PLASTIC SURGICAL RANDOMIZED CONTROLLED TRIALS:

A SYSTEMATIC REVIEW

PLASTIC SURGICAL RANDOMIZED CONTROLLED TRIALS: CHALLENGES AND OPPORTUNITIES FOR EVIDENCE-BASED PLASTIC SURGERY, A SYSTEMATIC SCOPING REVIEW

By

SOPHOCLES VOINESKOS

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree

Masters of Science

MASTER OF SCIENCE (2013) **McMaster University**

Health Research Methodology **Hamilton, Ontario**

Title: Plastic Surgical Randomized Controlled Trials: Challenges and Opportunities for Evidence-Based Plastic Surgery, A Systematic Scoping Review

Author: Sophocles Voineskos, MD

Supervisor: Dr. Mohit Bhandari

Number of Pages: x, 191

Abstract

Background: There is a shifting culture toward evidence-based plastic surgery. The use of high-quality evidence in patient decision-making is essential. To help achieve this goal, the best evidence in the field needs to be identified, and the validity of this evidence verified.

Objective: This systematic review was designed to evaluate the plastic surgery literature by focusing on the prevalence of, and examining key components of quality of, RCTs comparing surgical interventions.

Methods: An electronic search of the pertinent plastic surgery literature identified all RCTs published from 2000 to 2013 that compared one surgical intervention to another surgical intervention. Working in teams of two investigators independently, and in duplicate, assessed each manuscript for potential relevance and performed data extraction. Descriptive statistics, theory-driven multinomial regression, and independent samples t-test were used for data analysis.

Results: Of the 1664 hits obtained, 173 RCTs were included. These RCTs demonstrated the following data: 35% of RCTs performed and reported randomization properly, and 12% of RCTs reported proper allocation concealment methods. Outcome assessors were blinded in 48 (34%) RCTs, and patients blinded in 45 (26%) RCTs. Multinomial regression demonstrated that trials reporting an a *priori* sample size are significantly more likely to have a low risk of bias. One-third of trials did not state a primary outcome. The mean and median sample sizes were 73 and 43 patients respectively. Funding and conflict of interest reporting improved over time.

Conclusions: This systematic review establishes a baseline of the quality of evidence that currently guides practice for surgical interventions in plastic and reconstructive surgery. For the readers of plastic surgery literature to have confidence in the literature, risks of bias should be minimized and transparently reported. This will encourage plastic surgeons to apply the results and findings from published RCTs in their practice, providing patients them with the best possible treatments.

Acknowledgements

I would like to thank my supervisors and thesis committee, Dr. Bhandari, Dr. Thoma, and Dr. Meade who always made themselves available and provided continual guidance throughout my thesis and my Masters program. I am most appreciative for this invaluable experience. I would also like to thank the external reviewer, Dr. Pusic.

I am so grateful for the support I received from Dr. Singh and Dr. Kearon through both the Clinician Investigator Program and the Surgeon Scientist Program.

I received much advice and help along the way from a number of individuals including Lisa Buckingham, Qi Zhou and especially Dr. Jason Busse. The assistance of Laura Banfield, our medical librarian, was extremely helpful.

The reviewer team: Dr. Christopher Coroneos, Manraj Kaur, and Dr. Natalia Ziolkowski, dedicated countless hours to screening, reviewing and extracting data. I am most grateful for this effort and for all the suggestions that improved the end result of this project.

Throughout my Masters my family was consistently supportive and encouraging. Thank you so much for being there for me.

Financial Support

This study was supported through an Award from the Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare Hamilton.

Table of Contents

Declaration of Academic Achievement

As the primary author of this project I was responsible for most of the work presented. I designed the study, refined the research question and methods, and drafted the protocol. I was responsible for organizing the administrative aspects of the study which included the timeline of the project, recording all steps of the search and data extraction, assigning papers for title and abstract review, full text review, and for data extraction. I played a major role in article screening and data extraction, performing title and abstract screening, full text screening on every article, and data extraction on every RCT. I drafted all the questions, created the data extraction forms and the data dictionary (guidelines for extraction). I managed the data extraction database and prepared all data for statistical analysis. I calculated all reviewer agreement, performed most of the statistical analysis, and created all diagrams, tables, and charts. Finally, I drafted every section of this manuscript.

1. Introduction

1.1. Purpose

Randomized Controlled Trials (RCTs) are considered the gold standard for measuring a treatment's impact, among all forms of clinical trials. However, there exist unique challenges to the conduct of surgical RCTs that often are not present in RCTs of medical interventions. For example, cultural resistance to randomization, the challenge of blinding, variability in surgeon skill, surgical learning curves, and rare or life-threatening conditions are some of the unique challenges in performing surgical trials.

The objective of this systematic review was to evaluate the plastic surgery literature by focusing on the prevalence of, and providing an in depth examination of, the quality of RCTs comparing surgical interventions. Specifically, trial characteristics, risks of bias, trial outcomes, sample size, and funding were investigated in plastic surgery RCTs.

1.2. Background and Rationale for Review

The practice of surgery is entrenched in a tradition of "treating patients with practices based on rigidly held protocols learned in residency training or opinions presented by leaders in the field[1]." In July of 2010, the Editor-in-Chief of the highest impact plastic surgery journal, *Plastic and Reconstructive Surgery,* along with several specialty journal editors and plastic surgery Association presidents, met to put forth a challenge to the surgical community: "We invite, encourage, and challenge you to join with us to make Evidence-Based Medicine (EBM) part of our culture. Plastic surgery has

the opportunity to take a leading role in transforming medicine through EBM, and we personally solicit your involvement and help in this movement[2]." EBM has been defined as "conscientious, explicit, and judicious use of current best evidence, combined with individual clinical expertise and patient preferences and values, in making decisions about the care of individual patients[3]."

In the summer of 2012, a second summit took place bringing together leaders from various plastic surgery organizations, societies, boards, journals and foundations. Here, it was determined that an effort was needed to advance EBM in plastic surgery, which would improve the quality of care and patient safety[4].

1.3. Importance of RCTs in Surgery

Randomized controlled trials are generally accepted as the most scientifically rigorous study design to evaluate the existence of a cause-and-effect relationship between a therapeutic intervention and a predefined outcome when a genuine state of equipoise exists[5 6]. "Clinically and statistically, randomization is the single characteristic that most sharply distinguishes the controlled trial from other forms of scientific investigation in medicine[7]." Randomization itself is so powerful due to its ability to create groups of participants with similar known and unknown prognostic factors at the commencement of a trial[8]. This allows for the differences between groups at the completion of the trial to be attributable to the intervention under investigation[8]. High-quality, large multicentre RCTs are regarded as optimal in informing surgical decision-making[9], and are necessary to determine treatment efficacy when the benefits of a surgical intervention are expected to be small.

Not all questions faced in plastic surgery need to, or should be, answered with an RCT, for example due to feasibility issues (rare endpoints) or ethical considerations (measuring harmful outcomes)[5]. A study by Solomon *et al* reviewed gastrointestinal surgery operation articles published in 1990 found that in only 39% of studies could the posed question be answered by an RCT in an ideal clinical research setting[10]. However, they also found that only 5% of the studies actually were RCTs. While a similar study by Solomon *et al*[10] has not been performed with regards to plastic surgery literature, both publication rates and the evidence level of publications have been investigated in plastic surgery. Reviews of plastic surgery literature have estimated that RCTs comprised 2% of all original articles of all original articles in plastic surgery journals in September 2007[11], and represented 3.2% of aesthetic surgery articles published between 1998-2007[12]. Publication rates of "Level 1 evidence", which was defined as research consisting of RCTs or meta-analyses of RCTs, has been quoted at 1.5% for articles published in *Plastic and Reconstructive Surgery* in 2003[13]. While there is not one single study design that is appropriate to answer all plastic surgical questions, for example questions involving prognosis or diagnosis, it is reasonable to believe that many therapeutic questions remain that will best be addressed by using a well-designed, large RCT.

1.4. Risk of Bias

For surgeons to determine whether RCT findings will be beneficial in a practical sense, they must question 1) whether the research findings are convincing, and 2) whether the findings have clear application to their patients and clinical practice[14]. The design and conduct of the RCT must be considered to answer the first question, and can be evaluated

through an assessment of the internal validity of the trial. Specifically, the key methodological principles of randomization, allocation concealment, blinding, and ensuring adequate follow-up helps to ensure the low risk of bias of trial results[15].

The concept of "quality" has been used to refer to quality of reporting, quality of trial design, quality of trial conduct, or even its clinical relevance[16]. Assessments of the quality of reporting do not achieve a true evaluation of a randomized controlled trial, as such assessments are often evaluated with summary scores or quality checklists, which can be simplistic at best, and problematic at worst[16]. While evaluations of the key methodological principles of a trial are intertwined with the quality of reporting, it is preferable to evaluate these risks of bias. This preference of evaluation has been recommended based both on empirical evidence and theoretical considerations[16 17]. Furthermore, a more fulsome understanding of these risks of bias in surgical RCTs might allow for improved conduct of trials, thus producing results that are a closer approximation of the true effectiveness of a surgical intervention[18].

1.5. What is already known

An assessment of the risk of bias, using the Cochrane Risk of Bias tool[17], of plastic surgery RCTs has never been conducted. While a systematic review by Agha *et al*[19] assessed the methodological quality of plastic surgical RCTs published between January 1, 2009 and June 30, 2011, an examination of a significant time period of plastic surgery RCTs assessing surgical interventions using a comprehensive search strategy and the Cochrane Risk of Bias tool has not been performed.

Existing assessments of the "quality" of RCTs in plastic surgery are limited; in general, only quality of reporting is evaluated [20-22], only a small selection of journals are reviewed[20-25], and some of these reviews are now out of date[20 22-28]. However, some of these studies did use a comprehensive search strategy[28 29], and performed extensive assessments[21]. The assessment of plastic surgical RCTs by Agha *et al*[19] endeavoured to improve on existing assessment methods through their own adaptation of the Linde Internal Validity Scale[30]; the ELVIS (the Extended Linde Internal Validity Scale) which they report builds on the Jadad score[31]. A common theme discussed by most studies was the poor quality of reporting, and they agree that more high quality RCTs are needed in plastic surgery.

Scores obtained from certain quality scales when appraising clinical trials amalgamate quality of reporting with facets of trial conduct and weight scores in a manner that is difficult to justify[32]. Empirical evidence suggests that attempts to associate scores achieved in quality scale assessments with intervention effect estimates have been inconsistent and unpredictable[32]. The use of a quality scale in which a summary score is calculated can be appealing in its apparent simplicity. However, examining the influence of key components of methodological quality individually is a preferable method to assess RCTs[16].

1.6. Implications of this Study

A solid foundation for evidence-based plastic surgery is emerging as the volume of published level I studies continues to increase[21]. Meanwhile, readers are applying various methods to assess the plastic surgery literature. Plastic surgeons are expected to

appraise a randomized controlled trial, interpret the validity of the results, and combine this information with their clinical expertise and patient preferences to decide on the appropriate treatment. A goal of this systematic review is to understand the challenges unique to plastic surgeons when conducting an RCT addressing surgical interventions. The information and conclusions from this systematic review will be used to address shortcomings found in the literature. By evaluating the key methodological steps in the conduct of surgical RCTs, explaining their importance, and highlighting areas that are lacking can serve as a launch pad for future surgical RCTs. This study will help plastic surgeons succinctly evaluate an RCT, and will play a role in improving surgical research carried out by plastic surgeons.

2. Methods

The objective of this systematic review was to evaluate the plastic surgery literature by examining key components of the quality of RCTs comparing surgical interventions. This chapter will discuss the methodology for the systematic review, including the search strategy utilized, and the data collection process.

2.1. Systematic Review Methods

The general concepts and topics proposed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement[33] were adhered to. The focus of this systematic review was to assess key components of quality of surgical RCTs, rather than summarize the benefits and harms of a specific health care intervention. As a result of this focus, some modifications of the PRISMA checklist items were necessary, and are discussed within. The protocol of this systematic review was prepared in August 2012 for registration in the International Prospective Register of Systematic Reviews (PROSPERO)[34] (Appendix A), however, systematic reviews addressing methodological challenges were not eligible for registration at the time, and therefore this systematic review is not registered.

2.1.1. Types of Studies Eligible for Review

Prospective, non-pharmaceutical randomized controlled trials comparing two or more plastic surgical interventions to address the same patient problem were included. Arbitrary publication limits were set between January 2000 and February 2013.

2.1.2. *Types of Participants Eligible for Review*

All patients were considered of interest.

2.1.3. *Types of Interventions Eligible for Review*

All plastic surgical interventions were included in the initial study selection. For the purpose of this investigation, a surgical intervention was defined as "any procedure that involves cutting, abrading, suturing or physically changing body tissues". The surgeon's hands, or an extension of his/her hands via an instrument (e.g. scalpel, liposuction cannula, Kirschner wire, laser) must have traversed the dermal/epidermal junction as a key part of the described procedure. Non-surgical interventions or procedures, such as acupuncture, steroid injections or the use of injectables (e.g. Botox, hyaluronic acid) were excluded.

In order for the intervention to be considered a "plastic" surgical intervention, the procedure needed to be able to be classified into one of the ten domains of plastic surgery (Table 2.1). As well, the surgical interventions under comparison could differ by a single step; for example, an RCT comparing bilateral breast augmentation using triple antibiotic solution versus bacitracin solution would be eligible. Additionally, the RCT could compare two explicitly different surgical procedures to address the same patient problem; for example, deep inferior epigastric perforators (DIEP) flap versus transverse rectus abdominis myocutaneous (TRAM) flap for breast reconstruction.

2.1.4. *Types of Outcome Measures Eligible for Review*

All outcomes were considered of interest.

2.2. Search Methods for Identification of Studies

For this investigation, it was decided that the "plastic surgery literature" would encompass all journals pertinent to plastic and reconstructive surgery, with each journal being a publication that would have the possibility of being familiar to a practicing plastic surgeon.

For this investigation, two separate searches were required, which were created in consultation with, and under the direct supervision of a McMaster University Medical Librarian (Laura Banfield), experienced in the conduct of systematic reviews. Twenty-nine of the 30 journals included in this systematic review are fully indexed in Ovid MEDLINE®; therefore, Ovid MEDLINE® was searched, and a hand search was used for the remaining non-indexed journal.

Deleted: s

2.2.1. Search Strategy #1

The first search strategy involved obtaining RCTs from plastic surgery specific journals. Only two sets of search terms were required. First, an RCT search string was used to identify for the study design of interest. Since plastic surgery literature was specifically being evaluated, all health conditions and surgical interventions were to be included in this review as long as they were of an RCT study design and published within a journal that would be considered relevant to the plastic and reconstructive surgery field. Secondly, an additional set of search terms produced a list of relevant plastic surgery journals, which was created to define the plastic surgery literature.

Deleted: .

Together, the plastic surgery journals deemed relevant are listed, along with their 2011 ISI impact factors, in Table 2.2. The initial list consisted of 14 journals, and was

created from a table of "journals pertinent to plastic and reconstructive surgery", as discussed in Rorich and Sullivan, 2006[35]. Here, it was additionally noted that other journals exist to that help form the core literature for plastic and reconstructive surgery. However, at the time of their publication, these journals were not indexed by the Institute for Scientific Information. Therefore, under the supervision of two experienced academic plastic surgeons (Dr. A. Thoma and Dr. J.R. Bain), all surgical journals indexed in the Institute for Scientific Information (ISI) were reviewed and discussed for inclusion within the core plastic surgery literature. This was performed in October 2012, using the 2011 ISI impact factors. Of the indexed surgical journals, 11 were deemed to be pertinent to plastic and reconstructive surgery and added to the list of selected journals (Table 2.2, bolded) By including these 11 journals, the list of journals pertinent to plastic and reconstructive surgery consists of 25 unique journals. It is worth noting that 29 journal titles were searched, as 4 journals changed their name.

As a result, a search of the electronic database Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® (1946 to Present) was performed for these 25 unique journals to identify relevant RCTs. The search was restricted to "humans" and publications since the year 2000. An initial search was performed October 2012, with an updating search February 5, 2013. The full search strategy, highlighting specific search terms, is outlined in Table 2.3.

2.2.2. Search Strategy #2

The second search strategy was designed to obtain plastic surgical RCTs published in high impact medical journals, and the highest impact surgical journal. While

the 25 journals provided a list of subspecialty specific journals especially relevant to plastic and reconstructive surgery, five additional high impact journals were also considered relevant: the top surgical journal, Annals of Surgery, and general medical journals New England Journal of Medicine, The Lancet, Journal of the American Medical Association, and British Medical Journal. It is likely that plastic surgeons with high quality, ground-breaking research that might be relevant to several medical fields would pursue publication within these widely-read journals to communicate their findings and achieve visibility with their peers[36], as well as assist with professional advancement[37]. These additional "elite" journals were included in our list of pertinent journals, since any plastic surgery relevant RCT published within these journals would likely be noticed and read, creating a total of 30 relevant journals.

When searching the five high impact journals, three sets of search terms were used: (1) an RCT search string, (2) terms that search for plastic surgery health conditions, and (3) terms that searched for plastic surgery procedures. The terms used to search for plastic surgery health conditions and plastic surgery procedures were created using the Canadian Royal College Plastic Surgery Competencies (RCSPC Objectives) as a guideline. These terms were then modified and expanded upon in consultation with a McMaster University Medical Librarian (Laura Banfield) to create controlled vocabulary search terms for MEDLINE. In order to identify as many relevant records as possible[38], the search was comprised of a combination of subject terms selected from the controlled vocabulary, and a wide range of keyword terms. The full search strategy, highlighting specific search terms, is outlined in Table 2.4.

As the purpose of this systematic review was to evaluate the existing surgical RCTs within the plastic surgery literature, searching within these 30 plastic surgery relevant journals was determined to be the most appropriate search strategy, as opposed to searching for plastic surgery topics published in any existing journal.

2.2.3. Searching other resources

At the time of the final search (February 2013), the Canadian Journal of Plastic Surgery was only indexed electronically from January 2006 onward. Therefore, a hand search of this journal was performed, using the journal's website, from January 2000 to December 2005. Grey literature was not searched.

2.3. Study Selection

2.3.1. Titles and Abstract Screening

Three reviewers, in two pairs, Dr. S. Voineskos (SV) and Dr. C.J. Coroneos (CJC), (both plastic surgery residents, trained in health research methodology) and SV and Dr. N. Ziolkowski (NZ) independently, and in duplicate, read the retrieved titles and abstracts and assessed them for potential relevance. NZ was a senior medical student with experience in systematic reviews at the time of search, and is currently a plastic surgery resident.

Any article considered potentially relevant by either reviewer was obtained in full for complete assessment. To be considered potentially relevant, the title and abstract of the article had to (1) appear to be describing a non-pharmaceutical randomized controlled

trial that is comparing one plastic surgical intervention (or component/part thereof) to another plastic surgical intervention, (2) be able to be classified into one of the ten topics within the field of plastic surgery (Table 2.1), (3) be published between January 2000, and February 2013, (4) be published in one of the 30 journals decided upon a priori and (5) have the word random (or variation of) in the title, abstract, or Ovid extended reference of the manuscript. The title and abstract were excluded if they clearly were describing (1) an animal study (2) a cadaver study or (3) a non-randomized study.

2.3.2. Full Text Screening

Each full text article was read independently, and in duplicate, by both individuals within a pair of reviewers, either SV and CJC, or SV and M. Kaur (MK). MK is a plastic surgery research assistant with experience in systematic reviews. For a full text article to be included for data extraction and assessment, both reviewers had to confirm and agree that the article (1) described itself as a randomized controlled trial, or referred to the process of patient allocation as being random (or used a variation of the word "random"), (2) was a non-pharmaceutical trial comparing one surgical procedure (or component/part of one) to another surgical procedure, for a plastic surgical problem, performed on patients in an operating room, and (3) involved a topic of investigation identifiable as being relevant to the field of plastic and reconstructive surgery.

Any disagreements among reviewers regarding the potential relevance of a trial were discussed until a consensus was reached. If a consensus could not be reached, an arbitrator (AT) was consulted for a deciding opinion.

Full text screening was performed using electronic forms hosted through a central server, DistillerSR[39], an online application designed specifically for the screening and data extraction phases of a systematic review. The full text articles of potentially eligible RCTs were also available, to each reviewer, electronically on the central server.

Articles that were excluded fell into one or more of the following categories: (1) unsuitable study design: systematic review, meta-analysis, economic analysis based on an RCT, RCT of diagnostic tests, observational study, case series, case report, abstract, meeting proceeding, article summarizing the results of a previous study, any letter to an editor or correspondence whether or not results from an RCT are described within, (2) retrospective analyses of RCT data, (3) a surgical intervention that falls out of the domain of plastic surgery e.g. repair of tympanic membrane perforation, tonsillectomy, thyroidectomy, removal of submandibular hilar stone, dacryocrstorhinostomy, surgeries for sleep-disordered breathing, (4) comparisons between a surgical intervention and a non-surgical intervention e.g. a procedure (Botox, filler injections of any type, steroid injection, ultrasound, acupuncture), a non-surgical treatment (physiotherapy, manipulation, splinting, regular application of cream/spray), a "non-intervention" (delaying surgery and measuring outcomes before the surgery takes place), (5) comparisons of preoperative preparations e.g. comparisons of patient positioning on the operating table, draping/prepping styles, (6) any postoperative treatment (e.g. dressings) (7) any medication e.g. antibiotic, anesthetic or other that is administered outside the operating room or can be administered by the anesthesia team, or injections (including nerve blocks) administered by the surgeon just before or just after the surgery, (8) animal,

cadaver, or basic science studies, (9) an experimental (i.e. non-therapeutic) surgery on a human (e.g. administering an incision on a healthy patient, inserting a suture in a healthy patient's skin to measure dissolving time), and (10) a biopsy or fine needle aspiration.

Chance-corrected agreement (κ statistic) was measured for inter-reviewer agreement for full text trial inclusion. If fewer than 15%, or more than 85% of citations were included in the systematic review[15], agreement would also be measured using chance-independent agreement (ϕ statistic). Chance-independent agreement (ϕ statistic) is not susceptible to the distribution of agreement (e.g. 50% positive, 50% negative or 90% positive, 10% negative). At extreme values of chance agreement, the κ statistic can be low, even when reviewer agreement is almost perfect. The agreement statistics were interpreted using the guidelines recommended by Landis and Koch[40]: kappa values of 0 to 0.20 represent slight agreement, 0.21 to 0.40 represent fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.80 to 1 is almost perfect to perfect agreement. The same guidelines were used to interpret the ϕ statistic.

2.4. Data Collection Process

2.4.1. Data Extraction

Data extraction was performed individually by four reviewers, working in 3 pairs, (SV and CJC; SV and MK; SV and NZ) using electronic data collection forms created a priori. The electronic forms were hosted, and data was managed, on DistillerSR[39]. Data collection forms were designed and created with input from all authors. Details and information on methodological bias (e.g., allocation sequence generation, allocation

concealment, blinding of patients and trial team members, loss to follow-up), participants (e.g., total number, inclusion/exclusion criteria, country), interventions (e.g., total number of intervention groups, number of surgeons involved, standardization of intervention), outcomes (e.g., use of a primary outcome, type of outcome used, adverse events/complications), results (e.g., sample size, missing participants, estimate of effect with confidence intervals), and other RCT characteristics (e.g. funding source, trial registration, industry involvement) were collected. A sample of the final version of the data collection form can be viewed in Appendix B. A data dictionary was created and included precise definitions with specific instructions for reviewers when performing data extraction (Appendix B).

Before starting data abstraction, training exercises were performed to ensure consistency between reviewers. The data collection forms with specific and detailed instructions underwent two phases of pilot testing. In the first phase, December 2012, three pairs of reviewers (SV and CJC, SV and MK, SV and NZ) independently, and in duplicate, performed data abstraction on 18 unique RCTs (6 RCTs per pair). In the second phase, January 2013, the same three pairs of reviewers (SV and CJC, SV and MK, SV and NZ) independently and in duplicate performed data abstraction on 6 unique RCTs (2 RCTs per pair).

The unit of interest in this systematic review was the randomized controlled trial itself, not the manuscript. A “duplicate publication” has been defined as “the publication of an article that overlaps substantially with an article published elsewhere”. While duplication goes beyond simple copying, and characteristics of duplicates are not well

understood[41], when two or more publications were found to represent the same RCT, the information from these reports was collated. If any discrepancy was found between reports, information from the most recently published report was used. When recording items that could have been unique to the manuscripts (e.g. outcome, time horizon), the more recently published manuscript took precedence.

Once piloting of the data collection forms and the data dictionary was complete, all unique RCTs underwent data extraction independently and in duplicate by each individual within a pair of reviewers. Statistical software (SPSS) was used to randomly divide and assign all unique RCTs for data extraction among the other three reviewers, CJC, MK and NZ. Therefore, data extraction was performed on each RCT by SV, and a second time by one other reviewer (either CJC, MK, or NZ).

Explicit and simple decision rules were created and built into the data dictionary to make data extraction as objective as possible. The electronic data allowed the automatic comparison of disagreements, which were discussed until a consensus was reached. If a consensus could not be reached, an arbitrator (AT) was consulted for a deciding opinion. The presence and resolution of disagreements was carefully recorded. Three versions of data for each RCT exists: 2 versions of the "data as extracted" (1 per data extractor), and 1 version of the "final consensus data".

2.4.2. Plan for Data Analysis

The primary analysis was a theory-driven multinomial logistic regression. This is a model of logistic regression that uses a categorically distributed dependent variable. The successful completion of RCT methodological safeguards was used to create the

dependent variable. Information from participants, interventions, and other RCT characteristics was used to create the independent variables. Full details and results of this analysis are presented further in Chapter 4 (sections 4.3.2 and 4.4.6).

Descriptive statistics were used to present details and information on methodology (section 4.4), participants (sections 3.1.4 and 6.3), interventions (sections 5.3 and 6.3) , outcomes (section 5.3), results (section 6.3), and other RCT characteristics (sections 3.1.4 and 7.3).

Table 2.1. Domains of Plastic Surgery. The following list represents the surgical interventions which were considered a "plastic" surgical intervention for the purposes of this investigation[42]

i. Facial/head and neck reconstruction

ii. Craniofacial surgery

iii. Hand/upper extremity surgery

iv. Breast surgery

v. Trunk reconstruction

vi. Lower extremity surgery

vii. Genital/pelvic reconstruction

viii. Aesthetic surgery/body contouring

ix. Generalized cutaneous disorders

x. Burns

Table 2.2. Relevant Plastic Surgery Journals. The combined search strategies generated a list of 25 relevant plastic surgery journals, presented along with their 2011 ISI impact factor. An initial list of journals pertinent to plastic and reconstructive surgery, as identified by Rohrich and Sullivan[35], is identified by asterisks (*). The journals considered pertinent to plastic and reconstructive surgery after ISI review are highlighted are in bold.

Plastic Surgery Pertinent Journal	2011 ISI Impact Factor (as listed Oct 2012)
* *Plastic and Reconstructive Surgery*	3.832
* *Transplantation International*	2.921
Head and Neck - Journal for the Science and Specialties of the Head and Neck	2.403
Burns	1.962
British Journal of Oral & Maxillofacial Surgery	1.950
* *Otolaryngology Head and Neck Surgery*	1.718
* *Clinical Transplantation*	1.667
Archives of Facial Plastic Surgery	1.646
**Journal of Cranio-Maxillofacial Surgery*	1.643
Microsurgery	1.605
* *International Journal of Oral and Maxillofacial Surgery*	1.506
* *Journal of Plastic Reconstructive and Aesthetic Surgery* (formerly known as *British Journal of Plastic Surgery*)	1.494
Aesthetic Surgery Journal	1.469
**Journal of Reconstructive Microsurgery*	1.432
**Clinics in Plastic Surgery*	1.422
**Aesthetic Plastic Surgery*	1.407
Journal of Burn Care & Research (formerly known as *Journal of Burn Care & Rehabilitation*)	1.366
**Journal of Hand Surgery - American Volume*	1.354
* *Annals of Plastic Surgery*	1.318
Journal of Hand Surgery-European Volume (formerly known as *Journal of Hand Surgery - British Volume*)	1.171
Facial Plastic Surgery	0.963
Journal of Plastic Surgery and Hand Surgery (formerly known as *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*)	0.935
* *Journal of Craniofacial Surgery*	0.822
* *Cleft Palate-Craniofacial Journal*	0.822
Canadian Journal of Plastic Surgery	0.179

Table 2.3 Search Strategy #1. The full search strategy for identifying RCTs in plastic surgery relevant journals.

1	randomized controlled trial/
2	randomization/
3	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or method*)).mp.
4	1 or 2 or 3
5	plastic & reconstructive surgery.jn.
6	transplant international.jn.
7	clinical transplantation.jn.
8	"journal of cranio maxillo facial surgery".jn.
9	"international journal of oral & maxillofacial surgery".jn.
10	"journal of hand surgery american volume".jn.
11	"journal of hand surgery european volume".jn.
12	"journal of hand surgery british volume".jn.
13	otolaryngology head & neck surgery.jn.
14	"journal of plastic reconstructive & aesthetic surgery jpras".jn.
15	"british journal of plastic surgery".jn.
16	microsurgery.jn.
17	"archives of facial plastic surgery".jn.
18	"annals of plastic surgery".jn.
19	cleft palate craniofacial journal.jn.
20	aesthetic plastic surgery.jn.
21	clinics in plastic surgery.jn.
22	"journal of reconstructive microsurgery".jn.

23	"journal of craniofacial surgery".jn.
24	head & neck.jn.
25	burns.jn.
26	"journal of burn care & research".jn.
27	"journal of burn care & rehabilitation".jn.
28	"british journal of oral & maxillofacial surgery".jn.
29	aesthetic surgery journal.jn.
30	facial plastic surgery.jn.
31	"scandinavian journal of plastic & reconstructive surgery & hand surgery".jn.
32	"journal of plastic surgery and hand surgery".jn.
33	"canadian journal of plastic surgery".jn.
34	or/5-33
35	4 and 34
36	limit 35 to (humans and yr="2000 -Current")
37	limit 36 to (case reports or comment or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or meta analysis or practice guideline or "review")
38	36 not 37

Table 2.4. Search Strategy #2: Search strategy for identifying RCTs in five high impact journals.

1	randomized controlled trial/
2	randomization/
3	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or method*)).mp.
4	1 or 2 or 3
5	jama.jn.
6	"new england journal of medicine".jn.
7	lancet.jn.
8	bmj.jn.
9	"annals of surgery".jn.
10	5 or 6 or 7 or 8 or 9
11	exp plastic surgery/
12	((plastic or reconstruct* or cosmetic* or aesthetic* or esthetic*) adj4 (surg* or procedure* or technique* or method*)).mp.
13	(burn adj10 surg*).mp.
14	((moh or mohs or moh's) adj2 surgery).mp.
15	craniofacial surgery.mp.
16	exp orthognathic surgery/ or (orthognathic adj2 surg*).mp.
17	otoplast*.mp.
18	palatoplast*.mp.
19	dermabrasion*.mp.
20	hair transplant*.mp.
21	blepharoplast*.mp.
22	(facelift* or (face adj1 lift*) or rhytidoplast* or rhytidectom*).mp.

23	Endoscopic forehead lift.mp.
24	rhinoplast*.mp.
25	abdominoplast*.mp.
26	(liposuction or lipect* or lipoplast*).mp.
27	fat graft*.mp.
28	exp mammaplasty/ or mamm?plast*.mp. or breast augmentation*.mp.
29	(breast reduction* or mastopex*).mp.
30	breast reconstruct*.mp.
31	((nipple adj5 recon*) or (NAC adj5 recon*)).mp.
32	(tissue adj1 expansion*).mp.
33	microsurgery/ or microvascular surg*.mp.
34	hand surgery.mp.
35	exp tenosynovitis/
36	(tendon adj2 (repair or surgery)).mp. or tendon transfer/
37	(carpal adj2 release).mp.
38	decompression, surgical/ or microvascular decompression surgery/
39	nerve transfer/
40	replantation/
41	suture techniques/
42	or/11-41
43	exp melanoma/ or melanoma*.mp. or skin neoplasms/ or acanthoma/ or (skin adj3 (cancer* or neoplasm*)).mp.
44	exp carcinoma, squamous cell/ or neoplasms, squamous cell/ or (carcinoma* adj1 (epidermoid or squamous or planocellular)).mp. or (bowen* adj1 disease).mp.
45	neoplasms, basal cell/ or carcinoma, basal cell/ or carcinoma, basosquamous/ or (basal cell adj1 (cancer* or carcinoma*)).mp.
46	exp burn/
47	exp facial injuries/

48	((cleft adj1 lip*) or harelip*).mp.
49	(cleft adj2 palat*).mp.
50	exp temporomandibular joint/
51	skin transplantation/ or (skin adj2 transplant*).mp. or (skin adj2 graft*).mp.
52	exp surgical flaps/ or (free adj3 flap*).mp.
53	adipose tissue/ or ((adipose or fat) adj1 tissue*).mp. or body fat.mp.
54	exp brachial plexus/ or median nerve.mp. or musculocutaneous nerve.mp. or radial nerve.mp. or ulnar nerve.mp.
55	exp hand/ or exp hand injuries/
56	tendon injuries/
57	exp hand joints/
58	(trigger* adj2 finger*).mp.
59	carpal tunnel syndrome/
60	dupuytren*.mp.
61	osteoarthritis.mp.
62	exp arthritis, rheumatoid/ or rheumatoid arthritis.mp.
63	scar*.mp.
64	laceration/
65	soft tissue*.mp.
66	pressure ulcer/
67	reconstruct*.mp.
68	wound healing/ or wound infection/
69	exp "Wounds and Injuries"/
70	or/43-69
71	su.fs. or surg*.mp.
72	exp Specialties, Surgical/

73	exp Surgical Procedures, Operative/
74	71 or 72 or 73
75	4 and 10 and (42 or (70 and 74))
76	**limit 75 to (humans and yr="2000 -Current")**

3. Systematic Review Search Results and Summary of Studies

3.1. Results

3.1.1. Search Results

The flow of studies through the screening process is illustrated in Figure 3.1. The resulting 184 articles were categorized as RCTs assessing a surgical intervention within a plastic surgery domain. Each RCT underwent data extraction.

Of the 184 manuscripts that underwent review and data collection (by two reviewers independently and in duplicate), 173 were unique RCTs. In total, 21 manuscripts were found to represent 10 unique RCTs (see Table 3.1 for multiple reports of the same RCT).

3.1.2. Agreement Statistics

The raw agreement between reviewers during full text screening was 0.93. The calculated chance-corrected agreement (κ statistic) during full text screening was 0.682, representing substantial agreement. Since greater than 85% of citations (184/211 = 87%) were included in the systematic review, chance-independent agreement (ϕ statistic) was calculated as well, with a resulting value of 0.782, also representing substantial agreement.

3.1.3. Characteristics of Excluded Studies

Studies were excluded if: (1) the study either was not or did not describe itself as an RCT, (2) the RCT was not comparing two (or more) surgical interventions, or (3) the RCT was not assessing an operative procedure that is relevant to a plastic surgery

domain. The reason for exclusion of each of the 27 articles excluded during full text review are presented within the Flow Diagram (Figure 3.1).

3.1.4. Characteristics of Included Studies

The characteristics of the included RCTs are displayed in Figures 3.2-to-3.4 and Tables 3.2-to-3.9.

Over the 13 year time period investigated, the continent in which RCTs originated and were conducted the most, N=83 (48%), was Europe (including the UK), followed by Asia (including China and Japan), N=34 (20%). Approximately one in five RCTs originated and were conducted in the USA, N=33 (19%), while one in six RCTs were from the UK, N=30 (17%) (Figure 3.2). Canada conducted and published 7 (4%) plastic surgery RCTs assessing surgical interventions over the same time period. Plastic surgery domains found to be the most studied were Hand and Upper Limb surgery, N=46 (27%), Craniofacial surgery, N=43 (25%), Breast surgery, N=27 (16%), and Aesthetic surgery, N=24 (14%) (Figure 3.3).

Publication rates increased from an average of 2.5/year between 2000 and 2003, to an average of 18.1/year between 2004 and 2012 inclusive (Figure 3.4). Plastic surgery RCTs assessing surgical interventions were found in 22 of the 30 journals that were investigated. The greatest number of RCTs, N=38 (22%), were found in *Plastic and Reconstructive Surgery*, followed by the *Journal of Hand Surgery: European Volume* (formerly known as the *Journal of Hand Surgery: British Volume*), N=25 (14%), and by the *International Journal of Oral & Maxillofacial Surgery,* N=15 (9%) (Table 3.2). Four plastic surgical RCTs were found to be published in the following widely read, highly

regarded medical journals: *The Lancet*, N=2, the *British Medical Journal*, N=1, and the *New England Journal of Medicine*, N=1.

Publication titles identified the randomized trial design for 79 (46%) RCTs, and this information was reported within the abstract in 143 (83%) RCTs (Table 3.3). Some form of patient inclusion criteria were described in 160 RCTs (92%). Inclusion criteria were described explicitly, and in enough detail to be reproducible in 67 RCTs (39%) (Table 3.4). In 17 RCTs (10%), inclusion criteria were not described, though a statement embodying "all patients" or "consecutive patients were included" was present. Some inclusion criteria, while not being as clear or explicit as desirable, were described in 76 RCTs (44%), and inclusion criteria were not described at all in 13 RCTs (8%).

Patient exclusion criteria were described in 128 RCTs (74%). Exclusion criteria were described unequivocally, and in enough detail to be reproducible in 65 RCTs (38%) (Table 3.4). In 12 RCTs (7%), exclusion criteria were not described, though a statement embodying "all patients" or "consecutive patients were included" was present. Some exclusion criteria, while not being as clear or explicit as desirable, were described in 51 RCTs (29%), and exclusion criteria were not described at all in 45 RCTs (26%).

Of the 173 plastic surgical RCTs assessed, only 4 (2%) trials recruited patients internationally (Table 3.5). The majority of RCTs, N=117 (68%), were based out of, and operated on patients at, a single centre (Table 3.5). Thirty (17%) RCTs were multi-centre trials, but 26 (15%) RCTs did not describe their methodology in enough detail for the data abstractors to determine the number of centres involved.

Thirty-eight trials (22%) were single-surgeon RCTs, 12 (7%) had two operating surgeons, 13 (8%) had three operating surgeons, and 12 (7%) had four or more operating surgeons (Table 3.6). In 33 (19%) RCTs it was apparent that multiple operating surgeons were involved, however, the exact number of surgeons was not specified by the authors, and either a range of numbers was given or a "team" of surgeons was described. Sixty-five trials (38%) did not report the number of surgeons involved in their RCT. With the involvement of a plastic surgeon within an RCT being assessed through author reporting and author affiliation, it appeared that a plastic surgeon was involved in 93 (54%) of the RCTs, and 80 (46%) RCTs either did not have, or did not appear to have a plastic surgeon as part of the trial (Table 3.6).

Of the 173 RCTs examined, 12 (7%) reported a registration number for their trial (Table 3.7). One hundred-eight (62%) RCTs clearly started randomizing their patients in 2005, or earlier, 25 (14%) RCTs started randomizing their patients in 2006 or later, and in 40 (23%) RCTs the authors neither reported, nor could the reviewers decipher, the year at which randomization commenced. Of the 108 RCTs that started randomizing their patients to treatment groups either in 2005 or earlier, 5 (5%) reported a registration number for their trial. Of the 25 RCTs that started randomizing their patients to treatment groups either in 2006 or later, 5 (20%) reported a registration number for their trial (Table 3.7). In 125 (72%) RCTs authors reported that they obtained either Ethics or Institutional Review Board approval (Table 3.7).

Sixty-four (37%) RCTs reported that either one of their authors, or one of their contributors, had a graduate degree (Table 3.8). In 47 (27%) RCT manuscripts, a

methodologist (e.g. statistician, clinical epidemiologist) was acknowledged, either as an author, or a contributor to the trial (Table 3.8).

3.2. Discussion

3.2.1. Findings and Implications

In this systematic review of plastic surgical randomized control trials published since the year 2000, it was found that most plastic surgical RCTs originated and were conducted in Europe (48%), North America (24%), or Asia (20%). While this is generally consistent with the existing reviews of plastic surgery RCTs[20 22 23 25 29], in this review, it was found that a greater proportion of RCTs are originating and conducted in Asia when compared to other reviews. In this systematic review, hand and upper limb surgery (27%), craniofacial surgery (25%), breast surgery (16%) and aesthetic surgery (14%) accounted for the majority of the RCTs reviewed. This is likely due to the higher volumes that these areas of plastic surgery are exposed to. This varies greatly from the results of previously published reviews of plastic surgery literature, in which the majority of RCTs involved the domains of wound healing/dressing, anesthesia, aesthetic or breast[20 22]. The discrepancy is due to the purpose of this systematic review, which addressed RCTs specifically assessing surgical interventions.

The publication rates of surgical RCTs increased as expected over the 13 year period, however, an interesting finding was the sharp rise in publication rate from an average of 2.5/year between 2000 and 2003, to an average of 18.1/year between 2004 and 2012 inclusive. This is consistent with the spike in publication of RCTs reported in a

review of aesthetic plastic surgery RCTs[23] and the 4 reviews that assessed any type of plastic surgery RCT[21 22 25 29].

Between 2000 and 2013, the journal *Plastic and Reconstructive Surgery* published the most (N= 38, 22%) surgical RCTs. While some previous reviews used RCTs published in the 3 most prestigious plastic surgery journals[20 22 25], *Plastic and Reconstructive Surgery*, *Journal of Plastic and Reconstructive Surgery* (formerly known as the *British Journal of Plastic Surgery*), and *Annals of Plastic Surgery*, to evaluate the plastic surgery literature as a whole, these three journals only accounted for one-third (N=56, 32%) of the publications in this current study. It is possible that these results might be specific to plastic surgery RCTs assessing surgical interventions, however it is recommended that any future reviews of plastic surgery literature use a large number of plastic surgery journals.

When compared to a systematic survey by Berwanger *et al*[43] of RCTs published in NEJM, JAMA, BMJ, and the Lancet in the year 2006, plastic surgical RCTs do not report their study design in their title or abstract as well. Here, it was found that RCTs in medical journals identified themselves as RCTs in their title 55% of the time, and in their abstract 99% of the time[43]. In comparison, the plastic surgical manuscripts in this current systematic review identified themselves as RCTs in their title 46% of the time, and in their abstract 83% of the time. The importance of a manuscript identifying its study design in its title is straightforward. A reader simply might not bother to read the published report if it does not appear to be a study design that they are interested in. Furthermore, when a report is indexed in an electronic database, it might not be classified

under the appropriate study design if the authors do not include this information. The CONSORT guidelines recommend the identification of the study design and the use of the word "randomized" in the title allowing for the study to be easily indexed and identified[44].

The majority of plastic surgical RCTs identified their study design within their abstract. The significance of a clear, transparent, and detailed abstract cannot be overlooked as abstracts are often used a selection tools before deciding to read the full manuscript[44]. Since not all published reports are freely available, and not all physicians have access to the fully published manuscript, therefore healthcare decisions potentially can be, and sometimes are, made on based in the information contained in an abstract[44 45]. The abstracts reviewed in the Berwanger *et al*[43] were found to be structured, as it is a formal requirement in the medical journals they reviewed. Therefore it is certain that reporting of study design can be improved in the plastic surgical literature if structured abstracts, which are recommended by the CONSORT guidelines[44], become a requirement for consideration of publication.

A recent extension to the CONSORT statement provides a list of essential items that authors should include when reporting the main results of a randomised trial in a abstract[44]. The use of structured abstracts for reporting randomised trials is strongly recommended[44]. Some studies have found that structured abstracts are of higher quality than the more traditional descriptive abstracts and that they allow readers to find information more easily[44]. While journals have their own structure and word limit for reporting abstracts, following the recommendations of the CONSORT statement will help

plastic surgeons quickly assess the relevance and importance of a published manuscript though the abstract.

Inclusion and exclusion criteria are needed to define the patient group representative of the population of interest. The majority of RCTs were able to describe some form of their patient inclusion or exclusion criteria, 92% and 74% respectively. While this is helpful for the reader, unfortunately less than half of the RCTs described either their inclusion criteria or their exclusion criteria in sufficient detail, at 39% and 38%, respectively. Statements describing "inclusion of consecutive patients" are helpful, though are more suitable for observational studies. Inclusion and exclusion criteria need to be detailed enough so the reader can be confident that 1) decisions on whether or not to include a patient were objective and 2) the results of the RCT can be applied clinically, such that patients in their practice, who fit the inclusion criteria, are likely to be good candidates for the treatment.

Surgical RCTs recruiting and operating on patients at international sites appear to be rare in plastic surgery (N=4, 2%). These RCTs had at least one study centre in two or more countries where patients were recruited from and/or operated on. The existence of these four RCTs demonstrates that international, multicentre trials examining surgical interventions in plastic surgery are possible. Traditionally, surgeons have had the reputation of working in either a solitary, or small group arrangement[46]. In contrast with this viewpoint, the current study found that 30 (20%) RCTs were multicentre trials, and therefore composed a relatively significant proportion of plastic surgical RCTs. Large, international, multicentre trials have increased complexity; however, they are necessary in

order to provide reliable evidence of the moderate benefits provided to patients by most interventions[47 48].

When a large number of surgeons are involved in an RCT, the variability of their skills and of the experience of the operative teams may introduce greater variation in outcomes than from a single surgeon. These RCTs have the potential to be pragmatic trials, which are able to measure the benefit an intervention produces in the daily clinical setting. Many of the RCTs (N=70, 40%) in this investigation had multiple operating surgeons, which increases external validity, allowing the reader to interpret the results as theoretically being closer to "real-world" clinical practice. Single surgeon RCTs, when undertaken by a world expert, can be a component of an explanatory trial, potentially establishing whether a surgical technique can benefit a patient under ideal and controlled conditions.

In 2004, the International Committee of Medical Journal Editors (ICMJE) published a statement in the *New England Journal of Medicine*[49], announcing that any clinical trial starting enrolment after July 1, 2005 must register their RCT to be considered for publication within any ICMJE journal. The member journals of the Surgery Journal Editors Group (SJEG) followed suit to require registration of all prospective clinical trials[50]. Registering clinical trials is part of the ultimate goal of "full transparency with respect to performance and reporting of clinical trials[49]." Specific benefits of registering trials have been discussed previously[50 51]. At the time of writing, 18 of the 30 journals that were included in this systematic review advised prospective authors that trial registration is required. In this audit of reporting of plastic surgical trial

registration, only 20% of RCTs, which had started patient recruitment in 2006 or later, reported the registration number for their trial. While it is understood that statements regarding Ethics/Institutional Review Board (IRB) approval often depend on the specific journals' instructions to the author, it was found that the majority of RCTs (N=125, 72%) reported IRB approval. It is unlikely that 28% of trials did not obtain Ethics or IRB approval for their trial, rather this information is probably not reported in the manuscript. Since RCTs require IRB approval, and most (if not all) IRBs require the submission of a protocol before approval of a trial, most (if not all) RCTs will have a complete protocol. Therefore, the low rate or trial registration can be overcome since any IRB approved RCT will have a completed protocol that can be submitted to a trial registry.

3.2.2. Limitations of the Search Strategy

Plastic and reconstructive surgery overlaps with various specialties. It is appreciated that some RCTs answering questions which might be relevant to a plastic surgeon's practice are published in "non-plastic surgery journals" (for example Karounis *et al* in *Acad Emerg Med*[52] and Luck *et al* in *Pediatr Emerg Care*[53]). However the intent of this study was to evaluate surgical RCTs within the plastic surgery literature; in other words, the surgical RCTs that the members of our specialty are likely reading.

A single search engine was used in this systematic review. While a search of MEDLINE alone is not considered adequate for a systematic review of an intervention[38], this study is specifically targeting what has already been published in the 25 most relevant plastics journals and 5 major medical/surgical journals. Of these 30 journals, 29 were confirmed as being fully indexed on Ovid MEDLINE(R). The remaining journal, *CSPS*,

is indexed from January 2006 onward and therefore a hand search of titles and abstracts published in this journal from January 2000 to December 2005 was performed.

English language journals were considered for this review. In creating the list of 30 journals to search within, 3 potentially relevant, non-English language journals were identifiable but not included: *Handchirurgie Mikrochirurgie Plastische Chirurgie* (German, 2011 ISI Impact Factor: 0.875), *Chirurgie de la Main* (French, 2011 ISI Impact Factor: 0.529), and *Annales de Chirurgie Plastique Esthetique* (French, 2011 ISI Impact Factor: 0.410). These journals were not included for practical reasons, pertaining to logistics, as the inclusion of trials reported in languages other than English can significantly add to the costs of a review, and the time taken to complete it[38].

3.2.3. Limitations of Data Extraction

Plastic surgery divisions/departments were involved in 93 (54%) of the RCTs. The only objective method of ascertaining a plastic surgeon's involvement was through author reporting and author affiliation. Due to the overlap of plastic surgery as a specialty with other fields, (e.g. oral and maxillofacial surgery, orthopaedic surgery, otolaryngology) and vice versa, as well as differing practices of reporting author affiliations, (e.g. "department of surgery" may be reported, and "division of plastic surgery" is omitted), it is likely that the number of RCTs with a plastic surgeon involved is underreported. It would have been interesting to compare the characteristics of surgical RCTs published by plastic surgeons in the plastic surgery literature with those authored by surgeons from other specialties, and may be represent a further area of research that branches out from the foundations of these findings.

Data was collected on the reported involvement of an author with a graduate degree, and the involvement of a methodologist. Collecting these data from published reports was challenging. The aim was to investigate whether there was a link between high quality trials and either authors with a graduate degree or the involvement of a methodologist. Author qualifications were likely underreported, as it is also at the discrepancy of the journal how many degrees, if any, to report. Furthermore, the subject the actual degree conferred expertise in is unknown. Manuscripts also likely underreported the involvement of a methodologist. In addition, the extent to which the methodologist was involved in the design of the trial is unknown unless explicitly stated within the manuscript, which is rare.

3.2.4. Strengths of the Search Strategy and Data Extraction

This systematic review search spans 13 years, and is up to date, with the most recent search occurring February 5, 2013. These results are a comprehensive representation of the plastic surgery literature as all English language plastic surgery journals were included for review. The completion of a systematic review protocol *a priori* adds to the rigor and transparency of this systematic review. While it could not be registered, as it was not eligible for registration on PROSPERO, it is presented in its entirety in Appendix A.

The integrity and strength of this particular systematic review lies in how decisions were made relating to which studies would be included, and what data would be abstracted. Transparent and systematic methodology was used when searching for eligible RCTs, under the guidance and direct supervision of a medical librarian, and also while

selecting studies to undergo data extraction. All stages of RCT screening and data extraction were performed carefully, independently, and in duplicate, and substantial chance-corrected agreement (κ statistic) and chance-independent agreement (ϕ statistic) was achieved. The 2 stages of data extraction form piloting and the detailed written instructions (data dictionary) ensured consistency, and allowed judgments to be explicit during data extraction.

3.3. Conclusions

This systematic review uncovered many study characteristics of plastic surgery RCTs comparing two or more surgical interventions. Plastic surgical RCTs are being published at a much higher rate than they were 10 years ago, with the majority of productivity coming from Europe, USA, and an emerging Asia.

Plastic surgical RCTs are being published in a variety of plastic surgery journals, and future reviews of "plastic surgery literature" should not be limited to the 3 most read plastic surgery journals (*Plastic and Reconstructive Surgery*, *Journal of Plastic and Reconstructive Surgery,* and *Annals of Plastic Surgery)*[24]. International plastic surgery trials addressing a surgical intervention can be successfully completed, and multicentre trials are possible in plastic surgery. It is acknowledged that the specialty has increased the rate of surgical RCT publication seven-fold since the early 2000's. While it appears that there is still an opportunity for the quantity of surgical RCTs to increase, the quality of these plastic surgical RCTs still needs to be appraised, and this will be addressed in Chapter 4.

Figure 3.1. Flow Diagram of Study Selection. The most recent search was performed on February 5, 2013.

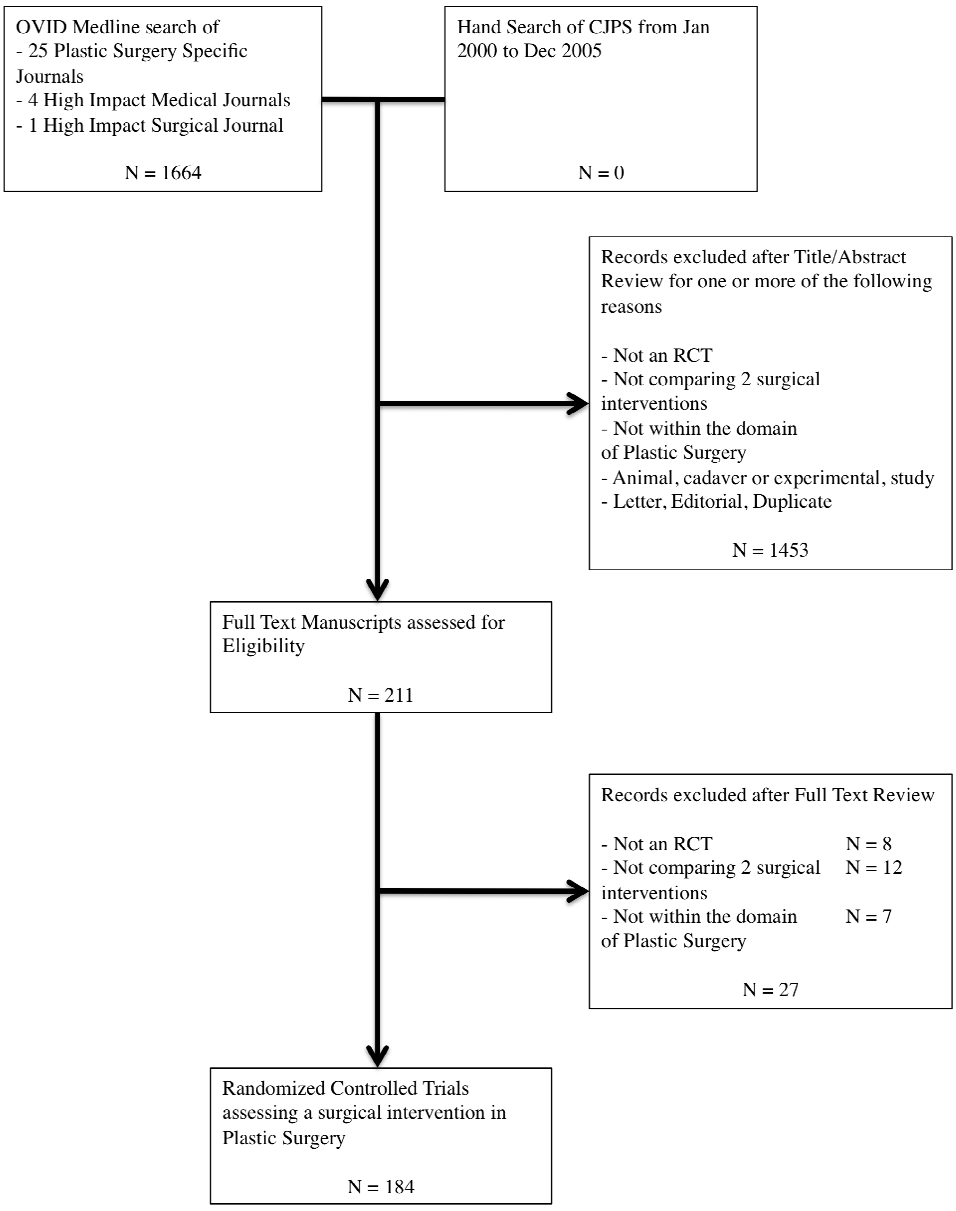


Figure 3.2. Geographical Location of Conduct and Origin of 173 Plastic Surgical RCTs

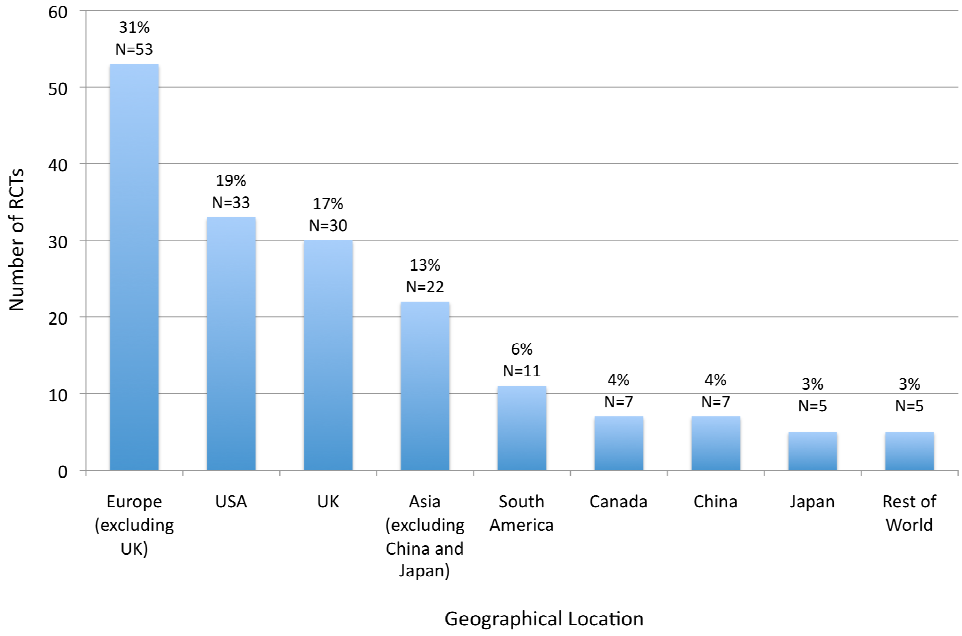


Figure 3.3. Domains of Plastic Surgery Studied in 173 Plastic Surgical RCTs

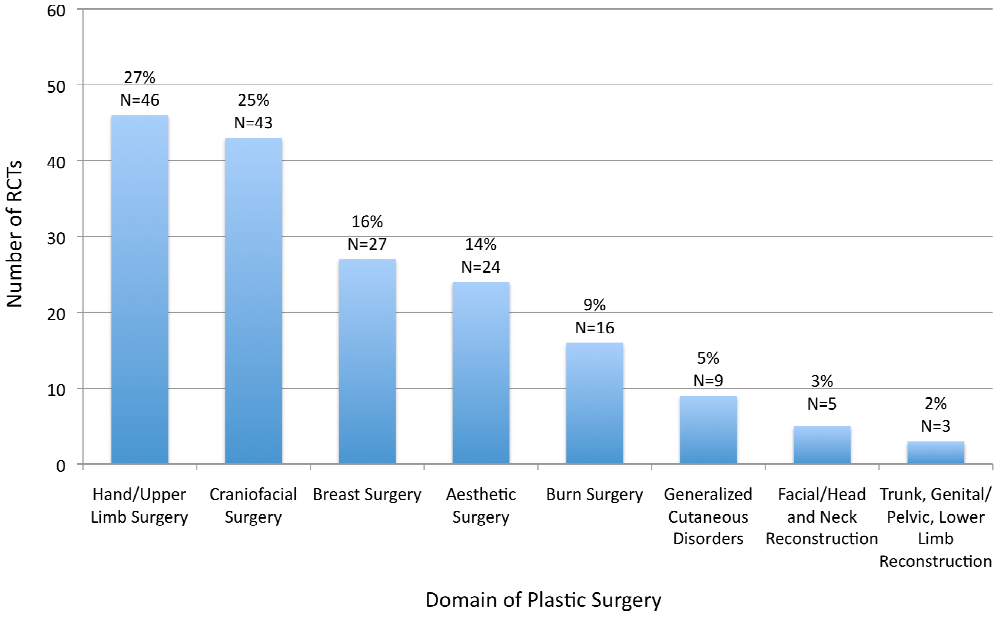


Figure 3.4. Publication Rate of Plastic Surgical RCTs in Plastic Surgery Relevant Journals

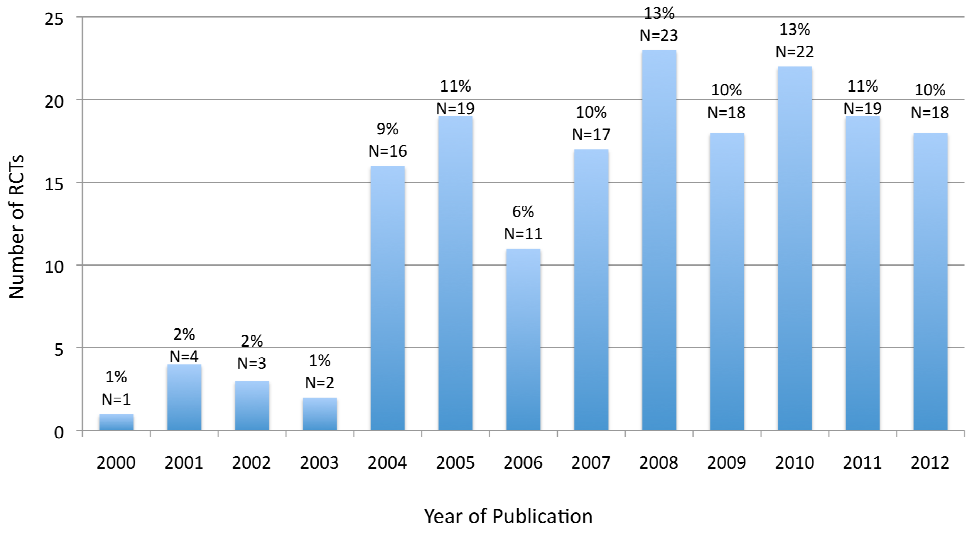


Table 3.1. Twenty-one manuscripts representing 10 unique RCTs

Unique RCT	Manuscript #1	Manuscript #2	Manuscript #3
1	Atroshi et al 2006	Atroshi et al 2009	
2	van Rijssen et al 2006	van Rijssen et al 2012	
3	Verhaegen et al 2011	Verhaegen et al 2011	
4	Parkkila et al 2005	Parkkila et al 2006	Parkkila et al 2006
5	Davis et al 2004	Gangopadhyay et al 2012	
6	Moller et al 2005	Tagil et al 2009	
7	Temple et al 2006	Temple et al 2009	
8	Cheung et al 2006	Chua et al 2010	
9	Bergenmar et al 2010	Gillgren et al 2011	
10	Davis and Pace 2009	Salem and Davis 2011	

Table 3.2. Number of Plastic Surgical RCTs Published by Journal

Journal	**N**	**Percent**
Plastic and Reconstructive Surgery	38	22
Journal of Hand Surgery-European Volume (formerly known as *Journal of Hand Surgery - British Volume*)	25	14
International Journal of Oral and Maxillofacial Surgery	15	9
Aesthetic Plastic Surgery	11	6
Journal of Hand Surgery - American Volume	10	6
Annals of Plastic Surgery	9	5
Burns	9	5
Journal of Plastic Reconstructive and Aesthetic Surgery (formerly known as *British Journal of Plastic Surgery*)	7	4
Journal of Craniofacial Surgery	7	4
British Journal of Oral & Maxillofacial Surgery	7	4
Journal of Burn Care & Research (formerly known as *Journal of Burn Care & Rehabilitation*)	6	3
Journal of Plastic Surgery and Hand Surgery (formerly known as *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*)	6	3
Cleft Palate-Craniofacial Journal	5	3
Aesthetic Surgery Journal	3	2
Archives of Facial Plastic Surgery	3	2
Journal of Cranio-Maxillofacial Surgery	3	2
Otolaryngology Head and Neck Surgery	3	2
The Lancet	2	1
British Medical Journal	1	1
New England Journal of Medicine	1	1
Journal of Reconstructive Microsurgery	1	1
Head and Neck - Journal for the Science and Specialties of the Head and Neck	1	1
Total	173	101*

*Percentage does not add up to 100 due to rounding

Table 3.3. Identification of Study Design as an RCT in the Title and Abstract

Identification as a randomized trial in the Title	**N**	**Percent**
Yes	79	46
No	94	54
Total	173	100
Identification as a randomized trial in the Abstract	**N**	**Percent**
Yes	143	83
No	30	17
Total	173	100

Table 3.4. Reporting of Inclusion and Exclusion Criteria

Reporting of Inclusion Criteria	**N**	**Percent**
Unequivocal, clear, and explicit criteria	67	39
Some criteria, but not as clear or explicit as desirable	76	44
Inclusion criteria was not described	13	8
Inclusion criteria was not described, but a statement embodying "all patients were included/consecutive patients were included" was present	17	10
Total	173	101*
Reporting of Exclusion Criteria	**N**	**Percent**
Unequivocal, clear, and explicit criteria	65	38
Some criteria, but not as clear or explicit as desirable	51	29
Exclusion criteria were not described	45	26
Exclusion criteria were not described, but a statement embodying "all patients were included/consecutive patients were included" is present	12	7
Total	173	100

*Percentage does not add up to 100 due to rounding

Table 3.5. International Patient Recruitment and Number of Centres in Each RCTs

International Patient Recruitment and Participation	**N**	**Percent**
Yes	4	2
No	169	98
Total	173	100
Number of Centres Involved	**N**	**Percent**
Single Centre	117	68
2 Centres	12	7
3 Centres	6	3
4 Centres	1	1
5 Centres	3	2
6 or more Centres	5	3
Multiple Centres, but unclear how many	3	2
Not Reported/Too Unlcear to reasonable estimate	26	15
Total	173	101*

*Percentage does not add up to 100 due to rounding

Table 3.6. Number of Operating Surgeons Involved, and Plastic Surgeon Involvement

Reported Number of Operating Surgeons	**N**	**Percent**
One	38	22
Two	12	7
Three	13	8
Four	7	4
Five	1	1
Six or more surgeons	4	2
Multiple surgeons, but number not specified	33	19
Not Reported	65	38
Total	173	101*
Clear Involvement of a Plastic Surgeon	**N**	**Percent**
Yes	93	54
No	80	46
Total	173	100

*Percentage does not add up to 100 due to rounding

Table 3.7. Plastic Surgical RCT Registration and Ethics/IRB Approval

Presence of RCT Registration Number	**N**	**Percent**
Registration Number Present	12	7
Registration Number Absent	161	93
Total	173	100
Commencement of Patient Randomization	**N**	**Percent**
2005 or earlier	108	62
2006 or later	25	14
Not ascertainable	40	23
Total	173	99*
Presence of RCT Registration Number in RCTs Commencing Patient Randomization in 2005 or earlier	**N**	**Percent**
Yes	5	5
No	103	95
Total	108	100
Presence of RCT Registration Number in RCTs Commencing Patient Randomization in 2006 or later	**N**	**Percent**
Yes	5	20
No	20	80
Total	25	100
Reporting of Ethics or IRB Approval	**N**	**Percent**
Yes, stated within manuscript	125	72
No statement present	48	28
Total	173	100

*Percentage does not add up to 100 due to rounding

Table 3.8. Reported involvement of an Author/Contributor with a Graduate Degree, and Involvement of a Methodologist in the RCT

Reported involvement of an author/contributor with a graduate degree	**N**	**Percent**
Yes	64	37
No	109	63
Total	173	100
Reported involvement of a Methodologist	**N**	**Percent**
Yes	47	27
No	126	73
Total	173	100

4. Risk of Bias in Plastic Surgery Clinical Trials: Let's Raise the Bar

4.1. Introduction

4.1.1. Background

Evidence-based medicine (EBM) is the dominant paradigm for health care in many medical subspecialties. On the other hand, evidence-based surgery (EBS) has been viewed as something difficult to implement due to the perceived low quantity and quality of RCTs assessing surgical interventions[54]. The quality of plastic surgery RCTs has been evaluated by proxy, through the assessment of reporting quality with checklists (i.e., specific questions are asked[20 21 23 25]), scales (i.e., components are scored and combined to give a final score), or both checklists and scales[22 28 29]. While many of these scales and checklists are based on items that are considered to be important criteria in clinical trial dogma, these scales and checklists often address items that are not directly related to the internal validity of a trial. The adequacy of reporting is often confused with the risk of bias present in the actual design and conduct of a trial[17]. While the use of a scale or checklist is appealing due to its simplicity, it is not supported by empirical evidence[17]. Indeed, "the use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews."[17] Instead, when assessing the validity of a trial, the Cochrane Collaboration recommends using a specific tool known as the 'Risk of bias' tool.

A distinguishing characteristic of the 'Risk of bias' tool is the assessment whether a methodological safeguard, such as allocation concealment, was performed appropriately in the trial. Conversely, checklists and scores from scales often record simply whether the

methodological safeguard, such as how patients were allocated, was reported. Failures to conceal allocation, failures to blind, losses to follow-up, and failures to appropriately consider the intention-to-treat principle, are widely accepted as methodological lapses in which bias can potentially be introduced to RCTs[55]. Trials that stop early for apparent benefit, and selective reporting of outcomes according to trial results, are missteps that have been more recently recognized as potential areas for concern[55]. The Cochrane Collaboration's tool for assessing risk of bias consists of an assessment of the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'[17]. Each of these domains are discussed further below.

4.1.2. Allocation Sequence Generation (Randomization)

With respect to allocation sequence generation, randomization can prevent systematic differences between baseline characteristics of participants in different intervention groups, in terms of both known and unknown prognostic factors[17]. Randomization allows for an unbiased comparison of the effects of two or more interventions, and also provides the foundation for the validity of testing for the statistical significance of an observed difference between the intervention groups[7]. The importance of appropriate sequence generation has been assessed empirically, and RCTs that did not generate their allocation sequence appropriately have been shown to be associated with larger estimates of intervention effects[56 57]. A true randomization process, when coupled with appropriately conducted allocation concealment, can minimize selection bias[8].

4.1.3. Allocation Concealment

Allocation concealment is a procedure that ensures the implementation of the randomization schedule while preventing the knowledge of forthcoming treatment assignments. Neither patients nor trial team members should be aware of the impending allocation. The efforts taken in creating a randomization sequence (i.e. an unpredictable and unbiased sequence) are likely to be lost if the trial does not protect this sequence by adequately concealing it from the trial personnel enrolling and assigning participants to their intervention groups[8 17].

Allocation concealment is always feasible[58]. Inappropriate allocation concealment can potentially allow for the selective assignment of participants, on the basis of prognostic factors, to treatment groups. Patients might be guided toward an "appropriate" treatment group, which can be achieved through the delay of the patient's entry into the trial until their "appropriate" allocation arises. RCTs with inadequate concealment of allocation, or unclear reporting of the technique used for concealment of allocation, have been shown to yield larger treatment effects when compared to those that used adequate concealment[59 60]. Furthermore, a meta-epidemiological study by Wood *et al*[58] revealed similar results. However, Wood *et al*[58] clarified that allocation concealment may play a more significant role in trials with subjective outcomes as they were more susceptible to exaggerated results. Little bias was found in trials with objective outcomes[58]. These findings were consistent both in trials assessing pharmacologic interventions, and those comparing non-pharmacologic interventions.

4.1.4. Blinding

Blinding differs from allocation concealment in that blinding is the process of masking the intervention received by the patient after randomization occurs and patients are assigned to their treatment groups. Where the adequate concealment of allocation hides the patient's upcoming intervention assignment from trial investigators and protects against selection bias, the goal of blinding is to reduce both performance bias and detection bias[61].

Blinding (or masking) of the trial participants and personnel can serve to minimize performance bias. Performance bias can occur due to differential behaviours. An example of such behaviours would be systematic differences between groups in the care that is provided (i.e. exposure to other treatments/interventions). It can also manifest in the participants, for example, due to a lack of expectations in one of the treatment arms. Adequate blinding of outcome assessors can reduce detection bias, in which outcome measurement can systematically differ between groups[17]. Blinding of outcome assessors is necessary to ensure that it is the intervention itself, rather than the knowledge of which intervention was received, that contributes to the final outcome measurement. When the treatment effect of outcome assessor blinding was evaluated in orthopaedic surgery RCTs, a significantly larger treatment effect was revealed in RCTs with unblinded outcome assessment[62]. Blinding of outcome assessors can be especially important for assessment of subjective outcomes, such as degree of postoperative pain. Granted, there are cases where blinding of outcome assessment can be impossible (e.g. when patients have received major surgery). In a systematic review of orthopaedic trauma literature,

blinding of outcome assessors was found to occur in less than 10% of RCTs[63]. However, this does not mean that these potential biases can be ignored, and while blinding of certain individuals is not always possible in surgical trials, the risk of bias should still be measured and considered when interpreting trial results[17].

The concern that well-conducted trials can occasionally omit reporting that methodological safeguards (e.g. concealment, blinding) were present throughout the trial is genuine, and has been described by Devereaux *et al*[64] and Chan *et al*[65]. Recently, specific instructions to evaluate unclear reported blinding status within RCTs have been published and were shown to be reliable and valid[66].

4.1.5. Incomplete Outcome Data

Incomplete outcome data is considered to be present if there is attrition (drop-outs) during the study or if participants are excluded from the analysis[17]. Measuring loss to follow-up, and assessing whether a trial used an intention-to-treat analysis, both are ways to evaluate the potential contribution of bias from incomplete outcome data in an RCT.

Well-designed RCTs can have biased results if the availability of outcome data is associated with the likelihood of outcome events[67]. If a surgical intervention results in poor outcomes, patients might drop out of the trial due to the adverse effects of the intervention. Patients lost to follow-up will contribute to bias if the number lost is imbalanced between groups, or if there are systematic differences in the patients lost to follow-up between the intervention and control groups[55 68]. Bias is also a concern when there is a large number of patients lost to follow-up as compared to the number of events

present in the trial[55]. Methods to limit loss to follow-up (LTFU) in surgical RCTs have been investigated in orthopaedic surgery[69], and it is reasonable to assume that they are applicable to surgical RCTs in plastic surgery. Ensuring that baseline characteristics of patients LTFU are presented, and accounting for all patients LTFU can be useful for the reader to make plausible assumptions regarding the implications of missing data.

The use of an intention-to-treat (ITT) analysis can provide an unbiased assessment of the efficacy of an intervention at the level of adherence present within that trial[70]. The prognostic balance provided by the randomization of patients in an RCT is essential to maintain. The use of an ITT analysis can help to maintain this distinguishing characteristic of an RCT. The creation and maintenance of balanced groups allows for any differences upon completion of the trial to be attributed to the interventions under investigation, and can avoid the influence of selection bias and confounding. An ITT analysis can also reduce the influence of loss to follow-ups and increase the generalizability of trial results[8]. There are limitations to the use of an ITT analysis (e.g. significant loss to follow-up), and there is considerable ambiguity in the use of the term "intention-to-treat"[71]. However, if the RCT study design is to be used to determine an unbiased, definitive assessment of a surgical interventions efficacy, the use of an ITT analysis is helpful[70].

Given the limitations of reporting, evaluating the potential risk of bias due to loss to follow-up can be difficult if it is unclear whether the patients included in the analysis are exactly those who were randomized to a treatment group. Concurrently, while the use of an ITT analysis is recommended as the least biased way to perform an analysis of an

RCT with missing data, it is also limited by reporting, and the inconsistent way with which ITT analyses are defined in the literature[71].

4.1.6. Selective Outcome Reporting

Selective outcome reporting can occur when: 1) multiple outcomes are recorded by trial investigators, and all the outcomes are not reported[72]; 2) multiple tools are used to measure the same characteristic, and the results from each tool are not reported[17]; or 3) if outcomes are recorded at multiple time points and only a proportion of the time points are reported[72]. Of RCT outcomes that are not reported, there are higher odds of non-statistically significant results being withheld[73]. To properly assess the risk of bias from selective reporting of outcomes, the outcomes stated in the trial protocol should be compared to the published report. Unfortunately, registered trials with a protocol are rare for plastic surgical RCTs (discussed in Chapter 3) and therefore, the risk of bias due to selective outcome reporting cannot be properly assessed in plastic surgical trials.

4.2. Purpose

This systematic review places an emphasis on evaluating the risk of bias using the Cochrane risk of bias tool. This allows for an assessment of the quality of the underlying research (i.e. the internal validity of the RCT), rather than the quality of reporting. While previous reviews of reporting quality of plastic surgery RCTs exist[20 22 23 25], an assessment of the risks of bias in plastic surgical RCTs has not been performed previously. The goal of this study was to investigate the following risks of bias in surgical RCTs in plastic surgery from 2000 to 2013 in depth: i) allocation sequence generation, ii) allocation

concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, and v) incomplete outcome data. A secondary goal was to identify trends in plastic surgical RCTs, with specific emphasis on how funding, multi-centre collaboration, a priori sample size calculation, involvement of a methodologist, and RCT registration are related to the level of bias.

4.3. Methods

The search strategy and study selection methodology used to identify the 173 unique surgical RCTs in the plastic surgery literature since the year 2000, along with the data collection process, has been described in Chapter 2. All risk of bias data collection was performed regarding the primary outcome. When a primary outcome was not explicitly stated by the author(s), an algorithm (discussed in Chapter 5; Figure 5.1) was used to determine one. To be judged as "low risk of bias" the method of random sequence generation or allocation concealment, had to be reported, and appropriate. Criteria for judging appropriate and inappropriate methods of random sequence generation and allocation concealment were created according to the Cochrane "Risk of Bias" assessment tool[17]. All reported methods of appropriate and inappropriate random sequence generation and allocation concealment were recorded. Assessment of the blinding status of the five relevant groups (outcome assessors, patients, surgeons, data collectors, data analysts) was performed based on an algorithm and the instructions from the assessment of blinding status of RCTs published in the five general medical journals with the highest impact factors[66]. These instructions were demonstrated to be valid and reliable when used to assess blinding in the five high impact medical journals[66]. Since this

systematic review is assessing surgical RCTs rather than non-surgical RCTs, the instructions were altered slightly. To be judged as "low risk of bias", blinding of the outcome assessor had to be classified as either "definitely yes" or "probably yes" using the blinding instructions. Whenever the blinding instructions led to a decision that a group (outcome assessors, patients, surgeons, data collectors, data analysts) was "probably not" or "definitely not" blinded, the two reviewers independently, and in duplicate, judged whether blinding of the group could realistically have occurred.

Risk of bias related to incomplete outcome data was assessed through follow-up rates. The number of participants randomized to treatment groups was recorded. The number of participants included in the analysis of the primary outcome was also recorded. This allowed for the calculation of follow-up rates. The definition of "loss to follow-up" was adapted from the LOST-IT systematic review[67]. Specifically, loss to follow-up was considered present when there was incomplete ascertainment of the primary outcome for any participant(s) that was randomized to a treatment group. If the authors excluded participants from the analysis, but still provided their primary outcome data (thus allowing others to conduct an analysis consistent with the intention-to-treat principle), loss to follow-up did not occur. Conversely, if the authors did not provide the primary outcome data of those excluded participants, it was considered that loss to follow-up did occur. All text was also scanned for clues that patients randomized to a treatment group did not undergo primary outcome assessment for any reason (e.g. patient withdrawal, death, drop-out). For RCTs stating that "loss to follow-up" occurred, yet presenting the same number of participants randomized and analyzed, the follow-up rate was not

calculated as the actual follow-up rate was thought to be unclear. To be classified as "low risk of bias", the patient follow-up rate for the primary outcome had to be 80% or greater.

The following information regarding missing outcome data was collected: Presence of loss to follow-up (LTFU), presence of patient flow diagram, patients LTFU accounted for, reporting of LTFU by treatment arm, comparison of patients LTFU vs. those not LTFU, comparison of patients LTFU between treatment groups, and, how missing data was handled. Author discussion of the implications of the missing outcome data (MOD) was discussed in the context of their results/findings.

4.3.1. Methods for Analysis

A descriptive analysis of allocation sequence generation, allocation concealment, blinding, and follow-up rate was conducted. For all data points, the percentage of studies falling into each category was calculated. Chance-corrected agreement (κ statistic) was measured for inter-reviewer agreement on the judgment of "low risk of bias" vs "high risk of bias" for allocation sequence generation, allocation concealment and blinding of the outcome assessor. If fewer than 15% or more than 85% of these risks of bias were rated as "low risk", agreement would also be measured using chance-independent agreement (ϕ statistic). The agreement statistics were interpreted using the guidelines outlined in Chapter 2.

4.3.2. Regression Analysis

A theory driven regression model was used to determine the relationship of five trial characteristics with risks of bias. To create the dependent variable required for

multinomial regression, the measurable risks of bias were categorized into four binary outcomes: i) generation of allocation sequence: reported and performed appropriately vs not reported or not performed appropriately, ii) concealment of allocation: reported and performed appropriately vs not reported or not performed appropriately, iii) blinding of the outcome assessor: reported and done properly vs not reported or not performed properly, iv) follow-up rate: judged to be 100% vs less 100%. Such categorization allowed for a multinomial logistic regression to be performed using a dependent variable with five categories based on how many risks of bias were performed appropriately:

1. None are performed appropriately → High Risk of Bias
2. One is performed appropriately → Medium to High Risk of Bias
3. Two are performed appropriately → Medium Risk of Bias
4. All three are performed appropriately → Medium to Low Risk of Bias
5. All four are performed appropriately → Low Risk of Bias

A priori the following five independent variables were chosen for inclusion into the model and the presence of each was hypothesized to be associated with low risk of bias: i) more recent year of publication, iii) multi-centre collaboration, iii) performance of an *a priori* sample size calculation, and iv) not for profit/government funding, and v) reporting of an RCT registration number.

A secondary regression analysis, for the purpose of generating hypotheses for future studies, was also performed. A correlation coefficient calculation was performed for the following 13 variables, each of which were prioritized by clinical reasoning: i) presence of a patient flow diagram, ii) sample size, iii) geographic location, iv) involvement of a methodologist, v) international trial, vi) journal of publication, vii) statistically significant primary outcome, viii) involvement of multiple operating surgeons

in the RCT, ix) use of a specified primary outcome, x) outcome class, xi) reporting of a confidence interval, xii) presence of co-interventions, xiii) presence of a graduate degree by author/collaborator.

A variable was considered statistically significant if it had a p-value ≤ 0.05 in the multinomial model. Correlation coefficients were interpreted as follows: low (< 0.45), moderate (0.45-0.7), high (>0.7). Analyses were performed with the help of a statistician, and SAS version 9.1 software[74] was used.

4.4. Results

4.4.1. Allocation Sequence Generation (Randomization)

The method of allocation sequence generation was described in sufficient detail in 71 (41%) RCTs to classify whether randomization was performed properly or not. In 102 (59%) RCTs, patients were simply described as randomized, and no further details were given. Allocation sequence generation was judged to have been performed adequately in 61 (35%) of all RCTs (Figure 4.1). These RCTs reported the method of randomization in enough detail to allow for judgment by the reviewers, allowing for a summarization of the randomization methods used (Table 4.1). The allocation sequence was not adequately generated in 10 (6%) RCTs, and a summary of these suboptimal methods of randomization is listed (Table 4.2). Of the 173 trials, 19 (11%) reported the use of an intention-to-treat analysis (Table 4.3).

4.4.2. Allocation Concealment

Allocation sequence generation was judged to be appropriately concealed in 21 (12%) RCTs (Figure 4.2). The appropriate methods of concealment used, and their frequencies are also presented (Table 4.4). The concept of allocation concealment was not acknowledged in 102 (59%) RCTs. The reported allocation sequence concealment method was inappropriate in 48 (28%) RCTs (Figure 4.2). The inappropriate methods chosen to conceal the allocation sequence in these RCTs are presented (Table 4.5). The most common inappropriate method of allocation concealment reported was the use of assignment envelopes with only one of three possible safeguards: either sealed or opaque or sequentially numbered envelopes.

4.4.3. Blinding

The structured inferences used to determine blinding status of the five relevant groups (outcome assessors, patients, surgeons, data collectors, data analysts) elicited the following results regarding the primary outcome of each surgical RCT. The outcome assessors were judged to have been blinded in 58 (34%) of RCTs (Figure 4.3). Of the 115 (67%) RCTs that did not blind the outcome assessor, 66 (57%) of these RCTs could realistically have blinded their outcome assessor (Table 4.6).

Patients were judged to have been blinded in 45 (26%) of RCTs (Figure 4.4). Of the 128 (74%) RCTs that did not blind the patient, 65 (51%) RCTs could have blinded the patient to the treatment they received (Table 4.6).

Only five (3%) RCTs blinded the surgeon performing the operation (Figure 4.5). In these RCTs, the intervention between the treatment arms was one similar surgical step

(injection/irrigation or exsanguination method, or indistinguishable sutures). The other 168 (97%) RCTs did not blind the surgeon. Of these 168 RCTs, it was determined that another five (3%) RCTs could have blinded the surgeon(s) to the intervention assessed in the trial (Table 4.6).

The data collector was judged to have been blinded in 48 (28%) of RCTs (Figure 4.6). Of the 125 RCTs that likely did not blind the data collector(s), it was reasoned that 95 (76%) RCTs could have blinded the data collector(s) (Table 4.6).

Data analysts were rarely blinded. In only 9 (5%) RCTs, the data analyst was blinded (Figure 4.7). Of the 164 (95%) RCTs that did not report blinding, it was judged that all could have blinded their data analyst.

4.4.4. Incomplete Outcome Data

Of the 173 RCTs examined, follow-up rates for the primary outcome could not be calculated for 10 RCTs. In these RCTs, reporting was such that either the number of units randomized or number of units included in the analysis of the primary outcome could not be determined. In the remaining 163 RCTs, follow-up rates were quite high, with 129 (79%) RCTs were able to follow-up on 90% or more of their patients, and 99 (61%) RCTs appeared to follow-up on all their patients (Figure 4.8).

Table 4.7 and Table 4.8 provide details on the presence and reporting of LTFU. LTFU occurred in 70 (40%) RCTs. In these 70 RCTs, authors acknowledged LTFU and provided a full explanation (i.e., reasons for each patient LTFU) in 31 (44%) RCTs, and a partial explanation (i.e., not accounting for all patients LTFU) in 14 (20%) RCTs. A simple statement that LTFU occurred, or the acknowledgement that fewer patients were

available for analysis than those that were randomized, without any further description, was present in 25 (36%) RCTs. Patient flow diagrams were presented in only 18 (10%) RCTs. Of the flow diagrams presented, 11 followed the CONSORT guidelines, demonstrating patient flow through the major stages of the RCT. Of the 70 RCTs in which patients were lost to follow-up, the patients lost were reported separately for each treatment arm in 40 (57%) RCTs. Differences in patients' baseline characteristics were compared between patients LTFU and patients not LTFU in 2 (3%) RCTs, and between patients LTFU in the intervention group and patients LTFU in the control in 1 (1%) RCT.

The analytic methods by which authors handled patients LTFU are outlined in Table 4.9. Excluding patients with missing outcome data from the analysis was the most common method, being performed by 65 (93%) of the 70 RCTs in which LTFU occurred. The implications or effects of missing outcome data were discussed in the context of the RCT's results or findings in 13 (19%) RCTs.

4.4.5. Risk of Bias Summary and Agreement

A summary of the four risks of bias examined in this systematic review is presented (Figure 4.9). The calculated chance-corrected agreement (κ statistic) between reviewers when assessing risk of bias in randomization was 0.843, representing almost perfect agreement. Fewer than 15% of the RCTs had a rating of "low risk of bias" for their allocation concealment; therefore, chance-independent agreement (ϕ statistic) was measured along with chance-corrected agreement (κ statistic). These values were ϕ = 0.792 and κ = 0.592, which indicate substantial agreement, and moderate agreement, respectively. Substantial agreement (κ = 0.679) was also found when calculating the

chance-corrected agreement between reviewers assessing blinding status of the outcome assessor.

4.4.6. Multinomial Regression Model

Of the 173 RCTs eligible for inclusion into the regression model, 10 were excluded as they inappropriately generated the allocation sequence used in the trial. Of the remaining 163 RCTs, 10 reported either patient recruitment or analysis in such a way that the follow-up rate could not be calculated. Therefore, data from 153 RCTs were available for inclusion in the regression model.

Due to the number of events present in each category of the multinomial dependent variable, the five risk of bias levels (Table 4.10) had to be compressed into three levels (Table 4.11):

1. None or One is performed appropriately → Medium to High Risk of Bias
2. Two are performed appropriately → Medium Risk of Bias
3. Three or four are performed appropriately → Medium to Low Risk of Bias

Furthermore, one independent variable (reporting of an RCT registration number) had to be removed from the model as power was present only for four independent variables. This variable was then included in the secondary analysis.

Odds ratios (ORs) with 95% confidence intervals (CIs) are presented for the five independent variables (Table 4.12). The odds of a study reporting an *a priori* sample size calculation were statistically significant and 2.76 times greater in a "Medium" risk of bias level compare to a "High" risk of bias (95% CI 1.12, 6.79). Similarly, the odds of an *a priori* sample size calculation being present in a "Low" risk of bias trial were 8.55 times greater than a "High" risk of bias trial (95% CI 2.73, 26.78). A statistically significant

difference was not present when "Low" and "Medium" risk of bias trials were compared. The other four independent variables did not demonstrate statistical significance. The correlation coefficients for the 14 variables in the secondary regression analysis are also presented (Table 4.13). None of these variables revealed strong correlations that were statistically significant.

4.5. Discussion

4.5.1. Allocation Sequence Generation (Randomization)

"Clinically and statistically, randomization is the single characteristic that most sharply distinguishes the controlled trial from other forms of scientific investigation in medicine."[7] It was found that just over one-third (35%) of surgical RCTs reported performing an appropriate method of randomization. Using an appropriate mechanism for randomization, such as those listed in Table 4.1, is important as prognostic factors will be balanced evenly across intervention groups with a large enough sample size[17]. While some of the mechanisms listed in Table 4.2 can potentially achieve this same balance, they are inadequate for truly random assignment as this type of systematic treatment assignment can be predicted.

In almost two-thirds (59%) of surgical RCTs, it was found that the manuscript contained the following statement (or similar): "we randomly allocated…", yet the authors did not provide any further detail. While it is possible that some of these RCTs actually performed the allocation sequence generation appropriately, it is "often insufficient to be confident that the allocation sequence was genuinely randomized."[17]

These situations may lead to doubt for the reader, and may potentially undermine the great amount of effort and care taken in the creation and execution of the RCT.

The intention-to-treat (ITT) principle has been recommended as the appropriate method to analyze RCT data by the Cochrane Collaboration, CONSORT and other trial methodology experts and organizations[71]. ITT can prevent biases that are potentially created if patients are removed after randomization[75]. Cross-overs, or patients LTFU, might result in disrupting the balance of both known and unknown prognostic factors created by randomization. Unfortunately, using an ITT analysis cannot truly minimize the bias introduced by patients lost to follow-up[70]. However an ITT analysis is a powerful tool, and "clinicians evaluating a randomized trial need to know whether the researchers followed the intention-to-treat principle."[75] The use of an ITT analysis can minimize bias if an adherent patient is more likely to have a better outcome and patients who do not receive the assigned treatment are omitted. In this case, an ITT analysis prevents the unbiased comparison created by randomization from being undermined[75]. The use of an ITT analysis was infrequent in plastic surgical RCTs (11%) and further clouding the picture is the ambiguity the way the term "intention-to-treat" is used. In a systematic review of methodological articles, Alshurafa *et al*[71] found that the term "intention-to-treat" is often used inappropriately, and they suggested that RCTs describe both how they dealt with patients who had complete data, and those who had missing outcome data[71].

4.5.2. Allocation Concealment

Only 21 (12%) RCTs reported using an adequate method of allocation concealment. In other fields, trials not reporting adequately concealed treatment

allocation are prone to an exaggeration of intervention effects[76-78]. Therefore, the large number of RCTs (N=152, 88%) in this systematic review that did not report the use of an appropriate method of allocation concealment was concerning. Furthermore, it is important to note that the treatment a patient has been allocated to should preferably be concealed until the patient receives the intervention. The effort taken to create and organize serially numbered, opaque, sealed envelopes is potentially lost when they are opened days, hours, or even minutes before the patient is brought to the operating room.

An interesting method of allocation concealment, which is unique to surgical RCTs, is intra-operative randomization. Since surgical interventions are a "one-time" treatment, waiting to randomize patients until just before the intervention step of the surgery is undertaken minimizes the risk of selection bias.

4.5.3. Blinding

Previously validated structured inferences were used to assess blinding status[66], even when blinding status was unclearly reported within the RCT manuscript. These instructions allowed for the determination of who was and was not blinded, as well as the risk of bias in the primary outcome due to lack of blinding.

Ensuring blinding of the outcome assessor is extremely important as bias can be introduced if those determining outcomes are aware of the treatment intervention applied. Using specific and standardized instructions to estimate blinding status, we found that 58 (34%) RCTs were able to blind their outcome assessors. It can be difficult, and sometimes impossible, to blind the outcome assessor in a surgical trial. Blinding was judged to be more difficult to both achieve, and maintain, in non-pharmacologic trials than in

pharmacologic trials in a review of RCTs evaluating treatments for hip and knee osteoarthritis[79]. Furthermore, in plastic surgical RCTs, the patient and the outcome assessor are sometimes the same person, depending on the outcome measure. In this systematic review, one-third of the RCTs blinded their outcome assessor, and of the 115 (67%) RCTs that did not, over half (57%, 66 RCTs) were judged to have been able to blind their outcome assessor. Therefore, one can surmise that the number of RCTs that can feasibly blind their outcome assessor can increase, and potentially double.

The amount of bias varies depending on whether the outcome is objective or subjective, and has been shown to be more biased, on average, in trials with more subjective outcomes[58]. In this systematic review, only 2 (1%) RCTs used mortality, which is truly objective, as the primary outcome, and in these cases, blinding (or lack of blinding) of the outcome assessor would not have any influence on the assessment of the outcome. The primary outcome of the remaining 171 (99%) RCTs lie on a spectrum of outcomes ranging from subjective toward objective, and will be discussed in greater detail in Chapter 6. While other potentially objective outcomes exist besides mortality, it has been shown that seemingly objective outcomes can actually be somewhat subjective in practice[80]. Therefore taking steps to ensure the outcome assessor is blinded should be a priority in plastic surgical RCTs.

Blinding of the patient is not always possible especially when the intervention is surgery. While the majority of RCTs (N=128, or 74%) did not appear to blind their patients, it was judged that half of these trials (N=65, 51%) could realistically have blinded their patients. Unfortunately, this also means that it was determined that blinding

of the patients was impossible for the remaining 63 RCTs, which make up 36% of the RCTs included in this systematic review. The inability to blind a patient can bias the results of an RCT by affecting the actual outcomes. The outcome can be directly affected due to differential behaviours between treatment groups (e.g. differential drop-out, or differential administration of co-interventions) or even by the lack of expectations in one of the treatment groups[17]. This is compounded by the fact that many outcomes in plastic surgery are subjective, or at least have a degree of subjectivity to them. Furthermore, since many outcomes involve quality-of-life, functional status, or symptoms, often times, the patients are the outcome assessor as well. However, these studies might be able to reduce this risk of bias, related to the inability to blind the patients, by adhering to strict protocols in an attempt to reduce the risk of differential behaviours by patients[17]. When it is impossible to blind the patient, who depending on the outcome might also be the outcome assessor, this limitation should be acknowledged, and readers of the these RCTs should be aware of the potential impact that the inability to blind these groups can have.

Blinding of the surgeon is rarely possible in surgical RCTs. Almost all the RCTs examined (N=168, 97%) did not blind their surgeon(s) and of these 168 RCTs, only 5 (3%) RCTs were judged to potentially have been able to blind the surgeon(s). It was determined that the only situations where surgeons were blinded, or could have been blinded, were when the interventions involved an item that looked and felt the same, and/or could have been prepared for the surgeon by another member of the surgical team. The inability to blind the surgeon can be a problem as bias might be introduced if the surgeon has a belief or opinion about the relative effectiveness of the procedures being

compared. There are many different ways in which this bias can manifest itself; for example, the application of co-interventions, the use of a more meticulous surgical technique[81], or even potentially un-blinding the patient during a follow-up visit. It appears that this potential limitation may have to be accepted as something inherent to surgical RCTs. Alternatively, "expertise based" RCT designs, in which the patient is randomized to a surgeon/group of surgeons committed to performing an intervention and therefore blinding of the surgeon is not necessary, can be implemented. The "expertise based" RCT design has further advantages, and they have been previously described in detail[81]. Another solution that has been proposed to limit bias when blinding of the surgeon is not possible is the assessment of the patient's outcome by two or more experts who are independent from providing any treatment[8].

Information on blinding the data analyst was rarely reported. Only 6 (3.5%) RCTs definitely blinded their data analyst, and 5 (3%) RCTs definitely did not blind their data analyst. While the results of estimating unclearly reported blinding status regarding the outcome assessor, patient, surgeon and data collector are convincing, it has been acknowledged that these instructions may not provide an accurate predict blinding status of the data analyst[66]. Therefore, one must regard with caution the results from the classification of "unclear" blinding of the data analyst into "probably yes" and "probably no" (Figure 4.7), as it is possible that the blinding status of the data analyst in these 162 (93.5%) RCTs could remain classified as "unclear". The importance and significance of blinding the data analyst has not been empirically quantified and is not explicitly covered by the Cochrane Risk of Bias tool[32].

4.5.4. Incomplete Outcome Data

The potential impact of plausible assumptions on the incidence of events among participants lost to follow-up has been assessed in RCTs published in five high quality medical journals (*NEJM, JAMA, BMJ, Lancet, Annals of Internal Medicine*)[67]. It was shown that in up to one-third of these RCTs, reporting significant results for binary primary outcomes would have lost statistical significance if a plausible assumption was made about event rates in the patients lost to follow-up. Additionally, the median and interquartile range for reported loss to follow-up rate was 6% (2-14%)[67]. In comparison, in this systematic review the median and interquartile range for loss to follow-up rate was 0% (0-8%).

Previously, studies had not been able to find evidence of statistically significant associations between the magnitude of a treatment effect and loss to follow-up[15]. RCTs with high rates of incomplete outcome data is concerning, since patients lost to follow-up often have worse outcomes than those who remain in the trial[15]. It has been suggested that the complete reporting of loss to follow-up has confounded efforts to uncover the relationship between loss to follow-up and treatment effect[15]. Trials clearly reporting exclusions are usually rated to have a higher methodological quality than those that do not[82]. Therefore, trials of lower methodological quality may not report the presence or absence of loss to follow-up, leaving the reader to falsely assume that full follow-up was achieved, clouding the relationship between treatment effect and loss to follow-up. This systematic review found that 99 (61%) RCTs appeared to have full (100%) follow-up of their patients. While this appears to be impressive, some RCTs neither reported the

presence nor absence of loss to follow-up, therefore it is unlikely that all 99 RCTs actually achieved 100% follow-up.

The method in which LTFU is handled can instil confidence in the reader regarding the trial results. The proportion of RCTs (44%) providing a full explanation and accounting for all the patients LTFU was suboptimal. LTFU can have an impact on results when it is extreme, or when the missing data is associated with outcome events. It is known that substantial LTFU can either lead to an overestimation, or underestimation of the effect of an intervention[67]. Plausible assumptions on patient outcomes can be made when the reasons patients were lost to follow-up are provided. For example, patients who were LTFU because they moved are more likely to have better outcomes than patients who were excluded from the trial for crossing over[67]. Therefore, providing the reader with details on patients lost to follow-up, including the reasons for, as well as the methods in which LTFU was handled, can at least allow the reader to decide what the effect of these patients LTFU was. The implications of patients LTFU were discussed in the context of the results of an RCT in 19% of the RCTs that had missing outcome data. The effect of this discussion by RCT authors is unclear, however providing more information is likely only to be useful.

The interpretation of RCT data can also be simplified if trial authors report “no loss to follow-up occurred”, or include this information in the patient flow diagram. For example, an RCT reporting “we recruited 100 patients for the clinical trial; of these, 87 received the allocated treatment” leaves the reader unclear on whether 13 patients did not meet the inclusion criteria, and 87 patients were randomized, or whether all 100 patients

were randomized but 13 patients dropped out of the trial or had to be excluded before receiving their treatment.

Information should be present for any patient that was involved in the trial, including patients in either intervention group who did not receive the surgery they were randomized to. A patient flow diagram, ideally one created according to the CONSORT guidelines, is a useful tool, though it is possible that their presence (or absence) in a manuscript can be influenced by the journal publishing the RCT. Unfortunately, patient flow diagrams were absent in 90% of the surgical RCTs reviewed, and only 6% of RCTs had a patient flow diagram that fulfilled the CONSORT requirements.

4.5.5. Regression Model

Trials that reported the calculation of an *a priori* sample size calculation were associated with lower risks of bias. What this could imply is that when reading a RCT comparing two plastic surgical interventions, the presence of an *a priori* sample size calculation can give the reader confidence that the RCT is more likely than most to have minimized potential risks of bias.

No secondary variables warranted further investigation with this sample, as all correlation coefficients were low.

While the association between RCT funding, of any kind, and methodological quality has not been quantified in the plastic surgery literature, it was surprising that reporting of a funding source was not found to be associated with a low risk of bias. In general, in can be assumed that to be awarded funding, an RCT needs to ask an important question and be well designed. Therefore, it was felt an RCT that has been awarded

funding, from any source (e.g. industry, government, non-profit), likely has gone through a rigorous process, with collaboration from a whole research team and judgment by the granting agency. This association was not found in this analysis; however, such a result is likely due to the poor reporting of funding status in general by plastic surgery RCTs, which is discussed further in Chapter 7.

4.5.6. Limitations

A limitation when undertaking the assessment of the risk of bias in an RCT is distinguishing between how the trial was conducted and how it was reported. While empirical evidence does support the relationship between minimizing risk of bias and the validity of an RCT[17], attempts to show systematic differences between studies that do and studies that do not minimize risk of bias have been inconsistent[55]. Well-conducted trials can be reported poorly[83], and it has been shown that actual trial methodology has a tendency to be better than it is reported[64 84]. However, it is likely that trial reporting has improved in the years since the trials examined in these reviews of reporting and actual trial methodology were published in 1997 and 1998[64 84]. Furthermore, RCTs with unclear reporting of methodology, specifically allocation concealment, were also found to have unclear descriptions of their allocation concealment methods in their trial protocol[85].

The risk of bias of blinding must be individually assessed by outcome as it may be high for certain outcomes, and low for others. All risk of bias data collection was performed regarding the primary outcome. When a primary outcome was not explicitly stated by the author(s), an algorithm (Chapter 5; Figure 5.1) was used to determine one. In 58 (34%) RCTs a primary outcome was not declared by the authors. Therefore, it is

possible that sometimes the primary outcome chosen by the algorithm was different than the primary outcome the authors had in mind when conducting their RCT. However, it is not expected that this would have changed the results for the risk of bias of blinding considerably.

The blinding decision tool used was an approach that identified whether strategies for blinding either are, or are not in place. This tool was not able to determine the extent to which the blinding strategies were successful since an attempt to blind does not ensure successful blinding in practice.

The interpretation of follow-up rate as "acceptable", greater than 80%, or "unacceptable", less than 80%, is more of a cut point rather than one based on evidence[55].

4.5.7. Limitations of the Regression Analysis

The regression analysis had three main limitations. First, the low event rate in the original lowest risk of bias category (all four risks of bias are performed properly) required collapsing five levels of the multinomial regression into three.

Second, in order to perform a multinomial regression using the available data, each risk of bias had to become a binary outcome due to the distribution of events in each category. Initially to perform the regression analysis, the follow-up rate was dichotomized in "acceptable", greater than 80%, or "unacceptable", less than 80%. However, due to the distribution of RCTs for this data it was required to use 100% follow-up to create a binary group. This is potentially problematic as it is likely that a number of trials with poor reporting, i.e. they neither reported the presence nor absence of LTFU, were included in the 100% follow-up group when in fact they might not have had full patient follow-up.

The third limitation involved reporting of the independent variables. That is, each variable had its own type of reporting limitation, whether the variable was likely to be journal dependent (e.g., presence of a flow diagram, or including author graduate degrees), culturally dependent (e.g., certain institutions acknowledge methodological or statistical assistance, whereas others do not), or simply items that are not commonly reported in plastic surgery (e.g., the presence or absence of co-interventions).

4.5.8. Strengths

Strengths of the search strategy and study selection process were described in Chapter 3. The careful creation of data extraction forms and detailed instructions along with the transparent reporting of the methods are strengths of this study. The strong level of agreement between pairs of reviewers likely reflects the objective decision rules used when extracting data from RCTs.

We provided risk of bias ratings for the primary outcome (an individual item) rather than using a scale in which quality components are scored and then a summary score is produced, which usually fails to consider the context of the individual items[55]. Our approach allowed for a domain-based evaluation of plastic surgical RCTs which is consistent with what is recommended by the Cochrane Collaboration.

4.5.9. Risk of Bias Summary

The validity of the findings of an RCT assessing a healthcare intervention can be questioned if there are problems with the design and execution of the RCT[17]. Although assessing risk of bias in an RCT is a relatively new approach, the importance of assessing

these methodological safeguards has been demonstrated previously[86], and studies with a high risk of bias can overestimate, or underestimate, an intervention's true effect. Tools exist to assess methodological quality, however the use of scales which provide a final summary score are not recommended[17]. It can reasonably be stated that the internal validity of the trials are probably better than what is reflected in the results of this systematic review. However, if plastic surgeons are going to apply the results of surgical RCTs in the plastic surgery literature when treating their patients, the conduct and reporting of these methodological safeguards need to be improved.

4.6. Conclusions

When applying the results of a randomized control trial to patients in one's clinical practice, the reliability of these results depends on the extent to which potential sources of bias were minimized or avoided. Intention-to-treat analyses can be used to reduce bias in plastic surgical RCTs. Reporting of details of LTFU can be improved with the presence of patient flow diagrams adhering to CONSORT guidelines.

RCTs require significant financial resources and time commitment from many individuals (e.g., surgeons, patients, hospital staff). For the readers of plastic surgery literature to believe what they are reading, risks of bias should be minimized, and information regarding risks of bias transparently reported. This will encourage plastic surgeons to apply the results and findings from published RCTs to their own patients. Through improvements in the performance and reporting of randomization, allocation concealment, blinding and follow-up, one can use plastic surgery RCTs that address

important surgical questions more efficiently, and provide plastic surgery patients with the best possible treatments.

Figure 4.1. Allocation Sequence Generation (Randomization)

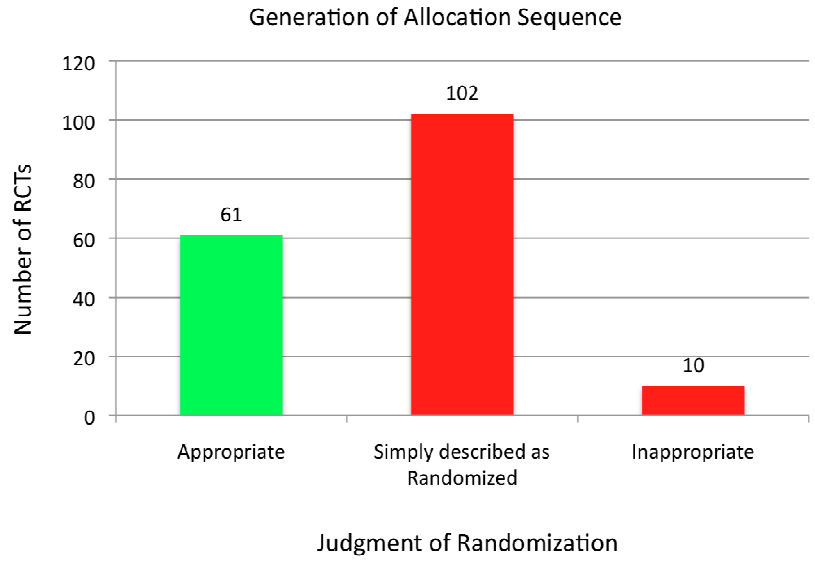


Figure 4.2. Allocation Concealment

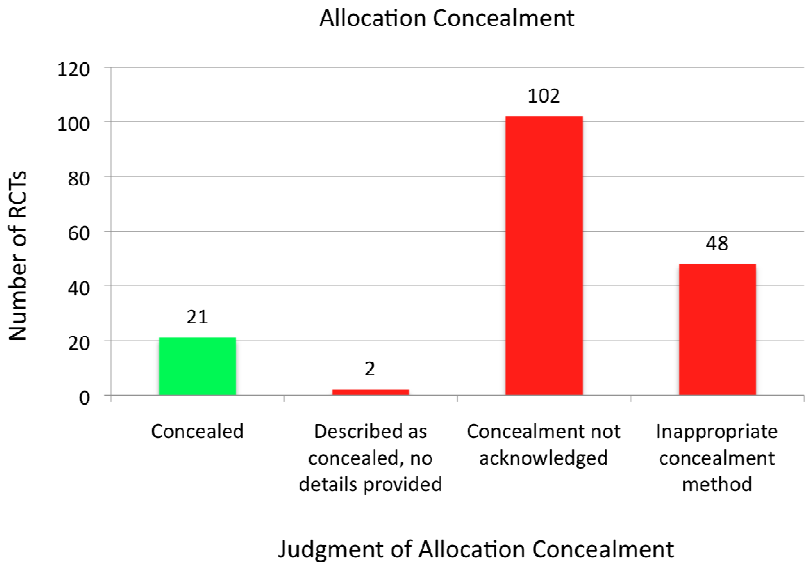


Figure 4.3. Blinding of the Outcome Assessor

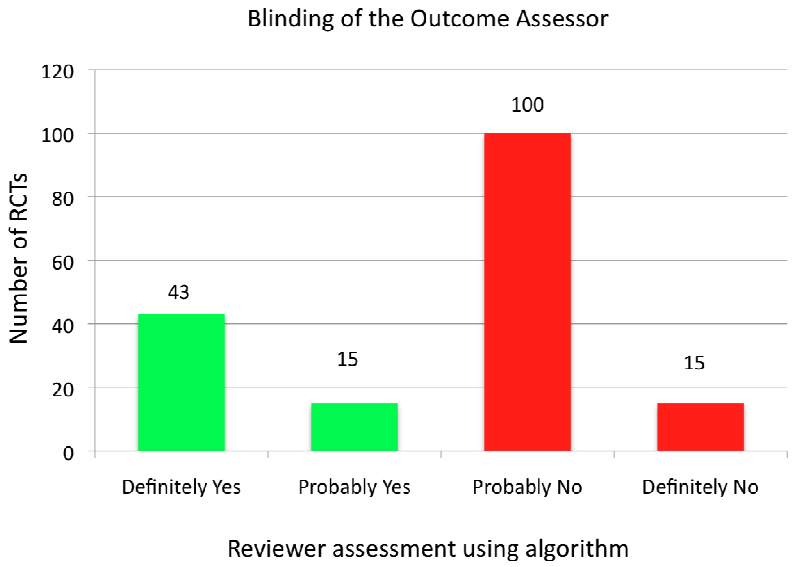


Figure 4.4. Blinding of the Patient

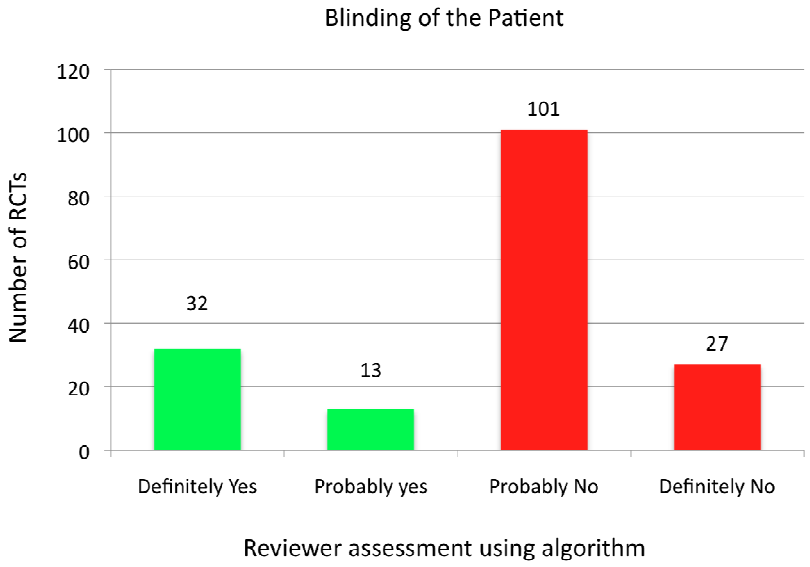


Figure 4.5. Blinding of the Surgeon

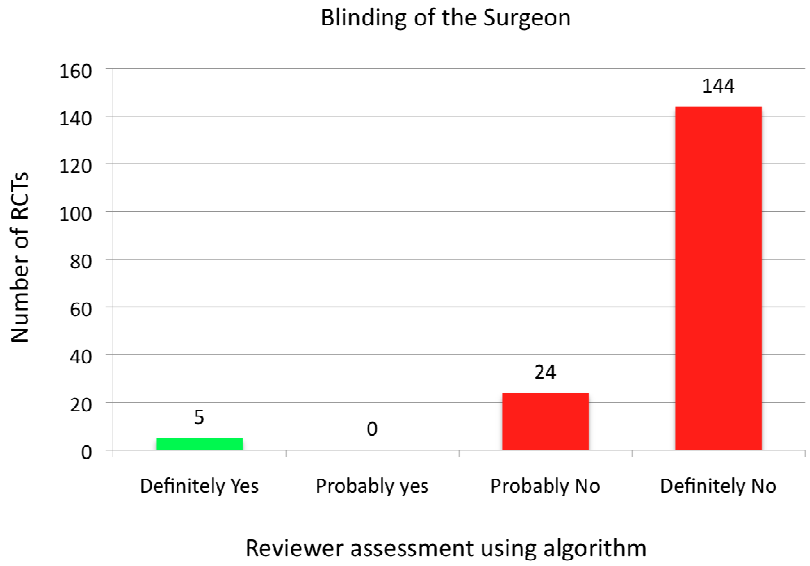


Figure 4.6. Blinding of the Data Collector

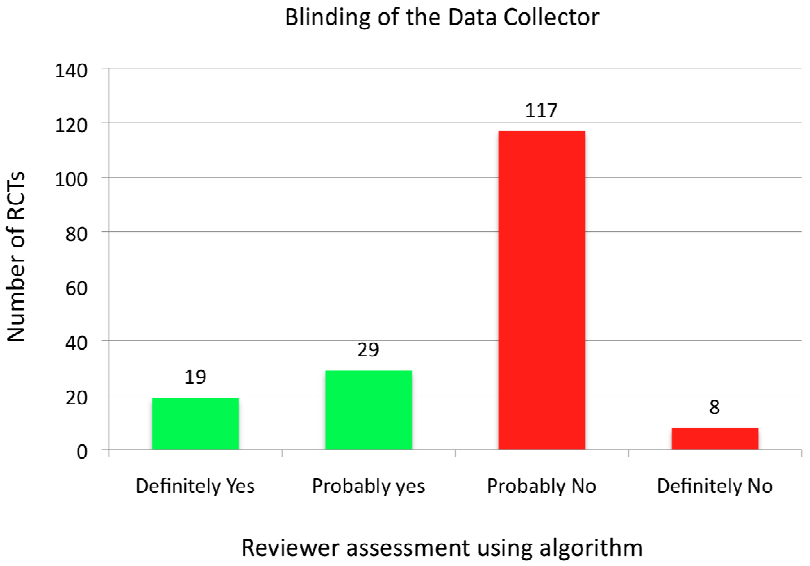


Figure 4.7. Blinding of the Data Analyst

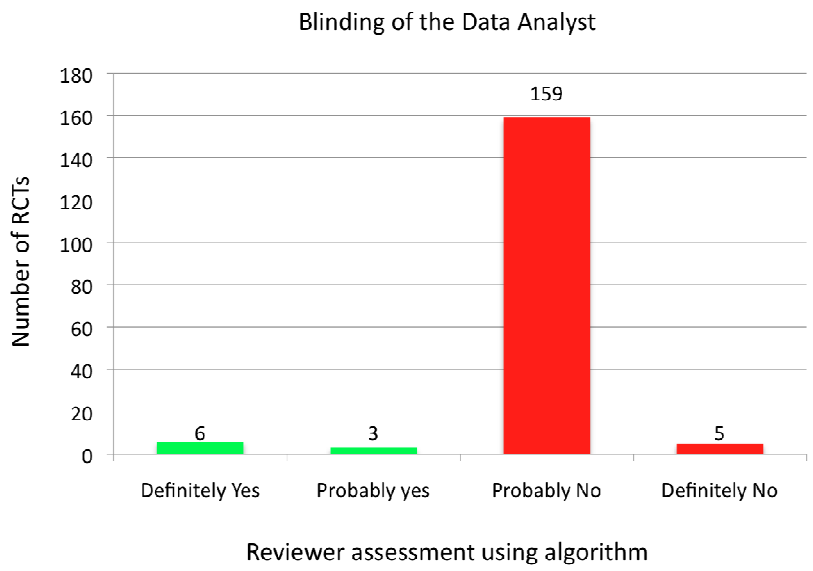


Figure 4.8. Follow-up

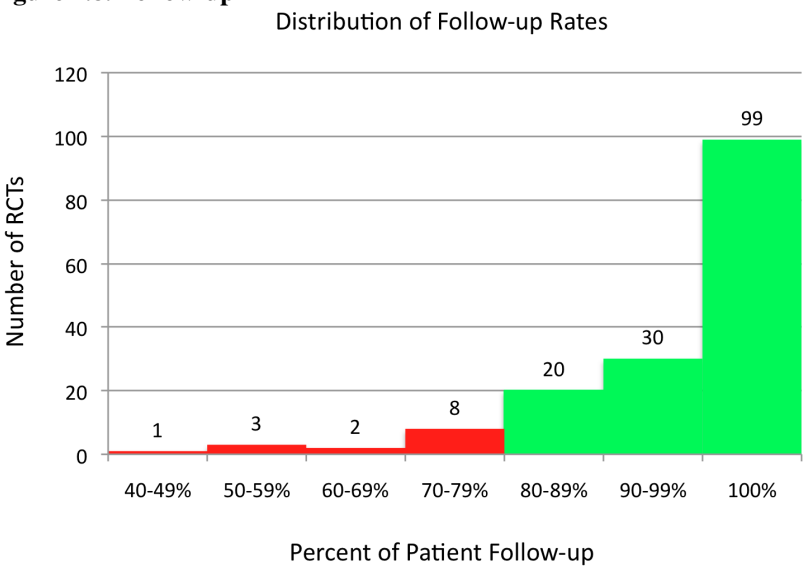


Figure 4.9. Summary of Risk of Bias in 173 Plastic Surgical RCTs

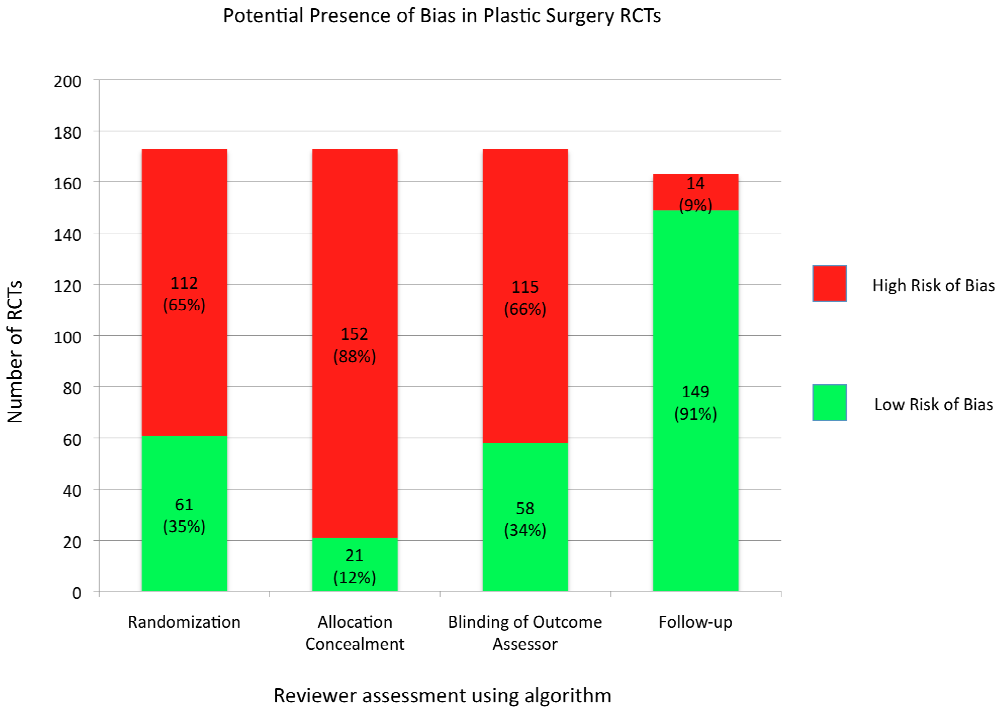


Table 4.1. Appropriate Methods of Randomization

	N	Percent
Random Number Table	7	11
Computer Random Number Generator	26	43
Unspecified Random Number Generator	7	11
Coin Tossing	3	5
Rolling of Dice	1	2
Drawing of Lots	11	18
Minimization	1	2
Other	5	8
Total	61	100

Table 4.2. Inappropriate Methods of Randomization

	N	Percent
Sequence generated by odd or even date of birth	1	10
Sequence generated by some rule based on date (or day) of admission	1	10
Sequence generated by some rule based on a medical record identifier (hospital number, clinic number etc)	3	30
Allocation by judgment of the clinician	3	30
Allocation by preference of the participant	0	0
Allocation based on the results of a laboratory test or a series of tests	0	0
Other	2	20
Total	10	100

Table 4.3. Author Description of Analysis as Intention-to-Treat (ITT)

Author report use of ITT	**Number of RCTs**	**Percent**
Yes	19	11
No	154	89
Total	173	100

Table 4.4. Appropriate Methods of Allocation Concealment

	N	Percent
Central allocation (including telephone, web-based, and pharmacy controlled randomization)	7	33
Sequentially numbered AND opaque AND sealed envelope	8	38
Other	6	29
Total	21	100

Table 4.5. Inappropriate Methods of Allocation Concealment

	N	Percent
Allocation concealment not acknowledged	102	68
An open random allocation schedule	3	2
Assignment envelopes with reporting ONLY TWO of the appropriate safeguards (2 of: envelopes being sealed, opaque, or sequentially numbered)	8	5
Assignment envelopes with reporting ONLY ONE of the appropriate safeguards (1 of: envelopes being sealed, opaque, or sequentially numbered)	25	17
Assignment envelopes NOT reporting ANY appropriate safeguards (NONE of: envelopes being sealed, opaque, or sequentially numbered)	5	3
Alternation or Rotation	2	1
Date of birth	1	1
Case record number	2	1
Other	2	1
Total	150	99

Table 4.6. Judgment on whether blinding was possible for RCTs that either did not, or probably did not blind the group of interest

	N	Percent
Outcome Assessor could have been blinded	66	57
Outcome Assessor could not have been blinded	49	43
Total	115	100
Patient could have been blinded	65	51
Patient could not have been blinded	63	49
Total	128	100
Surgeon could have been blinded	5	3
Surgeon could not have been blinded	163	97
Total	168	100
Data Collector could have been blinded	95	76
Data Collector could not have been blinded	30	24
Total	125	100
Data Analyst could have been blinded	164	100
Data Analyst could not have been blinded	0	0
Total	164	100

Table 4.7. Presence of Loss to Follow-Up (LTFU) in 173 RCTs

Evidence of Loss to Follow-up (LTFU)	**Number of RCTs**	**Percent**
Yes	70	40
No	103	60
Total	173	100
Author Statement about LTFU	**Number of RCTs**	**Percent**
Present, Full explanation given, all patients LTFU accounted for	31	44
Present, Partial explanation, not all patients LTFU accounted for	14	20
No description, simply stated LTFU occurred, or presented numbers allowing the reader to infer that LTFU occurred	25	36
Total	70	99
Presence of a Patient Flow Diagram	**Number of RCTs**	**Percent**
Present, Fulfills CONSORT Flow Diagram Requirements	11	6
Present, Does Not Fulfill CONSORT Flow Diagram Requirements	7	4
No Patient Flow Diagram Present	155	90
Total	173	100

Table 4.8. Details of Patient LTFU Reporting in 70 RCTs

Patients LTFU Reported Separately per Treatment arm	**Number of RCTs**	**Percent**
Yes	40	57
No	30	43
Total	70	100
Assessment of Baseline Characteristics, or Data Present for Reader, to Compare Patients LTFU and Patients not LTFU	**Number of RCTs**	**Percent**
Yes	2	3
No	68	97
Total	70	100
Assessment of Baseline Characteristics, or Data Present for Reader, to Compare Patients LTFU in the Intervention Group(s) and Patients LTFU in the Control Group(s)	**Number of RCTs**	**Percent**
Yes	1	1
No	69	99
Total	70	100

Table 4.9. Handling of Missing Data

Analytic Method for Handling LTFU applied by Authors	**Number of RCTs**	**Percent**
Individuals with Missing Outcome Data were not considered in the analysis (complete/available case analysis)	65	93
Imputation with Explicit Description	0	0
Assumed all experienced the outcome of interest	0	0
Assumed none experienced the outcome of interest	0	0
Assumed “worst case” scenario	1	1
Assumed “best case” scenario	1	1
Last observation carried forward	1	1
Multiple Imputation	0	
Authors own imputation method/Some other type of imputation method	2	3
Two or more of the above options (sensitivity analysis)	0	0
Total	70	99
Implications/Effects of Missing Outcome Data discussed in the context of the Results/Findings of the RCT	**Number of RCTs**	**Percent**
Yes	13	19
No	57	81
Total	70	100

Table 4.10. Frequency of RCTs in each Risk of Bias Level when using 5 Levels

Dependent Variable (Risk of bias in 5 levels)	Risk of Bias	N	Percent
None are performed appropriately	High	27	18
One is performed appropriately		55	36
Two are performed appropriately	Medium	51	33
Three are performed appropriately		14	9
Four are performed appropriately	Low	6	4

Table 4.11. Frequency of RCTs in each Risk of Bias Level when using 3 Levels

Dependent Variable (Risk of bias in 3 levels)	Risk of Bias	N	Percent
None or One are performed properly	High	82	54
Two are performed properly	Medium	51	33
Three or all Four are performed properly	Low	20	13

Table 4.12. Multinomial logistic regression in Risk of Bias (Medium vs High, Low vs High, Low vs Medium)

	Risk of Bias, OR (95% CI), p-value			Variable P-value
Independent Variables	**Medium vs High**	**Low vs High**	**Low vs Medium**	
Year of Publication (*per year increase*)	0.98 (0.86, 1.11), 0.72	0.99 (0.82, 1.19), 0.91	1.01 (0.80, 1.27), 0.93	0.94
Centre Collaboration (*multi vs single*)	0.74 (0.25, 2.19), 0.58	1.37 (0.35, 5.41), 0.65	1.85 (0.32, 10.59), 0.49	0.69
A priori sample size (*present vs absent*)	2.76 (1.12, 6.79), 0.03	8.55 (2.73, 27.78), 0.0002	3.10 (0.72, 13.27), 0.13	0.001
Funding Source (*government vs no report*) (*industry vs no report*)	0.76 (0.28, 2.10), 0.85 0.71 (0.23, 2.20), 0.72	0.89 (0.21, 3.67), 0.97 0.83 (0.17, 4.05), 0.86	1.17 (0.20, 6.78), 0.86 1.17 (0.17, 8.17), 0.87	0.97

Example of Interpretation:
Odds of a trial with *a priori* sample size calculation that has low risk of bias (compared to a trial that has high risk of bias) are 8.55 times those of a study without *a priori* sample size calculation.

Table 4.13. Secondary Analysis Correlation Coefficients

Variable	Correlation Coefficient with Risk of Bias*
RCT registration	0.24
Presence of a patient flow diagram	0.23
Sample size	0.007
Geographic location	-0.15
Involvement of a methodologist	0.11
International trial	0.45
Journal of publication	0.18
Statistically significant primary outcome	-0.01
Involvement of multiple operating surgeons	0.25
Use of a specified primary outcome	0.24
Outcome class	0.30
Reporting of a confidence interval	0.35
Presence of co-interventions	0.16
Presence of a graduate degree by author/collaborator	0.002

*All correlation coefficient values very low, thus p-values not presented.

5. Outcomes in Surgical RCTs in Plastic Surgery: 2000 – 2013

5.1. Introduction

Choosing the appropriate primary outcome measure is a crucial component to planning a randomized controlled trial. Morbidity and objective clinical outcomes have been reported as the most frequent endpoints, cited in 52% and 32% of studies respectively, as observed from the health outcome studies extracted from the journals *Plastic and Reconstructive Surgery* and *Annals of Plastic Surgery*[42]. The use of an appropriate primary outcome is imperative, as RCTs are resource intensive, both in practice (i.e., financially) and in effort (i.e., investment by many parties, including patients, surgeons, hospital staff and others). Furthermore, it is important to select a primary outcome that is valid, clinically relevant, and important to patients[87].

Approaches to measuring outcomes in plastic surgery, including aesthetic[88 89], breast[90], hand[91], lower limb[92], and craniofacial and pediatric[93] surgery, have been outlined together in a 2013 issue of *Clinics in Plastic Surgery*. This series of papers provided a detailed look into the specific outcome measurement tools available for each domain of plastic surgery, including how and when to use them. These patient reported outcome instruments aim not only to measure quality of life, but also patient expectations and satisfaction.

In comparison, this systematic review investigates the type of outcome measures used in existing plastic surgery RCTs comparing surgical interventions over the past 13 years (i.e., 2000 – 2013). One hundred seventy-three plastic surgical RCTs were

examined to determine the types of primary outcomes being used, as well as details of their reporting.

5.2. Methods

5.2.1. Search Methods and Study Selection

The search strategy and study selection methodology used to identify the 173 unique surgical RCTs in the plastic surgery literature since January 2000 has been described in Chapter 2.

5.2.2. Data Collection Process

The data collection process was summarized in Chapter 2. Specific to this discussion, information on outcomes collected included: statement of primary outcome, details of primary outcome, description of outcome measurement, patient reported outcomes, adverse events/complications, and reporting of confidence intervals.

The "primary outcome" was recorded verbatim (i.e., as stated by the author) if an explicit statement was present within the manuscript, such as: i) "the primary outcome of this study was…" ii) "the main endpoint of this study was…" or iii) the purpose of this study was…". A primary outcome was considered 'reported' if it was deemed specific by the data extractors (both SV and one of CJC, MK, or NZ). For example, general primary outcomes like "the effectiveness of this surgery" were not considered to be specific enough (unless a measurement of "effectiveness" was provided by the authors). In cases where the article authors did not explicitly state a primary outcome, it was noted, and a primary outcome was selected by the data extractors. The primary outcome was selected

using a primary outcome algorithm, modified from a similar algorithm in Bala *et al*[94], as described in Figure 5.1. Here, the most patient important outcome was defined as that which would be of greatest relevance to the patient. A hierarchy of outcomes (Table 5.1) was used to determine the most patient important outcome. This hierarchy is a modified version of the hierarchies of outcomes used in Bala *et al*[94] and Lubsen *et al*[95]. This hierarchy also incorporated information from a research group who examined outcomes used in plastic surgery over 17 years[42], as well as reviewed outcomes in hand surgery over the same time period[96].

Patient-reported outcome measures (PROM) were defined as described by Pusic *et al*[97]: "…a term that applies specifically to a questionnaire used in a clinical or research setting where responses are collected directly from patients. These questionnaires quantify quality of life and/or significant outcome variables (e.g. patient satisfaction, symptoms) from the patient's perspective".

5.2.3. Plan for Data Analysis

A descriptive analysis of the data collected on outcomes was conducted. Quantitative summaries of event totals and percentages are reported.

5.3. Results

The search strategy identified 173 unique RCTs. Table 5.2 provides information on primary outcomes explicitly stated in the manuscripts by the authors. A third (58/173 (34%)) of all trial reports did not define a primary outcome. One hundred-fifteen (66%) RCTs stated their primary outcome for the reader. Of these 115 RCTs, 58 (50%) used a

single primary outcome, 54 (47%) RCTs stated two or more primary outcomes and 3 (3%) RCTs used a composite outcome.

Table 5.3 provides details on the outcomes used. Half (N=85, 49%) of all trial reports used objective patient-important outcomes, which were assessed in a manner to limit bias. One hundred forty-six (84%) RCTs either used a well-known outcome measure, or described their outcome measure in enough detail for the reader.

Table 5.4 outlines the class of outcome that the primary outcome was categorized into. These outcomes consist of the authors' explicitly stated primary outcome, or in the cases when a single primary outcome was not stated, the outcome chosen using the primary outcome algorithm (Figure 5.1). Two (1%) RCTs used a Class I, Mortality, primary outcome. One RCT explicitly stated their primary outcome of comparing overall survival differences for 2-cm vs 4-cm excision margins in patients with cutaneous melanoma thicker than 2mm[98]. The other RCT[99] described multiple primary outcomes, and the primary outcome algorithm (Figure 5.1) was used to choose "survival" as the primary outcome. This RCT compared the timing of tracheostomy in burn patients[99]. Sixty-three (36%) RCTs used a Class II, Morbidity, primary outcome, 73 (42%) RCTs used a Class III, Symptoms/Quality of Life/Functional Status, primary outcome, and 35 (20%) RCTs used a Class IV, Surrogate Outcome, primary outcome.

Half (N=87, 50%) of all trial reports described using a patient-reported outcome measure as at least one of their trial outcomes. No consistent trend of an increasing proportion of RCTs using PROMs was present (Table 5.5). One hundred fifty-four (89%)

RCTs included a statement on either the presence or definite absence of any adverse events or complications associated with the treatment intervention (Table 5.6).

Appendix D contains a table in which the primary outcome all 173 RCTs are presented. They are arranged by domain of plastic surgery investigated, followed by whether the authors stated a primary outcome, or one was chosen for them using the primary outcome algorithm (Figure 5.1), and the corresponding primary outcome.

5.4. Discussion

5.4.1. Principal Findings of Study

Only two-thirds of RCTs (N=115, 66%) explicitly stated a primary outcome. It is surprising that one-third of RCTs did not explicitly report a primary outcome. Furthermore, it is necessary to differentiate a primary outcome from a secondary outcome. The identification of a primary outcome is required to make a decision on the overall result of a study[100] and is the basis from which the sample size is determined. If a primary outcome was used in the conception and execution of an RCT, but was not reported as such within the manuscript, the reader will be limited in the application of the results from this RCT to their own patients, and any researchers attempting a meta-analysis on the same intervention will be limited by this omission.

The ideal outcome measure is patient-important, reliable, accurate, and simple to measure[8]. The outcome measures chosen for an RCT comparing surgical interventions will impact the validity and applicability of the trial. Most plastic surgery interventions are not aimed at saving lives. Only in rare occasions is the “hard outcome” of mortality applicable for a plastic surgical RCT. This characteristic is reflected in this systematic

review where only 2 (1%) of the 173 RCTs used Mortality, Class I, outcomes as the primary outcome; indeed, such a low percentage is to be expected. Morbidity, Class II, outcomes (Table 5.1) are also considered "hard outcomes", however there are often different measures and definitions of the threshold the patient must reach before the patient is acknowledged as having the Class II outcome. For example, Symptoms/Quality of Life/Functional Status, Class III, outcomes can be as appropriate as a Morbidity, Class II, outcome when they are valid, reliable, and responsive[8]. Surrogate outcomes, Class IV, which used as the primary outcome in 35 (20%) of plastic surgical RCTs, can occasionally be useful when an important outcome is infrequent, or requires a long period of time to occur[101]. By definition, a surrogate outcome cannot be a patient-important clinical endpoint, and thus are less useful when creating treatment guidelines due to the indirectness of the quality of evidence[101].

The quantity and quality of patient-centric research has been increasing in plastic surgery[97]. While the number of surgical RCTs using at least one PROM has increased, it appears that this increase mirrors the increase in volume of surgical RCTs published per year. No obvious increase in the proportion of surgical RCTs using a PROM was noted. While the quality of the patient-reported outcome instruments used in each RCT was not assessed in this systematic review, valid and reliable condition-specific outcome instruments, such as the Breast-Q[102 103] and Face-Q[104], now exist to measure plastic surgery outcomes, and more, like the CLEFT-Q[93], are being developed.

Outcomes involving complications or adverse events, such as disability or hospitalization, are important[101]. While occasionally they may represent a surgical RCT's primary outcome, the presence of complications or adverse events should always be

acknowledged in the manuscript of an RCT. It is possible, and more likely, that no complications or adverse events are encountered in a surgical RCT of very small sample size. In these cases, the absence of complications or adverse events should be stated to ensure clarity. The majority, 154 (89%), of RCTs in this systematic review were able to report on the presence or absence of complications/adverse events in their trial.

5.4.2. Comparison with other Studies

No other study has reviewed, recorded, and presented outcomes of surgical RCTs in plastic surgery. Sears *et al*[42] examined the state of outcomes studies in plastic and reconstructive surgery. While outcomes research is different than research on outcomes of surgical RCTs, the proportion of study endpoints are similar to what was found in this review. The most common study end point was morbidity, closely followed by quality of life and subjective clinical measures, then objective clinical measures.

The prevalence of the use of PROMs in surgical RCTs does not appear to have been previously measured in plastic surgery. Half of the surgical RCTs published in plastic surgery used a PROM over the past 13 years (i.e., 2000 – 2013). The presence of PROMS in 50% of plastic surgical RCTs compares favourably to the field of gastric cancer surgery in which 11 (13%) of 87 RCTs included at least one PROM[105].

5.4.3. Limitations

This study was not able to answer the question: "Are we choosing the right outcomes in each surgical RCT?" However, it provided an overview of the distribution of primary outcomes in each outcome class. The distribution among outcome classes presented in this systematic review is a generous representation of the literature. In the 58

(34%) RCTs that did not declare a primary outcome, the Selection of Primary Outcome Algorithm (Figure 5.1) would have chosen the most patient-important outcome measured. This study does not provide data on outcome timelines, as presenting ranges or measures of central tendency for timelines of primary outcomes from procedures from various domains of plastic surgery is not informative. A future investigation will involve judgment by expert academic plastic surgeons on what the appropriate time horizon would be for the primary outcome, and then an assessment of whether the RCT successfully achieved this timeline.

5.5. Conclusions

A clear, patient-important primary outcome is necessary to allow an RCT to have an impact on patient care. In general, plastic surgical RCTs appear to be declaring primary outcomes and are using patient important class II and class III outcomes, however there is still room for improvement. Valid and reliable outcome measures that are responsive to change exist in plastic surgery, and research toward creating more high quality measurement tools has gained momentum. The volume of surgical RCTs using PROMs has increased, but the proportion has stayed the same. As the number of treatment options for plastic and reconstructive surgery patients increases, the use of evidence-based plastic surgery becomes even more important. Declaring a patient-important primary outcome, providing a clear description of what the outcome involves is essential to facilitate the incorporation of high-level evidence into every day clinical practice.

Figure 5.1. Algorithm for Selection of Primary Outcome

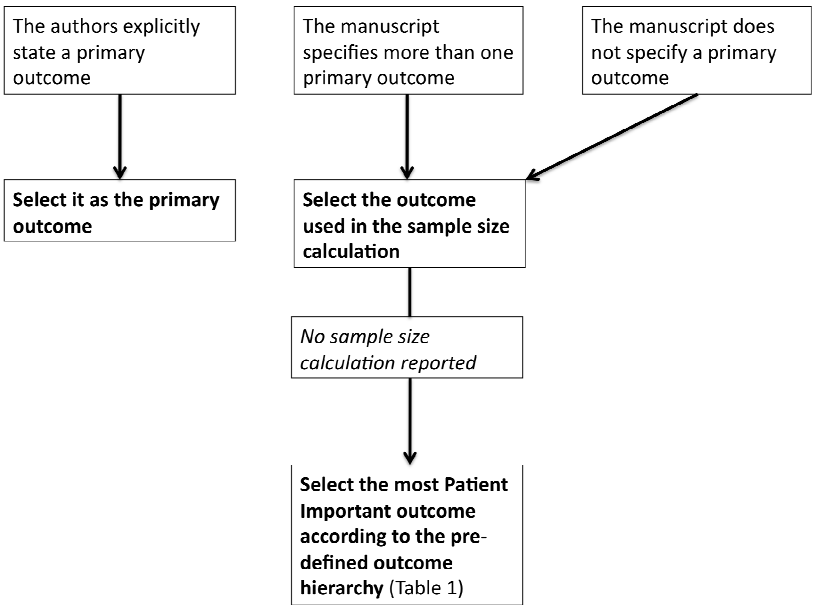

The authors explicitly state a primary outcome
The manuscript specifies more than one primary outcome
The manuscript does not specify a primary outcome
Select it as the primary outcome
Select the outcome used in the sample size calculation
No sample size calculation reported
Select the most Patient Important outcome according to the pre-defined outcome hierarchy (Table 1)

Table 5.1. Hierarchy of Outcomes

I	Mortality	- All Cause Mortality
	Mortality	- Disease Specific Mortality
II	Morbidity	- Major Surgery Required
	Morbidity	- Recurrence/Relapse/Remission of cancer or other chronic disease
	Morbidity	- Complication requiring any of the following: Hospitalization, Medical treatment or Minor surgical procedure
	Morbidity	- Other
III	Symptoms/Quality of Life/Functional Status	- Condition Specific QOL scale
	Symptoms/Quality of Life/Functional Status	- Generic QOL scale
	Symptoms/Quality of Life/Functional Status	- Assessment of functional status (disease specific or general)
	Symptoms/Quality of Life/Functional Status	- Return to Work
	Symptoms/Quality of Life/Functional Status	- Ad hoc scale/questionnaire/judgement
	Symptoms/Quality of Life/Functional Status	- Patient satisfaction
	Symptoms/Quality of Life/Functional Status	- Pain
	Symptoms/Quality of Life/Functional Status	- A symptom that does not involve pain
	Symptoms/Quality of Life/Functional Status	- Cost/Economic evaluation
	Symptoms/Quality of Life/Functional Status	- Other
IV	Surrogate Outcome	- Physical test/Biomechanical measurement/Anthropomorphic measurement
	Surrogate Outcome	- Laboratory test
	Surrogate Outcome	- Other

Table 5.2. Author Statement Regarding the Primary Outcome

Author Statement of a Primary Outcome	**N**	**Percent**
Present	115	66
Not present	58	34
Total	173	100
Number of Primary Outcomes Explicitly Stated by Author	**N**	**Percent**
Single Primary Outcome	58	50
Two or more Primary Outcomes	54	47
Composite Primary Outcome	3	3
Total	115	100

Table 5.3. Details on Outcomes Used

Were Outcomes Objective, Patient-Important, and Assessed in a Manner to Limit Bias?	**N**	**Percent**
Yes	85	49
Uncertain	75	43
No	13	8
Total	173	100
Was the description of the Outcome Measure Adequate?	**N**	**Percent**
Yes	146	84
No	27	16
Total	173	100

Table 5.4. Types of Primary Outcomes used in Plastic Surgical RCTs

Hierarchy of Outcomes	**N**	**Percent**
Class I: Mortality	2	1
Class II: Morbidity	63	36
Class III: Symptoms/Quality of Life/Functional Status	73	42
Class IV: Surrogate Outcomes	35	20
Total	173	99

Table 5.5. Were any of the outcomes in the RCT a Patient-Reported Outcome Measures?

Year of Publication	RCTs that used a Patient-Reported Outcome N (%)	RCTs that did not use a Patient-Reported Outcome N (%)	Total RCTs Published
2000	0 (0)	1 (100)	1
2001	2 (50)	2 (50)	4
2002	0 (0)	3 (100)	3
2003	1 (50)	1 (50)	2
2004	11 (69)	5 (31)	16
2005	7 (37)	12 (63)	19
2006	9 (82)	2 (18)	11
2007	10 (59)	7 (41)	17
2008	11 (48)	12 (52)	23
2009	9 (50)	9 (50)	18
2010	11 (50)	11 (50)	22
2011	5 (26)	14 (74)	19
2012	11 (61)	7 (39)	18
Total	**87 (50)**	**86 (50)**	**173**

Table 5.6. Details on Author Reporting of the Presence or Absence of any Adverse Events or Complications

Presence or absence of adverse events/complications	N	Percent
Reported	154	89
Not Reported	19	11
Total	173	100

6. Sample Size and Incomplete Outcome Data in Surgical RCTs in Plastic Surgery: 2000-2013

6.1. Introduction

While the distinguishing feature of randomizing patients to an intervention allows the RCT to be the gold standard for comparing interventions, other methodological features are necessary to maintain the credibility of an RCT. For example, an appropriate sample size can reduce the risk of an under-powered (false-negative) result[106].

While clinical drug trials have become known for large sample sizes, exceeding hundreds of patients, RCTs of surgical interventions in plastic surgery might be perceived as too small to have a meaningful impact on clinical practice. Thus, calculating a sample size using the appropriate level of power can give confidence to the reader that the trial was able to detect a difference between treatments if one truly existed. Surgical trials, like pharmacological trials, require the calculation of a sample size and the consultation of an epidemiologist or biostatistician for this purpose has been strongly recommended[8 106].

Essential to the sample size calculation is the declaration of a primary outcome. It is also important to incorporate the minimum clinically important difference (MCID) for this outcome when one is available. The MCID is the smallest measurable difference in outcome that a patient can perceive as important and that would persuade the physician, or policy maker, to change practice. When Ayeni *et al*[107] investigated the reporting of power and sample size in RCTs published between 1990 and 2010 in nine high impact plastic surgery journals, they found that most trials (81%) were not reporting power and sample size calculations.

In an extensive review of plastic surgery trials which failed to find a difference between intervention groups (i.e., "negative trials"), Chung *et al*[108] reported that many studies had less than 80% power, and warned readers that arriving at the conclusion of "no treatment effect" from these trials is not reasonable. Additionally, the reporting of trial results and the associated confidence interval (CI) can indicate whether the trial provides evidence which i) favours one intervention and is definitive, ii) favours one intervention but requires a larger sample size to be definitive, iii) favours neither intervention but requires a larger sample size to be definitive, or iv) the sample size of the trial is adequate and the trial is definitively negative[109].

This systematic review investigated sample sizes and their calculation in surgical RCTs published in the plastic surgery literature since the year 2000.

6.2. Methods

6.2.1. Search Methods and Study Selection

The search strategy and study selection methodology used to identify the 173 unique surgical RCTs in the plastic surgery literature since January 2000 has been described in Chapter 2.

6.2.2. Data Collection Process

The data collection process was summarized in Chapter 2. The following information regarding sample size was collected: Total number of participants randomized to a treatment, mean, median, range, total number of intervention groups, *a priori* sample size calculation, evidence used when calculating sample size, ability of

RCT to recruit the number of patients the sample size suggested, post hoc sample size calculation, and estimate of effect with confidence intervals.

The following information regarding issues related to analysis was collected: trials stopped early for benefit, missing participants, trials that operated on multiple body parts of the same patient, and, randomization type used in these multiple body part trials.

6.2.3. Plan for Data Analysis

A descriptive analysis of the data collected on outcomes was conducted. Quantitative summaries of event totals and percentages are reported. Independent samples t-test (significance set at alpha of 0.05) was used to compare sample sizes between RCTs that reported a significant primary outcome, and those that reported a non-significant primary outcome.

6.3. Results

The search strategy in Chapter 2 identified 173 unique RCTs. Table 6.1 provides information on measures of central tendency and measures of dispersion regarding the number of patients that trials were able to randomize. In two RCTs, it was not possible to confidently determine how many patients were randomized to treatment groups. Therefore, in the remaining 171 surgical RCTs, the mean number of patients included in a trial was 73, and the median was 43, with a range of 3 to 936. The interquartile range was 42 (Q_{25}: 28, Q_{75}: 70). Table 6.1 also provides details on the number of treatments arms present in each RCT, with 156 (90%) RCTs possessing two treatment arms.

Sample sizes of RCTs reporting a significant primary outcome (mean sample size 87) were not found to be significantly different (p-value = 0.76) than those reporting a non-significant primary outcome (mean sample size 79). The measures of dispersion of the sample sizes of both groups are similar, and presented in Table 6.2.

Table 6.3 outlines information regarding the sample size calculation. One hundred thirty (75%) RCTs did not report calculating a sample size *a priori*. Of the 43 (25%) RCTs that calculated a sample size *a priori*, 41 RCTs stated the number calculated, and provided some, or all, component(s) of the calculation for the reader. However two RCTs simply stated that a sample size was calculated *a priori*, and neither provided any component of the calculation, nor the actual sample size number calculated. For the 43 RCTs that calculated a sample size *a priori*, 16 (37%) RCTs used evidence from the literature to choose the MCID, 7 (16%) RCTs used evidence from their own pilot study, and 1 (2%) RCT conducted an informal survey of local plastic surgeons. The remaining 19 (44%) RCTs did not provide any information on how the MCID was chosen. Of the 41 trials that that calculated a sample size *a priori* and described the sample size with the reader, 30 (73%) RCTs were successful in randomizing at least as many patients as their sample size calculation had suggested.

Table 6.4 provides information on *post hoc* power analysis and the use of confidence intervals. Nine (5%) out of 173 RCTs performed a *post hoc* power analysis. In the 115 RCTs that reported a primary outcome, 25 (22%) RCTs reported the confidence interval with their results for the primary outcome. Thirty-seven (21%) of all 173 RCTs included a confidence interval when reporting at least one of their outcomes.

One (1%) RCT was stopped early for benefit (Table 6.5). In 71 (41%) RCTs, multiple sites of the same patient's body received a surgical intervention (Table 6.6). More specifically, in 39 (55%) of these 71 RCTs each body part received a different intervention, 25 (35%) RCTs had multiple body parts receiving the same intervention, and 5 (7%) RCTs used a combination in which multiple body parts received both interventions. In 2 (3%) RCTs not enough information was present to be able to classify the RCT into one of the previous categories.

6.4. Discussion

Sample sizes of plastic surgery RCTs comparing two or more surgical interventions were small, with the mean number of patients included in a trial being 73, and the median 43. Small trials that do not minimize the risks of bias of randomization, allocation concealment, or blinding, have been shown to significantly exaggerate intervention effects[110]. Such small trials can potentially lead to spurious conclusions if a few extra outcomes events randomly appear in one of the intervention groups, leaving the field with small RCTs that are inconclusive and sometimes contradictory. Thus, large RCTs are necessary if a treatment is to be evaluated definitively. A large sample size allows the trial to gain adequate precision, and becomes increasingly important when outcome events are infrequent[87].

Most trials (75%) did not report the calculation of a sample size *a priori*. The ability of a trial to detect smaller differences between interventions increases as the sample size increases. However, larger sample sizes come at a cost both financially, and the increased time taken to complete patient recruitment. Therefore sample size

evaluation and calculation for an RCT is often a compromise between the resources that are available, and the objectives of the trial (i.e. small or large effects desirable[111]). The calculation of the sample size *a priori* is essential to the trial's success to ensure that the trial has the power to detect a statistically significant difference between the intervention groups, and is especially important in the field of plastic surgery with its rather smaller sized RCTs.

The difference between the groups should also be larger than the MCID to ensure that this difference is relevant to the patient, and meaningful enough to change practice. The three accepted methods of determining the MCID include i) using evidence found in the literature, ideally by performing a systematic review of the available evidence, ii) conducting a pilot study to directly measure the MCID, or iii) surveying experts and/or patients[8]. Since the calculation of a sample size usually represents an initial estimate of the minimum participants required, adjustments (i.e. increases), should be built into the final estimate to account for potential patients lost to follow-up and any anticipated sub-group analyses to maintain an acceptable level of power[8].

It was reassuring that few (5%) RCTs performed a *post hoc* power analysis as there is concern that with a bit of manoeuvring, numbers can be chosen to contend that the a negative trial was adequately powered, when in fact it was not. Reporting of confidence intervals along with trial outcomes are important as the confidence interval represents the range of values in which the true difference between the intervention groups may lie. Confidence intervals (CIs), which were reported in one-fifth of plastic surgical RCTs, better inform the reader about the possibility the RCT had an inadequate

sample size than *post hoc* power analyses[112]. CIs are essential in helping the scientific literature move away from the dichotomizing force of the p-value. CIs can demonstrate both statistically differences, as well as clinically important information[109]. Finally, CIs allow the reader to evaluate whether the trial results were definitive or whether a larger sample size with more patients and events was needed[113].

RCTs that are stopped early (i.e., terminated) for an apparently beneficial treatment effect have been shown to be associated with greater effect sizes than RCTs that are not stopped early[101 114]. This is usually due to random fluctuations in treatment effect, which can occur early on in a trial, and was shown to be greatest in small trials[114]. RCTs stopping early for benefit does not appear to be a concern in surgical RCTs in the plastic surgery literature, as only one such trial was found over the past 13 years.

RCTs administering surgical interventions at multiple site of the body on the same patient represented 41% of all RCTs. When interpreting the results of a statistical analysis, it is important to be aware of whether the patient or the body site was randomized, and whether a separate outcome judgment is being performed for each site, or if there is a single outcome for the whole patient. When the patient is randomized, for example in a breast reduction surgery, and the outcome is infection, whereby either individual breast can have the outcome, an adjustment for non-independence between the breasts must be made. When multiple body parts receive the same intervention, it is similar to a cluster randomized trial, whereby the cluster is the patient. This is different from "split-mouth" study designs whereby, different surgical interventions are performed on multiple body parts of the same patient. For example patients with bilateral carpal

tunnel can be recruited, and two different surgical techniques are performed, one on each hand, in the same patient. The ability to perform within patient randomization, and having a perfectly matched comparison is an advantage that is unique to the field of plastic surgery, and few other specialties.

6.5. Conclusions

This study found that most surgical RCTs in the plastic surgery literature are not able to recruit an adequate number of patients. Small RCTs can be misleading, and if they are underpowered and poorly designed, they can cause harm as the simple association with the RCT study design provides them with tenuous credibility[115]. The majority of studies do not report an *a priori* sample size decision, and about half of those that do, need to provide more information on why this sample size was chosen. The MCID is a valuable component to incorporate when calculating a sample size estimate if one is available.

Confidence intervals allow the reader to determine statistical significance of a result, the variability present within the trial results, and the clinical importance of the conclusions. Confidence intervals need to be reported more in the plastic surgery literature as they are much more valuable than looking at a p-value. Unique opportunities are present in RCTs administering surgical interventions at multiple site of the body on the same patient.

Table 6.1. Number of patients included in plastic surgical RCTs (randomized to a treatment group)

Measures of Central Tendency	**Number of patients randomized in 171 RCTs***	
Mean	73	
Median	43	
Measures of Dispersion		
Min	3	
Q_{25}	28	
Q_{75}	70	
Max	936	
Number of Treatment Arms	**Number of RCTs**	**Percent**
2	156	90
3	12	7
4	3	2
5	0	0
6	1	1
7	0	0
8	1	1
Total	173	101

*In two RCTs it was not possible to confidently determine how many patients were randomized to treatment groups.

Table 6.2 Sample Sizes by Primary Outcome Significance

Measures of Central Tendency	**Significant Primary Outcome**	**Non-Significant Primary Outcome**
Mean	87	79
Median	47.5	44
Measures of Dispersion		
Min	8	10
Q_{25}	30	30
Q_{75}	70	70
Max	900	936

Table 6.3. Sample Size Calculation Information

***A priori* Sample Size Decision**	**Number of RCTs**	**Percent**
Present, number stated, some component of calculation present	41	24
Present, number stated, no component of calculation present	0	0
Present, authors do not share the number with the reader	2	1
Not Reported	130	75
Total	173	100
Evidence Used for choice of MCID used to Calculate Sample Size	**Number of RCTs**	**Percent**
Evidence from the Literature	16	37
Author's own Pilot Study	7	16
Unpublished Survey	1	2
None given/None reported	19	44
Total	43	99
Success of RCTs in Randomizing at Least as many Patients as Sample Size Calculation Suggested	**Number of RCTs**	**Percent**
Successful	30	73
Not Successful	11	27
Total	41	100

Table 6.4. Post hoc Sample Size Calculations and Use of a Confidence Interval (CI) When Reporting Outcomes

Post hoc Sample Size Calculation	**Number of RCTs**	**Percent**
Present	9	5
Not Present	164	95
Total	173	100
Was a CI included when reporting the primary outcome?	**N**	**Percent**
Yes	25	22
No	90	78
Total	115	100
Was a CI included in the reporting of ANY outcome?	**N**	**Percent**
Yes	37	21
No	136	79
Total	173	100

Table 6.5. Trials stopped early for Benefit

RCT Stopped early for Benefit	Number of RCTs	Percent
Yes	1	1
No	172	99
Total	173	100

Table 6.6. Unit of Analysis Issues: Multiple Body Parts

Sites of the Body Receiving an Intervention	Number of RCTs	Percent
Single	102	59
Multiple	71	41
Total	173	100
Type of Randomization in RCTs treating Multiple Body Parts	**Number of RCTs**	**Percent**
Split-Mouth: multiple body parts receive different interventions	39	55
Cluster: multiple body parts receive the same intervention	25	35
Combination of Split-Mouth and Cluster	5	7
Unclear	2	3
Total	71	100

7. Funding Sources, Conflict of Interest, and Outcome Direction in Surgical RCTs in Plastic Surgery: 2000 - 2013

7.1. Introduction

Inappropriate influence of any party that has a vested interest in the findings and conclusions of a trial can be regarded as a significant risk of bias. The influence of industry funding on trial outcomes and their subsequent conclusions has been investigated with varying levels of association being established[116-119]. The tendency of an industry-funded trial to favour a new therapy has been explored in the past, for numerous health care fields[120]. For example, in an analysis of oncology and cardiology trials, the declaration of industry funding has been shown to not only be associated with industry funding results, but additionally with an actual impact on medical literature, as measured by subsequent citation rate[121].

Indeed, the relationship of industry-funded studies with outcomes favourable to the funder has been demonstrated in both medical and surgical literature[110 119 26 122]. Furthermore, if the primary outcome of a trial was not statistically significant, industry funded trials have been shown to report subgroup analyses at a higher rate than non-industry funded trials[123]. These industry trials were also less likely to pre-specify their subgroup hypotheses, and tested for interaction less frequently than their non-industry counterparts[123].

In the plastic surgery literature, the association between research sponsorship and study outcome in RCTs and controlled clinical trials (CCTs) published between 1990 and

2005 has been described by Momeni *et al*[124]. Here, while a relationship between industry funded studies and outcomes favourable to the funder was not demonstrated, it is possible that trial funding in general was under-reported, and therefore the relationship could not be properly investigated[124].

The empirical study of Gøtzsche *et al*[125] described the presence of constraints in industry-initiated trials. The reviewed protocols and subsequent publications revealed that constraints on publication rights were present in 91% of protocols. Despite the fact that the sponsor either owned data, needed to approve the manuscript, or both owned data and had manuscript approval in 50% of protocols, none of this information regarding was stated in any of the trial publications. Ironically, in the same year of the publication of the Gøtzsche study, two prominent medical journals faced criticism over being misled by researchers who did not appropriately disclose financial conflicts of interest[126]. In the following months many journals, including *JAMA*, published editorials on the importance of financial disclosure and made changes to their disclosure and conflict of interest policies[126 127]. Rohrich described 'disclosure' as this: "Disclosure is the process whereby authors of manuscripts reveal their financial relationship(s) with manufacturers of any drugs or devices that are stated or discussed in their articles, or their relationship with companies that manufacture drugs or devices that are related to or compete with those mentioned in their articles."[126]

Plastic surgery journals were not immune to such criticisms; in 2006, *Plastic and Reconstructive Surgery* revised policies to incorporate a comprehensive and prominent disclosure. While financial disclosure is ultimately in the hands of the submitting author,

it is likely that these widespread changes improved reporting of funding and the disclosure of conflicts.

Clapham and Chung[128] characterized the existing literature involving the relationship between plastic surgery and the medical industry. They uncovered a need to examine the ethical implications of industry support and industry's overall engagement of the field of plastic surgery. They acknowledged that a systematic review of the level of industry support for clinical trials would be a suitable method to define the extent to which the plastic surgery is engaged by industry[128]. Randomized controlled trials are resource intensive, and the relative scarcity of resources allocated for RCTs has been identified as one of the key barriers to their conduct[47]. Therefore, the issue of funding, where funding comes from, and who is ultimately in control of the trial data and the decision to publish, continue to be essential matters to investigate.

Thus, the objectives of this systematic review were built upon the foundation of the work of Momeni *et al*[124], and more recent disclosure and conflict of interest policies, in order to examine the level of industry support for surgical RCTs in plastic surgery, the association between trial funding and trial outcome, and the reporting of conflicts of interest, from 2000 to 2013.

7.2. Methods

7.2.1. Search Strategy

The search strategy and study selection methodology used to identify the 173 unique surgical RCTs, along with the data collection process, has been described in Chapter 2. Two reviewers independently evaluated the presence of a primary outcome,

the statistical significance, and the direction of that primary outcome. Disagreements were resolved through discussion.

7.2.2. Funding Source, Conflict of Interest and Outcome Direction

All information on funding sources was collected from the self-reported information present within each manuscript. Industry funding was considered present if there was any acknowledgement of direct industry support for the research study, including direct funding of the study or supplying of medical devices. Industry funding was defined as support from for-profit companies, and excluded any government or non-profit agency. Conflicts of interest, such as authors owning shares in a for-profit company, were not considered to be "direct industry support" for the trial, and therefore were considered separately.

"Not for Profit/University/Government/Society Funding" was considered present when a reviewer would confirm the goals, description and mission statement of the funding agency, using Google as a search engine, as being a Not for Profit agency. University grants, government grants, and society funding (e.g. American Society of Plastic Surgeons, Canadian Society of Plastic Surgeons) were considered present when acknowledged by the trial authors.

No funding was considered to have been received by the trial author group only when an explicit statement embodying the idea "no funding was received" was present in the manuscript. If no statement regarding funding appeared in the publication, then "No Statement Regarding Funding Present" was recorded.

The presence of an industry product in the trial was recorded only if the product played a role in one or more of the interventions studied. The product had to be referenced either by its retail name, or along with the company name. Generic products without reference or allusion to an industry name (e.g. “absorbable mesh”, or “poly-L-D-lactic acid (PLDLA) implant) were not considered “industry products”. Statistical packages or computer programs used in data analysis were not considered relevant as a plastic surgery “industry product”.

All information collected regarding conflict of interest was self-reported by the manuscript authors and was taken at face value. Conflict of interest was considered to be present when items (e.g. royalties, consultant role, stock/stock options, position as company employee) were reported to be held by any member of the trial’s author group. Such conflicts of interest were treated differently from ‘direct industry support’.

Information on statistical significance of a primary outcome, and the direction of the primary outcome were only collected when a primary outcome was explicitly stated by manuscript authors. Reviewers classified the primary outcome as statistically significant if i) the authors stated that the outcome was significant, or ii) the reported p-value was less than 0.05, or iii) the reported 95% confidence interval excluded the null value (under a null hypothesis that no difference existed). If authors concluded superiority of one intervention over another despite a lack of supporting statistical evidence, the author statement took priority, and was recorded as a “positive/significant” outcome. For trials with a “positive outcome”, reviewers then classified the findings as favouring the “experimental” (new technique/industry product), or “control” (common/older technique

or standard of care) interventions. If it was not clear to the reviewers which were the "experimental" and "control" groups, this was simply recorded as "experimental/control group indeterminable".

7.2.3. Methods for Analysis

A descriptive analysis of funding sources, conflicts of interest, presence of industry products, and direction of primary outcome was conducted. For all data points, the percentage of studies falling into each category was calculated.

7.3. Results

The search strategy in Chapter 2 identified 173 unique surgical randomized controlled trials. The funding source reported in all 173 RCTs is outlined in Table 7.1, though the majority (n = 100, 58%) of surgical RCTs did not acknowledge the presence or the absence of any type of funding. The introduction of rigorous disclosure and conflict of interest policies in 2006 is used as a major milestone[126 127]. Thus, Figure 7.1 compares the reported funding sources in plastic surgical manuscripts published between 2000 and 2006, with those published between 2007 and 2013. RCTs reporting "no funding received" and "for profit/industry/private funding" increased from 1 (2%) RCT and 3 (5%) RCTs, to 17 (14%) RCTs and 22 (18%) RCTs respectively. The proportion of RCTs that did not acknowledge the presence or absence of a funding source decreased over the same time period, from 40 (70%) RCTs to 60 (50%) RCTs.

The relationship between reported trial funding and the significance of the primary outcome was examined (Figure 7.2). Of the trials with a significant difference in

their primary outcome, there is a greater presence of funded trials, 34 (44%) RCTs in total, compared to 20 (33%) funded RCTs that did not show a significant difference. However, the proportions of these trials are overshadowed by the large number of trials, 27 (50%) RCTs with a significant difference and 36 (59%) RCTs with a non-significant difference, which neither acknowledged the presence nor the absence of any type of funding. Of the 25 industry funded trials, 6 (24%) RCTs reported the authors having full and independent control of data, manuscript contents and the decision to submit for publication (Table 7.2). No trial reported the partial control of data, manuscript contents and or decision for publication. The other 19 (76%) RCTs did not include any type of statement regarding this issue. The outcome direction of trial results as compared to the funding source of the RCT, was also examined (Table 7.3).

The reporting of conflicts of interest was also described (Table 7.4). Nine (5%) RCTs reported a conflict of interest and 71 (41%) RCTs stated that no conflicts of interest were present. The majority of RCTs (N=93, 54%) did not report the presence or absence of conflicts of interest. When a trial was funded by industry or privately, 6 (24%) of RCTs reported a conflict of interest, 10 (40%) stated no conflicts were present, and in 9 (36%) RCTs neither the presence, nor absence of conflicts were reported. In trials where an industry product was mentioned, 7 (7%) RCTs reported a conflict of interest, 43 (41%) stated no conflicts were present, and in 55 (52%) RCTs neither the presence, nor absence of conflicts were reported. When conflicts of interest were compared over time, the proportion of RCTs not reporting the presence or absence decreased from 86% (48 RCTs) between 2000 and 2006, to 38% (45 RCTs) between 2007 and 2013 (Figure 7.3). Over

this same time period, the proportion of RCTs explicitly reporting no conflicts of interest increased from 13% (7 RCTs) to 55% (64 RCTs).

The presence of industry products in plastic surgical RCTs was described (Table 7.5). The majority of RCTs (N=105, 61%) mentioned the use of an industry product as part of one or more interventions. Some of these RCTs (N=16, 15%) used the same industry product in each of the surgical interventions. The most common domains of plastic surgery which mentioned an industry product were craniofacial surgery (N=26, 25%), followed by hand and upper limb surgery (N=23, 22%), then breast surgery (N=19, 18%), and aesthetic surgery (N=17, 16%). These proportions are similar to the overall presence of plastic surgery domains studied by the 173 surgical RCTs in Table 7.3 from Chapter 3, which were hand and upper limb surgery, (N=46, 27%), craniofacial surgery, (N=43, 25%), breast surgery, (N=27, 16%), and aesthetic surgery, (N=24, 14%).

7.4. Discussion

7.4.1. Principal Findings of the Study

This systematic review of plastic surgical RCTs published between 2000 and 2013 demonstrates an obvious improvement in reporting of funding sources (Figure 7.1) in the second half of the time period studied (2007-2013) when compared to the first half (2000-2006). This change is likely due to the significant changes that leading medical journals, like *JAMA*, and plastic surgery journals, like *Plastic and Reconstructive Surgery*, made to their disclosure and conflict of interest policies in the year 2006[126 127]. Since these changes, it appears that there is an approximately even split of trials reporting either “no funding received”, “for profit/industry/private” funding, or “not for

profit/university/government/society" funding, when funding source is provided. However, this can only give an estimate of funding sources actually being used by plastic surgical RCTs, as half (N=60, 50%) of the RCTs published since 2006 did not include any statement regarding the presence or absence of funding in their manuscript.

The study conducted by Momeni *et al*[124] investigated the association between research sponsorship and study outcome in all randomized controlled (RCT) and controlled clinical trials (CCT) published in four plastic surgery journals (*Plastic and Reconstructive Surgery, British Journal of Plastic Surgery, Annals of Plastic Surgery,* and *Aesthetic Plastic Surgery*) between 1990 and 2005. Here, the authors stated that the majority of trials reporting a statistically significant difference between treatment arms were industry funded.

This systematic review found a greater proportion of trials with any type of funding showing a significant difference in their primary outcome (44%) than those that did not show a significant difference (33%). However, there was too much statistical noise present from trials which neither acknowledged the presence nor the absence of any type of funding (50% of RCTs demonstrating a significant primary outcome, and 59% not demonstrating a significant primary outcome) to perform a statistically meaningfully comparison. Similarly, while the proportion of industry/privately funded trials demonstrating a significant difference (20%) was greater than industry/privately funded trials not demonstrating a significant difference (13%), a statistically meaningful comparison was not possible, due to the proportion of trials which neither acknowledged the presence nor the absence of any type of funding.

RCTs require significant financial resources, and while it has been shown that the results of both pharmacologic and surgical trials can be influenced by industry funding[26], it is also likely that by careful selection, industry will fund a trial that they are confident will reveal a benefit of their experimental intervention[119 26]. There have been cases in which the industry funding body has tried to, or even been successful in, suppressing trial results[124]. Therefore, when trials are industry funded, it is useful to include a statement reporting whether or not the authors had full and independent control of the data, manuscript contents and the decision to submit for publication. This practice can assuage concerns that might arise when deciding to apply results from an industry-funded trial to clinical practice and patient care.

A full disclosure of conflict of interest is necessary to address concerns regarding financial involvement in medical publications[126]. Reporting conflict of interest has improved immensely over time. The proportion of trials reporting either the presence or absence of any conflicts of interest increased from only 15% of RCTs published between 2000 and 2006 to 62% of RCTs published between 2007 and 2013. While this is a great improvement, and is likely due to journals changing their disclosure and conflict of interest policies in 2006, it still means that 38% of RCTs published between 2007 and 2013 did not report the presence or absence or any conflicts of interest within the manuscript. While the reporting of a conflict of interest ultimately lies with the submitting authors, the actual presence of a statement regarding disclosure of a conflict of interest is usually journal dependent. The inclusion of a statement regarding the trial authors' disclosure of conflicts of interest in each published manuscript by the publishing journal

would provide transparency to the relationship the authors have with any funding body, increase credibility and legitimacy of the authors, and allow readers to assess for themselves any potential biases that may be present in the trial[126].

Industry influence is not limited to solely providing funding. The presence of an industry product, referred to by its commercial name, was noted in the majority of plastic surgical RCTs (N=105, 61%) in this systematic review. It has been suggested that along with funding and conflict of interest disclosures, "a list of all products, devices, drugs, etc" should be included in each manuscript[126]. Consistent industry product placement in manuscripts, whether the product is being compared to the standard of care, or is being used in both treatment arms, can potentially have an effect on the surgical practice of a plastic surgeon. For example, if a craniofacial plate produced by a certain industry company repeatedly appears in published manuscripts, a craniofacial surgeon may incorporate that specific industry product into their practice due to its perceived popularity and repeated exposure of the surgeon to the product.

7.4.2. Limitations

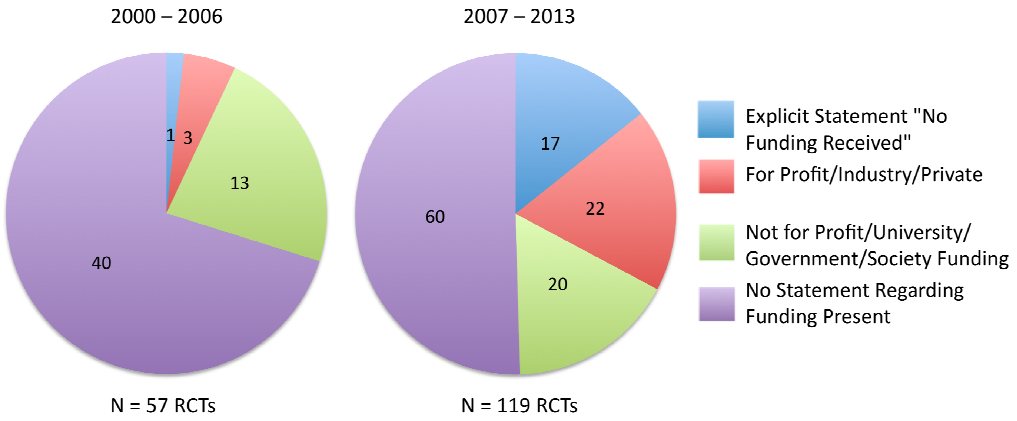
There are two major limitations present in a study assessing trial funding and conflicts of interest. First, both trial funding and conflict of interest are self-reported to the publishing journal and therefore are dependent on the trial authors. It is reasonable to assume that conflicts of interest, and even funding, are more likely to be under-reported (either intentionally or unintentionally) than adequately or over-reported. The second major limitation lies with the journal the surgical RCT was published in. The inclusion of statements within the actual published manuscript regarding i) trial funding, ii) conflicts

of interest, and iii) independent control of data, manuscript contents, and decision to publish lie solely with the editorial staff and the publication protocol of the journal. Together, these two limitations likely led to the under-reporting of trial funding, conflicts of interest and author control of the trial data, manuscript, and publication decision.

7.5. Conclusions

Funding is necessary to successfully complete large RCTs. For profit/industry/private funding appears to have increased over the past 13 years. The benefits of industry funding are apparent when valuable research is supported that could not have been possible otherwise. The findings of previous studies that demonstrated outcomes favourable to the funder[116 119 122] were not clearly seen in this current systematic review. An association between trial funding source and the statistical significance of the trial's primary outcome could not be properly investigated due to the proportion of trials (58%) that did not report any information regarding the presence or absence of trial funding. Reporting of the presence or absence conflicts of interest has greatly improved over the past 13 years, although it remains at only 62% over the last half of this time period (2007-2013). Complete reporting of trial funding, conflicts of interest, and author control over a manuscript and its contents appears to be an achievable goal that both authors and journals can accomplish.

Figure 7.1. Reported Funding Sources of Plastic Surgical RCTs over Time



*Total sum is 176 since 3 trials reported receiving multiple sources of funding

Figure 7.2. Reported Funding Source and Trial Primary Outcome Significance in Plastic Surgical RCTs

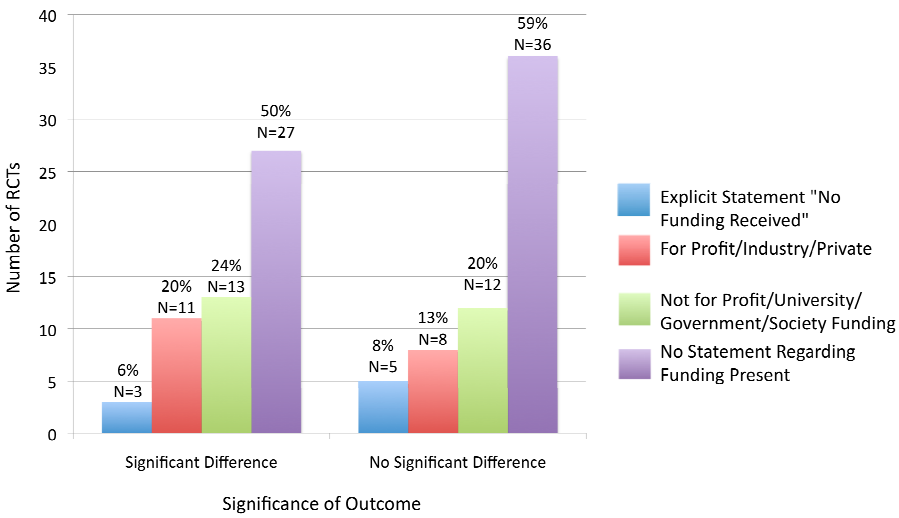


Figure 7.3. Reported Conflicts of Interest in Plastic Surgical RCTs over Time

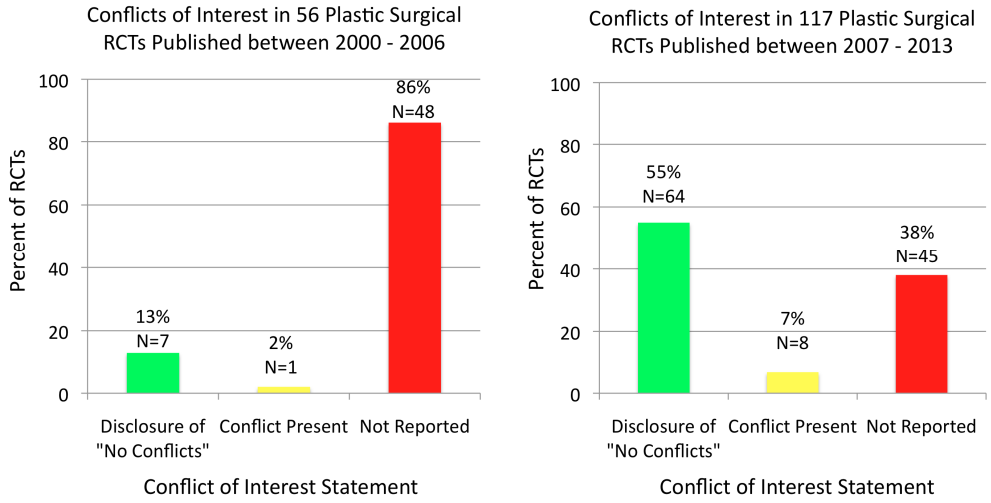


Table 7.1. Type of Funding Reported by 173 Plastic Surgical RCTs

Reported Funding Source	N	Percent
For Profit/Industry/Private	25	14
Not for Profit/University/Government/Society Funding	33	19
Explicit Statement "No Funding Received"	18	10
No Statement Regarding Funding Present	100	58
Total	176*	100

*Total sum is 176 since 3 trials reported receiving multiple sources of funding

Table 7.2. Of Trials Funded by Industry/For Profit/Private, did the Authors have Independent Control of Data, Contents of Manuscript and the Decision to Publish?

Reported Author Statement	N	Percent
Unequivocally yes	6	24
Yes, but authors did not have full control of all aspects	0	0
No statement regarding independent control present	19	76
Total	25	100

Table 7.3. Details on Direction of Primary Outcome Classified by Trial Funding Source in 173 Plastic Surgical RCTs

	Funding Source			
	Profit, Industry, Private	**Non-Profit, University, Government, Society**	**No Funding Received**	**Funding Source not Reported**
Favours Experimental	9 (36%)	9 (27%)	3 (17%)	24 (24%)
Favours Control	2 (8%)	4 (12%)	0	3 (3%)
Experimental/Control group indeterminable	0	0	0	3 (3%)
Non-Significant Result	8 (32%)	12 (36%)	5 (28%)	36 (36%)
No Primary outcome Stated by Authors	6 (24%)	8 (24%)	10 (56%)	34 (34%)
Total*	25 (100%)	33 (99%)**	18 (101%)**	100 (100%)

* Total number of RCTs represented are 173. Numbers add up to 176 because 3 RCTs received multiple sources of funding.
** Percentages do not add up to 100 due to rounding

Table 7.4. Reporting of Conflicts of Interest

Presence of Conflict in All RCTs	**N**	**Percent**
Conflict present	9	5
Statement that no conflicts are present	71	41
Not reported/disclosed	93	54
Total	173	100
Presence of Conflict in Industry Funded Trials	**N**	**Percent**
Conflict present	6	24
Statement that no conflicts are present	10	40
Not reported/disclosed	9	36
Total	25	100
Presence of Conflict in Trials where an Industry Product was Mentioned	**N**	**Percent**
Conflict present	7	7
Statement that no conflicts are present	43	41
Not reported/disclosed	55	52
Total	105	100

Table 7.5. Industry Products in Plastic Surgical RCTs

Mention of the use of an Industry Product as part of an Intervention	**N**	**Percent**
Yes	105	61
No	68	39
Total	173	100
Use of the same Industry Product in each Intervention	**N**	**Percent**
Yes	16	15
No	89	85
Total	105	100
Domain of Plastic Surgery for Trials that mentioned the use of an Industry Product	**N**	**Percent**
Craniofacial Surgery	26	25
Hand/Upper Limb Surgery	23	22
Breast Surgery	19	18
Aesthetic Surgery	17	16
Burn Surgery	12	11
Generalized Cutaneous Disorders	5	5
Facial/Head and Neck Reconstruction	2	2
Trunk, Genital/Pelvic, Lower Limb Reconstruction	1	1
Total	105	100

8. Conclusions

Several reporting deficiencies and methodological challenges in surgical RCTs were identified by this systematic review. It is difficult for readers of plastic surgery literature to assess the validity of trial results if the design and conduct of the trial is not completely and transparently reported. It is important to be able to differentiate trials with a low risk of bias, from those with potentially questionable results. Reinforcement of reporting guidelines among plastic surgery journals may be able to help readers interpret trial results better if factors contributing to risks of bias are clearly described.

The number of plastic surgery RCTs comparing surgical interventions have been increasing over the past 13 years. Certain risks of bias, like surgeon blinding, or outcome assessor blinding for a patient reported outcome, are difficult to minimize. Alternative strategies such as expertise based trials, or duplicate outcome assessment have been proposed as potential solutions. Patient-important primary outcomes are essential to plastic surgery RCTs, and should be explicitly stated within the published manuscript. Most plastic surgical RCTs are not able to recruit a large number of patients. These trials are then viewed with scrutiny, and are potentially dismissed by readers due to the potential of these trials to exaggerate treatment effects. Multicentre, and international collaboration is necessary to conduct and complete large surgical RCTs. The association between industry funding and trial results in favour of the funding source were not seen in this systematic review.

This systematic review uncovered several characteristics of plastic surgery RCTs and establishes a baseline of the quality of evidence that currently guides practice for surgical interventions in plastic and reconstructive surgery. Numerous reporting deficiencies and methodological challenges in surgical RCTs were identified. For the readers of plastic surgery literature to have confidence in the literature, risks of bias should be minimized and transparently reported. This will encourage plastic surgeons to apply the results and findings from published RCTs in their practice, providing patients with the best possible treatments.

9. References

1. Chung KC, Swanson JA, Schmitz D, Sullivan D, Rohrich RJ. Introducing evidence-based medicine to plastic and reconstructive surgery. *Plast Reconstr Surg* 2009;123(4):1385-9.
2. Rohrich RJ, Eaves FF, 3rd. So you want to be an evidence-based plastic surgeon? A lifelong journey. *Plast Reconstr Surg* 2011;127(1):467-72.
3. Swanson JA, Schmitz D, Chung KC. How to practice evidence-based medicine. *Plast Reconstr Surg* 2010;126(1):286-94.
4. Eaves FF, 3rd, Rohrich RJ, Sykes JM. Taking evidence-based plastic surgery to the next level: report of the second summit on evidence-based plastic surgery. *Plast Reconstr Surg* 2013;132(1):227-35.
5. Thoma A, Sprague S, Temple C, Archibald S. The role of the randomized controlled trial in plastic surgery. *Clin Plast Surg* 2008;35(2):275-84.
6. McCarthy CM. Randomized controlled trials. *Plast Reconstr Surg* 2011;127(4):1707-12.
7. Lachin JM. Statistical properties of randomization in clinical trials. *Control Clin Trials* 1988;9(4):289-311.
8. Farrokhyar F, Karanicolas PJ, Thoma A, Simunovic M, Bhandari M, Devereaux PJ, et al. Randomized controlled trials of surgical interventions. *Ann Surg* 2010;251(3):409-16.
9. Tornetta P, 3rd, Pascual M, Godin K, Sprague S, Bhandari M. Participating in multicenter randomized controlled trials: what's the relative value? *J Bone Joint Surg Am* 2012;94 Suppl 1:107-11.
10. Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 1995;118(3):459-67.
11. McCarthy CM, Collins ED, Pusic AL. Where do we find the best evidence? *Plast Reconstr Surg* 2008;122(6):1942-7; discussion 48-51.
12. Chang EY, Pannucci CJ, Wilkins EG. Quality of clinical studies in aesthetic surgery journals: a 10-year review. *Aesthet Surg J* 2009;29(2):144-7; discussion 47-9.
13. Loiselle F, Mahabir RC, Harrop AR. Levels of evidence in plastic surgery research over 20 years. *Plast Reconstr Surg* 2008;121(4):207e-11e.
14. Paradis C. Bias in surgical research. *Ann Surg* 2008;248(2):180-8.
15. Akl EA, Briel M, You JJ, Lamontagne F, Gangji A, Cukierman-Yaffe T, et al. LOST to follow-up Information in Trials (LOST-IT): a protocol on the potential impact. *Trials* 2009;10:40.
16. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *Bmj* 2001;323(7303):42-6.
17. Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2001]*: The Cochrane Collaboration., 2011.

18. Gurusamy KS, Gluud C, Nikolova D, Davidson BR. Assessment of risk of bias in randomized clinical trials in surgery. *Br J Surg* 2009;96(4):342-9.
19. Agha RA, Camm CF, Edison E, Orgill DP. The methodological quality of randomized controlled trials in plastic surgery needs improvement: a systematic review. *J Plast Reconstr Aesthet Surg* 2013;66(4):447-52.
20. Karri V. Randomised clinical trials in plastic surgery: survey of output and quality of reporting. *J Plast Reconstr Aesthet Surg* 2006;59(8):787-96.
21. McCarthy JE, Chatterjee A, McKelvey TG, Jantzen EM, Kerrigan CL. A detailed analysis of level I evidence (randomized controlled trials and meta-analyses) in five plastic surgery journals to date: 1978 to 2009. *Plast Reconstr Surg* 2010;126(5):1774-8.
22. Taghinia AH, Liao EC, May JW, Jr. Randomized controlled trials in plastic surgery: a 20-year review of reporting standards, methodologic quality, and impact. *Plast Reconstr Surg* 2008;122(4):1253-63.
23. Becker A, Blumle A, Antes G, Bannasch H, Torio-Padron N, Stark GB, et al. Controlled trials in aesthetic plastic surgery: a 16-year analysis. *Aesthetic Plast Surg* 2008;32(2):359-62.
24. Huemer GM, Bauer T, Gurunluoglu R, Sakho C, Oehlbauer M, Dunst KM. Analysis of publications in three plastic surgery journals for the year 2002. *Plast Reconstr Surg* 2004;114(5):1147-54.
25. Momeni A, Becker A, Antes G, Diener MK, Blumle A, Stark GB. Evidence-based plastic surgery: controlled trials in three plastic surgical journals (1990-2005). *Ann Plast Surg* 2008;61(2):221-5.
26. Bhandari M, Busse JW, Jackowski D, Montori VM, Schunemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *Cmaj* 2004;170(4):477-80.
27. Gummesson C, Atroshi I, Ekdahl C. The quality of reporting and outcome measures in randomized clinical trials related to upper-extremity disorders. *J Hand Surg Am* 2004;29(4):727-34; discussion 35-7.
28. Veiga Filho J, Castro AA, Veiga DF, Juliano Y, Castilho HT, Rocha JL, et al. Quality of reports of randomized clinical trials in plastic surgery. *Plast Reconstr Surg* 2005;115(1):320-3.
29. Veiga DF, Veiga-Filho J, Pellizzon RF, Juliano Y, Ferreira LM. Evolution of reports of randomised clinical trials in plastic surgery. *J Plast Reconstr Aesthet Surg* 2011;64(6):703-9.
30. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression--an overview and meta-analysis of randomised clinical trials. *Bmj* 1996;313(7052):253-8.
31. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.
32. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928.

33. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6(7):e1000100.
34. PROSPERO. National Institute for Health Reserach, National Health Service.
35. Rohrich RJ, Sullivan D. The role of the journal impact factor: choosing the optimal source of peer-reviewed plastic surgery information. *Plast Reconstr Surg* 2006;117(7):2495-8.
36. Dong P, Loh M, Mondry A. The "impact factor" revisited. *Biomed Digit Libr* 2005;2:7.
37. Labanaris AP, Vassiliadu AP, Polykandriotis E, Tjiawi J, Arkudas A, Horch RE. Impact factors and publication times for plastic surgery journals. *Plast Reconstr Surg* 2007;120(7):2076-81.
38. Lefebvre C, Manheimer E, Glanville J. *Chapter 6: Searching for studies*. Version 5.1.0 [updated March 2011] ed: The Cochrane Collaboration, 2011.
39. DistillerSR. http://systematic-review.net [program], 2013.
40. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-74.
41. von Elm E, Poglia G, Walder B, Tramer MR. Different patterns of duplicate publication: an analysis of articles used in systematic reviews. *Jama* 2004;291(8):974-80.
42. Davis Sears E, Burns PB, Chung KC. The outcomes of outcome studies in plastic surgery: a systematic review of 17 years of plastic surgery research. *Plast Reconstr Surg* 2007;120(7):2059-65.
43. Berwanger O, Ribeiro RA, Finkelsztejn A, Watanabe M, Suzumura EA, Duncan BB, et al. The quality of reporting of trial abstracts is suboptimal: survey of major general medical journals. *J Clin Epidemiol* 2009;62(4):387-92.
44. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;63(8):e1-37.
45. Barbour V, Chinnock P, Cohen B, Yamey G. The impact of open access upon public health. *Bull World Health Organ.* 2006;63(8):e1-37.
46. Thoma A. Challenges in creating a good randomized controlled trial in hand surgery. *Clin Plast Surg* 2005;32(4):563-73, vii.
47. Duley L, Antman K, Arena J, Avezum A, Blumenthal M, Bosch J, et al. Specific barriers to the conduct of randomized trials. *Clin Trials* 2008;5(1):40-8.
48. Chung KC, Burns PB. A guide to planning and executing a surgical randomized controlled trial. *J Hand Surg Am* 2008;33(3):407-12.
49. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Croat Med J* 2004;45(5):531-2.
50. Rohrich RJ, Longaker MT. Registering clinical trials in plastic and reconstructive surgery. *Plast Reconstr Surg* 2007;119(3):1097-9.
51. Dickersin K, Rennie D. Registering clinical trials. *Jama* 2003;290(4):516-23.

52. Karounis H, Gouin S, Eisman H, Chalut D, Pelletier H, Williams B. A randomized, controlled trial comparing long-term cosmetic outcomes of traumatic pediatric lacerations repaired with absorbable plain gut versus nonabsorbable nylon sutures. *Acad Emerg Med* 2004;11(7):730-5.
53. Luck RP, Flood R, Eyal D, Saludades J, Hayes C, Gaughan J. Cosmetic outcomes of absorbable versus nonabsorbable sutures in pediatric facial lacerations. *Pediatr Emerg Care* 2008;24(3):137-42.
54. Slim K. Limits of evidence-based surgery. *World J Surg* 2005;29(5):606-9.
55. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol* 2011;64(4):407-15.
56. Methodological quality and treatment effects in randomized trials: a review of six empirical studies. . 12th Cochrane Colloquium; 2004; Ottawa, Ontario.
57. Gluud LL. Bias in clinical intervention research. *Am J Epidemiol* 2006;163(6):493-501.
58. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *Bmj* 2008;336(7644):601-5.
59. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002;359(9306):614-8.
60. Pildal J, Hrobjartsson A, Jorgensen KJ, Hilden J, Altman DG, Gotzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol* 2007;36(4):847-57.
61. Altman DG, Schulz KF. Statistics notes: Concealing treatment allocation in randomised trials. *Bmj* 2001;323(7310):446-7.
62. Poolman RW, Struijs PA, Krips R, Sierevelt IN, Marti RK, Farrokhyar F, et al. Reporting of outcomes in orthopaedic randomized trials: does blinding of outcome assessors matter? *J Bone Joint Surg Am* 2007;89(3):550-8.
63. Karanicolas PJ, Bhandari M, Taromi B, Akl EA, Bassler D, Alonso-Coello P, et al. Blinding of outcomes in trials of orthopaedic trauma: an opportunity to enhance the validity of clinical trials. *J Bone Joint Surg Am* 2008;90(5):1026-33.
64. Devereaux PJ, Choi PT, El-Dika S, Bhandari M, Montori VM, Schunemann HJ, et al. An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. *J Clin Epidemiol* 2004;57(12):1232-6.
65. Chan S, Bhandari M. The quality of reporting of orthopaedic randomized trials with use of a checklist for nonpharmacological therapies. *J Bone Joint Surg Am* 2007;89(9):1970-8.
66. Akl EA, Sun X, Busse JW, Johnston BC, Briel M, Mulla S, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65(3):262-7.

67. Akl EA, Briel M, You JJ, Sun X, Johnston BC, Busse JW, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. *Bmj* 2012;344:e2809.
68. Farrokhyar F, Bajammal S, Kahnamoui K, Bhandari M. Practical tips for surgical research. Ensuring balanced groups in surgical trials. *Can J Surg* 2009;53(6):418-23.
69. Sprague S, Leece P, Bhandari M, Tornetta P, 3rd, Schemitsch E, Swiontkowski MF. Limiting loss to follow-up in a multicenter randomized trial in orthopedic surgery. *Control Clin Trials* 2003;24(6):719-25.
70. Montori VM, Guyatt GH. Intention-to-treat principle. *Cmaj* 2001;165(10):1339-41.
71. Alshurafa M, Briel M, Akl EA, Haines T, Moayyedi P, Gentles SJ, et al. Inconsistent definitions for intention-to-treat in relation to missing outcome data: systematic review of the methods literature. *PLoS One* 2012;7(11):e49163.
72. Hutton J, Williamson P. Bias in meta-analysis due to outcome variable selection within studies. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 2000;49(3):359-70.
73. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *Jama* 2004;291(20):2457-65.
74. SAS Softward [program]. 9.1 version.
75. *Chapter 9.4: The Principle of Intention to Treat. User Guides to the Medical Literature. A Manual for Evidence-Based Clinical Practice*. 2 ed. New York: McGraw Hill, 2008.
76. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama* 1995;273(5):408-12.
77. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352(9128):609-13.
78. Savovic J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med* 2012;157(6):429-38.
79. Boutron I, Tubach F, Giraudeau B, Ravaud P. Blinding was judged more difficult to achieve and maintain in nonpharmacologic than pharmacologic trials. *J Clin Epidemiol* 2004;57(6):543-50.
80. Noseworthy JH, Ebers GC, Vandervoort MK, Farquhar RE, Yetisir E, Roberts R. The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. *Neurology* 1994;44(1):16-20.
81. Devereaux PJ, Bhandari M, Clarke M, Montori VM, Cook DJ, Yusuf S, et al. Need for expertise based randomised controlled trials. *Bmj* 2005;330(7482):88.
82. Schulz KF, Grimes DA, Altman DG, Hayes RJ. Blinding and exclusions after allocation in randomised controlled trials: survey of published parallel group trials in obstetrics and gynaecology. *Bmj* 1996;312(7033):742-4.

83. Huwiler-Muntener K, Juni P, Junker C, Egger M. Quality of reporting of randomized trials as a measure of methodologic quality. *Jama* 2002;287(21):2801-4.
84. Hill CL, LaValley MP, Felson DT. Discrepancy between published report and actual conduct of randomized clinical trials. *J Clin Epidemiol* 2002;55(8):783-6.
85. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. *Bmj* 2005;330(7499):1049.
86. Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J, et al. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* 2009;339:b4012.
87. Slobogean GP, Sprague S, Bhandari M. The tactics of large randomized trials. *J Bone Joint Surg Am* 2012;94 Suppl 1:19-23.
88. Ching S, Rockwell G, Thoma A, Antony MM. Clinical research in aesthetic surgery. *Clin Plast Surg* 2008;35(2):269-73.
89. Alderman A, Chung KC. Measuring outcomes in aesthetic surgery. *Clin Plast Surg* 2013;40(2):297-304.
90. Lemaine V, McCarthy C. Measuring outcomes in breast surgery. *Clin Plast Surg* 2013;40(2):331-9.
91. Giladi AM, Chung KC. Measuring outcomes in hand surgery. *Clin Plast Surg* 2013;40(2):313-22.
92. Momoh AO, Chung KC. Measuring outcomes in lower limb surgery. *Clin Plast Surg* 2013
;40(2):323-9.
93. Wong KW, Forrest CR, Goodacre TE, Klassen AF. Measuring outcomes in craniofacial and pediatric plastic surgery. *Clin Plast Surg* 2013;40(2):305-12.
94. Bala MM, Akl EA, Sun X, Bassler D, Mertz D, Mejza F, et al. Randomized trials published in higher vs. lower impact journals differ in design, conduct, and analysis. *J Clin Epidemiol* 2013;66(3):286-95.
95. Lubsen J, Kirwan BA. Combined endpoints: can we use them? *Stat Med* 2002;21(19):2959-70.
96. Chung KC, Burns PB, Davis Sears E. Outcomes research in hand surgery: where have we been and where should we go? *J Hand Surg Am* 2006;31(8):1373-9.
97. Chung KC, Pusic AL. Patient-reported outcomes instruments. Outcomes measures in Plastic Surgery. *Clin Plast Surg* 2013;40(2):xi-xii.
98. Gillgren P, Drzewiecki KT, Niin M, Gullestad HP, Hellborg H, Mansson-Brahme E, et al. 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. *Lancet* 2011;378(9803):1635-42.
99. Saffle JR, Morris SE, Edelman L. Early tracheostomy does not improve outcome in burn patients. *J Burn Care Rehabil* 2002;23(6):431-8.
100. Stanley K. Design of randomized controlled trials. *Circulation* 2007;115(9):1164-9.
101. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011;64(4):395-400.

102. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plast Reconstr Surg* 2009;124(2):345-53.
103. Cano SJ, Klassen AF, Scott AM, Cordeiro PG, Pusic AL. The BREAST-Q: further validation in independent clinical samples. *Plast Reconstr Surg* 2012;129(2):293-302.
104. Pusic AL, Klassen AF, Scott AM, Cano SJ. Development and psychometric evaluation of the FACE-Q satisfaction with appearance scale: a new patient-reported outcome instrument for facial aesthetics patients. *Clin Plast Surg* 2013;40(2):249-60.
105. Karanicolas PJ, Bickenbach K, Jayaraman S, Pusic AL, Coit DG, Guyatt GH, et al. Measurement and interpretation of patient-reported outcomes in surgery: an opportunity for improvement. *J Gastrointest Surg* 2011;15(4):682-9.
106. Farrokhyar F, Reddy D, Poolman RW, Bhandari M. Why perform a priori sample size calculation? *Can J Surg* 2013;56(3):207-13.
107. Ayeni O, Dickson L, Ignacy TA, Thoma A. A systematic review of power and sample size reporting in randomized controlled trials within plastic surgery. *Plast Reconstr Surg* 2012;130(1):78e-86e.
108. Chung KC, Kalliainen LK, Spilson SV, Walters MR, Kim HM. The prevalence of negative studies with inadequate statistical power: an analysis of the plastic surgery literature. *Plast Reconstr Surg* 2002;109(1):1-6; discussion 7-8.
109. Cadeddu M, Farrokhyar F, Levis C, Cornacchi S, Haines T, Thoma A. Users' Guide to the Surgical Literature. Understanding confidence intervals. *Can J Surg* 2012;55(3):207-11.
110. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001;135(11):982-9.
111. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Control Clin Trials* 1981;2(2):93-113.
112. Levine M, Ensom MH. Post hoc power analysis: an idea whose time has passed? *Pharmacotherapy* 2001;21(4):405-9.
113. Montori VM, Kleinbart J, Newman TB, Keitz S, Wyer PC, Moyer V, et al. Tips for learners of evidence-based medicine: 2. Measures of precision (confidence intervals). *Cmaj* 2004;171(6):611-5.
114. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *Jama* 2010;303(12):1180-7.
115. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *Bmj* 2002;324(7351):1448-51.
116. Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. *Bmj* 2002;325(7358):249.

117. Clifford TJ, Barrowman NJ, Moher D. Funding source, trial outcome and reporting quality: are they related? Results of a pilot study. *BMC Health Serv Res* 2002;2(1):18.
118. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. *Lancet* 2000;356(9230):635-8.
119. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Bmj* 2003;326(7400):1167-70.
120. Davidson RA. Source of funding and outcome of clinical trials. *J Gen Intern Med* 1986;1(3):155-8.
121. Kulkarni AV, Busse JW, Shams I. Characteristics associated with citation rate of the medical literature. *PLoS One* 2007;2(5):e403.
122. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *Jama* 2003;290(7):921-8.
123. Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, et al. The influence of study characteristics on reporting of subgroup analyses in randomised controlled trials: systematic review. *Bmj* 2011;342:d1569.
124. Momeni A, Becker A, Bannasch H, Antes G, Blumle A, Stark GB. Association between research sponsorship and study outcome in plastic surgery literature. *Ann Plast Surg* 2009;63(6):661-4.
125. Gotzsche PC, Hrobjartsson A, Johansen HK, Haahr MT, Altman DG, Chan AW. Constraints on publication rights in industry-initiated clinical trials. *Jama* 2006;295(14):1645-6.
126. Rohrich RJ. Full disclosure: conflict of interest in scientific publications. *Plast Reconstr Surg* 2006;118(7):1649-52.
127. Flanagin A, Fontanarosa PB, DeAngelis CD. Update on JAMA's conflict of interest policy. *Jama* 2006;296(2):220-1.
128. Clapham PJ, Chung KC. A systematic review of the relationship between plastic surgery and the medical industry. *Plast Reconstr Surg* 2010;126(3):1098-105.

10. Appendix A

Surgical Randomized Controlled Trials: Challenges and Opportunities for Evidence Based Plastic Surgery
Systematic Review Protocol

Protocol Information:

Authors: Sophocles Voineskos[a], Natalia Ziolkowski[b], Maureen Meade[c], Jason Busse[c], Achilleas Thoma[acd], Mohit Bhandari[cde]

[a] Department of Surgery, Division of Plastic and Reconstructive Surgery, McMaster University, Hamilton, Ontario, Canada

[b] Medical University of Warsaw, Warsaw, Poland

[c] Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

[d] Surgical Outcomes Research Centre (SOURCE), McMaster University, Hamilton, Ontario, Canada

[e] Department of Surgery, Division of Orthopaedic Surgery, McMaster University, Hamilton, Ontario, Canada

Background and Rational for Review

Surgery is entrenched in a tradition of "treating patients with practices based on rigidly held protocols learned in residency training or opinions presented by leaders in the field". In July of 2010, the Editor-in-Chief of the highest impact plastic surgery journal, *Plastic and Reconstructive Surgery* along with several specialty journal editors and Association presidents met to put forth a challenge to the surgical community "*We invite, encourage, and challenge you to join with us to make Evidence-Based Medicine (EBM) part of our culture. Plastic surgery has the opportunity to take a leading role in transforming medicine through EBM, and we personally solicit your involvement and help in this movement.*"[1] In the summer of 2012, a second summit took place bringing together leaders from plastic surgery organizations, societies, boards, journals and foundations. It was determined that an effort was needed to advance EBM in plastic surgery, which would improve the quality of care and patient safety.

The quality of randomized contolled trials (RCTs) in plastic surgery has been assessed in different ways[2-6], but most commonly, quality of reporting is evaluated. These studies assessed RCTs from various sources (4 studies only looked at 3 journals: *PRS, BJPRS, APS,* 1 study performed their search using CCTR, EMBASE, MEDLINE and LILACS) over different time frames (1980-2004, 1990-2005, 1986-2006, 1984-2008, 1978-2009). These studies used one, or a combination, of the following scales to assess quality of reporting: Jadad scale, CONSORT checklist, Delphi list, or other scales developed by the authors (blinding, intention-to-treat, allocation concealment). Most studies commented on the poor quality of reporting and most have the same conclusion

"more high quality RCTs are needed in Plastic Surgery". It is important to note that there is inconsistency and unpredictability when associating different scales with intervention effect estimates[7]. Scores obtained from certain quality scales when appraising clinical trials amalgamate quality of reporting with facets of trial conduct and weight scores in a manner that is difficult to justify[7]. Therefore, examining the influence of key components of methodological quality individually is preferable[8].

This study is unique in that it will be a rigorously conducted systematic review assessing RCTs that involve a surgical intervention with a view to understanding the challenges that are unique to plastic surgeons when conducting an RCT addressing surgical interventions. "Clinically and statistically, randomization is the single characteristic that most sharply distinguishes the controlled trial from other forms of scientific investigation in medicine"[9]. The information and conclusions from this analysis will be used to develop practical suggestions and a framework of essential features that investigators can utilize when conducting RCTs in plastic surgery. If successful, this can address shortcomings found in the literature in a positive and meaningful way, and will help improve surgical research carried out by plastic surgeons.

This protocol describes a scoping systematic review of all randomized controlled trials (RCTs) involving surgical interventions for plastic surgery conditions published in 25 journals (20 plastic surgery relevant journals, 4 major medical journals and the surgical journal with the highest impact factor rating) from 2000-2012. Within this systematic review, an assessment of the methodological safeguards in plastic surgery trials will be performed. Specifically, an evaluation of risks of bias, issues involving

sample sizes and outcome measures, and practical challenges will be undertaken.

Purpose:

To evaluate the plastic surgery literature by examining predictors of quality of randomized controlled trials for surgical interventions in plastic surgery.

Methods

Criteria for Selecting Studies for this Review:

Types of studies: Nonpharmaceutical randomized controlled trials that compare one plastic surgical intervention (or component/part thereof) to another plastic surgical intervention, published between January 1, 2000 and present day.

Types of interventions: Any plastic surgical intervention, with a surgical intervention being defined as "any procedure that involves cutting, abrading, suturing or physically changing body tissues". To be considered a "plastic" surgical intervention, the procedure needed to able to be classified into one of the nine topics within the field of plastic surgery, see Appendix 1.

Types of outcome measures:

1. Assessment of Risks of Bias

    a) Generation of allocation sequence

    b) Concealment of allocation

    c) Blinding

    d) Loss to follow-up and adherence to ITT

    e) Selective outcome reporting

    f) Other potential sources of bias

2. Sample Size issues in Plastic Surgery: P-Value fragility

3. Choices and Selection of Outcome measures

    a) Use of Patient important outcome

    b) Use of Minimal Clinically Important Difference

4. Consideration of Surgical Learning Curve

5. Consideration of Surgical Expertise

6. Standardization of Surgical Procedure

7. Challenges authors had with Patient Recruitment

8. Surgeons and Patients' Preferences

9. Economic Considerations

Search Methods for Identification of Studies:

Electronic Searches:

A search of the electronic database Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Present) will be performed with the assistance of a McMaster University Medical Librarian to identify relevant RCTs (see Appendix 2 for planned search strategy) in 25 journals (see Appendix 3 for full list of journals). No language restrictions will be used. A final "updating" search will be performed in December 2012.

Searching Other Resources:

A search of grey literature is not necessary for this review since the goal is to assess RCTs already published in the 4 major medical journals, the highest impact surgical journal and 20 plastic surgery pertinent journals. All 25 journals assessed for this

review are fully indexed in the database Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Present). This was confirmed with a McMaster University Medical Librarian.

Data Collection and Analysis

Selection of Studies:

Two reviewers (SV and NZ) will independently read retrieved titles and abstracts and assess them for potential relevance. Any trial considered potentially relevant by either reviewer will be obtained in full for complete assessment. To be considered potentially relevant, the title and abstract of the article will have to (1) appear to be describing a nonpharmaceutical randomized controlled trials that is comparing one plastic surgical intervention (or component/part thereof) to another plastic surgical intervention, (2) be able to be classified into one of the nine topics within the field of plastic surgery, (3) be published between January 1 2000, and 2012, (4) be published in one of the 25 journals (See Appendix 3) decided upon *a priori* and (5) have the word random (or variation of) in the title, abstract section, or Ovid extended reference of the manuscript.

For a full text article to be included for data extraction and assessment, the article has to (1) have it's status as a nonpharmaceutical trial comparing one surgical procedure (or component/part of one) to another surgical procedure, for a plastic surgical problem, performed on patients in an operating room, confirmed by both reviewers, (2) have the topic within the field of plastic surgery it was classified into confirmed by both reviewers, and (3) refer to the process of patient allocation as being random (or a variation of the word "random").

N.B. Trials will be included for analysis even if the randomization process was not performed to the highest standard (e.g. randomization schedule by date or patient chart number). Article authorship (e.g affiliation with a plastic surgery department) is not relevant to inclusion or exclusion.

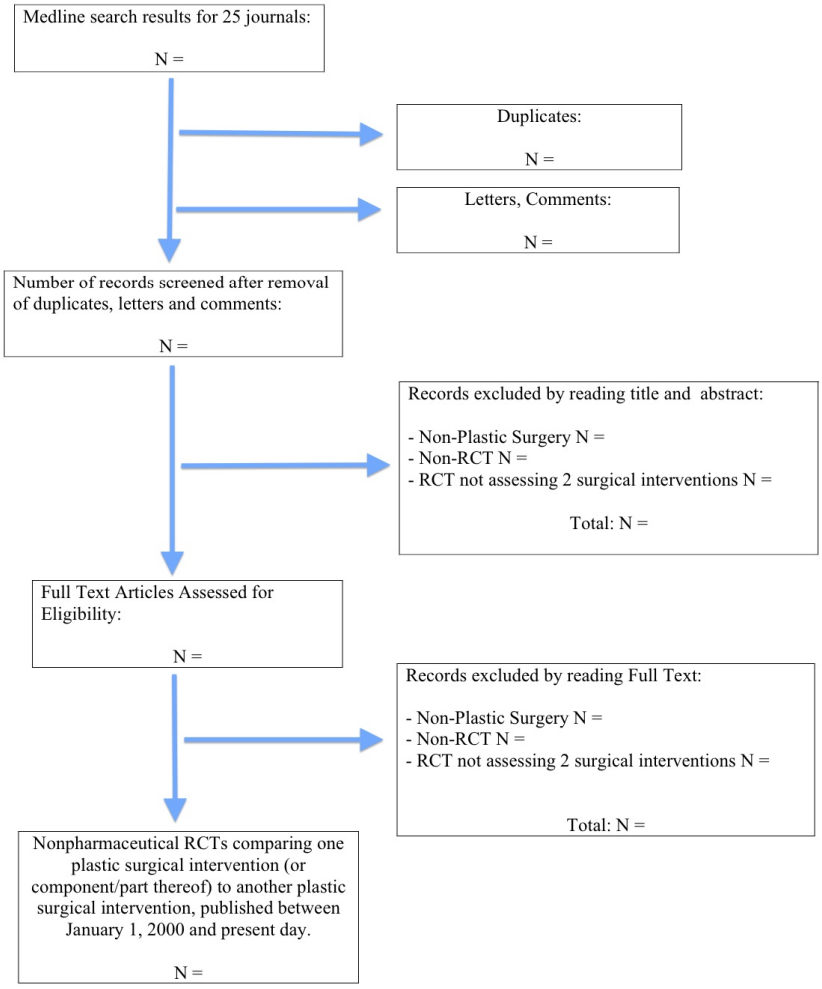
Exclusion Criteria:

Articles that will be excluded are: (1) systematic reviews, meta-analyses, observational studies, economic analyses based on RCTs, RCTs of diagnostic tests, (2) case reports, case series, abstracts, meeting proceedings, articles summarizing results of a previous study, any letter to an editor or correspondence whether or not results from an RCT are described within, (3) retrospective analyses of RCT data (4) a procedure that falls out of the domain of a plastic surgeon e.g. repair of tympanic membrane perforation, tonsillectomy, thyroidectomy, removal of submandibular hilar stone, dacryocrstorhinostomy, surgeries for sleep-disordered breathing. (5) physiotherapy, manipulation, ultrasound, dressings, regular application of cream/spray etc, or acupuncture, (6) any medication e.g. antibiotic, anesthetic or other that is administered outside the operating room or can be administered by the Anesthesia team, or injections (including nerve blocks) administered by the surgeon just before or just after the surgery (medicated irrigation, antibiotic impregnated gauzes, sprays etc. that are administered by the surgeon as part of the operation will not be excluded), (7) animal, cadaver, basic science studies, (8) an experimental procedure on a human (like administering an incision on a healthy patient), and (9) a biopsy or fine needle aspiration.

A chance-corrected agreement (κ statistic) and chance-independent agreement (ϕ statistic) will be performed on the inter-reviewer agreement for trial inclusion after independent full text assessment by each reviewer. If there is disagreement among reviewers in the potential relevance of a trial, a detailed discussion will follow. If further discussion is necessary, an arbitrator (AT) will be consulted for a deciding opinion.

Flow Diagram of Study Selection

Figure 1. Flow diagram of study selection.



Data Collection and Analysis:

Data Extraction and Management:

Data extraction will be performed individually be each reviewer (SV and NZ) using data extraction forms created *a priori*. Initially, each reviewer will individually perform data extraction on the same set of 5 papers, which will be chosen randomly. The data extracted will be reviewed and the process will be discussed in detail for the purpose of creating a "training set" of papers. After the completion of the "training set", the rest of the RCTs will be reviewed and assessed in random order as dictated by a computer-generated sequence. Discrepancies between extracted data will resolved through discussion between the reviewers. An arbitrator (AT) will be available if required.

The data extraction forms will be uploaded into the software program DistillerSR with the help of Lisa Buckingham, and thus will be performed electronically. Dr. J. Busse has created 2 licenses for the DistillerSR software, 1 for reviewer SV, and 1 for reviewer NZ. Author SV has been assigned as the Full Project Administrator, while Lisa Buckingham, Dr. J. Busse and author NZ all have access to the project account.

The following information will be recorded:

1. Trial Details:

a) Journal of publication

b) Country of origin

c) Topic within the field of plastic surgery

d) Number of centres involved

e) Involvement of a biostatistician – either an author or thanked

f) Funding received

2. Assessment of Risks of Bias using the Risk of Bias Tool

a) Generation of allocation sequence

b) Concealment of allocation

c) Blinding

d) Loss to follow-up and adherence to ITT

e) Selective outcome reporting

f) Other potential sources of Bias

3. Sample Size issues in Plastic Surgery: P-Value fragility using Dr. Walsh and Dr. Devereaux's Fragility Index

4. Choices and Selection of Outcome measures

a) Use of Patient important outcome

b) Use of Minimal Clinically Important Difference

5. Consideration of the Surgical Learning Curve

6. Consideration of Surgical Expertise

7. Standardization of Surgical Procedure

8. Challenges authors report with Patient Recruitment

9. Inclusion of Economic Analysis within the RCT

Assessment of Risk of Bias in Included Studies:

An assessment of each individual study's risk of bias will be performed. Information on allocation sequence generation, allocation concealment, blinding of patients and trial team members, loss to follow-up, selective outcome reporting, other

possible bias, and whether intention-to-treat analysis was used will be recorded and managed using Review Manager 5.1[10]. Dr. G. Guyatt's Tool to Assess Risk of Bias in Randomized Controlled Trials[11] will be used to judge and rate the risk of bias between 'low risk' and 'high risk' (see Appendix 4).

Statistic/Analysis Items to be Addressed:

Will any type of regression analysis add value to this project? (e.g. associating effect size with certain Risks of Bias). If so, this project will need to be powered to be able perform a regression analysis (approximately 10 trials for every outcome that will be addressed). However, I find this analysis problematic since the assumption is that the direction of bias is always the same when performing this type of regression. Furthermore, "right or wrong" cannot be proven, only "differences" can be demonstrated.

Dealing with Missing Data:

It is suspected that a potentially significant amount of information regarding our outcome measures will be missing. This is related to the quality of reporting of trials. When potentially relevant data is missing then it will be reported as such in relevant Figures and the Results. The potential impact of missing data on the findings of this review will be addressed in the Discussion section[12]. Contacting original investigators for missing data is be out of the scope of this review.

Assessment of Heterogeneity:

While assessment of heterogeneity is valuable for systematic reviews and meta-analyses assessing interventions for one clinical problem, this systematic review is a scoping review and thus clinical heterogeneity (variability in the participants,

interventions and outcomes studied) is expected. Methodological heterogeneity in terms of variability of study design should be minimal since all studies must be RCTs comparing 2 (or more) surgical interventions for a plastic surgical problem. Methodological heterogeneity in terms of variability in risk of bias will be assessed and recorded with Dr. G. Guyatt's Risk of Bias Tool[11] as described above.

Assessment of Reporting Biases:

Assessment of Publication bias with the traditional funnel plot is not possible since this is a scoping review and the RCTs will have been performed on various interventions. Therefore it may not be possible to gauge whether these published studies are a true representation of all valid studies undertaken. Realistically, however, due to the paucity of surgical RCTs in plastic surgery, it is likely that any RCT submitted to a plastic surgery journal will be published, whether the results are positive, negative, or inconclusive. As this systematic review is assessing surgical RCTs that have already been published in 25 specific journals the following types of reporting bias: Multiple publication bias, Citation bias and Language bias, are not applicable. Outcome Reporting bias can be assessed by comparing the original RCT protocol with the final published manuscript. Location bias is not relevant to this study, as only RCTs published within the 25 pre-specified journals are pertinent.

Data Synthesis:

Electronic search results will be organized and managed with Refworks 2.0[13]. Statistical analyses for chance-corrected agreement (κ statistic) will performed by hand. Chance-independent agreement (ϕ statistic) will be calculated by hand using the

formula[14]: $\phi = (\sqrt{OR} - 1)/(\sqrt{OR} + 1)$. Data will be synthesized and presented using Review Manager 5.1[10].

Subgroup Analyses:

The following subgroup analyses will be performed qualitatively if possible:

1) RCTs involving aesthetic surgery versus burn surgery versus non-aesthetic and non-burn surgery
2) Plastic surgery RCTs published in the 20 plastics surgery specific journals versus plastic surgery RCTs published in NEJM, The Lancet, JAMA, Annals of Internal Medicine and Annals of Surgery
3) Plastic surgery RCTs where one, or more, authors have an affiliation with a plastic surgery department versus plastic surgery RCTs where none of the authors have an affiliation with a plastic surgery department

Sensitivity Analysis:

A sensitivity analysis between RCTs that performed randomization properly versus those that did not will be undertaken. Other issues suitable for sensitivity analyses will likely arise during the review process when the "individual peculiarities of the studies under investigation are identified."[17]

Potential Tables:

Table 1: Journal of Publication (frequency and %)

Table 2: Country of Origin (frequency and %)

Table 3: Topic within field of Plastic Surgery (frequency and %)

Table 4: Characteristics of RCTs
- Number of centres involved
- Involvement of a biostatistician
- Funding received
- Consideration of Surgical Learning Curve
- Consideration of Surgical Expertise
- Standardization of Surgical Procedure

Table 5: P-Value Fragility specific table:
- Sample Size
- Number of outcome events
- Reported p-value
- Included outcome

Potential Figures:

Figure 1: Flow diagram of study selection (as existing in body above)

Figure 2: Figure of RCTs published per year – Bar graph

Figure 3: Risk of Bias diagram for all RCTs

Figure 4: Flow diagram of study eligibility for P-Value fragility analysis

Figure 5: Calculation of Fragility Index table

Figure 6: Distribution of Fragility Index for all trials

Figure 7: a) Fragility Index by trial sample size
b) Fragility Index by total number of events

Planned contributions of authors for Final Manuscript:

Sophocles Voineskos: Primary author, reviewer

Natalia Ziolkowski: Co-author reviewer

Maureene Meade: Advisor, Editor

Jason Busse: Advisor, Editor

Achilleas Thoma: Co-author, supervisor

Mohit Bhandari: Co-author, supervisor

Special Thanks:

Laura Banfield – McMaster Medical Librarian

Lisa Buckingham - DistillerSR

Declarations of interest: No conflicts of interest

Sources of support: This study is being supported through an Award from the Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare Hamilton.

References

1. Rohrich RJ, Eaves FF III. So You Want to be an Evidence-Based Plastic Surgeon? A Lifelong Journey. *PRS*. 127(1), 467-472. 2011.

2. Karri V. Randomised clinical trials in plastic surgery: Survey of output and quality of reporting. *JPRAS*. 59, 787-796. 2006.

3. Taghinia AH, Liao EC, May JW Jr. Randomized Controlled Trials in Plastic Surgery: A 20-Year Review of Reporting Standards, Methodologic Quality, and Impact. *PRS*. 122(4), 1253-1263. 2007.

4. Momeni A, Becker A, Antes G, Diener M, Bluemle A, Stark BG. Evidence-Based Plastic Surgery Controlled Trials in Three Plastic Surgical Journals (1990 to 2005). *Annals of Plastic Surgery*. 62(3), 293-296. 2009.

5. McCarthy JE, Chatterjee A, McKelvey TG, Jantzen EMG, Kerrigan CL. A detailed analysis of level I evidence (randomized controlled Trials and Meta-Analyses) in Five Plastic Surgery Journals to Date: 1978-2009. *PRS*. 126(5), 1774-1778. 2010.

6. Veiga DF, Veiga-Filho J, Pellizzon RF, Juliano Y, Ferreira LM. Evolution of reports of randomized clinical trials in plastic surgery. *JPRAS*. 64, 703-709. 2011.

7. Higgins JPT, Altman DG, G∅tzsche PC *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ*. 343:d5928. 2011.

8. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ*. 323, 42-46. 2001.

9. Lachin JM. Statistical Properties of Randomization in Clinical Trials. *CCT*. 9, 289-311. 1988.

10. Review Manager (RevMan) [Computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

11. Personal correspondence with Dr. G. Guyatt.

12. http://www.cochrane-handbook.org/ Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 Section 16.1.2

13. www.refworks-cos.com

14. Meade MO, Cook RJ, Guyatt GH, Groll R, Kachura JR, Bedard M, Cook DJ, Slutsky AS, Stewart TE. Interobserver variation in interpreting chest radiographs for the diagnosis

of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 161, 85-90. 2000.

15. http://www.cochrane-handbook.org/ Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 Section 9.7

16. Sears ED, Burns PB, Chung KC. Outcomes of Outcome Studies in Plastic Surgery: A Systematic Review of 17 Years of Plastic Surgery Research. *PRS*. 120(7), 2059-2065. 2007.

Appendix 1

Nine topics within the field of Plastic Surgery from Chung, 2007[16]

1. Facial/head and neck reconstruction

2. Craniofacial surgery

3. Hand/upper extremity surgery

4. Breast surgery

5. Trunk reconstruction

6. Lower extremity surgery

7. Genital/pelvic reconstruction

8. Aesthetic surgery/body contouring

9. Generalized cutaneous disorders/burns

Appendix 2

1. randomized controlled trial/
2. Randomized Controlled Trials as Topic/
3. randomized controlled trial*.mp.
4. randomised controlled trial*.mp.
5. Random Allocation/
6. random allocation*.mp.
7. randomized experimental trial*.mp.
8. randomised experimental trial*.mp.
9. controlled clinical trial/
10. controlled clinical trial*.mp.
11. Clinical Trial/
12. clinical trial*.mp.
13. experimental trial*.mp.
14. Single-Blind Method/
15. Clinical Trials as Topic/
16. Double-Blind Method/
17. randomized controlled trial.pt.
18. clinical trial.pt.
19. or/1-18

Appendix 3

ISI Web of Knowledge Journal Citation Reports, obtained January 2012
IF = Impact Factor

Highest Impact Medical Journals:

1. New England Journal of Medicine	2010 IF: 53.486
2. The Lancet	2010 IF: 33.633
3. Journal of the American Medical Association	2010 IF: 30.011
4. Annals of Internal Medicine	2010 IF: 16.729

Highest Impact Surgical Journal:

5. Annals of Surgery	2010 IF: 7.474

Journals Pertinent to Plastic and Reconstructive Surgery (Rohrich 2006):

6. Transplantation International	2010 IF: 3.211
7. Plastic and Reconstructive Surgery	2010 IF: 2.647
8. Clinical Transplantation	2010 IF: 1.751
9. Journal of Plastic Reconstructive and Aesthetic Surgery (formerly known as British Journal of Plastic Surgery)	2010 IF: 1.660
10. Otolaryngology Head and Neck Surgery	2010 IF: 1.565
11. Journal of Cranio-Maxillofacial Surgery	2010 IF: 1.540
12. Journal of Hand Surgery-American Volume	2010 IF: 1.439
13. International Journal of Oral and Maxillofacial Surgery	2010 IF: 1.302
14. Annals of Plastic Surgery	2010 IF: 1.274
15. Aesthetic Plastic Surgery	2010 IF: 1.252
16. Clinics in Plastic Surgery	2010 IF: 0.942
17. Journal of Reconstructive Microsurgery	2010 IF: 0.830
18. Journal of Craniofacial Surgery	2010 IF: 0.772
19. Cleft Palate-Craniofacial Journal	2010 IF: 0.770

Journals we think important when evaluating Plastic Surgery Literature

20. Burns	2010 IF: 1.718
21. Journal of Burn Care & Research	2010 IF: 1.563
22. Microsurgery	2010 IF: 1.555
23. Archives of Facial Plastic Surgery	2010 IF: 1.630
24. British Journal of Oral & Maxillofacial Surgery	2010 IF: 1.571
25. Journal of Hand Surgery-European Volume	2010 IF: 0.868

Appendix 4

Tool to Assess Risk of Bias in Randomized Controlled Trials

1. **Was the allocation sequence adequately generated?***

Definitely yes (low risk of bias) | Probably yes | Probably no | Definitely no (high risk of bias)

Examples of low risk of bias: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization with or without a random element.

Examples of high risk of bias: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number; Allocation by judgement of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention.

* Option to omit this item

2. **Was allocation adequately concealed?**

Definitely yes (low risk of bias) | Probably yes | Probably no | Definitely no (high risk of bias)

Examples of low risk of bias allocation concealment techniques: Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);

Examples of possible low risk of bias: Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.

Examples of high risk of bias allocation generation techniques: Using an open random allocation schedule (e.g. a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure.

3. **Blinding: Was knowledge of the allocated interventions adequately prevented?***

Definitely yes (low risk of bias) | Probably yes | Probably no | Definitely no (high risk of bias)

Examples of low risk of bias: No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the nonblinding of others unlikely to introduce bias.

Examples of high risk of bias: No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

* This global rating is challenging. May want to omit and use only the ratings below.

3.a) Were patients blinded?
Definitely yes | Probably yes | Probably no | Definitely no

3.b). Were healthcare providers blinded?
Definitely yes | Probably yes | Probably no | Definitely no

3.c). Were data collectors blinded?
Definitely yes | Probably yes | Probably no | Definitely no

3.d). Were outcome assessors blinded?
Definitely yes | Probably yes | Probably no | Definitely no

3.e). Were data analysts blinded?
Definitely yes | Probably yes | Probably no | Definitely no

4. **Was loss to follow-up (missing outcome data) infrequent?**

Definitely yes (low risk of bias) | Probably yes | Probably no | Definitely no (high risk of bias)

Examples of low risk of bias: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be

introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a important impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have an important impact on observed effect size; Missing data have been imputed using appropriate methods.

Examples of high risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce important bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.

5. **Are reports of the study free of suggestion of selective outcome reporting?***

Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias)

Examples of low risk of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Examples of high risk of bias: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided,
such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study

* This item sufficiently difficult to judge that may be omitted.

6. **Was the study apparently free of other problems that could put it at a risk of bias?***

Definitely yes (low risk of bias) | Probably yes | Probably no | Definitely no (high risk of bias)

Examples of low risk of bias: The study appears to be free of other sources of bias.
Examples of high risk of bias: Had a potential source of bias related to the specific study design used; Stopped early due to some data-dependent process (including a formal-stopping rule); Had extreme baseline imbalance; Has been claimed to have been fraudulent; Had some other problem.

* May omit this item.

11. Appendix B

Sample of Questions from the Data Extraction Form

1. Please Check your name:

   - ○ Sophocles Voineskos
   - ○ Chris Coroneos
   - ○ Manraj Kaur
   - ○ Mike Walsh
   - ○ Natalia Ziolkowski

2. Type the first page number of the manuscript

3. From reading the TITLE of the manuscript, (and only the TITLE) are you able to understand that this is a Randomized Control Trial?
   Guidance: Is the word "Random" (or a variation of it, with respect to the paper being an RCT) used in the TITLE? Would most readers understand that this is an RCT after reading the TITLE

   ○ Yes ○ No

4. From reading the ABSTRACT, (and only the ABSTRACT) are you able to understand that this is a Randomized Control Trial?
   Guidance: *Is the word "Random" (or a variation of it, with respect to the paper being an RCT) used in the ABSTRACT? Would most readers understand that this is an RCT after reading the ABSTRACT*

   ○ Yes ○ No

5. What type of funding was received:

   Multiple options available
   Check off all that apply

   - ☐ For Profit Industry/Private
   - ☐ Not for Profit/University/Governmnet Grant/Society funding (e.g. CSPS, ASPS)
   - ☐ Explicit statement that "No Funding" was received
   - ☐ No statement regarding funding source appears in the manuscript

7. Are any Conflicts of Interest present?
   (e.g. Royalties, Consultant, Stock/Stock Options, Company Employee)

   - ○ Yes, conflicts of interest are present
   - ○ Disclosure present AND embodies the idea that there are "no conflicts of interest"
   - ○ Not Reported/Not Disclosed

8. Is there any mention of an Industry created product within the manuscript?
   (This product should play some role in one or more of the interventions)

   ○ Yes ○ No

10. Is there evidence of involvement of a plastic surgeon/plastic surgery department/division anywhere in this manuscript?
    (Only "Plastic Surgery" or "Burn" counts,
    any other department e.g. Oral & Maxillofacial, or Otolaryngology DOES NOT COUNT)

    ○ Yes ○ No Clear Response

11. What country is the corresponding author giving their address from?

- ○ USA
- ○ Canada
- ○ Other North America (Mexico, Cuba, etc)
- ○ Brazil
- ○ Other South America (Chile, Argentina etc)
- ○ Japan
- ○ China
- ○ Other Asia (Turkey, India, Saudi Arabia, Singapore, Malaysia etc)
- ○ Australia
- ○ Other Oceania (e.g. New Zealand)
- ○ UK (England, Scotland, Wales, Ireland)
- ◉ Other Europe (Belgium, Italy, etc)
- ○ Africa (Egypt, South Africa, Morocco, etc)

12. Was this an International Study? i.e. Were patients recruited/operated on from/in 2 or more countries?
(Authorhip 2 or more countries DOES NOT COUNT)

◉ Yes ○ No

13. How many "Centres" appear to be involved in the study?
(remember to take the author's word at face value)

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ◉ 6 or more

14. If more than 5 were involved, type how many:

53

- ○ Multiple, but unclear exactly how many
- ○ Not Reported/Too unclear to reasonably estimate

15. Were the INclusion criteria for the patients made explicit?
Inclusion Criteria are used to define your population of interest

- ◉ Unequivolcal, clear, and explicit criteria
- ○ Some criteria, but not as clear or explicit as desirable
- ○ INclusion criteria was not described
- ○ INclusion criteria was not described, but a statement embodying "all patients were included/consecutive patients were included" is present

16. Were the EXclusion criteria for the patients made explicit?
Exclusion criteria describes unsuitable individuals who have the disease/problem you are interested in

- (•) Unequivolcal, clear, and explicit criteria
- ( ) Some criteria, but not as clear or explicit as desirable
- ( ) Exclusion criteria were not described
- ( ) Exclusion criteria were not described, but a statement embodying "all patients were included/consecutive patients were included" is present

17. What year did patient randomization start?
(use patient recruitment as a surrogate if randomization unknown)

- (•) 2004 or earlier
- ( ) 2005
- ( ) 2006 or later
- ( ) Not Reported

Clear Response

18. In what domain of Plastic Surgery does the patient's surgical problem lie?
(In what domain does the patient's problem/surgical issue that this RCT is trying to solve lie within?)

- ( ) Facial/Head and Neck Reconstruction
- ( ) Craniofacial Surgery
- ( ) Hand/Upper Extremity Surgery
- ( ) Breast Surgery
- ( ) Trunk Reconstruction
- ( ) Lower Extremity Surgery
- ( ) Genital/Pelvic Reconstruction
- ( ) Aesthetic Surgery/Body Contouring
- (•) Generalized Cutaneous Disorders (Including Skin Cancer)
- ( ) Burns/Skin Grafts

Clear Response

19. Was involvement of a methodologist (e.g. statistician, clinical epidemiologist) of some sort reported in the methods section, or as an author, or as a contribution acknowledged?

(•) Yes ( ) No Clear Response

20. Do ANY of the authors (or people who were thanked/acknowledged as contributors) have a graduate degree of any kind?
(e.g. MSc, MS, MPH, PhD, DSc, Ed. D, D.Ed)

(Excluding degrees of licensure like Medical/Osteopath/Nursing e.g. MD, DO, ARPN)

- (•) Yes
- ( ) No

12. Appendix C

Sample of the Instructions from the Data Dictionary

Part 1 - Baseline

1. Please Check your name
- Simply choose your name

2. Type the first page number of the manuscript
- Type the first page number of the manuscript exactly as you see it on the first page
- On occasion there may be different page numbers for the "electronic" version than for the "print" version. Please just record whichever is most prominent in the "header" or the "footer".
(e.g. the "electronic" version may be 8 pages long, and the first page will state "Page 1 of 8". Please record the first page as "1" IF you do not see the "print" page numbers anywhere)

3. From reading the TITLE of the manuscript, (and only the TITLE) are you able to understand that this is a Randomized Control Trial?
- Is the word "Random" (or a variation of it, e.g. Random, Randomized, RCT, with respect to the paper being an RCT) used in the TITLE?
- Would most readers understand that this is an RCT after reading the TITLE?

4. From reading the ABSTRACT, (and only the ABSTRACT) are you able to understand that this is a Randomized Control Trial?
- Is the word "Random" (or a variation of it, with respect to the paper being an RCT) used in the ABSTRACT?
- Would most readers understand that this is an RCT after reading the ABSTRACT

5. What type of funding was received?
CHECK OFF ALL THAT APPPLY
→ Please scan the whole manuscript for this information
- Specific places it might help to look:
    - the first page of the manuscript
    - the methods
    - the last page of the manuscript text where the conclusion ends

Last Resort: Use the "search" function and type in "fund"

- When the nature of the funding agency is not clear, Google it
- if the website is in a foreign language, use Google Translate:
http://translate.google.com/?hl=en

- "Industry" is defined as for-profit companies and excluded all government agencies and non-profit private agencies.
- Industry funding is considered present if there is any acknowledgement of direct industry support for the research study (including direct funding of the study or supplying of drugs or medical devices). This does not include author-declared conflicts arising from having received individual consultant fees, for example

6. HIDDEN – Although it was funded by industry, was a statement that embodies the idea that "the authors had independent control of the data, contents of the manuscript, and decision to publish" apparent within the publication?
→ Please scan the whole manuscript for this information
- Specific places it might help to look:
    - the first page of the manuscript
    - the last page of the manuscript text where the conclusion ends

7. Are any Conflicts of Interest Present?
- Examples include: Royalties, Consultant, Stock/Stock Options, Company Employee
- Listen to what the authors say (take it at face value) and just record their explicit statement
→ Places it might help to look: Author affiliations, the first page of the manuscript, the methods, the last page of the manuscript text where the conclusion ends.

8. Is there any mention of an Industry created product within the manuscript?
- This product should play some role in one or more of the interventions (statistical packages or computer programs used for data analysis do not count)
- They MUST use either the product's retail name, or they must reference the product with a company name e.g. "An intraoperative skin-stretching device (Humeca, Enschede, The Netherlands), originally developed by Hirshowitz et al. was used"

Choose "*Yes*" if: - an industry product/device is present that plays some type of role in one or more of the interventions

Choose "*No*" if: - no industry products are mentioned
- a product is mentioned but no industry name is used (for example, in RefID_570 a poly-L-D-lactic acid (PLDLA) implant is used, but no company name is given. This material is not specifically owned by any company in particular, therefore answer "No" for this reference since no industry name was used)

9. Is the same industry created product being used in all the treatment groups?

Choose "*Yes*" if: - all treatment groups at some point use/require/incorporate this industry product (e.g. RefID_988 both groups get a Blake Drain placed at the surgical site, or Ref_ID 1499 Botox is used to identify the treatment surgical site in all groups)

Choose "*No*" if: - There are multiple industry products being used, but two or more treatment arms are using different industry products (e.g. RefID_673 Caprosyn suture in one group and Novafil suture in the other group)
OR
- an industry product is only being used in one treatment arm (e.g. RedID_570 one arm uses

An example of how to answer #8 and #9 using RefID_747
→ 3 industry products are mentioned
1. Versajet (Smith and Nephew) → this product is only used in **one** treatment arm
2. Acticoat (Smith and Nephew) → this product is used in **both** treatment arms
3. Aquacel Ag (Convatec) → this product is used in **both** treatment arms

Therefore, using the above example of RefID_747
question #8 would be answered "Yes"
question #9 would be answered "No" (while Acticoat and and Aquacel Ag were used in both groups, Versajet was only used in one group, therefore #9 is answered "No")

10. Is there evidence of involvement of a plastic surgeon/plastic surgery department/division anywhere in this manuscript?
- Only "plastic surgery" or "Burn" counts
- Other departments e.g. Oral & Maxillofacial, Orthopaedic, Otolaryngology DOES NOT COUNT
→ Use the author affiliations to determine this information
- May exist as contribution thanked/acknowledged
- May exist in methods (e.g "we had our plastic surgeon colleague" assist us)

11. What country is the corresponding author giving their address from?
- We want to know "who is doing these trials?" so where is the investigator from, who is leading the trial
→ Use the author affiliations to determine this information

12. Was this an International Study? i.e. Were patients recruited/operated on from/in 2 or more countries?
- Author affiliation with 2 or more countries DOES NOT COUNT
- We are interested whether international collaboration existed for this trial

- Was there at least 1 study centre from 2 or more countries
- Were patients recruited from 2 or more countries

13. How many "Centres" appear to be involved in the study?
- How many "Centres" that have patients undergoing operations were involved in the study?
- Record this data as it is reported by the authors' use of the word "centre"
- If the authors do not use the word "centre", then for our purposes, the most basic unit of a "centre" is one hospital.
- If they do not provide details on the number of hospitals, the next basic unit of a "centre" is one city

Summary of Hierarchy:
- Authors statement of number of centres
- Authors statement of number of Hospitals
- Authors statement of number of Cities

If none of the above are present, then answer the most appropriate of the following:
- "Multiple, but unclear exactly how many"
- "Too unclear to reasonably estimate"
- "Not reported/Not obvious"

14. HIDDEN - If more than 5 were involved, type how many

13. Appendix D

Domain of Plastic Surgery	First Author	Title of Manuscript	Author Stated a Primary Outcome	Single Primary Outcome	Multiple Primary Outcomes	Composite Outcome	Outcome Chosen by Algorithm
Facial/head and neck reconstruction	S. Deo	A prospective randomized trial comparing harmonic scalpel versus electrocautery for pectoralis major myocutaneous flap dissection.	Yes		blood loss, operating time, postoperative drainage volume, and flap morbidity		
Facial/head and neck reconstruction	M. Omranifard	Follicular isolation technique with de-epithelialization for eyebrow and eyelash reconstruction.	No				satisfaction
Facial/head and neck reconstruction	C. J. Kerawala	Prospective randomised trial of the benefits of a sternocleidomastoid flap after superficial parotidectomy.	No				Facial nerve function
Facial/head and neck reconstruction	C. J. Kerawala	The pectoralis major myocutaneous flap: Is the subclavicular route safe?.	No				Flap necrosis
Facial/head and neck reconstruction	C. H. Huang	Comparison of the radial forearm flap and the thinned anterolateral thigh cutaneous flap for reconstruction of tongue defects: an evaluation of donor-site morbidity.	No				donor site morbidity/QOL
Craniofacial surgery	K. Ueki	Effect of self-setting -tricalcium phosphate between segments for bone healing and hypoaesthesia in lower lip after sagittal split ramus osteotomy.	Yes	hypoaesthesia of lower lip			
Craniofacial surgery	S. Laverick	Intraoral external oblique ridge compared with transbuccal lateral cortical plate fixation for the treatment of fractures of the mandibular angle: prospective randomised trial.	Yes	removal of infected plate			
Craniofacial surgery	C. Howley	Use of the alar base cinch suture in Le Fort I osteotomy: is it effective?.	Yes	width of alar base			
Craniofacial surgery	R. Rauso	Comparison of two techniques of cinch suturing to avoid widening of the base of the nose after Le Fort I osteotomy.	Yes	widening of the base of the nose			
Craniofacial surgery	M. Bashir	Comparison of suture and graft techniques in secondary unilateral cleft rhinoplasty.	Yes	tip projection			
Craniofacial surgery	W. Wu	Endoscopic transethmoidal and transconjunctival inferior fornix approaches for repairing the combined medial wall and orbital floor blowout fractures.	Yes		enophthalmos, diplopia, extraocular muscle function		

Craniofacial surgery	W. N. Williams	Prospective clinical trial comparing outcome measures between Furlow and von Langenbeck Palatoplasties for UCLP.	Yes		cul-de-sac hypernasal resonance and inappropriat e NAE
Craniofacial surgery	V. Tuovinen	Comparison of the stability of bioabsorbable and titanium osteosynthesis materials for rigid internal fixation in orthognathic surgery. A prospective randomized controlled study in 101 patients with 192 osteotomies.	Yes	stability of rigind internal fixation	
Craniofacial surgery	A. Ow	Bilateral sagittal split osteotomies versus mandibular distraction osteogenesis: a prospective clinical trial comparing inferior alveolar nerve function and complications.	Yes		neurosensor y function of inferior alveolar nerve
Craniofacial surgery	H. D. Chua	Maxillary distraction versus orthognathic surgery in cleft lip and palate patients: effects on speech and velopharyngeal function.	Yes	skeletal stability	
Craniofacial surgery	A. W. Sugar	A randomised controlled trial comparing fixation of mandibular angle fractures with a single miniplate placed either transbuccally and intra-orally, or intra-orally alone.	Yes	bony union without need for another intervention	
Craniofacial surgery	N. Pigadas	A randomized controlled trial on cross-infection control in maxillofacial trauma surgery: a comparison of intermaxillary fixation techniques.	Yes	glove perforations per operation	
Craniofacial surgery	D. B. Matic	Temporal hollowing following coronal incision: a prospective, randomized, controlled trial.	Yes		incidence and severity of temporal hollowing, and cause of temporal hollowing
Craniofacial surgery	B. P. Dickinson	Reduced morbidity and improved healing with bone morphogenic protein-2 in older patients with alveolar cleft defects.	Yes		bone healing and morbidity (pain)
Craniofacial surgery	J. de Lange	The effect of nasal application of cocaine/adrenaline on blood loss in Le Fort I osteotomies.	Yes	blood loss	
Craniofacial surgery	M. Gimbel	Repair of alveolar cleft defects: reduced morbidity with bone marrow stem cells in a resorbable matrix.	Yes		Morbidity of the harvest site (intensity and frequency of pain, functional disturbances , cosmetic outcomes)

Craniofacial surgery	M. E. Hassan	Does palatal muscle reconstruction affect the functional outcome of cleft palate surgery?.	Yes		eustachian tube function, velopharyngeal competence		
Craniofacial surgery	N. Chanchareonsook	Speech outcome and velopharyngeal function in cleft palate: comparison of Le Fort I maxillary osteotomy and distraction osteogenesis--early results.	Yes		speech (resonance and nasal emission) and VP status		
Craniofacial surgery	D. Takazakura	A comparison of postoperative hypoesthesia between two types of sagittal split ramus osteotomy and intraoral vertical ramus osteotomy, using the trigeminal somatosensory-evoked potential method.	Yes	lower lip hypoesthesia			
Craniofacial surgery	B. Richard	Results of randomized controlled trial of soft palate first versus hard palate first repair in unilateral complete cleft lip and palate.	Yes	maxillary growth			
Craniofacial surgery	J. G. Handschel	A prospective comparison of octyl-2-cyanoacrylate and suture in standardized facial wounds.	Yes	VAS			
Craniofacial surgery	F. Abyholm	Pharyngeal flap and sphincterplasty for velopharyngeal insufficiency have equal outcome at 1 year postoperatively: results of a randomized trial.	Yes		speech, incidence of sleep apnea, and surgical complications		
Craniofacial surgery	J. L. Segura-Castillo	Reduction of bone resorption by the application of fibrin glue in the reconstruction of the alveolar cleft.	Yes	bone graft resorption			
Craniofacial surgery	K. Panula	Neurosensory deficits after bilateral sagittal split ramus osteotomy of the mandible--influence of soft tissue handling medial to the ascending ramus.	Yes		subjective sensation, neurosensory function with 2-point discrimination (2-PD) and vitality scanner tests (VST)		
Craniofacial surgery	S. E. Norholt	Le Fort I miniplate osteosynthesis: a randomized, prospective study comparing resorbable PLLA/PGA with titanium.	Yes		maxillary stability, and morbidity		
Craniofacial surgery	K. O. Henkel	Veloplasty using the wave-line technique versus classic intravelar veloplasty.	Yes		lengthening of soft palate, speech, type of breathing		
Craniofacial surgery	V. Singh	Conventional versus 3-dimensional miniplate in management of mandibular fracture: a prospective randomized study.	No				occlusion

Craniofacial surgery	M. Bayat	Comparison of conchal cartilage graft with nasal septal cartilage graft for reconstruction of orbital floor blowout fractures.	No	diplopia
Craniofacial surgery	D. Mehrotra	Random control trial of dermis-fat graft and interposition of temporalis fascia in the management of temporomandibular ankylosis in children.	No	interincisal mouth opening
Craniofacial surgery	A. Siddiqui	One miniplate versus two in the management of mandibular angle fractures: a prospective randomised study.	No	"total morbidity"
Craniofacial surgery	S. Kruschewsky Lde	Fractured orbital wall reconstruction with an auricular cartilage graft or absorbable polyacid copolymer.	No	diplopia
Craniofacial surgery	E. Marukawa	Reduction of bone resorption by the application of platelet-rich plasma (PRP) in bone grafting of the alveolar cleft.	No	bone density/resorption
Craniofacial surgery	V. Singh	Comparative evaluation of 2.0-mm locking plate system vs 2.0-mm nonlocking plate system for mandibular fracture: a prospective randomized study.	No	complications
Craniofacial surgery	N. Thuaksuban	A comparison of autogenous bone graft combined with deproteinized bovine bone and autogenous bone graft alone for treatment of alveolar cleft.	No	time taken to walk again, with and without assistance
Craniofacial surgery	P. Stockmann	Resorbable versus titanium osteosynthesis devices in bilateral sagittal split ramus osteotomy of the mandible - the results of a two centre randomised clinical study with an eight-year follow-up.	No	complications
Craniofacial surgery	J. Yazdani	Comparison of clinical efficacy of temporalis myofascial flap and dermal graft as interpositional material in treatment of temporomandibular joint ankylosis.	No	Maximal incisal opening
Craniofacial surgery	S. T. Becker	Comparison of collagen membranes and polydioxanone for reconstruction of the orbital floor after fractures.	No	diplopia
Craniofacial surgery	M. M. Ardehali	Use of nasal packs and intranasal septal splints following septoplasty.	No	complication
Craniofacial surgery	B. Guyuron	A placebo-controlled surgical trial of the treatment of migraine headaches.	No	Elimination of Migraine headaches
Craniofacial surgery	L. K. Cheung	Stability and morbidity of Le Fort I osteotomy with bioresorbable fixation: a randomized controlled trial.	No	Stability of the Maxilla

Craniofacial surgery	J. K. Lee	Treatment outcomes of orthodontic treatment, corticotomy-assisted orthodontic treatment, and anterior segmental osteotomy for bimaxillary dentoalveolar protrusion.	No				skeletal radiograph measurements
Craniofacial surgery	K. Ueki	Changes in condylar long axis and skeletal stability after bilateral sagittal split ramus osteotomy with poly-L-lactic acid or titanium plate fixation.	No				skeletal stability
Craniofacial surgery	M. Peled	Treatment of osseous cleft palate defects: a preliminary evaluation of novel treatment modalities.	No				defect area
Hand/upper extremity surgery	I. Atroshi	Outcomes of endoscopic surgery compared with open surgery for carpal tunnel syndrome among employed patients: randomised controlled trial.	Yes	pain severity, and degree of limitation caused by pain			
Hand/upper extremity surgery	T. B. Hansen	Randomised controlled study of two different techniques of skin suture in endoscopic release of carpal tunnel.	Yes		postoperative wound pain and cosmesis		
Hand/upper extremity surgery	L. Rocchi	Articular ganglia of the volar aspect of the wrist: arthroscopic resection compared with open excision. A prospective randomised study.	Yes		risks of operating and time to healing		
Hand/upper extremity surgery	T. J. Parkkila	Survival and complications are similar after Swanson and Sutter implant replacement of metacarpophalangeal joints in patients with rheumatoid arthritis.	Yes		Survival , and fracture, and deformation rates of swanson and sutter implants		
Hand/upper extremity surgery	C. Theopold	A randomised controlled trial of absorbable versus non-absorbable sutures for skin closure after open carpal tunnel release.	Yes	6 week modified Patient and Observer Scar Assessment Scale			
Hand/upper extremity surgery	A. L. van Rijssen	Five-year results of a randomized clinical trial on treatment in Dupuytren's disease: percutaneous needle fasciotomy versus limited fasciectomy.	Yes	recurrence of dupuytren's disease			
Hand/upper extremity surgery	H. Kusuhara	Randomized controlled trial of the application of topical b-FGF-impregnated gelatin microspheres to improve tissue survival in subzone II fingertip amputations.	Yes	tissue survival			
Hand/upper extremity surgery	B. Rinker	A prospective randomized study comparing woven polyglycolic acid and autogenous vein conduits for reconstruction of digital nerve gaps.	Yes		sensory recovery, cost, complication profile		

Hand/upper extremity surgery	P. B. Honkanen	Bioreconstructive poly-L/D-lactide implant compared with Swanson prosthesis in metacarpophalangeal joint arthroplasty in rheumatoid patients: a randomized clinical trial.	Yes	active ROM of MP joint	
Hand/upper extremity surgery	M. Riccio	Efficiency of Hyaloglide in the prevention of the recurrence of adhesions after tenolysis of flexor tendons in zone II: a randomized, controlled, multicentre clinical trial.	Yes		Total Active Motion, Quick-DASH, Return to work, Complications
Hand/upper extremity surgery	B. G. Escott	NeuFlex and Swanson metacarpophalangeal implants for rheumatoid arthritis: prospective randomized, controlled clinical trial.	Yes	active MCP joint flexion	
Hand/upper extremity surgery	M. Tagil	Correlation between range of motion and implant fracture: a 5 year follow-up of 72 joints in 18 patients in a randomized study comparing Swanson and Avanta/Sutter MCP silicone prosthesis.	Yes	implant fracture rate	
Hand/upper extremity surgery	K. Howard	A prospective randomised trial of absorbable versus non-absorbable sutures for wound closure after fasciectomy for Dupuytren's contracture.	Yes		time spent attending to the wound, patient pain score, complications
Hand/upper extremity surgery	J. Braga-Silva	Randomized prospective study comparing reverse and direct flow island flaps in digital pulp reconstruction of the fingers.	Yes		2PD, PIPJ and DIPJ motion loss
Hand/upper extremity surgery	S. Tuzuner	Median nerve excursion in response to wrist movement after endoscopic and open carpal tunnel release.	Yes		longitudinal excursion and volar displacement of the median nerve
Hand/upper extremity surgery	A. Sonmez	Digital blocks with and without adrenalin: a randomised-controlled study of capillary blood parameters.	Yes		pH, PCO2, PO2, HCO3, and SaO2
Hand/upper extremity surgery	A. M. Navali	Zone 2 flexor tendon repair in young children: a comparative study of four-strand versus two-strand repair.	Yes		range of active motion and rupture rate
Hand/upper extremity surgery	L. Blond	Clinical consequences of different exsanguination methods in hand surgery. a double-blind randomised study.	Yes	VAS for exsanguination quality	
Hand/upper extremity surgery	T. R. Cresswell	Long-term outcome after carpal tunnel decompression - a prospective randomised study of the Indiana Tome and a standard limited palmar incision.	Yes	Levine-Katz Questionnaire	

Hand/upper extremity surgery	J. F. Ritchie	A comparison of trapeziectomy via anterior and posterior approaches.	Yes		Functional outcome and complicatio n rate	
Hand/upper extremity surgery	L. Kang	Arthroscopic versus open dorsal ganglion excision: a prospective, randomized comparison of rates of recurrence and of residual pain.	Yes	rate of ganglion recurrence		
Hand/upper extremity surgery	E. J. Strauss	A prospective, randomized, controlled trial of 2-octylcyanoacrylate versus suture repair for nail bed injuries.	Yes	time required for repair		
Hand/upper extremity surgery	A. W. Siegmeth	Standard open decompression in carpal tunnel syndrome compared with a modified open technique preserving the superficial skin nerves: a prospective randomized study.	Yes		incidence and severity of scar discomfort	
Hand/upper extremity surgery	N. D. Citron	Recurrence after surgery for Dupuytren's disease: a randomized trial of two skin incisions.	Yes	dupuytren's recurrence		
Hand/upper extremity surgery	M. J. Bertleff	A prospective clinical evaluation of biodegradable neurolac nerve guides for sensory nerve repair in the hand.	Yes	recovery of sensory nerve function		
Hand/upper extremity surgery	P. Cellocco	Mini-open blind procedure versus limited open technique for carpal tunnel release: a 30-month follow-up study.	Yes		safety and effectivenes s	
Hand/upper extremity surgery	N. Kharwadkar	Prospective randomized trial comparing absorbable and non-absorbable sutures in open carpal tunnel release.	Yes		pillar pain and scar tenderness, the extent of wound inflammatio n and the outcome of surgery	
Hand/upper extremity surgery	M. M. Al-Qattan	Vicryl Rapide versus Vicryl suture in skin closure of the hand in children: a randomized prospective study.	Yes			wound complicatio ns and suture reactions
Hand/upper extremity surgery	R. Delaney	A comparative study of outcome between the Neuflex and Swanson metacarpophalangeal joint replacements.	Yes		ROM, SODA (sequential occupationa l dexterity assessment)	
Hand/upper extremity surgery	J. J. Dias	Carpal tunnel decompression. Is lengthening of the flexor retinaculum better than simple division?.	Yes		gip strength, pinch strength, pain visual analogue score	
Hand/upper extremity surgery	N. W. Bulstrode	A prospective randomised clinical trial of the intra-operative use of 5-fluorouracil on the outcome of	Yes	recurrence rate		

		dupuytren's disease.		
Hand/upper extremity surgery	R. P. Tiihonen	Reconstruction of the trapeziometacarpal joint in inflammatory joint disease using interposition of autologous tendon or poly-L-D-lactic acid implants: a prospective clinical trial.	No	function
Hand/upper extremity surgery	K. Pettersson	NeuFlex compared with Sutter prostheses: a blind, prospective, randomised comparison of Silastic metacarpophalangeal joint prostheses.	No	Canadian Occupational Performance Measure
Hand/upper extremity surgery	S. Gangopadhyay	Five- to 18-year follow-up for treatment of trapeziometacarpal osteoarthritis: a prospective comparison of excision, tendon interposition, and ligament reconstruction and tendon interposition.	No	pain
Hand/upper extremity surgery	H. Salem	Six year outcome excision of the trapezium for trapeziometacarpal joint osteoarthritis: is it improved by ligament reconstruction and temporary Kirschner wire insertion?.	No	DASH score
Hand/upper extremity surgery	M. Aberg	Clinical evaluation of a resorbable wrap-around implant as an alternative to nerve repair: a prospective, assessor-blinded, randomised clinical study of sensory, motor and functional recovery after peripheral nerve repair.	No	sensorimotor testing
Hand/upper extremity surgery	J. Braga-Silva	A comparison of the use of distal radius vascularised bone graft and non-vascularised iliac crest bone graft in the treatment of non-union of scaphoid fractures.	No	range of motion
Hand/upper extremity surgery	M. Winter	Surgical treatment of the boxer's fracture: transverse pinning versus intramedullary pinning.	No	patient satisfaction
Hand/upper extremity surgery	J. Field	To suspend or not to suspend: a randomised single blind trial of simple trapeziectomy versus trapeziectomy and flexor carpi radialis suspension.	No	pain
Hand/upper extremity surgery	M. Rab	Intra-individual comparison between open and 2-portal endoscopic release in clinically matched bilateral carpal syndrome.	No	Levine Scale
Hand/upper extremity surgery	A. Nabhan	Simple decompression or subcutaneous anterior transposition of the ulnar nerve for cubital tunnel syndrome.	No	pain

Hand/upper extremity surgery	A. Aladin	Dorsal fracture-dislocation of the proximal interphalangeal joint: a comparative study of percutaneous Kirschner wire fixation versus open reduction and internal fixation.	No			Patient Evaluation Measure
Hand/upper extremity surgery	R. Bhattachary a	A randomized controlled trial of knifelight and open carpal tunnel release.	No			return to work
Hand/upper extremity surgery	G. Lundborg	Tubular repair of the median or ulnar nerve in the human forearm: a 5-year follow-up.	No			Model for Documentat ion of outcome after nerve Repair
Hand/upper extremity surgery	H. D. Skoff	The surgical treatment of Dupuytren's contracture: a synthesis of techniques.	No			DASH
Hand/upper extremity surgery	M. J. Mulcahey	Prospective evaluation of biceps to triceps and deltoid to triceps for elbow extension in tetraplegia.	No			ALDS
Breast surgery	C. M. McCarthy	The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial.	Yes	post-opertaive pain		
Breast surgery	K. Benediktsso n	Fluid retention in Bioplasty Misti Gold II breast prostheses with development of capsular contracture.	Yes	capsular contracture		
Breast surgery	A. Prado	Clinical trial evaluating the results of breast reduction with ancillary lipoplasty.	Yes	overall complicatio n rate		
Breast surgery	C. Eriksen	A prospective randomized study comparing two different expander approaches in implant-based breast reconstruction: one stage versus two stages.	Yes	number of operations needed to obtain patient satisfaction		
Breast surgery	J. G. Harper	The use of autologous platelet-leukocyte-enriched plasma to minimize drain burden and prevent seroma formation in latissimus dorsi breast reconstruction.	Yes		reduction of drain burden and incidence of seroma formation	
Breast surgery	T. E. Burdette	Harmonic scalpel versus electrocautery in breast reduction surgery: a randomized controlled trial.	Yes		operative time, fluid drainage, patient pain	
Breast surgery	J. Gahm	No differences in aesthetic outcome or patient satisfaction between anatomically shaped and round expandable implants in bilateral breast reconstructions: a randomized study.	Yes		evaluation of aesthetic outcome and patient satisfaction	
Breast surgery	A. L. Dancey	A prospective randomized trial of the efficacy of marginal quilting sutures and fibrin sealant in reducing the incidence of seromas in the extended latissimus dorsi donor site.	Yes	incidence of symptomati c seroma		

Breast surgery	C. L. Temple	Sensibility following innervated free TRAM flap for breast reconstruction: Part II. Innervation improves patient-rated quality of life.	Yes	Quality of Life		
Breast surgery	K. J. Cross	The absorbable dermal staple device: a faster, more cost-effective method for incisional closure.	Yes		speed and cost-effectiveness of the absorbable dermal stapler	
Breast surgery	L. U. Corion	Draining after breast reduction: a randomised controlled inter-patient study.	Yes		complications, and length of hospital stay	
Breast surgery	L. A. Rossetto	Quilting suture in the donor site of the transverse rectus abdominis musculocutaneous flap in breast reconstruction.	Yes		drain output, time to drain removal, complications	
Breast surgery	C. M. McCarthy	Efficacy of pocket irrigation with bupivacaine and ketorolac in breast augmentation: a randomized controlled trial.	Yes	patient reported postoperative pain (VAS)		
Breast surgery	M. D. Nipshagen	Use of 2-octyl-cyanoacrylate skin adhesive (Dermabond) for wound closure following reduction mammaplasty: a prospective, randomized intervention study.	Yes		VAS, Hollander Wound Evaluation Scale, POSAS	
Breast surgery	R. C. Mahabir	Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients: part II. 10-day follow-up.	Yes	pain		
Breast surgery	A. Anzarut	Completely autologous platelet gel in breast reduction surgery: a blinded, randomized, controlled trial.	Yes	24 hour wound drainage		
Breast surgery	S. S. Rayatt	Soft fluted silicone drains: a prospective, randomized, patient-controlled study.	Yes	pain		
Breast surgery	C. McCarthy	Use of abdominal quilting sutures for seroma prevention in TRAM flap reconstruction: a prospective, controlled trial.	Yes	Seroma formation		
Breast surgery	M. Tremp	Is ultracision knife safe and efficient for breast capsulectomy? A preliminary study.	No			seroma/hematoma
Breast surgery	M. Kaariainen	The significance of latissimus dorsi flap innervation in delayed breast reconstruction: a prospective randomized study-magnetic resonance imaging and histologic findings.	No			flap thickness

Breast surgery	D. Mu	The relationship between the thickness of de-epithelialization and occurrence of sebaceous cysts at the incision site after mastopexy and reduction mammaplasty.	No			incidence of sebaceous cysts
Breast surgery	A. E. Deliaert	The effect of triclosan-coated sutures in wound healing. A double blind randomised prospective pilot study.	No			wound dehiscence
Breast surgery	A. Soueid	Randomized clinical trial on the effects of the use of diluted adrenaline solution in reduction mammaplasty: same patient, same technique, same surgeon.	No			blood loss
Breast surgery	I. Niechajev	Prospective study comparing two brands of cohesive gel breast implants with anatomic shape: 5-year follow-up evaluation.	No			patient satisfaction
Breast surgery	M. A. Trelles	Erbium:YAG laser as a method of deepithelization in corrective and reductive breast surgery.	No			complications
Breast surgery	N. Collis	Drainage in breast reduction surgery: a prospective randomised intra-patient trail.	No			hematoma
Breast surgery	G. Di Benedetto	Which is the best position for the remote injection dome using the adjustable expander/prosthesis in breast reconstruction? A comparative study.	No			pain
Trunk reconstruction	P. Erba	Tip anchor flap in decubital surgery.	Yes	ulcer recurrence		
Lower extremity surgery	D. F. Kalbermatten	Sensate lateral arm flap for defects of the lower leg.	Yes		sensate recovery (pain, vibration, thermal, static and moving 2PD, Semmes-Weinstein	
Genital/pelvic reconstruction	P. Erba	Fibrin sealant for fasciocutaneous flaps.	Yes		drain output, and time to drain removal	
Aesthetic surgery/body contouring	B. E. DiBernardo	Randomized, blinded split abdomen study evaluating skin shrinkage and skin tightening in laser-assisted liposuction versus liposuction control.	Yes		skin shrinkage and skin tightening	
Aesthetic surgery/body contouring	K. J. Walgenbach	Randomized, prospective study of TissuGlu[REGISTERED] surgical adhesive in the management of wound drainage following abdominoplasty.	Yes		time to drain removal, device and non-device-related adverse events	

Aesthetic surgery/body contouring	M. E. Bercial	Suction drains, quilting sutures, and fibrin sealant in the prevention of seroma formation in abdominoplasty: which is the best strategy?.	Yes	seroma formation	
Aesthetic surgery/body contouring	M. W. Nagy	A multicenter, prospective, randomized, single-blind, controlled clinical trial comparing VASER-assisted Lipoplasty and suction-assisted Lipoplasty.	Yes	skin retraction	
Aesthetic surgery/body contouring	A. Kalantar-Hormozi	Can elimination of epinephrine in rhinoplasty reduce the side effects: introduction of a new technique.	Yes		amount of hemorrhage, duration of surgery, cardiac complications
Aesthetic surgery/body contouring	N. Naghshineh	A double-blind controlled trial of polyglytone 6211 versus poliglecaprone 25 for use in body contouring	Yes	suture extrusion	
Aesthetic surgery/body contouring	N. Chheda	The pain of nasal tampon removal after nasal surgery: a randomized control trial.	Yes	pain of removal	
Aesthetic surgery/body contouring	S. Lee	Efficacy of Crosseal fibrin sealant (human) in rhytidectomy.	Yes		ecchymosis and hematoma formation
Aesthetic surgery/body contouring	P. Andrades	Progressive tension sutures in the prevention of postabdominoplasty seroma: a prospective, randomized, double-blind clinical trial.	Yes	seroma formation	
Aesthetic surgery/body contouring	A. Araco	Comparison of power water--assisted and traditional liposuction: a prospective randomized trial of postoperative pain.	Yes	postoperative pain	
Aesthetic surgery/body contouring	A. Prado	Use of aerosolized bovine-prepared fibrin glue for skin fixation after primary open rhinoplasty: a prospective randomized and controlled trial.	Yes		Strasser score, control oozing, restrain flap movement, inflammation, edema, hematoma, ecchymosis
Aesthetic surgery/body contouring	A. P. Murtha	Evaluation of a novel technique for wound closure using a barbed suture.	Yes	scar cosmesis	
Aesthetic surgery/body contouring	D. Marchac	Early postoperative efficacy of fibrin glue in face lifts: a prospective randomized trial.	Yes		wound drainage, hematoma, ecchymosis, edema
Aesthetic surgery/body contouring	R. C. Mahabir	Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients.	Yes	Pain immediately post-op	

Aesthetic surgery/body contouring	F. X. Nahas	The use of tissue adhesive for skin closure in body contouring surgery.	Yes		application time, cosmetic outcome		
Aesthetic surgery/body contouring	J. M. Gryskiewicz	Nasal osteotomies: a clinical comparison of the perforating methods versus the continuous technique.	Yes		ecchymosis and edema		
Aesthetic surgery/body contouring	G. H. Sasaki	Quantification of human abdominal tissue tightening and contraction after component treatments with 1064-nm/1320-nm laser-assisted lipolysis: clinical implications.	No				tissue tightening
Aesthetic surgery/body contouring	U. Taskin	Efficacy of the combination of intraoperative cold saline-soaked gauze compression and corticosteroids on rhinoplasty morbidity.	No				edema and ecchymosis
Aesthetic surgery/body contouring	B. Salari	Evaluation of the Goldman tip procedure and suture technique in tip rhinoplasty.	No				Rhinoplasty Outcomes Evaluation
Aesthetic surgery/body contouring	L. H. Pereira	Transaxillary breast augmentation: a prospective comparison of subglandular, subfascial, and submuscular implant insertion.	No				patient satisfaction
Aesthetic surgery/body contouring	S. G. Pryor	Efficacy of fibrin sealant (human) (Evicel) in rhinoplasty: a prospective, randomized, single-blind trial of the use of fibrin sealant in lateral osteotomy.	No				patient questionnaire on efficacy
Aesthetic surgery/body contouring	B. M. Jones	The efficacy of surgical drainage in cervicofacial rhytidectomy: a prospective, randomized, controlled trial.	No				swelling, bruising, hematoma
Aesthetic surgery/body contouring	A. Prado	A prospective, randomized, double-blind, controlled clinical trial comparing laser-assisted lipoplasty with suction-assisted lipoplasty.	No				cosmetic result
Aesthetic surgery/body contouring	L. T. Calderon-Cuellar	Modified mattress suture technique to correct anterior septal deviation.	No				subjective composite outcome (respiration, rhinorrea, epistaxis, obstruction)
Generalized cutaneous disorders	D. Richter	A comparison of a new skin closure device and intradermal sutures in the closure of full-thickness surgical incisions.	Yes			cosmesis, and complications	
Generalized cutaneous disorders	P. Gillgren	2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial	Yes	overall survival			
Generalized cutaneous disorders	N. W. Smeets	Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial.	Yes	recurrence of carcinoma			

Generalized cutaneous disorders	J. M. Thomas	Excision margins in high-risk malignant melanoma.	Yes			Locoregional melanoma recurrence (rates of local or in-transit melanoma recurrence and rate of nodal recurrence)	
Generalized cutaneous disorders	C. Huang	Small-wave incision method for linear hypertrophic scar reconstruction: a parallel-group randomized controlled study.	Yes		scar size and recurrence		
Generalized cutaneous disorders	C. L. Kerrigan	Evaluation of a new wound closure device for linear surgical incisions: 3M Steri-Strip S Surgical Skin Closure versus subcuticular closure.	Yes		speed of wound closure, postoperative comfort, scar quality		
Generalized cutaneous disorders	A. J. Singer	Single-layer versus double-layer closure of facial lacerations: a randomized controlled trial.	Yes	3 month cosmetic appearance			
Generalized cutaneous disorders	G. J. Parell	Comparison of absorbable with nonabsorbable sutures in closure of facial skin wounds.	Yes		inflammation and scar		
Generalized cutaneous disorders	L. A. Dessy	Reconstruction of anterior auricular conchal defect after malignancy excision: revolving-door flap versus full-thickness skin graft.	No				Patient Satisfaction
Burns	P. D. Verhaegen	Sustainable effect of skin stretching for burn scar excision: long-term results of a multicenter randomized controlled trial.	Yes	scar surface area reduction			
Burns	A. A. Mohammadi	Early excision and skin grafting versus delayed skin grafting in deep hand burns (a randomised clinical controlled trial).	Yes	DASH score			
Burns	M. Omranifard	A trial on subcutaneous pedicle island flap for eyebrow reconstruction.	Yes		effectiveness, complications, and patient satisfaction		
Burns	P. Gacto	Haemostatic effects of adrenaline-lidocaine subcutaneous infiltration at donor sites.	Yes		intraoperative bleeding, number of days dressing remained on donor site, % re-epithelialised skin 1 week after surgery, viability of		

					skin graft		
Burns	K. Foster	Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study.	Yes	wound closure			
Burns	G. Gravante	A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns.	Yes		time for complete epithelialization, and aesthetic and functional quality of epithelialization		
Burns	G. Gravante	Versajet hydrosurgery versus classic escharectomy for burn debridment: a prospective randomized trial.	Yes		time for complete debridement, and efficacy of versajet system in reaching the correct bloody dermal plane		
Burns	M. S. O'Mara	The use of tourniquets in the excision of unexsanguinated extremity burn wounds.	Yes	decreased blood loss with unchanged graft take			
Burns	A. M. Munster	Acellular allograft dermal matrix: immediate or delayed epidermal coverage?	Yes	"graft take"			
Burns	M. Magnusson	Cultured autologous keratinocytes in suspension accelerate epithelial maturation in an in vivo wound model as measured by surface electrical capacitance.	Yes	transepidermal water loss			
Burns	J. R. Saffle	Early tracheostomy does not improve outcome in burn patients.	Yes		survival, length of stay, days of ventilator support, extubation by POD 14		
Burns	C. Nervi	A multicenter clinical trial to evaluate the topical hemostatic efficacy of fibrin sealant in burn patients.	Yes	time to hemostasis			
Burns	M. T. Omar	Evaluation of hand function after early excision and skin grafting of burns versus delayed skin grafting: a randomized clinical trial.	No			jebsen-taylor hand function test	

Burns	H. Ryssel	The use of MatriDerm in early excision and simultaneous autologous skin grafting in burns--a pilot study.	No	wound closure
Burns	N. Gibran	Comparison of fibrin sealant and staples for attaching split-thickness autologous sheet grafts in patients with deep partial- or full-thickness burn wounds: a phase 1/2 clinical study.	No	time to wound closure
Burns	R. Mann	Prospective trial of thick vs standard split-thickness skin grafts in burns of the hand.	No	patient satisfaction