# tPA Study

**Enrollment closed - March 2021**

<table>
<thead>
<tr>
<th>PI Name</th>
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<tr>
<td><strong>Project Title</strong></td>
<td>STARS (&quot;STudy of Alteplase for Respiratory failure in SARS-Cov2 (COVID-19)&quot;, a Phase Ila Clinical Trial)</td>
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<td><strong>NCT Information</strong></td>
<td>NCT04357730</td>
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**Study Population**
- Adult patients admitted to ICU severe respiratory failure (persisting PaO2/FiO2 ratio < 150 (>4 hours) despite ventilatory support)
- COVID+

**Treatment Summary**
- Step-wedge design comparing the following 3 regimens:
  1. 50 mg of tPA IV bolus over 2 hr (10 mg push followed 40 mgs over remainder 2hr) + heparin drip.
  2. 100 mg of tPA IV bolus administration over 2 hr (10 mg push followed by 90 mg over remaining 2 hr) + heparin drip.
  3. Control: standard of care

**Project Summary**

**OBJECTIVE:** To evaluate the change in respiratory function (PaO2/FiO2 from pre-to-post intervention at 48 hours post randomization) in acutely ill patients with COVID-induced ARDS receiving two different doses of tPA compared to standard of care.

**RATIONALE:** A new therapeutic approach capable of rapidly treating and attenuating ARDS secondary to COVID-19 is urgently needed.
- The dominant pathologic feature of viral-induced ARDS is fibrin accumulation in the microvasculature and airspaces. Substantial preclinical work suggests antifibrinolytic therapy attenuates infection provoked ARDS.
- In 2001, a phase I trial demonstrated the Urokinase and Streptokinase were effective in patients with terminal ARDS, markedly improving oxygen delivery and reducing an expected mortality in that specific patient cohort from 100% to 70%.
- A more contemporary approach to thrombolytic therapy is tissue plasminogen activator (t-PA) due to its higher efficacy of clot lysis with comparable bleeding risk.
- We therefore propose a phase Ila clinical trial with three intravenous tPA treatment arms to improve respiratory function and oxygenation. Additional secondary outcomes will include duration of mechanical ventilation and survival.

**DESIGN:** This is a Phase Ila clinical trial, open label, multi-center study with a modified stepped-wedge design, testing systemic administration of fibrinolytic therapy with alteplase (tPA) versus standard of care for patients infected with COVID-19 resulting in severe respiratory failure.

**TREATMENT:** The stepped-wedge randomization scheme is as follows: the first 10 patients will be randomly assigned to Group tPA50 (n=5) or Control (Standard-of-care) (n=5), at which time the first interim analysis occurs.
- If no stopping criteria are met, the next 10 patients are randomly assigned to Group tPA100 (n=5) or Control (n=5) when the second interim analysis is done.
- If no criteria for stopping or dropping an arm are met, the next 10 patients are randomly assigned to Group tPA50 (n=5) or Group tPA100 (n=5) (no Controls) when the third interim analysis is done. Finally, if no criteria for stopping or dropping an arm are met, the trial progresses with patients being randomized to Group tPA50 (n=10) or Group tPA100 (n=10) up to the final analysis at n=50.

**Group tPA50** (n=20) will receive 50 mg of tPA intravenous bolus administration over 2 hours, given as a 10 mg push followed by the remaining 40 mgs over a total time of 2 hrs. Immediately following the tPA infusion, 5000 U of UFH will be delivered and the heparin drip will be continued to maintain the activated partial thromboplastin time at 60-80 sec (2.0 to 2.5 times the upper limit of normal). This tPA protocol is a modification of the GUSTO I to III trials.

**Group tPA100** (n=20) will receive 100 mg of tPA intravenous bolus administration over 2 hours, given as a 10 mg push followed by the remaining 90 mgs over a total time of 2 hrs. Immediately following the tPA infusion, 5000 U of UFH will be delivered and the heparin drip will be continued to maintain the activated partial thromboplastin time at 60-80 sec (2.0 to 2.5 times the upper limit of normal). This tPA protocol is similar to that used by Konstantinides et al.

**Control:** standard of care according to the institution’s protocol for ARDS
- Re-bolusing of tPA, at the same dose, is permitted in the intervention groups in those patients who show an initial transient response (>20% improvement of PaO2/FiO2 over pre-infusion of alteplase, that is not sustained up to 24 hours after randomization); the repeat dose will be given only 24 hours after the initial tPA administration.

**Key Inclusion criteria**
1. Adult patients ages 18-75 years old
2. Known or suspected COVID-19 infection
3. PaO2/FiO2 ratio < 150 or inferred PaO2/FiO2 ratio from SpO2 if ABG is unavailable, persisting for > 4 hours, despite maximal mechanical ventilation management

**Key Exclusion Criteria**
1. Active bleeding or elevated bleeding risk:
   a. INR > 1.7 (with or without concurrent use of warfarin)
   b. Platelet count < 100 x 10^9/L or history of HITT
   c. Fibrinogen < 300mg/dL
   d. Known abdominal or thoracic aneurysm
   e. Major surgery or major trauma within the past 2 weeks
   f. GI or GU bleed within the past 3 weeks
   g. Known bleeding disorder
   h. Arterial puncture at a non-compressible site within the past 7 days
   i. Lumbar puncture within past 7 days
   j. Currently on ECMO
   k. CVA (stroke), history of severe head injury within prior 3 months, or prior history of intracranial hemorrhage
   l. Seizure during pre-hospital course or during hospitalization for COVID-19
   m. Acute myocardial infarction or history of myocardial infarction within the past 3 weeks or cardiac arrest during hospitalization
   n. Hemodynamic instability with Noradrenaline >0.2mcg/Kg/min
   o. Acute renal failure (escalating renal failure with creatinine >3 times baseline)
   p. Liver failure (escalating liver failure with ALT > 3 times baseline)

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**Co-enrollment in other trials permitted?**

YES, co-enrollment is permitted with other trials.