

Statistical Modeling Proposal  
for  
Continuous Monitoring of Pooled International Trials  
of Convalescent Plasma for COVID-19 Hospitalized Patients  
COMPILE

Version 1.2  
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# 1 Goals of the COMPILE study

The primary goal of the COMPILE study is to establish the efficacy (or lack there of) and safety of convalescent plasma (CP) for the treatment of COVID-19 in the target population. The target population is hospitalized patients that are not on ventilators at time of enrollment and treatment.

# 2 Qualifying RCT participants

To qualify for inclusion in the COMPILE study dataset, participants in the individual RCTs should satisfy the following conditions:

- Confirmed COVID-19 diagnosis by a diagnostic test
- Not on ventilator at time of treatment
- If the participant was randomized to CP (rather than the control arm of the RCT) there should be confirmation that the plasma the participant received contained antibodies. The confirmations should be by either of the following:
  - Prospective qualitative or quantitative assay prior to the transfusion
  - Retrospective qualitative or quantitative assay after the transfusion

# 3 Proposed minimal data set

Variable	Value
<b>Trial level</b>	
Blinding	0 = no; 1 = single blind; 2 = double blind
Randomization	0 = no; 1 = yes
Units of CP/control treatment	#
Control treatment	0 = standard of care; 1 = non-convalescent plasma; 2 = saline/LR with coloring agent
COMPILE trial number	character
Number of recruitment sites for RCT	#
Date the RCT opened enrollment	Date
<b>Patient baseline characteristics</b>	
Quarter during which patient was enrolled	1 = January-March, 2020; 2 = April-June, 2020; 3 = July-September, 2020; 4 = October-December, 2020; 5 = January-March, 2021; 6 = April-June, 2021; 7 = July-September, 2021; 8 = October-December, 2021
Treatment <sup>1</sup>	0 = control; 1 = convalescent plasma
Age in years	# ; NA= not available
Sex	0 = male; 1 = female; 2 = other; NA= not available

<sup>1</sup>The COMPILE study will collect antibody data when available.

Race	0 = American Indian/Alaska Native; 1 = Black or African American; 2 = White; 3 = Asian; 4 = Native Hawaiian or Pacific Islander; 5 = mixed race/other; NA= not available
Hispanic ethnicity	0 = no; 1 = yes; NA= not available
Blood group	0 = O; 1 = A; 2 = B; 3 = AB; 4 = not available
History of diabetes (all types)	0 = no; 1 = yes; NA= not available
History of pulmonary disease	0 = no; 1 = yes; NA= not available
History of cardiovascular disease	0 = no; 1 = yes; NA= not available
Days since symptoms onset at time of enrollment	1 = 0 to 3; 2 = 4 to 6; 3 = 7 to 14; 4 = more than 14; NA= not available
Days since COVID-19 diagnosis at time of enrollment	#; NA= not available
Status at time of enrollment	0 = outpatient; 1 = hospitalized non ICU; 2 = ICU
Time of treatment in days since enrollment	#; NA= not available
<b>Concomitant medications</b>	
Antibacterial	0 = no; 1 = yes; NA= not available
Antiviral	0 = no; 1 = yes; NA= not available
Anti-inflammatory	0 = no; 1 = yes; NA= not available
Steroids	0 = no; 1 = yes; NA= not available
Anticoagulants	0 = no; 1 = yes; NA= not available
<b>Adverse events</b>	
TRALI	0 = no; 1 = yes
TACO	0 = no; 1 = yes
Transfusion reaction (other than TRALI or TACO)	0 = no; 1 = yes
Arterial thrombotic event	0 = no; 1 = yes
Venous thrombotic event	0 = no; 1 = yes
<b>Outcomes</b>	
WHO ordinal 11-point scale at day 14 $\pm$ 1 day <sup>2</sup>	0 – 10
Mortality at day 14 $\pm$ 1 day	0 = no; 1 = yes
WHO ordinal 11-point scale at day 30 $\pm$ 2 days	0 – 10
Mortality at day 30 $\pm$ 2 days	0 = no; 1 = yes

Table 1: Minimal data set (MDS) for the COMPILE study

Information regarding the titers of antibodies in CP will be collected when available.

<sup>2</sup>The COMPILE study will collect daily WHO scores when available.

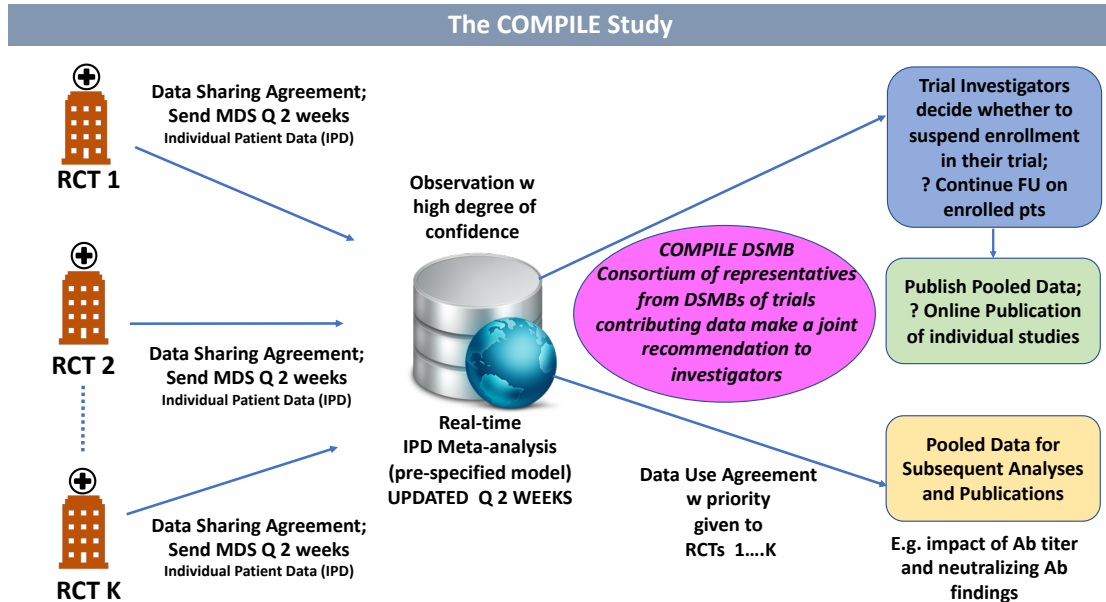


Figure 1: Schema of the COMPILE project as planned for trials of convalescent plasma in hospitalized patients with COVID-19. The Data Sharing Agreement will govern monitoring, publications and other aspects of the individual patient data pooling. A central repository for the pooled data will be established with continuous updating with new data at 2-week intervals. Unblinded biostatisticians will conduct the interim analyses and report to the COMPILE DSMB. When evidence with a high degree of confidence emerges, the DSMB will make a joint recommendation to the leadership of all trials. The plans for publication and subsequent analyses are shown on the right side of the schema. Ab: antibody, FU: followup; MDS: minimal data set; Q 2 weeks: every 2 weeks.

## 4 Proposed efficacy outcome

The outcome is the WHO COVID-19 ordinal scale with 11 levels: from 0 = not uninfected, to 10 = dead ([https://www.thelancet.com/action/showPdf?pii=S1473-3099\(20\)30483-7](https://www.thelancet.com/action/showPdf?pii=S1473-3099(20)30483-7)). There are earlier versions of this outcome; the most commonly used alternative versions have 7 or 8 levels scored in the opposite direction: 1 = dead. We have inverted the 7- and 8-point scales and show how to transform those scales into the 11-point WHO scale that will be used in the pooled data analysis.

### 4.1 7-point WHO scale: inverted

- 1: Not hospitalized without limitation in activity
- 2: Not hospitalized with limitation in activity
- 3: Hospitalized not on supplemental oxygen
- 4: Hospitalized on supplemental oxygen
- 5: Hospitalized on non-invasive ventilation or high flow nasal cannula

6: Hospitalized on invasive mechanical ventilation or ECMO

7: Death

## **4.2 8-point WHO scale: inverted**

1: No clinical or virological evidence of infection

2: Not hospitalized without limitations on activities

3: Not hospitalized with limitation on activities

4: Hospitalized not on supplemental oxygen

5: Hospitalized on supplemental oxygen

6: Hospitalized on non-invasive ventilation or high flow nasal cannula

7: Hospitalized, on invasive mechanical ventilation or ECMO

8: Death

## **4.3 11-point WHO scale**

0: Uninfected, no viral RNA detected

1: Asymptomatic, viral RNA detected

2: Symptomatic, independent

3: Symptomatic, assistance needed

4: Hospitalized, no oxygen therapy

5: Hospitalized, oxygen by mask or nasal prongs

6: Hospitalized, oxygen by non-invasive ventilation or high flow

7: Intubation & Mechanical ventilation,  $pO_2/FIO_2 \geq 150$  or  $SpO_2/FIO_2 \geq 200$

8: Mechanical ventilation,  $pO_2/FIO_2 < 150$  ( $SpO_2/FIO_2 < 200$ ) or vasopressors

9: Mechanical ventilation,  $pO_2/FIO_2 < 150$  and vasopressors, dialysis or ECMO

10: Dead

## 4.4 Converting 7-point and 8-point scales into the 11-point WHO scale

The following changes were made to align the WHO 11-point scale with the 7-point and 8-point scales

- “Intubation/mechanical ventilation” status (Score of 6 on 7-point scale and score of 7 on 8-point scale) is further divided into 3 categories depending on P/F ratio and vasopressor/dialysis/ECMO requirement
- “Not hospitalized without limitation status” (Score of 1 on 7-point scale and score of 1 or 2 on 8-point scale) is further divided into 2-3 categories depending on presence of symptoms and detection of viral RNA.

These factors will need to be taken into account when translating the 7- or 8-point scale to the 11-point scale. Table 2 shows the conversion of the 7- and 8-point scales to the 11-point WHO ordinal scale

7-point	8-point	11-point
1 (if no viral RNA detected)	1 (if no viral RNA detected)	0
1 (if asymptomatic)	1	1
1 (if symptomatic, independent)	2	2
2	3	3
3	4	4
4	5	5
5	6	6
6 (if pO <sub>2</sub> /FIO <sub>2</sub> ≥ 150 or SpO <sub>2</sub> /FIO <sub>2</sub> ≥ 200)	7 (if pO <sub>2</sub> /FIO <sub>2</sub> ≥ 150 or SpO <sub>2</sub> /FIO <sub>2</sub> ≥ 200)	7
6 (if pO <sub>2</sub> /FIO <sub>2</sub> < 150 (SpO <sub>2</sub> /FIO <sub>2</sub> < 200) or vasopressors)	7 (if pO <sub>2</sub> /FIO <sub>2</sub> < 150 (SpO <sub>2</sub> /FIO <sub>2</sub> < 200) or vasopressors)	8
6 (if pO <sub>2</sub> /FIO <sub>2</sub> < 150 and vasopressors, dialysis or ECMO)	7 (if pO <sub>2</sub> /FIO <sub>2</sub> < 150 and vasopressors, dialysis or ECMO)	9
7	8	10

Table 2: Rules for converting WHO 7- and 8-point scales into the 11-point scale

## 5 Proposed strategy for analyzing the pooled data and monitoring the pooled RCTs

### 5.1 Model for the efficacy outcome

#### 5.1.1 Cumulative odds model for the ordinal efficacy outcome

We now assume that all outcomes  $Y$  are scored on the WHO 11-point scale ( $Y=0, \dots, 10$ ).

Let  $q_y = P(Y = y)$ ,  $y = 0, \dots, 10$ ,  $\sum_{y=0}^{10} q_y = 1$  and let

$$p_y = P(Y \geq y) = \sum_{s=y}^{10} q_s, \quad y = 1, \dots, 10. \quad (1)$$

Assume that data from  $K$  studies are available. Only subjects randomized to the CP or the control condition from the studies will be used, i.e., patients randomized to other active treatments in a study with more than 1 treatment arm will be ignored. There are  $n_k$  subjects in the  $k$ -th study,  $k = 1, \dots, K$ . Denote the outcome for the  $i$ -th patient from the  $k$ -th study on the 11-point WHO ordinal COVID-19 scale at day 14 by  $Y_{ki} = y$ ,  $y = 0, \dots, 10$ , and that patient's baseline covariates (a vector of length  $m$ ) by  $\mathbf{x}_{ki}$ . Also, denote by  $p_{kiy}$  the respective probabilities in (1) for the  $i$ -th subject in the  $k$ -th study.

Because all studies will have the intervention arm of convalescent plasma but may have different control arms, we propose a statistical model with the following notation for treatment effect modeling. Let  $\mathbf{I}^{ctrl}$  be a 3-dimensional indicator vector for the treatment and let  $C$  denote the control treatment variable from Table 1, Part "Trial Level". Then

$$\begin{aligned} \mathbf{I}^{ctrl} &= (1, 0, 0) && \text{Control treatment } C = 0 \text{ (standard of care)} \\ \mathbf{I}^{ctrl} &= (0, 1, 0) && \text{Control treatment } C = 1 \text{ (non-convalescent plasma)} \\ \mathbf{I}^{ctrl} &= (0, 0, 1) && \text{Control treatment } C = 2 \text{ (saline/LR with coloring agent)} \\ \mathbf{I}^{ctrl} &= (0, 0, 0) && \text{Active treatment (convalescent plasma),} \end{aligned}$$

and  $\mathbf{I}_{ki}^{ctrl}$  will indicate the treatment assignment for subject  $i$  in the  $k$ -th study. The corresponding  $k$ -th study-specific control-arm effects are denoted by  $\mathbf{I}_{ki}^{ctrl} \boldsymbol{\delta}_k$ , where  $\boldsymbol{\delta}_k = (\delta_{k0}, \delta_{k1}, \delta_{k2})'$ , and the across-study control effects are denoted by  $\boldsymbol{\delta}_C = (\delta_0, \delta_1, \delta_2)'$ .

The following cumulative odds model for  $Y_{ki}$  will be considered:

$$\begin{aligned} Y_{ki} &\sim \text{Ordinal multinomial}(\mathbf{p}_{ki}), \quad \mathbf{p}_{ki} = \{p_{kiy}\}_1^{10} \\ \text{logit}(P(Y_{ki} \geq y)) &= \tau_{yk} + \boldsymbol{\beta}_k \mathbf{x}_{ki} + \mathbf{I}_{ki}^{ctrl} \boldsymbol{\delta}_k \\ \tau_{yk} &\sim \text{Normal}(0, 10), \text{ monotone within } k \\ \boldsymbol{\beta}_k &\sim \text{Normal}(\mathbf{0}, 10^3 I_{m \times m}) \\ \mathbf{I}_k^{ctrl} \boldsymbol{\delta}_k &\sim \text{Normal}(\delta_c, \eta^2), \quad c = 0, 1, 2 \text{ for the 3 control conditions} \\ \eta &\sim \text{Cauchy}(0, 2.5) \\ \delta_c &\sim \text{Normal}(-\Delta, 0.1), \quad c = 0, 1, 2 \\ -\Delta &\sim \text{Normal}(0, 0.354). \end{aligned} \tag{2}$$

The proposed model (2) conceptualizes the three control conditions as three treatments to be compared against the reference condition of convalescent plasma (CP). Being the reference treatment, the log odds defined from the cumulative probabilities of CP arm are estimated by  $\alpha_{yk}$  from (2), which corresponds to the  $k$ -th study's intercept associated with level  $y$  on the ordinal WHO outcome  $Y = y, y = 1, \dots, 10$ . We impose a very skeptical hyper-prior for these site-specific CP effects. All  $\alpha_{yk}, y = 1, \dots, 10$  and  $\alpha_y$  satisfy the monotonicity requirements for the intercepts of the proportional odds model. We impose a hyper-prior distribution for the three study-specific control treatment effects, which come from the same distribution with the overall treatment effect  $-\Delta$  being the parameter of primary interest. We take  $-\Delta$  as the mean of the distribution to which  $\delta_c$ 's belong so that  $\Delta$  will correspond to the difference of log-odds for CP minus log-odds for control, rather than control minus CP.

### 5.1.2 Stopping for efficacy, futility, or harm

We propose considerations for stopping the enrollment based on the following posterior probabilities for the ratio of the odds for higher severity on WHO score for CP vs. control ( $OR = e^\Delta$ )

- Stopping for efficacy

$$P(e^\Delta < 1) = P(\Delta < 0) \geq 0.95 \quad \text{and} \quad P(e^\Delta < 0.8) = P(\Delta < \ln(0.8)) > 0.5$$

- Stopping for futility or harm

$$P(e^\Delta > 1) = P(\Delta > 0) \geq 0.8.$$

## 5.2 Model for the safety outcome

We propose monitoring for safety based on adverse events related to the transfusion of plasma. Specifically we will compare the CP and control conditions with respect to the proportion of patients who experienced at least one of the adverse events in Table 1: TRALI, TACO, any other transfusion reaction, arterial or venous thrombotic effect.

### 5.2.1 Logistic regression model for the safety outcome

Let  $Z_{ki}$  be an indicator that the  $i$ -th subject in the  $k$ -th study experiencing safety related event. Similar to the consideration in Section 5.1.1, to accommodate the three different control conditions, we conceptualize the three different control conditions as three treatments to be compared against the reference condition (CP). The effects of the control conditions  $C = c, c = 0, 1, 2$  on the transfusion-related adverse events, will be denoted by  $\theta_c, c = 0, 1, 2$  and we will impose a hyper-prior distribution for those three estimated of the control conditions, that are coming from the same distribution. Being the reference treatment, the log odds of having the transfusion-related event in the CP arm is estimated by  $\gamma_k$  from (3), which corresponds to the  $k$ -th study's intercept. We impose a very skeptical hyper-prior for these site-specific CP safety effects.

The following logistic regression model will be used to model  $Z$ :

$$\begin{aligned}
 Z_{ki} &\sim \text{Bino}(r_{ki}), \quad 0 < r_{ki} < 1 \\
 \text{logit}(P(Z_{ki})) &= \gamma_k + \boldsymbol{\lambda}_k \mathbf{x}_{ki} + \mathbf{I}_{ki}^{ctrl} \boldsymbol{\theta}_k \\
 \gamma_k &\sim \text{Normal}(0, 10) \\
 \boldsymbol{\lambda}_k &\sim \text{Normal}(\mathbf{0}, 10^3 I_{m \times m}) \\
 \mathbf{I}_k^{ctrl} \boldsymbol{\theta}_k &\sim \text{Normal}(\theta_c, \eta^2), \quad c = 0, 1, 2 \text{ for the 3 control conditions} \\
 \eta &\sim \text{Cauchy}(0, 2.5) \\
 \theta_c &\sim \text{Normal}(-\Theta, 0.1), \quad c = 0, 1, 2 \\
 -\Theta &\sim \text{Normal}(0, 0.354),
 \end{aligned} \tag{3}$$

Similar to Section 5.1.1, we take  $-\Theta$  as the mean of the distribution to which  $\theta_c$ 's belong, so that  $\Theta$  will correspond to the difference of log-odds for CP minus log-odds for control, rather than control minus CP.



### 5.2.2 Stopping for safety

We propose stopping for safety if the posterior probability for the ratio of the odds for adverse events in the CP condition compared to the control condition satisfies:

$$P(e^{\Theta} > 1) = P(\Theta > 0) > 0.75.$$

### 5.3 Model for mortality outcome

An important secondary outcome will be mortality at day 14 ( $\pm 1$  day) and at day 30 ( $\pm 2$  days). This outcome will be analyzed using a logistic regression model similar to the model for the safety events (3).

### 5.4 Content of the DSMB reports

All reports to DSMB will include summary of the results from fitting model (2) for the WHO scores at day 14 and day 30 and model (3) for the safety events and for mortality at day 14 and day 30. In addition to reporting the prespecified posterior probabilities associated with the stopping rules in Section 5.1.2 and Section 5.2.2, we will present the posterior distributions for the odds ratios of interest as shown in Figure 2.

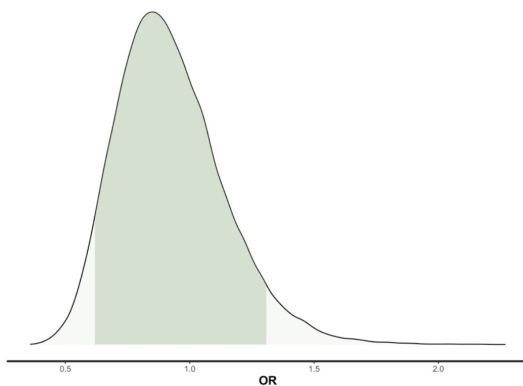


Figure 2: A made up example: the posterior distribution of the odds ratio (OR) for the effect of CP compared to all controls with respect to the WHO score at day 30. The shaded area corresponds for the 95% credible interval, on each side of which there are 0.025 probabilities. All probabilities of interest can be computed from the analyses. For example, in addition the the  $P(OR < 1)$  and  $P(OR < 0.8)$ , the DSMB will be able to see the posterior probability for any cut-off for the OR, such as  $P(OR < 0.98)$  and  $P(OR < 0.9)$ .