IOVERA° USE IN RIB FRACTURE
REQUEST FOR PROPOSAL

BACKGROUND

Pacira BioSciences, Inc. is committed to supporting independent research initiatives that foster the advancement of scientific and clinical information and improve patient care. To that end, Pacira extends a new grant opportunity by way of a request for proposal (RFP) focused on research trials that seek to result in optimized patient care. These research trials will provide valued information on the efficacy of the company's marketed products.

All proposals are reviewed for scientific merit, innovation, clinical impact on patients, and compliance with Pacira policy and requirements. If you are interested in applying for support of a research proposal, please review the submission process and apply online by clicking here. Pacira will review and consider all relevant research proposals but is not obligated to provide support for any research proposals received.

While the Pacira Grant Review Committee (PGRC) reviews all research proposals, the principal investigator (and ultimately the grantee) is responsible for the design, implementation, and conduct of the independent initiative supported by the grant. Pacira will not be involved in the conduct or monitoring of the proposed trial, including drafting the research study protocol.

PURPOSE AND INTENT

Pacira BioSciences, Inc. issues this RFP for a prospective clinical research study evaluating the iovera° system in the treatment of pain due to rib fracture. This RFP is funded through the investigator initiated trial (IIT) grant program at Pacira. Funding is available for the fiscal year 2020 and may be extended at the company's discretion.

ELIGIBILITY

To be eligible for consideration, the requestor must be an independent third party. Examples of appropriate requestors include, but are not limited to:

- Academic medical centers
- Healthcare institutions, including private practice settings and ambulatory care facilities

Note: If the research involves multiple departments within an institution and/or between different institutions/organizations/associations, please note each institution's role in the grant application.

TARGET AUDIENCE

Health care professionals involved in the care of patients with rib fracture.

TIMELINE

The RFP application will remain open until the grant has been awarded.

Note: The PGRC may award multiple awards at its discretion.

BURDEN

Epidemiology of rib fracture

Rib fractures are one of the most common and painful injuries following blunt chest wall trauma and can be more incapacitating than the injury itself (1). In this patient population, it is estimated that up to 39% of patients who have sustained blunt trauma and up to 10% of trauma admissions have sustained a rib fracture (2-5). Common mechanisms of injury include motor vehicle accidents, falls, indirect crush forces, and direct violence (2, 6). These fractures are generally not isolated but accompanied by internal thoracic injuries resulting in significant pain lending to inadequate respiratory function, the inability to clear sputum, and atelectasis resulting in the need for mechanical ventilation (7, 8).

The pain associated with traumatic rib fracture is often severe and may impair pulmonary function and clearance of secretion, contributing to major morbidities such as atelectasis and pneumonia (31-33). The impairments associated with pain may contribute to the mortality rates of 29%, which have been reported in patients with 7 or more rib fractures (30). Appropriate and adequate pain control has been shown to decrease rates of pneumonia, ventilator days, and mortality (33,34). However, studies have shown that 59% of patients with chest wall injuries have persistent pain at 2 months after injury (35). In addition, when followed to 6 months, 28% of isolated rib fracture patients still experienced chest wall pain 6 months after injury (36). Therefore traumatic rib fracture pain may require prolonged treatment.

While preventive measures have been implemented to reduce these types of injuries, the total number of rib fracture cases in the United States is estimated to be 350,000 where the average length of stay ranges from 12-16 days with most days spent in the intensive care unit (ICU) (3, 4, 9, 10).

Economic impact of rib fracture

The economic impact of rib fracture and its complications are significant with operative fixation having higher costs than non-operative treatment ($23,682 vs. $8629 per case, respectively) (11). Given decreased respiratory function, mechanical ventilation, and a prolonged ICU stay may be required. The reported average hospital cost of an ICU stay for trauma patients in the U.S. is approximately $3,500 per day and longer for those requiring mechanical ventilation (12). Thus, decreasing the length of ICU stay can generate dramatic cost savings (9).

In a retrospective cohort study assessing the impact of an expedited discharge protocol (LOS ≤ 3 days) in patients with multiple rib fractures. The review found that patients achieving expedited discharge status were more likely to be discharged home and had significantly lower mean hospitalization costs ($2865 [SD $1200] vs. $6085 [$3033], p < 0.001) (3). Productivity loss (ie, absenteeism and presenteeism) is also a considerable challenge within this population, contributing to significant lost workdays affecting patients for months after the initial injury (6).

Treatment of rib fracture pain

Current treatment options for traumatic rib fracture pain includes epidural catheters, patient controlled analgesia (PCA) pumps, blocks (eg, intercostal, paravertebral, intrathecal, interpleural, thoracic), topical analgesics (eg, lidocaine patches), oral analgesics (ie, opioids, non-narcotic pain medications), electrotherapy (eg, transcutaneous elective nerve stimulation), pulmonary hygiene, and cryoanalgesia (1, 3, 5, 13-15).

Thirteen RCTs have evaluated the efficacy of cryoneurolysis of the intercostal nerves for the management of post-thoracotomy pain (16-29). Seven of 13 RCTs showed that cryonanalgesia was superior to other pain relief methods (17, 18, 20, 22, 24-26). Studies varied in the comparator group, number of intercostal nerves treated, chest drain location, number of treatment cycles, duration of treatment, and cryonanalgesia temperature (29).

A case series reported results of 5 patients who received percutaneous cryoneurolysis of the intercostal nerves for traumatic rib fracture pain. One of the patients underwent rib plating. In each case, intercostal nerves associated with the fractured ribs were blocked (4-9 nerves). Each patient experienced improved pain after treatment, which could be managed with oral analgesics. Three months following treatment, none of the patients reported experiencing adverse events or neuropathic pain (37).

Current evidence does not support the use of one intervention over another, and as with all interventions, the least invasive methods with the greatest safety profile should be employed first.

SCOPE OF WORK

The successful applicant will prepare a research proposal for a feasibility study that adequately addresses the management of pain due to rib fracture with cryoanalgesia using the iovera° system.

The study proposal should focus on patients with rib fracture who require long lasting analgesia. The study will be a case series evaluating patients before and after cryoanalgesia treatment for up to six months with a 3-month enrollment period. Outcomes may include pain (eg, NRS, VAS, McGill Pain Questionnaire (MPQ)), hospital length of stay, ICU length of stay, ventilator days, pain interference (eg, Brief Pain Inventory (BPI), sleep interference (eg, The Medical Outcomes Study Sleep Scale (MOS-Sleep), The Pittsburgh Sleep Quality Index (PSQI)), health related quality of life, and adverse events.

Grant recipients will receive training on the use of the iovera° system and agree to provide data to Pacira at the time of study completion.

The Pacira Grant Review Committee will consider funding awards inclusive of indirect costs for the conduct of the study based on a budget within fair market value.

PROPOSAL SUBMISSION REQUIREMENTS

All requestors must submit a written proposal that addresses the following topics and includes required supporting documentation including:

- Organization's contact information
- Primary contact name, title, address, phone, and email
- Describe the organization's current activities relevant to the proposal including current standard of care and patient volume
- Project description and specific proposal objectives
- Available data/information relevant to proposal submission (eg, pilot data)
- Describe how the proposal will improve patient care in alignment with grant objectives
- Proposed timeline for completion with associated deliverables. If possible, attach a flow chart outlining the operational steps of the proposed program.
- Proposed budget that is within fair market value and reflects the scope of responsibilities to accomplish the goals of this project. No funding match is required; however, requestors will need to identify any other sources of funding, both in-kind and monetary, that will be used.

To apply for a grant, please click here.

A letter of intent on organizational letterhead should be included. The letter of intent should be single-spaced and not exceed four pages (not including the reference page).

The RFP process

Pacira maintains a stepwise process for review of RFPs. In brief, after registering on the online grant portal, the principal investigator submits a brief concept proposal and if accepted after a review by the PGRC, will be invited to submit a full proposal. Details on brief and full proposal contents are below.

Brief concept proposal:

A brief concept proposal must contain an adequate amount of information for the PGRC to determine interest in requesting a full study proposal. When submitting a brief concept proposal, the following information will be requested (if applicable):

- Principal investigator contact information
- Brief background for the study
- Method of administration of the marketed product
- Primary study objectives/endpoints
- Estimated study timelines

- Estimated total study budget
- Estimated study drug or device(s)
- Preliminary grant request: funding, drug, device, or a combination thereof
- Experience as sponsor-investigator
- Letter of intent on the requesting institution's letterhead
- Curriculum vitae from the principal investigator dated within the last calendar year

The PGRC will review all concept proposals for scientific merit, innovation, clinical importance/potential impact on patients, and compliance with company policy and requirements. The PGRC will extend contingent approval to individual applicants to proceed to the second step of the process, which is the submission of a full study proposal. Applicants will be notified of the PGRC's decision via email, and the status will also be available on the portal. Please note that an invitation to submit a full study proposal does not guarantee the approval of funding.

Full study proposal:
A full study proposal submission must contain enough detail about the research study to enable the PGRC to make an evaluation on support. When submitting a full study proposal, the following information will be requested (if applicable):

- Principal investigator contact information
- Study type: non-clinical or clinical
- Objectives: primary and secondary
- Key inclusion and exclusion criteria
- Study design
- Efficacy variables/measures
- Safety variables/measures
- Adverse event/Serious adverse event reporting
- Decision points/statistical methods/interim analysis
- Study product regimens
- Ethical rationale for the study
- Study deliverables
- Value of the study
- Applicable scientific references
- Publication plan
- Research Setting: single-site or multi-site
- Detailed budget
- Grant request: funding, product, or a combination thereof

Pacira reserves the right to reconsider its support if the research objectives outlined in the final protocol are materially different from the approved full study proposal. Pacira will not compensate for any work performed before the execution of a final contract or for impermissible costs, which include:

- Construction funds to build new facilities
- General education and training activities
- Hiring of staff that are not dedicated to the proposed research study
- Study to involve new investigational products or devices

- Studies that are designed to generate business for Pacira
- Purchase of capital equipment unrelated to the study or that would generate revenue
- Requests for support for ongoing or new research without an associated research study protocol
- Start-up funds to establish new clinical or research programs or to expand existing programs
- Support for ongoing clinical programs that are part of an organization's routine operations

PACIRA BIOSCIENCES, INC. CONTACT INFORMATION

If you have questions regarding this RFP, please email grants@pacira.com and include in the subject line *rib fracture RFP*.

CONFIDENTIALITY

This Request for Proposal constitutes the confidential and proprietary information of Pacira BioSciences, Inc. and may not, in whole or in part, be copied, reproduced, or otherwise used in any manner whatsoever without the prior express written permission of Pacira BioSciences, Inc. All information provided herein is proprietary to Pacira BioSciences, Inc. and is to be used only by your company in its response hereto. Any other use or communication of this information is prohibited.

REFERENCES

1. Karmakar MK, Ho AM. Acute pain management of patients with multiple fractured ribs. The Journal of trauma. 2003;54(3):615-25.
2. Barry R, Thompson E. Outcomes after rib fractures in geriatric blunt trauma patients. Am J Surg. 2018;215(6):1020-3.
3. Dalton MK, Minarich MJ, Twaddell KJ, Hazelton JP, Fox NM. The expedited discharge of patients with multiple traumatic rib fractures is cost-effective. Injury. 2019;50(1):109-12.
4. Pieracci FM, Majercik S, Ali-Osman F, Ang D, Doben A, Edwards JG, et al. Consensus statement: Surgical stabilization of rib fractures rib fracture colloquium clinical practice guidelines. Injury. 2017;48(2):307-21.
5. Lafferty PM, Anavian J, Will RE, Cole PA. Operative treatment of chest wall injuries: indications, technique, and outcomes. J Bone Joint Surg Am. 2011;93(1):97-110.
6. Liu X, Xiong K. Surgical management versus non-surgical management of rib fractures in chest trauma:a systematic review and meta-analysis. J Cardiothorac Surg. 2019;14(1):45.
7. Beks RB, de Jong MB, Sweet A, Peek J, van Wageningen B, Tromp T, et al. Multicentre prospective cohort study of nonoperative versus operative treatment for flail chest and multiple rib fractures after blunt thoracic trauma: study protocol. BMJ Open. 2019;9(8):e023660.
8. He Z, Zhang D, Xiao H, Zhu Q, Xuan Y, Su K, et al. The ideal methods for the management of rib fractures. J Thorac Dis. 2019;11(Suppl 8):S1078-s89.

9. Dehghan N, de Mestral C, McKee MD, Schemitsch EH, Nathens A. Flail chest injuries: a review of outcomes and treatment practices from the National Trauma Data Bank. J Trauma Acute Care Surg. 2014;76(2):462-8.
10. Martin TJ, Eltorai AS, Dunn R, Varone A, Joyce MF, Kheirbek T, et al. Clinical management of rib fractures and methods for prevention of pulmonary complications: A review. Injury. 2019;50(6):1159-65.
11. Swart E, Laratta J, Slobogean G, Mehta S. Operative Treatment of Rib Fractures in Flail Chest Injuries: A Meta-analysis and Cost-Effectiveness Analysis. J Orthop Trauma. 2017;31(2):64-70.
12. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med. 2005;33(6):1266-71.
13. Ilfeld BM, Preciado J, Trescot AM. Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves. Expert review of medical devices. 2016;13(8):713-25.
14. Ilfeld BM, Gabriel RA, Trescot AM. Ultrasound-guided percutaneous cryoneurolysis for treatment of acute pain: could cryoanalgesia replace continuous peripheral nerve blocks? British journal of anaesthesia. 2017;119(4):703-6.
15. Ilfeld BM, Gabriel RA, Trescot AM. Ultrasound-guided percutaneous cryoneurolysis providing postoperative analgesia lasting many weeks following a single administration: a replacement for continuous peripheral nerve blocks?: a case report. Korean J Anesthesiol. 2017;70(5):567-70.
16. Gwak MS, Yang M, Hahm TS, Cho HS, Cho CH, Song JG. Effect of cryoanalgesia combined with intravenous continuous analgesia in thoracotomy patients. Journal of Korean medical science. 2004;19(1):74-8.
17. Ju H, Feng Y, Yang B-X, Wang J. Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. European Journal of Pain. 2008;12(3):378-84.
18. Katz J, Nelson W, Forest R, Bruce D. Cryoanalgesia for post-thoracotomy pain. The Lancet. 1980;315(8167):512-3.
19. Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. Journal of cardiothoracic and vascular anesthesia. 1993;7(5):529-34.
20. Momenzadeh S, Elyasi H, Valaie N, Radpey B, Abbasi A, Nematollahi F, et al. Effect of cryoanalgesia on post-thoracotomy pain. Acta medica Iranica. 2011;49(4):241-5.
21. Mustola ST, Lempinen J, Saimanen E, Vilkko P. Efficacy of Thoracic Epidural Analgesia With or Without Intercostal Nerve Cryoanalgesia for Postthoracotomy Pain. The Annals of Thoracic Surgery. 2011;91(3):869-73.
22. Roberts D, Pizzarelli G, Lepore V, al-Khaja N, Belboul A, Dernevik L. Reduction of post-thoracotomy pain by cryotherapy of intercostal nerves. Scandinavian journal of thoracic and cardiovascular surgery. 1988;22(2):127-30.
23. Roxburgh JC, Markland CG, Ross BA, Kerr WF. Role of cryoanalgesia in the control of pain after thoracotomy. Thorax. 1987;42(4):292-5.
24. Yang MK, Cho CH, Kim YC. The effects of cryoanalgesia combined with thoracic epidural analgesia in patients undergoing thoracotomy. Anaesthesia. 2004;59(11):1073-7.
25. Moorjani N, Zhao F, Tian Y, Liang C, Kaluba J, Maiwand MO. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: a human prospective

randomized trial and a histological study. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2001;20(3):502-7.
26. Ba Y-F, Li X-D, Zhang X, Ning Z-H, Zhang H, Liu Y-N, et al. Comparison of the analgesic effects of cryoanalgesia vs. parecoxib for lung cancer patients after lobectomy. Surgery Today. 2015;45(10):1250-4.
27. Muller LC, Salzer GM, Ransmayr G, Neiss A. Intraoperative cryoanalgesia for postthoracotomy pain relief. Ann Thorac Surg. 1989;48(1):15-8.
28. Rooney SM, Jain S, McCormack P, Bains MS, Martini N, Goldiner PL. A comparison of pulmonary function tests for postthoracotomy pain using cryoanalgesia and transcutaneous nerve stimulation. Ann Thorac Surg. 1986;41(2):204-7.
29. Khanbhai M, Yap KH, Mohamed S, Dunning J. Is cryoanalgesia effective for post-thoracotomy pain? Interact Cardiovasc Thorac Surg. 2014;18(2):202-9.
30. Ziegler DW, Agarwal NN. The morbidity and mortality of rib fractures. J Trauma 1994;37:975-9.
31. Flagel BT, Luchette FA, Reed RL, Esposito TJ, Davis KA, Santaniello JM, et al. Half-a-dozen ribs: The breakpoint for mortality. Surgery 2005;138:717-23.
32. Dunham CM, Hileman BM, Ransom KJ, Malik RJ. Trauma patient adverse outcomes are independently associated with rib cage fracture burden and severity of lung, head, and abdominal injuries. Int J Burns Trauma 2015;5:46-55.
33. Bulger EM, Edwards T, Klotz P, Jurkovich GJ. Epidural analgesia improves outcome after multiple rib fractures. Surgery 2004;136:426-30.
34. Bulger EM, Arneson MA, Mock CN, Jurkovich GJ. Rib fractures in the elderly. J Trauma 2000;48:1040-6.
35. Fabricant L, Ham B, Mullins R, Mayberry J. Prolonged pain and disability are common after rib fractures. Am J Surg 2013;205:511-5.
36. Gordy S, Fabricant L, Ham B, Mullins R, Mayberry J. The contribution of rib fractures to chronic pain and disability. Am J Surg 2014;207:659-62.
37. Finneran JJ, Gabriel RA, Swisher MW, Berndtson AE, Godat LN, Costantini TW, Ilfeld BM. Ultrasound-guided percutaneous intercostal nerve cryoneurolysis for analgesia following traumatic rib fracture: a case series. Korean J Anesthesiol. 2019 Nov 5. doi: 10.4097/kja.19395. [Epub ahead of print]