**RESEARCH PROPOSAL**

**DClinDent (Oral Surgery)**

***Pre-emptive analgesic and anti-inflammatory effects of etoricoxib and sustained-release ibuprofen following impacted mandibular third molar surgery.***

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# Thesis topic

A comparison of the pre-emptive analgesic and anti-inflammatory effects of etoricoxib 120mg and sustained-release ibuprofen 1.6g[[1]](#footnote-2) on acute post-operative sequelae following bilateral impacted mandibular third molar surgery.

# Problem statement

Etoricoxib, a second-generation COX-2 inhibitor, is reported to be effective in reducing post-operative pain when given pre-emptively prior to orthopaedic and selected general surgical procedures. Sustained-release ibuprofen, a traditional non-steroidal anti-inflammatory drug (NSAID), is readily available over the counter and is more economical. There is a lack of research comparing the pre-emptive effectiveness of etoricoxib 120mg with sustained-release ibuprofen 1.6g (as a single dose) in third molar surgery. To date, the evidence for the superior efficacy of etoricoxib in third molar surgery is equivocal.

# Thesis overview

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| Scientific question: | Are there any differences in the pre-emptive analgesic and anti-inflammatory efficacy between etoricoxib 120mg and sustained-release ibuprofen 1.6g following impacted mandibular third molar surgery? |
| Hypothesis: | Pre-emptive etoricoxib 120mg will have a superior effect in reducing post-operative pain intensity over sustained-release ibuprofen 1.6g.  The pre-emptive anti-inflammatory effect of etoricoxib 120mg and sustained-release ibuprofen 1.6g on post-operative swelling and trismus will be comparable. |
| Statistical question: | What is the relative efficacy of pre-emptive etoricoxib and pre-emptive sustained-release ibuprofen in improving post-operative pain, swelling, and trismus in patients following impacted mandibular third molar surgery? |

# Introduction

Pre-emptive analgesia is defined as the administration of an anti-nociceptive agent prior to surgical insult with the intent to suppress nociceptive pathways before they are stimulated (Campiglia et al. 2010; Dahl and Møiniche 2005). The concept is based on the inhibition of surgery-mediated inflammation and neurophysiological insult of nociceptive pathways, and ultimately preventing the establishment of peripheral and central sensitisation that is responsible for the development of post-operative pain hypersensitivity and chronic pain (Dahl and Møiniche 2005). Therefore, the aims of pre-emptive analgesia are: (1) to reduce inflammation-mediated acute pain following surgical trauma/tissue injury; (2) to impede adverse central processing of noxious impulses and pain memory of the central nervous system; and (3) to establish good post-operative pain control and inhibit chronic pain development (Grape and Tramèr 2007).

A large proportion of patients experience moderate-to-severe pain following third molar surgery which negatively affects their quality of life, particularly during the first 72 hours post-operatively (Colorado-Bonnin et al. 2006).Early management of pain is shown to be associated with lower demand for re-medication and improved overall pain relief (Moore et al. 2014). Therefore, the use of effective and early post-operative pain relief is justified. To maximise the pre-emptive effectiveness, the literature recommends that an intervention agent have a prolonged duration of action to cover the intra-operative period during which the noxious stimuli is most intense, and that its effect should extend into the post-operative period to ensure suppression of the subsequent generation of inflammatory mediators. Lastly, the adoption of multimodal therapy combining several analgesics is advocated (Pogatzki-Zahn and Zahn 2006; Rosero and Joshi 2014).

Non-steroidal anti-inflammatory drugs (NSAIDs) are shown to inhibit peripheral and central sensitisation (Ong et al. 2005).Ibuprofen is arguably the most accessible and commonly used NSAID that is inexpensive and available over the counter in most countries (Derry et al. 2009). There is a substantial and valid body of evidence for its analgesic efficacy against mild-to-moderate post-operative pain (Derry et al. 2009) with opioid-sparing effects (Best et al. 2017). These features make ibuprofen an ideal control to compare the efficacy of other analgesics in clinical trials. However, ibuprofen is implicated in gastric irritation and bleeding in susceptible patients, and so impairment in gastric cytoprotection has prompted the emergence of selective COX-2 inhibitors (Clarke et al. 2014).

Etoricoxib, a highly selective COX-2 inhibitor, is available by prescription only (Clarke et al. 2014). Unlike ibuprofen, etoricoxib is not subsidised in New Zealand (Arcoxia (etoricoxib) film coated tablets). The effectiveness of a single dose of etoricoxib 120mg in the management of acute moderate-to-severe post-operative pain (including third molar surgery) has been reported on the latest Cochrane Database of Systematic Reviews (Clarke et al. 2014).Etoricoxib has a safer gastrointestinal profile (Clarke et al. 2014; Yuan and Hunt 2007) and its effects on renal function is reported to be comparable to that of traditional NSAIDs (Takemoto et al. 2008). However, little is known about its pre-emptive benefit in the oral surgery literature.

Single-dose oral etoricoxib 120mg and sustained-release ibuprofen 1.6g have a prolonged duration of blockade and maintain stable plasma concentrations over at least 20 hours (Clarke et al. 2014; Fernandes and Jenkins 1994).Taking these observations together, one may question whether a pre-emptive dose of these long-acting NSAIDs can help to reduce acute post-operative sequelae after mandibular third molar removal, and, if so, whether there would be any significant differences in efficacy between etoricoxib and ibuprofen.

# Specific objectives

*Primary objective*

To compare the effectiveness of etoricoxib 120mg with that of sustained-release ibuprofen 1.6g when administered pre-emptively for pain relief following third molar surgery.

*Secondary objectives*

* To compare the pre-emptive anti-inflammatory efficacy of etoricoxib 120mg and sustained-release ibuprofen 1.6g on clinical parameters including swelling and trismus following third molar surgery;
* To determine whether there are any differences in the need for rescue analgesia;
* To determine whether there are any differences in the adverse events; and
* To evaluate any differences in the participants’ overall satisfaction with pain control.

# Implications

*Potential benefits of this research*

To the best of my knowledge, no study has compared the pre-emptive efficacy of etoricoxib 120mg and sustained-release ibuprofen 1.6g against acute post-operative sequelae after third molar surgery. There is no convincing evidence to support or refute superior effectiveness of etoricoxib over ibuprofen, and so it requires further clinical investigation. The findings of the study will serve as a valuable addition to the current literature, in which the knowledge of pre-emptive analgesia in oral surgery is scarce.

Several benefits for clinical practice are anticipated if the proposed study demonstrates a significant positive outcome from the pre-emptive administration of etoricoxib and/or ibuprofen: (1) patients may benefit from a reduced burden of post-operative pain and discomfort; (2) a concomitant reduction in the analgesic consumption may reduce the risk of patients being subjected to unnecessary levels of analgesia and consequently reduce the risk of adverse effects, overdose, and toxicity; and (3) routine provision of pre-emptive analgesia prior to minor oral surgery may be encouraged in clinical practice. The findings may be extended to other surgical fields of dentistry, including implant surgery, periodontal open-flap debridement, and endodontic surgical procedures.

If the proposed study demonstrates that sustained-release ibuprofen is equal or better than etoricoxib, then routine pre-emptive use of ibuprofen in minor oral surgery may be more cost-effective than the use of unsubsidised etoricoxib. Conversely, if etoricoxib is found to be superior to ibuprofen, its preferential use would potentially lead to fewer gastrointestinal side effects. Moreover, such a finding would provide clinicians with the scientific rationale for the pre-emptive use of etoricoxib in third molar surgery.

On completion of the proposed research, I intend to publish its findings in a peer-reviewed scientific journal.

*Potential benefits for Māori*

The implications of our proposed study are the same for Māori patients.

# Preliminary literature review

The merit of pre-emptive analgesia in oral surgery remains a contentious issue. Some published series have exhibited beneficial effects of its pre-operative use in attenuating post-operative pain, swelling, trismus, and analgesic demand following surgical removal of third molars (Albuquerque et al. 2017; Costa et al. 2015; Mehra et al. 2013; Zor et al. 2014). Other studies state otherwise; some researchers have failed to show statistically significant pre-emptive efficacy of NSAIDs (Bauer et al. 2013; Kaczmarzyk et al. 2010) while others have documented equivocal effects for pre- and post-operative administration of NSAIDs (Aznar-Arasa et al. 2012; Mojsa et al. 2017).

Information on the pre-emptive efficacy of sustained-release ibuprofen in the oral surgery literature is scarce. Yong and Coulthard reported no difference between a pre-operative efficacy of 1.6g modified-release ibuprofen (intervention group) and conventional ibuprofen 400mg (control group) following surgical removal of third molars (Yong and Coulthard 2010). While the intervention lessened the demand for, and delayed the time to rescue analgesia, the difference was not statistically significant. It is important to highlight that bupivacaine was used in this study. Its prolonged anaesthesia may have outlasted the analgesic duration of the pre-operative conventional ibuprofen. Therefore, it can be argued that bupivacaine is a modifier in this study that may possibly have rendered the insignificant pre-emptive analgesic difference between modified-release and conventional ibuprofen. Moreover, five surgeons performed the surgery under general anaesthesia. Surgical inconsistencies amongst the surgeons are inevitable and the subsequent performance bias may also have inadvertently compromised the outcome of the study. Unfortunately, the pre-emptive anti-inflammatory effects of the two ibuprofen groups were not examined by these authors. Hence, whether or not sustained-release ibuprofen has better anti-inflammatory effect than conventional ibuprofen, when given pre-emptively, remains to be elucidated.

Additionally, there is a lack of evidence comparing the pre-emptive effectiveness of a selective COX-2 inhibitor with a traditional ibuprofen in third molar surgery. A Finnish study observed a superior analgesic effect of celecoxib 200mg over ibuprofen 400mg when administered pre-emptively (Al-Sukhun et al. 2012).

A multitude of researchers have demonstrated the efficacy of pre-emptive etoricoxib in orthopaedic surgical procedures (Boonriong et al. 2010; Lierz et al. 2012; Munteanu et al. 2016; Renner et al. 2012) and laparoscopic cholecystectomy (Sandhu et al. 2011). These studies show that a single pre-operative administration of etoricoxib 120mg have significantly alleviated post-operative pain, lessened the demand for rescue analgesia, and opioid use. However, there are only two placebo-controlled clinical trials to date that have investigated its pre-emptive benefit for third molar removal. Both have shown a significant ease in the post-operative pain intensity in the intervention group over a placebo group (Albuquerque et al. 2017; Costa et al. 2015). With respect to the clinical parameters of post-operative inflammatory sequelae, these studies have yielded conflicting findings. While Costa et al. failed to find any differences between intervention and control groups in post-operative oedema and trismus (Costa et al. 2015), Albuquerque et al. reported a significant improvement associated with the intervention group (Albuquerque et al. 2017). To date, the evidence for the superior efficacy of etoricoxib in third molar surgery is equivocal.

# Proposed methods

## *Study design*

The proposed research will be conducted as a double-blinded randomised control trial.

Ibuprofen is arguably the most accessible and commonly used analgesia that is inexpensive and available over the counter in most countries. Therefore, it is reasonable to select ibuprofen as the traditional NSAID to use as a control in determining the pre-emptive effectiveness of etoricoxib in third molar surgery.

## *Sample*

A clinical convenience sample will be gathered from patients needing to undergo the surgical extraction of impacted bilateral mandibular third molars at the School of Dentistry, University of Otago.

## *Sample size determination*

The sample size calculation was based on that described in the study conducted by Al-Sukhun et al (Al-Sukhun et al. 2012). 70% of patients who received celecoxib rated the study medication as good, very good, or excellent, while it was only 58% among patients who received ibuprofen and 15% among patients who received a placebo. Assuming an α value of 0.05 and 80% power to detect a difference, the estimated number of patients per group is 61. Thus, a minimum of 122 patients will be required.

## *Recruitment of participants*

The staff clinicians at the School of Dentistry, University of Otago, will be notified of this proposed study. Their cooperation will be solicited at staff meetings and via staff emails to identify patients deemed potentially suitable to meet study inclusion criteria from patients referred (internal/external referrals) to the Oral Surgery Unit, School of Dentistry, and from patients who attend the Urgent Care Unit with symptoms related to impacted wisdom teeth. These patients would then be provided with an initial briefing on the proposed study and invited to meet Jessica Lee (principal researcher/surgeon) for a detailed consultation. They will be informed that non-participation in the study will not adversely impact their treatment in any way.

Potential participants who agree for a consultation with Jessica Lee will attend a surgical consultation with Jessica Lee. During the consultation, the nature and purpose of the study and participant’s responsibility will be explained. A written participant information sheet and consent form will be provided. Upon receiving the participation consent for the proposed study, all participants will be taken through the standard consenting process used at the School of Dentistry for patients undergoing wisdom teeth surgery under intravenous (IV) sedation and local anaesthesia. This will be completed prior to scheduling their surgery appointment. The recruitment will commence from 1 January 2019 and continue until 150 participants are enrolled.

## *Inclusion criteria*

All prospective participants must be seen by Jessica Lee with the guidance from a Consultant Oral and Maxillofacial Surgeon at the School of Dentistry, University of Otago.

1. Patients must be deemed appropriately suitable for participation in the present study by Jessica Lee or a Consultant Oral and Maxillofacial Surgeon at the School of Dentistry, University of Otago.
2. The participant must be aged between 18 and 35 years.
3. The participant must legitimately require removal of at least two mandibular third molars (and may require removal of maxillary third molar/s) as per third molar surgical protocol at the School of Dentistry, University of Otago.
4. Expected bone removal and/or tooth sectioning for extraction of the impacted bilateral mandibular third molars.
5. The participant must be medically fit (American Society of Anaesthesiologist (ASA) physical status classification 1 or 2) to have their third molars removed.
6. The participant must be assessed as appropriate for an IV sedation.
7. The participant must consent to having their third molars removed under IV sedation and local anaesthesia.
8. There will be no discrimination based on gender, race, and ethnicity. Non-English-speaking patients will be given equal opportunity to participate; an accredited interpreter will be employed as required.

## *Exclusion criteria*

1. Patients under the age of 18 years and over 35 years of age
2. Patients are excluded if they meet any of the following criteria:
3. Any significant systemic disease/s classified as ASA 3, 4, or 5
4. Active/history of gastrointestinal bleeding or ulceration
5. Currently pregnant or lactating
6. Body weight >120kg
7. Cardiovascular disease
8. NSAID-sensitive asthma
9. Respiratory depression, COPD
10. Hepatic impairment
11. Renal impairment
12. Bleeding disorders
13. Therapeutic anticoagulation
14. Bone disorders
15. Metabolic diseases
16. Patients on bisphosphonates
17. Patients on long-term benzodiazepines, opioids, and liver enzyme induction agents/medications
18. Hypersensitivity to benzodiazepines, etoricoxib, ibuprofen, and codeine phosphate
19. Use of NSAIDs within 48 hours prior to the day of surgery
20. Presence of swelling, fever, trismus prior to third molar surgery
21. Opioid and illicit drug addiction
22. Alcoholism
23. Current smokers who refuse to stop smoking within 72 hours following third molar surgery
24. Patients opting to undergo third molar surgery under local or general anaesthesia
25. Patients unable to give informed consent
26. Patients who have third molars with following:
27. Associated pathologies
28. Third molar/s requiring coronectomy
29. Third molars with higher risk of mandibular fracture
30. Maxillary third molar/s with higher risk of oro-antral communication
31. Oral surgery requiring more than four third molars extracted

## *Interventions*

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| Intervention group (group A) | Etoricoxib 120mg |
| Control group (group B) | Sustained-release ibuprofen 1.6g |

## *Randomisation*

Block randomisation will be used to ensure balance in the assignment of participants to each treatment group. An independent biostatistician will generate a random allocation sequence. A hospital clinical trials pharmacist, the only non-blinded person involved in the proposed study, will hold this computer-generated randomisation code. Upon receiving participation consent, the pharmacist will randomly assign each participant to either the intervention group (group A) or the control group (group B) according to the randomisation code. Each participant will be given a unique identification number by the pharmacist and treatment will be provided via sealed opaque envelopes.

## *Obtaining patient consent for participation*

Patients who are deemed potentially suitable for participation in the study will be invited to the consultation appointment with the principal researcher/surgeon, Jessica Lee. During the consultation, the following will be explained:

1. The nature and purpose of the study (written participant information sheet will be provided);
2. Participant responsibility (see below);
3. Assurance to participants (see below); and
4. Participant incentive (see below).

Patients will be given the opportunity to ask questions for clarification prior to enrolment. Each participant will be given a unique identification number to ensure participant anonymity.

## *Participant responsibility*

In voluntarily choosing to participate in this research project, the patient will agree to:

1. Read in full the form entitled, *Participant Information Sheet* (Appendix 2). This form will be given to the patient to take home;
2. Complete a written consent form pertaining to participation in the study (Appendix 3);
3. Complete a pre-operative participant questionnaire (Appendix 4);
4. Attend the surgical appointment. The patients are required to:
   1. rate the pre-operative pain intensity;
   2. take the pre-operative dose of NSAID provided 2 hours prior to third molar surgery;
   3. have the facial dimension and mouth opening assessed;
   4. undergo third molar surgery under IV sedation.
5. Rate the pain intensity every 3 hours, while awake, for the first 48 hours post-surgery; and
6. Attend a 48-hour post-operative review appointment. During the review appointment, the extent of facial swelling and trismus will be assessed. The patients are also required to:
   1. hand in their completed visual analogue scale (VAS) diary;
   2. complete a post-operative participant questionnaire (Appendix 9).

## *Assurance to participants*

Patients will be informed:

1. All data collected will remain confidential and will only be used for the research project.
2. The names of participants will not appear in the thesis nor in any future journal articles which may arise from the research.
3. The study data will be retained in a de-identified format, which will be stored securely at the University of Otago for a period of 10 years, after which time it will be destroyed.
4. Participants may withdraw from the study at any time with no penalty or disadvantage to surgical care and management.
5. All the peri-operative drugs will be provided at an ethically acceptable doses for the surgical removal of mandibular third molars. All the intra-operative drugs are those routinely used at the School of Dentistry, University of Otago, for impacted third molar surgery.
6. Participants will be informed how and when to take their pre-emptive and post-operative pain relief medications.
7. All participants will be informed of potential side effects of etoricoxib and sustained-release ibuprofen.
8. If participants have any post-operative issues, they may phone the oral surgery team who performed their surgery during business hours or contact the on-call Dental House Surgeon after-hours via the Emergency Department of the Dunedin Public Hospital. The on-call Dental House Surgeon is part of the same oral surgery team responsible for this study and may contact the principal researcher if needed. Phone numbers of the oral surgery team and Dunedin Public Hospital are stated on the *Participant* *Information Sheet* (Appendix 2).
9. Participants will be offered a medical certificate as required.

## *Participant incentive*

Pre-emptive medications (etoricoxib and sustained-release ibuprofen) will be given to participants free of charge. Participants will be given a free 250ml bottle of 0.2% chlorhexidine gluconate mouthwash. This antibacterial mouthwash is commonly prescribed at the School of Dentistry, University of Otago, after minor oral surgery to prevent post-operative infection.

## *Obtaining and dispensing pre-emptive analgesic agents*

Etoricoxib 120mg and sustained-release ibuprofen 1.6g will be specifically prepared across 4 capsules by Optimus Healthcare Pharmacist in Auckland. Both drugs will be packed into bottles containing 4 capsules each for dispensing to individual patients. All medications have 1-year expiry from the date of preparation. They will be obtained in a single consignment to Jessica Lee at the Department of Oral Diagnostic and Surgical Sciences, School of Dentistry. The drugs will then be given to the clinical trials pharmacist at the Dunedin Public Hospital for randomisation coding as participants are recruited.

250ml bottle of 0.2% chlorhexidine gluconate mouthwash for dispensing will be obtained from the local pharmacy.

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| Intervention group | Etoricoxib 120mg (4 capsules in divided doses)   * *Each capsule contains 30mg of etoricoxib* |
|  | 0.2% chlorhexidine gluconate mouthwash 250ml |
| Control group | Sustained-release ibuprofen 1.6g (4 capsules in divided doses)   * *Each capsule contains 400mg of sustained-release* *ibuprofen* |
|  | 0.2% chlorhexidine gluconate mouthwash 250ml |

Participants are required to fast prior to IV sedation. The fasting guideline at the School of Dentistry for IV sedation is as follows:

* No food must be taken within 4 hours before IV sedation
* Clear fluids may be taken up to 2 hours before IV sedation.

To ensure adequate hydration and reduce the risk of potential renal adverse events, participants will be encouraged to drink sufficient amount of fluid prior to fasting. Jessica Lee will dispense the pre-emptive medication with a large glass of water 2 hours prior to the surgical appointment. If participants were to self-medicate, the variability in the timing of the drug administration will be inevitable. To limit this, the pre-emptive medication will be dispensed at the School of Dentistry, University of Otago. The date and time of dispense will be immediately recorded on a drug chart and signed by Jessica Lee and the supervising Consultant Oral and Maxillofacial Surgeon.

Renal function will not be checked in this proposed study. Participants will be young between the ages of 18 and 35 years and only ASA 1 and 2 patients will be recruited. ASA 2 patients will be carefully selected after reviewing their medical history. Patients with known renal impairment, poorly controlled diabetes, long-term antihypertensive therapy, and/or any conditions that may predispose to renal impairment, will be excluded.

At the School of Dentistry, University of Otago, IV sedation is strictly reserved for patients who are reasonably healthy with no significant systemic conditions. Hence, pre-operative renal function tests are not routinely performed. This conforms to the current Southern DHB Pre-operative Laboratory Investigations – Anaesthetic Guidelines (Otago). It states that: (1) no tests are indicated for asymptomatic patients having minor surgery; and (2) urea, creatinine, and electrolytes are indicated for those over 70 years, or those with dehydration[[2]](#footnote-3), pyloric stenosis, renal or diabetic disorders and/or on diuretics or potassium therapy or on long term antihypertensive therapy[[3]](#footnote-4) (Preoperative Laboratory Investigations - Anaesthetic Guidelines (Otago)). This protocol aligns favourably with the National Institute for Health and Care Excellence Clinical Guidelines for Routine Pre-operative Tests for Elective Surgery. The Guideline Development Group concluded **against** a routine baseline pre-operative renal function tests for ASA 1 and 2 patients, including well-controlled diabetic patients, as functional abnormalities of the kidneys are rarely detected in asymptomatic, fit and healthy young individuals and the risk of acute kidney injury (AKI) is very low. In contrast, a pre-operative renal function test is recommended to be considered for ASA grade 3 and 4 patients at risk of AKI (Routine preoperative tests for elective surgery).

Although getting the blood test is considered safe, it subjects our participants at unnecessary discomfort and pain. Moreover, a small risk of complications, such as haematoma, infection, and vasovagal reactions cannot be excluded (Routine preoperative tests for elective surgery). The current guidelines do not support the need for renal function tests for the participants in the proposed study.

## *Drug dose and administration*

**Pre-/intra-operative drugs**

All participants will undergo third molar surgery under IV sedation. Administration of the sedation will be performed by Jessica Lee and the patient will be monitored by a registered nurse trained in IV sedation. The entire operative procedure will be supervised by a Consultant Oral and Maxillofacial Surgeon.

The following medications are standard peri-operative drugs administered for those undergoing third molar surgery under IV sedation at the School of Dentistry, University of Otago:

* Dexamethasone 8mg
* Midazolam 5mg/5ml *titrated to effect (maximum total dose of 10mg as per recommendation by Malamed)* (Malamed 2010)
* 2.2ml lignocaine 2% with 1:80,000 adrenaline for each unilateral inferior alveolar nerve block
* 1.0ml lignocaine 2% with 1:80,000 adrenaline for each unilateral infiltration in the buccal sulcus near the third molar

**Post-operative analgesic regimen**

Jessica Lee will provide a prescription for the following post-operative analgesia:

* Paracetamol 1g QID 3/7 then as required
* Ibuprofen 400mg TID *(start 18 hours after pre-emptive drug administration)* 3/7 then as required
* Codeine phosphate 30mg – 60mg QID as required *(rescue medication)*

Regular dose of ibuprofen 400mg will commence 18 hours after pre-emptive NSAID administration. Etoricoxib and sustained-release ibuprofen have a long duration of action and maintain stable plasma concentration over at least 20 hours. Therefore, additional intake of NSAID may subsequently increase the risk of adverse renal effects.

Each participant will be given a 250ml bottle of 0.2% chlorhexidine gluconate mouthwash and a VAS diary prior to discharge home. All patients will be asked to use 10ml of 0.2% chlorhexidine gluconate 1-minute rinse three times daily for 7 days, commencing 24 hours post-operatively.

## *Surgical procedure*

The surgical removal of impacted bilateral mandibular third molars will be performed by Jessica Lee. All surgical procedures will be directly supervised by a Consultant Oral and Maxillofacial Surgeon employed by the University of Otago. The involvement of a single surgeon aims to eliminate operator variability and consequent performance bias from the proposed investigation.

## *Data collection*

1. Participants who meet the eligibility criteria will be provided with the participant information sheet. The first appointment will involve consultation with the surgeon/principal researcher. Upon receiving the participation consent, the pre-operative questionnaire will be completed. This questionnaire contains the Oral Health Impact Profile, OHIP-14 (Slade, 1997), Locker’s Global Oral Health Item (Thomson et al., 2012), and the Dental Anxiety Scale (Corah, 1969).
2. The type of third molar impaction according to the Winter’s classification (mesio-angular, disto-angular, vertical, horizontal, transverse bucco-lingual, inverted) will be recorded for each participant.
3. On the second appointment, third molar surgery will be completed under IV sedation. The following will be completed before surgery:
   1. Pre-operative pain rating on a 100mm VAS (Appendix 5)
   2. Assess facial swelling/dimension using 3-dimensional volumetric morphometric imaging software (3dMDtrio system)
   3. Assess maximum mouth opening (trismus) by measuring the distance between the mesio-incisal edges of the right maxillary and mandibular central incisor teeth during maximal mouth opening.
4. Participants will be asked to rate the pain intensity every 3 hours, while awake, for the first 48 hours post-surgery. A non-graduated 100mm VAS, printed one per page in a booklet, will be provided to each participant to take home after surgery (Appendix 5).

The VAS is an instrument that is widely accepted for the unidimensional, self-report measure of pain intensity. It comprises of a horizontal line of 100mm in length bounded by a pole at each extreme of the scale. The left end of the extreme is described as “no pain” and the other end as “worst pain imaginable.” It does not require any specific training; participants are to score the pain by placing a line perpendicular along the scale that best matches the individual’s pain experience. The score is then interpreted by using a ruler to measure the distance (in millimetres) from the “no pain” pole to the participant’s mark. The measure of pain intensity is represented by the range between 0 to 100 (Hawker et al. 2011).Accurate baseline measure of the parameters is paramount; this is not only to allow for objective comparisons and interpretation of the data after the surgery, but also to assess whether differences exist among the parameters that need to be controlled prior to the statistical analysis.

1. The VAS diary will also contain pages where participants will be asked to record the following details:
   1. The time elapsed between the end of the surgery and the first use of rescue medication
   2. Number of rescue analgesia consumed per day
   3. Any adverse events experienced post-surgery (e.g. headache, drowsiness, vomiting, and nausea) (Appendix 6 & 7)
2. Participants will be asked to attend post-operative review appointment with Jessica Lee at 48 hours post-surgery. The following will be completed:
   1. The extent of facial swelling will be assessed using 3dMDtrio system
   2. Trismus will be measured by the distance between the mesio-incisal edges of the right maxillary and mandibular central incisor teeth during maximal mouth opening
   3. Collect the VAS diary
   4. Complete a post-operative questionnaire (Appendix 9).

The post-operative questionnaire is comprised of a series of questions pertaining to their experience of post-operative pain, compliance with the prescribed analgesic regime, and whether rescue analgesia was required. The post-operative questionnaire will be completed by participants themselves during this appointment.

The timeframe of 48 hours is based on the finding that a large proportion of patients experience the greatest amount of pain and swelling during the first 48-72 hours following third molar surgery. Also, patient compliance in pain intensity recording is likely to decline the longer the study duration continues and hence may compromise the accuracy of data.

## *Data entry*

A Microsoft Excel spreadsheet will be used for data entry. All data entry will be double-checked for errors prior to data analysis.

## *Data analysis*

Statistical analysis will be undertaken using SPSS software. Baseline characteristics and categorical data will be compared using Chi-square tests. The summary data on VAS, swelling, and trismus between etoricoxib and ibuprofen groups will be compared and tested for statistical significance using Analysis of Variance (ANOVA). Pearson correlations will also be used to quantify the association between the sum of pain scores and the total intake of rescue medication. Linear regression will be used to control for confounders. The level of significance will be set at P < 0.05. Appropriate multivariate modelling will be undertaken.

# Bias and confounding

*Potential source of bias*

The proposed investigation is a double-blind study to minimise reporting/investigator bias. The proposed study is vulnerable to volunteer bias. There may be systematic differences in the characteristics between those who volunteer to participate in the study and those who decline to participate.

*Modifiers*

1. Age

The association between greater surgical difficulty and older age is well-documented in the literature (Renton et al. 2001).Alveolar bone is significantly denser and less elastic in older patients over the age of 35 years than among younger patients. This accounts for more bone removal, tooth sectioning, greater surgical time, and potentially increases the risk of post-operative complications (Renton et al. 2001). In order to minimise this age effect, we restrict the age group between 18 and 35 years of age.

1. Ethnicity

One study identified ethnic background as an independent predictor for difficulty of third molar extraction (Renton et al. 2001). The mean surgical time was longer amongst African-American and Caribbean patients when compared to Caucasian patients due to the high incidence of bone impaction, unfavourable root formation, angulation, and crown width (Renton et al. 2001). However, there is a paucity of data demonstrating the association between ethnicity and surgical difficulty pertaining to the New Zealand population. The available data failed to observe any significant differences in the rate of post-operative complications between Māori and NZ European patients following routine exodontia (Tong et al. 2014). Based on this finding, the heterogeneity in the ethnic background of the patients in the proposed study is unlikely to affect the findings.

1. Pre-operative dexamethasone

The peri-operative drug protocol for third molar surgery under IV sedation at the School of Dentistry, University of Otago, includes intravenous administration of dexamethasone. The proposed study aims to compare the pre-emptive anti-inflammatory efficacy of etoricoxib and sustained-release ibuprofen on clinical parameters including swelling and trismus. Thus, pre-operative dexamethasone will subsequently modify the potential association between the pre-emptive NSAIDs and the outcome. Administration of steroid prior to surgical removal of third molars under IV sedation or general anaesthesia is a common practice to help reduce post-operative swelling. Therefore, omitting this drug may subject participants to unnecessary discomfort.

1. Post-operative ibuprofen

The analgesic efficacy and opioid-sparing effects of ibuprofen in third molar post-operative pain is well-established in the literature. Post-operative administration of ibuprofen may potentially mask the pre-emptive anti-inflammatory effects of etoricoxib and sustained-release ibuprofen, hence modify the results of the proposed study. However, codeine is proven to provide poor analgesic effect and hence, a post-operative analgesic regimen of paracetamol and ibuprofen for pain after third molar surgery is a routine practice. Therefore, it is paramount that this research provides all the participants with a prescription for regular paracetamol and ibuprofen for at least 2 days post-operatively.

1. Alveolar osteitis and/or post-operative infection

Alveolar osteitis is a common post-operative complication following mandibular third molar extraction. The positive association between smoking and alveolar osteitis is well-established. To reduce the risk of alveolar osteitis, current smokers who refuse to stop smoking within 72 hours following third molar surgery will be excluded from this study.

Moreover, participants with clinical signs of pericoronitis will be treated at the time of the consultation to minimise the risk of post-operative infection. All participants will be provided with complimentary 0.2% chlorhexidine gluconate mouthwash to use post-operatively.

It should be noted that alveolar osteitis and post-operative infection generally occur 3 to 5 days post-operatively. Given the timeframe of the proposed study, the chance of these variables affecting the findings of the study is very low.

*Controlling for confounding variables*

Confounding variables will be controlled statistically using modelling techniques at the time of data analysis.

# Ethics approval and Māori approval

*Ethics approval*

Provisionally approved

*Māori approval*

Approved

# Funding

Application for the internal university funding is pending.

# Payment for treatment

Patients will bear the cost of surgical treatment according to the fee schedule guidelines of the School of Dentistry, University of Otago.

# Proposed supervisors

* Mr Harsha L De Silva
* Professor W Murray Thomson
* Associate Professor Rohana K De Silva
* Professor Darryl C Tong

# Thesis timeline

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **2018** | | **2019** | | | **2020** | | |
| **Sep** | **Dec** | **Jan** | **Jun** | **Dec** | **Jan** | **Apr** | **Aug** |
| **Grant application** |  |  |  |  |  |  |  |  |
| **Clinical trials registry** |  |  |  |  |  |  |  |  |
| **Ethics approval** |  |  |  |  |  |  |  |  |
| **Finalise preparation for commencement of research** |  |  |  |  |  |  |  |  |
| **Patient recruitment**  **Data collection** |  |  |  |  |  |  |  |  |
| **Data analysis** |  |  |  |  |  |  |  |  |
| **Report writing** |  |  |  |  |  |  |  |  |

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# Appendices

## *Appendix 1*

**OVERVIEW OF KEY STEPS IN THE STUDY DESIGN**

**Patients requiring surgical removal of third molar teeth who are deemed potentially suitable for participation in the study invited to the surgical consultation with Jessica Lee**

**Notify staff clinicians of the proposed study at staff meetings and via staff email**

***Appointment 1:***

**Consultation with Jessica Lee**

**Inclusion & exclusion criteria met**

**Patient records pain intensity on VAS diary every 3 hours (while awake) for the first 48 hours post-operatively**

**Patient records the number of rescue analgesia consumed and any adverse events for the first 48 hours post-operatively**

***Appointment 2:***

**Administration of pre-emptive medication 2 hours prior to surgery**

**Pre-operative VAS, swelling, mouth opening assessment**

**Third molar surgery under IV sedation**

**Block randomisation of patients**

***Appointment 3 (Day-2 post-operative review):***

**Swelling and trismus assessment**

**Complete post-operative questionnaire**

**End of participant commitment**

**Sign participation consent**

**Complete pre-operative questionnaire**

## *Appendix 2*



**PARTICIPANT INFORMATION SHEET**

***Pre-operative effects of anti-inflammatory drugs on pain and inflammation following wisdom teeth removal***

**Locality:** Department of Oral Diagnostic and Surgical Sciences, School of Dentistry

**Principal Researcher:** YJ Jessica Lee (Oral Surgery Doctorate Candidate)

**Primary Supervisor:** Mr Harsha De Silva (Senior Lecturer in Oral & Maxillofacial Surgery)

**Contact number:** (03) 479 7023

**Ethics Committee Ref:** 18/STH/139

We invite you to take part in a clinical study on the effects of pre-operative anti-inflammatory drugs on pain and inflammation following wisdom teeth surgery. Whether or not you take part is your choice. If you don’t want to take part, you don’t have to give a reason, and it won’t affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you’d like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 5 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

**What is the aim of the research project?**

This project is being undertaken as part of an Oral Surgery Doctorate degree at the University of Otago. The aim is to compare the pre-operative effectiveness of two different types of anti-inflammatory painkillers on pain, swelling, and mouth opening after wisdom teeth surgery. The medications involved in this project are **etoricoxib (Arcoxia) 120mg** and **sustained-release ibuprofen 1.6g**, two commonly used painkillers. Arcoxia is shown to be effective when given **before** bone and gall bladder operations but not much is known about its benefit in wisdom teeth surgery. Participants will be randomly assigned to a group. To help minimise bias, neither the researcher nor the participants will know which participants are receiving which medication.

**Who pays for the study?**

Application for the internal university funding is in progress.

Participants will bear the cost of surgical treatment according to the fee guidelines of the School of Dentistry, University of Otago, and the post-operative medications prescribed, except the study medications (Arcoxia, sustained-release ibuprofen) which will be provided free of charge.

**Who are we seeking to participate in the project?**

Anyone between 18 and 35 years of age who requires the removal of at least 2 impacted lower wisdom teeth are invited to participate. Participants must be healthy with no significant medical conditions and must not have any allergic reactions to anaesthetics/sedatives, anti-inflammatory painkillers (e.g. Nurofen, Voltaren), and codeine. Female patients who are pregnant or breastfeeding will not be able to participate.

**What will participants be asked to do?**

Should you agree to take part in this project, you will be asked to:

1. Complete a short questionnaire asking about things such as your age, gender, occupation, oral hygiene practice, past or present pain associated with your wisdom teeth, and whether you experience anxiety when receiving dental treatment.
2. Attend your surgical appointment. You will need to take a medication given to you 2 hours before the surgery. Before the wisdom teeth removal, your facial dimension will be assessed by a 3D-scanner and your mouth opening will be measured.
3. Fill in your pain diary. This involves scoring your pain level every 3 hours (while awake) for the first 2 days after the surgery. You will also need to answer questions relating to the use of painkillers and any side effects encountered. Each occasion will take only a moment of your time.
4. Attend a review appointment with Jessica Lee 2 days after the surgery, at which time she will:
5. Assess the extent of facial swelling and mouth opening;
6. Collect your pain diary; and
7. Ask you to complete a short questionnaire about to your experience of pain following the wisdom teeth surgery

**Benefits and risks of participating in this study**

Surgical removal of wisdom teeth is a common procedure provided at the School of Dentistry, University of Otago. The medications provided to you before your wisdom teeth surgery are known to have a good effect in controlling post-operative pain. The effective dose of the medication will remain the same; we will be giving the medication **before** the surgery rather than after the surgery. Like all anti-inflammatory painkillers, the side effects of ibuprofen and Arcoxia may include stomache pain in some people. Despite this, ibuprofen and Arcoxia are commonly prescribed following wisdom teeth surgery. Therefore, there are no increased risks by participating in this study. It’s important that you **DON’T** combine two types of anti-inflammatory painkillers as this could increase the risk of post-operative bleeding.

We will give you a free bottle of antibacterial mouthwash and a prescription for painkillers. These painkillers are no different to those given to patients undergoing wisdom teeth surgery at the School of Dentistry.

If you believe that the painkillers provided to you by the School of Dentistry are making you feel unwell, then you are advised to stop taking those tablets and contact your medical doctor for an alternative painkiller.

**What if something goes wrong?**

If you were injured in this study, which is unlikely, you would be eligible for compensation from ACC just as you would be if you were injured in an accident at work or at home. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.

**What about anonymity and confidentiality?**

Your participation in this study is strictly confidential. Any personal information such as your name, age, gender, and contact details will remain anonymous. The information collected from you will de deidentified and used only by the researchers involved in this project. The deidentified information (study data) will be stored securely at the University of Otago for a period of 10 years, after which time it will be destroyed.

The results of this study will be written up in the form of a thesis and may later be summarised and published in a dental journal in order that other dentists and their patients may benefit. Nothing that could identify you will be used in anything we publish.

**If I agree to participate, can I withdraw later?**

Your participation in this research is entirely voluntary and you can withdraw at any time with no disadvantage to you. To participate you will need to fill in the accompanying consent form. You are welcome to request a copy of the final results of this research project if you desire. You have the right to access your personal data.

**What if I have any questions about the research project?**

If you require additional information, please do not hesitate to contact Jessica Lee or Mr Harsha De Silva on (03) 479 7023 during business hours.

**What if I have any problems or require additional pain relief following my wisdom teeth surgery?**

If you need to contact the oral surgery team following your wisdom teeth surgery, you may do so during business hours on (03) 479 7023. For after-hours emergency, you may contact Dunedin Public Hospital on (03) 474 0999 and ask to be put through to the on-call Dental House Surgeon.

For Māori health support, please contact Professor John Broughton, Associate Dean (Māori), Faculty of Dentistry, on (03) 479 7639.

For Health and Disability Advocacy Service, please contact 0800 555 050 or [advocacy@advocacy.org.nz](mailto:advocacy@advocacy.org.nz)

## *Appendix 3*



**CONSENT FORM FOR PARTICIPANTS**

*Pre-operative effects of anti-inflammatory drugs on pain and inflammation following wisdom teeth removal*

**Please tick to indicate you consent to the following**

|  |  |  |
| --- | --- | --- |
| I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. | Yes 🞏 | No 🞏 |
| I have been given sufficient time to consider whether or not to participate in this study. | Yes 🞏 | No 🞏 |
| I have had the opportunity to use a legal representative, whānau/ family support or a friend to help me ask questions and understand the study. | Yes 🞏 No 🞏 N/A 🞏 | |
| I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet. | Yes 🞏 | No 🞏 |
| I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care. | Yes 🞏 | No 🞏 |
| I consent to the research staff collecting and processing my information, including information about my health. | Yes 🞏 | No 🞏 |
| If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed. | Yes 🞏 | No 🞏 |
| I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study. | Yes 🞏 | No 🞏 |
| I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study. | Yes 🞏 | No 🞏 |
| I understand the compensation provisions in case of injury during the study. | Yes 🞏 | No 🞏 |
| I know who to contact if I have any questions about the study in general. | Yes 🞏 | No 🞏 |
| I understand my responsibilities as a study participant. | Yes 🞏 | No 🞏 |
| I wish to receive a summary of the results from the study. | Yes 🞏 | No 🞏 |

**Declaration by participant:**

I hereby consent to take part in this study.

|  |  |
| --- | --- |
| Participant’s name: | |
| Signature: | Date: |

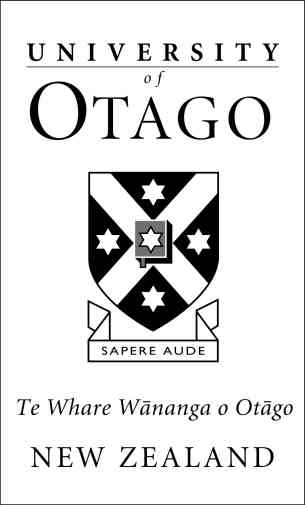
**Declaration by member of research team:**

I have given a verbal explanation of the research project to the participant, and have answered the participant’s questions about it.

I believe that the participant understands the study and has given informed consent to participate.

|  |  |
| --- | --- |
| Researcher’s name: | |
| Signature: | Date: |

## *Appendix 4*



**PRE-OPERATIVE PARTICIPANT QUESTIONNAIRE**

***General Information***

**Oral Surgery research project**

Department of Oral Diagnostic and Surgical Sciences, School of Dentistry, University of Otago

**Principal Researcher:** YJ Jessica Lee (Oral Surgery Doctorate Candidate)

**Primary Supervisor:** Mr Harsha De Silva (Senior Lecturer in Oral & Maxillofacial Surgery)

Thank you for taking the time to fill in this questionnaire.

You are kindly requested to complete this questionnaire during your wisdom teeth consultation appointment with YJ Jessica Lee.

***For information about this research project, please read the form entitled:***“Information sheet for participants: *Pre-operative effects of anti-inflammatory drugs on pain and inflammation following wisdom teeth removal.”*

***All personal information collected will remain strictly confidential.***

Please answer honestly. There will be no criticism or judgment of you for your answers.

**Question 1**

**How old are you?**

**Question 2**

**What is your gender?** (please circle)

|  |  |  |
| --- | --- | --- |
| Male | Female |  |

**Question 3**

**Which ethnic groups do you belong to?** (please circle all which apply)

New Zealand European

Māori

Samoan

Cook Island Māori

Tongan

Niuean

Chinese

Indian

Others (please state):

**Question 4**

**What is your occupation?**

**Question 5**

**What is the highest level of education you have attained?**

Primary school

Secondary school

Trade qualification

Tertiary education

**Question 6**

**Do you currently smoke?** (please circle)

|  |  |
| --- | --- |
| Yes | No |

**If yes, will you be able to stop smoking for the first 3 days after your wisdom teeth surgery?**

|  |  |
| --- | --- |
| Yes | No |

**Question 7**

1. **Have you ever had any pain or discomfort with your wisdom teeth?** (please circle)

|  |  |
| --- | --- |
| Yes | No |

1. **If so, how many times have you had pain or discomfort with your wisdom teeth?**
2. **In the last 4 weeks, have you had pain or discomfort with your wisdom teeth?** (please circle)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Always | Often | Sometimes | Occasionally | Never |

1. **How would you describe the usual intensity of that pain or discomfort?** (please circle)

|  |  |  |  |
| --- | --- | --- | --- |
| Mild | Moderate | Severe | Not applicable |

**Question 8**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **How would you describe the health of your teeth and mouth?** (please circle) | | | | |
| Excellent | Very good | Good | Fair | Poor |

**Question 9**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **How often do you usually brush your teeth?** (please circle) | | | | |
| More than once a day | Once a day | Not every day | Less than once a week | Never |

**Question 10**

**Place a vertical mark on the line below to indicate your current level of pain.**

No pain

Worst pain imaginable

**Question 11**

**Please circle the answer that BEST applies to you during the last 4 weeks.**

**Because of trouble with your teeth, mouth or dentures:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Have you had trouble pronouncing any words? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you felt that your sense of taste has worsened? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you had painful aching in your mouth? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you found it uncomfortable to eat any foods? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been self-conscious? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you felt tense? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Has your diet been unsatisfactory? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you had to interrupt meals? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you found it difficult to relax? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been a bit embarrassed? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been a bit irritable with other people? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you had difficulty doing your usual jobs? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you felt that life in general was less satisfying? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been totally unable to function? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |

**Question 12**

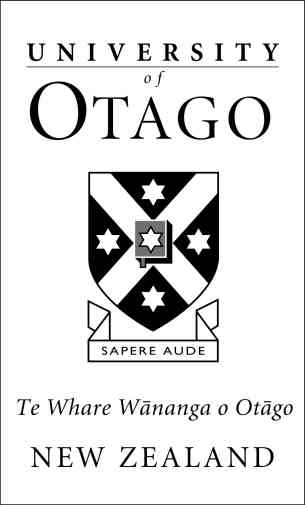
**For each question, please tick the box of the answer which comes closest to how you feel.**

|  |  |
| --- | --- |
| **If you had to go to the dentist tomorrow, how would you feel about it?** | |
| 1. I would look forward to it as a reasonably enjoyable experience |  |
| 1. I wouldn’t care one way or the other |  |
| 1. I would be a little uneasy about it |  |
| 1. I would be afraid that it would be unpleasant and painful |  |
| **When you are waiting in the dentist’s surgery for your turn in the chair, how do you feel?** | |
| 1. Relaxed |  |
| 1. A little uneasy |  |
| 1. Tense |  |
| 1. Anxious |  |
| 1. So anxious that I sometimes break out in a sweat or almost feel physically sick |  |
| **When you are waiting in the dentist’s chair while he gets his drill ready to begin working on your teeth, how do you feel?** | |
| 1. Relaxed |  |
| 1. A little uneasy |  |
| 1. Tense |  |
| 1. Anxious |  |
| 1. So anxious that I sometimes break out in a sweat or almost feel physically sick |  |
| **You are waiting in the dentist’s chair to have your teeth cleaned. While you are waiting and the dentist is getting out the instruments which he/she will use to scrape your teeth around the gums, how do you feel?** | |
| 1. Relaxed |  |
| 1. A little uneasy |  |
| 1. Tense |  |
| 1. Anxious |  |
| 1. So anxious that I sometimes break out in a sweat or almost feel physically sick |  |

***End of questionnaire.***

***Thank you.***

## *Appendix 5*



**Level of Pain *before* Wisdom Teeth Removal**

**Please complete on arrival at the School of Dentistry for your wisdom teeth surgery.**

***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

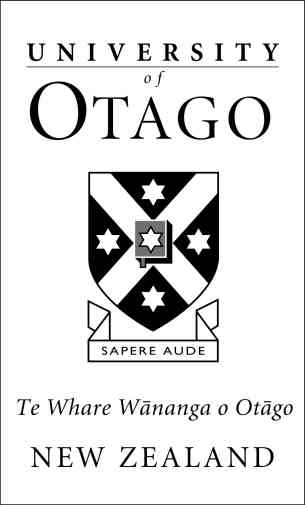
***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

Place a vertical mark on the line below to indicate your current level of pain.

Please answer honestly. There will be no criticism or judgment of you for what pain score you record below.

No pain

Worst pain imaginable



**PAIN SCORE**

**Level of Pain *following* Wisdom Teeth Removal**

**During awake hours, please complete every 3 hours for the first 48 hours following your wisdom teeth surgery. Use a separate page each time.**

***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

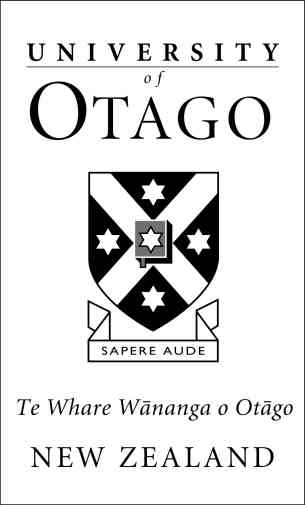
Place a vertical mark on the line below to indicate your current level of pain.

Please answer honestly. There will be no criticism or judgment of you for what pain score you record below.

No pain

Worst pain imaginable

## *Appendix 6*



**PAIN MEDICATION**

**The use of pain medication *on the day* following wisdom teeth removal**

**Please complete this questionnaire at the end of each day before going to bed.**

***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

1. How long did it take you to the first use of pain relief (paracetamol) after your wisdom teeth surgery?

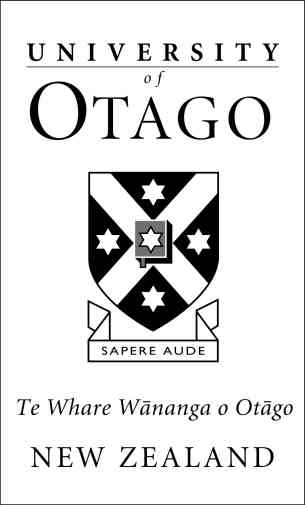
**hours**

1. How long did it take you to the first use of rescue pain relief (codeine phosphate) after your wisdom teeth surgery?

**hours**

1. If you have taken rescue pain relief (codeine phosphate), how may tablets did you take on the day of surgery?

**tablets**



**PAIN MEDICATION**

**The use of pain medication *1-day* following wisdom teeth removal**

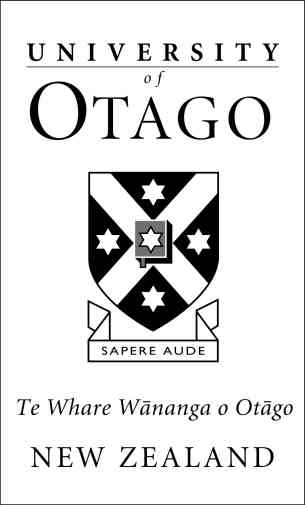
**Please complete this questionnaire at the end of each day before going to bed.**

***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

If you have taken rescue pain relief (codeine phosphate), how may tablets did you take on the 1st day following surgery?

**tablets**



**PAIN MEDICATION**

**The use of pain medication *2-days* following wisdom teeth removal**

**Please complete this questionnaire at the end of each day before going to bed.**

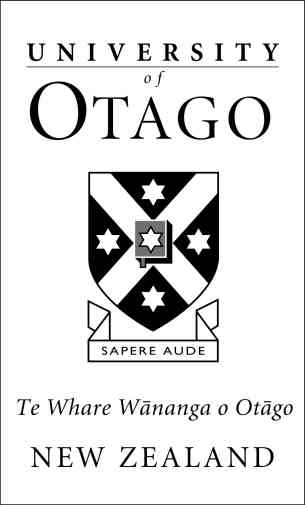
***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

If you have taken rescue pain relief (codeine phosphate), how may tablets did you take on the 2nd day following surgery?

**tablets**

## *Appendix 7*



**ADVERSE EVENTS PROFILE *(draft only)***

**Side effects following wisdom teeth removal**

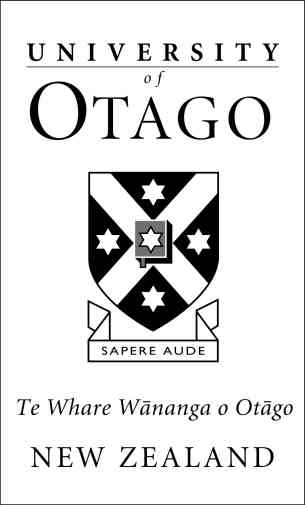
**Please complete this questionnaire on the 2nd day following surgery.**

***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

**Please indicate if you have experienced any of the following symptoms following your wisdom teeth surgery.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SYMPTOMS** | **YES** | **NO** | **IF “YES”, PLEASE COMMENT BELOW** | | | | | | | | | | | | |
| **Headache** |  |  | *Did you experience this symptom before your wisdom teeth surgery?* | | | | | | | | | | | | |
| YES | | | | | | | NO | | | | | |
| *When did you first experience this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *How often did you experience this side effect?* | | | | | | | | | | | | |
| HARDLY EVER | OCCASIONALLY | | | | | | FAIRLY OFTEN | | | | | VERY OFTEN |
| *How much influence did this side effect have on your daily functioning?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *What action did you take in relation to this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| **Drowsiness** |  |  | *Did you experience this symptom before your wisdom teeth surgery?* | | | | | | | | | | | | |
| YES | | | | | | NO | | | | | | |
| *When did you first experience this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *How often did you experience this side effect?* | | | | | | | | | | | | |
| HARDLY EVER | OCCASIONALLY | | | | | FAIRLY OFTEN | | | | | VERY OFTEN | |
| *How much influence did this side effect have on your daily functioning?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *What action did you take in relation to this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| **Dizziness** |  |  | *Did you experience this symptom before your wisdom teeth surgery?* | | | | | | | | | | | | |
| YES | | | | | NO | | | | | | | |
| *When did you first experience this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *How often did you experience this side effect?* | | | | | | | | | | | | |
| HARDLY EVER | OCCASIONALLY | | | | FAIRLY OFTEN | | | | | VERY OFTEN | | |
| *How much influence did this side effect have on your daily functioning?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *What action did you take in relation to this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| **Nausea** |  |  | *Did you experience this symptom before your wisdom teeth surgery?* | | | | | | | | | | | | |
| YES | | | | NO | | | | | | | | |
| *When did you first experience this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *How often did you experience this side effect?* | | | | | | | | | | | | |
| HARDLY EVER | OCCASIONALLY | | | FAIRLY OFTEN | | | | | VERY OFTEN | | | |
| *How much influence did this side effect have on your daily functioning?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *What action did you take in relation to this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| **Vomiting** |  |  | *Did you experience this symptom before your wisdom teeth surgery?* | | | | | | | | | | | | |
| YES | | | | NO | | | | | | | | |
| *When did you first experience this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *How often did you experience this side effect?* | | | | | | | | | | | | |
| HARDLY EVER | | OCCASIONALLY | | FAIRLY OFTEN | | | | | VERY OFTEN | | | |
| *How much influence did this side effect have on your daily functioning?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *What action did you take in relation to this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| **Stomache pain** |  |  | *Did you experience this symptom before your wisdom teeth surgery?* | | | | | | | | | | | | |
| YES | | | NO | | | | | | | | | |
| *When did you first experience this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *How often did you experience this side effect?* | | | | | | | | | | | | |
| HARDLY EVERY | | OCCASIONALLY | FAIRLY OFTEN | | | | | VERY OFTEN | | | | |
| *How much influence did this side effect have on your daily functioning?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |
| *What action did you take in relation to this side effect?* | | | | | | | | | | | | |
|  | | | | | | | | | | | | |

## *Appendix 8*



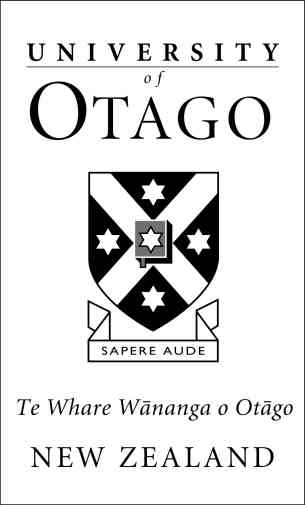
**Maximum Mouth Opening *before* Wisdom Teeth Removal**

***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

**The distance between the mesio-incisal edges of the right maxillary and mandibular central incisor teeth during maximal mouth opening:**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**



**Maximum Mouth Opening *2-days* following Wisdom Teeth Removal**

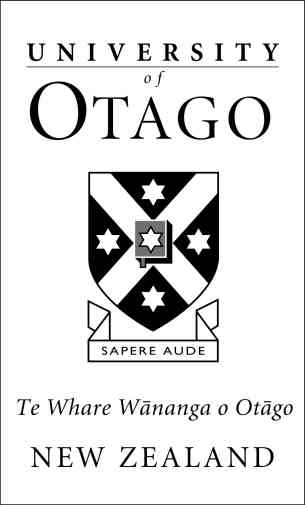
***Date: ­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

***Time: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***

**The distance between the mesio-incisal edges of the right maxillary and mandibular central incisor teeth during maximal mouth opening:**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

## *Appendix 9*



**POST-OPERATIVE PARTICIPANT QUESTIONNAIRE**

***General Information***

**Oral Surgery research project**

Department of Oral Diagnostic and Surgical Sciences, School of Dentistry, University of Otago

**Principal Researcher:** YJ Jessica Lee (Oral Surgery Doctorate Candidate)

**Primary Supervisor:** Mr Harsha De Silva (Senior Lecturer in Oral & Maxillofacial Surgery)

Thank you for taking the time to fill in this questionnaire.

You are kindly requested to complete this questionnaire during your review appointment with YJ Jessica Lee two days after surgery.

***For information about this research project, please read the form entitled:***“Information sheet for participants: *Pre-operative effects of anti-inflammatory drugs on pain and inflammation following wisdom teeth removal.”*

***All personal information collected will remain strictly confidential.***

Please answer honestly. There will be no criticism or judgment of you for your answers.

**Question 1**

**Did you take the pain relief medication prescribed to you?**

|  |  |
| --- | --- |
| Yes | No |

**Question 2**

**How long did it take for you to take the first pain relief after your surgery?**

**Question 3**

**Did the pain relief tablets give you sufficient pain relief?**

|  |  |
| --- | --- |
| Yes | No |

**Question 4**

**Overall, how would you rate your pain following your surgery?**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| No pain | Mild pain | Moderate pain | Severe pain | Excruciating pain & agony |

**Question 5**

**Did you take any *additional* pain relief medication other than the tablets prescribed to you?**

|  |  |
| --- | --- |
| Yes | No |

**If yes, please mention the name(s), dose, and duration \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Question 6**

**Did you need to see your medical GP about your pain or discomfort?**

|  |  |
| --- | --- |
| Yes | No |

**Question 7**

**Did you require the socket to be irrigated and dressed by a dentist?**

|  |  |
| --- | --- |
| Yes | No |

**Question 8**

Please circle the answer that BEST applies to you during the last 4 weeks.

**Because of trouble with your teeth, mouth or dentures:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Have you had trouble pronouncing any words? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you felt that your sense of taste has worsened? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you had painful aching in your mouth? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you found it uncomfortable to eat any foods? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been self-conscious? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you felt tense? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Has your diet been unsatisfactory? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you had to interrupt meals? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you found it difficult to relax? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been a bit embarrassed? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been a bit irritable with other people? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you had difficulty doing your usual jobs? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you felt that life in general was less satisfying? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |
| Have you been totally unable to function? | NEVER | HARDLY EVER | OCCAS-IONALLY | FAIRLY OFTEN | VERY OFTEN |

***End of questionnaire.***

***Thank you.***

1. Note that the selected dose of sustained-release ibuprofen 1.6g adheres to the Brufen SR modified-release 800mg New Zealand Data Sheet recommendation for adults. It states: “the recommended daily dosage is two Brufen SR tablets taken as a single dose, preferably in the early evening, well before retiring to bed. The tablets should be swallowed whole with plenty of fluids” (Brufen SR 800mg modified release tablet data sheet). In this proposed clinical trial, sustained-release ibuprofen 1.6g will be prepared in 4 capsules in divided doses (i.e. 4 x 400mg of sustained-release ibuprofen). All 4 capsules will be administered orally as a single dose 2 hours prior to surgery. [↑](#footnote-ref-2)
2. Participants will be encouraged to drink plenty of fluids prior to fasting. They will also be given a large glass of water to take with the pre-emptive medication 2 hours prior to the surgery, hence dehydration will not be an issue. [↑](#footnote-ref-3)
3. ASA 2 patients will be selected carefully after reviewing their medical history. Patients with known renal impairment, poorly controlled diabetes, and/or long-term antihypertensive therapy will be excluded *(“Exclusion criteria” p. 14-15).* [↑](#footnote-ref-4)