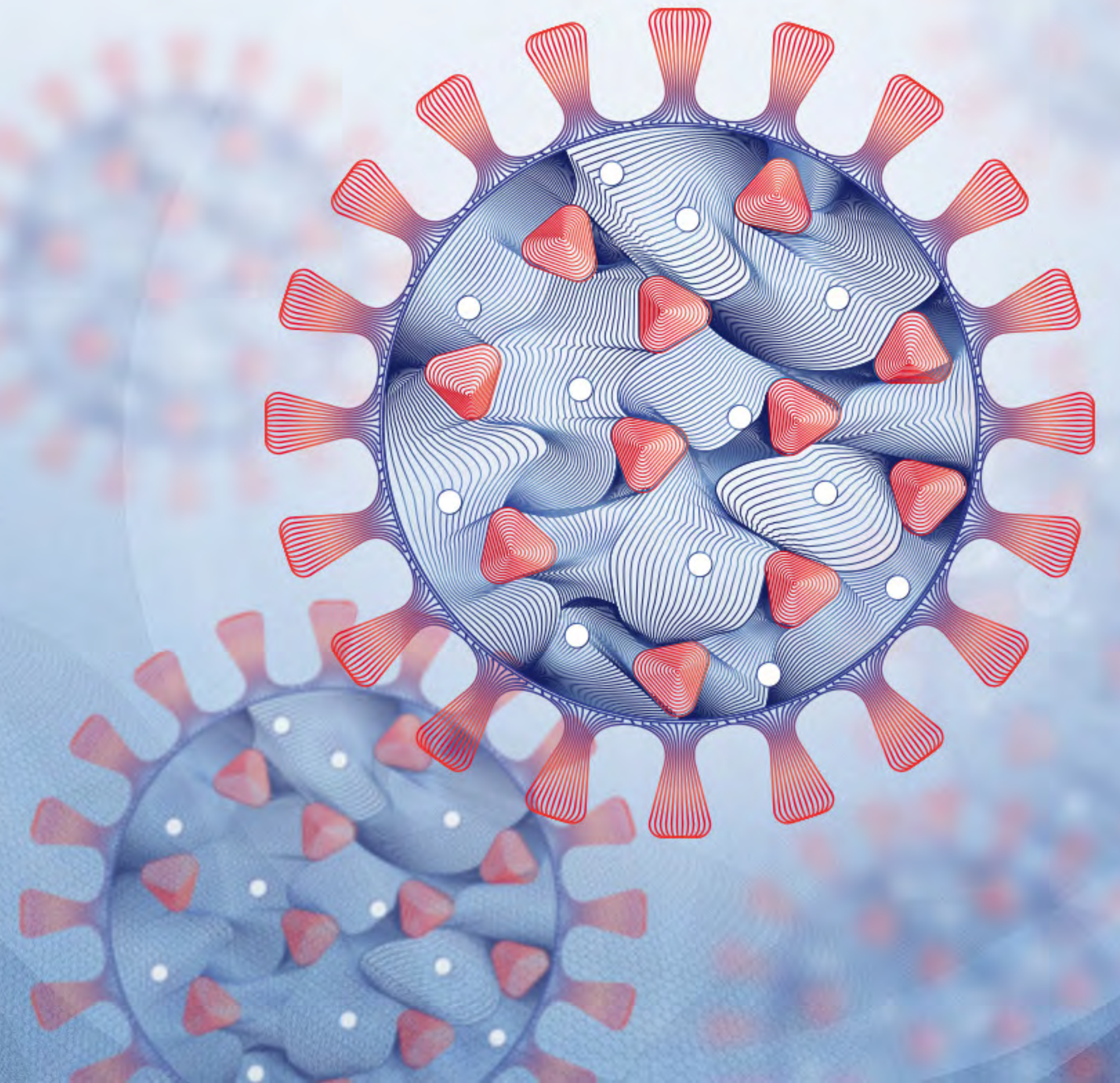


CytoSorb Therapy

Global decision support for
COVID-19 patients

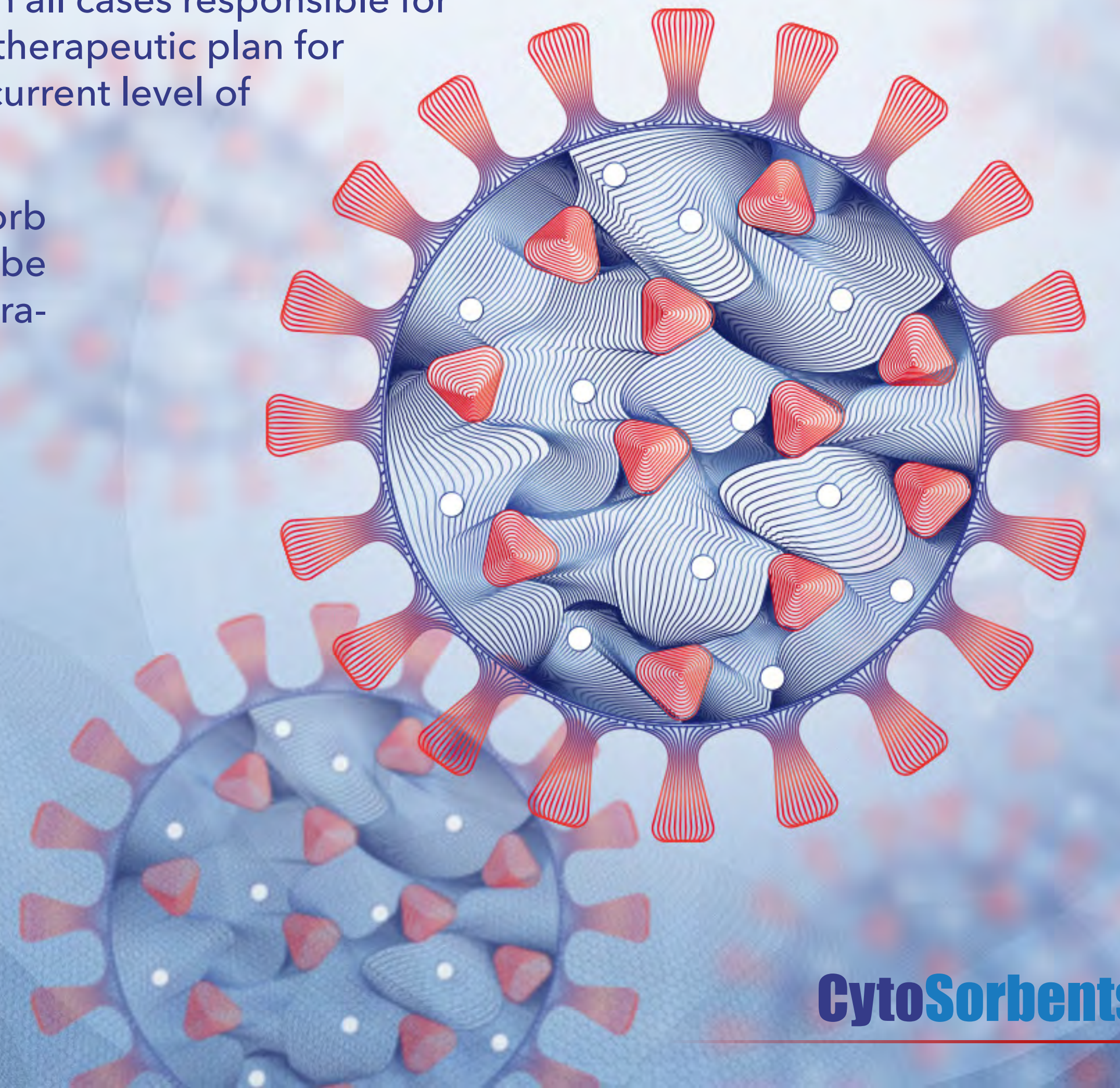


Disclaimer

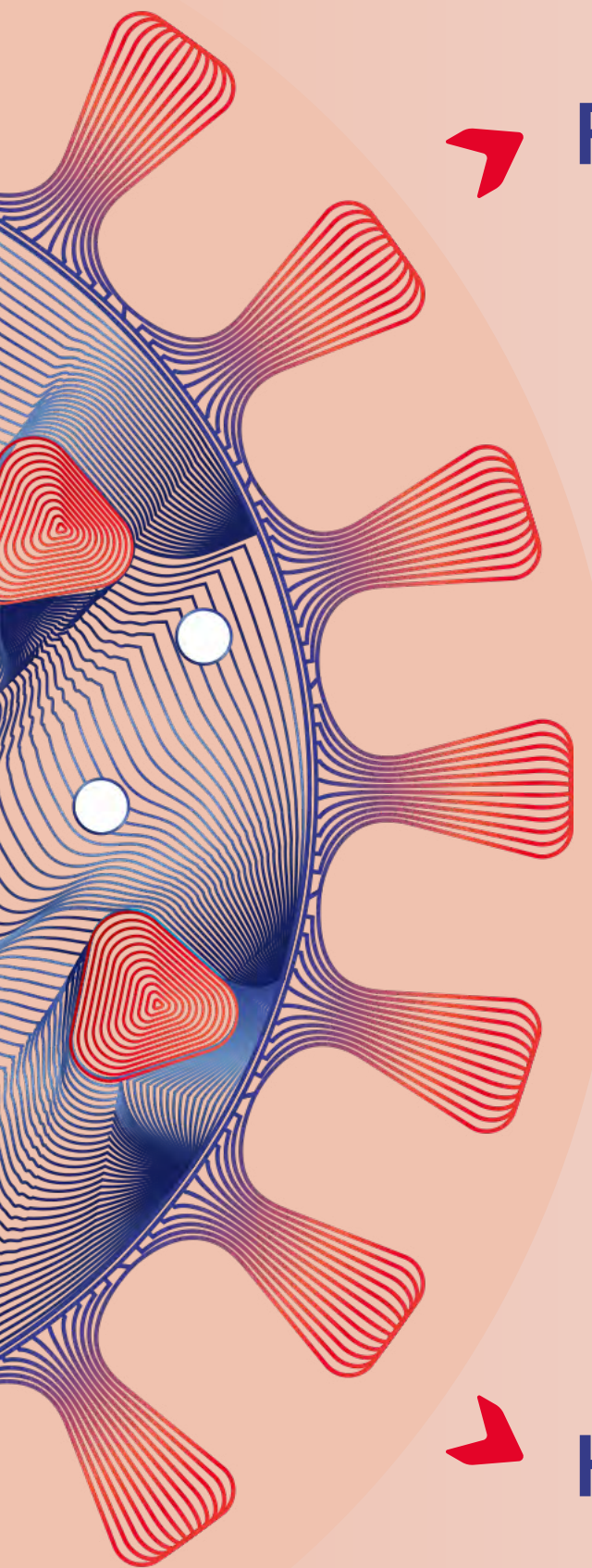
This decision guidance is for health care professionals outside the USA only. It is non-binding and cannot replace the therapy decisions of the treating physician, who is in all cases responsible for the development and implementation of an adequate diagnostic and therapeutic plan for each individual patient. It is a “best practice” collection, based on the current level of knowledge and expert opinion.

The clinical and preclinical data and results obtained with the CytoSorb adsorber are not transferable to other products. CytoSorb should only be administered by personnel who have been properly trained in administration of extracorporeal therapies.

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Criteria for considering CytoSorb in COVID-19 patients



- Refractory vasoplegic shock
- Moderate ARDS
- ECMO / ECLS
- AKI stage III with start CRRT
- H-Score suggesting sHLH



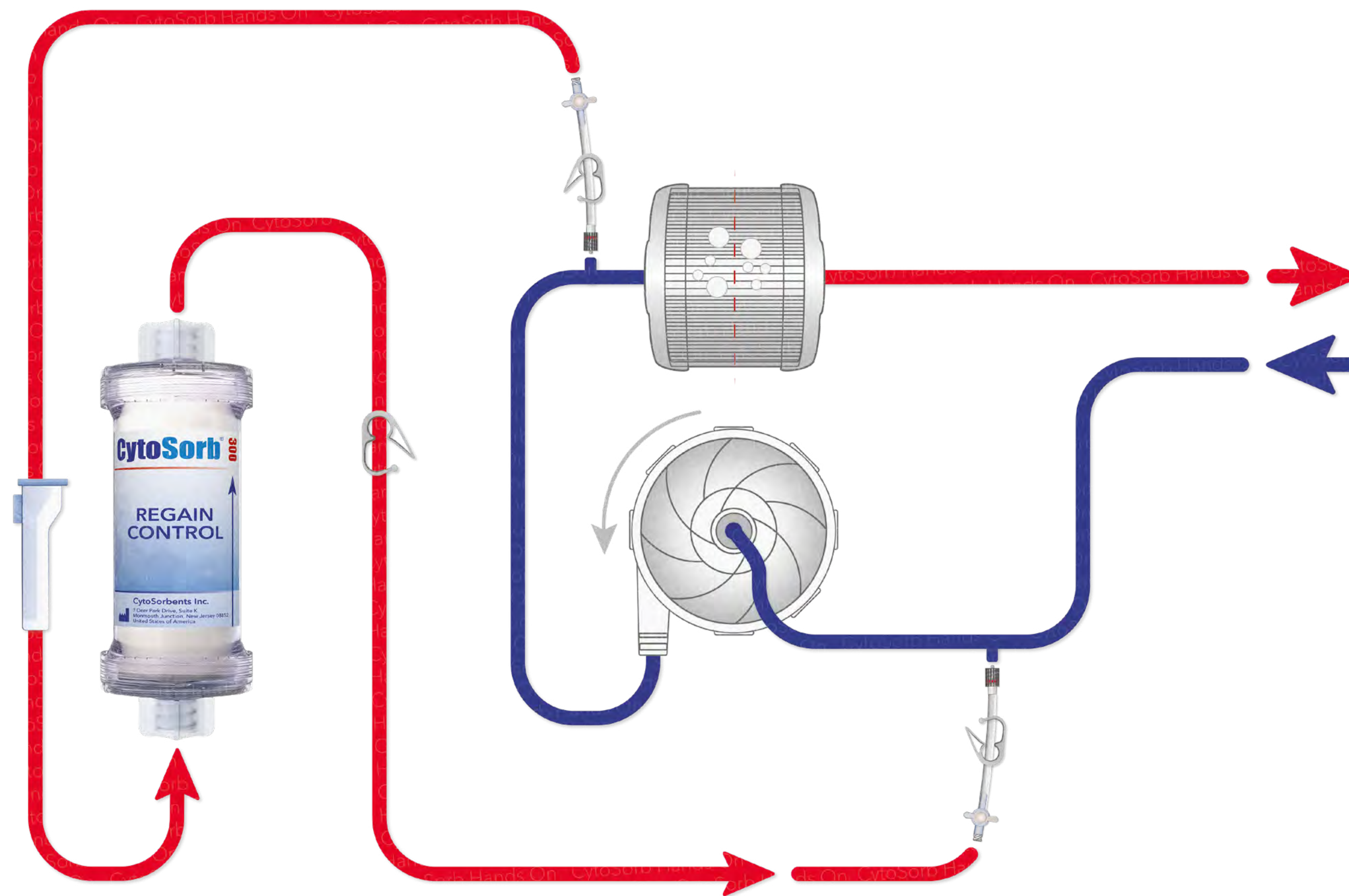
CytoSorb Therapy

Basic prerequisites for the use of CytoSorb therapy

- CytoSorb is to be employed as an adjunctive therapy to lower cytokine storm, not as a primary therapy removing the virus. Due to its concentration dependency CytoSorb does not completely eliminate cytokines from the body but rebalances the immune system to more physiologic levels.
- CytoSorb can be integrated into renal replacement therapy circuits or as a bypass in ECMO systems. Alternatively, use in stand-alone hemoperfusion is possible.
- Treatment duration and indication for exchange of adsorber depends on the clinical course. The maximum treatment time per adsorber is 24 hours.
- Usual contraindications for extracorporeal blood circuits apply.
- Installation must never be into the main-stream of an ECMO circuit, pressure or flow monitoring of CytoSorb line is recommended.
- Recommended blood flow rate 150-700 ml/min with a minimal flow of 100ml/min. Ideal flow rates using CRRT with systemic heparin anticoagulation seem to be 200-250 ml/min. Flow rates for regional citrate anti-coagulation are normally lower and should adhere to the corresponding protocols.
- Higher flow rates generally result in higher detoxification.

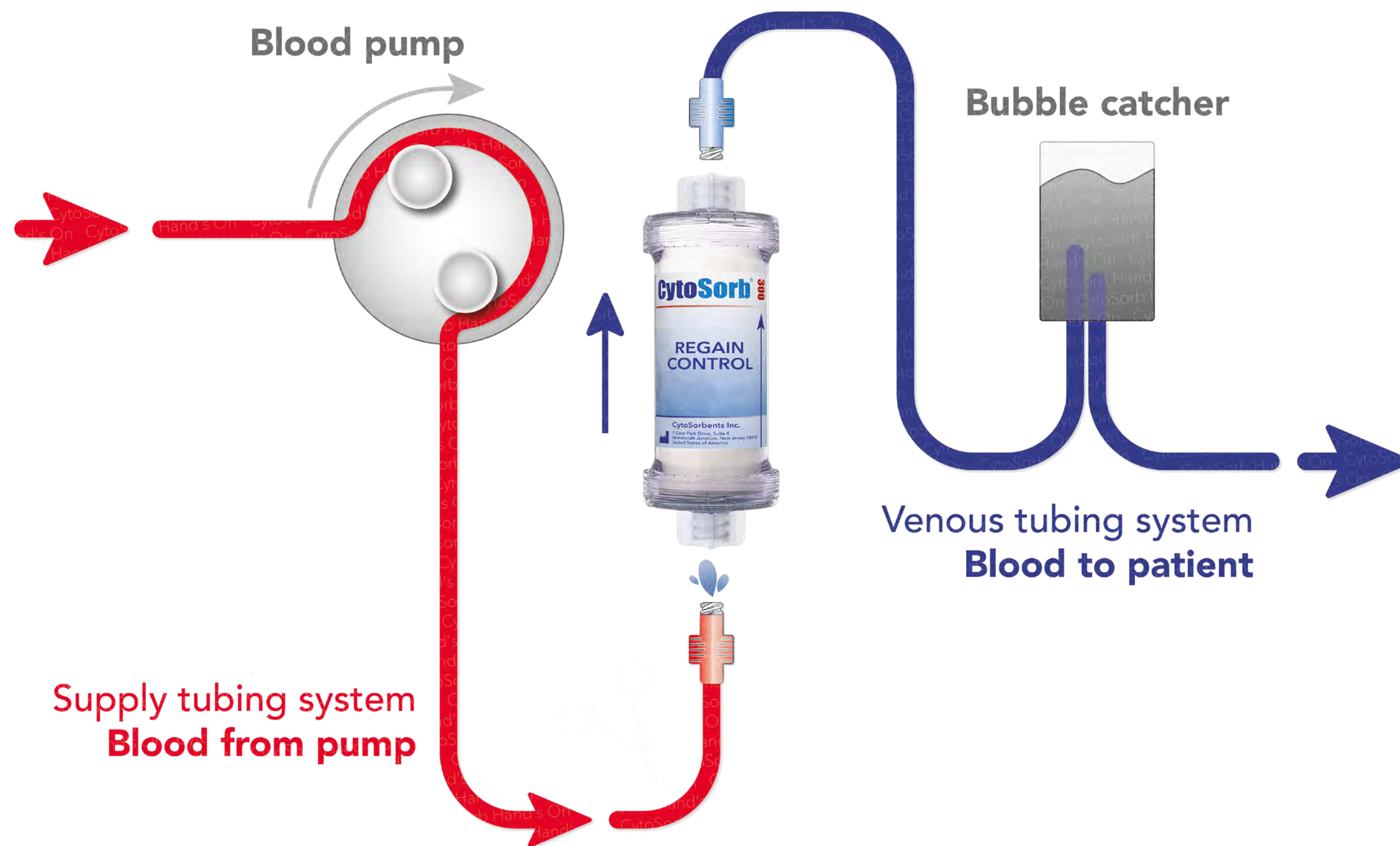


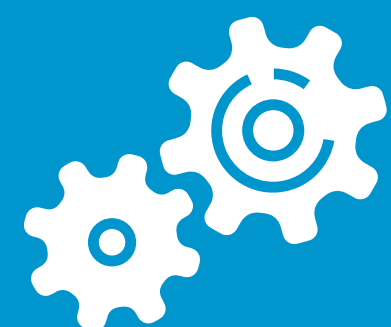
SETUP ECMO with CytoSorb



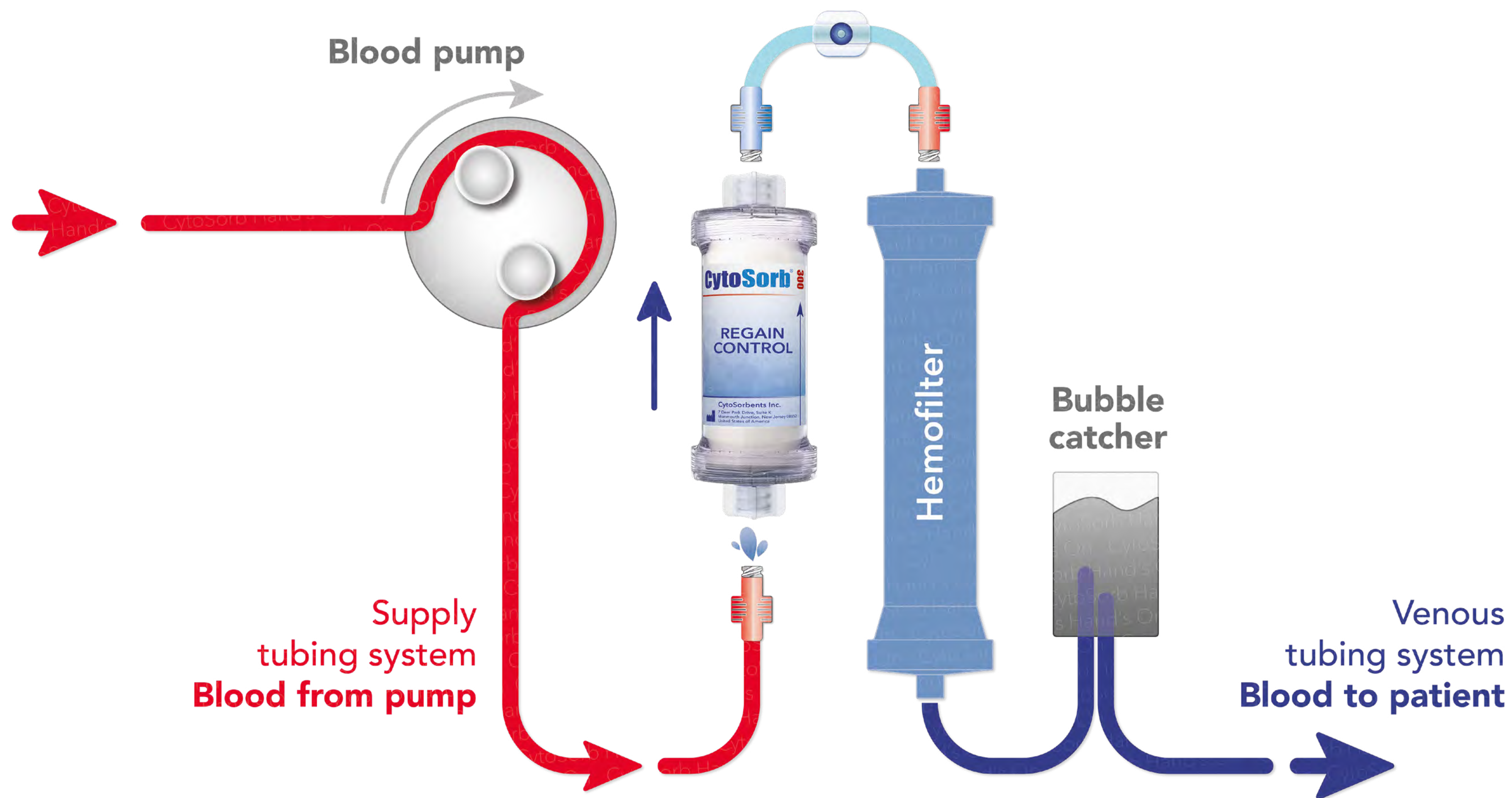


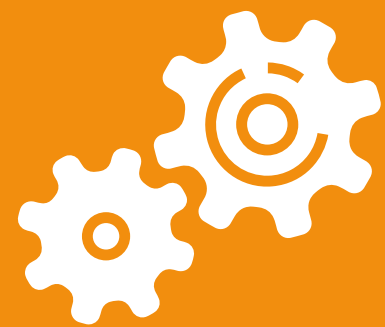
SETUP Hemoperfusion with CytoSorb



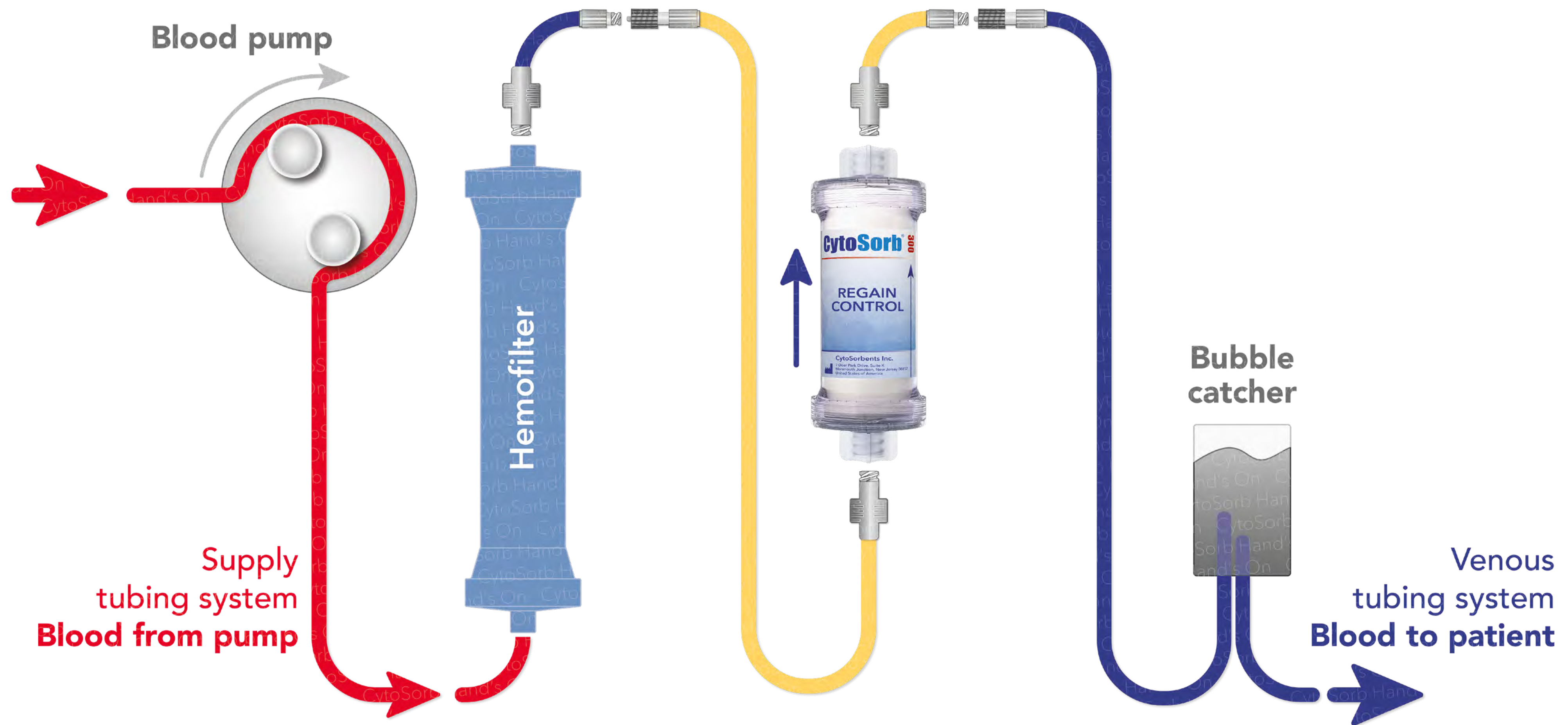


SETUP RRT with CytoSorb - Pre Filter





SETUP RRT with CytoSorb – Post Filter



Anticoagulation for CytoSorb therapy

- Clinical experience has shown that critically-ill patients with COVID-19 may be significantly hypercoagulable. This is supported by a recent publication on COVID-19 patients showing elevated D-Dimer levels in the critically ill. Standard dosing regimens for therapeutic anticoagulation during CRRT (see e.g. Dickie et al. Critical Care, 2015, 19:376), however, seem to be still sufficient. Close monitoring of anticoagulation is recommended.
- Therapeutic anticoagulation for CytoSorb is possible with heparin and citrate (if an additional hemofilter is present in the circuit) and must be fully effective at the start of treatment. When using heparin, PTT targets should be at the high end (i.e. PTT 80 sec).
- Clinical experience of clotting has found to be less of an issue with femoral vascular access, probably due to the generally higher possible flow rates.
- Generally, any decision on regimen, dosage, target values and monitoring intervals is the responsibility of the treating physician.

Follow up / Change of adsorber

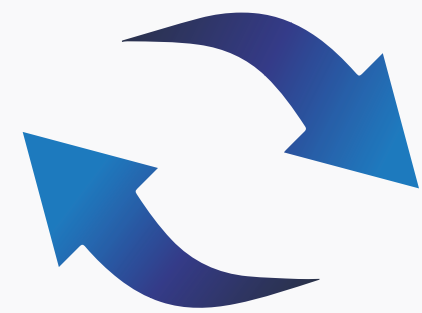
- After the start of the CytoSorb therapy, the first adsorber should be removed after 12 hours.
- Thereafter, the adsorber should be changed every 12-24 hours depending on the clinical course (e.g. degree of hemodynamic instability, pulmonary dysfunction).



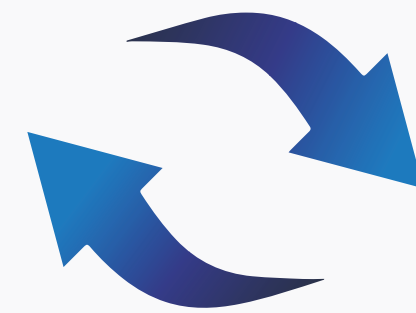
Termination of the therapy

- CytoSorb therapy should be re-evaluated after 2-3 days in cases of primarily respiratory problems.
- In cases of profound vasoplegia as the leading clinical problem, CytoSorb therapy should be continued (with new adsorbers every 12-24 hrs.) until shock reversal and reduction of vasopressor need is down to <10% of baseline need.

ARDS



12-24 hrs.



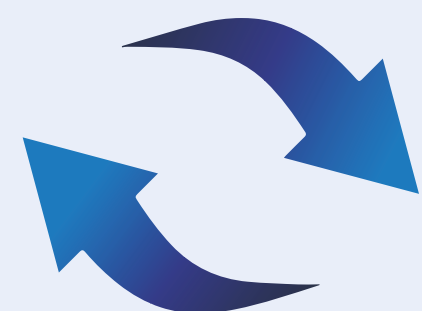
12-24 hrs.

...



Re-evaluate
on day 2-3

**Refractory
vasoplegic
shock**



12-24 hrs.



12-24 hrs.

...



Continue
until shock
reversal

Recommendations general treatment

Hemodynamic Support

Recommendations from ESICM / SSC

- In adults with COVID-19 and shock, we suggest using dynamic parameters skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness (weak recommendation, low quality evidence).
- For the acute resuscitation of adults with COVID-19 and shock
 - We suggest using a conservative over a liberal fluid strategy (weak recommendation, very low quality evidence).
 - We recommend using crystalloids over colloids (strong recommendation, moderate quality evidence).
 - We suggest using buffered/balanced crystalloids over unbalanced crystalloids (weak recommendation, moderate quality evidence).
- For adults with COVID-19 and shock
 - We suggest using norepinephrine as the first-line vasoactive agent, over other agents (weak recommendation, low quality evidence).
 - We suggest adding vasopressin as a second-line agent, over titrating norepinephrine dose, if target mean arterial pressure (MAP) cannot be achieved by norepinephrine alone (weak recommendation, moderate quality evidence).
 - We suggest titrating vasoactive agents to target a MAP of 60-65 mmHg, rather than higher MAP targets (weak recommendation, low quality evidence).
- For adults with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, we suggest adding dobutamine, over increasing norepinephrine dose (weak recommendation, very low quality evidence).

ARDS Berlin definition

Timing	Within one week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging ^a	Bilateral opacities - not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation ^b	
Mild	200 mmHg < PaO ₂ /FIO ₂ ≤300 mmHg with PEEP or CPAP ≥5 cmH ₂ O ^c
Moderate	100 mmHg < PaO ₂ /FIO ₂ ≤200 mmHg with PEEP ≥5 cmH ₂ O
Severe	PaO ₂ /FIO ₂ ≤100 mmHg with PEEP ≥5 cmH ₂ O

Abbreviations: CPAP, continuous positive airway pressure; FIO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure;

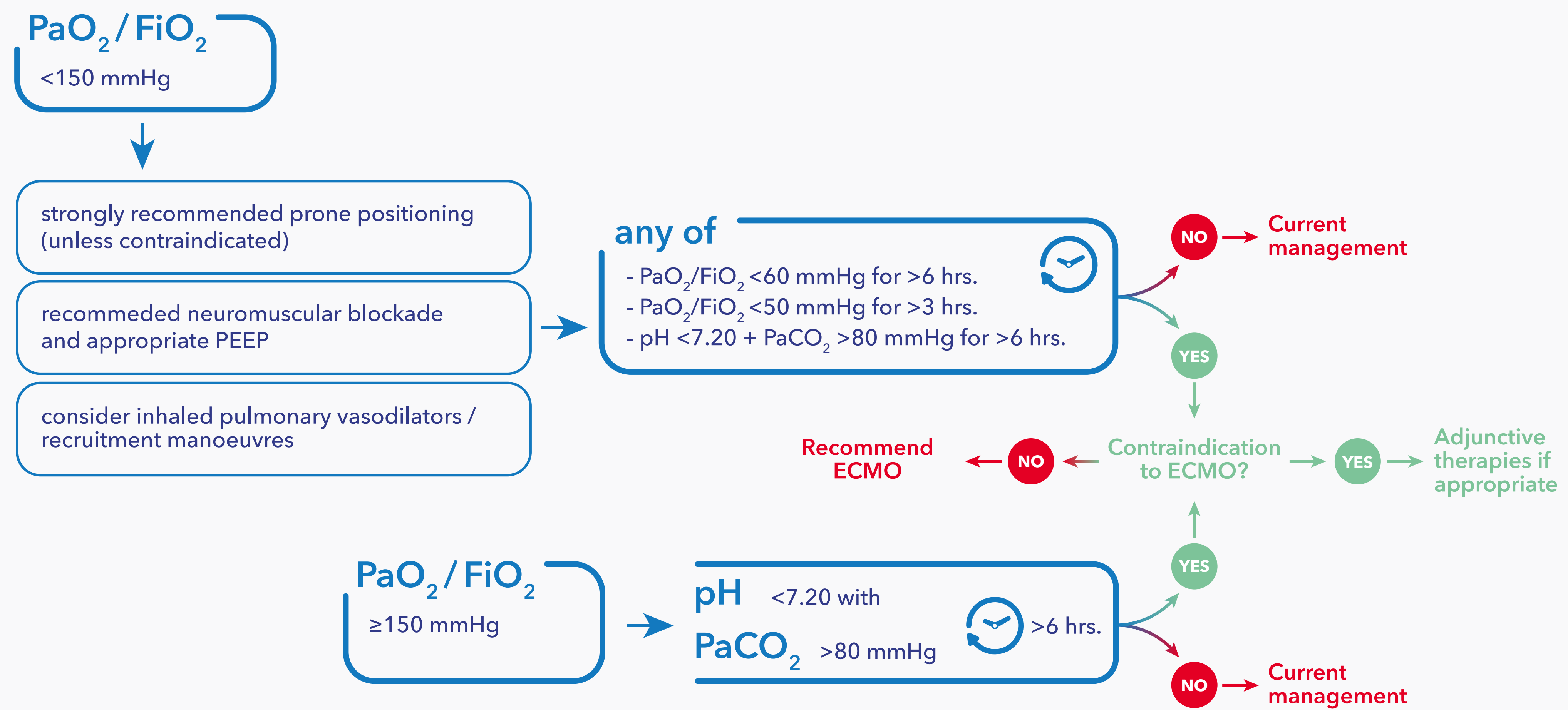
^aChest radiograph or computed tomography scan;

^bIf altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO₂/FIO₂ (barometric pressure/760)];

^cThis may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Ventilation and ECMO therapy

Recommendations from ELSO



Renal replacement therapy

Latest recommendations of the Brescia Renal Covid Task Force (Italy) for the treatment of patients on dialysis and kidney transplantation in the course of COVID-19 infection:

- Patients with AKI stage III should receive CVVH.
 - Defined as a 3-fold increase in creatinine levels from baseline or creatinine ≥ 4.0 mg/dl or defined based on amount of diuresis: diuresis < 0.3 ml/kg/h for ≥ 24 h or anuria for ≥ 12 h) hospitalized in ICU
 - Method: CVVH pre- and post-dilution with a prescribed dose > 25 ml/kg/h (to obtain an administered dose ≥ 25 ml/kg/h).
 - Anticoagulation:
 - First choice: regional citrate anticoagulation (RCA).
 - Second choice: systemic heparinization with unfractionated heparin (UFH).
 - Third choice: treatment with no anticoagulants.
 - NOTE: most COVID-19-infected patients requiring intensive care management show altered liver function values secondary to drug-induced hepatotoxicity as well as due to possible liver involvement. This is associated with an increased risk for citrate accumulation.

Diagnosis of secondary HLH

H-Score

	Number of points
Temperature	
< 38.4 °C	0
38.4 °C - 39.4 °C	33
> 39.4 °C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
< 1.5 mmol/L	0
1.5 - 4.0 mmol/L	44
> 4.0 mmol/L	64
Fibrinogen (g/L)	
> 2.5 g/L	0
≤ 2.5 g/L	30

	Number of points
Ferritin ng/ml	
< 2000 ng/ml	0
2000 - 6000 ng/ml	35
> 6000 ng/ml	50
Serum aspartate aminotransferase	
< 30 IU/L	0
≥ 30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The H-Score¹¹ generates a probability for the presence of secondary HLH. H-Scores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. H-Scores can be calculated using an online H-Score calculator.¹¹ HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 9.2 g/dL or less (≤5.71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

Table: H-Score for secondary HLH, by clinical parameter

H-Score > 169 points

- 93% sensitive for HLH
- 86% specific for HLH

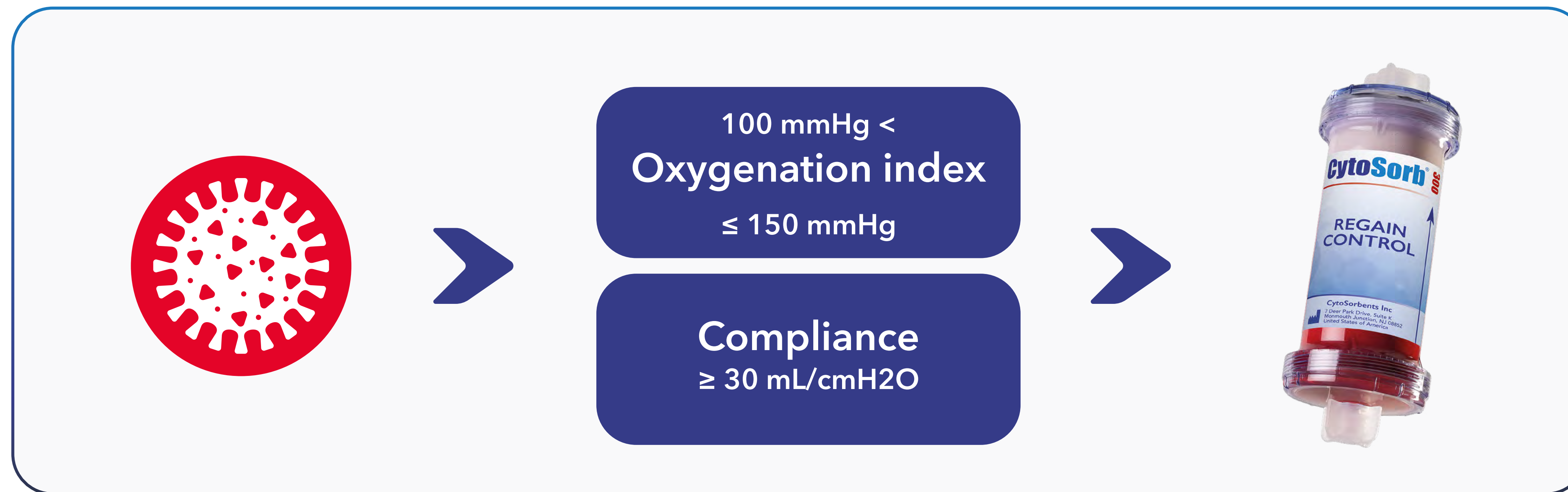
Recommendations anti-cytokine storm therapy



Recommendations from China

The recently published manual for prevention and treatment of COVID-19 reads as follows: Critical cases are classified into early, middle and late stages according to the oxygenation index and respiratory system compliance.

- Early stage: $100 \text{ mmHg} < \text{oxygenation index} \leq 150 \text{ mmHg}$; compliance of the respiratory system $\geq 30 \text{ mL/cmH}_2\text{O}$; without organ failure except the lung. The patient has a great chance of recovery through active antiviral, anti-cytokine storm therapy and supportive treatment.





Recommendations from Italy I

The latest recommendations of the Brescia Renal Covid Task Force (Italy) for the treatment of patients on dialysis and kidney transplantation in the course of COVID-19 infection are as follows:

- Patients with AKI stage III should receive CVVH.
- CytoSorb therapy is recommended for 48 hours (with change of adsorber after 24 hours) in patients for which tocilizumab (IL-6 receptor blocker) is not indicated or not available

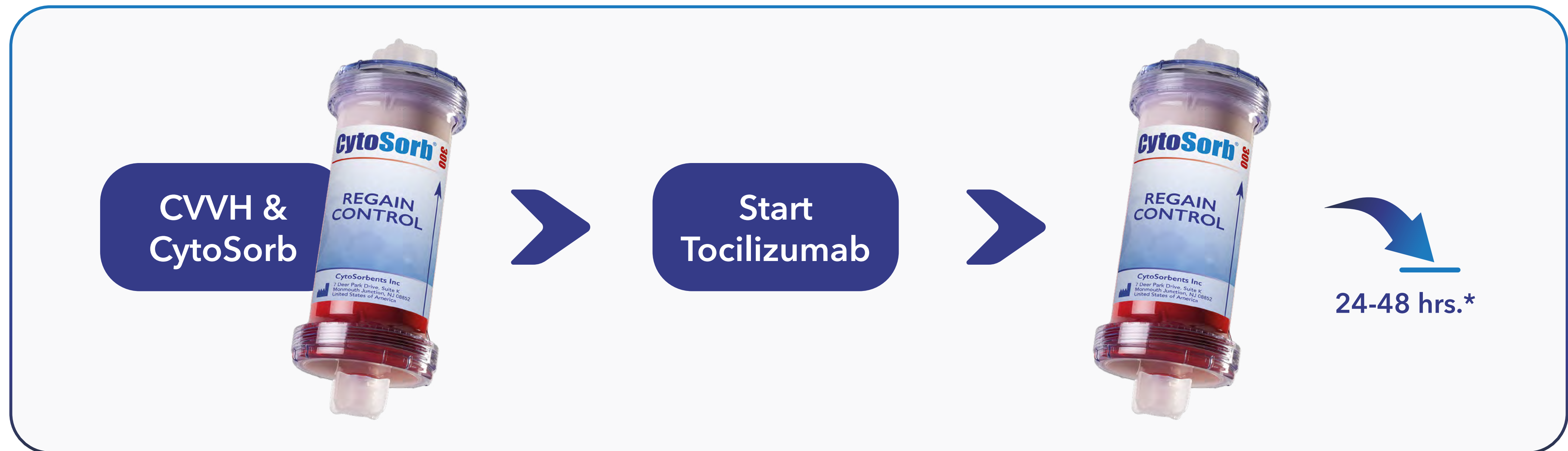


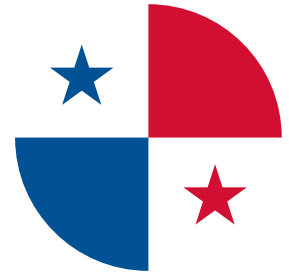


Recommendations from Italy II

In patients who are planned to receive Tocilizumab but haven't been given it at the time of CVVH start, CytoSorb therapy should be continued for 24 to 48 hrs. after the beginning of the Tocilizumab treatment.*

* Replace CytoSorb adsorber after every 24 hrs. of use with a new cartridge.

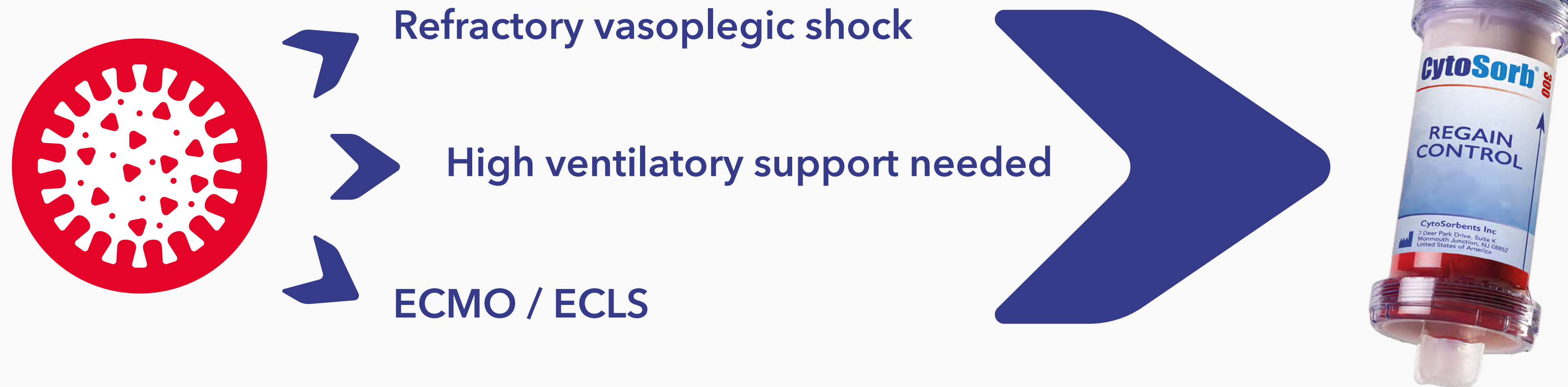




Recommendations from Panama

CytoSorb therapy should be considered if one or more of the following aspects occur:

- Deep vasoplegia with elevated lactate levels and high need for vasopressors (e.g. NE > 0.3 µg / kg / min) that do not respond to standard therapy. Therapy with CytoSorb should begin within the first 6, maximum 24 hours after the start of standard therapy.
- Very severe respiratory distress syndrome, requiring high ventilatory support
- Indication for use of ECMO / ECLS therapy



Reports suggest that **COVID-19** is associated with severe disease, that requires intensive care in approximately 5% of proven infections. The virus can result in a dysregulated immune response and this **cytokine storm** seems to be associated with disease severity, as it can lead to capillary leak syndrome, progressive lung injury, respiratory failure and acute respiratory distress syndrome (ARDS).

In addition to ARDS, further complications in the critically ill include shock, acute cardiac injury and AKI. This is in line with what is known from other viral infections like influenza and previous **coronavirus** infections (SARS, MERS), as well as with the general fact that infectious and non-infectious triggers can result in a cytokine storm, progressing to vasoplegic shock and finally multi organ dysfunction syndrome.

CytoSorb is a European Union-approved extracorporeal cytokine adsorber, designed to broadly reduce cytokine storm and other inflammatory mediators in the blood that could otherwise lead to uncontrolled systemic inflammation, organ failure, and death in many life-threatening illnesses. CytoSorb has been used safely in more than 80,000 treatments worldwide, primarily in the treatment of systemic hyperinflammation in a wide variety of life-threatening conditions.

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