Title: Perioperative Systemic Corticosteroids in Orthognathic Surgery: a Systematic Review and Meta-analysis

Article Type: Review Article

Section/Category: Craniomaxillofacial Deformities/Cosmetic Surgery

Keywords: orthognathic surgery; corticosteroids; steroids; preoperative procedures; perioperative management; systematic review; meta-analysis

Corresponding Author: Dr. Simon Jean, D.M.D.

Corresponding Author's Institution: Department of Oral and Maxillofacial Surgery, CHU de Québec - Université Laval, Hôpital de l'Enfant-Jésus

First Author: Simon Jean, D.M.D.


Abstract: Purpose
Perioperative systemic corticosteroids are broadly used in orthognathic surgery to prevent postoperative complications, but it is unclear whether this practice is beneficial and concerns about potential side effects were raised. The purpose of our systematic review and meta-analysis was to assess the effects of perioperative systemic corticosteroids on clinically significant outcomes in patients undergoing orthognathic surgery.

Methods
We conducted a systematic review of randomized controlled trials evaluating the effect of systemic corticosteroids in orthognathic surgery compared to placebo or any other intervention. We searched Medline, Embase, Cochrane Central, CINAHL, Lilacs, Scopus, and Web of science as well as references of included trials. Our primary outcome was the incidence of postoperative reintubation during the index hospitalization. Our secondary outcomes were hospital length of stay, facial edema reduction, and adverse events. We summarized data using Mantel-Haenszel random effect models.

Results
Of the 1098 trials retrieved, 8 were included (n=234). No trial evaluated the risk of postoperative reintubation. One trial evaluated the duration of hospital stay and showed no difference associated with the intervention. We observed a decreased in facial edema with the use of systemic corticosteroids (n=80, SMD -1.07, [-1.99, -0.16], I2=67%). Three trials reported side effects such as postoperative surgical site bleeding, hypersensitivity, and stomach discomfort with corticosteroids intake. The eight trials had an unclear risk of bias.
Conclusion
We observed no evidence of effect of systemic corticosteroids on the risk of reintubation and hospital length of stay in orthognathic surgery. Although facial edema reduction was observed to be improved with the intervention, adverse effects were inconsistently screened and reported. The use of systemic steroids in orthognathic surgery is thus not supported by strong evidence.
Reviewer Comments:

1) Please clarify the dollar amount in the Introduction
(Orthognathic surgery, performed to align the stomatognathic system and achieve adequate function and facial aesthetics, is a frequent procedure having an impact on the costs of the healthcare system in Canada. For comparison, in the United States of America, in 2008, there were 10 345 hospitalizations for orthognathic surgery, representing expenses amounting to US$466 800 000.(1)). Do you mean $466,800,000 ?

We thank the editor for his comments. Changes have been made to clarify the dollar amount. (Page 3)

2) Please cite all figures in numerical order in the text of the manuscript (Appendix 3 and 4 do not appear to be cited).

We cited supplementary files in our manuscript according to reviewers’ and editor’s comments. (Pages 10, 11, and 12)
Reviewer Comments:

1) Please clarify the dollar amount in the Introduction
(Orthognathic surgery, performed to align the stomatognathic system and achieve adequate function and facial aesthetics, is a frequent procedure having an impact on the costs of the healthcare system in Canada. For comparison, in the United States of America, in 2008, there were 10,345 hospitalizations for orthognathic surgery, representing expenses amounting to US$466,800,000.(1)). Do you mean $466,800,000?

We thank the editor for his comments. Changes have been made to clarify the dollar amount. (Page 3)

2) Please cite all figures in numerical order in the text of the manuscript (Appendix 3 and 4 do not appear to be cited).

We cited supplementary files in our manuscript according to reviewers’ and editor’s comments. (Pages 10, 11, and 12)
Title
Perioperative Systemic Corticosteroids in Orthognathic Surgery: a Systematic Review and Meta-Analysis

Authors
1. Simon Jean DMD, Resident in OMFS and Corresponding author, Department of Oral and Maxillofacial Surgery, CHU de Québec - Université Laval, Québec City, Québec, Canada. Mailing address: Hôpital de l’Enfant-Jésus, 1401 18e rue, Quebec, Quebec, Canada, G1J 1Z4, Telephone number: 1-514-452-3304, Fax number: 1-418-649-5964, e-mail address: simon.jean.4@ulaval.ca.

2. Pierre-Luc Dionne DMD, Resident in OMFS, Department of Oral and Maxillofacial Surgery, CHU de Québec - Université Laval, Québec City, Québec, Canada.

3. Carl Bouchard DMD MSc, Associate professor, Department of Oral and Maxillofacial Surgery, CHU de Québec - Université Laval, Québec City, Québec, Canada.

4. Luc Giasson PhD, Associate professor, Faculty of Dentistry - Université Laval, Québec City, Québec, Canada.

5. Alexis F. Turgeon MD MSc FRCPC, Associate professor and Research Director, Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Faculty of medicine - Université Laval, Québec City, Québec, Canada. Associate Director, Population Health and Optimal Health Practice Research Unit, Trauma - Emergency - Critical Care Medicine, CHU de Québec - Université Laval Research Center, CHU de Québec - Université Laval. Canadian Institutes of Health Research (CIHR) New Investigator and Scientific Director, Cochrane Canada Francophone.
Title
Perioperative Systemic Corticosteroids in Orthognathic Surgery: a Systematic Review and Meta-Analysis

Abstract

Purpose
Perioperative systemic corticosteroids are broadly used in orthognathic surgery to prevent postoperative complications, but it is unclear whether this practice is beneficial and concerns about potential side effects were raised. The purpose of our systematic review and meta-analysis was to assess the effects of perioperative systemic corticosteroids on clinically significant outcomes in patients undergoing orthognathic surgery.

Methods
We conducted a systematic review of randomized controlled trials evaluating the effect of systemic corticosteroids in orthognathic surgery compared to placebo or any other intervention. We searched Medline, Embase, Cochrane Central, CINAHL, Lilacs, Scopus, and Web of science as well as references of included trials. Our primary outcome was the incidence of postoperative reintubation during the index hospitalization. Our secondary outcomes were hospital length of stay, facial edema reduction, and adverse events. We summarized data using Mantel-Haenszel random effect models.
**Results**

Of the 1098 trials retrieved, 8 were included (n=234). No trial evaluated the risk of postoperative reintubation. One trial evaluated the duration of hospital stay and showed no difference associated with the intervention. We observed a decreased in facial edema with the use of systemic corticosteroids (n=80, SMD -1.07, [-1.99, -0.16], I²=67%). Three trials reported side effects such as postoperative surgical site bleeding, hypersensitivity, and stomach discomfort with corticosteroids intake. The eight trials had an unclear risk of bias.

**Conclusion**

We observed no evidence of effect of systemic corticosteroids on the risk of reintubation and hospital length of stay in orthognathic surgery. Although facial edema reduction was observed to be improved with the intervention, adverse effects were inconsistently screened and reported. The use of systemic steroids in orthognathic surgery is thus not supported by strong evidence.
**Introduction**

Orthognathic surgery, performed to align the stomatognathic system and achieve adequate function and facial aesthetics, is a frequent procedure having an impact on the costs of the healthcare system in Canada. For comparison, in the United States of America, in 2008, there were 10,345 hospitalizations for orthognathic surgery, representing expenses amounting to **US$466,800,000**.(1) Due to the risk of postoperative airway obstruction following the intervention, pain and inability to eat properly mainly due to the important facial and upper airway swelling, patients undergo a brief hospitalization to ensure the stabilization of their condition. To decrease the duration of endotracheal intubation after surgery, decrease pain, minimize risks and shorten hospital stay, short-term high doses of corticosteroids have been used for decades. Even if the most recognized oral and maxillofacial surgery associations do not provide recommendations for the use of corticosteroids in orthognathic surgery, this practice has become a standard of care throughout the years in most centers.(2-4) Some trials suggest that their use could minimize edema, but clear evidence is lacking and there is no standardized protocol.(3, 5)

A recent narrative review stated that there are still areas of debate in this practice.(2) Poor evidence actually support the efficacy of systemic corticosteroids in orthognathic surgery.(6) There is no ideal therapeutic regimen.(2) However, short-term high doses of corticosteroids seem safe and withholding their use on the lack of evidence is difficult to justify.(2) A recent systematic review on the effects of perioperative corticosteroids indicated that they significantly decrease postoperative facial edema in patients undergoing orthognathic surgery.(7) However, decisive outcomes of this trial may have
been inadequately chosen by not including airway related outcomes. Methodological flaws were also identified and data is probably insufficient to confirm their conclusion.

The use of perioperative systemic corticosteroids in orthognathic surgery is frequent. Even if potential harms may be uncommon, they can be serious: healing delay, adrenal suppression, peptic ulcer, allergic reaction, cutaneous lesion, hyperglycaemia, glaucoma, induced psychosis, cardiovascular event, immunity suppression, and wound infection.\(^2,\ 7-9\) We thus conducted a systematic review of randomized controlled trials to assess the effects of systemic corticosteroids compared to placebo or other interventions on clinically significant outcomes in patients undergoing orthognathic surgery. Our specific aims were to assess the effects of systemic corticosteroids on airway-related outcomes, hospital length of stay, facial edema, and adverse effects. We hypothesized that the use of perioperative systemic corticosteroids in orthognathic surgery is supported by limited evidence.

**Methods**

This systematic review protocol was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/)(CRD42015029817).

**Design and search strategy**

We conducted a systematic review and meta-analysis of randomized controlled trials. We searched Medline (OVID), Embase (OVID), Cochrane Central Register of Controlled Trials, CINAHL, Lilacs, Scopus, and Web of science up to May 1\(^{st}\), 2016. We utilized
text-terms, Mesh and Emtree descriptors characterizing population (patients undergoing orthognathic surgery) and intervention (perioperative corticosteroids) in the search strategies. We used highly sensitive validated strategies to retrieve randomized controlled trials in Medline(10) and Embase(11). We adapted the Medline strategy for other electronic databases.(10) We detailed each search strategy in the appendix 1. We consulted maxillofacial surgery experts for potentially missed other relevant literature. We scanned references of included trials and previous systematic reviews for relevant trials. Two reviewers (SJ and PLD) independently screened and assessed eligibility of trials based on their title and abstract, then full-text. A third researcher (CB) acted as a mediator and was consulted throughout the selection process when no consensus was obtained between both assessors. A flow diagram for trial selection with reasons for exclusion at each step is presented in Figure 1.

**Trial eligibility**

We included randomized controlled trials of parallel-group or cross-over designs. We included trials examining the effects of any corticosteroid administered systemically during the perioperative period. Every route of administration, dose, and duration of treatment were considered. We also considered comparators such as any intervention, no intervention or placebo. We included trials evaluating any outcome. We also considered abstracts, incomplete publication and publications ahead of print. There was no exclusion based on language of publication.

Our primary outcome was the incidence of postoperative reintubation during the index hospitalization. Our secondary outcomes were hospital length of stay, facial edema and
any reported adverse effects of systemic corticosteroids. Other reported outcomes were also considered.

**Data abstraction**

One reviewer (SJ) removed trial duplicates electronically and by handsearching. Two reviewers (SJ, PLD) independently performed data extraction from included trials. A third reviewer (CB) acted as a mediator in cases of disagreements. We used a data extraction form to standardise the data collection. We extracted data for trial characteristics, population, intervention, comparator, and outcomes. We converted each medication dose to its methylprednisolone equivalent based on its anti-inflammatory effect.(7) (Appendix 2) We decreased orally administered doses were by 20% to match bioavailability in order to compare them with intravenous doses.(7) We extracted data from techniques objectively evaluating edema of the mandible area as a priority when multiple systems were used for facial edema assessment. We contacted authors to obtain information or data when missing. We consulted a translator for trials published in languages other than English, French or Spanish.

**Assessment of risk of bias**

We used the Cochrane Collaboration’s tool for assessing risk of bias to assess the risk of bias within and across included trials at the study level. We evaluated sequence generation, allocation concealment, incomplete outcome data, selective outcome reporting, and blinding of participants, personnel, and outcome assessors. Two independent reviewers (SJ, PLD) assessed the risk of bias in duplicate.
**Data synthesis**

We performed all statistical analyses using Cochrane Review Manager version 5.3. We described dichotomic data as odds ratios with 95% confidence interval and continuous data as standardized mean differences with 95% confidence interval. An odds ratio greater than 1 suggests more complication in patients using corticosteroids and an odds ratio less than 1 suggests more complication in the control group. A positive standardized mean difference favours the control group and a negative standardized mean difference favours the intervention group. We applied an empirically correction of 0.5 when original value was 0 for a specific event. We summarized data using Mantel-Haenszel random effect models for meta-analyses of dichotomic data and inverse variance random effect models for meta-analyses of continuous data. We performed an I^2 statistical test to assess statistical heterogeneity. This test estimates the percentage of variation between trial results that is due to heterogeneity rather than sampling error.(12) We performed subgroup analyses for time of evaluation, type of fixation, type of surgery, route of administration, corticosteroid treatment length, type of comparator, and risk of bias to find out potential sources of heterogeneity. We compared the duration of the intervention according to four categories: 1) preoperative only, 2) preoperative and peroperative, 3) preoperative, peroperative, and postoperative, and 4) postoperative only to facilitate comparison. We used funnel plot analyses to assess publication bias.
Results

Search results

We identified 677 citations that were assessed for eligibility. Eight trials (3, 13-19) (n=234) met our inclusion criteria, but two were excluded from the quantitative analyses because of unclear data precluding extraction.(3, 14)

Trials characteristics

The included trials had sample sizes varying from 14 to 42 patients. Six of the included trials were published in English (3, 13-15, 17, 18), one in French (16), and one in Portuguese (19). Three trials were performed in Europe (13, 16, 18), 3 in America (3, 15, 19), and 2 in Asia (14, 17). Six trials were performed on adolescents and adults (3, 13, 16-19), one trial included children aged from 6 to 18 years old (15), and demographic data was not mentioned in one trial (14). Five trials compared systemic corticosteroids to no intervention (14, 16-19), 2 trials used a conventional saline placebo (3, 15) while one used another intervention (metoclopramide) (13). Dexamethasone was used in 5 trials (3, 13-15, 19), methylprednisolone in one trial (16), prednisone in one trial (17), and betamethasone in one trial (18). Steroids dosage was fixed in 6 trials (3, 13, 14, 17-19) and calculated according to patients’ weight in the 2 others (15, 16). The intravenous route of administration was used in 7 of the 8 trials (3, 13-16, 18, 19). Corticosteroids were administered via a single dose (13, 14) or via multiple doses for 1 day (3), 2 days (15, 19), 3 days (16, 18) or 14 days (17). Six trials evaluated monomaxillary procedures (3, 14, 16-19), one trial evaluated bimaxillary surgeries (15), and one trial did not specify the type of procedure performed (13). The latter was an abstract for which no full-text
publication was available. Non-rigid fixation was used in one trial (15), rigid fixation in 2 trials (16, 18), and 5 trials did not mention the type of fixation used (3, 13, 14, 17, 19). Most trials used facial edema as the main outcome. (3, 14, 16, 18, 19) Other outcomes were postoperative nausea and vomiting (13), duration of intubation (15), sensory return (14, 17), delay before oral intake (15), laboratory inflammation values (3, 14, 16), and maximum incisal opening (14). Financial support was not mentioned in 6 trials. (3, 13-16, 19) One trial was supported by its affiliated hospital (18) and one trial by a grant for the ‘promotion of science’ (17). Potential conflict of interest of the investigators was not mentioned in 7 trials (3, 13-17, 19) and authors had no conflict of interest to declare in the other trial (18). Key characteristics of the included trials are presented in table 1.

**Risk of bias assessment**

We assigned an unclear risk of bias to eight trials (3, 13-19). Two trials (16, 18) had an adequate sequence generation while the others did not mention randomization technique (3, 13-15, 17, 19). Three trials (3, 15, 18) had an appropriate method of allocation concealment. Four trials were blinded. (3, 15, 16, 18) Three trials did not mention reasons for attrition and missing data. (15-17) We performed a risk of bias summary to identify bias for each evaluated outcomes. (Figure 2)

**Incidence of postoperative reintubation**

No trial evaluated the risk of postoperative reintubation.
**Hospital length of stay**

One trial evaluated the duration of hospital stay, showing no difference between the corticosteroid and placebo groups.(18) The hospital stay was 2.3 ± 0.9 days for patients receiving the placebo, while it was 2.6 ± 0.7 days for those receiving only preoperative medication, and 2.0 ± 0.4 days when preoperative and postoperative systemic corticosteroids were given. Patients receiving the latter treatment had a shorter hospital stay versus patients receiving preoperative medication only (p=0.049). Another trial reported an hospital stay ranging from 8 to 10 days, even though it was not an intended outcome.(16) Measurement of inflammatory markers for 7 days postoperative in the latter trial may explain the large difference in hospital stay observed between the two trials.(16)

**Facial edema**

Five trials evaluated the effect of corticosteroids on facial edema.(3, 14, 16, 18, 19) (Table 2) Two trials were excluded from quantitative analysis because data was only presented as percentages precluding extraction.(3, 14) One trial evaluated facial edema at multiple time points (1 day, 7 days, 2 months, 6 months) and showed no significant treatment effect with the use of systemic corticosteroids.(18) One trial showed significant decrease of edema in the masseter muscle area with a 16 mg preoperative dose of dexamethasone compared with a placebo.(14) Our statistical analyses showed a beneficial effect of systemic corticosteroids for facial edema (3 trials, n=80, SMD -1.07, [-1.99, -0.15], I²=68%).(16, 18, 19) (Supplementary file 1) Subgroup analyses showed that these results seem to be associated with the evaluation of edema at 48 hours
postoperatively and when corticosteroids were administered by intravenous route (2 trials, n=46, SMD -1.49, [-2.40 to -0.58], $I^2=32\%$).(16, 19) (Supplementary file 2 and 3)

**Adverse effects**

Three of the 8 included trials reported side effects. Among these effects, there were two cases of postoperative surgical site bleeding(15), one case of gastro-intestinal discomfort(17), and one case of hypersensitivity(19) associated with corticosteroids intake. One of the two reported bleeding cases needed nasal packing and subsequent rewiring, and both cases required blood transfusions.(15) As for the gastro-intestinal episode, it occurred during the two-week corticosteroid treatment and no further complication ensued.(17) No details were given on the hypersensitivity case.(19) Side effects were not systematically screened and reported in any trial. The overall incidence of adverse events was not mentioned in any trial.

**Duration of intubation**

One trial evaluated the duration of intubation before an air leak around the nasotracheal tube was audible.(15) A subjective positive effect of corticosteroids in patients having maxillary osteotomies was reported without statistical comparison.

**Postoperative nausea and vomiting**

One trial evaluated the incidence of early postoperative nausea and vomiting following orthognathic surgery.(13) Corticosteroids seemed to have a statistically significant effect on this outcome when compared with metoclopramide.
**Time until oral intake**

One trial evaluated the postoperative length of time before fluid intake. (15) No statistical difference was observed.

**Inflammatory markers**

Three trials evaluated inflammatory markers following orthognathic surgery. (3, 14, 16) C-reactive protein, fibrinogen, granulocytes, and lymphocytes statistically were statistically decreased with corticosteroids. (3, 16) The other trial did not mention details on the examined markers. (14)

**Tactile sensation**

Three trials evaluated mechanical, thermal or pain sensation in the chin and lower lip region following orthognathic surgery. (14, 17, 18) One trial showed a statistical improvement in mechanical-touch threshold with postoperative corticosteroids. (17) One trial did not observe a treatment effect on neurosensory disturbances. (18) The other trial did not mention details on the evaluated submental sensation. (14)

**Publication bias**

Visual inspection using a funnel plot revealed that retrieved trials were of small sample size and that the absence of large sample size trials was obvious. (Supplementary file 4) We could not conclude on publication bias.
Discussion

In our systematic review, we retrieved no trial on the effect of systemic corticosteroids on the risk of reintubation following orthognathic surgery and thus no evidence of effect for this clinically significant outcome measure. We observed no evidence of effect on hospital length of stay, but a reduction of facial edema. Healing delay, infections, or other potential side effects were not systematically screened or reported.

Our results are in contrast with current beliefs and opinions in the oral and maxillofacial surgery community. We realize that systemic corticosteroid administration in patients undergoing orthognathic surgery is a controversial topic. As stated decades ago, very few trials present a postoperative morbidity reduction or an improvement of the global end result associated with this intervention. (20) Postoperative airway compromise associated with facial edema has been a concern in orthognathic surgery for a long time. (21) A health care survey revealed that steroids appear to be a factor in permitting early extubation. (21) A narrative review promoted the use of corticosteroids among oral and maxillofacial surgeons to prevent lip, facial, and parapharyngeal edema causing respiratory complications. (22) A more recent survey performed in Finland reported that 100% of oral and maxillofacial surgeon respondents use perioperative corticosteroids for orthognathic surgery procedures to reduce swelling. (23) A recent systematic review suggested a potential effect of perioperative corticosteroid on facial edema reduction. (7)

In our systematic review, we observed a treatment effect of systemic corticosteroids on facial edema, but not for more clinically significant outcomes. Our systematic review was more comprehensive, included more trials, and was designed following strict methodological standards for conducting systematic reviews based on the Cochrane...
Handbook for Systematic Reviews of Interventions. We must however be cautious with the conclusions we draw from our observations. Our analyses are mainly based on three trials with small sample size and an unclear risk of bias. Complications were not screened for in a thorough manner in the included trials, but we identified potential side effects associated with the intervention. The latter are sparsely described in the current literature. As an example, in a retrospective trial, two cases of gastrointestinal complications associated with steroid administration were reported.(24) Both were managed adequately with medication cessation.

**Limitations and Strengths**

Our systematic review has some limitations. First, the limited literature in the field, the fact that most trials looked at a small number of outcomes, that most of them were surrogates of clinically significant ones and that none looked at our primary outcome measure, precluded to evaluate the impact on clinically significant outcomes that should drive practice changes. The absence of data on our primary outcome measure is an important finding showing that the intervention is currently based on surrogate outcomes or outcomes with lower clinical significance. Second, the limited number of trials and the small sample size of these trials made that the whole current body of evidence come from 234 patients only. Also, included trials were considered having an unclear risk of bias, thus limiting the quality of the evidence and the strength of our conclusion. Moreover, our meta-analysis showed important statistical heterogeneity that could not be explained by our planned subgroup analyses. Although planned a priori, some of these analyses could not be performed due to the limited number of trials. One of them is the impact of the type of surgery (monomaxillary vs bimaxillary). This again highlights
the limited amount of data on the topic. Important secondary outcome measures, such as duration of intubation, postoperative nausea and vomiting, time until postoperative oral intake, postoperative inflammatory markers, and postoperative tactile sensation, were considered in our systematic review. Again, these outcomes could not be further evaluated on a quantitative meta-analytical manner because of the small number of trials assessing them. Even though limited observations can be withdrawn from these evaluated outcomes, the consideration of these outcomes in our review exemplifies our exhaustive methodology. Nonetheless, our systematic review was conducted following a rigorous standardized methodology and followed the publication of the protocol. Our search strategy was comprehensive and highly sensitive thus ensuring that the data retrieved represent the current literature.

**Conclusions and implications for practice**

We observed no evidence of perioperative systemic steroids on the risk of reintubation and hospital length of stay in orthognathic surgery. However, facial edema reduction was improved with steroids, but adverse effects were not systematically screened and reported, and published trials are at unclear risk of bias. In this context, the use of systemic steroids in orthognathic surgery is thus not supported by strong evidence. Further research must be performed to evaluate outcomes that are more pertinent for patients such as airway-related outcomes or hospital length of stay, but more so, the potential risks on significant adverse events such as infections and non-healing.
Acknowledgments

We thank Mrs. Marie-Claude Laferrière for her help with the search strategies and Mrs. Kaoutar Ennour-Idrissi for her help with the research methodology. Alexis Turgeon is the Canada Research Chair in Critical Care Neurology and Trauma.

Declarations of interest

Authors declare none.
References

10. Glanville JM, Lefebvre C Fau - Miles JNV, Miles Jn Fau - Camosso-Stefinovic J, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. (1558-9439 (Electronic)).
11. Lefebvre C, Eisinga A Fau - McDonald S, McDonald S Fau - Paul N, Paul N. Enhancing access to reports of randomized trials published world-wide--the contribution of EMBASE records to the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. (1742-7622 (Electronic)).
20. Bourke DL. Use of steroids during orthognathic surgery. (0278-2391 (Print)).
21. Haber-Cohen A, Rothman M. A survey of extubation practices following orthognathic surgery. (0278-2391 (Print)).
22. Guernsey Lh Fau - DeChamplain RW, DeChamplain RW. Sequelae and complications of the intraoral sagittal osteotomy in the mandibular rami. (0030-4220 (Print)).
**Figure Legends**

Figure 1. Flow diagram of trials

Figure 2. Risk of bias of included trials

[Green=Low risk of bias. Yellow=Unclear risk of bias].

Supplementary file 1. Forest plot of facial edema

Supplementary file 2. Forest plot of facial edema by time of evaluation

Supplementary file 3. Forest plot of facial edema by route of administration

Supplementary file 4. Funnel plot of facial edema comparison
<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Type of surgery</th>
<th>Type of fixation</th>
<th>Drug regimen</th>
<th>Comparator</th>
<th>Side effects (Number)</th>
<th>Outcome measures</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gecaj-Gashi et al. (2012)</td>
<td>21</td>
<td></td>
<td>U</td>
<td>Dexamethasone 8mg IV 1 minute prior to induction</td>
<td>Other intervention (Metoclopramide)</td>
<td>NM</td>
<td>PONV</td>
<td>Albania</td>
</tr>
<tr>
<td>Munro et al. (1986)</td>
<td>17</td>
<td>M + B</td>
<td>NR</td>
<td>Dexamethasone 0.5mg/kg IV at induction; 0.25mg/kg/day IV in 4 divided doses for 48 hours</td>
<td>Placebo (Saline)</td>
<td>Yes (2 in IG)</td>
<td>Mean intubation time; Time until oral intake; Facial edema</td>
<td>Canada</td>
</tr>
<tr>
<td>Peillon et al. (1996)</td>
<td>16</td>
<td>M</td>
<td>R</td>
<td>Methylprednisolone 1.5mg/kg IV at induction; 1.5mg/kg/day IV for 3 days</td>
<td>No intervention</td>
<td>No</td>
<td>Facial edema</td>
<td>France</td>
</tr>
<tr>
<td>Seo et al. (2004)</td>
<td>20</td>
<td>M</td>
<td>U</td>
<td>Prednisone 30mg PO for 7 days; 15mg PO for 4 days; 5mg PO for 3 days</td>
<td>No intervention</td>
<td>Yes (1 in IG)</td>
<td>Mechanical and thermal sensitivity</td>
<td>Japan</td>
</tr>
<tr>
<td>Silveira et al. (1988)</td>
<td>8</td>
<td>M</td>
<td>U</td>
<td>Dexamethasone 20mg IV 15-30 minutes prior to induction; 10mg IV q8h for 48 hours</td>
<td>No intervention</td>
<td>Yes (1 in IG)</td>
<td>Facial edema</td>
<td>Brazil</td>
</tr>
<tr>
<td>Weber et al. (1994)</td>
<td>16</td>
<td>M</td>
<td>U</td>
<td>2 protocols: Dexamethasone 16mg IV immediately before induction or Dexamethasone 16mg IV immediately before induction; 8mg IV q6h x 3 doses</td>
<td>Placebo (Saline)</td>
<td>Yes (1 in CG)</td>
<td>Facial edema; Inflammatory markers</td>
<td>USA</td>
</tr>
<tr>
<td>Widar et al. (2015)</td>
<td>25</td>
<td>M</td>
<td>R</td>
<td>2 protocols: Betamethasone 4mg PO day before surgery; 8mg IV at induction; 4mg PO on POD 1 or 16mg IV at induction</td>
<td>No intervention</td>
<td>No</td>
<td>Facial edema; Pain and mechanical sensitivity</td>
<td>Sweden</td>
</tr>
<tr>
<td>Abukawa et al. (2015)</td>
<td>16</td>
<td>M</td>
<td>U</td>
<td>2 protocols: Dexamethasone 8mg IV preoperative or Dexamethasone 16mg IV preoperative</td>
<td>No intervention</td>
<td>NM</td>
<td>Facial edema (rate of increase in masseter muscle thickness); Maximum incisal opening; Submental sensation; Inflammatory markers</td>
<td>Japan</td>
</tr>
</tbody>
</table>

U=Unknown; M=Monomaxillary; B=Bimaxillary; R=Rigid fixation; NR=Non-rigid fixation; NM=Not mentioned; CG=Control group; IG=Intervention group; PONV=Postoperative nausea and vomiting; POD=Postoperative day; USA=United States of America
Table 2. Subgroup analyses and overall estimate for the effect of steroids on facial edema

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Number of trials</th>
<th>Number of participants</th>
<th>Standardized mean difference (95% CI)</th>
<th>$I^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours postoperative</td>
<td>1</td>
<td>34</td>
<td>-0.32 (-1.03 to 0.39)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>48 hours postoperative</td>
<td>2</td>
<td>46</td>
<td>-1.49 (-2.40 to -0.58)</td>
<td>32</td>
</tr>
<tr>
<td><strong>Type of fixation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid</td>
<td>2</td>
<td>66</td>
<td>-0.74 (-1.58 to 0.10)</td>
<td>62</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>14</td>
<td>-2.18 (-3.60 to -0.75)</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomaxillary</td>
<td>3</td>
<td>80</td>
<td>-1.07 (-1.99 to -0.15)</td>
<td>68</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-venous</td>
<td>2</td>
<td>46</td>
<td>-1.49 (-2.40 to -0.58)</td>
<td>32</td>
</tr>
<tr>
<td>Combined</td>
<td>1</td>
<td>34</td>
<td>-0.32 (-1.03 to 0.39)</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Treatment length</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative, peroperative,</td>
<td>3</td>
<td>80</td>
<td>-1.07 (-1.99 to -0.15)</td>
<td>68</td>
</tr>
<tr>
<td>and postoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of comparator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No intervention</td>
<td>3</td>
<td>80</td>
<td>-1.07 (-1.99 to -0.15)</td>
<td>68</td>
</tr>
<tr>
<td><strong>Methodological quality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear risk of bias</td>
<td>3</td>
<td>80</td>
<td>-1.07 (-1.99 to -0.15)</td>
<td>68</td>
</tr>
<tr>
<td><strong>Overall estimate</strong></td>
<td>3</td>
<td>80</td>
<td>-1.07 (-1.99 to -0.15)</td>
<td>68</td>
</tr>
</tbody>
</table>
Appendix 1

Search strategies

Cochrane Central Register of Controlled Trials:

#1 methapred:ti,ab,kw or betaject:ti,ab,kw or decadron:ti,ab,kw or medrol:ti,ab,kw or celestone:ti,ab,kw or betamethasone:ti,ab,kw or methylprednisolone:ti,ab,kw or dexamethasone:ti,ab,kw or steroid:ti,ab,kw or glucocorticoid:ti,ab,kw or corticosteroid:ti,ab,kw or corticoid:ti,ab,kw or "adrenal cortex hormone":ti,ab,kw or solumedrol:ti,ab,kw or depomedrol:ti,ab,kw

#2 MeSH descriptor: [Steroids] explode all trees

#3 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#4 #1 or #2 or #3

#5 mandibular:ti,ab,kw or maxillary:ti,ab,kw or craniomaxillofacial:ti,ab,kw or bimaxillary:ti,ab,kw or cleft:ti,ab,kw or orthognathic*:ti,ab,kw or zygomatic:ti,ab,kw or lefort:ti,ab,kw or "sagittal split":ti,ab,kw or maxillomandibular:ti,ab,kw or ramus:ti,ab,kw or jaw:ti,ab,kw

#6 Repositioning:ti,ab,kw or advancement:ti,ab,kw or surger*:ti,ab,kw or osteotom*:ti,ab,kw or impaction:ti,ab,kw or setback:ti,ab,kw or distraction:ti,ab,kw or procedure*:ti,ab,kw

#7 MeSH descriptor: [Osteotomy] explode all trees

#8 MeSH descriptor: [Bone Lengthening] explode all trees

#9 #6 or #7 or #8

#10 #5 and #9

#11 ivro:ti,ab,kw or bsso:ti,ab,kw or lefort:ti,ab,kw or "sagittal split ramus":ti,ab,kw or "palatal expansion":ti,ab,kw or surgical orthodontic*:ti,ab,kw or genioplasty:ti,ab,kw

#12 MeSH descriptor: [Orthognathic Surgical Procedures] explode all trees

#13 MeSH descriptor: [Cleft Palate] explode all trees and with qualifier(s): [Surgery - SU]

#14 MeSH descriptor: [Mandible] explode all trees and with qualifier(s): [Surgery - SU]

#15 MeSH descriptor: [Maxilla] explode all trees and with qualifier(s): [Surgery - SU]

#16 MeSH descriptor: [Chin] explode all trees and with qualifier(s): [Surgery - SU]

#17 MeSH descriptor: [Mandibular Advancement] explode all trees

#18 MeSH descriptor: [Retrognathia] explode all trees and with qualifier(s): [Surgery - SU]
MeSH descriptor: [Alveolar Ridge Augmentation] explode all trees

MeSH descriptor: [Orthognathic Surgery] explode all trees

#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#10 or #21

#22 and #4 in Trials (Word variations have been searched)

Embase:

#1 methapred:ab,ti OR betaject:ab,ti OR decadron:ab,ti OR medrol:ab,ti OR celestone:ab,ti OR betamethasone:ab,ti OR methylprednisolone:ab,ti OR dexamethasone:ab,ti OR steroid:ab,ti OR glucocorticoid:ab,ti OR corticosteroid:ab,ti OR corticoid:ab,ti OR 'adrenal cortex hormone':ab,ti OR solumedrol:ab,ti OR depomedrol:ab,ti OR 'steroids'/exp

#2 mandibular:ab,ti OR 'mandible'/exp OR 'chin'/exp OR maxillary:ab,ti OR 'maxilla'/exp OR craniomaxillofacial:ab,ti OR bimaxillary:ab,ti OR cleft:ab,ti OR orthognathic*:ab,ti OR zygomatic:ab,ti OR lefort:ab,ti OR 'sagittal split':ab,ti OR maxillomandibular:ab,ti OR ramus:ab,ti OR jaw:ab,ti OR 'jaw'/exp OR 'cleft palate'/exp AND (repositioning:ab,ti OR advancement:ab,ti OR surger*:ab,ti OR osteotom*:ab,ti OR impaction:ab,ti OR setback:ab,ti OR distraction:ab,ti OR procedure*:ab,ti)

#3 'mandible osteotomy'/exp OR 'mandible reconstruction'/exp OR 'maxilla osteotomy'/exp OR 'orthognathic surgery'/exp OR 'palatoplasty'/exp OR 'maxillofacial surgery'/exp OR 'orthodontics'/exp OR ivro:ab,ti OR bsso:ab,ti OR lefort:ab,ti OR 'sagittal split ramus':ab,ti OR 'palatal expansion':ab,ti OR surgical AND orthodontic*:ab,ti OR genioplasty:ab,ti OR 'orthodontics'/exp

#4 #2 OR #3

#5 #1 AND #4

#6 random$ OR factorial$ OR crossover$ OR cross AND over$ OR 'cross over'$ OR placebo$ OR double$ AND adj AND blind$ OR single$ AND adj AND blind$ OR assign$ OR allocate$ OR volunteer$

#7 'crossover procedure'/exp

#8 'double blind procedure'/exp

#9 'randomized controlled trial'/exp

#10 'single blind procedure'/exp

#11 #7 OR #8 OR #9 OR #10

#12 #6 OR #11

#13 #5 AND #12
**Medline:**

#1 ([(methapred or betaject or decadron or medrol or celestone or betamethasone or methylprednisolone or dexamethasone or steroid or glucocorticoid or corticosteroid or corticoid or "adrenal cortex hormone" or solumedrol or depomedrol).mp. or exp steroids/ or exp adrenal cortex hormones/) and (((mandibular or maxillary or craniomaxillofacial or bimaxillary or cleft or orthognathic* or zygomatic or lefort or "sagittal split" or maxillomandibular or ramus or jaw).mp. and ((Repositioning or advancement or surger* or osteotom*).mp. or exp Osteotomy/ or exp Bone Lengthening/ or impaction.mp. or setback.mp. or distraction.mp. or procedure*.mp.)) or ((ivro or bsso or lefort or "sagittal split ramus" or "palatal expansion" or surgical orthodontic* or genioplasty).mp. or exp Orthognathic Surgical Procedures/ or exp Cleft Palate/su or exp Mandible/su or exp Maxilla/su or exp Chin/su or exp Mandibular Advancement/ or exp Retrognathia/su or exp Alveolar Ridge Augmentation/ or exp Orthognathic Surgery/))

#2 randomized controlled trial.pt.

#3 controlled clinical trial.pt.

#4 randomized.ab.

#5 placebo.ab.

#6 drug therapy.fs.

#7 randomly.ab.

#8 trial.ab.

#9 groups.ab.

#10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

#11 exp animals/ not humans.sh.

#12 10 not 11

#13 1 and 12

**LILACS:**

(tw:((tw:(estud$)) OR (tw:(clin$)) OR (ab:(grupo$)) OR (CT:(comparative study)) OR (tw:(placebo$)) OR (tw:(random$)) OR (ti:(compara$)) OR (ti:(tratamiento)) OR (tw:(control$)) OR (mh:(/dt))))) AND (tw:(methapred) or tw:(betaject) or tw:(decadron) or tw:(medrol) or tw:(celestone) or tw:(betamethasone) or tw:(methylprednisolone) or tw:(dexamethasone) or tw:(steroid) or tw:(glucocorticoid) or tw:(corticosteroid) or tw:(corticoid) or tw:("adrenal cortex hormone") or tw:(solumedrol) or tw:(depomedrol) or mh:("steroids" or "adrenal cortex hormones") and (((tw:(mandibular) or tw:(maxillary) or
tw:(craniomaxillofacial) or tw:(bimaxillary) or tw:(cleft) or tw:(orthognathic$) or tw:(zygomatic) or tw:(lefort) or tw:("sagittal split") or tw:(maxillomandibular) or tw:(ramus) or tw:(jaw)) and (tw:(repositioning) or tw:(advancement) or tw:(surgery$) or tw:(osteotom$) or mh:("Osteotomy" or "Bone Lengthening") or tw:(impaction) or tw:(setback) or tw:(distraction) or tw:(procedure$)) or (tw:ivr$) or tw:bss$ or tw:lefort or tw:"sagittal split ramus") or tw:"palatal expansion") or tw:(surgical orthodontics) or mh:("Orthognathic Surgical Procedures" OR "Cleft Palate/SU" OR "Mandible/SU" OR "Maxilla/SU" OR "Chin/SU" OR "Mandibular Advancement" OR "Retrognathia/SU" OR "Alveolar Ridge Augmentation" OR "Orthognathic Surgery"))

CINAHL:

S14  S1 and S13
S13  S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12
S12  TX allocat* random*
S11  (MH "Quantitative Studies")
S10  (MH "Placebos")
S9   TX placebo*
S8   TX random* allocat*
S7   (MH "Random Assignment")
S6   TX randomi* control* trial*
S5   TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doub* n1 blind*) or (doub* n1 mask*)) or TX ( (tripl* n1 blind*) or (tripl* n1 mask*) ) or TX ( (trebl* n1 blind*) or (trebl* n1 mask*) )
S4   TX clinic* n1 trial*
S3   PT Clinical trial
S2   (MH "Clinical Trials+")
S1   (TI methapred OR TI betaject OR TI decadron OR TI medrol OR TI celestone OR TI betamethasone OR TI methylprednisolone OR TI dexamethasone OR TI steroid OR TI glucocorticoid OR TI corticosteroid OR TI corticoid OR TI "adrenal cortex hormone" OR TI solumedrol OR TI depomedrol OR AB methapred OR AB betaject OR AB decadron OR AB medrol OR AB celestone OR AB betamethasone OR AB methylprednisolone OR AB dexamethasone OR AB steroid OR AB glucocorticoid OR AB corticosteroid OR AB corticoid OR AB "adrenal cortex hormone" OR AB solumedrol OR AB depomedrol OR (MH "steroids+") OR (MH "adrenal cortex hormones+") OR (MH "Antiinflammatory Agents, Steroidal+") AND (((TI mandibular OR TI maxillary OR TI craniomaxillofacial OR TI bimaxillary OR TI cleft OR TI orthognathic* OR TI zygomatic OR TI lefort OR TI "sagittal split" OR TI maxillomandibular OR TI ramus OR TI jaw OR AB mandibular OR AB maxillary OR AB craniomaxillofacial OR AB bimaxillary OR AB cleft OR AB orthognathic* OR AB zygomatic OR AB lefort OR AB "sagittal split" OR AB maxillomandibular OR AB ramus OR AB jaw) AND (TI Repositioning OR TI advancement OR TI surgery* OR TI osteotom* OR (MH "Osteotomy+") OR (MH "Bone Lengthening+") OR TI impaction OR TI setback OR TI distraction OR TI procedure* OR AB Repositioning OR AB advancement OR AB surgery* OR AB osteotom* OR AB impaction OR AB setback
Scopus:

((TITLE(methapred) OR ABS(methapred) OR TITLE(betaject) OR ABS(betaject) OR TITLE(decadron) OR ABS(decadron) OR TITLE(medrol) OR ABS(medrol) OR TITLE(celestone) OR ABS(celestone) OR TITLE(betamethasone) OR ABS(betamethasone) OR TITLE(methylprednisolone) OR ABS(methylprednisolone) OR TITLE(dexamethasone) OR ABS(dexamethasone) OR TITLE(steroid) OR ABS(steroid) OR TITLE(glucocorticoid) OR ABS(glucocorticoid) OR TITLE(corticosteroid) OR ABS(corticosteroid) OR TITLE(corticoid) OR ABS(corticoid) OR TITLE(adrenal cortex hormone) OR ABS(adrenal cortex hormone) OR TITLE(solumedrol) OR ABS(solumedrol) OR TITLE(depomedrol) OR ABS(depomedrol)) AND (((TITLE(mandibular) OR ABS(mandibular) OR TITLE(maxillary) OR ABS(maxillary) OR TITLE(craniomaxillofacial) OR ABS(craniomaxillofacial) OR TITLE(bimaxillary) OR ABS(bimaxillary) OR TITLE(cleft) OR ABS(cleft) OR TITLE(orthognathic*) OR ABS(orthognathic*) OR TITLE(zygomatic) OR ABS(zygomatic) OR TITLE(lefteft) OR ABS(lefteft) OR TITLE("sagittal split") OR ABS("sagittal split") OR TITLE(maxillomandibular) OR ABS(maxillomandibular) OR TITLE(ramus) OR ABS(ramus) OR TITLE(jaw) OR ABS(jaw)) AND (TITLE(repositioning) OR ABS(repositioning) OR TITLE(advancement) OR ABS(advancement) OR TITLE(surger*) OR ABS(surger*) OR TITLE(osteotom*) OR ABS(osteotom*) OR TITLE(impaction) OR ABS(impaction) OR TITLE(setback) OR ABS(setback) OR TITLE(orthognathic surgery*) OR TITLE(surgical orthodontic*) OR TITLE(genioplasty) OR ABS(genioplasty)))) AND (((TITLE-ABS(randomized controlled trial)) OR (TITLE-ABS(controlled clinical trial)) OR (TITLE-ABS(placebo)) OR (TITLE-ABS(drug therapy)) OR (TITLE-ABS(randomly)) OR (TITLE-ABS(trial)) OR (TITLE-ABS(groups))) AND NOT (exp animals/ not humans))

Web of science:

#1 (TS=methapred OR TS=betaject OR TS=decadron OR TS=medrol OR TS=celestone OR TS=betamethasone OR TS=methylprednisolone OR TS=dexamethasone OR TS=steroid OR...
TS=glucocorticoid OR TS=corticosteroid OR TS=corticoid OR TS="adrenal cortex hormone" OR TS=solumedrol OR TS=depomedrol) AND (((TS=mandibular OR TS=maxillary OR TS=craniofacial OR TS=bimaxillary OR TS=cleft OR TS=orthognathic* OR TS=zygomatic OR TS=lefort OR TS="sagittal split" OR TS=maxillomandibular OR TS=ramus OR TS=jaw) AND (TS=repositioning OR TS=advancement OR TS=surger* OR TS=osteotom* OR TS=impaction OR TS=setback OR TS=distraction OR TS=procedure*)) OR (TS=ivro OR TS=bsso OR TS=lefort OR TS="sagittal split ramus" OR TS="palatal expansion" OR TS=surgical orthodontic* OR TS=genioplasty))

#2 TS="randomized controlled trial"

#3 TS="controlled clinical trial"

#4 TS=randomized

#5 TS=placebo

#6 TS="drug therapy"

#7 TS=randomly

#8 TS=trial

#9 TS=groups

#10 #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2

#11 #10 AND #1
## Appendix 2

### Equivalent doses of corticosteroids with regard to anti-inflammatory effect

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Equivalent dose with regard to anti-inflammatory effect (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>5</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Records identified through database searching (n=1097)
  - Cochrane Central Register of Controlled Trials (n=83)
  - Embase (n=65)
  - Medline (n=371)
  - Lilacs (n=9)
  - CiNAHL (n=30)
  - Scopus (n=137)
  - Web of science (n=402)

Records after duplicates removed (n=676)

Records screened (n=676)

Records excluded (n=663)
  - Not a randomized controlled trial (n=4)
  - Local administration of corticosteroid treatment (n=1)
  - Duplicate results (n=1)

Full-text articles assessed for eligibility (n=13)

Full-text articles excluded (n=6)

Studies included in qualitative synthesis (n=7)

Full-text articles excluded (n=1)
  - Data presented in figures only, precluding extraction

Studies included in quantitative synthesis (n=6)
Figure 2

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

Legend:
- Green: Low risk of bias
- Yellow: Unclear risk of bias
- Red: High risk of bias
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Corticosteroid Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>SD</th>
<th>Total Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfill et al. 1996</td>
<td>3.4631</td>
<td>16</td>
<td>3.9833</td>
<td>16</td>
<td>37.9%</td>
<td>-1.18 [-1.94, -0.42]</td>
<td></td>
</tr>
<tr>
<td>Silveira et al. 1988</td>
<td>1.25</td>
<td>.89</td>
<td>8</td>
<td>.3</td>
<td>23.0%</td>
<td>-2.18 [-3.60, -0.75]</td>
<td></td>
</tr>
<tr>
<td>Widar et al. 2015</td>
<td>262.6818</td>
<td>22</td>
<td>271</td>
<td>273.996</td>
<td>12</td>
<td>39.2%</td>
<td>-0.32 [-1.03, 0.39]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>46</td>
<td>34</td>
<td>100%</td>
<td></td>
<td>-1.07 [-1.99, -0.15]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.43; Chi² = 6.16, df = 2 (P = 0.05); I² = 68%
Test for overall effect: Z = 2.29 (P = 0.02)
### Supplementary file 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Corticosteroid Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widar et al. 2015</td>
<td>262.68 ± 23.97</td>
<td>22</td>
<td>271</td>
<td>27.39 ± 9.6</td>
<td>12</td>
<td>39.2%</td>
<td>-0.32</td>
<td>[-1.03, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td></td>
<td>271</td>
<td>27.39 ± 9.6</td>
<td>12</td>
<td>39.2%</td>
<td>-0.32</td>
<td>[-1.03, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.89 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.2 48h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peillon et al. 1996</td>
<td>3 ± 2.46 ± 31</td>
<td>16</td>
<td>7</td>
<td>3.98 ± 3.3</td>
<td>16</td>
<td>37.9%</td>
<td>-1.18</td>
<td>[-1.94, -0.42]</td>
<td></td>
</tr>
<tr>
<td>Silveira et al. 1988</td>
<td>1.25 ± 0.89</td>
<td>8</td>
<td>3</td>
<td>0.5</td>
<td>6</td>
<td>23.0%</td>
<td>-2.18</td>
<td>[-3.60, -0.75]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td></td>
<td>22</td>
<td>60.8%</td>
<td></td>
<td>1.49</td>
<td>-2.40</td>
<td>-0.58</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.16; Chi² = 1.48, df = 1 (P = 0.22); I² = 32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.22 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.4 More than 72h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>46</td>
<td></td>
<td>34</td>
<td>100.0%</td>
<td></td>
<td>-1.07</td>
<td>[-1.99, -0.15]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.43; Chi² = 6.16, df = 2 (P = 0.05); I² = 68%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.29 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 3.95, df = 1 (P = 0.05), I² = 74.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study or Subgroup</td>
<td>Corticosteroid</td>
<td>Control</td>
<td>Std. Mean Difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>---------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
<td></td>
</tr>
<tr>
<td>1.5.1 PO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5.2 IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellow et al. 1996</td>
<td>3</td>
<td>2.4631</td>
<td>16</td>
<td>7</td>
<td>3.9833</td>
<td>16</td>
<td>37.9%</td>
<td>-1.18 [-1.94, -0.42]</td>
<td></td>
</tr>
<tr>
<td>Silveira et al. 1988</td>
<td>1.25</td>
<td>0.89</td>
<td>8</td>
<td>3</td>
<td>0.5</td>
<td>6</td>
<td>23.0%</td>
<td>-2.18 [-3.60, -0.75]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td></td>
<td></td>
<td>22</td>
<td>50.8%</td>
<td></td>
<td></td>
<td>-1.49 [-2.40, -0.58]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau^2 = 0.16; Chi^2 = 1.48, df = 1 (P = 0.22); I^2 = 32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 3.22 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5.3 Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widar et al. 2015</td>
<td>262.6818</td>
<td>23.975</td>
<td>22</td>
<td>271</td>
<td>27.3996</td>
<td>12</td>
<td>39.2%</td>
<td>-0.32 [-1.03, 0.39]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 0.89 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>46</td>
<td>34</td>
<td>100.0%</td>
<td>-1.07 [-1.99, -0.15]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau^2 = 0.43; Chi^2 = 6.16, df = 2 (P = 0.05); I^2 = 68%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 2.29 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 3.95, df = 1 (P = 0.05), I^2 = 74.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Financial Relationships Disclosure Form**

**For Faculty, Authors, Committee/Board Members, Reviewers and Staff**

Organizations accredited by the American Dental Association Continuing Education Recognition Program (ADA CERP) and Accreditation Council for Continuing Medical Education (ACCME) are required to identify and resolve all potential conflicts of interest with any individual in a position to influence and/or control the content of CDE/CME activities. A conflict of interest will be considered to exist if: (1) the individual has a *relevant financial relationship*; that is, he/she has received financial benefits of any amount, within the past 12 months, from a *commercial interest* (an entity producing, marketing, re-selling, or distributing health care goods or services consumed by or used on, patients), and (2) the individual is in a position to affect the content of CDE/CME regarding the products or services of the commercial interest.

All individuals in a position to influence and/or control the content of AAOMS CDE/CME activities are required to disclose to the AAOMS, and subsequently to learners: (1) any relevant financial relationship(s) they have with a commercial interest, or (2) if they do not have a relevant financial relationship with a commercial interest.

Failure to provide disclosure information in a timely manner prior to the individual’s involvement will result in the disqualification of the potential Faculty, Author, Committee/Board Member, or Staff, from participating in the CDE/CME activity.

**Type of CME activity:** JOMS Manuscript Submission

**Title of Submission:** Perioperative Systemic Corticosteroids in Orthognathic Surgery: a Systematic Review and Meta-Analysis

**Name:** Simon Jean  
**Date:** 2016-11-21

Please check one to indicate your role:

- [ ] Faculty  
- [x] Author  
- [ ] Committee Member (specify: ______________________)  
- [ ] Board of Trustees  
- [ ] Reviewer  
- [ ] Staff  
- [ ] Other (specify: ______________________)

**E-mail (required):**

<table>
<thead>
<tr>
<th>DISCLOSURE OF FINANCIAL RELATIONSHIPS WITHIN 12 MONTHS OF DATE OF THIS FORM</th>
</tr>
</thead>
<tbody>
<tr>
<td>[X] <strong>NO</strong>- Neither I, nor any member of my immediate family, has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>[ ] <strong>YES</strong>- I have or ___ an immediate family member has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The financial relationships are identified as follows (if needed, attach an additional list):</td>
</tr>
</tbody>
</table>

| Commercial Interest(s) (any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.) | RELEVANT FINANCIAL RELATIONSHIP(S) RELATED TO YOUR CONTENT (CHECK ALL THAT APPLY) |
| --- |
| [ ] Research Grant (including funding to an institution for contracted research) |
| [ ] Speakers’ Bureau |
| [ ] Stock/Bonds (excluding Mutual Funds) |
| [ ] Consultant |
| [ ] Other (Identify) |

I affirm that the foregoing information is complete and truthful, and I agree to notify the AAOMS immediately if there are any changes or additions to my relevant financial relationships. During my participation in this activity, I will wholly support the AAOMS’ commitment to conducting CDE activities with the highest integrity, scientific objectivity, and without bias. I agree that I will not accept any honoraria, additional payments or reimbursements beyond what has been agreed upon to be paid directly by the AAOMS in relation to this educational activity.

**Electronic Signature**: Simon Jean  
**Date:** 2016-11-21  
**Corresponding author**
Electronic signature required from corresponding author only. It is the responsibility of the corresponding author to collect and submit all relevant conflicts of interest (or lack thereof) of all contributing authors at the time of the submission.

___ 1st Co-Author (if applicable)
Name: Pierre-Luc Dionne

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITHIN 12 MONTHS OF DATE OF THIS FORM

<table>
<thead>
<tr>
<th>Commercial Interest(s)</th>
<th>Research Grant (including funding to an institution for contracted research)</th>
<th>Speakers' Bureau</th>
<th>Stock/Bonds (excluding Mutual Funds)</th>
<th>Consultant</th>
<th>Other (Identify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

___ 2nd Co-Author (if applicable)
Name: Carl Bouchard

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITHIN 12 MONTHS OF DATE OF THIS FORM

<table>
<thead>
<tr>
<th>Commercial Interest(s)</th>
<th>Research Grant (including funding to an institution for contracted research)</th>
<th>Speakers' Bureau</th>
<th>Stock/Bonds (excluding Mutual Funds)</th>
<th>Consultant</th>
<th>Other (Identify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

X NO—Neither I, nor any member of my immediate family, has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

OR

YES—I have or an immediate family member has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The financial relationships are identified as follows (if needed, attach an additional list):
**3rd Co-Author (if applicable)**

Name: **Luc Giasson**

**DISCLOSURE OF FINANCIAL RELATIONSHIPS WITHIN 12 MONTHS OF DATE OF THIS FORM**

**X NO**—Neither I, nor any member of my immediate family, has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

**OR**

**YES**—I have or an immediate family member has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The financial relationships are identified as follows (if needed, attach an additional list):

<table>
<thead>
<tr>
<th>Commercial Interest(s) (any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.)</th>
<th>RELEVANT FINANCIAL RELATIONSHIP(s) RELATED TO YOUR CONTENT (CHECK ALL THAT APPLY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Research Grant (including funding to an institution for contracted research)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**4th Co-Author (if applicable)**

Name: **Alexis F. Turgeon**

**DISCLOSURE OF FINANCIAL RELATIONSHIPS WITHIN 12 MONTHS OF DATE OF THIS FORM**

**X NO**—Neither I, nor any member of my immediate family, has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

**OR**

**YES**—I have or an immediate family member has a financial relationship or interest (currently or within the past 12 months) with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The financial relationships are identified as follows (if needed, attach an additional list):

<table>
<thead>
<tr>
<th>Commercial Interest(s) (any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.)</th>
<th>RELEVANT FINANCIAL RELATIONSHIP(s) RELATED TO YOUR CONTENT (CHECK ALL THAT APPLY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Research Grant (including funding to an institution for contracted research)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
American Association of Oral and Maxillofacial Surgeons
Disclosure Statement Regarding Dual Commitment

It is the policy of the American Association of Oral and Maxillofacial Surgeons to ensure balance, independence, objectivity and scientific rigor in scientific/educational activities. This requirement includes relationships with pharmaceutical companies, biomedical device manufacturers or distributors, or others whose products or services may be considered to be related to the subject matter of the scientific/educational activity. The principal intent of requiring disclosure is not to prevent an author with dual commitments from submitting a publication. Disclosure is requested so that the reader may reasonably formulate their own judgments regarding the paper in the light of full disclosure of related information.

SUMMARY OF OPERATING PRINCIPLES GOVERNING DISCLOSURE OF DUAL COMMITMENT

1. The expression “dual commitment” describes the dilemma faced by authors when their responsibility to remain unbiased may be compromised, or perceived to be compromised, by a simultaneous commitment to commercial interests related to the subject of a specific scientific/educational activity. “Conflict of Interest” refers to a degree of dual commitment that may be strong enough to produce reservations regarding potential loss of objectivity.

2. Dual commitments governed by the AAOMS Policy on Dual Commitment include but are not limited to:
   - special customer preferences (material donations, clinical materials, special discounts, special gifts, etc.)
   - financial interest (honoraria for lectureships or other teaching activities; stipends)
   - consultancies (paid or unpaid)
   - governance (corporate responsibility, corporate allegiances, e.g. through service on governing boards)
   - research contracts or other support for investigation
   - ownership of patents or companies, royalties, stock options, equity
   - by virtue of past or present employment of immediate family or relatives

3. AAOMS requires disclosure of dual commitments. In determining the significance of a dual commitment, AAOMS considers the following:
   - scope of the relationship or commitment
   - frequency and timing, i.e. whether past or recent, occasional or long-standing
   - number, i.e. a single, exclusive relationship rather than multiple, competing relationships

4. If a dual commitment is related to the submission, it must be disclosed to the readers, regardless of scope, frequency, timing, or number.

5. Penalties for failure to disclose will be considered at the discretion of the AAOMS Commission on Professional Conduct.

Disclosure of Unlabeled and/or Investigational Product Usage

The American Association of Oral and Maxillofacial Surgeons requires all authors to disclose whether any product discussed in their submission is unlabeled for the use discussed or is investigational.

Definitions:

Unlabeled: Any use of a product or device for purposes other than those specifically stated by the manufacturer and approved by the Food and Drug Administration.

Investigational: Any product or device that has not yet received approval for general use by the Food and Drug Administration.
American Association of Oral and Maxillofacial Surgeons
Disclosure Statement

Publication: Journal of Oral and Maxillofacial Surgery
Author: Simon Jean (Co-authors: Pierre-Luc Dionne, Carl Bouchard, Luc Giasson, Alexis F. Turgeon)
Article Title: Perioperative Systemic Corticosteroids in Orthognathic Surgery: a Systematic Review and Meta-Analysis

Disclosure of Dual Commitment

I have read the operating principles governing dual commitment and potential conflict of interest and the policy governing unlabeled and investigational commercial product usage. As it pertains to the article listed above, I declare that (select one by marking the space with an “X”):

- [X] I have no dual commitment (as defined on the reverse of this page).
- [ ] I may have an area of dual commitment that I affirm will not influence my objectivity.

<table>
<thead>
<tr>
<th>Type of Commitment</th>
<th>Company</th>
<th>Type of Commitment</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special Customer Preferences</td>
<td>Governance</td>
<td>Consultantship (paid)</td>
<td>Company</td>
</tr>
<tr>
<td>Honoraria</td>
<td>Governance</td>
<td>Stock Options/Holdings</td>
<td>Governance</td>
</tr>
<tr>
<td>Consultantship (unpaid)</td>
<td>Research Contracts/Grants</td>
<td>Company</td>
<td>Governance</td>
</tr>
<tr>
<td>Equity</td>
<td>Family Employment</td>
<td>Company</td>
<td>Governance</td>
</tr>
<tr>
<td>Company Ownership</td>
<td>Royalties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent Ownership</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please explain):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disclosure of Unlabeled and/or Investigational Product Usage

1. In the course of your article, do you intend to discuss any unlabeled and/or investigational use of any commercial product, as defined above? (select one by marking the space with an “X”):

   Yes [ ] No [X]

2. If you have answered “Yes” to item 1, please identify the product and describe the specific product usage you intend to discuss:

<table>
<thead>
<tr>
<th>Product</th>
<th>Usage</th>
<th>FDA Approval Status (select one)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unlabeled / Investigational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled / Investigational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled / Investigational</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unlabeled / Investigational</td>
</tr>
</tbody>
</table>

Signature  Simon Jean  
(type name)  Date  2017/23/02  
(enter date)