

# **Clinical Protocol**

*Trauma-PC<sup>2</sup>: Treatment of Adult Traumatic Rib Fractures With Percutaneous Cryoneurolysis  
for Pain Control*

**NCT:** NCT05330611

**Principal investigator:** Drs. Joseph Forrester

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## Pacira Iovera Investigator Initiated Trial

### ***Brief concept proposal:***

*A brief concept proposal must contain an adequate amount of information in order for the PGRC to determine interest in requesting a full study proposal.*

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- Title of the proposed research study  
Treatment of Adult **Traumatic** Rib Fractures with Percutaneous Cryoneurolysis for **Pain Control** (Trauma-PC<sup>2</sup> study)

- Brief background and rationale for the study

Rib fractures are common injuries sustained after trauma<sup>1-3</sup> – in 2017, nearly 500,000 emergency department visits in the United States involved a patient with a rib fracture<sup>4</sup>. In addition to causing morbidity and mortality in injured patients<sup>2</sup>, rib fractures have been associated with chronic pain and prolonged disability<sup>5-7</sup>. A number of institutions<sup>13-15</sup>, including our own<sup>16</sup>, have implemented evidence-based, multidisciplinary care pathways to improve clinical outcomes in patients with rib fractures.

Treatment modalities offered to patients with rib fractures have included a multimodal approach including non-opioid and opioid pharmacologic agents, neuraxial or regional anesthesia blocks, as well as surgical stabilization of rib fractures (SSRF) in select patients. SSRF requires open reduction and fixation of rib fractures to restore anatomic alignment of fracture fragments in order to decrease pain and restore respiratory mechanics<sup>15</sup>. Current consensus guidelines<sup>18</sup> recommend SSRF in patients with physiologic flail chest and multiple rib fractures with bi-cortical displacement. Although surgical fixation may help select patients with certain patterns of rib fractures, others may not qualify for the procedure or be deemed poor surgical candidates.

There are also inadequacies associated with pharmacologic components of existing rib fracture care pathways. Oral and intravenous pain medications can be problematic as adequate analgesia must be balanced with the risks of over-sedation and respiratory depression. Non-steroidal anti-inflammatory drugs can exacerbate underlying renal dysfunction. Neuraxial<sup>24</sup> and regional anesthesia<sup>25</sup> blocks are effective but technically demanding and relatively short-lived. There is, therefore, a critical need for durable, long-term pain control for patients with rib fractures that are unable to undergo surgical fixation in order to minimize their risk of complication and return to baseline functional capacity as soon as possible.

Cryoneurolysis of intercostal nerves offers a minimally-invasive method to deliver long term pain control. Direct application of cold to nerves destroys nerve axons,

resulting in Wallerian degeneration of the distal nerve without distorting epineurial or perineurial tissue. Preservation of peri- and epineurium provides a scaffold for peripheral nerve regeneration which provides reversible anesthesia lasting months<sup>27</sup>. Cryoneurolysis of intercostal nerves under direct visualization has been validated for long-term analgesia after video assisted thoracoscopic surgery (VATS) for pectus excavatum in children reducing procedural pain and length of stay<sup>28,29</sup>. More recently, case reports have explored use of VATS to perform intercostal nerve cryoablation as an anesthetic adjunct following SSRF<sup>30</sup>. Image-guided cryoneurolysis of intercostal nerves has been shown in case-reports and series to decrease chronic pain following thoracotomy<sup>31,32</sup>. These findings suggest a role for percutaneous, imaging guided intercostal nerve cryoanalgesia in patients with rib fractures who are not candidates for SSRF and subsequently VATS-guided intercostal nerve cryoneurolysis.

In 2019, Stanford received 3,132 trauma activations. Of these, 489 patients had rib fractures, and 236 (50%) were < 65 years. Over the last year, we have used intrathoracic intercostal nerve cryoneurolysis as an analgesic adjunct to SSRF in over 40 patients with promising results. We have also begin enrolling patients in a prospective, randomized investigator-initiated clinical trial among patients  $\geq 65$  with traumatic rib fractures comparing standard of care (SOC) to CT guided percutaneous cryoneurolysis plus SOC (<https://clinicaltrials.gov/ct2/show/NCT04482582>). Given our experience with VATS-guided cryoablation of intercostal nerves and our experience so far with CT-guided percutaneous cryoneurolysis, we hypothesize that ultrasound-guided intercostal nerve cryoneurolysis will provide a minimally invasive method of long-term pain control for adult trauma patients 18-64, affording the benefits of cryoanalgesia of the intercostal nerves to those patients who aren't surgical candidates.

We propose a randomized-controlled study comparing ultrasound-guided percutaneous cryoanalgesia of the intercostal nerves with SOC to SOC care alone in adult patients with acute rib fractures following chest wall trauma.

- **Method of administration of marketed product**

Ultrasound-guided percutaneous targeted cryoanalgesia of intercostal nerves (ribs 3-9)

- **Primary study objectives/endpoints**

Primary endpoints of the study would be daily numeric pain score, daily narcotic equivalents, and length of hospital stay. Secondary endpoints for the study would include 30-day mortality, need for ICU admission, 30-day rib-specific (delayed hemothorax, pneumothorax, pneumonia, pain) readmission, as well as long term pain and quality of life as measured by MPQ PRI, GOS-E and SF-12 scores at 30, 90, and 365 days.

- Study population including estimated number of subjects and preliminary justification

**Study Inclusion criteria include:**

- patients ages 18-64 with any acute rib fracture between rib 3 and rib 9
- pain score  $\geq 5$  with deep inspiration

-Presenting to the Stanford Adult Emergency Department, having a trauma consult and being admitted to the Trauma floors of SHC for their inpatient stay

**Study Exclusion criteria include:**

- radiographic evidence of metastasis to ribs
- Glasgow Coma Scale (GCS) score <13
- patients undergoing SSRF
- rib fractures located <3 cm from spinous process
- coagulopathy (INR>1.5, Plt<100)
- inability to be positioned for the procedure
- other factors precluding cryoneurolysis at discretion of trauma attending
- - If the patient has the following conditions that the manufacturer of the Iovera device advises AGAINST using the device if present
  - Cryoglobulinemia
  - Paroxysmal cold hemoglobinuria
  - Cold urticaria
  - Raynaud's disease
  - Open and/or infected wounds at or near the treatment site

**Power calculation:**

Forty (40) patients will be enrolled: 20 will receive the intervention and 20 will receive SOC. Using a two-sample t-test with 5% significance, 80% statistical power, and assuming a standard deviation of 2 in pain scores (based on the pooled standard deviation of pain scores among the first 50% of enrolled EPERC patients), a 20% difference in mean pain scores between SOC and treatment patients can be identified with a total of 34 patients (17 in each group). Accounting for 15% attrition (which we believe to be on the high end due to 1) the short duration between enrollment and the primary outcome and 2) the fact that at the 50% enrollment mark of the EPERC trial, only 1 of the 59 patients did not have the primary outcome available), we will enroll a total of 40 patients.

**Enrollment:**

Patients will be prospectively enrolled by the trauma service at admission and followed through their hospital course. A random number generator will be used to assign patients to either SOC or ultrasound-guided percutaneous cryoanalgesia with SOC .

**Treatment group:**

Patients who are deemed to be adequate candidates will have a bedside procedure of ultrasound-guided percutaneous cryoanalgesia (<72 hours from presentation to the ED) performed by the trauma service. All subsequent care will be carried out by the trauma service. Once a patient receives cryoneurolysis, they will no longer be candidates for additional neuroaxial blockade.

**Control group:**

All patient care will be carried out by the trauma service according to standard of care. This includes admission to the ICU or ward at the discretion of the attending physician, and multimodal pain control including acetaminophen, gabapentin, and narcotics, and evaluation for neuraxial or regional nerve block by the anesthesia service as dictated by the current clinical protocol.

Estimated total length of the study: 1 year for enrollment, 1 year for longitudinal follow-up. 0.5 year for data analysis and manuscript writing. **2.5 years total.**

In 2019, 489 patients with rib fractures were admitted to Stanford Hospital. Of these, 236 were between 18-64 years of age. Assuming conservatively 1/3 of these patients would be eligible, there would be 78 potential candidates per year. Assuming 2/3 of these patients consent to participate (which is consistent with our current enrollment with our ongoing E-PERC trial), we will enroll the required 40 patients for this pilot study in a year.

- Estimated study drug or device(s)  
Iovera cryoanalgesia (+/- bupivacaine injection)
- Preliminary grant request: funding, drug, device, or a combination thereof  
Combination of device, drug, funding
- Experience as sponsor-investigator

Dr. Forrester is the principal investigator for a similar investigator-initiated trial in older adults, E-PERC (<https://clinicaltrials.gov/ct2/show/NCT04482582>). Dr. Forrester is also the site PI for the Chest Wall Injury Society Traumatic Brain Injury Multicenter Trial (CWIS-TBI), and the CWIS chest tube thoracostomy multicenter trial (CWIS T-REX). Additionally, Dr. Forrester has extensive administrative experience as the associate trauma medical director for Stanford Healthcare and the Medical Director of the Chest Wall Injury Center. Dr. Forrester has national recognition through his work with the Chest Wall Injury Society and the Surgical Infection Society. He recently received the Surgical Infection Society Clinical Faculty Research Award for his accomplishments.