Interventions for reducing the use of opioids in breast reconstruction (Protocol)

Siotos C, Cheah MA, Karahalios A, Seal SM, Manahan MA, Rosson GD


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Interventions for reducing the use of opioids in breast reconstruction

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effect of different peri-operative interventions designed to reduce the need for postoperative opioids for women with breast cancer undergoing breast reconstruction.
**BACKGROUND**

**Description of the condition**

Breast reconstruction is a common procedure performed on over 40% of women undergoing mastectomy (Ballard 2017). Breast reconstruction following mastectomy provides numerous benefits for patients interested in having reconstruction (Rubano 2019), including physical, psychosocial, and sexual well-being (Dean 2016; Nano 2005; Siotos 2019a). Overall, this has contributed to the growth of breast reconstruction following mastectomy from approximately 24%, prior to the passage of the Women’s Healthcare and Cancer Rights Act (WHCR) in 1998, to approximately 40% in 2005 (Morrow 2005). According to a study published in 2017, almost 90% of patients scheduled to undergo breast reconstruction are prescribed opioids peri-operatively and 10% continue using opioids for three months postoperatively (Marcusa 2017).

In addition to the progressive dosage tolerance often observed with opioid use, multiple adverse effects have been well-documented. These include sedation, respiratory depression, impaired cognitive function, as well as gastrointestinal and urologic dysfunction (Benyamin 2008; Nelson 2015). For surgical patients, these adverse effects are significant given the frequent prescription of opioids in the perioperative period and the stressors of surgical recovery and pain. Furthermore, excessive use of opioids after surgery exposes patients to adverse events, such as nausea, vomiting, constipation, drowsiness, lightheadedness, fatigue, headaches, and addiction (Zhao 2004). In the orthopedic and general surgery literature, chronic opioid use has been linked to increased morbidity and mortality, poorer patient outcomes, prolonged hospital stays, and overall increased healthcare utilization costs (Cron 2017; Menendez 2015). These can be worsened in patients with concomitant mental health issues. For example, breast reconstruction patients with pre-existing depression have been linked to higher dosages and longer utilization of perioperative narcotics (Marcusa 2017).

The continued reliance on prescription opioids for perioperative pain control exposes patients to potential dependence and misuse. It also places a significant strain on both healthcare systems and the society at large, perhaps contributing to the growing opioid epidemic. Narcotic-related overdose deaths have more than tripled in the period of 2001 to 2016 (Gomes 2018).

In light of these findings, our interest is to evaluate available strategies and techniques to reduce opioid use among women undergoing breast reconstruction, avoid the adverse effects, improve patient outcomes, and limit its impact on society.

**Description of the intervention**

We plan to perform a systematic review of current strategies for reducing opioid use in women undergoing breast reconstruction. Some of these strategies may include pharmaceutical alternatives or replacement therapy, or both; the use of anesthetic nerve blocks; and novel techniques of breast reconstruction, such as pre-pectoral placement of tissue expanders. These may offer opportunities to reduce narcotic use postoperatively and impact on the following.

- Patient outcomes including postoperative complications, length of hospital stay, and quality of life.
- Healthcare system burden and costs. Prolonged opioid use places significant financial strain on the overall healthcare system, potentially increasing both the length of postoperative hospital stay and total cost (Oderda 2003; Oderda 2007).

**How the intervention might work**

For patients, the benefits of opioid use are under increased scrutiny. There are significant questions regarding their effectiveness and concerns over their substantial risk profile. An evidence-based summary of current strategies to reduce opioid use is vital. For women undergoing breast reconstruction, there are multiple options to be explored and these may involve any combination of the following.

- Technical: operative interventions may include pre-pectoral tissue expander placement (Walia 2018), or local anesthesia blocks (Jablonska 2017; Parikh 2016).
- Pharmacological: opioid alternatives or anti-opioid medications (Demsey 2017; Satija 2014).
- Postoperative management: prescribing practices, psychological support, or enhanced recovery after surgery (ERAS) pathways (Chiu 2018; Dumestre 2017; Offodile 2019).

We aim to identify any clinical means to assist with opioid cessation, dose reduction, or reliance in the perioperative period.

**Why it is important to do this review**

The negative impact of opioids has been observed in health care and society. With increasing focus being placed on curbing the opioid crisis, surgeons are in a unique position to effect a change. Previously published work in orthopedics and general surgery has explored the detrimental effects of opioids on surgical patients (Cron 2017; Menendez 2015). In light of these developments, evaluating current therapies to reduce opioid use has significant potential to improve outcomes for women undergoing breast reconstruction, as well as reduce the overall detrimental on society.

**OBJECTIVES**

To assess the effect of different peri-operative interventions designed to reduce the need for postoperative opioids for women with breast cancer undergoing breast reconstruction.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All randomised controlled trials (RCTs) and cluster-RCTs looking at pre- or intra-operative interventions to reduce the need of opioids after breast reconstruction. The interventions may include utilization of specific anesthetics, fast-track protocols, or enhanced recovery pathway protocols. In the absence of RCTs, we will include well-designed cohort or case-control studies.

**Types of participants**

Women with breast cancer, aged ≥ 18 years, who are undergoing unilateral or bilateral therapeutic mastectomy and immediate or delayed breast reconstruction (of any technique). We will also include women at high-risk of breast cancer (e.g. BRCA1 or BRCA2 mutations, personal history of ductal or lobular carcinoma in situ,
history of chest radiation, Li-Fraumeni syndrome, Cowden/PTEN syndromes) undergoing risk-reducing mastectomy and immediate or delayed breast reconstruction (of any technique).

We will exclude studies that report on other participants and do not report results separately on those participants relevant to this review.

Types of interventions
The peri-operative phase is defined as immediately pre-operative and a few days postoperative.

Interventions
We will categorise these into three groups.

• Technical e.g. surgical interventions such as pre-pectoral tissue expander placement and local anaesthesia blocks.
• Pharmacological e.g. alternatives to opioid medications.
• Postoperative management: ERAS protocols.

Comparisons
These can include placebo interventions, historical/pre-interventional protocols, or opioid versus non-opioid protocols.

We will not apply limits to the type of opioid regimen or route of administration.

We will include multicomponent interventions where multiple interventions may be combined in order to enhance the effect of the intervention, such as the implementation of fast-track or enhanced recovery pathways. In addition, we will analyse interventions separately. Also, we will analyse each comparison group separately.

We will include studies that measure rates of postoperative opioid use.

Types of outcome measures
Primary outcomes
• Postoperative opioid use (measured as morphine equivalent units using opioid conversion tables, from immediately after surgery to up to a month following surgery).
• Postoperative pain intensity within 24 hours after surgery (measured with validated pain scales, such as the numerical rating scale (NRS), visual analogue scale (VAS), and the verbal categorical rating scale (VRS)).

Secondary outcomes
• Postoperative nausea and vomiting (defined as antiemetic use and measured on Likert scales, VAS, postoperative nausea and vomiting (PONV) intensity scale or PONV impact scale, and reported as incidence rate or severity or both).
• Operation time (in minutes).
• Length of hospital stay (in days).
• Overall complications (in number of complications).
• Cost of care (in USD).

Search methods for identification of studies
Electronic searches
We will search the following databases.

• The Cochrane Breast Cancer Specialised Register. Details of the search strategies used by the Cochrane Breast Cancer Group for the identification of studies and the procedure used to code references are outlined in the Group's module (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials with the key words "opioids", "oxycodone", "morphine", "breast reconstruction", "mammaryplasty" will be extracted and considered for inclusion in the review.
• CENTRAL (the Cochrane Library, latest issue) (see Appendix 1).
• MEDLINE (via OvidSP) from 1946 to present (see Appendix 2).
• EMBASE (via OvidSP) from 1947 to present (see Appendix 3).
• World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/ttrialsearch/Default.aspx) for all prospectively registered and ongoing trials (see Appendix 4).
• ClinicalTrials.gov (http://clinicaltrials.gov/) (see Appendix 5).

Searching other resources
• Bibliographic searching.

We will try to identify further studies from reference lists of identified relevant trials or reviews. We will obtain a copy of the full article for each reference reporting a potentially eligible trial. Where this is not possible, we will try to contact study authors to obtain additional information.

Data collection and analysis
Selection of studies
Following removal of duplicate references, two review authors (CS, MAC) will independently screen all titles and abstracts and discuss the results of the first step of screening. A third review author (GDR) will resolve any disagreements regarding eligibility. Two review authors (CS, MAC) will screen the selected references based on the full-text publication, and we will follow a similar process to resolve any disagreements. The result of the selection process will be recorded in the PRISMA flow diagram. In addition, we will record the reasons for excluding key full-text articles in the ‘Characteristics of excluded studies’ table. We will apply no language restrictions and, if necessary, we will translate non-English papers.

Data extraction and management
Two review authors (CS, MAC) will develop a standard data extraction form and independently extract data from the included studies. A third review author (GDR) will resolve any disagreements regarding data collection and extraction. We will collect information on study design, participants, setting, interventions, outcomes, follow-up, methods employed to control for confounders and biases, sources of funding, and notable conflicts of interest of trial authors, amongst other items. For observational studies where we extract adjusted estimates, we will select the most fully adjusted model. Should we identify multiple papers that report results from the same study during the data extraction process, we will select a single paper as the primary
reference based on the completeness of reporting and sample size if overlapping population exists.

Assessment of risk of bias in included studies

For RCTs, two review authors (CS, MAC) will assess risk of bias using Cochrane’s ‘Risk of bias’ tool described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). This will include an evaluation of the following items that are reported in a ‘Risk of bias’ table:

- Random sequence generation (to assess possible selection bias).
- Allocation concealment (to assess possible selection bias).
- Blinding of participants and personnel (to assess possible performance bias).
- Blinding of outcome assessment (to assess possible detection bias).
- Incomplete outcome data (to assess possible attrition bias).
- Selective outcome reporting (to assess possible reporting bias).
- Other bias.

For non-randomised studies, we will assess risk of bias using the Risk of Bias in Non-randomized studies of Interventions (ROBINS-I) tool (Sterne 2016). This includes an evaluation of multiple items at the pre-intervention period, intervention period, and post-intervention period. In particular, it will cover participant baseline demographics and clinical characteristics (to assess for possible selection bias), heterogeneity of surgical interventions, adherence to interventional protocols, missing data, reported results, and adjustment for potential confounding variables (to assess for bias due to confounding).

Examples of possible confounding factors include the following.

- Demographic characteristics, such as younger age (age < 50 years, Katz 2005), higher body mass index (Spivey 2018), unmarried status (Katz 2005).
- Presence of pre-operative pain (Wang 2016) and pre-operative use of opioids.
- Comorbidities that alter the metabolism of pain medications, such as liver or kidney disease.
- Pre-existing psychiatric conditions, such as anxiety (Katz 2005) or depression (Spivey 2018).
- Types of surgical interventions, such as sentinel lymph node biopsy versus axillary dissection (Spivey 2018) where intraoperative nerve division may be related with reduced pain (Bruce 2012), type of breast reconstruction performed, type of implant used (Siotics 2019b), and volume of implant or tissue expander inserted.
- Receipt of neoadjuvant or adjuvant therapy, such as chemotherapy (Bruce 2014), or radiotherapy (Poleshuck 2006).

We will classify items as either ‘low’, ‘moderate’, ‘serious’, or ‘critical’ risk of bias or ‘no information’, and will record the reasons for each classification. A third author (GDR) will be involved in the process to resolve any disagreements.

Measures of treatment effect

For dichotomous outcomes (e.g. opioid use, presence of pain, postoperative nausea and vomiting, anti-emetic use, number of complications), we will measure the effect using risk ratios (RRs) and 95% confidence intervals (CIs). We will report the ratios of treatment effects for response so that RRs less than 1.0 favor the intervention.

For continuous outcomes collected using different scales (e.g. opioid use, intensity of pain, severity of postoperative nausea and vomiting), we will measure the effect using standardized mean differences (SMD) with 95% CIs. For continuous outcomes collected using the same scale (e.g. operation time, length of hospital stay, cost of care), we will measure the effect using mean differences (MD) with 95% CIs. We will report the differences of treatment effects for response so that mean difference values of less than 0.0 favor the intervention.

Unit of analysis issues

We will conduct the analysis per participant. If we identify both cluster and individually-based RCTs, we will adjust the cluster’s sample size using appropriate methods, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will also consider whether the matching technique used in the included studies may impact the analysis. In non-randomised studies, matching refers to selecting study participants in a way that the distribution of specific confounders are more similar among the comparative groups (Costanza 1995).

In those studies contributing more than one intervention group, we will combine the intervention groups to create a single pair-wise comparison in order to overcome the unit-of-analysis error.

Dealing with missing data

Where missing data occurs (e.g. effect estimates are reported without their corresponding standard error), one review author will contact the corresponding author or co-authors of the study and request further information. If we do not receive a response within four weeks after initial email contact, we will send a follow-up email.

We will perform the analysis on an intention-to-treat basis (i.e. all participants are analysed according to the groups to which they were randomised). We will perform a sensitivity analysis to assess the impact of missing data on our results. We will stratify the included studies into the three categories of low missing data (≤ 10% of the original sample size), medium missing data (> 10% and < 50%), and high missing data (≥ 50%), and will compare the results in each category.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity among included trials by reviewing patient characteristics, types of interventions, and types of breast reconstruction.

Statistical heterogeneity will be assessed using the Chi² test, the Tau² and the I² statistic (Higgins 2003). We will consider P values < 0.05 (generated by the Chi² test) to indicate statistically significant heterogeneity, and I² values as follows.

- < 40%: heterogeneity might not be important.
• 30 to 60%: moderate heterogeneity.
• 50 to 75%: substantial heterogeneity.
• > 75%: considerable heterogeneity.

We will perform subgroup analysis to investigate substantial heterogeneity if appropriate. However, if there is considerable heterogeneity, meta-analyses may not be appropriate.

Assessment of reporting biases
If we have 10 or more studies in our meta-analysis of the primary outcome, we will assess reporting bias by generating funnel plots (Higgins 2011) and evaluating the results of the Egger’s test (Egger 1997).

Data synthesis
We will perform statistical synthesis of data using Review Manager 5 (RevMan 5) software (Review Manager 2014). Dichotomous outcomes will be synthesized using the Dersimonian and Laird model, and continuous outcomes will be synthesized using the inverse-variance method. If data are available to perform meta-regression, we will undertake this in Stata (Stata 2015).

We will perform all analyses using the random-effects model. If different estimates of effect are available (e.g. odds ratios and RRs), we will perform the appropriate conversions before pooling the data, according to the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Main outcomes of ‘Summary of findings’ table for assessing the certainty of the evidence
We will use the GRADE approach to assess the certainty of the evidence for the main outcomes (Schünemann 2011). The main outcomes assessed using GRADE and presented in the ‘Summary of findings’ table will be: postoperative opioid use, postoperative pain intensity within 24 hours after surgery, postoperative nausea and vomiting, operation time, length of hospital stay, overall complications, and cost of care.

Two review authors (CS, MAC) will prepare the ‘Summary of findings’ table using GRADEproGDT (GRADEpro GDT).

Subgroup analysis and investigation of heterogeneity
If there are 10 or more studies included in our meta-analysis and we observe high heterogeneity, we will fit a meta-regression model using the study characteristics provided below to investigate heterogeneity.

• Type of intervention (i.e. technical, pharmacological, and postoperative management).
• Study design if trial studies are available (i.e. experimental versus observational studies).
• Type of breast reconstruction (i.e. implant-based versus autologous-based versus other methods of reconstruction).
• Timing of breast reconstruction (i.e. immediate versus staged versus delayed).
• Type of mastectomy (i.e. risk-reducing mastectomy versus therapeutic mastectomy).

We will compare the heterogeneity (i.e. $I^2$ and $\tau^2$) from each of these meta-regression models to a model without any covariates. This will give an indication of the degree of variation between the studies explained by the covariate.

Sensitivity analysis
If an adequate number of studies are available, we plan to perform a sensitivity analysis by excluding studies with high risk of bias. Also, we will perform a sensitivity analysis based on the presence of missing data in the included studies. We will stratify the included studies into three categories of low missing data (≤ 10% of the original sample size), medium missing data (> 10% and < 50%), and high missing data (≥ 50%), and will compare the results in each category.

For each sensitivity analysis, we will report the effect estimate and associated CI, and heterogeneity for each outcome, and compare the results to those from the meta-analyses prior to each sensitivity analysis.

Acknowledgements
We thank Ava Grace Tan-Koay for developing the search strategies. We also thank the Nicola Rocco (MD, PhD, Scientific Director of the Group for Reconstructive and Therapeutic Advancements (GReTA), Italy; Clinical Editor), Sandra Finestone PsyD, Executive Director of the Association of Cancer Patient Educators (Consumer), Cecilia Farbizio (Consumer Editor), and Sarah Hodgkinson (Associate Editor, Editorial and Methods Department, Cochrane Central Executive Team).
REFERENCES

Additional references

Ballard 2017

Benyamin 2008

Bruce 2012

Bruce 2014

Chiu 2018

Costanza 1995

Cron 2017

Dean 2016

Demsrey 2017

Demestre 2017

Egger 1997

Gomes 2018

GRADEpro GDT [Computer program]

Higgins 2003

Higgins 2011

Jablonka 2017

Katz 2005

Marcusa 2017

Menendez 2015
Menendez ME, Ring D, Bateman BT. Preoperative opioid misuse is associated with increased morbidity and mortality after

**Morrow 2005**

**Nano 2005**

**Nelson 2015**

**Oderda 2003**

**Oderda 2007**

**Offodile 2019**

**Parikh 2016**

**Poleshuck 2006**

**Review Manager 2014 [Computer program]**

**Rubano 2019**

**Satija 2014**

**Schünemann 2011**

**Siotos 2019a**

**Siotos 2019b**

**Spivey 2018**

**Stata 2015 [Computer program]**
StataCorp. Stata. Version 14. College Station, TX, USA: StataCorp, 2015.

**Sterne 2016**

**Stone 2019**

**Walia 2018**

**Wang 2016**


**Zhao 2004**


**APPENDICES**

**Appendix 1. CENTRAL**

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near neoplasm*
#3 breast near carcinom*
#4 breast near cancer*
#5 breast near tumour*
#6 breast near tumour*
#7 breast near malignan*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Mammaplasty] explode all trees
#10 mammaplast* or mammoplast*
#11 mastoplast*
#12 breast reconstruct*
#13 breast reconstructive surger*
#14 #9 OR #10 OR #11 OR #12 OR #13
#15 #8 OR #14
#16 MeSH descriptor: [Analgesics, Opioid] explode all trees
#17 opioid*
#18 MeSH descriptor: [Codeine] explode all trees
#19 codeine
#20 MeSH descriptor: [Fentanyl] explode all trees
#21 fentanyl
#22 MeSH descriptor: [Morphine] explode all trees
#23 morphine
#24 MeSH descriptor: [Oxycodone] explode all trees
#25 oxycodone or endone or oxycontin
#26 MeSH descriptor: [Buprenorphine] explode all trees
#27 (buprenorphine or Subutex or Suboxone)
#28 MeSH descriptor: [Methadone] explode all trees
#29 methadone
#30 MeSH descriptor: [Tramadol] explode all trees
#31 tramadol
#32 MeSH descriptor: [Opiate Alkaloids] explode all trees
#33 (reduc* and opioid*)
#34 MeSH descriptor: [Opiate Substitution Treatment] explode all trees
#35 ((opioid* or opiat*) near substitut*)
#36 (Enhanced recovery after surgery)
#37 ERAS
#38 (Enhanced recovery pathway)
#39 ((fast track or fast-track) near (recovery or surgery))
#40 MeSH descriptor: [Perioperative Care] explode all trees
#41 MeSH descriptor: [Postoperative Care] explode all trees
#42 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 #15 AND #42

**Appendix 2. MEDLINE**
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<tr>
<td>1</td>
<td>exp Breast Neoplasms/</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(breast adj6 cancer$).tw.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(breast adj6 neoplasm$).tw.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(breast adj6 carcinoma$).tw.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(breast adj6 tumo?r$).tw.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>or/1-5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>exp Mammoplasty/</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(mammoplast* or mammoplast* or mastoplast*).tw.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(breast adj6 reconstruct$).tw.</td>
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<tr>
<td>10</td>
<td>(breast adj6 reconstruct$ adj6 surger$).tw.</td>
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<td>11</td>
<td>(breast adj6 reconstruct$ adj6 surgical adj6 procedure$).tw.</td>
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<td>or/7-11</td>
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<tr>
<td>46</td>
<td>randomized controlled trial.pt.</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>controlled clinical trial.pt.</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>randomized.ab.</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>placebo.ab.</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Clinical Trials as Topic/</td>
<td></td>
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<tr>
<td>51</td>
<td>randomly.ab.</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>trial.ti.</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>(crossover or cross-over).tw.</td>
<td></td>
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<tr>
<td>54</td>
<td>Pragmatic Clinical Trials as Topic/</td>
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<tr>
<td>55</td>
<td>pragmatic clinical trial.pt.</td>
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</tbody>
</table>
(Continued)

56  or/46-55

57  Case-Control Studies/

58  Control Groups/

59  Matched-Pair Analysis/

60  Retrospective Studies/

61  ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

62  or/57-61

63  Cohort Studies/

64  Longitudinal Studies/

65  Follow-Up Studies/

66  Prospective Studies/

67  Retrospective Studies/

68  cohort.ti,ab.

69  longitudinal.ti,ab.

70  prospective.ti,ab.

71  retrospective.ti,ab.

72  or/63-71

73  45 and 56

74  45 and 72

75  45 and 62

Appendix 3. Embase

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
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<tbody>
<tr>
<td>1</td>
<td>exp breast/</td>
</tr>
<tr>
<td>2</td>
<td>exp breast disease/</td>
</tr>
<tr>
<td>3</td>
<td>(1 or 2) and exp neoplasm/</td>
</tr>
<tr>
<td>4</td>
<td>exp breast tumor/</td>
</tr>
</tbody>
</table>
(Continued)

5 exp breast cancer/

6 exp breast carcinoma/

7 (breast$ adj5 (neoplasm$ or cancer$ or carcin$ or tumor$ or metastas$ or malig$)).ti,ab.

8 or/3-7

9 mammoplast$ or mastoplast$.tw.

10 exp breast reconstruction/

11 (breast adj6 reconstruct$).tw.

12 (breast adj6 reconstruct$ adj6 surgeon$).tw.

13 (breast adj6 reconstruct$ adj6 surgical adj6 procedure$).tw.

14 or/9-13

15 8 or 14

16 exp opiate/

17 exp narcotic analgesic agent/

18 opioid*.mp.

19 exp codeine/

20 Codeine.mp.

21 exp fentanyl/

22 Fentanyl.mp.

23 exp morphine/

24 Morphine.mp.

25 exp oxycodone/

26 (oxycodone or endone or oxycontin).mp.

27 exp buprenorphine/

28 (buprenorphine or Subutex or Suboxone).mp.

29 exp methadone/

30 Methadone.mp.

31 exp tramadol/

32 Tramadol.mp.
(Continued)

33  (reduc* and opioid*).tw.

34  exp opiate substitution treatment/

35  ((opioid* or opiat*) and substitut*).tw.

36  Enhanced recovery after surgery.tw.

37  ERAS.tw.

38  Enhanced recovery pathway.tw.

39  ((fast track or fast-track) and (recovery or surgery)).tw.

40  exp perioperative period/

41  exp postoperative care/

42  or/16-41

43  15 and 42

44  limit 43 to (human and (conference abstracts or embase))

45  Randomized controlled trial/

46  Controlled clinical study/

47  Random$.ti,ab.

48  randomization/

49  intermethod comparison/

50  placebo.ti,ab.

51  (compare or compared or comparison).ti.

52  (open adj label).ti,ab.

53  ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

54  double blind procedure/

55  parallel group$.1.ti,ab.

56  (crossover or cross over).ti,ab.

57  ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

58  (assigned or allocated).ti,ab.

59  (controlled adj7 (study or design or trial)).ti,ab.

60  (volunteer or volunteers).ti,ab.
(Continued)

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<table>
<thead>
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<tbody>
<tr>
<td>61</td>
<td>trial.ti.</td>
</tr>
<tr>
<td>62</td>
<td>or/45-61</td>
</tr>
<tr>
<td>63</td>
<td>exp case control study/</td>
</tr>
<tr>
<td>64</td>
<td>case control study.ti,ab.</td>
</tr>
<tr>
<td>65</td>
<td>((case control or case base or case matched or retrospective) adj1 (analys* or design* or evaluation* or research or stud* or survey* or trial*)).ti,ab.</td>
</tr>
<tr>
<td>66</td>
<td>or/63-65</td>
</tr>
<tr>
<td>67</td>
<td>exp retrospective study/</td>
</tr>
<tr>
<td>68</td>
<td>exp prospective study/</td>
</tr>
<tr>
<td>69</td>
<td>((cohort or concurrent or incidence or longitudinal or followup or 'follow up' or prospective or retrospective) adj1 (analys* or design* or evaluation* or research or stud* or survey* or trial*)).ti,ab.</td>
</tr>
<tr>
<td>70</td>
<td>or/67-69</td>
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<tr>
<td>71</td>
<td>44 and 62</td>
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<tr>
<td>72</td>
<td>44 and 70</td>
</tr>
<tr>
<td>73</td>
<td>44 and 66</td>
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</tbody>
</table>

**Appendix 4. WHO ICTRP**

Basic search:

1. Breast reconstruction AND opioid*
2. Breast surgery AND opioid*
3. Breast cancer surgery AND opioid*
4. Breast* AND enhanced recovery after surgery
5. Mastectomy AND opioid*

**Appendix 5. ClinicalTrials.gov**

Basic search:

1. Condition or disease: breast cancer OR breast reconstruction OR breast surgery
   Other terms: Opioid or opiate
2. Condition or disease: mastectomy
   Other terms: Opioid or opiate

Advanced search:

1. Condition or disease: breast cancer OR breast reconstruction OR breast surgery
   Outcome measures: Opioid or opiate
2. Condition or disease: mastectomy
   Outcome measures: Opioid or opiate
CONTRIBUTIONS OF AUTHORS

• Developed the protocol: CS, MAC, AK, SMS, MAM, GDR

For the review:

• Study selection: CS, MAC, GDR
• Extract data from studies: CS, MAC
• Enter data into Review Manager 2014: CS, AK
• Carry out the analysis: CS, AK
• Interpret the analysis: CS, MAC, AK, SMS, MAM, GDR
• Draft the final review: CS, MAC, AK, SMS, MAM, GDR
• Disagreement resolution: GDR
• Update the review: CS, MAC, AK, SMS, MAM, GDR

DECLARATIONS OF INTEREST

CS has no financial interest in any of the products, devices, or drugs mentioned in this protocol.
MAC has no financial interest in any of the products, devices, or drugs mentioned in this protocol.
AK has no financial interest in any of the products, devices, or drugs mentioned in this protocol.
SMS has no financial interest in any of the products, devices, or drugs mentioned in this protocol.
MAM has no financial interest in any of the products, devices, or drugs mentioned in this protocol.
GDR has no financial interest in any of the products, devices, or drugs mentioned in this protocol.

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The Johns Hopkins Department of Plastic Surgery receives research support from LifeCell Corp (Branchburg, NJ, USA). The Department also receives educational support from LifeCell Corp (Branchburg, NJ, USA), Mentor Corp (Santa Barbara, CA, USA), AxoGen Inc (Alachua, FL, USA), and Integra LifeSciences (Plainsboro, NJ, USA), which make products used in plastic surgery reconstruction procedures.

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• No sources of support supplied, Other.

External sources

• No sources of support supplied