Final PROTOCOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Prophylactic removal of impacted third molars

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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ABBREVIATIONS LIST

3M	Third molar
AE	Adverse events
CPG	Clinical practice guideline
HRQoL	Health related quality of life
HTA	Health technology assessment
I3M	Impacted third molar
LR*i*G	Liverpool Reviews and Implementation Group
NICE	National Institute for Health and Care Excellence
RCT	Randomised controlled trial
TA	Technology appraisal
TAR	Technology appraisal report

GLOSSARY

Decision analysis	Decision analysis is a systematic, quantitative and interactive method used to address and evaluate important choices confronted by decision-makers. Decision analysis is interdisciplinary and incorporates theories from the disciplines of psychology, economics, and management science
Dry socket	Dry socket (alveolar osteitis) occurs when a blood clot fails to develop (or is dislodged) in the tooth socket as a normal part of healing, and can cause a dull, aching pain in the gum or jaw. It can also cause a bad taste or smell to come from the tooth socket
Impacted third molar	Third molars that have failed to erupt completely
Mandibular	Relating to the lower jaw
Maxillary	Relating to the upper jaw

1 TITLE OF PROJECT

Prophylactic removal of impacted third molars

2 TAR TEAM

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3 PLAIN ENGLISH SUMMARY

Wisdom teeth (third molars) are located at the very back of the mouth on both the upper and lower jaws, and four molars usually appear in the mouth between the ages of 18-24 years. About 15-20% of people never develop at least one of these four molars. Wisdom teeth often grow through the gums (erupt) without problems; however, sometimes, the wisdom tooth is unable to erupt properly and becomes “impacted”. When wisdom teeth become impacted there is an increased risk of decay and disease. Wisdom teeth can be surgically removed if they are diseased, or if they are likely to become diseased in the future. There are risks involved when surgically removing wisdom teeth. Risks include infection, delayed healing, and nerve damage. Current NHS guidelines recommend that impacted wisdom teeth should only be removed if there is evidence of disease or if there are repeated episodes of infection associated with the tooth. The guidance states that healthy wisdom teeth should not be removed as a preventive measure against future disease and that people with disease-free impacted wisdom teeth should visit their dentist for regular check-ups.

The aim of this review is to assess the clinical and cost effectiveness of the prophylactic removal of impacted mandibular wisdom teeth compared with standard care without prophylactic removal of wisdom teeth. The evidence for clinical effectiveness will be derived from a systematic review of published randomised controlled trials, clinical studies and literature reviews. The key outcomes will be pathology (disease) associated with retention of wisdom teeth, complications following surgical removal, adverse effects of surgical treatment, and health related quality of life. The evidence for cost effectiveness will be derived from a systematic review of published economic evaluations and costing studies.

4 DECISION PROBLEM

4.1 Clarification of research question and scope

The remit of this review is to appraise the clinical and cost effectiveness of the prophylactic removal of impacted mandibular third molars. The objective is to partially update the first Technology Appraisal carried out by the National Institute for Health and Care Excellence (NICE): Guidance on the Extraction of Wisdom Teeth (TA1).[1]

4.2 Background

The four hindmost molars, known as third molars (3Ms) are the last teeth to erupt in the mouth and this usually happens during young adulthood between the ages of 18 and 24. Third molars can either erupt in correct dental alignment and function but they can also erupt out of alignment, or fail to erupt completely. Third molars that have failed to erupt completely

are said to be impacted. Impaction can occur completely (enclosed in the soft tissue or jaw bone) or partially (break through or erupt through the gum).

Impacted third molars (I3Ms) may be associated with pathological changes such as infection (pericoronitis), periodontal (gum) disease, dental caries, destruction of adjacent teeth, cysts and tumours. Pericoronitis is an infection of the soft tissue surrounding the crown of the tooth and is caused by an accumulation of bacteria and debris beneath the soft tissue. This can result in inflammation and pain. Where wisdom teeth are impacted, this creates an area that is difficult to clean properly with a toothbrush, making the molar in front of the wisdom tooth, as well as the wisdom tooth itself, vulnerable to periodontal disease. Periodontal disease is caused by bacteria in the mouth, which, when not removed by tooth-brushing, sets up some chronic inflammation in the gum and bone which support the teeth in the mouth. Bone loss can result in the tooth becoming loose, and possibly lost. Dental caries are cavity formations in teeth, caused by bacteria which metabolise sugar in the diet to form acids. There is some evidence to suggest that I3Ms at an angle facing towards the front of the mouth (mesioangular), away from the adjacent tooth or impacted horizontally may increase the risk of decay and cause possible damage to adjacent teeth.[2] Cysts and tumours may develop around I3Ms though research has shown that the risk is low and reduces with age.[3] The prevalence of pathological changes in I3Ms is higher in I3Ms that erupt in the mandibular (lower jaw) compared with I3Ms that erupt in the maxillary (upper jaw).[4]

4.2.1 Epidemiology

The prevalence of I3Ms in the UK is unknown. Internationally, the prevalence of I3Ms is reported to range from 18–68%.[5] Prior to the introduction of NICE guidance,[1] the removal of 3Ms was one of the most common of all surgical procedures performed in the UK with over 36,000 inpatient and 60,000 day case admissions for 'surgical removal of tooth' in the period 1994-5.[1] During this period, the cost to the NHS in England of 3M surgery was estimated at £30 million per year, with additional estimated costs of £20 million in the private sector.[1]

The UK National Third Molar project[4] was set up in 1997 to assess the management of 3Ms in UK clinical practice. Clinical data were collected prospectively from all of the patients referred for assessment of 3Ms to oral and maxillofacial consultant surgeons during July 1995.[4] Completed questionnaires were returned from 181 consultants and 8298 patients (with 25,001 3Ms) who were referred to hospital for assessment. Details of eruption and symptoms status of all 3Ms at the time of presentation are shown in Table 1. Where data were available, the majority of mandibular 3Ms were impacted. Whereas maxillary 3Ms were either present and functional, or absent.

Table 1 State of eruption and symptoms status of all third molar teeth at the time of presentation

Status	Maxillary right (n=5191)	Maxillary left (n=5700)	Mandibular left (n=7049)	Mandibular right (n=7061)
Present and functional	18.9	19.4	8.5	4.2
Absent	34.7	40.5	16.6	6.1
Impacted and symptomatic	12.6	13.3	17.6	11.3
Impacted and asymptomatic	4.1	4.1	41.9	24.4
Buried	7.9	8.2	4.2	2.7
Unrecorded	22.0	14.7	11.3	51.5

Source: UK National Third Molar Project: the initial report[4]

The authors of the study[4] reported that, after assessment, a total of 19,971 (80%) of the 25,001 3Ms were extracted and mandibular 3Ms were more likely to be extracted than maxillary 3Ms (87% versus 71% respectively). The most frequent indication for extraction was prophylactic removal (n=8772, [44%]), followed by pericoronitis (n=7896, [40%]). There were differences in rates between mandibular and maxillary 3Ms: 22% of mandibular 3Ms were extracted prophylactically compared to 79% of maxillary 3Ms, whereas 60% of mandibular 3Ms were removed due to pericoronitis compared to 8% of maxillary 3Ms.

Authors of a recent study[6] investigating the effects of NICE guidance[7] on the management of 3Ms reported that, since the introduction of the NICE guidance,[7] the number of 3M removals in secondary care (in-patient/day-case) reduced from ~60,000 in the 1990s to ~40,000 in 2003. However, after 2003, the number of removals appears to have increased to ~65,000 during 2009/10 (in-patient/day-case only).

The results of the UK National Third Molar Project[4] showed that the most common age for the removal of 3Ms was between 21 and 25 years. However, in 2012, McCardle[6] reported that the mean age of patients having 3Ms removed had increased from age 25 years in 2000 to age 32 years in 2010, with the most common age increasing from 26 to 29 years.

4.2.2 Current treatment options

Treatment options for people with I3Ms include either surgical removal or standard care without prophylactic removal of third molars.

Surgical removal

A study[8] by the Royal College of Surgeons of England states that, “Third molar surgical procedures are generally suitable for day case management, and it is recognised that treatment under local anaesthesia with or without sedation is associated with reduced complication rates.”

Removal of I3Ms can be carried out by a dentist, or patients can be referred to an oral surgeon in cases where the degree of impaction or position of the tooth indicates a more complex surgical procedure. In cases where general anaesthetic is required (which is rare), the surgical removal is conducted in hospital.

Generally, recovery from surgery to remove 3Ms is straightforward. The immediate side effects of 3M surgery such as pain and swelling resolve within a few days and tooth sensitivity and jaw stiffness usually subside within 1-2 weeks.[9] However, there may be potential additional complications associated with the removal of I3Ms including damage to surrounding teeth, infection and dry socket (which can manifest as a throbbing pain in the gum or jaw and also cause bad breath). Also, nerve damage may occur and is a serious complication that can cause pain or a tingling sensation and numbness in the tongue, lower lip, chin, teeth and gums.

Overall, the rate of complications following the removal of 3Ms is reported to vary between 2.6% and 30.9%.[10] The removal of mandibular 3Ms (regardless of eruption status) is much more likely to be associated with post-surgical complications than the removal of maxillary 3Ms.[11] The risk of infection following extraction of I3Ms is approximately 10% in healthy patients, however, this risk increases by up to 25% in patients in patients with low immunity.[12] Dry socket occurs in 5-10% of patients having a 3M removed and presents within 3-5 days after the initial pain from surgery has subsided. Nerve damage occurs in up to 2% of patients and is generally temporary, but in 0.5% (1 in 200) patients, the damage is permanent.[9] The risk of nerve injury is more common if the mandibular I3M is located close to the lingual nerve, with 20% of patients likely to then have temporary nerve damage and 2% to experience permanent damage.[9]

Standard care without removal

The alternative to surgical removal of an I3M is standard care without removal of the tooth. Standard care is typically patient-centred and comprises regular oral health reviews, oral health advice, dental care plans and a decision on the length between recalls.[13] Standard care is carried out without the removal of the I3M.

However, without the removal of the I3M there is a risk that pathological changes, as previously described, could lead to future surgical removal of the impacted tooth.

Indications for removal or retention

The decision to remove or retain an I3M depends on whether it is asymptomatic (pathology/trouble-free). Where there are pathological changes, current NICE guidance[7] states that the I3M should be removed.[14]

Even if an I3M is pathology/trouble-free, the dentist may decide to remove the tooth to prevent future risk of pathological changes. Removal of a pathology/trouble-free tooth is termed prophylactic removal. However, there is disagreement on the operational definition of what constitutes a pathology/trouble-free wisdom tooth and there are a variety of clinical guidelines[7, 8, 15-24] that make recommendations on this topic. The rationale for the prophylactic removal of I3Ms is also much debated in the published literature.{McArdle, 2013 #53} The current NICE guidance[7] is presented in Box 1.

Box 1 NICE guidance (TA1) on the extraction of wisdom teeth

1.1 The practice of prophylactic removal of pathology-free impacted third molars should be discontinued in the NHS
1.2 The standard routine programme of dental care by dental practitioners and/or paraprofessional staff, need be no different, in general, for pathology-free impacted third molars (those requiring no additional investigations or procedures)
1.3 Surgical removal of impacted third molars should be limited to patients with evidence of pathology. Such pathology includes unrestorable caries, nontreatable pulpal and/or periapical pathology, cellulitis, abscess and osteomyelitis, internal/external resorption of the tooth or adjacent teeth, fracture of tooth, disease of follicle including cyst/tumour, tooth/teeth impeding surgery or reconstructive jaw surgery, and when a tooth is involved in or within the field of tumour resection
1.4 Specific attention is drawn to plaque formation and pericoronitis. Plaque formation is a risk factor but is not in itself an indication for surgery. The degree to which the severity or recurrence rate of pericoronitis should influence the decision for surgical removal of a third molar remains unclear. The evidence suggests that a first episode of pericoronitis, unless particularly severe, should not be considered an indication for surgery. Second or subsequent episodes should be considered the appropriate indication for surgery

Source: Guidance on the Extraction of Wisdom Teeth (TA1)[7]

A systematic review[14] of the literature on the prophylactic removal of pathology-free wisdom teeth (search dates 2000 and 2010, limited to English, Dutch, French and German language papers) identified 10 clinical practice guidelines (CPG)[7, 8, 15-18, 20-23] and two health technology assessment (HTA) reports.[19, 24] Only the guidance issued by NICE[7] was considered to be of high quality and was summarised in the report.[14] The HTA reports and guidelines[7, 8, 15-24] (minus the guidance issued by NICE[7] and the superseded guidelines) are summarised in Appendix 1.

The NICE TA 1[1] was completed in 2000 and the resultant guidance was that the prophylactic removal of pathology-free I3Ms was not to be recommended. A review of the existing NICE guidance via a 'Review Proposal' in 2014 concluded that no new trial data on this topic were available. As a result, a decision was made that that the NICE guidance did not need to be revisited and the topic should remain on the static list. However, as the recommendations

set out in the NICE guidance[7] were increasingly being perceived as controversial by the dental profession, a NICE consultation with relevant stakeholders was then undertaken. Consultation responses highlighted that additional pertinent trial data were available and therefore should be assessed. In response, NICE instructed that the current guidance[7] should be partially updated (i.e. prophylactic indications only) via the Multiple Technology Appraisal (MTA) process.

4.3 The present appraisal

The present appraisal will be conducted in line with the decision problem issued by NICE in the final scope.[2] This is reproduced in Table 2. The intervention under consideration is the prophylactic removal of 3Ms, and the relevant patient population is people with pathology/ trouble-free impacted mandibular I3Ms. The intervention will be compared with standard care without the prophylactic removal of 3Ms. The outcomes of interest will be: pathology associated with retention of third molars, post-operative complications following extraction, adverse effects (AEs) of treatment, and health related quality of life (HRQoL). If evidence allows, people with mesioangular third molars will be considered as a subgroup. The evidence for cost effectiveness will be derived from a systematic review of published economic evaluations and costing studies.

Table 2 Decision problem issued by NICE

Interventions	Prophylactic removal of third molars
Population	People with pathology-free or trouble-free impacted mandibular third molars
Comparators	Standard care without prophylactic removal of third molars
Outcomes	The outcome measures to be considered include: • Pathology associated with retention of third molars • Post-operative complications following extraction (for example, pain, dry socket, nerve injury) • Adverse effects of treatment • Health related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective
Other considerations	If evidence allows, consideration may be given to the following subgroups: • •People with mesioangular or horizontally impacted third molars

5 METHODS FOR SYNTHESISING CLINICAL EVIDENCE

5.1 Search strategy

The TAR team will identify clinical studies and systematic reviews by searching major medical databases such as MEDLINE, EMBASE and the Cochrane Library from 1999 onwards. In addition, information on studies in progress will be sought by searching a range of relevant databases including the National Research Register and Controlled Clinical Trials.

An example of the draft search strategy to be used in MEDLINE is presented in Appendix 2. Citation searches of key articles will be undertaken. A database of published literature will be assembled from the aforementioned sources and will be held in the Endnote X7 software package.

5.2 Study selection

Two reviewers will independently screen all titles and abstracts identified by the initial search. Full text copies of any titles/abstracts that may be eligible for inclusion will be obtained and will be assessed for inclusion by two reviewers according to the inclusion and exclusion criteria listed in Table 3. Any discrepancies will be resolved by consultation with a third reviewer. Studies that do not meet the inclusion criteria will be excluded and their bibliographic details will be listed with reasons for exclusion.

Table 3 Inclusion criteria (clinical effectiveness)

	Inclusion	Exclusion
Study design	Clinical trials (randomised and non-randomised) Observational studies Systematic reviews Decision analyses	Case studies Non-systematic reviews
Patient population	People with impacted mandibular third molars	
Interventions	Prophylactic removal of impacted mandibular third molars (as defined by study authors)	
Comparators	Standard care without prophylactic removal of impacted mandibular third molars	
Outcomes	The outcome measures to be considered include: • Pathology associated with retention of third molars • Post-operative complications following extraction • Adverse effects of treatment • Health related quality of life	
Setting	Europe North America Australasia	
Other considerations	If evidence allows, consideration may be given to the following subgroups: • •People with mesioangular or horizontally impacted third molars	
Limits	1999 onwards English language only	

5.3 Data extraction and quality assessment strategy

Data relating to study characteristics and outcomes will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus, and if necessary a third reviewer will be consulted. Time permitting, study authors will be contacted for missing data. Data from multiple publications will be extracted and reported as a single study.

The quality of the included studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted. The quality of the randomised controlled trials (RCTs) will be assessed according to criteria based on Centre for Review and Dissemination's Guidance[25] for undertaking reviews in healthcare. For other study designs, data related to study quality will be tabulated and discussed using appropriate assessment tools.

5.4 Methods of analysis/synthesis

The results of the data extraction and quality assessment for each included study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed.

The TAR team anticipates that, in the included studies, the outcomes measured for each individual patient will differ according to the intervention/control group to which they belong. Therefore comparative estimates of treatment effect for intervention groups relative to control groups are unlikely to be reported in the papers themselves. The TAR team will not be able to calculate comparative treatment effects using reported data as outcomes will differ according to the intervention/control group. Consequently, it will not be possible to perform meta-analyses of treatment effects.

The TAR team will consider synthesising data for each intervention/control group separately, i.e. if appropriate, the TAR team will perform meta-analyses to summarise outcomes across the included studies, but only for a single intervention. Single arm data are by definition non-randomised and therefore are likely to be heterogeneous. The TAR team will consider clinical and methodological heterogeneity between the included studies by considering differences in (a) study population, (b) intervention, (c) outcome measures, and (d) study quality. If there are important differences between the included studies that mean it would not be clinically meaningful to pool results, the TAR team will present individual study results on forest plots but the TAR team will not perform any meta-analyses.

Where pooling is an appropriate approach, the TAR team will use the generic inverse variance method in R to pool data using a fixed effects model, or the DerSimonian and Laird method[26] using a random effects model in the case of substantial heterogeneity. The I^2 statistic will be used to assess heterogeneity of trial results, with a value of $I^2 \geq 50\%$ indicating substantial heterogeneity.

The TAR team will explore possible sources of heterogeneity by performing subgroup analyses. The TAR team will perform subgroup analyses for factors that may affect study outcomes, such as differences in patient populations, interventions and how outcomes are measured.

6 METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

6.1 Identifying and systematically reviewing published cost studies

The cost and cost effectiveness evidence presented in TA1[7] was limited. It comprised UK cost information extracted from three journal articles[4, 27, 28] and a submission of evidence to NICE.[29] The results of the scoping searches recently carried out by the TAR team indicate that published cost and cost effectiveness evidence in this area remains limited and only basic costing information is available. The TAR team's literature review will, therefore, focus primarily on published UK costs associated with the extraction and/or retention of I3Ms.

6.2 Search strategy

The search strategy detailed in Section 5.1 will be used to identify studies reporting the costs (and where possible, the benefits) associated with extracting/retaining I3Ms. Other searching activities, including electronic searching of online health economic journals, conference proceedings and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report.

6.2.1 Study selection and inclusion criteria

Two reviewers will independently examine the titles and abstracts of potentially eligible publications. Potentially relevant studies will then be obtained in full text and examined carefully by two independent reviewers using the inclusion criteria specified in Table 4. Any disagreement will be resolved by consensus and, if necessary, a third reviewer will be consulted. Although the review will focus on costs, relevant outcome information will be collated and discussed narratively in the final report, as appropriate.

Table 4 Inclusion criteria (costs and outcomes)

	Inclusion
Patient population	People with impacted molars
Costs	UK costs
Outcomes	Any health outcomes, health related quality of life
Study design	All study designs
Date	2000 - present
Language	English language only

6.2.2 Data extraction

Where available, data relating to both study design and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. If time

constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

6.2.3 Quality assessment

The quality of the individual cost effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of cost effectiveness studies will be assessed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[30] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[31] The information will be tabulated and summarised within the text of the final report.

6.3 Health economic modelling

Examination of the results of the recent scoping searches conducted by the TAR team has highlighted an absence of robust RCT evidence linking the extraction/retention of I3Ms with future (measurable) outcomes. It would, therefore, be premature to attempt a full economic modelling and cost effectiveness evaluation exercise for this procedure at this time. However, depending on the design and volume of the evidence identified via the clinical and cost effectiveness literature reviews, the TAR team might be in a position to describe the cost and benefit information that would be required if a full economic evaluation were to be undertaken.

7 EXPERTISE IN THE TAR TEAM AND COMPETING INTERESTS

This TAR team comprises the individuals listed in Table 5. A panel of clinical/dental experts will also be consulted during the review process. The experts will provide insight into a range of issues relating to clinical/dental practice, potential patient characteristics that may influence clinical/dental heterogeneity and relevant patient subgroups.

Table 5 TAR team members

Team lead/clinical systematic reviewer	Gerlinde Pilkington
Team lead/clinical systematic reviewer	Juliet Hounsome
Systematic reviewer (economics)	Sophie Beale
Systematic reviewer (economics)	Dr Angela Boland
Information specialist	Eleanor Kotas
Methods advisor	Prof Rumona Dickson
Clinical/dental advisor	Prof Rebecca Harris
Clinical/dental advisor	TBC

None of the review team has any competing interests. Any competing interests relating to any external reviewers will be declared in the final report. All e-mail correspondence should be sent to the team leaders and the Director.

8 PROJECT TIMELINES

Table 6 Timetable/milestones

Submission and approval of final protocol	07/04/2016
Stakeholder information meeting	26/04/2016
Progress report to NETSCC, HTA	04/07/2016
Assessment report	21/09/2016

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10 APPENDICES

Appendix 1 Summary of published clinical practice guidelines and health technology assessments

Table 7 Clinical practice guidelines and health technology assessments

Guidelines/HTA	Country	Recommendation
Faculty of Dental Surgery - RCS(eng) 1997[8] (reviewed in 2014 and currently under review)	England	Indications for removal • Overt or previous history of infection including pericoronitis • Unrestorable caries • Non-treatable pulpal and/or periapical pathology • Cellulitis, abscess and osteomyelitis • Periodontal disease • Orthodontic abnormalities • Prophylactic removal in the presence of specific medical and surgical conditions • Facilitation of restorative treatment including provision of prosthesis • Internal/external resorption of tooth or adjacent teeth • Pain directly related to a third molar • Tooth in line of bony fracture or impeding trauma management • Fracture of tooth • Tooth/teeth impeding orthognathic surgery or reconstructive jaw surgery • Tooth involved in/ within field of tumour resection • Satisfactory tooth for use as donor for transplantation A4.1 An impacted tooth which is totally covered by bone and which does not meet the above indications for surgery should not be removed; however it is generally recognised that it should be monitored periodically by clinical and radiographic examination (usually dental panoramic tomograph) because of the potential for change in position and/or development of pathology. The relative risk of retaining/delaying removal of impacted third molars should be considered in all cases. However surgical intervention in the absence of pathology is not usually indicated. A4.2 Consideration may be given to removal of an unerupted third molar by the third decade when a high probability of disease or pathology exists and when the risks associated with early removal are less than the anticipated risks of later removal (i.e.: increased morbidity). Two situations in which a high probability of consequential local disease is present are: a. When a vertical or distoangular impacted tooth is at or close to the occlusal plane but the occlusal surface has been half or more covered for an extended period by soft tissue, pericoronitis is more likely, b. When a partly-erupted impacted wisdom tooth in mesioangular or horizontal impaction has a contact point at or close to the amelocemental junction of the second molar the risk of caries of the latter is increased especially in the absence of a high standard of oral hygiene. A4.3 In a patient who has borderline indications for third molar excision and whose occupation will necessitate long periods away from civilisation (e.g. astronauts, nuclear submariners and explorers) consideration may be given to earlier rather than later third molar removal
AAPD 2010 Adolescents[17] (Revised 2015)	US	Evaluation of third molars, including radiographic diagnostic aids, should be an integral part of the dental examination of the adolescent. For diagnostic and extraction criteria, refer to AAPD's Guideline on Pediatric Oral Surgery. Referral should be made if treatment is beyond the treating dentist's scope of practice

Guidelines/HTA	Country	Recommendation
AAPD 2005 Paediatric[18] (Revised 2015)	US	A systematic review of research literature from 1984 to 2013 concluded there is no evidence to support or refute the prophylactic removal of disease-free impacted third molars. Factors that increase the risk for surgical complications (e.g., coexisting systemic conditions, location of peripheral nerves, history of temporomandibular joint disease, presence of cysts or tumors) and position and inclination of the molar in question should be assessed. The age of the patient is only a secondary consideration. Referral to an oral and maxillofacial surgeon for consultation and subsequent treatment may be indicated. When a decision is made to retain impacted third molars, they should be monitored for change in position and/or development of pathology, which may necessitate later removal
ZZQ 2006[16]	Germany	**Removal is indicated in the following cases**: a) Acute or chronic infection (acute pericoronitis) b) Exposed pulp due to caries c) Non-restorable caries-damaged teeth or untreatable pulpitis d) If it appears that the third molar is a significant source of pain e) Untreatable periapical changes f) Manifest pathological structures associated with dental follicles (e.g. cysts or a tumour) or suspicion of such changes g) Resorption of adjacent teeth h) In connection with the treatment of periodontal disease or limitation of its progression i) Teeth that impede orthodontic and reconstructive surgery j) Teeth in the fracture gap that impede fracture treatment k) Where the tooth is to be used for transplant purposes l) If the elongated or inclined third molar presents a manifest disturbance of dynamic occlusion **Indications for the removal of clinically and radiologically asymptomatic third molars having regard to the local risks of surgery** Removal may be indicated in the following cases: a) Prophylactic removal for higher-level reasons associated with the patient's life situation (e.g. non-availability of medical care) b) If other measures are being conducted under anaesthetic and further anaesthesia would be necessary for removal of a third molar c) Where prosthetic treatment is planned and secondary eruption due to further atrophy of the alveolar ridge or to pressure of the removable prosthesis is likely d) To facilitate orthodontic treatment such as tooth movement and/or retention **Indications for non-removal of clinically and radiologically asymptomatic third molars** Removal is not indicated in the following cases: a) Where spontaneous regular positioning of the third molars in the dental arch is likely b) If the extraction of other teeth and/or orthodontic treatment with correct positioning of the tooth is appropriate c) Deeply impacted and malposed teeth without associated pathology, where a high risk of surgical complications exists
NGC-7156 2008[22] (Updated 2013)	US	In summary, the committee have the following suggestions for treatment, referral, and monitoring asymptomatic impacted third molars: • If the patient is over 30 years of age, third molars should be monitored. Suggested monitoring regimen is an annual radiograph and clinical examination • If the patient is between 14 and 30 years of age and root formation is at least 1/2 to 2/3 complete, the examining dentist should review treatment options including risks and benefits. Referral to an oral and maxillofacial surgeon for consultation can be made as indicated • If there are multiple third molars present, the treating general dentist or oral surgeon will consult on the advisability of removal of all third molars simultaneously. The decision to have asymptomatic teeth removed should be made by the well informed patient in consultation with their care provider.
Clinical Evidence 2010 based on Dodson 2010[20]	Sweden	**Extraction of asymptomatic impacted wisdom teeth:** When managing asymptomatic, disease-free wisdom teeth, no RCT data are available to guide therapeutic choices. Consistent with the application of evidence-based medicine principles, after a thorough review of the risks and benefits of the treatment alternatives, patient preference should be the factor driving the clinical decision **Active surveillance of asymptomatic impacted wisdom teeth**: Based on non-RCT evidence, when active surveillance is the recommended management option, the interval for follow-up should be 24 months. In addition to assessing the patient's

Guidelines/HTA	Country	Recommendation
		symptoms, the examination should include physical and radiographical components
SIGN 43 1999[23] (This guideline has now been removed at is >10 years old)	Scotland	**Removal of unerupted and impacted third molars is not advisable:** • In patients whose third molars would be judged to erupt successfully and have a functional role in the dentition • In patients whose medical history renders the removal an unacceptable risk to the overall health of the patient or where the risk exceeds the benefit • In patients with deeply impacted third molars with no history or evidence of pertinent local or systemic pathology • In patients where the risk of surgical complications is judged to be unacceptably high, or where fracture of an atrophic mandible may occur • Where the surgical removal of a single third molar tooth is planned under local anaesthesia the simultaneous extraction of asymptomatic contralateral teeth should not normally be undertaken **Removal of unerupted and impacted third molars is advisable:** • In patients who are experiencing or have experienced significant infection associated with unerupted or impacted third molar teeth • In patients with predisposing risk factors whose occupation or lifestyle precludes ready access to dental care • In patients with a medical condition when the risk of retention outweighs the potential complications associated with removal of third molars (e.g. prior to radiotherapy or cardiac surgery) • In patients who have agreed to a tooth transplant procedure, orthognathic surgery, or other relevant local surgical procedure • Where a general anaesthetic is to be administered for the removal of at least one third molar, consideration should be given to the simultaneous removal of the opposing or contralateral third molars when the risks of retention and a further general anaesthetic outweigh the risks associated with their removal **There are strong indications for removal when:** • There have been one or more episodes of infection such as pericoronitis, cellulitis, abscess formation; or untreatable pulpal/periapical pathology • There is caries in the third molar and the tooth is unlikely to be usefully restored, or when there is caries in the adjacent second molar tooth which cannot satisfactorily be treated without the removal of the third molar • There is periodontal disease due to the position of the third molar and its association with the second molar tooth. • In cases of dentigerous cyst formation or other related oral pathology • In cases of external resorption of the third molar or of the second molar where this would appear to be caused by the third molar **Other indications for removal**: • For autogenous transplantation to a first molar socket • In cases of fracture of the mandible in the third molar region or for a tooth involved in tumour resection • An unerupted third molar in an atrophic mandible • Prophylactic removal of a partially erupted third molar or a third molar which is likely to erupt may be appropriate in the presence of certain specific medical conditions • Atypical pain from an unerupted third molar is a most unusual situation and it is essential to avoid any confusion with temporomandibular joint or muscle dysfunction before considering removal • An acute exacerbation of symptoms occurring while the patient is on a waiting list for surgery may be managed by extraction of the opposing maxillary third molar

Guidelines/HTA	Country	Recommendation
		• A partially erupted or unerupted third molar, close to the alveolar surface, prior to denture construction or close to a planned implant
ANAES 1997[15]	France	• The extraction of impacted or misaligned mandibular wisdom teeth, with signs of pericoronitis, is recommended for patients with a risk of chronic or acute infectious endocarditis • The extraction of the four third molar buds is recommended for adolescents with a risk of infectious endocarditis and who present tooth-jaw disharmony • For patients with a risk of infectious endocarditis, the operation should take place in the best conditions of asepsis and with respect to the protocol on prophylactic antibiotherapy concerning infectious endocarditis • A course of antibiotics can follow if local infection persists
MoH Malaysia 2005[21]	Malaysia	• Assessment of the unerupted and impacted third molar must involve history taking (including medical history), clinical examination and radiological investigations • Asymptomatic and pathology-free impacted third molars need not be removed but would advise periodic review • Impacted third molars should not be removed to prevent late anterior crowding • The main indications for removal of impacted third molars are dental caries and third molar associated infections • Proper case assessment and careful surgical technique can prevent unwanted complications • In third molar surgery, the buccal approach with minimal lingual soft tissue retraction minimizes the likelihood of lingual nerve injury • Excessive bone removal is not recommended • The routine use of antibiotics in third molar surgery is not recommended
CADTH 2010[19]	Canada	There is currently insufficient evidence supporting or refuting the practice of prophylactic removal of asymptomatic third molars. Regarding clinical practice, the decision to remove asymptomatic wisdom teeth appears to be best based on careful consideration by practitioners of the potential risks and benefits for individual patients, as well as their attitude toward a potentially unnecessary surgical procedure
HTA Centre Sweden Suska 2010[24]	Sweden	Prophylactic removal of third molar teeth to prevent possible future complications is seriously questioned due to lack of supporting data of beneficial effects and the documented complications. There is still no scientific documentation available to either support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults

RCS(eng)=The Royal College of Surgeons of England; AAPD=American Academy of Paediatric Dentistry; ZZQ=Agency for Quality in Dentistry; NGC=National Guideline, Clearinghouse; SIGN=Scottish Intercollegiate Guidelines Network; ANAES=Agence Nationale d'Accréditation et d'Evaluation en Santé; MoH=Ministry of Health; CADTH=Canadian Agency for Drugs and Technologies in Health; HTA=Health technology appraisal

Source: Belgian Health Care Knowledge Centre (KCE). KCE Reports 182C[14]; ANAES 1997[15] is translated from the original French

Appendix 2 Draft search strategy (MEDLINE)

	Searches
1	Molar, Third/
2	((third or three) adj1 molar*).tw.
3	(wisdom adj1 (tooth or teeth)).tw.
4	Tooth, Impacted/
5	(impact* adj1 (tooth or teeth)).tw.
6	(itm or itms).tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	M3.tw.
9	(tooth or teeth).tw.
10	8 and 9
11	7 or 10
12	limit 11 to yr="1999 -Current"
13	Limit 12 to english language