NOME EM LETRA DE FORMA: Augusto César de Mendonça Brasil

FUNÇÃO: Diretor-Presidente

DATA: 16/11/2022

**ANEXO A-1**

A Expansão COMPILE solicita dados que podem ter sido obtidos no momento em que os pacientes foram randomizados no teste clínico randomizado COMPILE. Nenhum dado novo dos pacientes precisa ser coletado.

| Dados | | Tipo |
|---|---|---|
| Pressão arterial sistólica | | Número; ND = não disponível |
| Peso (em kg) | | Número; ND = não disponível |
| **Histórico Médico** | | |
| Histórico de asma | | 0 = não; 1 = sim; ND = não disponível |
| Histórico de terapia renal substitutiva | | 0 = não; 1 = sim; ND = não disponível |
| **Medicação na randomização** | | |
| Agente antiplaquetário | | 0 = não; 1 = sim; ND = não disponível |
| Anticoagulante intravenoso | | 0 = não; 1 = sim; ND = não disponível |
| Anticoagulante oral | | 0= não; 1 = sim; ND = não disponível |
| **Medição de anticorpos pré-tratamento** | | |
| IgG | | 0 = abaixo do cutoff[1]; 1 = acima do cutoff; ND = não disponível |
| IgM | | 0= abaixo do cutoff[2]; 1 = acima do cutoff; ND = não disponível |
| IgA | | 0= abaixo do cutoff[3]; 1 = acima do cutoff; ND = não disponível |
| **Pre-treatment antigen measurements** | | |
| Proteína Spike | | = abaixo do cutoff[4]; 1 = acima do cutoff; ND = não disponível |
| Nucleocapsídeo | | = abaixo do cutoff[5]; 1 = acima do cutoff; ND = não disponível |

1Este é um valor específico da análise – e ECR – abaixo do qual se considera que uma pessoa está negativa e acima do qual se considera que uma pessoa está positiva à presença de IgG

2 Este é um valor específico da análise – e ECR – abaixo do qual se considera que uma pessoa está negativa e acima do qual se considera que uma pessoa está positiva à presença de IgM

3 Este é um valor específico da análise – e ECR – abaixo do qual se considera que uma pessoa está negativa e acima do qual se considera que uma pessoa está positiva à presença de IgA

4 Este é um valor específico da análise – e ECR –acima do qual se considera que a proteína spike está presente

5 Este é um valor específico da análise – e ECR – acima do qual se considera que a proteína do nucleocapsídeo está presente

**ANEXO A-2**

**Definição de termos para os fins deste formulário:**

Episódio Indexado: enfermidade COVID-19 quando o paciente participou no ERC de plasma convalecente
Alta do Hospital: alta da internação hospitalar durante o episódio indexado

Informação a ser obtida de relatórios clínicos, relatos do paciente ou membros da família

Complete este formulário com informações sobre eventos, tratamentos, sintomas e status vitais **APÓS alta hospitalar durante o episódio indexado durante o qual o paciente foi registrado no estudo controlado randomizado (ECR) original e foi randomizado como plasma convalescente ou controle**

COMPILE ERC ID N._____ COMPILE Local ID N._____ COMPILE Paciente ID N._____
Data da randomização no estudo controlado randomizado (ECR) de plasma convalescente: Mês___ Ano___
Data de preenchimento deste formulário: Mês____ Ano_____

| Eventos (marque todos que se aplicam) | | | |
|---|---|---|---|
| O paciente experenciou algum dos seguintes eventos? | Sim | Não | Incerto |
| Infecção Recorrente por SARS – CoV 2 | | | |
| Infarto do Miocárdio | | | |
| AVC | | | |
| Trombose venosa profunda | | | |
| Embolia Pulmonar | | | |
| Internação por insuficiência cardíaca | | | |
| Internação por comprometimento respiratório, exacerbação de asma ou de DPOC | | | |

| Tratamentos (Marque todos que se aplicam) | | | |
|---|---|---|---|
| O paciente recebeu algum dos seguintes tratamentos? | Sim | Não | Incerto |
| Vacina para SARS-CoV 2 (qualquer dose, qualquer vacina) | | | |
| Início de terapia renal substitutiva (mesmo que temporária) | | | |
| Transplante: | | | |
| Coração | | | |
| Pulmão | | | |
| Rim | | | |

| Sintomas (Marque todos que se aplicam) | | | | |
|---|---|---|---|---|
| | Sim | | | |
| O paciente experenciou algum dos seguintes sintomas? | Ainda presente | Resolvido | Não | Incerto |
| Fadiga | | | | |
| Se sim, a fadiga limitou o desempenho diário | | | | |
| Falta de ar | | | | |
| Disfunção cognitiva/confusão mental/perda de memória | | | | |
| Ansiedade | | | | |
| Depressão | | | | |
| Dor no peito | | | | |
| Dor nas articulações | | | | |
| Alterações na audição | | | | |
| Alterações no olfato | | | | |
| Alterações no paladar | | | | |

| Status Vital | | | |
|---|---|---|---|
| Indique o status do paciente | Sim | Não | Desconhecido |
| Vivo | | | |
| Se falecido: Mês do falecimento ..... Ano do falecimento..... | | | |

Anexo B

Orçamento

| Meta | Custo por Meta | Custo total Máximo |
|---|---|---|
| ***Conjunto de dados da Expansão COMPILE*** Conforme estabelecido nos Anexos A-1 e C-1 | US$30.000,00 | US$30.000,00 |
| ***Conjunto de dados de Seguimento COMPILE*** Conforme estabelecido nos Anexos A-2 e C-2 | US$2.750,00 por paciente<br>Número máximo de pacientes: 31 | US$85.250,00 |

As faturas registradas na forma de Fatura de Exemplo anexadas a este serão geradas pela NYUGSoM e enviadas para a Instituição do Consórcio para certificação antes da autorização de pagamento. Os pagamentos serão feitos trimestralmente.

O contrato financeiro da NYUGSoM será:
Norka Rappoport, Office of Science and Research
One Park Ave., 6th floor
New York, NY 10016
929-455-2408(Office)
Norka.Rappoport@nyulangone.org

O contato financeiro do Pesquisador do Consórcio será:

Nome: _____
E-mail: _____
Phone: _____

Anexo B Fatura Exemplo

PARA: Dr. Eva Petkova
COMPILE COVID Projeto PI

DE: [INSERIR LÍDER DO ECR AQUI]
[INSERIR PAÍS DO ECR AQUI]

DATA: [INSERIR DATA AQUI]

REF.: Transferência de Dados para o Estudo COMPILE COVID

Onde aplicável para o ECR do nosso País, completamos a(s) seguinte(s) tarefa(s) para a Transferência de Dados COMPILE COVID durante o período do projeto iniciado em 1/1/2022:

O detalhamento por tarefas é o seguinte:

| | | | |
|---|---|---|---|
| | | | Total |
| Tarefa 1 | Expansão COMPILE | US$30.000,00 | |
| Tarefa 2 | Seguimento COMPILE | N. de participantes: _____ (US$2.750,00 Para cada) | |

Por gentileza, remeta o pagamento para o total de US$ _____ to:

[INSERIR INFORMAÇÕES DO ECR AQUI]
[ENDEREÇO]
[CIDADE, PAÍS]
ATENCIOSAMENTE: [INSERIR LÍDER DO ECR AQUI]

Em caso de dúvidas, favor enviar e-mail [INSERIR O E-MAIL DO PESQUISADOR PRINCIPAL AQUI].

# COMPILE Expand

Title: COMPILE Expand – Additional baseline data prior to treatment in a COMPILE CCP RCT

Short title: COMPILE Expand

Protocol version: 1.0

Date: 5/6/2022

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Authors: The COMPILE Consortium

Principal Investigator: Andrea B. Troxel, ScD, NYU Grossman School of Medicine

Steering Committee:

Andrea B. Troxel, ScD, New York University Grossman School of Medicine, NY, USA
(Chair) Liise-Anne Pirofski, MD, Albert Einstein College of Medicine, NY, USA
Mila Ortigoza, MD, New York University Grossman School of Medicine, NY,
USA Cristina Ave˜ndano Sol´a, MD, Universidad Aut´onoma de Madrid, Spain
Rafael F. Duarte Palomino, MD, Universidad Aut´onoma de Madrid,
Spain Priscilla Hsue, MD, University of California San Francisco, CA,
USA Annie Luetkemeyer, MD, University of California San Francisco,
CA, USA Katharine Bar, MD, University of Pennsylvania, PA, USA Andre
Moraes Nicola, MD, University of Bras´ılia, Brazil
Bart JA Rijnders, Erasmus University Medical Center, The Netherlands
Aparna Mukherje, PhD, Indian Council of Medical Research, India
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Hyung Park, PhD, New York University Grossman School of Medicine, NY, USA
Mengling Liu, PhD, New York University Grossman School of Medicine, NY,
USA Danni Wu, MS, New York University Grossman School of Medicine, NY,
USA Yi Li, MS, New York University Grossman School of Medicine, NY, USA
Eva Petkova, PhD, New York University Grossman School of Medicine, NY, USA

Advisors:

Elliott Antman, MD (cardiovascular medicine), Harvard School of Medicine, Boston, MA, USA

# PROTOCOL SYNOPSIS

## Title: COMPILE Expand – Additional baseline data prior to treatment in a COMPILE CCP RCT

## Short title: COMPILE Expand

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Background: COMPILE is a consortium of randomized controlled trials (RCTs) of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19 who were not on mechanical ventilation at the time of randomization. The primary objective was to pool individual patient data (IPD) from the different RCTs in order to obtain conclusive results regarding the efficacy of CCP faster than the individual trials would have allowed. Patients in the COMPILE study were enrolled from early 2020 to March 2021 and were observed until day 28(±2) after treatment initiation. The COMPILE database was locked in April 2021. Ultimately, 8 RCTs from 6 countries and 4 continents provided data on 2341 patients. The main results from the study were published [1]. The study also developed a treatment benefit index (TBI) that uses patients' pre-treatment characteristics to predict the specific benefit of acute treatment with CCP compared to treatment without CCP with respect to short-term outcomes at days 14(±1) and 28(±2) post-treatment [2]. An online calculator is available to facilitate the use of this tool in practice http://covid-convalescentplasma-tbi-calc.org.

This current COMPILE Expand study seeks to pool additional baseline data that has been collected as part of the COMPILE RCTs. This additional baseline patient information will be used in an attempt to refine the TBI developed in [2].

Research hypothesis: We hypothesize that combined with the COMPILE pooled dataset, the additional baseline data from COMPILE Expand will improve the initially developed TBI in [2], which would allow more precise guidance of treatment recommendations.

Primary objective: Our primary objective is to enrich the COMPILE dataset with additional baseline patient information. The COMPILE-Expand data will enrich the MDS pooled by COMPILE with additional baseline patient information. From the existing databases of the RCTs participating in COMPILE Expand will pool data on patients' pre-treatment antibodies as well as concomitant medication, and pre-existing health conditions that were not collected as part of the COMPILE MDS.

Secondary Objectives: A secondary objective is to examine whether different patients benefit from different amount of titers in the donors' plasma. One can think of this question as whether different doses of treatment are beneficial for different patients. COMPILE has assembled titers data from the donor's plasma transfused to 50% of the CCP treated patients and those data will be used to investigate the question about optimal "dose" of titers depending on patient characteristics.

Study design: De-identified additional baseline IPD from the COMPILE RCTs will be pooled and merged with the existing COMPILE dataset.

Statistical methods: The COMPILE TBI described in [3] was developed using a specific precision medicine approach described in [4], but several other approaches were tested also to ensure that optimal treatment recommendations can be made based on the TBI. We will use the same approach [4] in the attempt to refine the TBI with the additional baseline information. As in [3], we will also test alternative precision medicine techniques to compare and select the optimal approach.

The methods derived in [4] also allow the selection of optimal dose depending on patients' baseline characteristics and will be used for selecting optimal amount of titers in the donor's plasma for individual patients.

Data sharing: The pooled COMPILE-Expand data will be merged with the existing COMPILE data dataset and will be shared under the same rules.

Governance: The COMPILE-Expand study will be conducted under the governing documents for the COMPILE study.

Abbreviations

| | |
|---|---|
| COMPILE | Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients |
| CCP | COVID-19 Convalescent Plasma |
| FTP | File Transfer Protocol |
| GDPR | General Data Protection Regulations |
| HIPAA | Health Insurance Privacy and Accountability Act |
| IPD | Individual Patient Data |
| MCIT | Medical Center Information Technology |
| MDS | Minimal Data Set |
| MFT | Managed File Transfer |
| NYU | New York University |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| RCT | Randomized Clinical Trial |
| SAP | Statistical Analysis Plan |
| SC | Steering Committee |
| TBI | Treatment benefit index |
| VDI | Virtual Device Infrastructure |

# Contents

# 1 Introduction

## 1.1 Study hypotheses

We hypothesize that additional baseline variables will enable us to refine the treatment benefit index (TBI) [2] that we developed using the original COMPILE minimal data set (MDS). The additional baseline information will include patients' pre-treatment levels of antibodies, concomitant medications and pre-existing health conditions not assessed in the MDS. We also hypothesize that different patients have optimal response when transfused with convalescent plasma containing different amounts of titers and we will study how patient baseline characteristics and titers in donors' plasma jointly determine the benefit from treatment with CCP for individual patients.

## 1.2 Background

COMPILE is a consortium of randomized controlled trials (RCTs) of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19 who were not on mechanical ventilation at the time of randomization. The primary COMPILE objective was to pool individual patient data (IPD) from different RCTs in order to obtain conclusive results regarding the efficacy of CCP faster than the individual trials would have allowed. Patients in the COMPILE study were enrolled from early 2020 to March 2021 and were observed until day 28 (±2) after treatment initiation. The COMPILE database was locked in April 2021. Ultimately, 8 RCTs from 6 countries and 4 continents provided data on 2341 patients.

The main results from the study were published in [1]. The study also developed a treatment benefit index (TBI) that uses patients' pre- treatment characteristics to predict the specific benefit of acute treatment with CCP compared to treatment without CCP with respect to short -term outcomes at days 14(±1) and 28(±2) post-treatment [2]. An online calculator is available to facilitate the use of this tool in practice http://covid-convalescentplasma-tbi-calc.org.

The COMPILE study was conceived early on in the COVID-19 pandemic and collected only a minimal data set (MDS) of patients characteristics at baseline in order to reduce the burden on the RCTs' research teams extracting the information. The MDS was designed based on the existing knowledge at the time (Summer of 2020). Almost two years since the start of the COMPILE study has passed, and the knowledge about the COVID-19 and the accumulating information about the mechanisms of action of CCP, as well as other treatments for COVID-19, suggests that additional baseline patient information might be able to address remaining important questions regarding the efficacy of CCP and specifically, help identify patients who are expected to benefit most from CCP treatment.

Thus, the current COMPILE Expand study seeks to pool additional baseline data that has been collected as part of the COMPILE RCTs. This additional baseline patient information will be used in an attempt to refine the TBI developed in [2].

# 2 Study objectives

## 2.1 Primary objective

The primary objective of this expanded study is to refine the TBI developed using the original COMPILE dataset [2]. This therapeutic index predicts the expected relative treatment benefit from CCP compared with treatment without CCP for patients hospitalized for COVID-19 using patients' baseline characteristics. From the COMPILE RCTs, we will pool the following existing pre-treatment patient data that were not collected under the MDS used in the COMPILE study: concomitant medications (any antiplatelet agents, any intravenous anticoagulant agents, and any oral anticoagulant agents), vital signs (weight and systolic blood pressure (SBP)), pre-existing health conditions (receiving renal replacement therapy and asthma), and antibody and antigen measurements in the COMPILE patients pre-treatment.

#### 2.1.1 Primary outcome

All outcomes in the COMPILE-Expand study (including the primary ones) will be the same as the outcomes in the COMPILE study

## 2.2 Secondary objective

The secondary objective of this extended study is to generate an expanded COMPILE dataset of de-identified IPD from the COMPILE Consortium RCTs, to enable analyses to address additional related questions.

#### 2.2.1 Differential effect of CP

Another secondary objective is to assess the effect of specific patient characteristics on the efficacy of CP compared to control treatment. For this expanded study, these characteristics include the additional baseline variables: concomitant medications (any antiplatelet agents, any intravenous anticoagulant agents, and any oral anticoagulant agents), vital signs (weight, SBP), whether receiving renal replacement therapy, history of asthma, antibody and antigen measurements in recipients. A specific focus of COMPILE-Expand is to assess the effect of patients' pre-treatment antibody and antigen measurements. We will investigate whether and how these antibody and antigen measurements are related to the efficacy of CP compared to control treatment.

#### 2.2.2 Joint effect of patient characteristics and donors' plasma characteristics on CCP efficacy

Another objective is to examine whether different patients benefit from different amount of titers in the donors' plasma. One can think of this question as whether different doses of treatment are beneficial for different patients. COMPILE has assembled titers data from the donor's plasma transfused to 50% of the CCP treated patients and those data will be used to investigate the question about optimal "dose" of titers depending on patient characteristics. This is an enhanced precision medicine question that acknowledges that the best dose of a given treatment might be different between patients.

Usually, the question of dose comes in the context of adverse events, which have not been reported with transfusion of plasma. Recent literature [5, 6] indicates that the concentrations of titers in the donor's plasma is related to the efficacy of this treatment, which has led to the FDA recommendation that only CCP with high titers is used for treatment [7]. We will investigate the evidence that optimal titers' concentrations are different for patients with different characteristics.

# 3 Ethical considerations

## 3.1 Informed consent

All subjects or their legally authorized representatives have given informed consent for the RCT in which they are participating. All patient data will be de-identified (de-identification process described below in Section 4.4) and no additional patient data, that is not part of the data obtained for the qualifying trial in which the patient is participating, will be requested. Therefore, no additional informed consent is necessary.

## 3.2 Protected health information

No protected health information (PHI), as defined by the Health Insurance Portability and Accountability Act (HIPAA) or the General Data Protection Regulations (GDPR), will be contained in the pooled datasets. COMPILE-Expand uses the same procedures to protect patient health information as the original COMPILE protocol.

## 3.3 Risk to subjects

As COMPILE, the protocol for the COMPILE-Expand study will use de-identified, pre-existing data. Patients or their legally authorized representatives have already signed informed consent. No study subject

contact will take place, no additional data will be obtained outside of already collected data for the trial in which the subject is participating, and no PHI will be obtained. Therefore, risk to subjects is minimal.

### 3.4 Data storage

As in the original COMPILE study, the accumulating dataset and the final merged dataset will be hosted at NYU DataCore and stored in a secure location at NYU.

## 4 Investigational plan

### 4.1 Study population and sample

The study population for COMPILE-Expand is the population for the COMPILE study. The study sample consists of all 2341 COMPILE patients on whom data was reported in [1].

### 4.2 Data sources

Individual RCTs will transfer IPD to NYU's MCIT Research DataCore by secure file transfer protocol (FTP) using the GlobalScape managed file transfer (MFT) solution, using the same process as the COMPILE study.

The COMPILE RCTs, site and patient IDs assigned in the COMPILE study will be used in COMPILE-Expand.

### 4.3 Data merger

NYU maintains the COMPILE Consortium data in a secure environment. The data collected in COMPILE-Extpand will pooled across RCTs and merged with the COMPILE dataset in that secure environment.

### 4.4 Ensuring complete data de-identification

To ensure complete data deidentification in compliance with HIPPA and GDPR, the same processes used in COMPILE will be used in COMPILE-Expand

### 4.5 Variables collected in COMPILE-Expand

The COMPILE-Expand will collect the following baseline information on the COMPILE patients:

| Data | Type |
|---|---|
| Vital Signs | |
| Systolic blood pressure | # ; NA = not available |
| Weight (in kg) | # ; NA = not available |
| Disease history | |
| History of asthma | 0 = no; 1 = yes; NA = not available |
| History of receiving renal replacement therapy | 0 = no; 1 = yes; NA = not available |
| Pre-treatment antibodies measurements | |
| IgG | 0= below cutoff[1]; 1= above cutoff; NA = not available |
| IgM | 0= below cutoff[2]; 1= above cutoff; NA = not available |
| IgA | 0= below cutoff[3]; 1= above cutoff; NA = not available |
| Pre-treatment antigen measurements | |
| Spike protein | 0= below cutoff[4]; 1= above cutoff; NA = not available |
| Nuclocapsid | 0= below cutoff[5]; 1= above cutoff; NA = not available |
| Medications at randomization | |
| Any antiplatelet agent | 0 = no; 1 = yes; NA = not available |
| Any intravenous anticoagulant | 0 = no; 1 = yes; NA = not available |
| Any oral anticoagulant | 0 = no; 1 = yes; NA = not available |

# 5 Statistical considerations

## 5.1 Analysis data set

In the COMPILE-Expand study, the following baseline variables: concomitant medications (any antiplatelet agents, any intravenous anticoagulant agents, and any oral anticoagulant agents), vital signs (weight, SBP), whether receiving renal replacement therapy, history of asthma, antibody and antigen measurements in recipients, will be requested from the RCT teams. These variables combined with the original COMPILE MDS forms the analysis data set.

A separate document that defines these variables is attached as an appendix to this protocol.

## 5.2 Statistical analysis plan

The statistical analysis plan (SAP) of the original COMPILE study will be followed in the COMPILE-Expand study, as described in [3].

The strategy for refining the TBI will follow the derivations of the expanded TBI from the basic TBI in [2].

To explore the benefit from CCP as a function of both patient characteristics and titers concentrations in the donors' plasma, we will follow the approach described in [4].

[1] This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgG

[2] This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgM

[3] This is an assay- and RCT-specific value below which a person is considered negative and above which a person is considered positive presence of IgA

[4] This is an assay- and RCT -specific value above which spike protein is considered present [5] This is an assay- and RCT-specific value above which nucleocapsid is considered present

# 6 Administrative considerations

## 6.1 Compliance

This study will be conducted in accordance with all applicable laws and regulations related to human subjects' research, institutional research policies and procedures, and data privacy and security standards. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Ethics Committee, as applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed any required Human Subjects Protection Training.

## 6.2 Data sharing

The data from the COMPILE study have been stored in a secure platform (sandbox ), where the dataset can be analysed with a provided set of analytic software. Access to the sandbox is provided after submission of a summary of the proposed research question and analytic approach and subsequent approval by the COMPILE Publications Committee (contact Chang.Yu@nyulangone.org and cc Renata.Schwartz@nyulangone.org). NYU provides to the approved requestor a snapshot or data dump of the COMPILE database, which will be cre - ated and stored within a virtual device infrastructure (VDI), or virtual machine, residing within NYU's DataCore. Designated analysts/programmers working with the approved requestor are provided with an NYU Kerberos ID and password, enabling remote access to the VDI; all analyses will be performed within the VDI. All statistical applications, analysis datasets, and programming will remain within the secure VDI.

At the completion of COMPILE Follow Up data collection and transfer, the updated COMPILE dataset hosted by NYU DataCore will be finalized, harmonized, curated, and made available for additional analyses under the same rules at those currently used for access to the COMPILE data.

## 6.3 Governance

See the governance document.

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# COMPILE Follow Up

Title: COMPILE - A Follow Up of Patients 13 to 33 Months After Enrolment in the Convalescent Plasma Trials

Short title: COMPILE Follow Up

Protocol version: 1.0

Date: 5/6/2022

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# PROTOCOL SYNOPSIS

## Title: COMPILE - A Follow Up of Patients 13 to 33 Months After Enrolment in the Convalescent Plasma Trials

## Short title: COMPILE Follow Up

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Background: COMPILE is a consortium of randomized controlled trials (RCTs) of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19 who were not on mechanical ventilation at the time of randomization. The primary goal objective was to pool individual patient data (IPD) from the different RCTs in order to obtain conclusive results regarding the efficacy of CCP faster than the individual trials would have allowed. Patients in the COMPILE study were enrolled from early 2020 to March 2021 and were observed until day 28(±2) after treatment initiation. The COMPILE database was locked in April 2021. Ultimately, 8 RCTs from 6 countries and 4 continents provided data on 2341 patients. The main results from the study were published [1]. The study also developed a therapeutic benefit index that uses patients' pre-treatment characteristics to predict the specific benefit of acute treatment with CCP compared to treatment without CCP with respect to short-term outcomes at days 14(±1) and 28(±2) post-treatment. [2]. An online calculator is available to facilitate the use of this tool in practice http://covid-convalescentplasma-tbi-calc.org.

This current COMPILE Follow Up study seeks to collect data on the COMPILE patients 13 to 33 months after their participation in the RCTs with the goal of assessing the long-term efficacy of CCP.

Research hypothesis: We hypothesize that pooling systematic uniform follow-up information across COM-PILE patients 13 - 33 months after their participation in the CCP RCTs that were part of the COMPILE consortium, would allow the evaluation of the efficacy of CCP with respect to long-term outcomes, including long-COVID symptoms.

Primary objective: Our primary objective is to collect individual patient data (IPD) at follow up from the original COMPILE patients, a sample that is very well characterized at the time of patients' participation in the COMPILE CCP RCTs. Obtaining 13 to 33 month follow up data on a sample of patients who have detailed information prior to treatment with CCC for COVID-19, will allow us to evaluate whether CCP has effects in a long term. Patients will be contacted and assessed for specific clinical characteristics and events that occurred since they participated in the COMPILE RCTs. The follow-up data collected from COM-PILE patients will include information about vaccination, COVID-19 reinfection and symptoms, currently considered to be associated with long-COVID syndrome and major health events. The collected data will be de-identified employing the previously used COMPILE IDs, which would allow us to link the COMPILE data records with the follow-up patient information. We acknowledge that the follow-up intervals will differ between subjects which makes accurate assessment of the effects of CCP on the clinical characteristics com- plicated. Appropriate analytic methods will be employed to draw valid inferences regarding the long-term effects of CCP treatment.

Secondary objectives: A secondary objective is to study the potentially heterogeneous effects of CCP on long-term clinical status of patients infected with COVID-19 who survived. The analysis of the the COMPILE study identified wide heterogeneity of the acute treatment effect of CCP. Similar investigation is planned to identify patients that in a long-term might benefit from CCP more than other individuals infected with COVID-19. We will also investigate the effects of intermittent treatments, such as vaccination, on the CCP long-term efficacy.

Study design: COMPILE patients will be contacted and assessed for a set of clinical characteristics relevant to long-term health status after COVID-19 illness. The de-identified data will be pooled to construct and continuously update a COMPILE follow-up dataset. The follow-up dataset will be merged with the existing COMPILE dataset, containing baseline patient characteristics and 14 and 28 days outcomes.

Statistical methods: The analytic methods developed for and used in the main analysis of the COMPILE study [3] will be adapted for analysis of COMPILE-FollowUp data to accommodate the unequal follow-up

intervals for COMPILE patients (13 to 33 months) as well as the different treatments that patients might have received in the intermittent period.

Data sharing: The data from the COMPILE study have been stored in a secure platform (sandbox ) and access to the platform is provided upon approval by the COMPILE Consortium. The data from COMPILE FollowUp will be merged with the COMPILE dataset and made available in the same sandbox with the approval process for access.

Governance: The COMPILE-FollowUp study will be governed by the COMPILE governing bodies, including the Steering Committee (SC) and the Publications Committee (PC).

Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| COMPILE | Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients |
| CCP | COVID-19 Therapeutic Convalescent Plasma |
| FDA | Food and Drug Administration |
| FTP | File Transfer Protocol |
| GDPR | General Data Protection Regulations |
| HIPAA | Health Insurance Privacy and Accountability Act |
| IPD | Individual Patient Data |
| MCIT | Medical Center Information Technology |
| MFT | Managed File Transfer |
| NYU | New York University |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| RCT | Randomized Clinical Trial |
| SAP | Statistical Analysis Plan |
| SC | Steering Committee |
| VDI | Virtual Device Infrastructure |

# Contents

# 1 Introduction

## 1.1 Definitions

COMPILE CCP RCTs denotes the eight RCTs from Belgium, Brazil, India, the Netherlands, Spain and the USA (at UPenn, at UCSF and the multisite CONTAIN study at NYU).

COMPILE patients refers to the 2341 patients, data from whom was used in the COMPILE study and reported in [1].

A patient's index hospitalization refers to the hospitalization during which the patient participated in a COMPILE CCP RCT.

A patient's index COVID-19 illness refers to the illness episode during which the patient participated in a COMPILE CCP RCT.

Long COVID or what doctors refer to as post-acute sequelae of COVID-19 (PASC), is a condition marked by the continuation of COVID -19 symptoms—or the emergence of new ones—after recovery from acute (or the initial phase of illness of) COVID-19. While there is not yet a formal definition of long COVID, it generally refers to the persistence of symptoms four weeks or longer after the onset of COVID-19.

## 1.2 Study hypothesis

We hypothesize that data on the health status of COMPILE patients 13 to 33 months after the index COVID-19 illness will allow us to evaluate the long-term efficacy of CCP and to assess whether CCP treatment has effect on long COVID symptoms. The compilation of a pooled dataset of de-identified individual patient data (IPD) from COMPILE patients assessed at 13 - 33 months post their index illness will provide evidence regarding the long-term efficacy (or harm) of CCP as a treatment for COVID-19.

## 1.3 Background and rationale

Since the onset of the COVID-19 pandemic, there have been reports of people experiencing persistent symp-toms weeks to months after initial infection. Early studies in Europe reported persistence of symptoms in 87% of patients discharged from the hospital, although it is becoming evident that persistent symptoms after COVID-19 are not restricted to those who were critically ill or hospitalized but can occur in patients who had mild disease and never needed to be hospitalized. The Centers for Disease Control and Prevention (CDC) calls such cases "post-COVID conditions," an umbrella term that refers to a range of "new, returning, or ongoing health problems" experienced by people four or more weeks after initial coronavirus infection. Post-COVID conditions also go by several other names, including long COVID, long-haul COVID, chronic COVID, and post-acute COVID-19.

Given that, theoretically, treatment with polyclonal antibody could help retaining activity against evolving mutant strains, there is a reason to expect that treatment with CCP might be protective against new variants and/or against long COVID, see [4].

COMPILE- FollowUp protocol builds on the success of the COMPILE study, which has assembled systematic baseline characterization of 2341 patients, participants in the CCP trials mostly early on in the pandemic, likely infected with Alpha and Delta variants, and who received CCP from donors with those SARS-CoV-2 variants (the last participants in the COMPILE study was randomized in March 2021). This protocol calls for assessing COMPILE patients in 2022, which will constitute an interval of 13 to 33 months after each patient's index COVID-19 illness and treatment with CCP.

Data collected on the COMPILE patients will be transferred to the COMPILE data team at NYU in the same manner as in the COMPILE study.

COMPILE-FollowUp will be conducted under the same governing rules as COMPILE.

We recognize that the unequal time interval for follow-up for patients as well as the events patients experienced from their index COVID-19 illness to the follow-up assessment (e.g., vaccination and new infections)

will make the evaluation of the long-term efficacy of CCP statistically challenging. However, this problem is not insurmountable and the potential gains from finding answers regarding the long-term efficacy of CCP for COVID-19 treatment using the COMPILE sample, which is very well-characterized at baseline, makes this effort worth.

# 2 Study objectives

## 2.1 Primary objective

The primary objective of this study is to conduct follow-up assessments on COMPILE patients 13-33 months after their index COVID-19 illness when they participated in randomized RCTs evaluating the acute treat-ment efficacy of CCP for COVID- 19; to assemble those data and merge them with the existing COMPILE dataset, which contains baseline patient information and outcomes at days 14 (±1) and 28 (±2,); and to evaluate the long-term efficacy of CCP.

The follow up patient data will be transferred to the COMPILE-FollowUp data team on a regular bi-weekly basis. The data will be de-identified and patients will be assigned the same COMPILE ID number as in the COMPILE study.

### 2.1.1 Clinical assessment at follow-up

The clinical assessment will cover the period since hospital discharge from the index COVID-19 illness when the patient participated in the CCP RCT to the day of the assessment. The information can be obtained from the patients in person, or over the phone, from informers (e.g., spouse, parent, child, partner) of from medical records.

Information about the following health events will be obtained: Recurrent SARS-CoV- 2 Infection; Myocardial Infarction; Stroke; Deep Venous Thrombosis; Pulmonary Embolus; Hospitalization for Heart Failure; and Hospitalization for respiratory compromise, exacerbation of asthma or COPD;

The following symptoms, that are currently most frequently associated with long-COVID will be assessed: Fatigue; Shortness of breath; Cognitive dysfunction/brain fog/memory loss; Anxiety; Depression; Chest pain; Joint pain; Change in hearing; Change in smell; and Change in taste;

The following intermittent treatments will be assessed: Vaccine for SARS-CoV 2 (any dose, any vaccine); Initiation of renal replacement therapy (even temporarily); Transplant of Hearth; Transplant of Lung; and Transplant of Kidney.

### 2.1.2 Outcomes of interest

Outcome of interest are each of the major clinical events and the potential long-COVID symptoms assessed at follow-up, listed in Section 2.1.1.

## 2.2 Secondary objective

The secondary objective of this study is to investigate factors possibly related to the long- term efficacy of CCP and to assess if the CCP effects are heterogenious. Another secondary question is to evaluate the effects of intermittent treatments on the long-term CCP efficacy.

### 2.2.1 Differential effect of CP

One secondary goal is to assess the effect of specific patient baseline characteristics on the long-term efficacy of CP compared to control treatment. Such heterogeneous treatment effect was detected with respect to the efficacy of CCC with respect to acute COVID-19 treatment, [2 ], and we will employ similar approach to study the heterogeneity of the long-term CCP effects. The analysis of the COMPILE study identified wide heterogeneity of the treatment effect of CCP on the 14 and 28 days outcomes and we developed an index that was associated with this heterogeneity. Those investigations suggested that the larges benefit was experienced

by patients with pre-existing health conditions, such as diabetes, cardiovascular and pulmonary disease and who were treated at early stage of the COVID-19 disease. We plan to perform similar investigation to identify patients that in a long-term might benefit from CCP more than other individuals infected with COVID-19.

#### 2.2.2 Effect of intermittent treatments on the long-term effects of CCP

Patients could have received various treatments during the time interval from discharge from the index hospitalization to the follow up assessment time. Such treatments will be outside the COMPILE RCTs protocol and are likely to be imbalanced between the randomized treatment conditions in the COMPILE RCTs. We will assess the potential effect of those treatments on the long-term CCP efficacy. To address the lack of randomization in the receipt of those treatments, approached from causal inference for observational studies will be employed [5], including sensitivity analyses.

#### 2.2.3 Effect of antibodies in the donors' CCP

Information on the titers in the donor's plasma from half of the COMPILE patients treated with CCP is available. We will assess the evidence that the amount of titers in the donors' plasma is related to the long-term efficacy of CCP.

# 3 Ethical considerations

## 3.1 Informed consent

As required by local regulations, subjects or their legally authorized representatives will provide the necessary consent for collection of follow- up assessments. All patient data will be de-identified (the same de-identification process as the one used in the COMPILE study will be followed).

## 3.2 Protected health information

No protected health information (PHI), as defined by the Health Insurance Portability and Accountability Act (HIPAA) or the General Data Protection Regulations (GDPR), will be contained in the pooled datasets. No PHI from the RCT data will be transferred for this protocol. It will not be possible to identify patients from the pooled datasets. Key codes used to identify subjects will be retained only by participating RCT institutions and will not be available to members of this protocol as was done in the COMPILE study.

## 3.3 Risk to subjects

This protocol will re-assess the COMPILE patients. Data will be used only from patients who have signed informed consent. Follow-up data will be obtained through an interview with the patients, or an informant, or from medical records. No procedures other than an interview will be performed. Only de-identified data will be transferred to the COMPILE-FollowUp study. Therefore, risk to subjects is minimal.

## 3.4 Data storage

The accumulating dataset and the final dataset will be hosted at NYU DataCore and stored in a secure location at NYU.

# 4 Investigational plan

## 4.1 Study population

The COMPILE-FollowUp study will collect 12-33 months follow-up information of the COMPILE patients. The goal is to evaluate the long-term efficacy of CCP 13 - 33 months after the index COVID-19 illness.

In general, we will be analyzing the data on an intent- to-treat basis. However, the COMPILE patients might have received different treatments in the intermittent period between the end of the COMPILE CCP RCTs and the follow- up assessment. Therefore, special causal inference approaches, including sensitivity analysis, will be employed to obtain valid inferences regarding the long-term effects of CCP [5].

### 4.2 Data sources

Individual RCTs will transfer IPD to NYU's MCIT Research DataCore by secure file transfer protocol (FTP) using the GlobalScape managed file transfer (MFT) solution. The same process employed in the COMPILE data transfer protocol will be used in the COMPILE-FollowUp study.

### 4.3 Data merger

NYU maintains the COMPILE dataset in a secure environment. Follow-up data on COMPILE patients will be merged with the COMPILE dataset, which will be maintained by NYU as a common database within a secure Hadoop or MCIT-managed network drive.

### 4.4 Ensuring complete data de-identification

To ensure complete data de-identification in compliance with HIPPA and GDPR, the same process of de-identifying as the one used in COMPILE will be employed. Compile patients will be assigned the same COMPILE IDs as in the COMPILE study.

## 5 Statistical considerations

### 5.1 Follow-up data collection

Figure 1 shows the clinical research form (CRF) that will be used for follow-up assessments of COMPILE patients. Where required, the RCTs will translate this CRF in the local language. The researchers will be instructed to carefully communicate to the patients or their informers the time interval for which the reporting is required, as specified in the header of the CRF.

### 5.2 Data transfer

The information for formatting the data transferred to the COMPILE data repository is presented in the instructions for data transfer document.

### 5.3 Statistical analysis plan

See the most current version of the statistical analysis plan (SAP).

## 6 Administrative considerations

### 6.1 Compliance

This study will be conducted in accordance with all applicable laws and regulations related to human subjects' research, institutional research policies and procedures, and data privacy and security standards. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Ethics Committee, as applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed any required Human Subjects Protection Training.

**Definition of terms for the purposes of this form:**

Index COVID illness: COVID-19 illness when the patient participated in the convalescent plasma RCT
Hospital discharge: discharge from hospital stay during the index COVID illness

Information to be obtained from clinical records, patient report, or family member report

Complete this form with information regarding events, treatments, symptoms and vital status **AFTER hospital discharge from index episode during which the patient was enrolled in the original randomized controlled trial (RCT) and was randomized to convalescent plasma or control**

COMPILE RCT ID #_____ COMPILE Site ID #_____ COMPILE Patient ID #_____
Date of randomization in the convalescent plasma randomized controlled trial (RCT): Month___ Year___
Date this form is completed: Month____ Year_____

| **Events (Check all that apply)** | | | |
|---|---|---|---|
| **Has the patient experienced any of the following events?** | **Yes** | **No** | **Unsure** |
| Recurrent SARS – CoV 2 Infection | | | |
| Myocardial Infarction | | | |
| Stroke | | | |
| Deep Venous Thrombosis | | | |
| Pulmonary Embolus | | | |
| Hospitalization for Heart Failure | | | |
| Hospitalization for respiratory compromise, exacerbation of asthma or COPD | | | |

| **Treatments (Check all that apply)** | | | |
|---|---|---|---|
| **Has the patient received any of the following treatments?** | **Yes** | **No** | **Unsure** |
| Vaccine for SARS-CoV 2 (any dose, any vaccine) | | | |
| Initiation of renal replacement therapy (even temporarily) | | | |
| Transplant: | | | |
| Heart | | | |
| Lung | | | |
| Kidney | | | |

| **Symptoms (Check all that apply)** | | | | |
|---|---|---|---|---|
| **Has the patient experienced any of the following symptoms?** | **Yes** | | **No** | **Unsure** |
| | **Still present** | **Resolved** | | |
| Fatigue | | | | |
| If yes, did the fatigue limit everyday functioning | | | | |
| Shortness of breath | | | | |
| Cognitive dysfunction/brain fog/memory loss | | | | |
| Anxiety | | | | |
| Depression | | | | |
| Chest pain | | | | |
| Joint pain | | | | |
| Change in hearing | | | | |
| Change in smell | | | | |
| Change in taste | | | | |

| **Vital Status** | | | |
|---|---|---|---|
| **Indicate the patient status** | **Yes** | **No** | **Unknown** |
| Alive | | | |
| If dead: Month of Death……__ Year of Death……__ | | | |

Figure 1: Clinical research form for follow-up data collection

## 6.2 Data sharing

The data from the COMPILE study have been stored in a secure platform (sandbox ), where the dataset can be analysed with a provided set of analytic software. Access to the sandbox is provided after submission of a summary of the proposed research question and analytic approach and subsequent approval by the COMPILE Publications Committee (contact Chang.Yu@nyulangone.org and cc Renata.Schwartz@nyulangone.org). NYU provides to the approved requestor a snapshot or data dump of the COMPILE database, which will be cre - ated and stored within a virtual device infrastructure (VDI), or virtual machine, residing within NYU's DataCore. Designated analysts/programmers working with the approved requestor are provided with an NYU Kerberos ID and password, enabling remote access to the VDI; all analyses will be performed within the VDI. All statistical applications, analysis datasets, and programming will remain within the secure VDI.

At the completion of COMPILE Follow Up data collection and transfer, the updated COMPILE dataset hosted by NYU DataCore will be finalized, harmonized, curated, and made available for additional analyses under the same rules at those currently used for access to the COMPILE data.

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