To: Rita Reik, MD (22 January 2022 – Updated 8 April 2022)

From: Michael J. Joyner, MD & Arturo Casadevall MD/PHD

Re: Efficacy of Convalescent Plasma (CP) and COVID-19 – Working Draft

Background: In early 2020, CP was the first passive immunity strategy used to treat patients with active COVID-19 infections. It was deployed at scale in the United States. There is population-based data demonstrating that as the pandemic progressed in 2020, consistent with the well-established principles of antibody therapy, clinicians at the bedside used high titer CP early in the course of disease. An epidemiologic analysis of correlating CP use and mortality suggests that CP saved as many as 100,000 lives in the USA. As the pandemic continues information from an impressive array of randomized controlled trials, retrospective studies, case series, and case reports have accrued to define key parameters associated with effective use of CP. *A holistic view of the entirety of the data indicates that if sufficient antibodies are administered early in the course of disease, disease progression can be limited, and a mortality benefit is seen.*

Outpatient Trials: There are four major outpatient trials showing signals of efficacy for CP. The Libster Trial in the NEJM and the Hopkins Trial also in the NEJM both administered high titer plasma to patients very early after symptom onset and diagnosis and reduced hospital admissions by ~50%. The C3PO study was reported as negative but an inordinately large number of patients in the plasma treatment arm were admitted on the index visit. When the data is analyzed excluding patients admitted on the index visit, CP administration reduces admissions by ~35%. A report from Europe that combined two similar trials that were terminated early due to slowing enrollment as the first wave of the pandemic waned, reported evidence that CP administered within five days of symptom onset reduced hospital admissions and death. ***Summary of Outpatient Trials:*** *Two of four outpatient trials of CP clearly demonstrate efficacy. When design and analysis issues are considered four of four trials demonstrate efficacy. This data should also be viewed in the context of 1) the loss of efficacy of some monoclonal antibodies, and 2) observations indicating that plasma from individuals who have been infected and vaccinated or experienced breakthrough infections is likely effective against a wide array of variants.* The Infectious Disease Society of America guidelines have recently been updated to support the outpatient use of CP in some circumstances.

Inpatient Trials: There are five major inpatient trials that were reported relatively early in the course of the pandemic. Top line results for all were categorized as "negative", but all violated the principles of antibody therapy by either focusing on later use and in some cases the quality of the CP was marginal. In essence these trials tested CP in patients where it was unlikely to work and then concluded that it was ineffective creating a futile logical cycle. Of note RECOVERY demonstrated signals of efficacy in patients requiring minimal supplemental oxygen, not on steroids and/or treated within seven days of diagnosis. Both Simonovich and Agarwal demonstrated symptomatic improvement. CONCOR-1 showed a clear dose response curve for CP with improved outcomes with the highest quality plasma. REMAPCAP showed evidence of benefit with early treatment and in immunosuppressed patients. More recently the TSUNAMI trial reported no overall benefit, but clear evidence of efficacy in less severely ill patients treated early. Additionally, the CONTAIN trial shows evidence of efficacy – especially early in the pandemic – in patients with less severe disease. Detailed commentaries and critiques of some of these and other trials are available at https://ccpp19.org/news/index.html. In addition to the "negative" trials with signals of efficacy embedded in them noted above, there are RCTs that clearly show benefit when high titer plasma is given early and in several there is some evidence of efficacy with later use. Noteworthy examples include O'Donnell, Bar, and Körper. ***Tables 1 & 2*** are Chalmers style analyses of the papers just reviewed and data from additional trials categorized by optimal and suboptimal use of CP. A validated

Treatment Benefit Index calculator is available based a patient level meta-analysis to identify inpatients most likely to benefit from CP,

Summary Inpatient Trials: *All major negative RCTs show signals of efficacy especially in subgroups treated consistent with the principles of antibody therapy. RCTs that tested the earlier use case and/or higher doses of plasma have been more uniformly positive. A treatment benefit index calculator is available to aid clinical decision making about the use of CP.*

Retrospective Matched Control Trials: A number of retrospective matched control studies have been performed. These have been graphically summarized and in general demonstrate a relative mortality benefit of 25-50% when – consistent with the principles of antibody therapy, high titer plasma is administered early in the course of hospitalization. Two of the most sophisticated analyses include a large nationwide real world data set from the Hospital Corporation of America and also data From Houston Methodist Hospital. The high titer early use case is also supported by data from the US EAP. Two additional large EAP-like studies from Argentina and Italy yielded similar observations that early use of CP in hospitalized patients was associated with reduced mortality.

Immunosuppressed Patients: There are numerous case series and case reports showing that CP can have dramatic effects when administered as *replacement therapy* to patients who are unable to generate endogenous antibodies. These have been summarized as of the middle of 2021 with an update in the progress. Importantly, two matched control trials (one from the US and one from France) focused primarily on B-Cell depleted COVID-19 patients with heme-malignancies demonstrate a marked mortality benefit when patients are treated with CP.

Caveats: There is also evidence that plasma obtained in close proximity to where it was used has increased efficacy. Additionally, data from numerous sources indicates that CP obtained from individuals who have recovered from infection and been vaccinated or experienced breakthrough infections is extremely high titer and covers a wide array of variants. This “hybrid” or “Vax” plasma appears to be widely available in the standard blood donor pool and the number of potential donors is almost certainly increasing dramatically.

Overall Summary: Convalescent Plasma when used in a manner consistent with the principles of antibody therapy is effective in reducing disease progression and mortality in patients with COVD-19. As the pandemic continues, very high titer and “broad spectrum” plasma is available from the many donors who have both recovered from disease and been vaccinated or vaccinated donors who have experienced breakthrough infections. Of note, in contrast to monoclonal antibodies, CP also adapts within a matter of weeks to novel variants. The use case for CP as replacement therapy for patients unable to generate endogenous antibodies is strong. CP is also potentially available worldwide. Two years into the COVID-19 pandemic, the knowledge base, experience, and potential supply of CP means that it can be used optimally during the next phases of the pandemic and when COVID-19 becomes endemic. Many lessons have been learned that can be applied in preparation for future outbreaks of novel infectious diseases.

Table 1.*

Mortality rates among randomized clinical trials of optimal use convalescent plasma therapy for COVID-19

	Convalescent Plasma			Control					
Study	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	**Mechanical ventilation (%)**	**Titer**	**Time to transfusion (days)**
Avendaño-Solà et al.	172	7	4%	157	14	8%	0%	High titer	1 (admission)
Bar et al.	38	2	5%	29	10	26%	0%	High titer	1 (admission)
Bennett-Guerrero et al.	43	16	27%	10	5	33%	19%	High titer	4 (admission)
Devos et al.	310	10	3%	155	8	5%	0%	High titer	7 (symptoms)
Gharbharan et al.	37	6	14%	32	11	26%	12%	High titer	2 (admission)
Korper et al.	42	11	21%	35	17	33%	30%	High titer	2 (admission)
Libster et al.	78	2	3%	76	4	5%	0%	High titer	3 (symptoms)
Menichetti F et al.	217	14	6%	221	19	8%	0%	High titer	7 (symptoms)
O'Donnell et al.	131	19	13%	55	18	25%	11%	High titer	9 (symptoms)
Ortigoza et al. (No corticosteroids subgroup)	85	9	10%	69	18	21%	0%	High titer	1 (admission)
Simonovich et al.	197	25	11%	93	12	11%	0%	High titer	8 (symptoms)
Sullivan et al.	592	0	0%	289	3	1%	0%	High titer	6 (symptoms)
The CONCOR-1 Study Group (high titer subgroup)	268	75	22%	133	40	23%	0%	High titer	5 (diagnosis)
The RECOVERY Collaborative Group (No corticosteroids subgroup)	317	74	19%	313	100	24%	5%	High Titer	2 (admission)
The REMAP-CAP Investigators (Moderate state subgroup)	54	8	13%	17	7	29%	0%	High titer	2 (admission)
The SIREN-C3PO Investigators	256	5	2%	253	1	0%	0%	High titer	4 (symptoms)
Overall	**2837**	**283**	**9.1%**	**1937**	**287**	**12.9%**			

$\chi^2 = 20.13$, $P < 0.001$; 41.7% relative mortality reduction associated with convalescent plasma therapy

Table 2.

Mortality rates among randomized clinical trials of non-optimal use convalescent plasma therapy for COVID-19

	Convalescent Plasma			Control					
Study	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	**Mechanical ventilation (%)**	**Titer**	**Time to transfusion (days)**
Agarwal et al.	201	34	14%	198	31	14%	8%	Not high titer	4 (admission)
Ali Shaukat et al.	30	10	25%	4	6	60%	3%	Not high titer	8 (symptoms)
AlQahtani et al.	19	1	5%	18	2	10%	0%	-	-
Bajpai et al.	11	3	21%	14	1	7%	0%	Not high titer	3 (symptoms)
Bandopadhyay et al.	30	10	25%	26	14	35%	-	Not high titer	-
Gonzalez et al.	60	70	54%	28	32	53%	85%	-	-
Kirenga B et al.	59	10	14%	59	8	12%	0%	-	7 (symptoms)
Li et al.	43	8	16%	38	12	24%	30%	Not high titer	33 (symptoms)
Ortigoza et al. (Corticosteroids subgroup)	334	17	5%	333	24	7%	0%	High titer	1 (admission)
Pouladzadeh et al.	27	3	10%	25	5	17%	10%	Not high titer	0 (admission)
Rasheed et al.	20	1	5%	20	8	29%	81%	Not high titer	4+ (admission)
The CONCOR-1 Study Group (not high titer subgroup)	205	66	24%	101	23	19%	0%	Not high titer	5 (diagnosis)
The RECOVERY Collaborative Group (Corticosteroids subgroup)	4056	1314	24%	4012	1299	24%	5%	High titer	2 (admission)
The REMAP-CAP Investigators (Severe state subgroup)	679	407	37%	557	347	38%	0%	High titer	2 (admission)
Sekine et al.	62	18	23%	67	13	16%	30%	Not high titer	10 (symptoms)
Overall	**5836**	**1972**	**25.3%**	**5500**	**1825**	**24.9%**			

$\chi^2 = 0.23$, $P = 0.63$; - indicates data not available

**Analysis performed by S. Klassen, PHD and J. Senefeld, PHD*