Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Peripheral Nerve Blocks for Postoperative Pain Management in Cardiothoracic Surgery***

I. Background and Objectives for the Systematic Review

Millions of surgeries are performed in the United States annually[1–4] and most people experience postoperative pain, especially after major surgery. Inadequate pain management is a major component of postoperative morbidity, which in turn contributes to longer hospital stays, patient anxiety and dissatisfaction, adverse endocrine and neurovascular responses, cardiac stress, and a longer physiologic surgical stress response.[5–8] Opioids are the mainstay of acute postoperative pain management.[9,10] However, opioids are associated not only with adverse physiologic effects—respiratory depression, urinary retention, delirium, immunosuppression, impaired wound healing, nausea, and constipation[11–14] —but also physiologic dependence and chronic opioid use disorder originating from postoperative opioid use.[15–18] Patients prescribed opioids after surgery have a 2.5-fold higher risk of developing opioid use disorder than those not discharged with opioid prescriptions.[16,19]

Peripheral nerve blocks (PNBs) have gained significant attention in perioperative pain management as a method to reduce systemic opioid consumption, improve pain control, decrease postoperative complications, and improve patient outcomes.[20,21] A growing body of evidence supports the use of PNBs for orthopedic surgery, but their use for non-orthopedic surgery remains unclear, and is therefore a key decisional dilemma for this evidence review. PNBs, also called *regional* (non-systemic) *anesthesia*, involve the injection of local anesthetics (or numbing agents) with or without other neuromodulating drugs (i.e., steroids) near the nerve(s) supplying the surgical site. PNBs provide targeted pain relief to the surgical area, without the negative systemic effects of opioids. PNBs may also reduce the risk of chronic postoperative pain by preventing central sensitization and dysfunctional neuronal plasticity, [17] two key mechanisms contributing to ongoing pain after surgery. PNBs are not an option for all types of surgery or in all body areas. When feasible, PNBs are nearly always used as part of a *multimodal* approach to postoperative pain control. Multimodal pain management includes combinations of analgesic classes (opioid and nonopioid) and sometimes nonpharmacological interventions, and aims to

rely on non-opioid pain control techniques as much as possible.[22–24] PNBs also have potential adverse effects such as nerve damage, infection, hematoma formation, local anesthetic toxicity, and failure to achieve adequate pain relief.[25–28] Additionally, most PNBs require specialized clinical training by anesthesiologists,[29] as well as extra perioperative time and postoperative monitoring, and expensive equipment and supplies.[30,31]

Some but not all studies suggest that PNBs reduce opioid consumption and improve pain control in nonorthopedic surgery.[32–35] Furthermore, the optimal timing, duration, and type of PNBs remain unclear, as does their impact on postoperative complications and patient satisfaction. This lack of clarity calls for a rigorous comparative effectiveness review to summarize clinical evidence on the use of PNBs in multimodal pain management. This comparative review will synthesize evidence of PNB effects in intrathoracic surgery, including cardiac, lung, other chest surgeries, and includes open, minimally invasive, and video assisted thoracoscopic surgery in adults. This topic was nominated by the American Society of Anesthesiologists, and is funded by the Patient-Centered Outcomes Research Institute (PCORI) in partnership with the Agency for Healthcare Research and Quality (AHRQ) for systematic review. The American Society of Anesthesiologists (ASA) intends to use this evidence report to inform their next published guidelines on this topic.

II. Key Questions

The key questions and PICOTS were posted for public comment, which ended on May 19, 2023. These components were also reviewed by our Key Informants and Technical Expert Panel. Below is a summary of comment themes and how we incorporated them. We identified an extremely large amount of evidence for the original posted key questions, which also included pediatric populations and abdominal surgeries. Based on TEP and expert input, we narrowed the scope of the population to adults undergoing intrathoracic procedures.

- **Population:** Questions and comments commonly addressed the need to delineate between included versus excluded surgical populations, and to uniformly define these populations. These comments specifically focused on the need to include both minimally invasive surgery (MIS) and open surgery, and to define MIS and open in a standard fashion. Comments also addressed the need to specifically exclude orthopedic, spine,

cranial, and other surgeries of the orthopedic or neurosurgical specialties. To incorporate these comments, we have defined our included population to include MIS and open approaches, and have specifically excluded orthopedic, spine, and other neurosurgical procedures. We have also discussed the need for uniform definitions of these populations with our Key Informants (KIs), and we have decided on definitions consistent with other related systematic reviews underway.

Additionally, commenters expressed concerns that subgrouping populations by socioeconomic status and other health equity indicators would be difficult due to sparsity of data. We agree this likely will be rarely reported, but we will attempt to identify outcome correlations with socioeconomic status and other demographic information.

- **Intervention:** Many comments highlighted the need to clarify several intervention inclusion/exclusion and grouping criteria: 1) specify the inclusion/exclusion status of local anesthesia (LA) infiltration at the incision site, 2) evaluate continuous peripheral nerve blocks (cPNBs) (a subcutaneous catheter placed under the skin to continuously deliver local anesthetic) separately from single-shot peripheral nerve blocks (ssPNBs), 3) explicitly exclude neuraxial blocks (spinals and epidurals along with paravertebral blocks), and 4) examine liposomal bupivacaine as a separate intervention. We have incorporated these by explicitly excluding LA infiltration at the surgical incision site as an intervention of interest. We will separate results by cPNBs and ssPNBs, and we will exclude all neuraxial nerve blocks. We have consulted with our KIs about the long-acting liposomal bupivacaine (and recently FDA-approved bupivacaine extended release), and, after much discussion, most KIs agreed *not* to examine the long-acting LAs separately. This aligns with our decision not to compare different types of LA drugs or additives against each other. Rather, we will assess for the effect of PNB versus other type (different nerve blocked, cPNB vs. ssPNB) or no PNB.
- **Comparator:** Several comments pertained to comparator selection. KIs pointed out the need to define distinct comparators, and secondly, if multimodal analgesia without PNB is to be used as a comparator, then multimodal analgesia needs to be defined and standardized to the best extent possible across comparators. To incorporate this comment into our key question and PICOTS, we sought to identify distinctly different approaches to perioperative pain management as well as those we expect to see commonly reported

as a comparator. Of note, in the current U.S. practice environment "multimodal analgesia" is almost ubiquitous and will likely be synonymous with "usual care" or "standard of care." Many different strategies are used to achieve a multimodal pain management regimen, so we will not define a multimodal analgesia regimen *a priori*. We defined comparators as: neuraxial blocks, local anesthetic infiltration at the surgical incision site, standard of care or usual care or multimodal analgesia without PNB, PNB of differing type(s), and sham or placebo.

- **Outcome:** Comments on outcomes highlighted a need for defining efficacy and narrowing the scope of the outcomes, as well as defining harms. To incorporate these comments, we have gathered information from the initial scope, our KI calls, and a preliminary literature scan, and have defined outcomes as: pain intensity scores, opioid consumption in morphine milliequivalents, pain trajectory, pain interference scores, in-hospital length of stay, and all-cause return to the emergency department (ED) within 30 days of surgery. The KIs noted that the main outcomes of interest are pain intensity and opioid consumption post-surgery. We will report any harms or complications of PNBs noted in the studies. These will likely include complications of the PNB procedure, including but not limited to nerve damage, bleeding/hematoma, infection, and local anesthetic toxicity. A TEP member with expertise in anesthesia suggested the particular focus on pain intensity *increase* relative to controls seen when the PNB wears off around 12-24 hours after surgery. This phenomenon of increased pain relative to controls with dissipation of the PNB is called "rebound pain," and we have added it as a specific outcome. On the recommendation of a KI, we will also report cost to the patient and/or payor approval if we find it in the literature.
- **Timing:** We received requests to better define the surgical time period we will be examining, and one specific request to further subdivide the 3 months postoperative period into acute and subacute. To incorporate these requests, we have defined our time periods of interest as acute (within 72 hours of surgery or during the inpatient stay), subacute (discharge up to and including three months postoperatively), and chronic (greater than 3 and up through 12 months postoperatively). Our KIs pointed out that most of the research would be focused on acute outcomes, and that there will likely be little reported on post-discharge or chronic pain in relation to PNB interventions.

- **Settings:** One KI requested that we define the perioperative environment and explicitly state whether we will include sites outside of the operating room (OR) for initiation of PNBs (e.g., postoperatively). We will include PNBs performed postoperatively (within 24 hours of surgery), because some PNBs are given immediately after surgery. We will also separate inpatient surgery (or patients admitted after surgery) from outpatient surgery (patients who go home on the day of surgery). We will explicitly exclude nerve blocks or any procedure performed on a nerve for the purpose of *chronic* pain treatment outside of the immediate perioperative period.

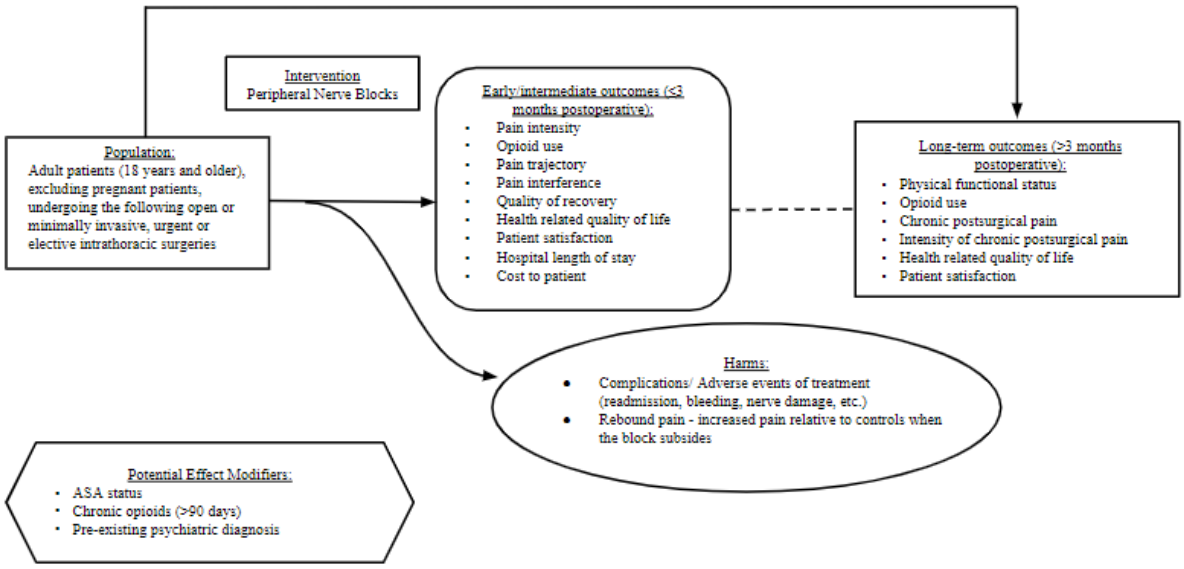
Key Questions

- KQ 1. In adult intrathoracic surgical patients, what are the effectiveness, comparative effectiveness, and harms of peripheral nerve blocks for managing postoperative pain and its sequelae — including opioid use?
    - KQ 1a. How do findings vary by baseline patient clinical characteristics (e.g., ASA status, chronic opioids (>90 days), pre-existing psychiatric diagnoses)?

Table 1 provides details on the populations, interventions, comparators, outcomes, timing, and settings (PICOTS) for the research key questions.

III. Logic Model

Figure 1: Analytic framework for the systematic review of peripheral nerve blocks for postoperative pain management



A. Criteria for Inclusion/Exclusion of Studies in the Review

Studies will be included in the review based on the PICOTS framework in Table 1.

Table 1. Population, intervention, comparator, outcome, timing, and setting (PICOTS)

KQ1	Inclusion	Exclusion
Population	Adult patients (18 years and older) undergoing the following open or minimally invasive (laparoscopic/thoracoscopic), elective, or urgent intrathoracic surgeries*: ● Cardiac ● Lung ● Other intrathoracic KQ 1a Subgroups: Patients taking opioid medications for chronic pain, those with preexisting psychiatric diagnoses, and ASA status.	-Pediatric patients under the age of 18 years -Patients undergoing spine, head/neck, orthopedic, breast, abdominal, pelvic, peritoneal, retroperitoneal, or obstetric surgery -Pregnant patients -Other surgery not listed -Emergency surgery
Intervention	Peripheral nerve block (PNB) either alone or as part of multimodal analgesia for postoperative pain management	-Other pain management strategies not considered peripheral nerve blocks -Cryoanesthesia/ cryoanalgesia -PNBs used for limb or excluded surgery -Neuraxial blockade (epidural, spinal, caudal, and paravertebral nerve blocks)

Comparators	Placebo, sham, usual care, multimodal analgesia without peripheral nerve block, other peripheral nerve block administration (e.g., differing location, continuous vs. single shot), local anesthesia infiltration at surgical incision, neuraxial blockade (epidural, spinal, caudal, and paravertebral nerve blocks)	Same peripheral nerve block but with different dose/additives or different local anesthetic (bupivacaine vs. ropivacaine or vs. liposomal/long-acting local anesthetic)
Outcomes	<u>Early//intermediate (72 hours or time of discharge to ≤3 months postoperative):</u> ● Pain intensity ● Opioid use ● Pain trajectory ● Pain interference ● Quality of recovery ● Health-related quality of life (HRQoL) ● Patient satisfaction ● Hospital length of stay ● Cost to patient <u>Long-term (>3 months postoperative):</u> ● Physical functional status ● Opioid use ● Chronic postsurgical pain ● Intensity of chronic postsurgical pain ● HRQoL ● Patient satisfaction <u>Harms:</u> ● Complications/adverse events of treatment (nerve damage, bleeding, all-cause return to ED/hospital within 30 days, etc.) ● Rebound pain- increased pain relative to controls when the block subsides	Outcomes not listed Studies excluded if postoperative pain intensity is not reported
Outcome Timing	Post-operative period ≤3 months subdivided into 72 hours or less; >72 hours or discharge up to <30 days; 30 days up to ≤3 months Post-operative period 3-12 months	Other timing
Setting	Perioperative (inpatient or outpatient) setting for intervention Perioperative and all follow-up settings for outcomes	Nerve blocks performed in the outpatient clinic. Nerve blocks performed outside of the preoperative day-of-surgery to the 24-hours postoperative.
Study design	Randomized controlled trials (RCTs) Minimum sample size per arm of ≥30 participants. If a particular intervention/comparator is not represented in the studies of 30/ arm or greater, we will include studies of smaller size for that unique intervention/comparator.	Non-randomized, observational, non-controlled study designs, cross-sectional, prevalence, qualitative, case reports, opinions/letters, pilot studies, feasibility studies Studies with a sample size <30 participants analyzed in any arm.
Publications	English-only peer-reviewed publications from 2013. (Consistent with other current ASA systematic reviews on regional anesthesia.)	Comments, editorials, and letters

*EMERGENCY – A surgical, therapeutic, or diagnostic procedure that cannot be delayed without causing a significant risk of death or permanent impairment. Note: The American Society of Anesthesiologists (ASA) Physical Status should include "E". The designation of a procedure as an emergency is determined by a surgeon and/or an anesthesiologist.
URGENT – A surgical, therapeutic, or diagnostic procedure that must be performed to prevent death or permanent impairment but that can be delayed. Note: The procedure may be delayed to allow for medical optimization of the patient or to permit better availability of resources (e.g., personnel or equipment).
ELECTIVE – A surgical, therapeutic, or diagnostic procedure that can be performed at any time or date with an agreement between the surgeon and the patient.

B. Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We will search MEDLINE, Embase, and Cochrane Central Register of Controlled Trials for peer-reviewed literature published in English from 2013 to the current date. Searches will include controlled vocabulary terms (e.g., MeSH), along with free-text words, related to peripheral nerve blocks. All searches will be updated during the public comment period of the draft report. The proposed search strategy for Medline (via Ovid) is included in Appendix A and will be submitted for librarian peer review.

The reference lists of relevant existing systematic reviews and included studies will be scanned for additional eligible studies. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria.

To improve efficiency and accuracy of the screening process and management of the process, we will upload all search results to a web-based screening tool, PICO Portal™ (www.picoportal.net). PICO Portal uses machine learning to sort and present first those citations most likely to be eligible. Initially, two team members will independently screen titles and abstracts of results. As the machine learning system is trained, will we move to one human title and abstract screener when we reach a 90 percent recall rate of citations eligible for full-text screen. We will then not screen citations remaining past a 95 percent recall rate of citations eligible for full-text screen, and will fully report articles excluded based solely on the machine learning algorithm. Citations identified by title/abstract will undergo full-text level screening by two team members independently using the same online system.

A Supplemental Evidence and Data for Systematic review (SEADS) portal will be available, and a Federal Register Notice will be posted for this review.

C. Data Abstraction and Data Management

Data fields that will be extracted include author, year of publication, sponsorship, country, setting, sample selection criteria, intervention and control characteristics, sample size, reported outcomes, outcome timing, adverse events, and follow-up period. Participant baseline demographic and clinical characteristics including age, race/ethnicity, sex, BMI, ADA status, pre-existing psychiatric diagnosis, and chronic opioid use (>90 days); and clinical characteristics including type of surgery, level of urgency of surgery (urgent vs

elective), and duration of surgery will also be extracted. One investigator will extract data into standardized extraction forms in Microsoft Excel, and a second investigator will verify for accuracy.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess risk of bias of eligible studies by outcome using the Cochrane Risk of Bias 2 Tool 2.0.[55] One investigator will independently assess the risk of bias for eligible studies by outcome; a second investigator will review each risk of bias assessment. Investigators will consult to reconcile any discrepancies in the risk of bias assessments. Overall risk of bias assessments for each study outcome will be classified as low, moderate, or high, based upon the collective risk of bias across components and confidence that the study results for a given outcome are believable given the study's limitations.

E. Data Synthesis

Results will be organized by intervention comparison, targeted outcome, and outcome timing. We will qualitatively summarize results in evidence tables and synthesize evidence for each unique intervention-outcome comparison with meta-analysis when possible and appropriate. We will assess the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[56] We will synthesize data using a Hartung, Knapp, Sidik, and Jonkman (HKSJ)[57] random effects model if three or more studies can be pooled. We will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs for continuous outcomes if combining similar outcomes measured with different instruments. The HKSJ method is more conservative than the commonly used DerSimonian-Laird approach which may result in overly narrow confidence intervals that can lead to Type 1 error.[57] If meta-analysis is not possible, we will present results in a narrative "Summary of Findings" table. A sensitivity analysis will be conducted to compare the results from the full set to the results with high risk of bias studies removed.

We will identify heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis.[58]

When we find heterogeneity, we will attempt to determine possible reasons for it by examining individual study and subgroup characteristics.

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will present the overall strength of the evidence for each prioritized outcome according to EPC methods. This approach assesses five criteria which measure either internal validity (risk of bias, inconsistency, imprecision, publication bias) or external validity (directness of results).[59] RCTs start out as high certainty and may be rated down for any one of the five criteria. For each comparison, one review author will rate the certainty of evidence for each outcome as high, moderate, low, or insufficient. These ratings will then be reviewed by a second investigator. We will resolve any discrepancies by consensus, or, if needed, by discussion with a third reviewer.

We will present a summary of the evidence for the main outcomes in a "Summary of Findings" table as well as a full Evidence Profile. The Evidence Profile will provide key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and the rating of the overall confidence in effect estimates for each outcome.[60] For outcomes measured on a scale, we will consider minimal clinically important differences (MCID), which represent the threshold of clinically significant change, to be a directly validated value for a particular measure, obtained from peer-reviewed literature. If we are unable to find directly validated minimal clinically important difference for a particular measure, we will rely on the conventional value, which is one half the standard deviation of the baseline score.[61] When documenting results that were not statistically significant, we will state that we did not detect a systematic effect, although we cannot rule out that the intervention may work for some patients, across participants, and the study's effects were indistinguishable from chance. For all interventions and outcomes that reported a continuous and a categorical effect estimate, we will review both estimates for each key outcome.

G. Assessing Applicability

Applicability of studies is generally determined according to the PICOTS framework. Study characteristics that might affect applicability include, but are not limited to, the

population from which the study participants are enrolled, narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies.[62] In particular, we will consider surgery type and the presence or absence of subgroups of interest when determining study groupings and potential sensitivity analyses to best approximate for whom the review findings may apply.

V. References

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VI. Definition of Terms

Peripheral Nerve Block - Injection of local anesthetic (numbing medicine) in close proximity to a nerve or bundle of nerves intended to numb the area of the body the nerve(s) supply usually for surgical pain control.

Continuous Peripheral Nerve Block - A peripheral nerve block in which a small catheter is tunneled under the skin and lies in close proximity to the nerve(s) being blocked (numbed). A continuous infusion of local anesthetic (numbing medicine) is given through the catheter to continually numb the nerves. This can be left in place for up to seven days.

Single Shot Peripheral Nerve Block - A peripheral nerve block in which the local anesthetic (numbing medicine) is injected at one single time without a catheter and continuous infusion left in place.

Neuraxial Nerve Block/Neuraxial Blockade - Injection of local anesthetic (numbing medicine) in or near the spinal canal to interrupt sensation from the legs or abdomen. This includes spinal anesthesia, epidural and paravertebral anesthesia nerve blocks.

Local Anesthetic - A medication which interrupts neural transmission and effectively numbs the area of the body supplied by the nerve(s).

Local Anesthetic Infiltration/Local Infiltration - The injection or infiltration of local anesthetic (numbing medicine) subcutaneously in the area immediately surrounding the surgical incision.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

VII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The EPC refined and drafted the key questions after review of the public comments, and input from Key Informants. This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who help the EPC to define populations, interventions, comparisons, and outcomes, and to identify particular studies or databases to search. Selection criteria for Technical Experts focus on assembling a group that has broad expertise as well as perspectives specific to the topic under development. Divergent and conflicting opinions are common and valued as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent

the views of any individual technical or content expert. Technical Experts also help the EPC to identify literature search strategies and specific approaches to particular issues as needed. Technical Experts do not conduct analysis or contribute to the writing of the report. They have not reviewed the report, except through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts, and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project is funded by the Patient-Centered Outcomes Research Institute (PCORI) and executed under AHRQ, U.S. Department of Health and Human Services through Contract No. 75Q80120D00008. The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by PCORI, AHRQ, or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A: Search Strategy

Ovid MEDLINE® ALL

1. nerve block/ or brachial plexus block/ or (nerve block* or ((brachial plexus or erector spinae or fascial or iliohypogastric or ilioinguinal or intercostal or interfascial or parasternal or PEC? or pecto or pectoral or pectointercostal or pectoserratus or peripheral or PIFB or quadratus lumborum or rectus sheath or thoracic fascial or transvers* abdominis or TAP or transversalis fascia or TFP or truncal) adj2 block*) or ((pecto or serratus or transversus thoracic) adj4 block*) or PECS I or PECS1 or PECS II or PECSII).mp.

2. Breast/su or exp mastectomy/ or exp mammaplasty/ or ((breast adj2 surg*) or breast augmentation or breast reconstruct* or breast reduction or mamm?plast* or mastectom*).ti,ab,kf.

3. exp Cardiovascular Surgical Procedures/ or exp coronary artery bypass/ or Defibrillators, Implantable/ or heart transplantation/ or heart-lung transplantation/ or heart valve prosthesis implantation/ or Mitral Valve/su or (coronary surg* or coronary artery bypass or cardia implant* or implant* cardioverter-defibrillator or heart surg* or heart procedure?).ti,ab,kf. or (cardiac adj2 (operation or procedure or surg*)).ti,ab,kf. or (cardio* adj2 (operati* or procedure? or surg*)).ti,ab,kf.

4. Sternotomy/ or exp Thoracic Cavity/su or Thoracic Wall/su or Thoracic Surgery/ or thoracic surgery, video-assisted/ or exp Thoracic surgical procedures/ or Thorax/su or funnel chest/su or (intrathoracic surg* or intra-thoracic surg* or retroperitoneal surg* or sternotom* or thorascosop* or thoracostom* or thoracotom* or thoracic surg* or thoracic wall surg* or thorax surg*).ti,ab,kf. or (Nuss adj (bar or method or procedure? or repair? or surger*)).ti,ab,kf.

5. lung/su or lobectomy/ or Pneumonectomy/ or (lung surg* or lung transplant* or lobectomy or pneumonectomy).ti,ab,kf.

6. or/2-5

7. 1 and 6

8. case reports/ or comment/ or editorial/ or letter/ or news/ or patient education handout/ or legal case/ or legislation/ or newspaper article/ or overall/ or festschrift/ or periodical index/ or resource guide/ or study guide/

9. 7 not 8

10. exp animals/ not humans.sh.

11. 9 not 10

12. limit 11 to (english language and yr="2013 -Current")

13. Cryoanesthesia/ or (cryoan?esthesia or cryoanalgesia or intercostal nerve cryoablation).mp.

14. Breast/su or exp mastectomy/ or exp mammaplasty/ or ((breast adj2 surg*) or breast augmentation or breast reconstruct* or breast reduction or mamm?plast* or mastectom*).ti,ab,kf.

15. exp Cardiovascular Surgical Procedures/ or exp coronary artery bypass/ or Defibrillators, Implantable/ or heart transplantation/ or heart-lung transplantation/ or heart valve prosthesis implantation/ or Mitral Valve/su or (coronary surg* or coronary artery bypass or cardia implant*

or implant* cardioverter-defibrillator or heart surg* or heart procedure?).ti,ab,kf. or (cardiac adj2 (operation or procedure or surg*)).ti,ab,kf. or (cardio* adj2 (operati* or procedure? or surg*)).ti,ab,kf.

16. Sternotomy/ or exp Thoracic Cavity/su or Thoracic Wall/su or Thoracic Surgery/ or thoracic surgery, video-assisted/ or exp Thoracic surgical procedures/ or Thorax/su or funnel chest/su or (intrathoracic surg* or intra-thoracic surg* or retroperitoneal surg* or sternotom* or thorascosop* or thoracostom* or thoracotom* or thoracic surg* or thoracic wall surg* or thorax surg*).ti,ab,kf. or (Nuss adj (bar or method or procedure? or repair? or surger*)).ti,ab,kf.

17. lung/su or lobectomy/ or Pneumonectomy/ or (lung transplant* or lobectomy or pneumonectomy).ti,ab,kf. or (lung adj3 surg*).ti,ab,kf.

18. or/14-17

19. 13 and 18

20. case reports/ or comment/ or editorial/ or letter/ or news/ or patient education handout/ or legal case/ or legislation/ or newspaper article/ or overall/ or festschrift/ or periodical index/ or resource guide/ or study guide/

21. 19 not 20

22. limit 21 to (english language and yr="2003 -Current")

23. 19 not 20

24. 12 or 23