MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Prophylactic removal of impacted third molars

This report was commissioned by the NIHR HTA Programme as project number 15/69/16

Completed 15/02/2017

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Prophylactic removal of impacted third molars

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Date completed: 15/02/2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/69/16.

Declared competing interests of the authors: None

Acknowledgements: The authors would like to thank Tara Renton, Paul Coulthard, Rebecca Harris and Margaret Raison for clinical input and Joanne Fisher for assistance with data extraction.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Hounsome J, Pilkington G, Mahon J, Boland A, Beale S, Kotas, E, Dickson R, et al. Prophylactic removal of impacted third molars Health Technology Assessment. 2017; In press.

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Data sharing statement
All available data can be obtained by contacting the corresponding author.

SCIENTIFIC SUMMARY

Background

The four hindmost molars, known as third molars (3Ms) are the last teeth to erupt in the upper (maxillary) and lower (mandibular) jaws, and this usually happens during young adulthood between the ages of 18 and 24. Third molars can be either impacted or non-impacted, and an impacted 3M (I3M) can be classed as erupted, partially erupted or unerupted. Impaction occurs when the eruption of the tooth is blocked either by soft tissue (gum) or bone. Impacted third molars can be potentially problematic to the individual by causing pain and disease; however, many I3Ms are asymptomatic (trouble-free) and/or disease-free/pathology-free.

Impacted third molars may be associated with pathological changes such as infection (pericoronitis), periodontal (gum) disease, dental caries, destruction of adjacent teeth, cysts and tumours.

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

The decision to remove or retain an I3M depends on whether it is asymptomatic and/or pathology-free. Where there are pathological changes, current National Institute for Health and Care Excellence (NICE) guidance states that the I3M should be removed. Even if an I3M is pathology-free, the dentist may decide to remove the tooth to prevent future risk of pathological changes; this is termed prophylactic removal.

Objectives

The remit of this review is to appraise the clinical and cost effectiveness of the prophylactic removal of impacted mandibular 3Ms (IM3Ms) compared with standard care without prophylactic removal.

Methods

Clinical effectiveness review

Five electronic databases were searched for: clinical trials (randomised and non-randomised), observational studies, systematic reviews (SRs), decision analyses and UK costs. Studies comparing the prophylactic removal of IM3Ms with standard care without prophylactic removal or studies assessing the outcomes of either approach were considered. The outcomes of interest were: pathology associated with retention of third molars, post-operative complications following extraction, adverse effects of treatment and health-related quality of life. Two reviewers independently screened all titles and/or abstracts including economic

evaluations, applied inclusion criteria to relevant publications and quality assessed the included studies. The results of the data extraction and (clinical) quality assessment are summarised in structured tables and as a narrative description. No meta-analysis or network meta-analyses were undertaken.

Cost-effectiveness review

The search strategy developed for the clinical searches, with the addition of an economics filter, was used to identify studies reporting the costs and benefits associated with extracting/retaining I3Ms. As part of the search strategy, the NHS Economics Evaluation Database (NHS EED), located within the Cochrane Library, and EconLit (EBSCO) were also interrogated. Two reviewers independently screened all titles and/or abstracts, and applied inclusion criteria to identify relevant studies.

Economic model

Due to the absence of cost-utility analyses relevant to the decision problem and generalisable to the NHS in England, the AG constructed a de novo economic model. Two pathways are considered, the intervention (prophylactic removal of IM3Ms) and the comparator, current standard of care (watchful waiting). The pathways were modelled as a combination of Markov processes and decision trees. The model perspective was that of the UK NHS, the time horizon was a life-time (80 years), outcomes were measured in quality adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%. A wide range of one-way sensitivity analyses were carried out to test parameter uncertainty and scenario analyses were carried out to test structural assumptions.

Results

Clinical effectiveness

Thirteen studies from 22 publications were included in the SR (four cohort studies and nine SRs).

Cohort studies

The four cohort studies included one observational cohort investigating the prophylactic removal of pathology-free or asymptomatic IM3Ms in comparison with the standard care and retention of these pathology-free or asymptomatic IM3Ms. Annual assessment over 5 years identified patients as: requiring and subsequently having an IM3M removed, requiring and refusing extraction of an IM3M, and not requiring removal of the IM3M.

No serious surgical complications were reported in the 52 participants who had an IM3M removed. Of those requiring removal but refusing, 5/7 required extraction within the follow-up

period. Finally, of those not requiring removal, 0/25 required extraction within the follow-up period

Two single cohort studies investigated the standard care without removal of pathology or asymptomatic IM3Ms. For one study assessments were conducted by telephone every 6 months for 5 years, and for the other a clinician questioned and assessed clinical outcomes at 1 year. The difference in length of follow-up periods explains the differences in the rates of extraction reported by each paper: 5.5% and 31.4%. The reasons for extraction also varied between the studies. One study reported that at 1 year, 46% of participants did not know the reason for the removal of the IM3M. Of those who did know, 50% were removed for pain and 20% for symptoms of pericoronitis. The other study reported that at 5 years, pericoronitis was the most frequent reason for removal (62.5%) followed by cosmetic/orthodontic reasons (12.5%).

One single prospective cohort study investigated the prophylactic removal of pathology or asymptomatic IM3Ms. Assessment of periodontal health was conducted prior to and 6 months after removal, and post-surgical complications were reported. There was no statistically significant change in plaque index and gingiva index but there was statistically significant reduction in mean probing pocket depth and probing attachment level. A total of 20 post-surgical complications were reported, most frequently intense pain for more than one day (12/78), post-operative infection (5/78), and wound dehiscence (3/78). No instances of secondary bleeding or nerve damage were reported.

Systematic reviews

Nine SRs of the management of 3Ms were included in this review, though none were limited to IM3Ms. The inclusion criteria for the SRs differed, resulting in a wide range of included primary studies. Despite the differences in SRs, the conclusions were similar, with seven of the nine stating that there was insufficient evidence on which to base a decision. One SR that looked at the risk of future extraction following the retention of trouble-free 3Ms found that the mean incidence rate of future extraction was 3.0% annually (range 1-9%), with a cumulative incidence rate of 5% at 1 year and 64% at 18 years

Cost-effectiveness

Three studies were identified that provide economic evidence on the cost-effective prophylactic removal of I3Ms. Two of the papers report details about the cost effectiveness of the prophylactic removal of I3Ms. One is a cost-effectiveness study from a UK NHS perspective, whilst one is of less direct relevance as estimates are based on the Australian health care system and results are presented in Australian dollars. The third paper reports findings relating to an assessment of oral HRQoL after the removal of I3Ms.

Economic model

For the comparison of a prophylactic removal strategy with watchful waiting, model results show that the incremental cost per person associated with prophylactic extraction is £55.71 and the incremental QALY gain is 0.005 per person. Combining the cost and QALY results generated by the model suggests an incremental cost effectiveness ratio (ICER) for the comparison of a prophylactic removal strategy versus a watchful waiting strategy of £11,741 per QALY gained for people aged 20 years with asymptomatic IM3Ms. The base case ICER per QALY gained was found to be robust when a range of one-way sensitivity analyses were carried out to test parameter uncertainty and when scenario analyses were carried out to test structural assumptions.

Discussion

Despite extensive searching of the literature the SR of clinical evidence found no RCT data to support or refute the prophylactic removal of pathology-free/trouble-free IM3Ms. The review however did identify evidence from two longitudinal studies demonstrating the outcomes when asymptomatic IM3Ms are left in situ. No studies reported the impact of retention on the status of the second molars although this may have been due to the narrow inclusion criteria which included “People with pathology-free or trouble-free impacted mandibular third molars”. This criteria severely limited the number of studies that met the inclusion criteria of this review.

As there is very limited clinical effectiveness evidence comparing the prophylactic removal of pathology-free IM3M versus a watchful waiting strategy, it is unsurprising that economic evidence relating to this comparison is also limited. The two published cost-effectiveness studies that directly consider this comparison conclude that there is currently no economic evidence to support the prophylactic removal of I3Ms. This is in contrast to the results generated by the AG economic model which suggest that prophylactic removal may be the more cost-effective strategy.

The strengths of the AG’s economic model include its simplicity and the minimal use of assumptions. It is constructed around two key parameters – the annual rates of symptom development and the extraction of pathology-free/trouble-free IM3Ms. Unfortunately, the economic model is limited by the lack of utility evidence around IM3M symptoms. However, suitable proxies were found and the cost-effectiveness findings are robust across a range of values that could be used.

Conclusions

Clinical effectiveness conclusions

The findings from this review are consistent with previous systematic reviews in that there is no available RCT evidence to support or refute the practice of the prophylactic removal of asymptomatic/pathology-free IM3Ms. However, the review did identify evidence from longitudinal studies demonstrating what happens when asymptomatic IM3Ms are left in situ.

Cost effectiveness conclusions

Only two published cost-effectiveness studies that directly consider the study question were identified. In both cases, the authors conclude that there is currently no economic evidence to support the prophylactic removal of I3Ms.

The base case results generated by the AG economic model indicate that the ICER per QALY gained for the comparison of the cost effectiveness of a prophylactic removal strategy versus a watchful waiting strategy is markedly less than the £20,000 per QALY gained threshold widely accepted by NICE Appraisal Committees.

Implications for service provision

The reintroduction of the prophylactic removal of pathology-free/trouble-free IM3Ms will have resource implications both in primary and secondary care settings, with the rate of pathology-free I3M3 extractions increasing.

The results generated by the economic model show that most people with IM3Ms will have their impacted teeth removed at some point and that, while prophylactic removal is probably more costly than a watchful waiting strategy, the improvements in HRQoL for people from a reduction in IM3M symptoms mean that prophylactic removal is a cost effective strategy for the NHS.

Suggested research priorities

There remains a lack of head-to-head trial evidence comparing a prophylactic removal strategy with a watchful waiting strategy. The practical difficulties (including, time, cost, and the need for extended follow-up) associated with undertaking such studies means that it is unlikely that this type of study will be conducted.

Future longitudinal studies on the pathology of retained IM3Ms could be designed to record the impaction status and health of the retained IM3M with results being presented separately for maxillary and mandibular teeth.

PLAIN ENGLISH SUMMARY

Third molars, commonly known as wisdom teeth may come through the gum (erupt) without any problems, usually during young adulthood (age 18-24). However, in some cases they are unable to erupt because they are poorly aligned, or obstructed by other teeth, gums or bone. They are then referred to as ‘impacted’. Historically, dentists often recommended that these teeth be removed so as not to cause problems later in life. This is referred to as ‘prophylactic’ removal. In 2000 the National Institute for Health and Care Excellence (NICE) reviewed this practice and recommended that these teeth not be removed if they were not bothersome to the person. Many dentists and oral surgeons have disagreed with this decision, believing that it is more difficult to remove these teeth and that there are more complications for the patient if they are removed later in life.

Our review group carried out a systematic review of the available clinical and cost-effectiveness evidence of the prophylactic removal of impacted third molars.

The review identified four clinical studies. None of which provided strong evidence for or against the prophylactic removal of these teeth. These findings are similar to nine previous reviews. There is also very little research reported relating to the cost-effectiveness of the procedure, with only three studies identified.

We built an economic model to assess the cost-effectiveness. Results from the model suggest that a prophylactic removal strategy costs more than a watchful waiting strategy but leads to improvements in quality of life. When the costs and quality of life measures associated with the two strategies are compared, the resulting statistic is £11,741 per quality adjusted life year gained. This means that NICE may consider that a prophylactic removal strategy can deliver value for money to the NHS.

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ABBREVIATIONS AND GLOSSARY

ABBREVIATIONS LIST

2M	Second molar
3M	Third molar
AAOMS	American Association of Oral and Maxillofacial Surgeons
AG	Assessment Group
BAOS	British Association of Oral Surgeons
BAOMS	British Association of Oral and Maxillofacial Surgeons
BDA	British Dental Association
CADTH	Canadian Agency for drugs and Technologies in Health
CI	Confidence interval
CPG	Clinical practice guidelines
DCC	Distal cervical caries
FDS	Faculty of Dental Surgery
FGDP	Faculty of General Dental Practice
GI	Gingiva index
HES	Hospital Episode Statistics
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
I3M	Impacted third molar
ICER	Incremental cost-effectiveness ratio
IM3M	Impacted mandibular third molar
LRiG	Liverpool Reviews and Implementation Group
M2M	Mandibular second molar
M3M	Mandibular third molar
MTA	Multiple Technology Appraisal
NHS EED	NHS Economics Evaluation Database
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PAL	Probing attachment level
PD	Periodontal probing depth
PPD	Probing pocket depth
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review
TA	Technology appraisal
TAR	Technology Appraisal Report
TMD	Temporomandibular disorder
UDA	Unit of Dental Activity

GLOSSARY

Decision analysis	A systematic, quantitative and interactive method used to address and evaluate important choices confronted by decision makers
Distal cervical caries	Decay of the back surface of the neck of the tooth
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	A third molar that has failed to erupt completely due to being blocked by another tooth, bone or tissue
Mandibular	Relating to the lower jaw
Maxillary	Relating to the upper jaw
Roentgenology	Branch of medicine dealing with diagnosis and therapy through x-rays.
Treatment episode	Period of time between the first and last treatment for a given diagnosis

1 BACKGROUND

1.1 Description of health problem

The four hindmost molars, known as third molars (3Ms) or wisdom teeth, are the last teeth to erupt in the upper (maxillary) and lower (mandibular) jaws, and this usually happens during young adulthood between the ages of 18 and 24. Third molars can be either impacted or non-impacted, and an impacted 3M (I3M) can be classed as erupted, partially erupted or unerupted. Impaction occurs when the eruption of the tooth is blocked either by soft tissue (gum) or bone.

For some patients, 3Ms erupt fully, while for others 3Ms could remain unerupted and impacted throughout the life of the tooth. Third molars can be potentially problematic to the individual by causing pain and disease; however, many 3Ms are asymptomatic (trouble-free) or disease-free/pathology-free. There has been significant debate over the past few decades surrounding the management of 3Ms, and historically, the practice has been to surgically extract 3Ms prophylactically to avoid potential problems in the future. However, 3M surgery is not without risk to the patient. Despite the substantial amount of literature dedicated to the debate on whether or not to prophylactically remove 3Ms, there is still disagreement and controversy among dentists and oral surgeons as to what constitutes best practice.[1] Current National Institute for Health and Care Excellence (NICE) guidance[2] advises against the routine prophylactic removal of 3M teeth.

Kandasamy et al 2009[3] assert that “the literature pertaining to the extraction of third molars is extensive. There is a large individual variation and a multitude of practitioners’ beliefs and biases relating to the extraction of especially asymptomatic and pathology-free third molars. With the current emphasis in dentistry being placed on clinicians to make evidence-based decisions, the routine removal of third molars has been re-assessed and questioned.”(page 284)[3]

There is disagreement on the operational definition of what constitutes an asymptomatic or pathology-/trouble-/disease-free 3M. In part, this is due to some inconsistent and misleading use of vague terminology.[1,4] In some studies “asymptomatic” denotes teeth that have no associated pathology, in others it denotes an absence of symptoms.[4] There is a significant difference between disease-free and asymptomatic – asymptomatic does not equal disease-free. It is argued that pathology always precedes symptoms, so it is therefore prudent for decision makers to assume the development of pathology if teeth are symptomatic.[1] The terminology that is used in clinical research studies needs to convey the precise condition

being described (i.e. the presence or absence of pathology), otherwise inconsistent findings will always be reported.[4]

To be clear, in this report, prophylactic removal of I3Ms is considered as relating to the removal of pathology-free 3Ms to avoid potential problems in the future.

1.1.1 Aetiology, pathology and prognosis

Impacted third molars are classified on the basis of location (mandibular or maxillary), eruption status, nature of impaction, angulation of impaction, and the depth of impaction relative to the adjacent tooth. An impacted tooth can be visible in the mouth, can be explored with a periodontal probe, or may only be observed through radiographic assessment.[5] Eruption status is described in Table 1.

Table 1 Eruption status

Erupted	Partially erupted	Unerupted

Crown is visible in mouth
• Functional position
• Non-functional position
  • Unlikely to erupt into functional position
  • Likely to develop into functional position
	Part of crown is visible in mouth
	• Partial bone impacted
	• Soft tissue impacted
		Crown not visible BUT
		• May be soft tissue impacted and communicating with the mouth (probeable)
		• Hard tissue impacted, i.e. under bone not communicating with the mouth

The nature of the impaction can be when the tooth is covered only by soft tissue and is referred to as ‘soft tissue impaction’. The tooth can also be covered by bone, and this is known as either ‘partial bony impaction’ when partially erupted or ‘complete bony impaction’ when unerupted and not communicating with the mouth.

Angulation can be based on Winter’s classification[6] and the 3M could be:

- Mesioangular (angled towards the second molar)
- Distoangular (away from the second molar)
- Horizontal
- Vertical
- Buccal (angled towards the cheek)
- Lingual (angled towards the tongue)

Based on Pell and Gregory’s classification[7] relating to depth, the I3M can be class 1, 2, or 3 according to the amount of tooth covered by the mandibular ramus, or A, B, or C depending on the depth of the impacted tooth compared with the second molar (2M).

Pathological changes

Impacted third molars may be associated with pathological changes such as infection (pericoronitis), periodontal (gum) disease, dental caries, destruction of adjacent teeth, and cysts and tumours. According to Worrall et al, the prevalence of pathological changes in I3Ms is higher in impacted mandibular 3Ms (IM3Ms) compared with impacted maxillary 3Ms.[8]

Pericoronitis

This 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 3Ms are impacted, this creates an area that is difficult to clean properly with a toothbrush, making the molar in front of the 3M, as well as the 3M itself, vulnerable to plaque accumulation, inflammation and infection. It is reported that 20-30% of partially erupted, and 10% of completely unerupted teeth are associated with pericoronitis. Partial soft bony impaction and vertical or distal angulation are additional risk factors for pericoronitis.[9]

Gum/periodontal disease

Early stages of gum disease include red and swollen gums, and bleeding gums after tooth brushing and is known as gingivitis. More advanced disease, known as periodontal disease or periodontitis, can lead to bad breath, loose teeth, and gum abscesses. Periodontal disease/gum disease is caused by bacteria in the mouth, which, when not removed by tooth brushing, sets up chronic gum inflammation, which can affect the bone that supports the teeth in the mouth.

Dental caries (decay)

Dental caries or decay is the demineralisation of tooth enamel or dentine caused by bacteria, which metabolise sugar in the diet to form acids. A longitudinal study in the US followed patients with at least one 3M below the occlusal plane at baseline, which had erupted during the follow-up period (median 5.1 years). The study found that of the 49 patients who had no 3M caries at baseline, 36 (73%) had no caries experience at follow-up, and 13 (27%) had at least one 3M with caries.[10]

Pathology in adjacent teeth

There is some evidence to suggest that horizontal or mesioangular I3Ms may increase the risk of decay and cause possible damage to adjacent teeth.[11] Longitudinal data from the U.S. Department of Veterans Affairs Dental Longitudinal Study of 1,231 non-veteran volunteers, revealed that the presence of a 3M that was soft tissue impacted increased the risk of incident 2M pathology 4.88-fold (95% confidence interval (CI): 2.62 to 9.08); however, the prevalence of soft tissue impaction in the study population was only 3%. The relative risk for pathology in

the 2M was 39.6% for those with absent 3Ms, 52.8% for those with erupted 3Ms, and a similar rate for those with bony impaction (56.6%).[12] There appears to be a link, therefore, between the presence of 3Ms and the development of 2M distal cervical caries (DCC), particularly with mesioangular 3Ms.[13]

Cysts and tumours

Cysts and tumours may develop around I3Ms, though research has shown that the risk is low and reduces with age.[14] A study of surgically removed asymptomatic I3Ms found that histological examination of the dental follicles showed the following pathological conditions: 14.1% were diagnosed as dentigerous cysts, 6.6% were calcifying odontogenic cysts, and 2.5% were odontogenic keratocysts.[15]

1.1.2 Natural history with no treatment

Little is known about the natural history of I3Ms left *in situ.* This is due in part to the historical routine extraction of I3Ms, which means we have limited data on which to make reliable estimates of the onset of pathology when the asymptomatic teeth are left in place.[3] Collecting the required data is also problematic in the UK, as clinical reporting systems are not sensitive enough to capture information relating to 3M management.[16] In addition, it would be costly to conduct a non-interventional/observational study to gather data on untreated I3Ms, as it would take decades because of the size of the study cohort needed to determine the occurrence of pathological conditions.[4]

1.1.3 Epidemiology

The prevalence of I3Ms in the UK is unknown. Internationally, the prevalence of I3Ms is reported to range from 18% to 68%.[17] According to the results of a recent meta-analysis[18] of 49 studies (83,484 individuals), the prevalence of 3M impaction worldwide in individuals aged >17 years is 24.4% (95% CI: 18.97 to 30.80). The authors of the study also found that the risk of having IM3Ms was higher than having impacted maxillary 3Ms – 57.6% (95% CI: 43.3 to 68.3; p<0.0001), and there was no difference in the incidence of impaction for men and women (18.6%, 95% CI: –4.9% to 48.0%; p=0.12). The most common angulation of impaction was found to be mesioangular (41.2%, 95% CI: 33.8 to 49.0).

The UK National Third Molar project[8] was a cross-sectional survey that 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.[8] 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 symptom status of all 3Ms at the time of presentation are

shown in Table 2. Where data were available/recorded, the majority of mandibular 3Ms (M3Ms) (69.4%) were impacted, whereas maxillary 3Ms were more likely to be classified as 'present and functional', or 'absent'.

Table 2 State of eruption and symptom status of all third molar teeth

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[8]

The authors of the study[8] reported that, after assessment, a total of 19,971 (80%) of the 25,001 3Ms were extracted and M3Ms 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 and reasons for extraction between mandibular and maxillary 3Ms: 22% of M3Ms were extracted prophylactically compared with 79% of maxillary 3Ms, whereas 60% of M3Ms were removed due to pericoronitis compared with 8% of maxillary 3Ms.

The results of the UK National Third Molar project[8] showed that the most common age for the removal of 3Ms was between 21 and 25 years. However, in 2012, McArdle et al[19] 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 (CIs not reported).

1.1.4 Impact of the health problem

Prior to the introduction of NICE guidance in 2000,[2] 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.[20] During this period, the cost to the NHS in England of 3M surgery was estimated to be £30 million per year, with additional estimated costs of £20 million in the private sector.[20]

Authors of a recent study[19] investigating the effects of NICE guidance[2] on the management of 3Ms reported that, since the introduction of the NICE guidance,[2] the number of 3M removals in secondary care (inpatient/day case) reduced from ~60,000 in the 1990s to ~40,000 in 2003.

However, since 2003, the number of removals appears to have increased to ~65,000 during 2009/10 (inpatient/day case only).

Information provided to NICE in the British Dental Association (BDA)[21] and the Faculty of General Dental Practice (FGDP)[22] submissions, suggest that the prophylactic removal of 3Ms prevents future harm to patients. They argue that the introduction of NICE guidance[2] initially resulted in a reduction in the number of 3Ms extracted. However, this figure has since increased. It is argued that irrespective of the NICE guidance in 2000[2], the need for surgical extraction was not negated, but postponed until a later date. It is further argued that patients over the age of 25 years are at a higher risk of surgical morbidity relating to 3M extraction.[22] Another possible explanation for the increase in 3M extractions could be that patients who may have more than one I3M undergo multiple treatment episodes, as and when other 3Ms become problematic (BDA).[21]

1.2 Current service provision

1.2.1 Management of disease

Treatment options for people with I3Ms include either surgical removal or standard care without prophylactic removal of 3Ms.

Surgical removal

A report[23] 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.” (page 10)

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 that a more complex surgical procedure is required. In cases where general anaesthetic is required, the surgical removal is conducted in hospital.

Generally, recovery from surgery for the removal of 3Ms is straightforward. The immediate side effects of 3M surgery such as pain and swelling resolve within a few days, and jaw stiffness usually subsides within 1-2 weeks.[24] 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 short- and long-term pain or a tingling sensation and numbness in the tongue, lower lip, chin, teeth and gums.

Overall, the rate of complications following the surgical removal of 3Ms is reported to vary between 2.6% and 30.9%.[25] 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.[26] The risk of infection following extraction of I3Ms is approximately 10% in healthy patients; however, it may be up to 25% in patients with low immunity.[27] Dry socket occurs in 5-10% of patients who have undergone a 3M removal, 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.[24] The risk of nerve injury is more common if the IM3M is located close to the inferior alveolar nerve, with 20% of patients likely to then have temporary nerve damage and 2% to experience permanent damage.[24]

Standard care without prophylactic 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.[28] 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- or trouble-free). Where there are pathological changes, current NICE guidance[2] states that the I3M should be removed.

1.2.2 Variation in services and/or uncertainty about best practice

Internationally, there is a vast quantity of published literature relating to the management of 3Ms, and many published international guidelines with recommendations for best practice relating to asymptomatic, or disease-free, 3Ms. However, there is still debate, and it remains a contentious subject. According to the FGDP submission,[22] there are differences of opinion between professionals in the UK relating to best practice. However, the submission authors assert that most UK dentists believe that erupted, non-functional, low-risk M3Ms should be removed at a young age to prevent increased surgical morbidity in older age, and to prevent future harm to the patient.[22]

There is significant geographical variation in current practice when international guidelines are examined. The American[29] guidelines recommend a more interventional approach to 3M management. In the UK NHS setting, there is a ‘no intervention’ policy unless there are distinct

therapeutic indications, although there are differences of opinion between professionals. A table summarising international guidelines is provided in Appendix 1.

There is variation in the services relating to the use of general anaesthesia or local anaesthesia and sedation. There are published data[30] which illustrate that only 3% of IM3M cases in a London teaching hospital required general anaesthetic, with 40% of cases needing intravenous sedation. However, our clinical advisor has pointed out that not all district general hospitals offer sedation services for dental extractions, and therefore the proportion of patients receiving higher-risk general anaesthetic is greater. In terms of service provision, many dental practices in the UK do not provide intravenous sedation, which results in these patients being referred to hospital to undergo surgical extraction under general anaesthetic. There is also considerable variation in the perioperative care provided; for example, the provision of informed consent, patient information, pre-operative mouth rinses, provision of analgesia, and rates of antibiotic prescription.[22]

1.2.3 Relevant UK guidelines

The NICE TA1[20] was completed in 2000 and the resultant NICE guidance[2] was that the prophylactic removal of pathology-free I3Ms was not recommended (see Box 1).

Box 1 Current NICE guidance 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, non-treatable 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)[2]

A review of the existing NICE guidance[2] 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 the NICE guidance[2] 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[2] 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[2] should be partially updated (i.e. prophylactic indications only) via the Multiple Technology Appraisal (MTA) process.

1.3 Description of technology under assessment

1.3.1 Summary of intervention

The surgical extraction of IM3Ms with evidence of pathology (see Box 1) can be undertaken in primary care, secondary care, and specialist clinics. The NHS commissioning oral surgery pathway[31] clearly outlines social, medical and dental factors that dictate the optimal setting.[22]

Specialist radiographic equipment and assessment can be required for risk assessment of IM3Ms, including panoral and cone beam computed tomography radiography which requires the input of a radiologist. For patient requiring sedation (primary care), specialist nursing is required. Intravenous sedation services require additional staff training, the correct facilities and indemnity costs.

1.3.2 Identification of important subgroups

There is intrapatient variance in the presentation of I3Ms, i.e. a single patient can have multiple 3Ms (maxillary as well as mandibular and bilateral presence) with different types of impaction (vertical, horizontal, distoangular, and mesioangular). These are the most common impaction types considered as subgroups, though a smaller proportion of patients may have ectopic impactions. The variability of 3M impactions results in different secondary disease distribution, which is dependent on the nature of the impaction.[21]

Patients with high-risk M3Ms (the roots cross the inferior dental canal) could be 10 times more likely to develop temporary or permanent inferior alveolar nerve injury.[22]

2 DEFINITION OF THE DECISION PROBLEM

The remit of this review was to appraise the clinical and cost-effectiveness of the prophylactic removal of IM3Ms.

2.1 Decision problem

This MTA has been conducted in line with the decision problem issued by NICE in the final scope.[11] This is reproduced in Table 3.

Table 3 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 (e.g. 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

Source NICE Final scope[11]

2.2 Overall aims of assessment

The aim of this assessment report is to synthesise the clinical and cost-effectiveness of the prophylactic removal of IM3Ms compared with standard care without prophylactic removal.

2.2.1 What is not included in the assessment

It is beyond the remit of this assessment report to comment on or draw conclusions relating to the wider topic of the management of 3Ms; this assessment report focusses primarily on summarising the relevant evidence relating to the surgical extraction or retention of asymptomatic IM3Ms.

It is worth noting that the aims of the original assessment report conducted by Song et al,[20] which contributed to the NICE guidance[2] issued in 2000, were not exactly the same as the aims of this assessment, which is a partial update of TA1.[20] Song et al[20] aimed to "provide a summary of existing evidence on prophylactic removal of impacted wisdom teeth, in terms of the incidence of surgical complications associated with prophylactic removal, and the morbidity associated with retention."

3 ASSESSMENT OF CLINICAL EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 Identification of studies

Search strategy

The assessment group (AG) identified relevant clinical studies, systematic reviews (SRs) and decision analyses by searching the following major medical databases: MEDLINE, EMBASE, Cochrane Library, NHS Economics Evaluation Database (NHS EED) and EconLit, from 1999 onwards. The search strategies used are presented in Appendix 2.

In addition to the electronic databases, information on studies in progress were sought by searching the Current Controlled Clinical Trials database.

Citation searching was conducted using all references in key articles and all identified SRs. The sources referenced in the professional stakeholder submissions received as part of the standard NICE process were cross checked to identify relevant references.

A database of the published literature was assembled from the aforementioned sources and was held in the EndNote X7 software package.

3.1.2 Inclusion and exclusion criteria

Two of three reviewers (JH, GP, RD) independently screened all titles and abstracts identified by the initial search using Covidence.[32] Full-text copies of any titles/abstracts that may have been eligible were obtained and assessed for inclusion by two reviewers (JH, GP), according to the inclusion and exclusion criteria listed in Table 4. Discrepancies were resolved by consultation with a third reviewer/clinical advisor. Studies that did not meet the inclusion criteria were excluded and the reasons for exclusion summarised. For studies that were identified as not meeting the criteria at the data abstraction stage, bibliographic details and reasons for exclusion were summarised.

Table 4 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/location	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	

3.1.3 Data abstraction strategy

Data relating to study characteristics and outcomes were extracted by one of two reviewers (JF or JH) and independently checked for accuracy by a second reviewer (JF or JH). Disagreement was resolved through consensus, and where necessary a third reviewer was consulted. Study data reported in multiple publications were extracted and reported as a single study.

3.1.4 Critical appraisal strategy

The quality of the included studies was assessed by one reviewer (JH or JF), and independently checked for agreement by a second reviewer (JH or JF). Disagreements were resolved through consensus. The quality of the cohort studies were assessed using an adapted version of the Newcastle–Ottawa quality assessment scale for cohort studies,[33] and SRs were assessed according to criteria outlined by the Centre for Reviews and Dissemination.[34]

3.1.5 Methods of data synthesis

The results of the data extraction and quality assessment for each included study are presented in structured tables and as a narrative summary.

3.2 Results

3.2.1 Quantity and quality of research available

The results of the electronic searches and the application of the inclusion criteria are shown in Figure 1.

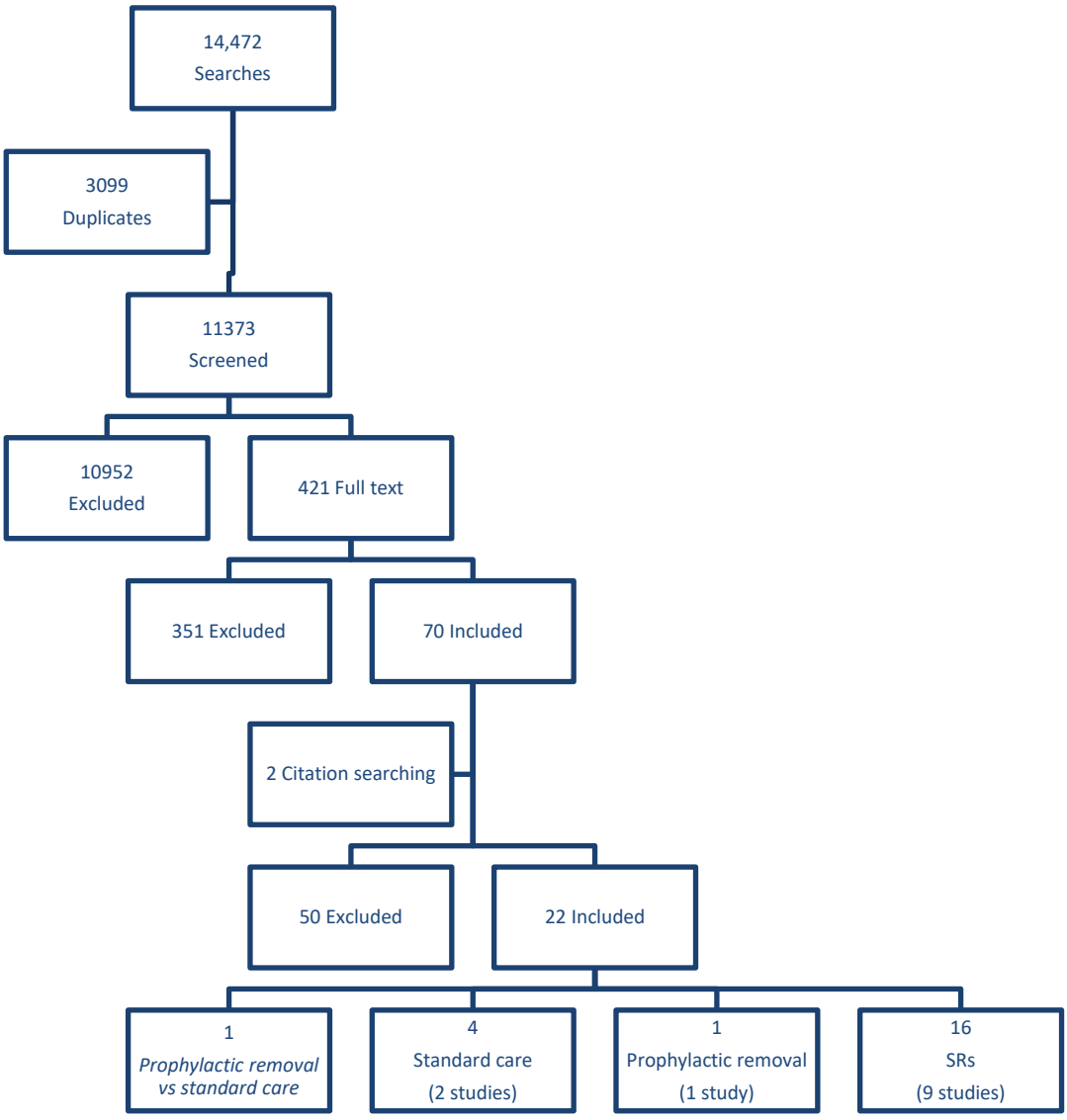

Figure 1 PRISMA flow diagram: clinical evidence review

In total, 22 citations[20,35-55] reporting results of nine SRs[20,36,38-42,46,52] and four cohort studies[43,44,54,55] were included in the review. No randomised controlled trials (RCTs) were identified.

The reasons for excluding papers at the full-text review stage are summarised in Appendix 3. As shown in

Figure 1, 50 papers were initially included at full-text review but on further inspection no relevant data for the specific population of interest for this review were available and these papers were subsequently excluded. The bibliographic details with reasons for exclusion for these 50 studies are also reported in Appendix 3.

One study[54] reported on outcomes both for standard care with and without prophylactic removal of IM3Ms. Four papers[35,43,44,53] reported on two studies assessing the outcomes of standard care without prophylactic removal of IM3Ms, and one paper[55] reported on a study of prophylactic removal of IM3Ms. A further 16 papers[20,36-42,45-52] reported on nine SRs assessing whether I3Ms should be removed prophylactically.

Quality assessment – Cohort studies

The quality of the four included cohort studies[43,44,54,55] was assessed using an adapted version of the Newcastle–Ottawa quality assessment scale for cohort studies[33] and the results are tabulated in Table 5.

Table 5 Quality assessment of cohort studies

Study	**Vares et al 2014[54]**	**Fernandes et al 2010[44]**	**Hill et al 2006[43]**	**Petsos et al 2016[55]**
Representative of cohort	No description	Truly representative	Truly representative	Truly representative
Ascertainment of exposure	Clinical records	Clinical records	Clinical records	Clinical records
Outcome present at start	Yes	Yes	Yes	Yes
Assessment	No description	Record linkage	Record linkage	Record linkage
Length of follow-up	Adequate	Adequate	Adequate	Adequate
Attrition	No description	31%	9%	14%

All but the Vares et al 2014 study[54] had patients who were representative of the population of interest. Clinical records were used in all four studies[43,44,54,55] to ascertain whether patients were 'exposed' to the intervention (either standard care or prophylactic removal), and all studies demonstrated that the outcome of interest (e.g. pathology) was not present at the start of the study and the assessment of outcome was through clinical assessment. None of the studies used a blinded assessment as this was not possible. The length of follow-up was adequate in all studies. The attrition rates differed between three studies; 9%,[43] 14%[55] and 31%.[44] No details of study attrition were reported by Vares et al 2014.[54] To conclude, the AG

considered all but one[54] of the studies to be generally good-quality cohort studies. However, missing information in the Vares et al 2014[54] paper meant it was not possible to adequately assess the quality of this study.

Quality assessment – Systematic reviews

The quality of the nine SRs[20,36,38-42,46,52] was assessed according to criteria outlined by the Centre for Reviews and Dissemination.[34] The results of the quality assessment are shown in Appendix 4.

Seven of the SRs had clear review questions defined in terms of population, interventions, comparators and outcomes.[20,36,38-40,42,46] However these details were missing in two SRs.[41,52] Only three reviews had an adequate search strategy without language or date restrictions.[20,41,42] Two reviews were limited by language, one to English, Dutch, French, or German[36] and one to English[40]. One review was restricted by language (English, Danish, Norwegian or Swedish) and date (1999-2003).[39] Another review restricted by date only (1999-2003).[46] The search terms used were not reported in the Clinical Evidence publications[52] nor in the CADTH SR,[38] which also restricted by date and language. Three SRs provided adequate information to facilitate assessment of whether preventative steps had been taken to minimise bias and errors in the selection process.[20,36,42] Four SRs reported adequate methods for assessing the quality of included studies.[20,36,41,42] One SR reported using a recognised quality assessment tool but did not provide details on how it was used.[39] The remaining four SRs[38,40,46,52] did not report whether they had conducted a quality assessment of included studies. Adequate details of the primary studies were presented in seven of the SRs.[20,36,39,40,42,46,52] In the CADTH publication, details were only presented narratively for each primary study,[38] and although Costa et al 2013[41] presented some details of the primary studies no details of the outcomes of the primary studies were presented. Statistical data synthesis was not appropriate for any of the SRs; instead, the authors of two SRs reported a narrative synthesis,[40,52] three summarised each study individually[20,36,38] and one did not include any studies.[42] Costa et al 2013[41] only reported the results of the quality assessment and Suska et al 2010[39] did not provide any synthesis. It was not possible to assess the SMM Report for this item.[46]

3.2.2 Assessment of effectiveness from included studies

Prophylactic removal versus *standard care*

One study[54] reported on outcomes both for surgical complications of the prophylactic removal of asymptomatic IM3Ms and standard care without prophylactic removal of asymptomatic IM3Ms. The study was an observational cohort study conducted in Ukraine between 2009 and

2013. It was designed to develop and assess a pre-operative assessment and create a rationale for the prophylactic removal of asymptomatic IM3Ms. The assessment included clinical and roentgenological parameters, and the 84 included patients were assigned to one of three groups: requiring removal and subsequently had the tooth removed (n=52), requiring removal but the patient refused (n=7), and those not requiring removal as determined by the assessment (n=25). The first group (n=52) was then separated further into three age groups: 18-25 years (n=41), 25-45 years (n=10), and one patient of 68 years. Patients were followed up annually for 5 years.

At the end of 5 years, the study authors reported that there were "No considerable intra- or post-operative complications in the first subgroup" only "minor complications in the second subgroup", and "in the case of 68 year-old patient surgery, all complications were related to considerable bone atrophy of the operated area".

Of the seven patients who refused extraction, five required the tooth to be extracted within the 5 years. Of the 25 patients who were assessed at baseline as not requiring extraction, none had the tooth extracted during the 5 years' follow-up.

The study authors concluded that "The low-to-no percentage of intra- and post-operative complications does not give any reason to leave a wisdom tooth with minor clinical manifestations or an asymptomatic wisdom tooth with bad prognosis in place, since early surgical procedures generate fewer complications, having shorter operative time and post-operative period" (page 35).

Further details of the study characteristics and outcomes are reported in Appendix 5.

Standard care

We included two studies, Fernandes et al[44] and Hill et al[43] (reported in four publications[35,43,44,53]), that reported relevant outcomes for the comparator of standard care without prophylactic removal of IM3Ms. Both studies were single-cohort studies with follow-up periods of 1 year[44] and 5 years.[43] Both studies were conducted in the UK and the number of patients with trouble-free IM3Ms was 421[44] and 153.[43] The number of trouble-free IM3Ms examined was only reported by one study (n=676).[44] Participants were patients aged 16-30 years (median age 23 years)[43] and 18-70 years (18-34.9 years, n=400; 35-49.9 years, n=149; and 50-70 years, n=64).[44] The percentage of males was 41%[44] and 34%[43] (Table 6). Further study and participant characteristics are reported in Appendix 5.

Table 6 Study and participant characteristics of standard care studies

Study	Setting	Follow-up	Description of I3Ms N	Demographics
Fernandes et al 2010[44]	Multicentre, Scotland, UK (primary care setting)	1 year	IM3Ms=676 613 patients assessed at baseline, 583 patients eligible, 421 patients with follow-up	Full sample n=613 Males: 40.1% Age: 18-34.9=400 35-49.9=149 50-70=64
Hill et al 2006[43]	Unclear but likely single centre Cardiff, UK	5 years	IM3Ms 153 patients had no history of pericoronitis	Males=34% Median age=23 years Age range 16-30

IM3M=impacted mandibular third molar

Outcomes were assessed by Hill et al[43] using a questionnaire or telephone call every 6 months and a clinical examination every year if the patients were willing to attend. A research dentist questioned and assessed the clinical outcomes of patients in Fernandes et al[44] at 1 year.

Both studies reported the rates of extraction during the study period, the reasons for extraction and the rate of the IM3M surviving asymptomatically. A summary of these outcomes is shown in Table 7. Over 1 year, Fernandes et al**[44]** reported an extraction rate of 5.5%, whereas Hill et al[43] reported an extraction rate over 5 years of 31.4% for those without a history of pericoronitis. The reasons for extraction also differed between the studies. Fernandes et al**[44]** reported that the reason for removal was unknown by patients in 46% of cases but that for those patients who knew the reason, pain was the most frequent reason for removal (27%, 50% of known reasons) followed by pericoronitis (13.5%, 25% of known reasons). Hill et al[43] reported that pericoronitis was the most frequent reason for removal (62.5%), followed by cosmetic/orthodontic reasons (12.5%). Both studies reported the number of patients having teeth removed due to caries in the 2M: 2.7%[44] and 8.3%.[43]

The number of patients who did not experience any symptoms over the period of the studies was 83.1%[44] and 67.6%.[43] Fernandes et al[44] also reported the number of patients who did not experience symptoms indicative of the need for removal according to the Scottish Intercollegiate Guidelines Network (SIGN) guidelines[56] as (92.2%). The authors also reported the rates for the different symptoms, with discomfort/irritation, not a symptom that SIGN includes as a reason for removal, being the most frequently reported reason (47.4%).[44]

Fernandes et al[44] also investigated the relationship between symptoms and several factors. The authors found a statistically significant relationship between the presence of symptoms and age, angulation, eruption status, and the reason for last visit to the general dental

practitioner. They found no relationship between the presence of symptoms and sex, average number of teeth, maximum basic periodontal examination score, average gingival bleeding index, 'average mean plaque', education after minimum school-leaving age, employment status, frequency of brushing teeth, occasional use of mouthwashes, occasional teeth flossing, frequency of dental appointments, length of time since patient last visited the dentist, smoking, drinking >14 units/week, and deprivation category.

Table 7 Outcomes of standard care studies

Study	Outcomes assessed	Rate n (%)
Extraction rate	***Fernandes et al 2010[44]**	37/676 (5.5)
	Hill et al 2006[43] Without a history of pericoronitis With a history of pericoronitis	 48/153 (31.4) 23/66 (34.8)
Reasons for extraction	***Fernandes et al 2010[44]**	
	Pericoronitis	5/37 (13.5)
	Pain	10/37 (27.0)
	Caries in distal of adjacent molar	1/37 (2.7)
	Caries in the third molar	2/37 (5.4)
	Contralateral	2/37 (5.4)
	Unknown	17/37 (46.0)
	***Hill et al 2006[43](Without a history of pericoronitis)**	
	Pericoronitis after start of study	30/48 (62.5)
	Cosmetic/orthodontic	6/48 (12.5)
	Food impacted/difficult to clean	4/48 (8.3)
	Early caries in second molar	4/48 (8.3)
	Painful when eating	2/48 (4.2)
	Earache/TMJ pain	2/48 (4.2)
Survived asymptomatically	**Fernandes et al 2010[44]**	
	From any symptom	562/676 (83.1)
	From SIGN symptoms only	623/676 (92.2)
	Hill et al 2006[43]	150/222[+] (67.6)
Symptoms developed by tooth	**Fernandes et al 2010[44]**	
	Pericoronitis	15/114 (13.2)
	Severe pain (SIGN)	16/114 (14.0)
	Mild pain (SIGN)	22/114 (19.3)
	Discomfort/irritation (non-SIGN)	54/114 (47.4)
	Food stagnation (non-SIGN)	7/114 (6.1)

*per tooth; [+]Includes 66 patients with a history of pericoronitis
TMJ=temporomandibular joint; SIGN=Scottish Intercollegiate Guidelines Network

Prophylactic removal

The final included study by Petsos et al[55] assessed the effects of the prophylactic removal of trouble-free IM3Ms. It was identified during forward citation searching as it was published after

the date of the review searches. Details of the study, patient characteristics and outcomes are reported in Appendix 5.

The study[55] was a prospective cohort study conducted in Germany that was self-funded and recruited patients after extraction of asymptomatic IM3Ms over 5 months in 2014. The study[55] was designed to assess changes in the periodontal health of adjacent 2Ms 6 months after the removal of the asymptomatic IM3Ms. Results from 78 patients were included in the analyses. Of these 78 patients, 58 had a submucosal IM3Ms removed and 20 of the 78 teeth were fully impacted. The mean age of patients was 16 years and 37% were male. Only four patients were smokers. At baseline, the plaque index, gingiva index (GI), probing pocket depth (PPD) and probing attachment level (PAL) were measured. With measurements being obtained at six sites around the M2 (i.e. mesiobuccal, buccal, distobuccal, distolingual, lingual, mesiolingual).

To assess the change in periodontal health of the 2M at follow-up, the mean PPD and PAL scores at the three sites located closest to the distovestibular incision (buccal, distobuccal, distolingual) were used.

Whereas no significant change was reported in PII and GI scores, the mean PPD score of the three sites improved from 3.25±0.65 (range 2-5.7) to 2.57±0.5 (range 1.3-3.7). This was a statistically significant reduction. Similarly, mean PAL score across the three sites significantly improved, with a reduction from 2.96±0.53 (range 2.0-5.0) to 2.55 ±0.5 (range 1.3-3.7).

Surgical complications following the prophylactic removal of the IM3M were recorded. A total of 20 patients (25.6%) reported complications. Intense pain for more than 1 day was the most frequent complication, reported by 12 patients. A further five patients (6.4%) reported post-operative infection (infiltrate or abscess) and the remaining three experienced wound dehiscence. No incidences of secondary bleeding or nerve damage were reported.

The authors concluded that “Young patients may benefit from an early removal of mandibular M3, especially in the presence of certain cofactors”. (page 453)

Systematic reviews

Nine SRs[20,36,38-42,46,52] that were reported in 16 publications[20,36-42,45-52] met the review inclusion criteria and details are summarised in Table 8 and Table 9 with further details shown in Appendix 5.

Two[36,38] were rapid reviews that applied SR methodology. All but one[40] attempted to assess the evidence for the prophylactic removal of 3Ms compared with standard care without

prophylactic removal. Bouloux et al[40] only assessed whether retention of asymptomatic 3Ms led to future extraction.

No review restricted the population to trouble-free IM3Ms. Instead, four[36,38,40,41] included all trouble-free 3Ms regardless of impaction status or location, two[42,52] included trouble-free I3Ms regardless of location, one[20] included all 3Ms regardless of symptoms or not, and one[39] included I3Ms regardless of symptoms or location. A further review was published in Norwegian and only had an English summary[46] so the specific population was unclear. Different types of study designs were included across the SRs: five[36,38,39,41,52] included SRs and five[38-40,46,52] included non-RCTs (e.g. cohort studies and case series). One[42] SR limited inclusion to RCTs, and another[40] limited to cohort studies only. One[20] review also included literature reviews. The dates of the searches ranged from 1950[42] to 2014.[52]

The different inclusion criteria adopted by the SRs meant that the studies identified and included in the SRs differed. In total, 84 studies were identified across the nine SRs, with only seven studies[20,45,46,57-60] being identified by more than one review.

- Mettes et al[45](SR) was included in five SRs[36,38,39,41,52]
- Harradine et al[58] (RCT) was included in four SRs[20,41,42,52]
- NICE Guidance/Song et al publications[2,20,61] were identified by three SRs[36,38,52]
- Senter for medisinsk metodevurdering (SMM)'s[46] report was included in three SRs[38,39,52]
- Lindqvist et al[60] (RCT) was included in three SRs[41,45,52]
- Edwards et al[57] (decision analysis) was included in two SRs[20,46]
- Kruger et al[59] (cohort study) was included in two SRs[40,46]

Despite the differences in inclusion criteria across the SRs, the conclusions were similar. Seven SRs[20,36,38,39,41,42,52] stated that there was insufficient evidence to support or refute the prophylactic removal of trouble-free 3Ms. Two[38,52] SRs recommended that the decision to remove an asymptomatic 3M should be based on careful consideration of the risks and benefits, and that patient preferences should be taken into account. Two[20,36] SRs recommended that in light of insufficient evidence, retention/"first do no harm" may be appropriate. Watchful monitoring was recommended in the Cochrane review by Mettes et al.[42] The Norwegian SMM report[46] recommended the prophylactic removal of 3Ms "when the likelihood of 3Ms causing problems in the future is high and the incidence of post-operative complications are low." They restrict this to partially erupted 3Ms and state that this approach

is not recommended for people with fully retained (i.e. complete bony impacted) teeth. They also state that patient preferences should be decisive.

The one[40] SR that looked at the risk of future extraction following the retention of trouble-free 3Ms found that the mean incidence rate of future extraction was 3.0% annually (range 1-9%) leading to a cumulative incidence rate of 5% at 1 year and 64% at 18 years. The reasons for extraction were caries, periodontal disease, and other inflammatory conditions. The authors concluded that: “The cumulative risk of M3 extraction for young adults with asymptomatic M3s is sufficiently high to warrant its consideration when reviewing the risks and benefits of M3 retention as a management strategy”.[40] (page 806)

Table 8 Systematic review characteristics

Study	Publication type Date of search	Objective/Research questions	Inclusion criteria
Bouloux et al 2015[40] AAOMS M3Taskforce	SR NR	To determine clinically whether young adults who elect to retain their asymptomatic 3Ms have a risk of undergoing one or more 3M extractions in the future	English language publication Prospective study design with >50 patients Recorded the number of patients or 3Ms requiring extraction during study period Follow-up duration of ≥1 year Aged ≥18 years old At least 1 3M present at enrolment Only asymptomatic 3Ms at enrolment Assumption that the teeth had been retained because they were asymptomatic and disease-free 3Ms
CADTH 2010[38]	Rapid review/HTA 2000-2010	What is the evidence for the clinical benefit of prophylactic removal of asymptomatic wisdom teeth compared with retention of asymptomatic wisdom teeth? What are the evidence-based guidelines for the prophylactic removal of asymptomatic wisdom teeth?	English language Study design: • HTAs • SRs • RCTs • Non-RCTs Comparing clinical outcomes between one group underwent prophylactic surgery for 3M removal, while the other group retained their asymptomatic teeth
Clinical evidence[37,47-52]	SR (updated yearly) 1966-2014	Should asymptomatic and disease-free impacted wisdom teeth be removed prophylactically?	Study design: • Published SRs of RCTs • RCTs • Prospective cohort studies with a control group Any language More than 20 patients
Costa et al 2013[41]	SR Up to 30 August 2012	To investigate whether there is evidence justifying the prophylactic extraction of 3Ms	Study design: • RCT • SR and meta-analyses All languages

Study	Publication type Date of search	Objective/Research questions	Inclusion criteria
			The effect of prophylactic third molar extraction The non-intervention (maintenance) of asymptomatic impacted third molars
Mettes et al 2012[42]	SR 1950-30 March, 2012	To evaluate the effect of prophylactic removal of asymptomatic impacted wisdom teeth in adolescents and adults compared with the retention (conservative management) of these wisdom teeth	Study design: • RCT • Random allocation Compare the effect of prophylactic removal of asymptomatic impacted wisdom teeth with retention Data on at least one of the selected clinical outcomes as a part of the primary outcome measure
SMM Rapport 2003[46]	SR/HTA (English summary only) 1999-2003	To assess the scientific evidence on prophylactic removal of impacted wisdom teeth, in terms of the incidence of surgical complications associated with prophylactic removal, the morbidity associated with retention, quality of life and economic aspects	NR in English summary
Song et al 2000[20]	SR/HTA/Clinical guidance 1984-1999	To provide a summary of existing evidence on prophylactic removal of impacted wisdom teeth, in terms of the incidence of surgical complications associated with prophylactic removal, and the morbidity associated with retention	Study design: • RCT • Literature review • Decision analyses Population • Unerupted or impacted 3Ms, or undergoing surgical removal of 3Ms either as prophylaxis or due to associated pathological changes Outcomes • Pathological changes associated with retention of 3Ms, or post-operative complications following extraction
Stordeur & Eyssen 2012[36]	Rapid assessment December 2010/March 2011	To present the existing scientific evidence on the prophylactic extraction of 3Ms in the absence of local disease, and to formulate clinically relevant recommendations What are the benefits and risks (complications) of prophylactic extraction of pathology-free wisdom teeth (3Ms) in adolescents and adults in the absence of local disease? What is the related good clinical practice for the prophylactic removal of pathology-free wisdom teeth?	English, French, German and Dutch languages Study design: • SRs with or without meta-analyses • RCT • Non-randomised clinical trials • HTA • CPGs

Study	Publication type Date of search	Objective/Research questions	Inclusion criteria
			Comparing the effect of prophylactic removal of pathology-free wisdom teeth with no-treatment Existing guidelines of high quality
Suska et al 2010[39]	HTA/SR May 2003 up to December 2009 Based on the Norwegian HTA so searches only conducted after 2003	Does removal of 3M teeth reduce the risk of infections and other local disease/pathological conditions in patients with asymptomatic or symptomatic impacted 3Ms compared with no intervention?	Study design: • Studies with some kind of control group • Case series etc. if ≥ 300 patients Healthy individuals of all ages with totally or partially impacted wisdom teeth without symptoms, or healthy individuals of all ages with totally or partially impacted wisdom teeth with any kind of symptom or condition Extraction of 3M tooth, or no extraction or any other treatment of 3M tooth English, Danish, Norwegian and Swedish language only

3M=third molar; AAOMS=American Association of Oral and Maxillofacial Surgeons; CADTH=Canadian Agency for Drugs and Technologies in Health; HTA=health technology assessment; SR=systematic review; RCT=randomised controlled trial; CPG=clinical practice guidelines

Table 9 Systematic review results and conclusions

Study	Number/type of studies included	Author conclusions as quoted in publications
Bouloux et al 2015[40]	Cohort studies=7	The cumulative risk of 3M extraction for young adults with asymptomatic 3Ms is sufficiently high to warrant its consideration when reviewing the risks and benefits of 3M retention as a management strategy
CADTH 2010[38]	SRs=4 Non-RCTs=1 Guidelines=2	Based on evidence and guidelines from the past ten years of evidence identified for inclusion in this review, 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
Clinical evidence[37,47-52]	Extraction of asymptomatic I3Ms: SR=5 Active surveillance of asymptomatic I3Ms: No studies	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

Study	Number/type of studies included	Author conclusions as quoted in publications
Costa et al 2013[41]	SR=1 RCT=3	The results of the present review indicate a lack of scientific evidence to justify the indication of the prophylactic extraction of third molars
Mettes et al 2012[42]	RCT=1	Insufficient evidence was found to support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults. A single trial comparing removal *versus* retention found no evidence of a difference on late lower incisor crowding at 5 years, however no other relevant outcomes were measured Watchful monitoring of asymptomatic third molar teeth may be a more prudent strategy
SMM Rapport 2003[46]	Patient series=13 Cohort studies=3 Case–control studies=2 Cross-sectional studies=6 Decision analysis=1	This report is based on evidence from studies that use small selected patient groups, and therefore it is difficult to conclude and give recommendations. Norwegian dentists recommend prophylactic removal of third molars when the likelihood of third molars causing problems in the future is high and the incidence of post-operative complications are low. This includes partially erupted wisdom teeth. Removal of asymptomatic fully retained wisdom teeth is not recommended. Since this report is based on studies that are not optimal the patient's preferences need to be decisive
Song et al 2000[20]	RCT=2 Decision analysis=4 Literature reviews=34	There is no reliable research evidence to support the prophylactic removal of disease-free impacted third molars. Available evidence suggests that retention may be more effective and cost-effective than prophylactic removal, at least in the short to medium term
Stordeur & Eyssen 2012[36]	SRs=2 HTAs=2 CPG=1	There is mostly little debate on the fact that third molars associated with clinical and/or radiological pathology, such as unrestorable caries, should be removed. However, there is a lack of proven benefit from the systematic prophylactic removal of pathology-free third molars, impacted or not, in all adolescents or (young) adults, and the procedure is not free of risk. Preventive actions at the level of the population are only recommended if the benefits outweigh the disadvantages, and if this is not the case it is preferable not to intervene. If there is no scientific evidence that an intervention is beneficial, the largely accepted principle of medicine: "*primum non nocere*", "first, do no harm", should be respected
Suska et al 2010[39]	HTA-report/SRs=2 Case series=16 (None reported on asymptomatic teeth)	A systematic literature search and review of published data has revealed that there is still no scientific documentation available to either support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults

3M=third molar; I3M=impacted third molar; AAOMS=American Association of Oral and Maxillofacial Surgeons; CADTH=Canadian Agency for Drugs and Technologies in Health; HTA=health technology assessment; SR=systematic review; RCT=randomised controlled trial; CPG=clinical practice guidelines

3.2.3 Additional evidence

References from included SRs

We reviewed all references included in the identified SRs for inclusion in this review. Of the 84 cited references, nine met our inclusion criteria and all had been identified through our searches. However, the AG feels that another nine of these references warrant further discussion as they are papers often cited in the debate on the management of 3Ms. Therefore, study details and summaries of these nine studies are provided in Appendix 6.

Professional stakeholder's submissions

As part of the NICE process three submissions from professional stakeholders were received. One on behalf of the BDA, the second, a combined submission on behalf of the Faculty of Dental Surgery (FDS), the FGDP, and the British Association of Oral Surgeons (BAOS), and the third on behalf of the British Association of Oral and Maxillofacial Surgeons (BAOMS).

The submission forms provided by NICE to professional stakeholders enables healthcare professionals to provide their perspectives on the technology in the context of clinical practice, and includes questions within a predefined template to prompt and guide the process. The submissions can also include references to additional sources of evidence that may not be found by a technology-focussed SR. This could be information on recent and informal unpublished evidence, registry and audit data. The information must include sufficient detail to allow a judgement to be made as to the quality of the evidence, and to determine any potential sources of bias.

The information from the submissions was reviewed to ascertain whether they included any data that could inform this appraisal report.

Much of the content of the submissions were professional opinions and perspectives and the full submissions are available for the committee to consider. Where references were provided, no additional studies meeting our review inclusion criteria were identified and many were excluded from this review as they did not meet all of our inclusion criteria. A summary of the more pertinent papers is provided for information in Appendix 6

The key points from each submission are summarised below.

BDA

The BDA highlights that the treatment of 3Ms should be undertaken in a holistic manner, rather than for each 3M in isolation. It is argued that NICE guidance,[2] which does not recommend the prophylactic removal of I3Ms, has led to an increase in the rate of 3M removal overall,

which causes a financial burden to the NHS and disadvantages patients. The submission authors suggest that savings could be realised if repeat treatment episodes were reduced by removing potentially problematic 3Ms at the same time as treating the symptomatic 3M.

FDS, FGDP and BAOS

The key points highlighted in the submission are that as a result of NICE guidance,[2] patients are retaining mandibular 3Ms, which results in problems for the surrounding teeth. There is variation in surgical techniques used, in the sedation and anaesthetic used for patients, and in the quality of follow-up care after the surgical removal of IM3Ms.

BAOMS

The key points highlighted in the submission are that as a result of NICE guidance,[2] there is little difference in clinical practice in the UK regarding the removal of 3Ms; however, there is a difference in opinion between professionals in how these teeth should be managed. The Finnish longitudinal study[62] often cited to advocate the interventional removal of 3Ms to prevent problems does not report the rationale for removal in the study and weakens the rationale for interventional removal of 3Ms. Two subgroups with different prognoses are described (i.e. those taking anti-resorptive or anti-angiogenic drugs, and those who are to receive radiotherapy to the head and neck). The routine prophylactic removal of third molars would put significant strain on NHS resources in both primary and secondary care.

3.3 Summary of clinical results

Searching of major electronic databases identified 14,472 citations; after screening and the application of inclusion/exclusion criteria, 13 studies from 22 publications were included in the SR (nine SRs[20,36-42,45-52] and 4 cohort studies[35,43,44,53-55]).

Of the four cohort studies, one investigated the prophylactic removal of pathology or asymptomatic IM3Ms in comparison with the standard care and retention of these pathology-free or asymptomatic IM3Ms, two investigated the prophylactic removal of pathology or asymptomatic IM3Ms without a comparison group, and one studied the retention and standard care of pathology-free or asymptomatic IM3Ms. All studies described teeth as asymptomatic. All four studies were European, and the two studies looking at the prophylactic removal of pathology-free or asymptomatic IM3Ms, without a comparison group, were UK based. Follow-up across the studies varied from 6 months to 5 years, with outcomes assessed through clinical assessment for three of the studies. Of the two studies reporting on surgical complications no serious complications were reported, though intense pain and post-operative infection were reported by one study. The pathological changes due to retention of pathology-free or asymptomatic IM3Ms were reported by three studies. The extraction rate for retained

teeth varied from 5.5% and 31.4% though this variation can be explained by the differing follow-up periods (1 and 5 years).

3.4 Discussion of clinical effectiveness results

This SR aimed to identify and appraise the relevant evidence relating to the clinical effectiveness of the prophylactic removal of IM3Ms in comparison with standard care without the removal of IM3Ms. The rationale for the prophylactic removal of I3Ms is much debated in the published literature in the UK and worldwide, with variation as to what is considered as the best approach to the treatment of I3Ms. There are dental professionals who advocate for the prophylactic removal of 3Ms, and those who argue for a more conservative approach. There is a plethora of literature debating the controversies surrounding the prophylactic removal of 3Ms[1,3,4,16,63-66] and there are a number of international clinical guidelines[2,23,29,37-39,56,67-73] that make recommendations on this topic. These clinical guidelines focus on the management of 3Ms in general and report indications for removal rather than reviewing the evidence for the prophylactic removal of asymptomatic, pathology-free 3MS. The SR literature is consistent in reporting a lack of evidence for or against the prophylactic removal of these teeth. The results of this review have been limited by the decision problem set by NICE, focussing on people with pathology-free or trouble-free, IM3Ms, which represents a more specific population than the populations of all patients with 3Ms or I3Ms that were considered in much of the relevant literature on the management of third molars.

Discussion of the results of the cohort studies are hampered by the different outcomes reported by the studies; as different approaches to third molar management require different outcome measures (e.g. the rate of infection of retained IM3Ms and the rate of surgical complications following removal of IM3Ms). This means the different interventions cannot be directly compared. However, from the included studies it appears that retention of asymptomatic IM3Ms may lead to future symptoms and consequential extraction at a rate of between 6% and 31% over a period of 1-5 years. For participants who had asymptomatic IM3Ms removed, no major surgical complication rates were reported, though intense pain and infection were reported at a rate of 15% and 6%, respectively.

None of the nine SRs reviews that were identified by this SR restricted their research question to pathology-free or trouble-free IM3Ms; however, most were restrictive in the time periods covered and/or languages included. The inclusion criteria for the SRs also differed especially in relation to study design. This led to a disparate collection of studies being included, with 73 of the 84 studies only being included in one SR. This heterogeneity reflects the heterogeneity in the literature in general and the lack of robust primary evidence. Despite these differences,

most reviews concluded that there was insufficient evidence to make a decision, regardless of how inclusive an approach was used.

In conclusion, our findings are consistent with previous systematic reviews in that there is no available RCT evidence to support or refute the practice of the prophylactic removal of asymptomatic/pathology-free IM3Ms. However, the review did identify evidence from longitudinal studies demonstrating what happens when asymptomatic IM3Ms are left in situ.

4 ASSESSMENT OF COST-EFFECTIVENESS

4.1 Systematic review of existing cost-effectiveness evidence

This section presents the methods and results of a systematic review of the published literature comparing the cost-effectiveness of prophylactic removal of I3Ms *versus* no prophylactic removal.

4.1.1 Search strategy

The search strategy developed for the clinical searches (see Appendix 2), with the addition of an economics filter, was used to identify studies reporting the costs and benefits associated with extracting/retaining I3Ms. As part of the search strategy, NHS EED, which is located within the Cochrane Library, and EconLit (EBSCO) were also interrogated. All databases were searched on 29th April 2016. The results were entered into an Endnote X7.4 library, de-duplicated and exported into Covidence.

Informal searching activities were carried out to identify economic evaluations relevant to the decision problem. These included contacting experts in the field and a search of Google Scholar. The Google Scholar search was updated on 1st February 2017 and revealed no relevant results.

The two clinical submissions from professional stakeholders that were submitted to NICE as part of the MTA process were also checked for cost-effectiveness data.

4.1.2 Study selection and inclusion criteria

Studies were selected based on their relevance to the decision problem and the specific economic criteria displayed in Table 10. Two reviewers (AB/SB) independently examined the titles and abstracts of all studies identified by the search to find potentially eligible publications (Stage 1). During the next stage (Stage 2), two reviewers (AB/SB) examined the full texts of studies that were identified as being potentially relevant at Stage 1. During Stage 2, two modifications were made to the inclusion criteria:

- due to only limited information about UK costs being available, studies that included any costs were included in the review
- to align HRQoL outcomes with the outcomes reported in the clinical papers, papers reporting short-term HRQoL outcomes were excluded from the review (i.e. only papers with long-term HRQoL outcomes were included).

Disagreements about inclusion were resolved through discussion and, in all cases, a consensus was reached; it was, therefore, not necessary to consult a third reviewer during the screening and selection process.

Table 10 Economic inclusion criteria (costs and outcomes)

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

4.1.3 Quantity of included evidence

From the main searches, the AG identified 493 potentially relevant papers for inclusion in the review of economic evidence. Of these, 34 papers were considered for inclusion after Stage 1. As shown in Figure 2, eight studies[17,20,74-79] were initially included at Stage 2. However, on further inspection, five[74-78] of the eight studies did not include information that was relevant to the population of interest and these papers were, therefore, subsequently excluded from the review. Bibliographic details and summary data from these five studies[74-78] are available in Appendix 3. So, of the 34 papers considered for inclusion after Stage 1, 31 papers were excluded during Stage 2, leaving three papers[17,20,79] to be included in the review. The reasons for excluding the 31 studies are listed in Table 11.

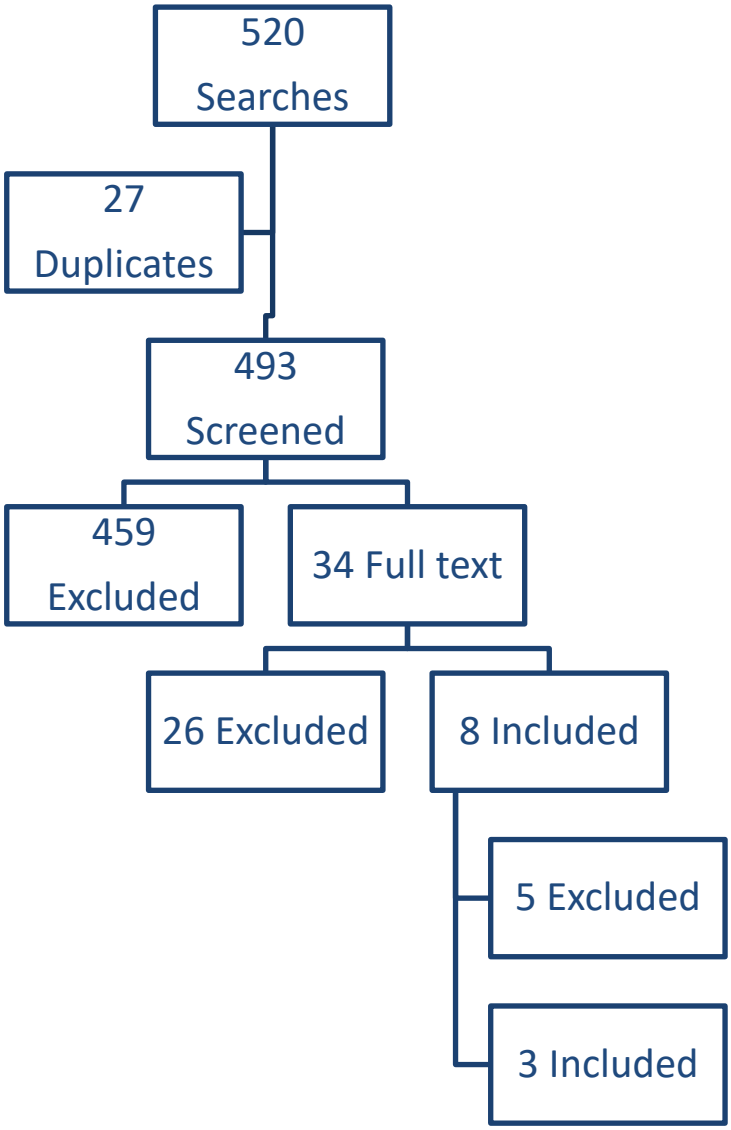

Figure 2 PRISMA flow diagram: economic evidence review

Table 11 Reasons for excluding papers from the cost-effectiveness review at Stage 2

Reference	Reason for exclusion
Aravena 2015[80]	Literature review describing the signs and symptoms used to evaluate post-operative complications in third-molar surgery. Abstract only
Bienstock et al 2011[81]	Short-term study of duration of disability after 3M surgery (mean 1.4±1.8 days) and risk factors associated with prolonged recovery (maximum 26 days)
Bienstock 2012[82]	Indirect costs (mean number of work days missed and risk factors associated with prolonged return to work after 3M surgery)
Chuang et al 2007[83]	Estimates of post-surgery complication rates and risk factors after removal of 3Ms
Chuang et al 2008[84]	Risk factors for post-surgery inflammatory complications after removal of 3Ms
Colorado-Bonnin et al 2006[85]	Short-term (7-day) post-operative HRQoL data
Conrad et al 1999[86]	Short-term (14-day) patients' perceptions of recovery after 3M surgery
Deepti et al 2009[87]	Short-term (7-day) post-operative HRQoL data after impacted 3M removal
Edwards et al 1999[57]	Data were included in HTA review by Song that informed TA1
Gutierrez-Perez 2004[88]	Signs and symptoms of 3M infections. Written in Spanish
Inverso et al 2014[89]	The value of telephone *vs* clinical follow-up after 3M surgery
Inverso et al 2014[74]	No information relating to I3Ms
Koumaras 2012[75]	No information relating to I3Ms
Kunkel et al 2006[77]	No information relating to I3Ms
Kunkel et al 2007[76]	No information relating to I3Ms
Liedholm et al 2010[90]	No figures relating to I3Ms were specifically reported
Leidholm et al 2005[78]	No information relating to I3Ms
Matijevic et al 2014[91]	Comparison of the effect on patient-reported HRQoL of detailed written and oral instructions *vs* written instruction only about treatment after surgical removal of a lower 3M
Offenbacher et al 2012[92]	A study of visible 3Ms and probing depths
Osunde et al 2011[93]	A review of literature on different modalities for minimising inflammatory complications associated with 3M surgery
Panduric et al 2009[94]	Short-term (14-day) post-operative HRQoL data reported for patients (after 3M surgery) in Croatia
Phillips et al 2003[95]	Short-term (14-day) diary designed to assess a patient's perception of recovery after removal of all four 3Ms
Phillips et al 2010[96]	Short-term (14-day) diary used to study the effect of age and sex on recovery after 3M surgery
Ruvo et al 2005[97]	Short-term (14-day) outcomes after removal of all four 3Ms
Sancho-Puchades et al 2012[98]	Short-term (7-day) study of HRQoL after 3M surgery when using conscious sedation
Sato et al 2009[99]	Short-term (7-day) outcomes – data about post-operative signs and symptoms collected daily from patients and surgeons
Shugars & White 2003[100]	Editorial linked to McGrath paper – no rates, frequencies or other statistics provided
Shugars et al 2006[101]	Short-term (14-day) HRQoL outcomes collected using two different instruments
Slade et al 2004[102]	Short-term (pre- and 7-day post) oral health outcomes after removal of 3Ms
White et al 2003[103]	Short-term (14-day) clinical and HRQoL outcomes after removal of all four 3Ms
White 2004[104]	List of citations (with comments) summarising clinical and HRQoL outcomes after 3M surgery

3M=third molar; HRQoL=health-related quality of life; HTA, Health Technology Assessment; I3M=impacted third molar

The three papers that were included in the review are listed in Table 12. Two studies[17,20] provided information on costs and one study[79] provided information on patient HRQoL. The characteristics of these studies are presented in Table 13.

Table 12 Three studies included in the Assessment Group's economic evidence review

Reference	Title
Cost and cost-effectiveness	
Anjrini et al 2015[17]	Cost-effectiveness modelling of a 'watchful monitoring strategy' for impacted third molars vs prophylactic removal under general anaesthetic: an Australian perspective
Song et al 2000[20]	The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth
HRQoL	
McGrath et al 2003[79]	6-month study of patients' perceptions of oral HRQoL after removal of impacted 3Ms

HRQoL=health-related quality of life

Table 13 Characteristics of studies that were included in the economic evidence review

Study	Country	3Ms or I3Ms	Study design/ purpose	Comparators	Reported measures	Cost/outcome source	Time horizon	Cost year
Anjrini et al 2015[17]	Australia	I3Ms	National cost model	Watchful monitoring strategy for I3Ms *vs* prophylactic removal of I3Ms under GA	Number of hospitalisations for impacted wisdom teeth (population aged 15-34 years); direct, indirect and total costs of hospitalisation	Australian Refined Diagnosis Related Group (AR-DRG) costs from private and public hospitals	20 years	2009 (unless otherwise stated)
Song et al 2000[20]	UK	I3Ms	Systematic review (and decision analysis)			NHS		NA
McGrath et al 2003[79]	UK	I3Ms	Evaluation of patients' perceptions of changes in (OHQOL) over a 6-month period after I3M surgery	Patients awaiting I3M surgery	Change in OHQOL as measured by (OHIP-14 and OHQOL-UK scores)	Patient questionnaires and patient 'recovery log' diaries	From the day of the I3M surgery until 7 days after I3M surgery	NA

OHIP=oral health impact profile; GA=general anaesthetic; NA=not applicable; 3M=third molar; I3M=impacted third molar; OHQOL=oral health-related quality of life; UK=United Kingdom

4.1.4 Quality of the included evidence

Contrary to the review protocol, the AG made the decision not to quality assess the papers included in the review of cost-effectiveness evidence using a cost-effectiveness checklist. This decision was made as only one paper directly considers the cost-effectiveness of prophylactic removal of I3Ms in a UK setting (Song et al[20]), and a summary of this paper and its quality are located in the clinical evidence section of this report (see section 3.2).

4.1.5 Economic review: overview of included papers

The AG concludes that relevant data on I3Ms are limited to three studies.[17,20,79] Two of the papers report details about the cost-effectiveness of the prophylactic removal of I3Ms. The review by Song et al[20] includes details about cost-effectiveness from a UK NHS perspective, whilst the material presented in the study by Anjrini et al[17] is of less direct relevance as estimates are based on the Australian health care system and results are presented in Australian dollars. The third paper[79] reports findings relating to an assessment of oral HRQoL after the removal of I3Ms.

4.1.6 Key results: cost-effectiveness of prophylactic removal of I3Ms

Cost-effectiveness: Song et al[20]

This publication is the AG report for TA1 (title: *The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth*). It includes a summary of findings from a study reported by Edwards et al,[57] who estimated the cost-effectiveness of removal and retention of disease-free 3Ms and concluded that the cost of prophylactic removal of I3Ms was about 33% higher than the cost of retention. The Song et al[20] report also includes findings from a paper by Walters,[105] who identified that the compensation awarded for permanent nerve damage after 3M surgery ranged from £4,000 to £14,000 per case, or higher (Walters).

Song et al[20] conclude that in the short- to medium-term, based on available evidence, retention of I3Ms may be more cost effective than prophylactic removal.

Cost-effectiveness: Anjrini et al[17]

The objective of the study reported by Anjrini et al[17] was to develop a model to compare the direct (and indirect) costs associated with a watchful monitoring strategy for I3Ms *versus* prophylactic removal under general anaesthetic. Data were obtained from the Western Australian Hospital Morbidity Data System. All episodes of discharge from all hospitals (private and public) in Western Australia for the financial year 2008/2009 for the removal of impacted or embedded teeth as the principal oral condition, as classified by the International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM), were

included. The rate calculations for Western Australian Hospitalisation were measured using population data obtained from the Australian Bureau of Statistics 2006 Census.

The annual direct cost to the state for I3M removal in hospital was estimated to be AUS$259million, which equates to a direct cost of AUS$2,644 for each hospitalisation (i.e. £1,536 using 22/08/16 conversion rate). The time frame for the analysis was 20 years. The average watchful waiting strategy cost per participant was AUS$1,077. This cost included clinical examinations (AU$60.30) and panoramic radiographs (AUS$47.40), both of which were undertaken every 2 years. Thus, the estimated annual cost was AUS$53.80 per individual, which is approximately 1% of the estimated cost of removal. The authors conclude:

> *'With no evidence to support the prophylactic removal of asymptomatic wisdom teeth, a proposed watchful monitoring strategy is a more cost effective alternative in the Australian context. (page19)*

Health-related quality of life: McGrath et al[79]

The study by McGrath et al[79] in 2003 assessed oral HRQoL in patients after removal of I3Ms over a period of 6 months using two specific oral HRQoL tools and a patient diary. Patients in the study were a mix of people with asymptomatic (n=19) and symptomatic (n=69) 3Ms. Study results demonstrated that people who had previously reported having pericoronitis symptoms achieved greater oral HRQoL gains after I3M surgery than people who had not; the authors considered the findings to be both statistically and clinically significant.

4.1.7 Cost-effectiveness review: conclusions

As there is very limited clinical effectiveness evidence comparing the prophylactic removal of I3M *versus* a 'watchful waiting' strategy, it is unsurprising that economic evidence relating to this comparison is also limited. There are only two published cost-effectiveness studies that directly consider this comparison and, in both cases, the authors conclude that there is currently no economic evidence to support the prophylactic removal of I3Ms. However, Song et al[20] restrict their conclusion to a short- to medium-term time frame.

4.2 Independent economic assessment

There are no existing cost–utility analyses that are relevant to the decision problem and generalisable to the NHS in England. For these reasons, the AG constructed a de novo economic model to determine the cost-effectiveness of the prophylactic removal of IM3Ms compared with standard care where standard care refers to what is currently being done (i.e. no prophylactic removal, referred to as 'watchful waiting') in a population with pathology-free or trouble-free IM3Ms.

The model perspective is that of the UK NHS only, as Personal Social Services costs are not relevant to the decision problem. Outcomes were measured in quality-adjusted life years (QALYs), and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE in the Methods Guide to Technology Appraisal.[106]

In the AG model, in line with the age of the youngest patient recruited to the Fernandes et al study,[44] the AG has chosen to use a starting age of 20 years in the base case; sensitivity analyses are used to explore the impact of using starting ages of 30, 40 and 50 years.

In the AG model, the base case time horizon is 80 years (i.e. up to the point when people reach the age of 100 years, when less than 1% of patients are still alive). The time horizon is varied in scenario analyses (10, 20, 30, 40, 50 years) to assess the impact that this change has on model outputs.

4.2.1 Model pathways

The elements of both the intervention (prophylactic removal) and comparator (watchful waiting) pathways were determined through consultation with clinical experts and examination of clinical data identified via the AG's systematic review of clinical effectiveness evidence.

In the NHS, the watchful waiting pathway (current standard of care) is complicated and, in parts, unclear. There are many different points at which a tooth may, or should, be extracted. For example, the decision to extract a tooth may be determined by a specific number of instances of pericoronitis, the degree of severity of pericoronitis, a decayed adjacent tooth or the amount of tooth pain. Following several searches of the literature and consultation with experts, the AG concluded that data to populate the current watchful waiting pathway are lacking. The AG has, therefore, chosen to design an economic model that is based on what happens (i.e. use available data) rather than on what might happen. This approach minimises the use of assumptions.

A visual representation of the intervention pathway (prophylactic removal) is shown in Figure 3. The pathway is modelled as a combination of a Markov process and decision trees. The cycle length is one year. In each cycle, a person can develop IM3M symptoms but not have the IM3M extracted, have the IM3M extracted (either with or without complications) or die from any cause.

For every person with an IM3M in situ, there is a probability that, in each cycle, the person will die (from any cause), their IM3M will develop symptoms and/or will be extracted. The probability of extraction is independent of symptom development. The possible symptoms are pericoronitis, mild pain and severe pain.

When a tooth is extracted the person might develop a DCC in the adjacent M2M. The AG has assumed that varying the probability of developing an M2M DCC due to an IM3M does not alter the probability of IM3M extraction. This assumption has been made because data are only available describing the proportion of people with M2M DCC in a population who had an IM3M extracted, and not on whether this was the reason for the extraction[107]. If a M2M DCC is present, the tooth can be extracted, be simply restored or have more complex restoration, including root canal treatment.

Extraction of an IM3M can be complication-free or result in mandibular fracture, temporary nerve damage, permanent nerve damage or alveolar osteitis ('dry socket'). After extraction, people can either enter an 'extracted with permanent nerve damage' state or an 'extracted with no nerve damage' state. They will then remain in either of these states for the lifetime of the model or until death.

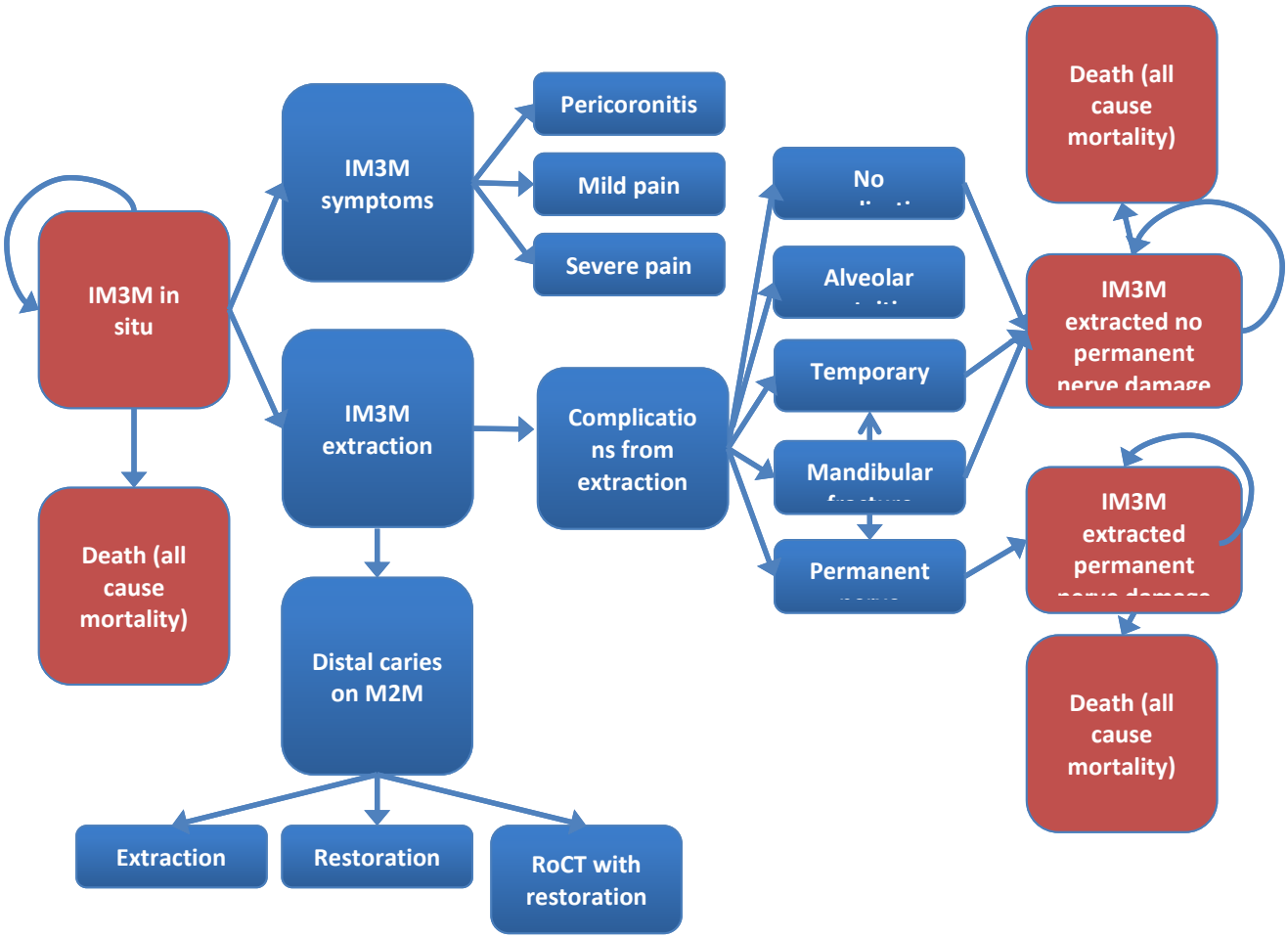

Figure 3 Prophylactic removal of IM3M model pathway

IM3M=impacted mandibular third molar; M2M=mandibular second molar; RoCT=root canal treatment

4.2.2 Model transition probabilities

The transition probabilities used in the AG model have been drawn from published studies identified in the clinical evidence review and evidence identified by clinical experts. Where data are absent, assumptions based on clinical advice have been used.

Evidence presented by Fernandes et al[44] has been used to represent the annual rate of tooth extraction and the development of symptoms for people who have asymptomatic IM3Ms. In this 1-year prospective cohort study, the authors collected data from patients with at least one IM3M. All of the participants were registered with general dental practices in Scotland where SIGN guidelines[56] recommending a watchful waiting pathway have been in place since 2000. The AG considered that these data were generalisable to an English NHS setting.

In the paper by Fernandes et al[44] the annual rate of extraction (5.47%) was found to be independent of age. The inclusion criteria in terms of age of the cohort studied by Fernandes et al[44] was 18-70, but only those aged 20 to 63 years were actually recruited into the study. This determined the model start age of 20. It was assumed that annual rate of extraction continued at 5.47% after the age of 63. A scenario analysis explores where no extractions were undertaken after the age of 63.

An annual rate of extraction of 5.47% gives a five year extraction rate of 24.5% which is lower than that reported by Hill et al[43] at 31.4%. To check the impact of varying the annual rate of extraction, the upper (7.39%pa equivalent to a five year extraction rate of 32.0%) and lower (3.94%pa) bounds of the 95% CI quoted in the paper by Fernandes et al[44] were used in the AG's sensitivity analysis.

For the prophylactic removal pathway, the AG's base case assumption is that not all people will accept the recommendation that the IM3M(s) should be extracted and, therefore, these teeth will remain in situ. Fernandes et al[44] reports that 45.9% of patients who had their IM3Ms extracted did not know why the tooth had been extracted and so the extraction could have been prophylactic (despite the SIGN guideline[56] recommendation). Based on this finding, the AG chose a base case value of 46.95% to represent the proportion of people who would accept prophylactic removal of asymptomatic IM3Ms, if it were offered to them. The AG recognises that it is likely that this figure overestimates the true rate of non-prophylactic removal, as it is unlikely that all of the 46.95% of patients who could not recall why their IM3M was extracted had the tooth extracted when the IM3M was asymptomatic. However, it could also be an underestimate if future guidelines were to suggest that prophylactic removal were to be recommended. Due to these uncertainties, the AG carried out sensitivity analyses to

explore the impact of different levels of acceptance of prophylactic removal (10%, 25%, 50%, 75% and 100%).

Findings from the Fernandes et al[44] study suggest that symptom development is age dependent (at least up the age of 63 years), declining as a patient ages. In the base case, the AG assumes that the rate of symptom development follows a linear trend from ages 53 to 63 years and this trend is applied beyond the age of 63 years. A scenario analysis explores the impact of symptom development no longer occurring past the age of 63 years. The probabilities, by age, of experiencing symptoms can be found in Appendix 7.

The probability of a person who, on having an IM3M extracted, is found to have an associated M2M DCC, and the likelihoods of the M2M being extracted, simply restored or undergoing complex restoration, have been taken from the a study by McArdle et al.[107] In this study, the investigators undertook a retrospective review of 339 people in England across two cohorts from 2006 and 2014 who had IM3Ms removed due to having an M2M DCC.

Probabilities of specific complications associated with tooth extraction were derived from the Chuang et al study.[83] Chuang et al[83] also reported an odds ratio for all complications (OR=1.46) for patients aged 25 years and over compared with those younger than 25 years. The AG has adjusted the individual complication rates reported by Chuang et al[83] by this odds ratio to estimate the probability of specific complications for those younger than 25 years and for those 25 years old and over.

One complication for which there is no evidence available in the study by Chuang et al[83] is the rate of permanent nerve damage. The AG has used a value reported by Valmaseda-Castellón et al.[108] This value has been adjusted for age (people younger than 25 years and 25 years old or over) using the odds ratio reported by Chuang et al.[83]

Table 14 shows a full list of probabilities used in the AG model. Rates for death from any cause have been taken from Office for National Statistics life tables.[109]

Table 14 Probabilities of symptom, extraction complication and distal cervical caries of the mandibular second molar used in the Assessment Group's model base case

Parameters		Probability	Source
Symptoms	Pericoronitis	13.16%	Fernandes et al 2010[44]
	Severe pain	14.04%	
	Mild pain	19.30%	
DCC of M2M on extraction of IM3M	DCC of M2M	15.00%	McArdle 2016[107]
	M2M extracted	42.00%	
	M2M restored	42.00%	
	M2M root canal treatment and restored	16%	
IM3M extraction complications	Mandibular fracture (<25 years)	0.019%	Chuang et al 2007[83]
	Mandibular fracture (≥25 years)	0.03%	
	Permanent nerve damage (<25 years)	0.22%	Valmaseda-Castellón et al 2001[108] Chuang et al 2007[83]
	Permanent nerve damage (≥25 years)	0.33%	
	Temporary nerve damage (<25 years)	2.89%	Chuang et al 2007[83]
	Temporary nerve damage (≥25 years)	4.16%	
	Alveolar osteitis (<25 years)	5.61%	
	Alveolar osteitis (≥25 years)	7.98%	

DCC=distal cervical caries; M2M=mandibular second molar; IM3M=impacted mandibular third molar

The use of annual transition probabilities for symptom development within the AG model results in a person only being able to experience IM3M symptoms once per year for each tooth. Given people may develop symptoms more than once a year in each IM3M, the model may underestimate the actual annual symptom burden for people with IM3Ms. This will result in the AG model underestimating the annual cost of treating IM3M symptoms and the impact of IM3M symptoms on HRQoL.

As a watchful waiting strategy leaves people with more IM3Ms *in situ* than prophylactic removal, the results of the AG model will underestimate the potential reduction in costs and gains in HRQoL from reductions in IM3M symptoms when these two pathways are compared. The incremental cost-effectiveness ratio (ICER) per QALY gained generated by the model for prophylactic removal compared with watchful waiting will therefore be an overestimate as people can develop IM3M symptoms more than once per year.

By designing the model around the available data and excluding complicated pathology that can occur if IM3Ms are left *in situ*, the model is biased towards generating more favourable results for a watchful waiting strategy. For example, with an IMSM left *in situ*, pericoronitis can develop into a severe infection that can spread to the throat and lead to severe cellulitis causing airway blockage resulting in hospitalisation, intensive care unit admission and in some cases death. Pericoronitis can also lead to abscess formation and is accompanied by a potential risk of developing sepsis.

No published data could be found to estimate the risk of these serious events occurring. However, one of the AG's clinical experts reports treating one person per month who has been admitted to the intensive care unit with life-threatening cellulitis due to having had an IM3M. Although there is no way to generalise this experience into a probability that can be included in the AG model, if such a complication were to be included it would result in a reduction in QALYs and increase in costs for the watchful waiting strategy.

4.2.3 Resource use and unit cost estimation

The total number of patients with IM3M extractions each year in the NHS is unknown. However, McArdle et al[107] have estimated that, in 2014/15, there were 152,000 people with IM3M extractions: 67,000 (44.1%) were carried out during inpatient admissions; 38,000 (25.0%) during outpatient attendances and 47,000 (30.9%) during a primary care appointment. The AG has used these estimates as the basis for estimating the cost, to the NHS, of IM3M extractions. Unit costs of extraction in an acute setting have been taken from NHS Reference Costs (2015/16). The cost of an extraction in primary care is a Band 2 treatment and is charged to the NHS as three Units of Dental Activity (UDA).

The AG has assumed that 75% of M2Ms with DCC are extracted at the same time as the IM3M, with no additional cost. For those M2Ms extracted independently, the cost of extraction is assumed to be the same as the estimated cost of IM3M extraction. Sensitivity analyses have been used to explore the impact of this assumption on model results. Values of concurrent IM3M and M2M extraction of between 0% and 100% have been used in these analyses.

To estimate the cost associated with pericoronitis and severe pain, in the absence of any published information of clinical advice, the AG has assumed that 25% of people will self-medicate and that symptoms will resolve without the need for dental or medical intervention. For the 75% that require treatment, dental care will be required. Based upon clinical advice, this dental care would comprise a Band 2 treatment (3 UDAs) plus an antibiotic prescription for erythromycin (a further 0.75 UDAs for issuing a prescription). For the 75% of patients with severe pain, the AG has assumed that an emergency dental appointment will be required (1.2 UDAs) and that people will be prescribed codeine (incurring a further 0.75 UDAs for issuing a prescription). The AG has undertaken sensitivity analyses to explore the impact on model results of varying the proportion of people self-treating from 0% to 100%.

The cost of a UDA varies across England. In the base case, the AG has used a figure of £25. The BDA quotes this figure as being the mean UDA cost across England.[110] The AG has undertaken sensitivity analyses to explore the impact on model results of lower and higher

UDA costs. The figures used in the sensitivity analyses are based on a freedom of information request[1] made in 2009, and ranged from £11.08 to £105.58.

Antibiotic and analgesic prescription costs have been sourced from Prescription Cost Analysis data.[111] The AG has assumed that the cost of all other aspects of treatment is covered either by the relevant NHS Reference Cost or by the payments received for UDAs. The AG has undertaken sensitivity analyses to explore the impact of varying these costs on model results. Upper and lower quartile NHS Reference Cost[112] figures have been used in these analyses.

The AG has assumed that mild pain does not result in any cost being incurred by the NHS and that the treatment of alveolar osteitis is included in the cost of the initial extraction. The AG has assumed that everyone with permanent nerve damage receives surgery to try to correct the damage, and that no one with temporary nerve damage receives corrective surgery. No litigation costs from permanent nerve damage are included in the model. However, as it is likely that some people with permanent nerve damage will receive compensation and that some people with temporary nerve damage will receive surgery (indeed the nerve damage may only be temporary because of corrective surgery), these assumptions mean that the AG's model will underestimate the true cost to the NHS that arises from nerve damage.

A full list of costs used in the AG model is provided in Table 15.

Table 15 Base case costs included in the model

Cost element	Value	Calculation details and source
UDA	£25.00	BDA (http://www.gdpuk.com/news/latest-news/432-uda-values-vary-hugely-across-uk-claim-tories)
Tooth extraction: hospital admission	£801.81	NHS Reference Costs (2015/16) HRG code: major surgical removal of tooth CD04A (weighted by activity of day case/elective inpatient/non-elective inpatient)
Tooth extraction: outpatient	£148.00	NHS Reference Costs (2015/16) HRG code: major surgical removal of tooth CD04A (outpatient)
Tooth extraction: primary care	£75.00	Band 2 treatment (3 UDAs)
Average cost of tooth extraction (based on weighted average of location of extraction)	£413.62	McArdle 2016[107]
Average cost of M2M DCC extraction	£103.41	£413.62/4, as 75% of extractions undertaken concurrently with I3M3 extraction (see source above)
Pericoronitis treatment	£70.31	3.75 UDAs (see source above) × 75% seeking treatment (assumption)
Antibiotics	£2.25	Erythrocin_B-Pack 10 Filmtab 500mg[111]
Severe dental pain treatment	£36.56	1.95 UDAs (see source above) × 75% seeking treatment (assumption)
Analgesic	£3.56	Codeine Phos_Tab 30mg[111]
Fixation of jaw following fracture	£2,854.00	NHS Reference Costs (2015/16) HRG code: Reduction or fixation of jaw CA96Z (inpatient)
Surgery for permanent nerve damage	£5,507.00	NHS Reference Costs (2015/16) HRG code: Complex maxillofacial procedures CA91B (inpatient)
Restoration of M2M	£75.00	Band 2 treatment (3 UDAs) (assumption)
M2M endondically treated and restored	£300.00	Band 3 treatment (12 UDAs) (assumption)

BDA=British Dental Association; HRG=healthcare resource group; M2M=mandibular second molar; PCA=Prescription Cost Analysis; UDA=unit of dental activity

4.2.4 Health measurement and valuation estimation

No IM3M-specific utilities, or utility values related to IM3M symptoms, or extraction complications, could be identified from a targeted search of the published literature (search strategy in Appendix 8). The AG, therefore, used values from a working paper[113] to populate these parameters in the model. It is reported within this paper[113] that people with teeth, mouth or tongue conditions in the UK have an EQ-5D utility score that is 0.345 less than those who do not report having any teeth, mouth or tongue conditions. This is comparable to a utility decrement for Level 3 pain based on the EQ-5D-3L questionnaire ("I have extreme pain or discomfort") of 0.386.[113]

The AG model includes a 0.345 utility decrement to represent the experience of people with any IM3M complication(s) or any complication(s) following extraction. For people experiencing mild pain, the decrement was assumed to be 50% of 0.345 (i.e. 0.1725). Sensitivity analyses were undertaken to explore the impact of varying these figures on model results. The decrements were varied individually over the 95% CI (0.102 to 0.549) reported in the paper by Ara and Brazier.[113] The AG has assumed that M2M restoration is not associated with any loss of utility and that extraction of the M2M would only result in a loss of utility if it occurred independently of an IM3M extraction.

To generate a QALY loss when a person experiences a complication, the duration of symptoms from the complication is required. The AG was not able to identify any evidence describing the duration of symptoms associate with extraction complications. Thus, it was necessary to make a number of assumptions about the durations of symptoms; the AG's clinical experts were contacted to verify these assumptions. The AG has undertaken sensitivity analyses to assess the impact of varying these estimates of duration on model results (duration varied by ±50%). To reflect declining HRQoL as people age in the model, utility declines with age in line with age-related population norms described in the paper by Ara and Brazier.[113]

Details of the values used in the model to represent utility decrement, duration of symptoms assumed, and the resulting QALY loss associated with symptoms and complications are shown in Table 16.

Table 16 Base case utility decrements and symptom duration

Cause of utility decrement		Utility decrement	Duration of symptoms	QALY loss
Symptoms	Pericoronitis	0.345	9 days	0.009
	Severe pain	0.345	30 days	0.028
	Mild pain	0.1725	30 days	0.014
Extraction	IM3M or M2M	0.345	7 days	0.007
Complications following IM3M extraction	Mandibular fracture	0.345	42 days	0.040
	Permanent nerve damage	0.345	Lifetime	0.345
	Temporary nerve damage	0.345	30 days	0.028
	Alveolar osteitis	0.345	9 days	0.009

IM3M=impacted mandibular third molar; M2M=mandibular second molar; QALY=quality-adjusted life year

4.2.5 Analysis of uncertainty

The AG explored the uncertainty surrounding model assumptions using deterministic sensitivity analyses and scenario analyses. Probabilistic sensitivity analysis was not undertaken as the only parameter for which a distribution could be drawn based solely on published evidence was the annual rate of extraction. Creating distributions around the central value of other parameters would not be meaningful either because the parameter values are essentially fixed (e.g. in the case of costs) or because the central values are, at least partly, based on assumptions due to lack of data (e.g. the actual utility values associated with symptoms or the duration of symptoms). Furthermore, a probabilistic sensitivity analysis could potentially lead to confounding results, as the uncertainty around most of the assumptions used in the AG model is not known and, therefore, from a statistical perspective, cannot be confidently modelled.

The parameter ranges explored in deterministic sensitivity analysis are summarised in Table 17, and the scenario analyses performed are summarised in Table 18.

Table 17 Parameter values in deterministic sensitivity analyses

Analysis		Base case value	Range in sensitivity analysis	Range source
Utility decrement (QALY)	Pericoronitis	0.345	0.102 to 0.549	Fernandes et al 2010[44] (95% CI)
	Severe pain	0.345	0.102 to 0.549	
	Mild pain	0.1725	0.051 to 0.275	
	Alveolar osteitis	0.345	0.102 to 0.549	
	Tooth extraction	0.345	0.102 to 0.549	
	Mandibular fracture	0.345	0.102 to 0.549	
	Permanent nerve damage	0.345	0.102 to 0.549	
	Temporary nerve damage	0.345	0.102 to 0.549	
Duration of symptoms	Pericoronitis	9 days	4.5 to 13.5 days	Assumption (base case +-50%)
	Severe pain	30 days	15 to 45 days	
	Mild pain	30 days	15 to 45 days	
	Alveolar osteitis	9 days	4.5 to 13.5 days	
	Tooth extraction	7 days	3.5 to 10.5 days	
	Mandibular fracture	42 days	21 to 63 days	
	Temporary nerve damage	30 days	15 to 45 days	
Unit costs	UDA	£25	£11.08 and £105.58	BDA (http://www.gdpuk.com/news/latest-news/432-uda-values-vary-hugely-across-uk-claim-tories)
Discount rate	Annual rate	3.5%	1.5% and 5.0%	NICE Reference Case
Proportion seeking treatment for IM3M symptoms	Pericoronitis	75%	0% to 100%	Assumption
	Severe dental pain	75%	0% to 100%	
Annual rate of extraction	IM3M	5.47%	3.94% to 7.39%	Fernandes et al 2010[44] (95% CI)
Extraction of M2M	Percentage of patients having M2M with DCC extracted at same time as IM3M	75%	0% to 100%	McArdle 2016[107]

CI=confidence interval; DCC=distal cervical caries; FOI=freedom of information; IM3M=impacted mandibular third molar; M2M=mandibular second molar; UDA=unit of dental activity

Table 18 Scenario analyses

Scenario variant	Base case value	Value(s) used in scenario(s)
Vary model start age	20 years	30, 40, 50 years
Vary model time horizon	Lifetime	10, 20, 30, 40, 50 years
No IM3M symptoms after age 63 years	Same rate of symptoms as those aged 53 to 63 years	0
No extractions after age 63	5.47%pa	0% per annum
Modifying patient acceptance of prophylactic removal	45.95%	10%, 25%, 50%, 75%, 100%
All extractions occur in primary care	30.9% (making average cost of extraction £413.62)	100.0% (making average cost of extraction £565.13)
No extractions occur in primary care	30.9% (making average cost of extraction £413.62)	0.0% (making average cost of extraction £75.00)

IM3M=impacted mandibular third molar

4.2.6 Base case results

Costs

For the modelled population, the AG model results predict that, compared with a watchful waiting strategy, a prophylactic removal strategy will result in 2.14% more people with IM3Ms having their impacted teeth removed over their lifetime. For the prophylactic removal strategy, this results in the average discounted cost of extraction per person being £71.49 higher compared with the watchful waiting strategy.

The AG model results show that, compared with a watchful waiting strategy, a prophylactic removal strategy leads to lower rates of permanent nerve damage and jaw fracture following extraction. However, the actual discounted cost of treating these extraction complications will be higher with a prophylactic removal strategy than for a watchful waiting strategy as the costs of these complications will, predominantly, occur in the first year of the model. With a watchful waiting strategy these costs will accrue across decades, resulting in the discounted costs being lower than for the prophylactic removal strategy, even though more complications occur with a watchful waiting strategy.

The model results show that, compared with a watchful waiting strategy, a prophylactic removal strategy results in lower IM3M symptom treatment costs. These cost savings lead to the total cost of a prophylactic removal strategy being £55.71 higher per person compared to a watchful waiting strategy.

The base case costs generated by the AG model for a cohort of 1000 people with asymptomatic IM3Ms are shown in Table 19.

Table 19 Base case cost results for 1000 people with symptomatic impacted mandibular third molars

Complication or symptom	Watchful waiting		Prophylactic removal		Change	
	Number	Cost	Number	Cost	Number	Cost
IM3Ms extracted	955.4	£258,014	975.9	£329,503	20.5	£71,489
Permanent nerve damage	2.9	£9,874	2.6	£10,979	-0.3	£1,106
Jaw fracture	0.2	£428	0.2	£481	-0.02	£52
Number of M2Ms with DCC	143.3		77.5		-65.9	
M2Ms extracted	60.2	£4,064	32.5	£2,196	-27.7	-£1,867
M2Ms restored	60.2	£2,947	32.5	£1,593	-27.7	-£1,354
M2Ms RoCT and restoration	22.9	£4,491	12.4	£2,427	-10.5	-£2,064
Pericoronitis	295.9	£15,946	160.0	£8,620	-135.9	-£7,326
Severe pain	315.7	£9,408	170.7	£5,085	-145.0	-£4,322

DCC=distal cervical caries; M2M=mandibular second molar; RoCT=root canal treatment

Health-related quality of life results

More people have an IM3M extracted under a prophylactic removal strategy and more extractions happen earlier, compared with a watchful waiting strategy. The AG model predicts that the expected discounted QALY loss per person from IM3M extraction is greater with a prophylactic removal strategy than with a watchful waiting strategy. As was the case with costs, when comparing results from a prophylactic removal strategy with those from a watchful waiting strategy, although complications from extraction will be lower when a prophylactic removal strategy is employed (because these complications occur earlier in the model) the discounted QALY loss from extraction complications will be higher than with a watchful waiting strategy.

However, the QALY loss from IM3M symptoms is lower when using a prophylactic removal strategy compared with a watchful waiting strategy, and outweighs the QALY loss from the greater number of IM3M extractions with prophylactic removal. This results in an overall expected QALY gain from prophylactic removal of 0.005 compared with watchful waiting.

The base case QALY results generated by the AG model for a cohort of 1000 people with asymptomatic IM3Ms are shown in Table 20.

Table 20 Base case QALY results for 1000 people with symptomatic impacted mandibular third molars

Complication or symptom	Watchful waiting		Prophylactic removal		Change	
	Number	QALY loss	Number	QALY loss	Number	QALY loss
IM3Ms extracted	955.4	4.124	975.9	5.267	20.5	1.143
Permanent nerve damage	2.9	0.619	2.6	0.688	-0.3	0.069
Temporary nerve damage	36.6	0.653	33.1	0.729	-3.6	0.076
Jaw fracture	0.2	0.006	0.2	0.007	-0.02	0.001
Alveolar osteitis	70.4	0.377	63.8	0.423	-6.6	0.046
Number of M2Ms with DCC extracted	60.2	0.155	32.5	0.084	-27.7	-0.071
Pericoronitis	295.9	1.868	160.0	1.010	-135.9	-0.858
Severe pain	315.7	6.644	170.7	3.591	-145.0	-3.052
Mild pain	434.0	4.566	234.6	2.468	-199.4	-2.098

DCC=distal cervical caries; IM3M=impacted mandibular third molar; M2M=mandibular second molar; QALY=quality-adjusted life year

Cost-effectiveness results

Combining the cost and QALY results generated by the model suggests an ICER for the comparison of a prophylactic removal strategy versus a watchful waiting strategy of £11,741 per QALY gained. The incremental costs and benefits for a cohort of 1000 people with asymptomatic IM3Ms is shown in Table 21.

Table 21 Base case incremental cost-effectiveness ratios for 1000 people with asymptomatic impacted mandibular third molars

Total costs		Total QALYs		Incremental		
Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Cost	QALY	ICER per QALY gained
£305,173	£360,885	22615	22620	£55,713	4.74	£11,741

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

4.2.7 Deterministic sensitivity analysis

Tornado diagrams summarising the results of the one-way deterministic sensitivity analyses detailed in Table 17 are shown in Figure 4.

The tornado diagram shows that the most important parameters that affect model results are the discount rate, the cost of a UDA, the annual extraction rate for IM3Ms, the utility decrements applied to IM3M symptoms and the duration of the symptoms.

Although the results are most sensitive to changes in the discount rate – which is to be expected given that the prophylactic strategy effectively 'front loads' extraction costs in the model compared with the watchful waiting strategy, which spreads those cost over many years – the ICER is still under £20,000 per QALY gained even when the discount rate is 5% per annum. The AG considers that although the 3.5% per annum discount rate is the correct one to apply, an argument could be made that prophylactic removal constitutes a public health intervention similar to vaccination and so a 1.5% per annum discount rate should be applied instead. At this lower rate, the model predicts an ICER of £3,377 per QALY gained for the prophylactic removal strategy.

Given that there is no direct evidence on the QALY loss from symptoms of IM3Ms, it is potentially concerning that the ICER per QALY gained is sensitive to values used in the AG model to estimate the IM3M symptom QALY loss. However, over all of the parameter ranges considered, only the lower bound for the utility decrement for severe pain (0.102 as opposed to 0.345 in the base case) results in an ICER above £20,000 per QALY gained for prophylactic removal (£21,469 per QALY gained).

As stated previously there is evidence from Hill et al[43] that the annual rate of extraction of IM3Ms is closer to the upper bound of 7.39%pa reported by Fernandes et al[44] rather than the 5.47%pa used in the base case. If the annual rate of extraction was 7.39%pa then the ICER would be £9,944 per QALY gained. However, even if the annual rate of extraction was at the lower bound suggested by Fernandes et al[44]of 3.94%, the ICER would be £13,847 per QALY gained which is still below the £20,000 per QALY gained threshold.

As stated previously, the cost of a UDA varies widely across the country. The value used in the AG base case (£25) is at the lower end of the potential range used in England (£11.08 to £105.58). At the lower UDA price (£11.08), the ICER for prophylactic removal is £12,925 per QALY gained and thus remains below the £20,000 per QALY gained threshold. For geographical areas where the UDA price is higher than the £25 base case value, the ICER per QALY gained increasingly favours a prophylactic removal strategy.

The AG model results are insensitive to several parameters where no information was available and assumptions had to be made. For example, the duration of symptoms for complications from extraction, the percentage of patients seeking treatment for pericoronitis

and the percentage of patients having an M2M extraction at the same time as IM3M extraction. This finding suggests that the lack of robust information on these parameters does not impact on the conclusions that can be drawn from the AG model.

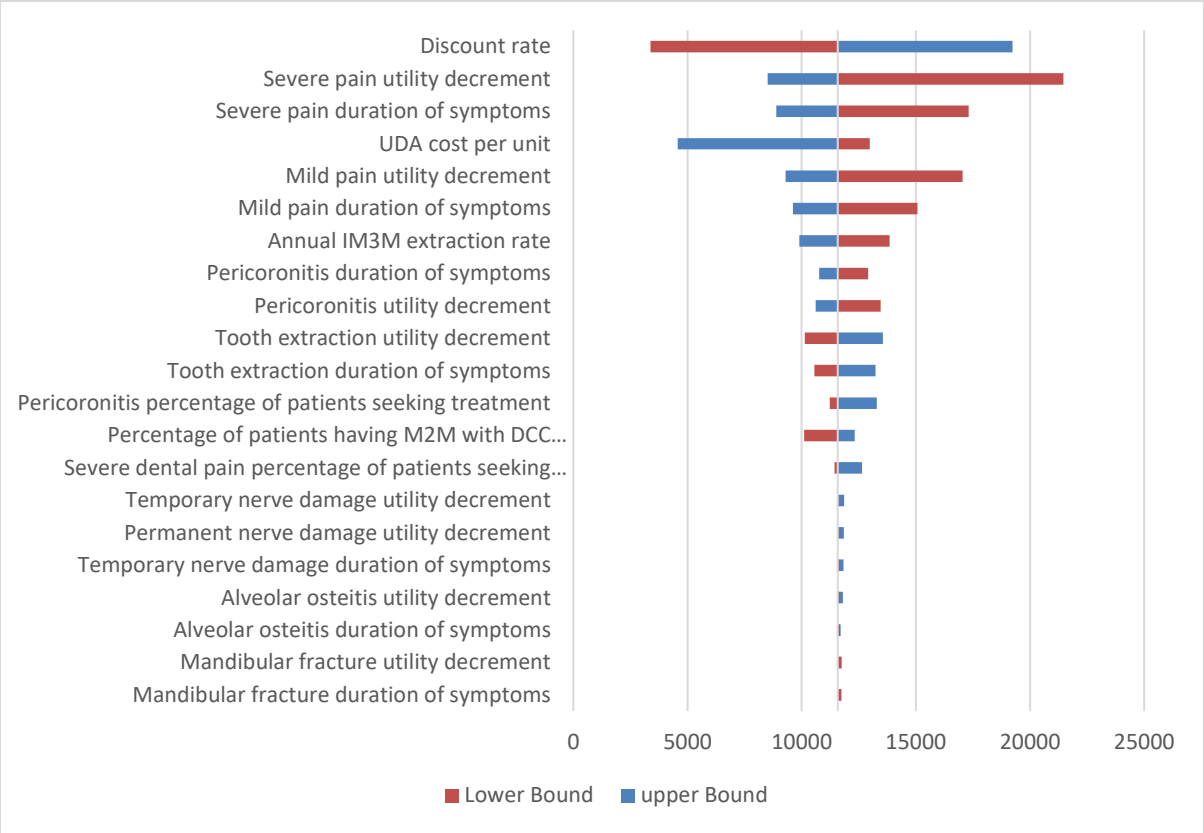

Figure 4 Deterministic sensitivity analyses results

UDA=unit of dental activity; IM3M=impacted mandibular third molar; M2M=mandibular second molar; DCC=distal cervical caries

4.2.8 Scenario analyses

The total number of patients with IM3M extractions each year in the NHS is unknown. However, McArdle et al[107] have estimated that, in 2014/15, there were 152,000 people with IM3M extractions: 67,000 (44.1%) were carried out during inpatient admissions; 38,000 (25.0%) during outpatient attendances and 47,000 (30.9%) during a primary care appointment. The AG has used these estimates as the basis for estimating the cost, to the NHS, of IM3M extractions. Unit costs of extraction in an acute setting have been taken from NHS Reference Costs (2015/16).[114] The cost of an extraction in primary care is a Band 2 treatment and is charged to the NHS as three Units of Dental Activity (UDA). Whilst the number of extractions in an acute setting was derived from published statistics, McArdle et al[107] estimated the number of extractions in primary care from a historical data source as primary care IM3M extractions have not been recorded since 2004/05. McArdle et al[107] state that they believe that their estimate of 47,000 extractions in primary care is probably an underestimate. However, given the potential uncertainty around the number of primary care extractions,

scenario analyses were undertaken where (i) no extractions occurred in primary care and (ii) all extractions occurred in primary care.

Proportion of extractions occurring in primary care

Increasing the proportion of people having extractions in primary care reduces the average cost of extraction per person and vice versa.

If all extractions were to take place in primary care, the average cost per extraction decreases to £75 and the ICER per QALY gained decreases such that prophylactic removal becomes a dominant strategy compared to watchful waiting. If no extractions take place in primary care, the average cost per extraction increases to £565.13 and the ICER increases to £17,116 per QALY gained for prophylactic removal. The results of this scenario analysis are shown in Table 22.

Table 22 Impact on cost-effectiveness results from assuming 100% and 0% of impacted mandibular third molars extractions occur in primary care

	Total costs		**Total QALYs**		**Incremental**		
IM3M symptoms	**Watchful waiting strategy**	**Prophylactic removal strategy**	**Watchful waiting strategy**	**Prophylactic removal strategy**	**Cost**	**QALY**	**ICER per QALY gained**
Base case	£305,173	£360,885	22615	22620	£55,713	4.74	£11,741
100% of extractions in primary care	£90,616	£89,331	22615	22620	-£1,285	4.74	Dominates
0% of extractions in primary care	£401,173	£482,388	22615	22620	£81,215	4.74	£17,116

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio

Model start age

The age at which people enter the model was varied between 30 and 50 years (base case=20 years). As the age at the start increases, so does the ICER per QALY gained for the comparison of a prophylactic removal strategy with a watchful waiting strategy. However, even when the starting age was set at 50 years, the ICER for this comparison remains below £20,000 per QALY gained. The results of these sensitivity analyses are presented in Table 23.

Table 23 Impact on cost-effectiveness results of varying the start age

Model start age	Total costs		Total QALYs		Incremental		
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Cost	QALY	ICER per QALY gained
Base case (20 years)	£305,173	£360,885	22615	22620	£55,713	4.74	£11,741
30 years	£303,175	£362,483	20616	20620	£59,308	4.36	£13,609
40 years	£296,341	£358,764	18190	18194	£62,423	4.22	£14,787
50 years	£283,219	£351,611	15335	15339	£68,392	3.94	£17,348

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

Time horizon

The time horizon used in the AG model was varied in 10-year increments between 10 and 50 years. The results of these scenarios compared with the base case results are shown in Table 24.

As the prophylactic removal strategy 'front loads' the costs of extraction compared to a watchful waiting strategy, the ICER per QALY gained is sensitive to the time horizon employed in the model. The shorter the time horizon, there are fewer people in the watchful waiting strategy who have an extraction and develop symptoms due their IM3Ms. By 21 years, the ICER per QALY gained for the comparison of a prophylactic removal strategy with a watchful waiting strategy has fallen below £20,000.

Table 24 Impact of varying the model time horizon on cost-effectiveness results

	Total costs		Total QALYs		Incremental		
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Cost	QALY	ICER per QALY gained
Base case (Lifetime)	£305,173	£360,885	22615	22620	£55,713	4.74	£11,741
10 years	£186,095	£296,515	7364	7365	£110,419	1.57	£70,310
20 years	£259,364	£336,122	13102	13106	£76,758	3.72	£20,620
30 years	£288,021	£351,613	16987	16992	£63,593	4.42	£14,401
40 years	£299,141	£357,625	19538	19543	£58,484	4.64	£12,598
50 years	£303,325	£359,886	21184	21188	£56,562	4.72	£11,994

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

No IM3M symptoms after the age of 63 years

The assumption that people continue to have IM3M symptoms after the age of 63 years makes a minor difference to the size of the ICER per QALY gained. When comparing a prophylactic removal strategy with a watchful waiting strategy, removing the assumption so that no people

experience IM3M symptoms after the age of 63 increases the ICER per QALY gained by £51. The results of this scenario analysis are shown in Table 25.

Table 25 Impact on cost-effectiveness results from assuming no symptoms from impacted mandibular third molars after the age of 63 years

IM3M symptoms	Total costs		Total QALYs		Incremental		
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Cost	QALY	ICER per QALY gained
Base case	£305,173	£360,885	22615	22620	£55,713	4.74	£11,741
No IM3M symptoms post 63 years	£305,097	£360,844	22615	22620	£55,747	4.73	£11,793

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

No extractions after the age of 63 years

The assumption that people continue to have IM3Ms extracted after the age of 63 years also makes only a minor difference to the size of the ICER per QALY gained. This is unsurprising as, by the age of 63 years (annual extraction rate of 5.47%), approximately 91% of patients will have had their IM3M removed with watchful waiting and both costs and benefits by this age are substantially discounted. When comparing a prophylactic removal strategy with a watchful waiting strategy, removing the assumption that people continue to have IM3Ms extracted after the age of 63 increases the ICER per QALY gained by £437. The results of this scenario analysis are shown in Table 25.

Table 26 Impact on cost-effectiveness results from assuming no extraction from impacted mandibular third molars after the age of 63 years

IM3M symptoms	Total costs		Total QALYs		Incremental		
	Watchful waiting strategy	Prophylactic removal strategy	Watchful waiting strategy	Prophylactic removal strategy	Cost	QALY	ICER per QALY gained
Base case	£305,173	£360,885	22615	22620	£55,713	4.74	£11,741
No IM3M extractions post 63 years	£301,435	£358,865	22615	22620	£57,430	4.71	£12,180

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

Proportion of people accepting prophylactic removal of IM3Ms

Varying the proportion of people accepting prophylactic removal of IM3Ms resulted in no change to the base case cost-effectiveness results, as the increase in costs that accompanied an increase in the number of prophylactic removals resulted in a directly proportional increase in QALYs. As such, the ICER per QALY gained for the comparison of a prophylactic removal

strategy with a watchful waiting strategy remained the same, irrespective of the proportion of patients accepting prophylactic removal.

4.2.9 Summary of cost-effectiveness results

The results generated by the AG's economic model indicate that the ICER per QALY gained for the comparison of the cost-effectiveness of a prophylactic removal strategy versus a watchful waiting strategy is £11,741 per QALY gained for people aged 20 with asymptomatic IM3Ms. The incremental cost per person associated with prophylactic extraction is £55.71 with an incremental QALY gain of 0.005 per person. The base case ICER per QALY gained was found to be robust when a range of one-way sensitivity analyses were carried out to test parameter uncertainty and when scenario analyses were carried out to test structural assumptions.

4.3 Discussion of cost-effectiveness results

The AG's review of cost-effectiveness evidence only identified two published cost-effectiveness studies[17,20] that directly consider the decision problem. The authors of both studies[17,20] conclude that there was no economic evidence to support the prophylactic removal of IM3Ms. However, the AG notes that Song et al[20] restrict their conclusions to a short- to medium-term time frame. More importantly, none of the studies was a cost–utility analysis and therefore the relevance of the reported results to the decision problem is limited.

The results generated by the AG's economic model indicate that the ICER per QALY gained for the comparison of the cost-effectiveness of a prophylactic removal strategy versus a watchful waiting strategy is markedly less than the £20,000 per QALY gained threshold widely accepted by NICE Appraisal Committees.

Although the ICER was determined to be robust when a range of scenario and one-way sensitivity analyses were carried out, uncertainty exists around the magnitude of utility loss from IM3M symptom development (either through the utility decrement or duration of symptoms). As no direct values for these parameters could be drawn from the published literature, parameter values had to be derived from generic studies of utility and from expert clinical opinion. This inevitably places a limit on the robustness of the AG model results. However, the AG notes that a central model assumption is that symptoms can only develop once a year, which is likely to underestimate the true symptom burden arising from IM3Ms.

The ICER per QALY gained for prophylactic removal also increases as the percentage of people having an extraction in an acute setting rises. However, it is noted that the percentage of extractions in primary care in the base case of the model (30.9%) was considered to likely

be an underestimate by the authors of the study (McArdle et al[105]) from where the proportions of location of extraction were derived. The greater the percentage of people that can have their IM3Ms extracted in a primary care setting, the more cost effective prophylactic removal becomes.

In addition to the limit of only developing symptoms once a year, eight other model assumptions also suggest that the base case ICER per QALY gained generated by the model may be conservative:

1. No serious complications arising from IM3M symptoms (e.g. from severe infection) are included in the model.
2. No disutility from M2M decay and restorative treatment (including root canal treatment) is included in the model.
3. Expert clinical advice to the AG is that tooth extraction becomes much more difficult as people age, which could result in the extraction being more complex and, therefore, more costly. The only way that this increase in difficulty is represented in the model is through an increase in the complication rate.
4. No litigation costs from permanent nerve damage and/or fracture are included in the model.
5. No surgical treatment costs for temporary nerve damage or ongoing costs of treating permanent nerve damage are included in the model.
6. No costs of additional check-ups or x-rays are included for a watchful waiting strategy. Routine dental care costs are assumed to be identical regardless of whether the IM3M is *in situ* or not.
7. All people with IM3Ms are treated equally in the model regardless of impaction status (i.e. whether partially erupted or a bony impaction). Expert clinical advice to the AG is that it is only partially erupted teeth that tend to cause problems. If this is the case, then both the extraction and complication rates reported by Fernandes et al[44] (this study included people with both bony and partially erupted IM3Ms) would be an underestimate of the rates for people with partially erupted IM3Ms. The base case ICERs generated by the model are, therefore, overestimates for those with partially erupted IM3Ms and underestimates for those with bony impaction.
8. Patients who develop symptoms in the model but do not have their teeth removed have the same risk of developing symptoms in future years as if they had stayed asymptomatic. It may be the case that patients who develop symptoms are either

inherently more prone to symptom development, or prior symptoms and treatment increase the likelihood of developing future symptoms.

The AG model results are ultimately driven by the finding that most individuals with asymptomatic IM3Ms will eventually have their IM3Ms extracted. This finding arises from the AG's long-term extrapolation of the annual extraction data reported in the study by Fernandes et al.[44] In this sense, a watchful waiting strategy may be more accurately described as 'putting off the inevitable'. The findings reported by Fernandes et al[44] on the rate of extraction of IM3Ms are supported by the results of Hill et al.[43] Importantly, even if the annual rates of extraction are substantially lower then used in the model base case, the ICER per QALY gained remains below £20,000.

5 DISCUSSION

5.1 Statement of principle findings

The SR of clinical evidence found no RCT data to support or refute the prophylactic removal of pathology-free/trouble-free IM3Ms. The authors of the two included studies[54,55] investigating the rate of surgical complications concluded that no serious complications were reported, and the three longitudinal studies[43,44,54] assessing outcomes of retained IM3Ms reported varying extraction rates due to the different lengths of follow-up. No studies reported the impact of retention on the status of the second molars.

As there is very limited clinical effectiveness evidence comparing the prophylactic removal of I3M versus a watchful waiting strategy, it is unsurprising that economic evidence relating to this comparison is also limited. The two published cost-effectiveness studies[17,20] that directly consider this comparison conclude that there is currently no economic evidence to support the prophylactic removal of I3Ms.

The results generated by the AG's de novo economic model indicate that the ICER per QALY gained for the comparison of the cost-effectiveness of a prophylactic removal strategy versus a watchful waiting strategy is £11,741 per QALY gained for people aged 20 with asymptomatic IM3Ms. The incremental cost per person associated with prophylactic extraction is £55.71 with an incremental QALY gain of 0.005 per person. The base case ICER per QALY gained was found to be robust when a range of one-way sensitivity analyses were carried out to test parameter uncertainty and when scenario analyses were carried out to test structural assumptions.

While the available published economic evidence is limited, the findings that prophylactic removal is not cost-effective would seem to be contradicted by the findings from the results of the AG's de novo model. There are several reasons that may explain this apparent contradiction. First, the model time horizon is important, as shown by the results of the scenario analysis in Table 24. It is unlikely that economic models that only consider the short- and medium-term would show that a prophylactic removal strategy was more cost effective than a watchful waiting strategy. Second, there are data available[43,44] on the annual rate of extraction and symptom development in the UK under a watchful waiting strategy that were not available at the time of the Song et al study.[20] Additional sources of information[107] are also now available on, for example, the rate of M2M DCCs due to IM3Ms. Third, the costs of extraction have now been robustly estimated and are significantly lower than those previously estimated (see, for example, Anjrini et al[17]). Lower costs of extraction will make it more likely that a prophylactic removal strategy will be more cost effective than a watchful waiting

strategy. Finally, the studies included in the review of cost-effectiveness evidence were not cost–utility analyses and so the analysis of effectiveness in these studies is fundamentally different to that considered here. The AG is, therefore, not surprised that the results generated by the de novo model differ from those published previously.[17,20]

5.2 Strengths and limitations of the assessment

The main strength of this review is the breadth of literature that was considered. All clinical study designs and SRs were included in an attempt to identify all relevant literature. However, two limitations were the date of the search and the very specific population outlined in the decision problem. As this review was an update of the current NICE guidance[2] published in 2000, the conducted searches were from 2000 to 2016. The population outlined in the decision problem was "People with pathology-free or trouble-free impacted mandibular third molars"; much of the literature cited by the professional stakeholders and the identified SRs did not provide data on the position of the tooth (maxillary or mandibular), whether teeth were impacted or not, and several did not provide information on the state of the tooth (i.e. pathology-free or trouble-free). This severely limited the number of studies relevant to this review.

The findings of this review were in line with those from the other nine identified SRs,[20,36,38-42,46,52] suggesting that the limitations of this review did not overly affect the conclusions.

The strength of the de novo economic model is the use of existing evidence[44] on the annual rates of symptom development and on the annual rates of extraction of IM3Ms that are currently pathology-free/trouble free. All of the assumptions employed in the model suggest that the base case ICER per QALY gained for the comparison of prophylactic removal versus watchful waiting may be conservative. An additional strength of the model is that it is robust to variations across the range of parameter values that could be considered clinically plausible.

The economic model was limited by the lack of direct utility evidence around IM3M symptoms. However, suitable proxies could be found and the cost-effectiveness findings were robust across a range of potential values that could be chosen.

5.3 Uncertainties

The AG model results are driven by figures reported by Fernandes et al[44] and McArdle et al.[107] While the results reported by Fernandes et al[44] on the rate of extraction of IM3Ms are supported by results reported by Hill et al,[43] the results reported by McArdle et al[107] on the different proportions of people having IM3Ms extracted in non-acute NHS settings have yet to be confirmed by other studies. However, even if all extractions were carried out in the acute

setting, the size of the ICER for prophylactic removal versus watchful waiting would still remain below £20,000 per QALY gained.

Model results show that the difference in costs between the prophylactic removal strategy and the watchful waiting strategy is £55.71 per person. With such a small difference in the cost, the level of confidence in the utility associated with the two strategies gains importance. Although the model has been shown to be robust to variations in utility values, all of the utility values used in the model are based on a figure published in 2010 study by Ara and Brazier;[113] this figure has been adjusted for use in the AG model using assumptions verified by a clinical expert.

6 CONCLUSIONS

6.1 Implications for service provision

The reintroduction of the prophylactic removal of pathology-free/trouble-free IM3Ms will have resource implications both in primary and secondary care settings, with the rate of pathology-free I3M3 extractions increasing. Expert clinical advice to the AG is that it can be argued that the cost would be offset by the reduction in the number of complicated extractions being performed when people are older. There is no published evidence that this is the case, although there is evidence that complications associated with extraction increase with age.[83]

The results generated by the economic model show that most people with IM3Ms will have their impacted teeth removed at some point and that, while prophylactic removal is probably more costly than a watchful waiting strategy (although this may not be the case if, for example, compensation pay-outs for permanent nerve damage are taken into consideration), the improvements in HRQoL for people from a reduction in IM3M symptoms mean that prophylactic removal is a cost effective strategy for the NHS.

6.2 Suggested research priorities

The AG was able to produce a robust economic model using the limited clinical evidence relating to the prophylactic removal of pathology-free/trouble-free IM3Ms. However, there remains a lack of head-to-head trial evidence comparing a prophylactic removal strategy with a watchful waiting strategy. The practical difficulties (including, time, cost, and the need for extended follow-up) associated with undertaking such studies means that it is unlikely that this type of study will be conducted.

Future longitudinal studies on the pathology of retained IM3Ms could be designed to record the impaction status and health of the retained IM3M with results being presented separately for maxillary and mandibular teeth.

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8 APPENDICES

Appendix 1 International guidelines

International clinical practice guidelines

Guidelines	Country	Recommendation
AAOMS 2016[29]	US	Position statement: Predicated on the best evidence-based data, third molar teeth that are associated with disease, or are at high risk of developing disease, should be surgically managed. In the absence of disease or significant risk of disease, active clinical and radiographic surveillance is indicated In the absence of evidence regarding current associated symptoms or disease to support surgical management, the surgeon should review the likelihood of pathology developing in the future, functionality, risks of removal, risks of retention, and protocol for active surveillance. Removal should be favoured when the third molar is currently or likely to be non-functional, there is an overlying removable prosthesis, orthodontic removal is justified (such as when the tooth is preventing the eruption of the second molar) and in the case of planned orthognathic surgery. Patients should also be informed of the greater difficulty and increased rate of complications associated with third molar removal as they age
AAPD 2005 Paediatric[70] (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 tumours) 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
AAPD 2010 Adolescents[69] (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
ANAES 1997[67]	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
Faculty of Dental Surgery - RCS(eng) 1997[23] (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

Guidelines	Country	Recommendation
		• 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 2.1 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. 2.2 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. 2.3 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 2.4 Opposing and contralateral teeth: If there are indications for removal of one 3M it is in the patient's best interests to determine whether the other three are present and if so whether their excision is required on the grounds of the clinical indications listed under items above. It is suggested that removal of other teeth should only be carried out when treatment under general anaesthetic is planned or selected by the patient and where there is no evidence of increased risk of post-operative complications such as sensory nerve impairment. It is important to recognise that medico-legal cases have arisen in relation to complications arising from removal of such opposing and/or contralateral teeth
MoH Malaysia 2005[71]	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

Guidelines	Country	Recommendation
		• 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 minimises the likelihood of lingual nerve injury • Excessive bone removal is not recommended • The routine use of antibiotics in third molar surgery is not recommended
NGC-7156 2008[72] (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
SIGN 43 2000[56] (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

Guidelines	Country	Recommendation
		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 that 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 • A partially erupted or unerupted third molar, close to the alveolar surface, prior to denture construction or close to a planned implant
ZZQ 2006[68]	Germany	**Removal is indicated in the following cases**: • Acute or chronic infection (acute pericoronitis) • Exposed pulp due to caries • Non-restorable caries-damaged teeth or untreatable pulpitis • If it appears that the third molar is a significant source of pain • Untreatable periapical changes • Manifest pathological structures associated with dental follicles (e.g. cysts or a tumour) or suspicion of such changes • Resorption of adjacent teeth • In connection with the treatment of periodontal disease or limitation of its progression • Teeth that impede orthodontic and reconstructive surgery • Teeth in the fracture gap that impede fracture treatment • Where the tooth is to be used for transplant purposes • If the elongated or inclined third molar presents a manifest disturbance of dynamic occlusion

Guidelines	Country	Recommendation
		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: • Prophylactic removal for higher-level reasons associated with the patient's life situation (e.g. non-availability of medical care) • If other measures are being conducted under anaesthetic and further anaesthesia would be necessary for removal of a third molar • 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 • 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: • Where spontaneous regular positioning of the third molars in the dental arch is likely • If the extraction of other teeth and/or orthodontic treatment with correct positioning of the tooth is appropriate • Deeply impacted and malposed teeth without associated pathology, where a high risk of surgical complications exists

AAOMS=American Association of Oral and Maxillofacial Surgeons; AAPD=American Academy of Paediatric Dentistry; RCS(eng)=The Royal College of Surgeons of England; 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; Source: Belgian Health Care Knowledge Centre (KCE). KCE Reports 182C[36]; ANAES 1997[67] is translated from the original French and AAOMS White paper[29]

Appendix 2 Literature search strategies

Cochrane library

Cochrane Database of systematic reviews/Central/ DARE/HTA

ID	Search	Hits
#1	MeSH descriptor: [Molar, Third] explode all trees	836
#2	((third or three) near/1 molar*)	1756
#3	(wisdom near/1 (tooth or teeth))	180
#4	(itm or itms)	69
#5	M3 and (tooth or teeth)	19
#6	MeSH descriptor: [Tooth, Impacted] explode all trees	506
#7	(impact* near/1 (tooth or teeth))	598
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7 Publication Year from 1999	1318
#9	age determin*	39875
#10	MeSH descriptor: [Age Determination by Teeth] explode all trees	5
#11	#9 or #10	39875
#12	#8 not #11	1206

N.B databases included Cochrane Database of systematic reviews (CDSR), Cochrane central register of controlled trials (Central), Database of abstracts of reviews of effects (DARE), Health Technology Assessments (HTA)

MEDLINE

:	Strategy used	Hits
1	Molar, Third/	5258
2	((third or three) adj1 molar*).tw.	6535
3	(wisdom adj1 (tooth or teeth)).tw.	937
4	Tooth, Impacted/	5989
5	(impact* adj1 (tooth or teeth)).tw.	1066
6	(itm or itms).tw.	491
7	1 or 2 or 3 or 4 or 5 or 6	12952
8	M3.tw.	17929
9	(tooth or teeth).tw.	114879
10	8 and 9	147
11	7 or 10	13039
12	limit 11 to yr="1999 -Current"	7043
13	animal/ not human/	4178280
14	12 not 13	6746
15	limit 14 to english language	6312
16	comment/ or editorial/ or letter/ or news/	1532370
17	15 not 16	6033
18	Age Determination by Teeth/	1410
19	"age determin*".tw.	898
20	18 or 19	2146
21	17 not 20	5895

EMBASE

	Searches	Results
1	Molar, Third/	24449
2	((third or three) adj1 molar*).tw.	7130
3	(wisdom adj1 (tooth or teeth)).tw.	1068
4	Tooth, Impacted/	16122
5	(impact* adj1 (tooth or teeth)).tw.	1162
6	(itm or itms).tw.	825
7	1 or 2 or 3 or 4 or 5 or 6	42489
8	M3.tw.	34492
9	(tooth or teeth).tw.	123929
10	8 and 9	231
11	7 or 10	42616
12	limit 11 to yr="1999 -Current"	20887
13	animal/ not human/	1297895
14	12 not 13	19854
15	limit 14 to english language	18383
16	comment/ or editorial/ or letter/ or news/	1398219
17	15 not 16	17982
18	Age Determination by Teeth/	5092
19	(age adj2 (determin* or estimat*)).tw.	15389
20	18 or 19	18641
21	17 not 20	17719
22	limit 21 to embase	6238

EconLit

	Strategy used	Hits
S10	(S6 NOT S9)	32
S9	(S7 OR S8)	6
S8	"age determin*"	6
S7	age determination on teeth	0
S6	S1 OR S2 OR S3 OR S4 OR S5	32
S5	M3 AND (teeth or tooth)	0
S4	(itm or itms)	32
S3	(impact* N1 (tooth or teeth))	0
S2	(wisdom N1 (tooth or teeth))	0
S1	((third or three) N1 molar*)	0

NHS EED

04/04/2016	3

Appendix 3 Excluded studies

Reasons for exclusion of clinical studies excluded at full-text review

Reason for exclusion	Number of studies
Wrong design	61
Non-systematic review	24
Non-English	8
Wrong setting	87
No relevant outcomes	20
Not mandibular third molar	24
Not impacted	13
Not pathology- or trouble-free	114
Total	**351**

Full bibliographic details of studies are available from the authors

Reasons for exclusion of clinical studies excluded at data abstraction

Study	Reason for exclusion
Ahmad et al 2008[10]	Not impacted
Al-Belasy et al 2009[115]	Not pathology-free or trouble-free
Allen et al 2009[116]	No data for impacted pathology-free/trouble-free
Anonymous 1999[117]	Reprint of an article based on Song 1997
Baykul et al 2005[118]	Not pathology-free or trouble-free
Blakey et al 2010[119] Blakey et al 2009[120] Blakey et al 2007[121] Blakey et al 2006[122] Blakey et al 2002[123] Blakey et al 2009a[124] Divaris et al 2012[125] Phillips et al 2007[126] Shugars et al 2005[127] Shugars et al 2004[128]	Not all impacted, not all mandibular third molars, no relevant outcomes reported byIM3Ms
Bloomer 2000[129]	Not pathology-free or trouble-free
Brann et al 1999[130]	Not pathology-free or trouble-free
Chaparro-Avendano et al 2005[131]	No results for impacted pathology-free or trouble-free
Cunha-Cruz et al 2014[132] Huang et al 2014[133]	Not all impacted pathology-free or trouble-free mandibular 3Ms
Dicus et al 2010[134]	Not results for impacted, mandibular pathology-free or trouble-free teeth
Faria et al 2012[135] Faria et al 2013[136]	No relevant outcomes
Figueiredo et al 2005[137]	Not pathology-free or trouble-free
Guven et al 2000[138]	No results for impacted pathology-free or trouble-free
Hanson et al 2004[139]	Not impacted
Juhl et al 2006[140]	Not pathology-free or trouble-free
Juhl et al 2008[141]	Not pathology-free or trouble-free

Study	Reason for exclusion
Kucukkolbasi et al 2014[142]	No relevant outcomes
Monaco et al 2009[143]	Not pathology-free or trouble-free
Montevecchi et al 2014[144]	Not pathology-free or trouble-free
Naghipur et al 2013[145]	Not pathology-free or trouble-free
Naghipur et al 2014[146]	Not pathology-free or trouble-free
Nunn et al 2013[12]	No results for impacted pathology-free or trouble-free mandibular 3Ms
Ozec et al 2009[147]	No results for impacted pathology-free or trouble-free
Pepper et al 2012[148]	Not pathology-free or trouble-free
Phillips et al 2003[95]	No relevant outcomes
Phillips et al 2012[149]	No relevant outcomes
Poeschl et al 2004[150]	94% Impacted but not pathology-free/trouble-free
Polat et al 2008[151]	Not pathology-free or trouble-free
Sarikov et al 2014[152]	Not pathology-free or trouble-free
Simsek-Kaya et al 2011[153]	Premolars
Venta et al 1999[154] Venta et al 2001[155] Venta et al 2000[156] Venta et al 2004[62]	No relevant outcomes reported by impacted mandibular 3Ms
Vondeling et al 1999[157]	Not impacted
Yildirim et al 2008[15]	No relevant outcomes

Bibliographic details and data summaries of five studies initially included in the economic evidence review and then subsequently excluded

Study	Country	3Ms or I3Ms	Study design/ purpose	Comparators	Reported measures	Cost/outcome source	Time horizon	Cost year
Inverso et al 2014[74]	USA	3Ms	Micro-costing analysis	S1: Extraction of 4 symptom-free, disease-free 3Ms S2: Active surveillance of 4 symptom-free, disease free 3Ms	S1: Average time and cost by visit type (consultation, operative and post-operative) for extraction of 4 × 3M S2: Cost of surveillance visit by an oral and maxillofacial surgeon every 2 years	Private health care	10, 20 and 30 years for S2	2013 estimates
Koumaras et al 2012[75]	USA	3Ms and I3Ms	Financial analysis of claims data	Operative *vs* non-operative management of asymptomatic disease-free 3Ms and I3Ms	S1: Retention of asymptomatic, disease-free M3s for 20 years S2: Removal of asymptomatic, disease-free I3Ms S3: Removal of previously asymptomatic, disease-free I3M that was monitored for 10 years	Insurance claims data	S1: 20 years S2: Not provided S3: 10 years	Services provided in the 2009 calendar year
Kunkel et al 2006l[77]	Germany	3Ms	Prospective cohort study of patients admitted to hospital for management of 3M-associated complications	A: Prophylactic 3M removal B: Non-elective 3M removal C: 3M present at time of admission	Infection parameters, treatment costs, length of hospital stay, days of disability, post-operative complications (A and B) were compared with complications based on pericoronitis	German NHS: Diagnostic Related Group rates for hospital treatment	Patients presenting over a 2-year period	2004/2005
Kunkel et al 2007[76]								NA
Leidholm et al 2005[78]	Sweden and Wales (UK)	3Ms	Comparison of patient preferences using the multi-attribute utility method	Patients referred (1997/8) for removal of one or both mandibular 3Ms	Home and social life General health and well-being Job and studies Health and comfort of mouth, teeth and gums Your appearance	Patient interviews	Interviews took place in clinic immediately after consultation	NA

NA=not applicable; 3M=third molar; I3M=impacted third molar; UK=United Kingdom

Appendix 4 Quality assessment

Quality assessment of systematic reviews

Study	Bouloux et al 2015[40]	Clinical evidence[52]	CADTH 2010[38]	Costa et al 2013[41]	Mettes et al 2012[42]	*SMM Rapport[46]	Song et al 2000[20]	Stordeur & Eyssen 2012[36]	Suska et al 2010[39]
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs (PICOS)?	Yes	Partially	Yes	Partially	Yes	Unclear	Yes	Yes	Yes
Was the search strategy adequate and appropriate? Were there any restrictions on language, publication status or publication date?	Partially	Partially	No	Yes	Yes	Partially	Yes	Partially	Partially
Were preventative steps taken to minimise bias and errors in the study selection process?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear
Were appropriate criteria used to assess the quality of the primary studies, and were preventative steps taken to minimise bias and errors in the quality assessment process?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Partially
Were preventative steps taken to minimise bias and errors in the data extraction process?	Yes	NS	NS	Yes	Yes	Unclear	Yes	Yes	Unclear
Were adequate details presented for each of the primary studies?	Yes	Yes	Partially	Partially	Yes	Yes	Yes	Yes	Yes
Were appropriate methods used for data synthesis? Were differences between studies assessed? Were the studies pooled, and if so was it appropriate and meaningful to do so?	Yes	Yes	No	No	NA	Unclear	No	No	No
Do the authors' conclusions accurately reflect the evidence that was reviewed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NS=not stated; NA=not applicable; * English summary only

Appendix 5 Data abstraction tables

Characteristics of the study comparing prophylactic removal *versus* standard care

Study	**Vares et al 2014[54]**
Aim	The aim of our investigation was to systematise a scheme of objective pre-operative clinical and roentgenological assessment of mandibular impacted symptom-free 'wisdom teeth' to create a rationale for their prophylactic removal
Conclusion	All the chosen criteria facilitate the formation of indications for a proper treatment tactic regarding asymptomatic impacted lower third molars without any considerable pathological changes. The low-to-no percentage of intra- and post-operative complications does not give any reason to leave a wisdom tooth with minor clinical manifestations or an asymptomatic wisdom tooth with bad prognosis in place, since early surgical procedures generate less number of complications, having shorter operative time and post-operative period
Design	Observational cohort
Setting	Department of Surgical Dentistry and Maxillofacial Surgery of Lviv Danylo Halytsky National Medical University, Ukraine
Recruitment period/Follow-up	2009-2013/ Annual follow-up, 5 years
Sponsorship/ Conflict of interests	NR/ NR
Power	NR
Description of IM3Ms, N	84 patients asymptomatic IM3Ms with no considerable pathological changes
Inclusion/exclusion criteria	NR
Demographics	NR
Baseline assessments (Assessment of requirement for removal)	General criteria: operator's experience, age, weight, sex of a patient, frequency of acute respiratory diseases, readiness of a patient to systematic observation, bad habits, and severity of gag reflex Clinical parameters: oral hygiene state, presence of an erupted opposite upper third molar, presence (in anamnesis) of pericoronitis, presence of plaque distally on a third molar, results of periodontal probe distally to a third molar Roentgenological parameters: degree of third molar follicle enlargement, root morphology, proximity to the mandibular canal, angulation, depth according to the occlusal line, position in relation to the anterior edge of mandibular ramus, evaluation of contact with the second molar, presence of bone and risk of its loss distally along the second molar
Results of assessment and description of groups	Group 1: Identified as requiring removal of IM3Ms and IM3Ms were removed=52 patients (subgroups by age 18-25 [n=41], 25-45 [n=10], 68-year old [n=1]) Group 2: Identified as requiring removal of IM3Ms but refused removal of IM3Ms=7 patients Group 3: Identified as not requiring removal of IM3Ms=25 patients
Details of surgery/Anaesthesia/Surgeon	The third molar removal was conducted using the surgical bur technique. In accordance with the severity of impaction, a proper incision and tooth sectioning were made following the strict conventional scheme and with a minimisation of the distal bone removal and the operative time

NR=not reported; IM3M=impacted mandibular third molar

Outcomes of prophylactic removal *versus* standard care study

Group	Outcomes	Results
Removal (n=52)	Surgical complications	NR "No considerable intra- or post-operative complications in the first subgroup (41 cases of patients 18-25 years old); minor complications in the second subgroup (10 cases of 25-45 year old patients). In the case of 68 year-old patient surgery, all complications were related to considerable bone atrophy of the operated area"
Retention though requiring removal (n=7)	Removed during follow-up because of the appearance of indications	5/7
Retention (n=25)	Removed during follow-up because of the appearance of indications	0/25

NR=not reported

Study characteristics of standard care studies

Study	Aim	Conclusion	Design	Setting	Recruitment period Follow-up	Sponsorship Conflict of interests	Power	Outcomes
Fernandes et al 2010[44]	The aim of this study was to create an actuarial life-table and related survival analysis that would shed light on the natural history of an impacted lower third molar To determine the potential of a pathology-free impacted lower third molar to cause symptoms within a year and whether these symptoms can be linked to clinical characteristics, lifestyle or socio-demographic status	The study indicates that older patients are less likely to develop the symptoms studied. In addition the authors believe that there is evidence to suggest that general dental practitioners might not be following current guidelines when deciding whether or not to extract an impacted lower third molar in the centres studied	Prospective cohort study	Multicentre, Scotland, UK (primary care setting)	1995-2002 12 months	The Wellcome Trust (061636/HS/SH/MW/sf). Professor Pitts acknowledges support from the Chief Scientist Office, which core funds the Dental Health Services Research Unit	NR	Presence of impacted lower tooth Caries in 3M Visibly detectable caries in the distal of adjacent tooth Pericoronitis Infection Pain
Hill et al 2006[43]	Find out what happened over a period of 5 years to fully or partially impacted M3Ms that were left alone	Examination of a number of factors including smoking, extent of eruption, depth of periodontal pocket, and history of pericoronitis failed to show any predictive factors that would	Single cohort	Unclear but likely single centre, Cardiff, UK	NR 5 years	Partly funded by a grant from the Leeds Oral Surgery Trust	Based on various assumptions about the incidence of pericoronitis, a minimum of 200 patients would be	Extraction rates Reasons for extraction Clinical factors: • visible plaque

Study	Aim	Conclusion	Design	Setting	Recruitment period Follow-up	Sponsorship Conflict of interests	Power	Outcomes
		indicate which teeth would subsequently require removal. However, about one-third of the teeth in this series had to be removed within the 5-year period. Although this does not allow a 'lifetime extrapolation', it blurs the edges of our current thinking about asymptomatic wisdom teeth and certainly suggests that further (possibly longer-term) studies need to be completed. It does, however, provide little support for the reintroduction of prophylactic removal of wisdom teeth					needed to complete the study	• depth of pocket distal to the 2M • bleeding on probing • intra-bony defect • evaluation of the position of the upper 3M • any evidence of resorption • radiographic measurement of the follicular space

2M=second molar; 3M=third molar; M3M=mandibular third molar; NR=not reported

Participant characteristics of standard care studies

Study	Description of I3MS N	Inclusion/exclusion criteria	Demographics	Baseline assessments
Fernandes et al 2010[44]	N=421 (69% of 613 assessed at baseline) Lower I3Ms examined=676	Inclusion: • Be a registered patient within the dental primary care system of one of the three regions involved • Aged 18 to 70 years • Have at least one lower I3M • Have had a panoramic radiograph taken between 1995 and 2002 • No current or past symptoms associated with impaction of 3Ms	Full sample Males: 40.78 Age: 18-34.9=400 35-49.9=149 50-70=64	Clinical characteristics (reported by sex and age group): • angulation • degree of impaction Other variables: • average age number of teeth • basic periodontal examination • gingival bleeding • presence of plaque • sex • age • postcode • education • employment • frequency of brushing • use of mouthwashes • tooth flossing • frequency of attending dental check-ups • time of last dental appointment • reason for last dental appointment • smoking • alcohol intake
Hill et al 2006[65]	Lower I3M and no criterion for its immediate removal 228 patients analysed/250 recruited 427 3Ms (19 fully erupted)	Inclusion: • Aged 16 to 30 years • At least one lower I3M and no criterion for its immediate removal Exclusion: • Patients with one or more of the NIH (and subsequently NICE) or Cardiff criteria • Those outside the declared age range • Those with fully erupted 3Ms	Males=34% Median age=23 years Age range 16-30 years	Clinical and radiographic examination. • Eruption state • Sericoronitis or history of pericoronitis • Smoking • History of swelling • Trismus • Orthodontic considerations such as crowding or cross bites • Presence and location of any caries The clinical examination was also used to record: • Visible plaque • Depth of pocket distal to the 2M

Study	Description of I3MS N	Inclusion/exclusion criteria	Demographics	Baseline assessments
	153 patients had no history of pericoronitis	• Patients who were unwilling to be followed up for 5 years or who moved away from the geographical area were withdrawn		• Bleeding on probing • Intra-bony defect • Evaluation of the position of the upper 3M • Any evidence of resorption • Radiographic measurement of the follicular space

2M=second molar; 3M=third molar; I3M=impacted third molar; NIH=National Institute of Health; NICE=National Institute for Health and Care Excellence

Outcomes of standard care studies

Study	Outcomes assessed		Measured by/timing/Analysis	Rate n (%) unless otherwise stated
Fernandes et al 2010[44]	Teeth extracted		Questioned and assessed by research dentist 1 year NA	37 (5.47%)
	Reasons for extraction	Pericoronitis		5 (13.5%)
		Pain		10 (27.0%)
		Caries in distal of adjacent molar		1 (2.7%)
		Caries in the 3M		2 (5.4%)
		Contralateral		2 (5.4%)
		Unknown		17 (46.0%)
	Survived asymptomatically			562/676 (83.1%)
	Symptoms developed by tooth	Pericoronitis (SIGN)		15 (13.2%)
		Severe pain (SIGN)		16 (14.0%)
		Mild pain (SIGN)		22 (19.3%)
		Discomfort/irritation (non-SIGN)		54 (47.4%)
		Food stagnation (non-SIGN)		7 (6.1%)
	Distribution of lower I3Ms according to survival and the development of symptoms in 1 year	Survived symptom-free		552 (81.7%)
		Survived with symptoms (SIGN)		31 (4.6%)
		Survived with symptoms (non-SIGN)		55 (8.1%)
		Extracted symptom-free		10 (1.5%)
		Extracted with symptoms (SIGN)		23 (3.4%)

Study	Outcomes assessed		Measured by/timing/Analysis	Rate n (%) unless otherwise stated	
		Extracted with symptoms (non-SIGN)		5 (0.7%)	
	Some form of symptoms	18-34.9 years of age	Questioned and assessed by research dentist 1 year Pearson chi square test	83 (22.6%)	p=0.0028
		35-49.9 years of age		28 (20.9%)	
		≥50 years of age		3 (5%)	
		Sex		NR	p>0.05
		Vertical angulation		34 (22.7%)	p≤0.001
		Mesial angulation		43 (13.15%)	
		Distal angulation		31 (30.7%)	
		Horizontal angulation		6 (6.5%)	
		Unerupted		10.49%	p≤0.001
		Partially erupted		23.05%	
		Average number of teeth	Questioned and assessed by research dentist 1 year NR	NR	p=>0.05
		Maximum BPE scores		NR	p=>0.05
		Average gingival bleeding index		NR	p=>0.05
		Average mean plaque		NR	p=>0.05
		Reason for last visit to the general dental practitioner	Questioned and assessed by research dentist 1 year t-test	NR	p=0.041
		Education after minimum school-leaving age		NR	p=0.191
		Employment status		NR	p=0.560
		Frequency of brushing teeth		NR	p=0.305
		Occasional use of mouthwashes		NR	p=0.116
		Occasional teeth flossing		NR	p=0.124
		Frequency of dental appointments		NR	p=0.133
		Length of time since patient last visited the dentist		NR	p=0.335
		Smoking		NR	p=0.291

Study	Outcomes assessed		Measured by/timing/Analysis	Rate n (%) unless otherwise stated	
		Drinking >14 units/week		NR	p=0.447
		Deprivation category		NR	p=0.058
	Symptoms as SIGN symptoms only (infection, severe pain and caries)	Vertical angulation	Questioned and assessed by research dentist 1 year Pearson chi square test	10.29%	p≤0.001
		Mesial angulation		5.48%	
		Distal angulation		24.69%	
		Horizontal angulation		3.34%	
		Unerupted		NR	p=0.004
		Partially erupted		NR	
Hill et al 2006[65]	Extraction rates (per patient)		Questionnaire/telephone (every 6 months) Clinical examination (or telephone) Every year NA	48/153 (no history of pericoronitis) 23/66 (history of pericoronitis)	
	Reasons for extraction				
	Pericoronitis after start of study			30/48(62.5%)	
	Cosmetic/orthodontic			6/48 (12.5%)	
	Food impacted/difficult to clean			4/48(8.3%)	
	Early caries in 2M			4/48(8.35)	
	Painful when eating			2/48(4.2%)	
	Earache/TMJ pain			2/48(4.2%)	
	Clinical factors		Clinical examination (or telephone) Every year NA		
	Visible plaque			NR	
	Depth of pocket distal to the second molar			NR	
	Bleeding on probing			NR	
	Intra-bony defect			NR	
	Evaluation of the position of the upper 3M			NR	
	Any evidence of resorption			0/NR	
	Radiographic measurement of the follicular space			NR	
	Remained symptomless			150/228	

2M=second molar; 3M=third molar; I3M=impacted third molar; NA=not applicable; NR=not reported; BPE=basic periodontal examination; TMJ=temporomandibular joint; SIGN=Scottish Intercollegiate Guidelines Network
*results for full sample but 91% were mandibular

Study and participant characteristics of the prophylactic removal study

Study	**Petsos et al 2016[55]**
Aim	To investigate the effect of M3M removal on periodontal health of adjacent 2Ms. PPD and PAL have been described for primary outcome. As cofactors involved, sex, complications, two suture materials and two types of impaction were chosen as secondary outcomes
Conclusion	Young patients may benefit from an early removal of M3M, especially in the presence of certain cofactors
Design	Prospective cohort study
Setting	Unclear on number of sites, Germany
Recruitment period/Follow-up	2nd June to 31th October 2014/ 6 months
Sponsorship/ Conflict of interests	Self-funded/no conflicts
Power	NR
Description of IM3Ms, N	78/91 recruited patients with a randomly selected 78/148 removed teeth selected for analysis Submucosal=58, fully impacted=20
Inclusion/exclusion criteria	Inclusion: Completely impacted (entirely within the bone) or submucosal (completely below the mucous membrane), had a close positional relationship with the adjacent 2M (teeth 47 or 37, respectively), and no contact with the oral cavity. Completed root growth of the adjacent 2M was a prerequisite Exclusion: Presence of systemic disease (e.g. diabetes mellitus, cardiovascular, kidney, liver or lung disease), withdrawal of written consent, or failure to appear at the follow-up appointment
Demographics	37% male Mean age=16.0±2.0 years Non-smokers=74
Baseline assessments	PII=NR GI=NR PPD (measured from the gingival margin to the base of the pocket) mean=2.97±0.47 (range 2.0-4.2) PAL (measured from cemento-enamel junction to the base of the pocket) mean=2.47±0.44 (range 1.5-3.3) (Measurements were obtained at six sites around the 2M: mesiobuccal, buccal, distobuccal, distolingual, lingual, mesiolingual)
Details of surgery/Anaesthesia/Surgeon/other interventions	A mucoperiostal flap was reflected on the basis of a marginal incision on the 2M with a distovestibular releasing incision. A bone raspatorium was introduced on the lingual side to protect the lingual nerve. The wisdom tooth was horizontally dissected with rotary instruments using continuous sterile saline irrigation, and removed. The wound was closed with either pseudo-

Study	Petsos et al 2016[55]
	monofilament silk or monofilament sutures after previous randomisation by numbers to assess a possible effect of the suture material on the post-operative soft-tissue healing and the periodontal conditions Local or general anaesthesia Oral surgeon All patients received oral hygiene instruction and were prescribed clindamycin 300 mg every 8 h for 5 days, ibuprofen 400 mg every 8 hours for 3 days, dexamethasone 4 mg every 8 h for 3 days (tapering off on the 4th day) and a rinsing solution (chlorhexidine digluconate 0.1%) twice daily for 10 days

M3M=mandibular third molar; 2M=second molar; PII=plaque index; GI=gingiva index; PPD=probing pocket depth; PAL=probing attachment level; NR=not reported

Outcomes for the prophylactic removal study

Outcomes assessed by Pestos et al 2016[55]		Rate	p
PII	Baseline	NR	>0.5
	6 Months	NR	
GI	Baseline	NR	>0.05
	6 Months	NR	
Mean±SD (range) PPD (mm) of 3 sites*	Baseline	3.25±0.65 (2-5.7)	<0.05
	6 Months	2.57±0.5 (1.3-3.7)	
Mean±SD (range) PAL (mm) of 3 sites*	Baseline	2.96±0.53 (2.0-5.0)	<0.05
	6 Months	2.55 ±0.5 (1.3-3.7)	
Any complication		20/78	
Intense pain for >1 day		12/78	
Post-operative infection (infiltrate or abscess)		5/78	
Wound dehiscence		3/78	
Secondary bleeding		0/78	
Nerve damage		0/78	

PII=plaque index; GI=gingiva index; PPD=probing pocket depth; PAL=probing attachment level; NR=not reported
*3 sites located closest to the distovestibular incision (buccal, distobuccal, distolingual)

Systematic reviews

Systematic review characteristics

Study	Publication type Date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
Bouloux et al 2015[40] AAOMS M3Taskforce	SR NR	To determine clinically whether young adults who elect to retain their asymptomatic 3Ms have a risk of undergoing one or more 3M extractions in the future	English language publication Prospective study design More than 50 patients Recorded the number of patients or 3Ms requiring extraction during study period Follow-up duration of ≥1 year Aged ≥18 years old ≥1 3M present at enrolment Only asymptomatic 3Ms at enrolment Assumption that the teeth had been retained because they were asymptomatic and disease-free M3s	Number of 3Ms removed during follow-up period or Number of patients who required one or more 3Ms removed during that period	• Pt age • Number of 3Ms or patients present at the baseline examination • Predictor variable=follow-up duration, recorded in years
CADTH 2010[38]	Rapid review July 9, 2010	1. What is the evidence for the clinical benefit of prophylactic removal of asymptomatic wisdom teeth compared with retention of asymptomatic wisdom teeth? 2. What are the evidence-based guidelines for the prophylactic removal of asymptomatic wisdom teeth? N.B. this rapid review did not restrict to impacted teeth	English language Publication date 2000-2010 Study design: HTAs SRs RCTs Non-RCTs Comparing clinical outcomes between one group underwent prophylactic surgery for 3M removal, while the other group retained their asymptomatic teeth	Clinical outcomes summarised narratively	Each study was summarised narratively

Study	Publication type Date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
Clinical evidence[37,47-52]	SR (updated yearly) 1966-2014	Should asymptomatic and disease-free impacted wisdom teeth be removed prophylactically?	Study design: Published SRs of RCTs RCTs Prospective cohort studies with a control group Any language More than 20 patients	Dental disease Complications or adverse effects of extraction	NR
Costa et al 2013[41]	SR Up to 30 August 2012	To investigate whether there is evidence justifying the prophylactic extraction of 3Ms	RCT, SR and meta-analyses All languages The effect of prophylactic 3M extraction The non-intervention (maintenance) of asymptomatic I3Ms	Quality evaluation of studies Adequate sample size Adequate description of selection process Valid measurement methods Use of method of error analysis Blinded measurement evaluation Valid statistical methods Confounding factors included in analysis	NR
Mettes et al 2012[42]	SR 1950-30 March 2012	To evaluate the effect of prophylactic removal of asymptomatic impacted wisdom teeth in adolescents and adults compared with the retention (conservative management) of these wisdom teeth	Study design: RCT Random allocation Compare the effect of prophylactic removal of asymptomatic impacted wisdom teeth with retention Data on at least one of the selected clinical outcomes as a part of the primary outcome measure	Primary outcome: Health-related quality of life measures associated with retention or removal Pathological changes associated with retention Pericoronitis (inflammation of the gum around the crown of a tooth) Caries (tooth decay) Cysts Tumours Root resorption	• Year of the publication • Date and duration of the study • Age of the participants • Sample size • Numbers of participants randomised to each group

Study	Publication type Date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
				Dimensional changes in the dental arch (crowding) Symptoms associated with removal of wisdom teeth Pain/swelling/trismus Alveolar osteitis Nerve damage Costs Costs associated with treating symptoms associated with retention Direct costs associated with the removal of wisdom teeth and treating any associated symptoms Days off work or study	
SMM Rapport 2003[46]	SR (English summary only) 1999-2003	To assess the scientific evidence on prophylactic removal of impacted wisdom teeth, in terms of the incidence of surgical complications associated with prophylactic removal, the morbidity associated with retention, quality of life and economic aspects	NR in English summary	Complications related to prophylactic removal Complications related to retention	• Author • Year of publication • Country • Aims • Study design • Intervention • Population • Age • Observation time • Quality
Song et al 2000[20]	Clinical guidance/SR 1984-1999	To provide a summary of existing evidence on prophylactic removal of impacted wisdom teeth, in terms of the incidence of surgical complications associated with prophylactic removal, and the morbidity associated with retention	Study design: • RCT • Literature review • Decision analyses Population • Unerupted or impacted 3Ms, or undergoing surgical removal of 3Ms either as prophylaxis or due to	Narrative description of included studies:	RCTs • Study aims • Method of randomisation • Use of *a priori* power calculation • Selection criteria for participants • Baseline characteristics of groups • Intervention details

Study	Publication type Date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
			associated pathological changes Outcomes • Pathological changes associated with retention of 3Ms or post-operative complications following extraction		• Numbers allocated to each group • Setting of treatment • Outcome measurements • Statistical methods • Results per group for each outcome • Follow-up • Withdrawals • Authors' main conclusions Literature reviews: • Review aims • Total number of references • Authors' main conclusions
Stordeur & Eyssen 2012[36]	Rapid assessment No restriction to December 2010/March 2011	• To present the existing scientific evidence on the prophylactic extraction of 3Ms in the absence of local disease, and to formulate clinically relevant recommendations • What are the benefits and risks (complications) of prophylactic extraction of pathology-free wisdom teeth (3Ms) in adolescents and adults in the absence of local disease? • What is the related good clinical practice for the prophylactic removal of pathology-free wisdom teeth?	English, French, German and Dutch languages Study design: • SRs with or without meta-analyses • RCT • Non-randomised clinical trials (• HTA • CPGs Comparing the effect of prophylactic removal of pathology-free wisdom teeth with no-treatment Existing guidelines of high quality	NR	SRs and HTAs: • Search date • Publication year • Searched databases • Availability of evidence tables • Included studies • Main results CPGs: • Search date • Publication year • Searched databases • Availability of evidence tables • Recommendations and referenced evidence. • The recommendations from the identified SRs

Study	Publication type Date of search	Objective	Inclusion criteria	Outcomes reported	Other study variables
					• Quality appraisal using checklists of the Dutch Cochrane Centre and Appraisal of Guidelines • Research and Evaluation in Europe for clinical guidelines and GRADE
Suska et al 2010[39]	May 2003 up to December 2009 Based on the Norwegian HTA so searches only conducted after 2003	Does removal of 3M teeth reduce the risk of infections and other local disease/pathological conditions in patients with asymptomatic or symptomatic I3Ms compared with no intervention?	Healthy individuals of all ages with totally or partially impacted wisdom teeth without symptoms, or healthy individuals of all ages with totally or partially impacted wisdom teeth with any kind of symptom or condition Extraction of 3M tooth, or no extraction or any other treatment of 3M tooth English, Danish, Norwegian and Swedish language only ≥300 patients	Primary: • Infection Secondary: • Root resorption • Crowding • Caries on adjacent tooth • Loss of adjacent tooth • Complications related to the surgical procedure	• Author • Year of publication • Country • Aims • Study design • Intervention • Population • Age • Observation time • Quality

3M=third molar; I3M=impacted third molars; AAOMS=American Association of Oral and Maxillofacial Surgeons; CADTH=Canadian Agency for Drugs and Technologies in Health; HTA=health technology assessment; SR=systematic review; RCT=randomised controlled trial; CPG=clinical practice guidelines

Systematic review results

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Bouloux et al 2015[40] AAOMS M3Taskforce	Cohort studies=7 von Wowern et al 1989[158] Garcia &Chauncey 1989[159] Venta et al 2000[156] Kruger et al 2001[59] Venta et al 2004[62] Hill & Walker 2006[43] Fernandes et al 2010[44]	Mandibular only=3 Both maxillary and mandibular=4 Range of sample sizes=70-821 Range of mean ages=18-47 years Range of % male=31-100 Range of follow-up=1-18 years	Seven studies met the inclusion criteria. The samples sizes ranged from 70 to 821 patients, and the follow-up period ranged from 1 to 18 years. The mean incidence rate for 3M extraction of previously asymptomatic 3Ms was 3.0% annually (range 1-9%). The cumulative incidence rate for 3M removal ranged from 5% at 1 year to 64% at 18 years. The reasons for extraction were caries, periodontal disease, and other inflammatory conditions	The cumulative risk of 3M extraction for young adults with asymptomatic 3Ms is sufficiently high to warrant its consideration when reviewing the risks and benefits of 3M retention as a management strategy
CADTH 2010[38]	SRs=4 Song et al 2000[20] Norwegian Knowledge Centre for the Health Services 2003[46] Mettes 2005[45] Dodson & Susarla 2010[37] Non-RCTs=1 Kunkel et al 2007[76] Guidelines=2 NICE 2000[2] Agency for Quality in Dentistry 2006[68]	NR	Overall, seven relevant articles were identified from the electronic search of databases and grey literature. This included four SRs, one non-randomised study, and CPG. No relevant HTA reports or RCTs were identified	Based on evidence and guidelines from the past 10 years of evidence identified for inclusion in this review, there is currently insufficient evidence supporting or refuting the practice of prophylactic removal of asymptomatic 3Ms. 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

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Clinical evidence[37,47-52]	Extraction of asymptomatic impacted wisdom teeth: SR=5 Song et al 1997[61] Song et al 2000[20] Norwegian Knowledge Centre for the Health Services 2003[46] Mettes 2005[45] Costa et al 2013[41] Between them 1 RCT was identified Harradine et al 1998[58] An RCT on incisor crowding was excluded in latest update Lindqvist & Thilander 1982[60] Active surveillance of asymptomatic impacted wisdom teeth: No studies	Extraction: Mandibular only=1 RCT Range of sample sizes=164 Age range=14-18 years Follow-up=66 months	We found five SRs evaluating the extraction of impacted wisdom teeth which between them identified one RCT that met Clinical Evidence inclusion criteria	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
Costa et al 2013[41]	SR=1 Mettes et al 2005[45] RCT=3 Van der Sanden et al 2005[160] Harradine et al 1998[58] Lindqvist & Thilander 1982[60]	Mandibular only=3 Not specified=1 Range of sample sizes=36 (simulated patient cases) -164 Range of mean ages=NR for simulated patients,	Four papers qualified for the final analysis. A medium degree of quality and methodological consistency was found in three studies, and low quality was found in one study. No studies showed a high degree of consistency. The most significant flaw was an inadequate sample size	The results of the present review indicate a lack of scientific evidence to justify the indication of the prophylactic extraction of third molars

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
		Mean age 14 years 10mths and 13-19 years 13-60 Range of % male=44-45 (NR for simulated cases) Follow-up=36-66 months		
Mettes et al 2012[42]	RCT=1 Harradine et al 1998[58] NB. The original version review had found two RCTs (Harradine et al 1998,[58] Lindqvist & Thilander 1982[60]) and one ongoing study (van de Waal 1999[161])	Maxillary only Sample size=164 Completed trial=77 Mean length of follow-up=66 months +/-12.6 months Mean age=14 years and 10 months % male=45	No RCTs were identified that compared the removal of asymptomatic wisdom teeth with retention and reported quality of life. One RCT on adolescents was identified that compared the removal of impacted mandibular wisdom teeth with retention and only examined the effect on late lower incisor crowding. This study at high risk of bias provided no evidence that extraction of wisdom teeth had an effect on lower incisor crowding over 5 years The included Lindqvist & Thilander study[60] in the original published version was excluded in the updated review, because we think that a split-mouth study is not an appropriate design to assess crowding. The ongoing van de Waal study[161] in the original published version of this review could not be further assessed and therefore is not listed in this review. The trial stopped early and despite several attempts to contact the investigators no details of the study design or outcome data were available	Insufficient evidence was found to support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults. A single trial comparing removal *vs* retention found no evidence of a difference on late lower incisor crowding at 5 years, however no other relevant outcomes were measured Watchful monitoring of asymptomatic 3M teeth may be a more prudent strategy
SMM Rapport 2003[46]	Patient series=13 (11 reported in summary) Berge 2002[162] Blakey et al 2002[123]		Studies on complications related to prophylactic removal report relatively high prevalence of deep residual periodontal defects at the distal surface of the mandibular 2M after the surgical extraction of the adjacent impacted 3M.	This report is based on evidence from studies that use small selected patient groups, and therefore it is difficult to conclude and give recommendations. Norwegian dentists recommend prophylactic removal of 3Ms when the likelihood of 3Ms

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
	Conrad et al 1999[86] Gülicher & Gerlach 2001[163] Hill et al 2001[164] Rakprasitkul 2001[165] Renton & McGurk 2001[166] Tay 2000[167] Valmaseda-Castellón et al 2000[168] Valmaseda-Castellón 2001[108] White et al 2002[169] Yamaoka et al 1999[170] Yoshii et al 2001[171] Cohort studies=3 (5 reported in summary) Kruger et al 2001[59] Ventä et al 1999[154] Ventä et al 2001[155] Case-controlled studies=2 Güngörmüs 2002[172] Shafer et al 1999[173] Cross-sectional studies=6 Güven et al 2000[138] Kan et al 2002[174] Libersa et al 2002[175] Ma'aita & Alwrikat 2000[176] Perry & Goldberg 2000[177] Punwutikorn et al 1999[178] Decision analysis=1 Edwards et al 1999[57]		However, there was found low incidences of pain, permanent nerve damage (more than 6 months) on inferior alveolar and lingual nerve, fractures or serious infection Studies on complications related to retention report a relatively high incidence of pericoronitis and caries, with higher incidence of pericoronitis related to partially erupted third molars compared to fully retained. Only low incidence of root resorption of 2M teeth, cysts and tumours was found	causing problems in the future is high and the incidence of post-operative complications are low. This includes partially erupted wisdom teeth. Removal of asymptomatic fully retained wisdom teeth is not recommended. Since this report is based on studies that are not optimal the patient's preferences need to be decisive

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
Song et al 2000[20]	RCT=2 Harradine et al 1998[58] Vondeling et al 1999[157] Decision analysis studies=4 Brickley et al 1995[179] Edwards et al 1999[57] Tulloch et al 1987[180] Tulloch et al 1990[181] Literature reviews=34 Toth 1993[182] Stephens et al 1989[183] Mercier et al 1992[184] Daley 1996[185] Vasir & Robinson 1991[186] Anderson 1998[187] Bertrand 1989[188] Bishara 1999[189] Bonetti et al 1988[190] Bramante 1990[191] Brokaw 1991[192] Cade 1992[193] Chikhani et al 1994[194] Denes et al 1993[195] ECRI 1993[196] Flick 1999[197] Forssel &Miettinen 1988[198] Garattini et al 1990[199] Goia et al 1990[200] Pajarola 1994[201] Kugelberg 1992[202]	Only available for Harradine 1998[58] Sample size=164 Completed trial=77 Follow-up=66 months Mean age=14 years and 10 months	One RCT in the UK focused on the effects of retained 3Ms on incisor crowding (predominantly a cosmetic problem) in patients who had previously undergone orthodontic treatment. The results of this trial suggested that the removal of 3Ms to prevent late incisor crowding cannot be justified. Another on-going RCT in Denmark compares the effects and costs of prophylactic removal of 3Ms with removal according to morbidity. So far, this trial has recruited 200 participants, and preliminary results indicate that watchful waiting may be a promising strategy. However, more data and longer follow-up of patients are needed to conclude which treatment strategy is the most cost effective. It is also known that a trial is ongoing in the USA but no results are available so far The methodological quality of the literature reviews was generally poor, and none of the reviews was systematic. Conclusions from nine reviews on anterior crowding suggested that there was only a weak association between retention of 3Ms and crowding. Six out of 21 reviews with a more general scope also concluded that the prophylactic removal of 3Ms was unjustified. 12 general reviews did not conclude with a clear message about the management of 3Ms. Three reviews suggested that prophylactic removal of 3Ms is appropriate, but these reviews were of poorer methodological quality than the majority of other reviews. Three out of four papers focusing on surgical management expressed uncertain conclusions relating to the prophylactic extraction of 3Ms. It is difficult to compare prophylactic removal of I3Ms with retention in the absence of disease, partly because these two strategies are related to different types of	There is no reliable research evidence to support the prophylactic removal of disease-free I3Ms. Available evidence suggests that retention may be more effective and cost effective than prophylactic removal, at least in the short to medium term

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
	Lechien 1995[203] Mommaerts & Jacobs 1991[204] Peterson 1992[205] Robinson & Vasir 1993[206] Robinson 1994[207] Sands et al 1993[208,209] Southard 1992[210] Tate 1994[211] Tealdi & Domini 1986[212] Torres 1997[213] van der Linden et al 1993[214] Waite & Reynolds 1998[215] Weisenfeld & Kondis 1991[216]		outcomes. By using utility methods, four decision analyses made it possible to compare different outcomes directly in the coherent models. Although there were important differences in the structure and methods for estimating input values, the findings of the decision analyses (by two groups of researchers) consistently suggested that retention of 3Ms was cost saving and more cost effective compared with prophylactic removal of I3Ms	
Stordeur & Eyssen 2012[36]	SRs=2 Mettes et al 2005[45] Song et al 2000[20] HTAs=2 CADTH 2010[38] Suska 2010[39] CPG=1 NICE 2000[2]	NA	Evidence of good quality in this domain is sparse. The methodological quality of the primary studies is low to very low. The three randomised controlled trials that could be included are more than 10 years old, but a search for primary (randomised or not) controlled clinical trials of more recent date yielded no results. Most of the included studies explicitly focus on impacted wisdom teeth only The message emerging from this evidence is that prophylactic removal of pathology-free impacted wisdom teeth for orthodontic reasons in adolescents neither reduces nor prevents late problems of front teeth misalignment. The single RCT dealing with the management of non-orthodontic indications concludes that watchful waiting might be the more beneficial approach. The SR dealing with non-orthodontic indications concludes that existing reviews	There is mostly little debate on the fact that 3Ms associated with clinical and/or radiological pathology, such as unrestorable caries, should be removed. However, there is a lack of proven benefit from the systematic prophylactic removal of pathology-free 3Ms, impacted or not, in all adolescents or (young) adults, and the procedure is not free of risk. Preventive actions at the level of the population are only recommended if the benefits outweigh the disadvantages, and if this is not the case it is preferable not to intervene. If there is no scientific evidence that an intervention is beneficial, the largely accepted principle of medicine: "*primum non nocere*", "first, do no harm", should be respected

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
			favouring prophylactic removal, are generally of poorer methodological quality than those concluding that prophylactic removal is unjustified. Two HTA reports conclude that there is still no scientific documentation available to either support or reject routine prophylactic removal of pathology-free wisdom teeth Decision analysis models compare prophylactic with symptomatic extraction for I3Ms, including frequencies and ratings of severity of complications in both cases. They consistently suggest that patients' well-being is maximised if surgical removal is confined to wisdom teeth with pathological changes. Several of the included publications stress the importance of clear communication with patients about expected benefits and potential side effects and complications of the prophylactic removal of pathology-free 3Ms	
Suska et al 2010[39]	HTA-report/SRs=2 Mettes et al 2005[45] Norwegian Knowledge centre 2003[46] Case series=16 (None reported on asymptomatic teeth)	NR	The literature search did not find any randomised or non-randomised, adequately controlled trial in which prophylactic removal of 3M teeth has been compared with no intervention Both the SRs were of adequate quality according to the AMSTAR criteria. The Norwegian HTA-report stated "removal of asymptomatic fully retained wisdom teeth is not recommended", whereas the Cochrane review concluded that "no evidence was found to support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults" The level of evidence of prophylactic removal of asymptomatic 3M teeth as well as for removal of symptomatic 3M teeth is very low according to the GRADE system	Prophylactic removal of 3M teeth to prevent possible future complications is still frequently performed in Sweden. This intervention has been seriously questioned due to lack of supporting data of beneficial effects and the documented complications A systematic literature search and review of published data has revealed that there is still no scientific documentation available to either support or refute routine prophylactic removal of asymptomatic impacted wisdom teeth in adults

Study	Number/type of studies included	Summary of population characteristics	Summary of results	Author conclusions
			None of the case series reported the distribution of asymptomatic and symptomatic patients or the outcome of the extraction according to the presence or absence of symptoms at the time of the procedure	

2M=second molar; 3M=third molar; I3M=impacted third molar; AAOMS=American Association of Oral and Maxillofacial Surgeons; CADTH=Canadian Agency for Drugs and Technologies in Health; HTA=health technology assessment; SR=systematic review; RCT=randomised controlled trial; CPG=clinical practice guidelines; NR=not reported

Appendix 6 Additional excluded studies

As mentioned earlier, many of the references included in previously published SRs and the submissions from the BDA and the FDS, FGDP, and BAOS were excluded from this review. However, due to the paucity of information available, the AG feels it would be pertinent to discuss and summarise the results from some of these studies. The studies we have summarised here are studies that nearly met our inclusion criteria but did not specifically report results for the specific population of interest to this review (i.e. trouble-free IM3Ms).

References from included systematic reviews

Of the 84 references reported in the included SRs, only nine[2,20,37,39,41,43-46] met the inclusion criteria for this review, meaning that 75 references, previously included in SRs, were excluded. For 41 of these references[58,60,61,158,159,179-188,190-196,198-216] the date of publication was prior to 1999 and the studies were therefore published prior to the date limits of this SR. The remaining 34 references and the reasons for exclusion are shown in Table . Nine of these references did not met our specific inclusion criteria but warrant further discussion as papers often cited in the debate. The details of the study aims, the results and conclusions are summarised narratively below and in Table .

Blakey et al 2002[123] is one in a series of publications that report on a longitudinal clinical trial including patients between 14 and 45 years of age, who had four asymptomatic 3Ms with adjacent 2Ms. The Blakey et al 2002[123] paper assessed the periodontal probing depth (PD) of these molars at enrolment and found that 64 of the 329 patients had PD ≥5mm on any 3M, 35 of which were only on the M3M. However, two-thirds of all 3Ms in patients studied were erupted to the occlusal plane (i.e not impacted or partially erupted/unerupted). Moreover, these fully erupted teeth were found to be just as likely as teeth below the occlusal plane to exhibit a change in probing depth. The White et al 2002[169] paper is also part of this series of papers, and reports on the detection and levels of pathogenic bacteria in subgingival plaque of the same patients. The authors reported results in relation to position and angulation. However, the results section did not include outcomes separately for mandibular and maxillary 3Ms.

The papers by Venta et al[62,154-156] are based on a longitudinal study that followed 181 first-year students at the University of Helsinki. Participant's teeth were clinically examined and panoramic radiographs were taken at baseline and 18 years later at the end of the study (n=118). Some students were also examined at 6 years and 12 years (n=81). Not all teeth were impacted and both mandibular and maxillary 3Ms were included. Not all were pathology-free or trouble-free, though two of the published papers do report the results of a questionnaire

in which students were asked about symptoms. The authors of the studies conclude that 3Ms "undergo continuous clinical change on a reduced scale at least up to the age of 38 years" and that "considerable radiographic changes, without notable symptoms, may occur involving inclination of the tooth and state of impaction in impacted third molars after the usual age of eruption". One paper[156] reporting the results of the need for removal, reported that 33/54 3Ms removed were asymptomatic and concluded that "Because need for surgical removal decreases during early adulthood, routine prophylactic extraction of asymptomatic third molars in young adults cannot be recommended. Well-defined indications for prophylactic removals are needed". (page 288)

The study by Edwards et al[57] is a decision analysis that was identified by two SRs.[20,46] The study aimed to identify the "least costly, most effective and most cost-effective management strategy for asymptomatic, disease free mandibular third molars". Though the authors did conduct a review to identify information to populate the model, no details on the results of the clinical review are reported. The study did not restrict analyses to I3Ms. Further details on the cost-effectiveness elements of the study are discussed in further details in the cost-effectiveness section of this report (Section 4).

It was not possible to access any published data on either the Van de Waal et al[161] or Vondeling et al[157] papers. However, both reported on discontinued trials, according to the SRs citing them. The Van de Waal[161] citation was a reference to an ongoing trial and was identified by the original Cochrane review by Mettes et al 2005[45], but Van de Waal is also listed as an author of the Vondeling et al abstract.[157] As both have similar titles it is possible that the citations are for the same study, which has been discontinued, and so no results have been published. From the details reported in the citing SRs[45,207] neither of the studies were restricted to I3Ms.

Table 27 Studies included in previous systematic reviews and reasons for exclusion from this review

Study id	Design and reason for exclusion
Agency for Quality in Dentistry (ZZQ) 2006[68]	Guidelines German summary. Does not seem to be based on SR 'Impaction' refers to a tooth that has remained fully embedded in the bone; 'retention' denotes a position of a 3M in which the occlusal plane is not reached on completion of root growth; 'malposed' is if axis or position deviates No mention of mandibular or not
Berge 2002[162]	Retrospective single cohort IM3Ms no mention of prophylactic removal Outcome is pain
Bishara 1999[189]	Literature review Some of the pertinent studies related to the management of 3Ms in an orthodontic context

Study id	Design and reason for exclusion
Blakey et al 2002[123]	Longitudinal single cohort Not all impacted Not all M3Ms
Conrad et al 1999[86]	Prospective patient series No details of impaction All 3Ms were removed in 175 of 201 patients, and at least both lower 3Ms were removed in 182 of 201 patients Teeth were symptomatic
Edwards et al 1999[57]	Decision analysis Impaction status not mentioned
Flick 1999[197]	Literature review
Gulicher & Gerlach 2001[163]	Prospective cohort Indications for surgery were (1) pathological findings as caries, cysts, pericoronitis or abscess formation; (2) facilitation of orthodontic therapy, and (3) prevention No data for prevention group
Gungormus 2002[172]	Retrospective case–control study Evaluate the changes in M3M position and pathological status associated with 3Ms after extraction of four first premolars
Guven et al 2000[138]	Retrospective cross-sectional study 3:1 Mandibular:maxillary 3621/7582 teeth removed prophylactically but outcomes assess how many had pathology
Hill et al 2001[164]	Prospective patient series Comparing general and local anaesthesia for unilateral or bilateral removal of IM3Ms
Kan et al 2002[174]	Retrospective cross-sectional study Not asymptomatic Pathology of 2Ms after removal of 3Ms
Kruger et al 2001[59]	Prospective single cohort Change in eruption status from 18 to 26 years No data on asymptomatic or symptomatic wisdom teeth
Kunkel et al 2007[76]	Prospective cohort study, patients admitted for management of acute M3-associated complications Clinical status of the 3M was defined as (1) prophylactic 3M removal, (2) therapeutic (non-elective) 3M removal, or (3) 3M present at the time of admission No mention of impaction or whether mandibular
Libersa et al 2002[175]	Retrospective cross-sectional study Patients with immediate or late fracture after removal of IM3Ms No details on whether they are removed prophylactically
Ma'aita et al 2000[176]	Retrospective cross-sectional study 86% were impacted Outcome is risk of fracture with/without a 3M No mention on whether it was prophylactic removal
Perry et al 2000[177]	Retrospective cross-sectional study Patients with late fracture were selected All grades of impaction included 18 of the 28 fracture patients had a history of infection before the extractions
Punwutikorn et al 1999[178]	Retrospective cross-sectional study Unerupted though eruption status and angle are reported 62% asymptomatic Thailand

Study id	Design and reason for exclusion
Rakprasitkul 2001[165]	Patient series Unerupted no mention of impaction 65.38% M3Ms Removed for any indication apart from infection and enlarged tissues Measured pathological changes in pericoronal tissues
Renton et al 2001[166]	Prospective patient series 90% impacted 87% had therapeutic indications for operation
Shafer et al 1999[173]	Prospective case–control study All four 3Ms were removed Outcome taste change
Tay 2000[167]	Retrospective patient series Both mandibular and maxillary 56.2% were removed prophylactically Singapore
Valmaseda-Castellón et al 2000[168] Valmaseda-Castellon et al 2001[108]	Prospective patient series 5% erupted no details on impaction? Angulation? 36% vertical No mention of prophylactic removal or retention
van de Waal 1999[161]	No results Excluded in Mettes[42] update
van der Sanden et al 2005[160]	Decision-making tool
Venta et al 1999[154]	Not all impacted or mandibular or pathology-free or trouble-free No relevant outcomes reported
Venta et al 2000[156]	Not all impacted and mandibular No relevant outcomes reported However, details on symptoms are reported
Venta et al 2001[155]	All impacted and many results reported for mandibular subgroup 74% of the whole group were asymptomatic No relevant outcomes
Venta et al 2004[62]	Not all impacted and mandibular or pathology-free or trouble-free No relevant outcomes reported
Vondeling et al 1999[157]	Not all impacted Cannot get hold of paper Originally included in Song[20]
White et al 2002[169]	Longitudinal single-cohort study Not all impacted Not all M3Ms
Yamaoka et al 1999[170]	Retrospective patient series Not all impacted Both 2Ms and 3Ms removed No mention of prophylactic removal or retention
Yoshii et al 2001[171]	Retrospective patient series Data available for impacted subgroup Not prophylactic removal

SR=systematic review; 3M=third molar;IM3M=impacted mandibular third molar; M3M=mandibular third molar

Table 28 Studies included in identified systematic reviews but excluded by the Assessment Group

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
Blakey et al 2002[123]	Not all impacted, not all M3Ms	We report the prevalence of PD as a clinical measure of the extent of periodontitis associated with asymptomatic 3Ms at the initial examination in a cohort of patients enrolled in an institutional review board-approved longitudinal clinical trial	Our data indicating that 25% of patients with retained asymptomatic 3Ms have considerable periodontal pathology in the 3M region were unexpected National epidemiological surveys indicate a much lower rate of periodontitis in the population younger than 35 years	Total of 329 healthy patients were enrolled during a 30-month period. Full mouth periodontal probing that included 3Ms was conducted to determine periodontal status. Panoramic radiographs were taken to assess the degree of eruption of the 3Ms and the angulation of 3Ms compared with the adjacent 2M. Vertical bitewing radiographs were analysed to detect alveolar bone levels relative to the cementoenamel junction on the distal 2Ms Results: 25% (82 of 329) of all enrolled patients, and 34% (14 of 41) of black patients, had at least one PD ≥5 mm on the distal 2M or around a 3M. PD ≥5 mm was associated with periodontal attachment loss of at least 1 mm in every patient; PD ≥5 mm was associated with attachment loss ≥2 mm in 80 of 82 patients. A higher proportion of patients 25 years old or older had a PD ≥5 mm on the distal 2Ms or around 3Ms compared with patients younger than 25 years (33% *vs* 17%; p<0.002). The distals of 2Ms and 3Ms in the mandible were affected more often than in the maxilla (25% *vs* 5%; p<0.0001)
White et al 2002[169]	Not all impacted, not all M3Ms	Our goal was to report the detection and levels of pathogenic bacteria in subgingival plaque samples taken from the distal of all 2Ms in 295 patients with asymptomatic 3Ms	The clinical findings of increased PDs and PAL coupled with colonisation of periodontal pathogens support the concept that clinical and microbial changes associated with the initiation of periodontitis may present first in the 3M region in young adults	Subgingival plaque samples were taken from the distal of all 2Ms before periodontal probing. The presence and levels of 11 bacterial species were determined using whole chromosomal DNA probes and checkerboard DNA-DNA hybridisation. Detected bacterial species were grouped into clusters of periodontal pathogens designated as 'red' or 'orange' complex microorganisms Results: As a group these relatively young patients were periodontally healthy. 'Orange and red' complex microorganisms were detected at levels ≥105 more often if patients had a PD ≥5 mm with periodontal attachment loss at the distal of 2Ms or around 3Ms at their entry examination. In patients

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
				with no PD ≥5 mm in the 3M region, 'orange and red' complex microorganisms were detected at levels ≥105 more frequently than would be anticipated in patients with little clinical evidence of periodontal disease
Venta et al 1999[154]	Not all impacted or mandibular or pathology-free or trouble-free No relevant outcomes reported	The aim of the study was to follow the clinical changes in 3M status during a 12-year period in patients aged 20 to 32 years	3Ms undergo continuous clinical change at least up to the age of 32 years	The study was based on a follow-up of 81 university students (32 men, 49 women). They were clinically examined and panoramic radiographs were taken at baseline (mean age, 20.7±?0.5 years) and at the end of the study (mean age 32.6 t 0.6 years) The students had 285 unerupted, partially erupted, or fully erupted 3Ms at the beginning of the study, and 150 at the end. On final examination, 115 teeth were erupted. During the first 6 years from age 20 to 26, various clinical changes took place in the status of the 3Ms. In the second 6 years, until age 32, the two main changes were either removal or eruption. During the 12-year follow-up, 22% of 3Ms erupted, a few even after 26 years of age; the percentage of 3Ms removed was 42%
Venta et al 2000[156]	Not all impacted and mandibular and no relevant outcomes reported However, details on symptoms are reported	The aim of this study was to evaluate the estimates on need for 3M removals made at age 20 after 12 years	Because need for surgical removal decreases during early adulthood, routine prophylactic extraction of asymptomatic 3Ms in young adults cannot be recommended. Well-defined indications for prophylactic removals are needed	During the follow-up, one or more 3Ms had been removed from 67% of the former students. A total of 155 3M removals had been estimated, but by age 32 years the percentage actually removed was only 59%. Of the 79 3Ms taken out at the Finnish Student Health Service, 77% were initially estimated to need a surgical procedure, but actually 66% were simply extracted. Most were removed at around age 27 years. According to the questionnaire, 67% of the students were asymptomatic in the 3M region during 12 years Of the 54 teeth extracted, 33 (61%) were symptom-free. Of the 24 teeth retained 19 (79%) were symptom-free
Venta et al 2001[155]	All impacted and many results reported for mandibular subgroup	To examine radiographic changes in I3Ms in adults from 20 to 32	Considerable radiographic changes, without notable symptoms, may occur involving inclination of the tooth and	8 women and six men with IM3Ms following 12 years' follow-up. At baseline, the follicle was enlarged around three M3Ms. At age 32, one had a

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
	74% of the whole group were asymptomatic No relevant outcomes	years, with special interest on sagittal changes in inclination	state of impaction in I3Ms after the usual age of eruption	follicle enlarged around a M3M different from the situation at baseline. Resorption of the crown of 3Ms or resorption of any 2M due to 3M impact was not seen in any of the teeth. In the mandible at baseline, development of the root was incomplete in 13 teeth. At the end of the study, all root ends were completed Detailed longitudinal analysis showed that a change of more than 5 degrees in inclination had taken place for 76% of the teeth in the mandible The M3Ms changed their angulation both in the distal and the mesial direction. The mean change in the mandible was 19 (SD 11.5) and in the maxilla 12 (SD 2.7), difference not statistically significant (*t*=1.03; df=17). In the mandible, all the teeth that moved were initially inclined in a mesial direction
Venta et al 2004[62]	Not all impacted and mandibular or pathology-free or trouble-free No relevant outcomes reported	The aim of the present study was to follow the clinical changes in 3M status during an 18-year period in patients aged 20 to 38 years	3Ms undergo continuous clinical change on a reduced scale at least up to the age of 38 years	The series consisted of 118 patients (37 men and 81 women). In the beginning of the study, the mean age was 20.2 years (SD 0.6), and at the end, it was 38.6 years (SD 6). Panoramic radiographs were taken at baseline and at age 38. All patients were clinically examined at baseline and at the end of the study. A portion of the patients (n=69) were also examined at age 32 Results: Most of the initially unerupted 3Ms were removed during the follow-up period (73%, maxilla and mandible together). More than half of the initially partially erupted 3Ms were removed during the follow-up period (64%, maxilla and mandible together). The percentage of erupted 3Ms found in the mouth at age 38 increased significantly depending on the initial status. Of the initially unerupted, partially erupted, or erupted 3Ms, 10%, 33%, and 50%, respectively, were erupted at age 38 (maxilla and mandible together). Changes in the status of 3Ms continued from age 32 to age 38, although to a lesser extent (8%). The three 3Ms with advanced eruption were all maxillary teeth in men

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
Edwards et al 1999[57]	Not impacted	The study was undertaken to identify the least costly, most effective and most cost-effective management strategy for asymptomatic, disease-free M3Ms	M3M retention is less costly to the NHS, more effective for the patient and more cost-effective to both parties than removal. However, should the likelihood of developing pericoronitis, periodontal disease and caries increase substantially then removal becomes the more cost-effective strategy	Decision tree model University of Wales Dental Hospital "The various outcomes of lower third molar retention and removal, together with their incidences were obtained from a comprehensive computerised (Medline) and manual search of the medical literature (1966 to 1998)." No further details of the results of the search are reported "The effectiveness of mandibular third molar management was rated as being greater for third molar retention (69.5) than for removal (63.3) giving a marginal effectiveness of -6.2"
van de Waal 1999[161]	An ongoing trial identified in Mettes review It was stopped early in 2004 and no reports published so was subsequently excluded from Mettes update	NR	NR	NR
Vondeling et al 1999[157]	An ongoing trial identified by Song in 2000 No further results have been published and we have not been able to access the conference abstract identified by Song	NR	NR	NR

M3M=mandibular third molar; 3M=third molar; 2M=second molar; I3M=impacted third molar; IM3M=impacted mandibular third molar; PD=periodontal probing depth; PAL=periodontal attachment loss; DNA= deoxyribonucleic acid; SD=standard deviation; df=degrees of freedom; NR=not reported

References from submissions

The main reference lists included in the submissions (n=26) were checked by the AG to ensure that a complete and thorough review of the available evidence could be conducted. Three references had already been included by the AG. The remaining 23 references did not meet the criteria for inclusion in this review; a list of these references, with comprehensive reasons for exclusion is supplied in Table .

There were five references[13,116,147,217,218] included in the submissions that partially met the inclusion criteria for this SR and which warrant further discussion. In addition to the main submission forms, the additional sources provided in the combined FDS, FGDP and BAOS submission were also checked and a further nine references[62,83,84,122,126,151,154,156,219] were identified, which also fell into this category. The AG has therefore summarised these 14 studies[13,62,83,84,116,122,126,147,151,154,156,217-219] in Table . Six studies[13,116,147,151,217,218] were retrospective in design, five publications[62,122,126,154,156] reported the outcomes of longitudinal studies, and three publications[83,84,219] reported outcomes of prospective cohort studies. Six of the studies[13,116,147,151,217,218] reported outcomes relating to DCC in the 2M. The position of 3Ms, and probing depth or clinical changes were reported in three publications.[122,126,154] Clinical complications of 3M surgery were reported by three,[83,84,219] and one study[156] reported the estimation of the need for removal of 3Ms.

The publications by Blakey et al[122] and Phillips et al[126] report on different outcomes from the same longitudinal study conducted in the US at the University of Kentucky and the University of North Carolina. Two other linked publications[123,169] from the same longitudinal study were discussed in the previous section and are not repeated here. Blakey et al[122] assessed the changes in periodontal health over time, and it was concluded that for asymptomatic patients with at least one PD ≥4 mm at enrolment, there were increased periodontal PDs ≥2 mm often found in the 3M region. Phillips et al[126] reported on the changes over time in the position of 3Ms relative to the occlusal plane, and concluded that the anatomic position of 3Ms was not static over time; therefore, unerupted 3Ms should be monitored for changes in position and periodontal pathology.

There were also three linked publications by Venta et al,[62,154,156] which report on outcomes from a longitudinal study conducted in Finland, at the University of Helsinki, which were also discussed in detail in the previous section. Briefly, Venta et al[154] followed the clinical changes in 3M status in patients aged 20-32 years, and similarly to Phillips et al,[126] found that 3Ms undergo continuous clinical change. During the follow-up period, it was reported that 22% of

3Ms had erupted, and 42% of 3Ms were removed. In a subsequent publication,[156] it was reported that 67% of patients had one or more 3Ms removed during the follow-up period.

The publications by Chuang et al[83,84] are linked to a series of publications,[81,82,220] which report the outcomes of the AAOMS Age-Related Third Molar Study, a prospective cohort study. Chuang et al[83] reports on the frequency of complications following 3M surgery, and it was concluded from the results that increased age appears to be associated with a higher rate of complications – patients aged 25 to 35 years were statistically significantly more likely to have a complication compared with patients <25 years (OR=1.63; 95% CI: 1.12 to 2.37; p=0.01). The level of impaction, evidence of periodontal condition, and pathology were also associated with an increased risk of complications. Chuang et al[84] reported the frequencies of inflammatory complications after 3M surgery, and it was found that the level of impaction, pre-existing infection and pathology were associated with inflammatory complications. Full bony impacted teeth (OR=6.01; 95% CI: 4.7 to 7.7), followed by partially bony impacted teeth (OR=4.7; 95% CI: 3.6 to 6.1), and soft tissue impacted teeth (OR=2.5; 95% CI: 1.7 to 3.7) were more likely to have inflammatory complications compared with patients with erupted teeth. Blondeau et al[219] evaluated the incidence of post-surgical complications, and reported that the overall complication rate differed significantly between men and women (2.2% and 10.2%, respectively; χ^2=13, p=0.0003).

Six studies[13,116,147,151,217,218] reported outcomes relating to DCC in the 2M; all the studies reported a relationship between I3Ms, in particular mesioangular I3Ms, and the presence of 2M DCC. Allen et al[116] concluded that if 3Ms were left *in situ*, there is a need for close monitoring and regular bitewing radiographs. McArdle et al[13,218] and Ozec et al[147] recommend prophylactic removal of the 3M to prevent CDD of the 2M.

Table 29 Studies identified in the submissions and reasons for exclusion from this review

Study	Design and reason for exclusion
AAOMS 2016[29]	Wrong study design
Allen et al 2009[116]	Retrospective review of patient records Not all patients pathology-free/trouble-free and no results for specific population of pathology-free/trouble-free, IM3M
Chang et al 2009[221]	Retrospective cohort M3Ms Not all impacted not all pathology-free or trouble-free Wrong setting (Korea)
Devine et al 2016[30]	Wrong study design
Falci et al 2012[217]	Retrospective review of patient records All M3M Unclear whether all patients pathology-free or trouble-free
Draft FDS RCS M3M Guidance	Wrong study design

Study	Design and reason for exclusion
Finnish Guidelines 2014[73]	Wrong study design
HES online[222]	Wrong study design
Internal audit 2016[223]	Wrong study design
Kang et al 2016[224]	Wrong setting (China) Not all patients pathology-free/trouble-free and no results for specific population of pathology-free/trouble-free, IM3M
McArdle et al 2006[218]	Retrospective review of patient records All IM3M Unclear whether all patients pathology-free/trouble-free
McArdle et al 2012[19]	Wrong study design
McArdle 2013[225]	Wrong study design
McArdle et al 2014[13]	Retrospective cohort All IM3M Unclear whether all patients pathology-free/trouble-free
McArdle et al 2016[107]	Retrospective cohort All IM3M Unclear whether all patients pathology-free/trouble-free
McArdle PhD data	No access to reference
Oderinu et al 2012[226]	Wrong setting(Nigeria), withdrawn from publication
ONS statistics[109]	Wrong study design
Ozeç et al 2009[147]	Retrospective review of patient records All M3M Unclear whether all patients pathology-free/trouble-free
Ozgun et al [227]	AIC data Wrong study design
SIGN 2000[56]	Wrong study design
WHO 2010[228]	Wrong study design
Worrall et al 1998[8]	Pre-1999

AAOMS=American Association of Oral and Maxillofacial Surgeons; IM3M=impacted mandibular third molar; M3M=mandibular third molar; HES=Hospital Episode Statistics; AIC=???; SIGN=Scottish Intercollegiate Guidelines Network; WHO=World Health Organisation

Table 30 Studies identified in the submissions and excluded from this review

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
Allen et al 2009[116]	Not all patients pathology-free/trouble-free and no results for specific population of pathology-free/trouble-free, IM3M	To identify the prevalence of caries in lower 3Ms and the distal aspect of corresponding lower 2M in patients referred for lower 3M assessment	Distal caries in lower 2M related to a mesioangular 3M is a common finding in oral and maxillofacial patients in secondary care, especially if the 3M is fully or partially erupted. If such a 3M is left *in situ*, close monitoring and regular bitewing radiographs are recommended	Data were recorded for 439 consecutive patients over the 5-month data collection period The median age of patients was 28 years (range 14-88, SD=11.0) and the median DMFT score was 5 (range 0-27, SD=4.9). As the majority of patients had two lower wisdom teeth present, 776 lower wisdom teeth were analysed in total. Of these, 136 teeth were classified as unerupted, 493 as partially erupted and 147 as fully erupted. In total 183 of the 776 lower 3Ms (23.6%) were carious. Distal caries was identified in the 2M in 150/776 (19.3%). 3M caries was significantly associated with mesioangular 3Ms (x^2=7.2, p<0.007). Distal 2M caries was also significantly associated with mesioangular 3Ms (x^2 (1)=138.0, p <0.0001)
Blakey et al 2006[122]	Not all mandibular and impacted, results unclear	To assess the change in periodontal status over time by PD in the 3M region	Increased PDs ≥2 mm were often found in the 3M region for asymptomatic patients with at least 1 PD ≥4 mm at enrolment, clinical measures that indicated increased periodontal pathology, and a deteriorating periodontal condition	254 patients had at least 2 follow-up visits as of May 2005. The majority were female (56%) and Caucasian (80%). African–American patients (13%) were similar in percentages to the US population, but Asian and Hispanic patients were under-represented. Slightly more than half of the patients were older than 25 years at enrolment. Median follow-up from enrolment to second follow-up visit was 2.2 years (interquartile range 2.0, 2.6 years). At baseline 61% of 3Ms were at the occlusal plane; 85% were vertical or distoangular If patients had at least 1 PD ≥4 mm at baseline, 38% of these had at least 1 PD deepen by 2 mm or more at follow-up. Only 3% of those with all teeth in the 3M region with <4 mm PD at baseline exhibited the same extent of change (p<.001). Although not statistically significant, those at least 25 years old at enrolment were more likely to have at least 1 increased PD ≥2 mm at follow-up (27% *vs* 20%). Of those with a PD ≥4 mm at baseline in the mandible, an increased PD ≥2 mm was more likely on the distal of a 2M (34%) than around a 3M (23%).

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
Blondeau et al 2007[219]	All IM3Ms Not pathology-free or trouble-free	To evaluate the incidence of various complications, including alveolitis, infection and paresthesia of the inferior alveolar nerve, in association with removal of IM3Ms	Surgical removal of IM3Ms should be carried out well before the age of 24 years, especially for female patients. Older patients are at greater risk of post-operative complications and permanent sequelae. A surgeon's lack of experience could also be a major factor in the development of post-operative complications	A total of 550 IM3Ms were extracted. The 327 patients (191 [58.4%] females and 136 [41.6%] males) were between the ages of 12 and 55 years (average 24.4 years). The complication rate was 6.9%. The overall complication rate differed significantly between men and women (2.2% and 10.2%, respectively, χ^2=13, p=0.0003) The 3 patients with permanent paresthesia (0.5% of the whole cohort) were at least 24 years of age (24, 27 and 36 years, respectively)
Chuang et al 2008[84]	Not all mandibular or impacted or pathology-free or trouble-free	To estimate the frequency of inflammatory complications (surgical site infection and alveolar osteitis) following 3M extraction and identify risk factors for such complications	Level of impaction, pre-existing infection, and pathology were associated with increased risk for post-operative inflammatory complications following 3M surgery	4004 patients having 8748 3Ms extracted met the study inclusion criteria. The mean age was 39.8±13.6 years (range 13-98 years) and 48% of the sample was female. Most patients were above the age of 25 years (93.9%) Full bony impacted teeth (OR=6.01; 95% CI: 4.7 to 7.7), followed by partially bony impacted teeth (OR=4.7; 95% CI: 3.6 to 6.1), and soft tissue impacted teeth (OR=2.5; 95% CI: 1.7 to 3.7) were more likely to have inflammatory complication in comparison to the reference group of erupted teeth. Patients with pre-existing infection were 25% more likely to experience post-operative inflammatory complications (OR=1.25; 95% CI: 1.01 to 1.6). Patients with pathology associated with the extracted 3M were 3 times more likely to develop post-operative inflammatory complications (OR=3.0; 95% CI: 2.2 to 4.3)
Chuang et al 2007[83]	Not all mandibular, results unclear	The purpose of this study was to estimate the frequency of complications after 3M surgery, with age as the primary risk factor	The results of these analyses suggest that increased age (>25 years) appears to be associated with a higher complication rate for 3M extractions	The study sample was comprised of 4004 patients who had 8748 3Ms extracted during the study period. The mean age of the sample was 39.8±13.6 years (range 13-98 years), with 245 patients (6.1%) under age 25 and 3759 patients (93.9%) over age 25. A total of 798 patients (19.9%) had at least 1 3M with caries, 692 (17.3%) had at least 1 3M with a periodontal condition, 656 (16.4%) had at least 1 3M with an associated infection, 294 (7.3%) had at least 1 3M with associated pathology, and 71 (1.8%) had at least 1 3M with an associated cyst

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
				The overall complication rate was 18.3%; the intraoperative and post-operative complication rates were 3.9% and 16.3%, respectively. The most common complications were alveolar osteitis (7.4%), inferior alveolar nerve injury (1.6%), unexpected trismus (1.2%), and post-operative infection (1.1%). Patients aged 25 to 35 were statistically significantly more likely to have a complication compared with those under 25 (OR=1.63; 95% CI: 1.12 to 2.37; p=0.01). In this model, level of impaction, evidence of periodontal condition, and pathology were associated with an increased risk of complications
Falci et al 2012[217]	Unclear whether all patients pathology-free free/trouble free	The objective of this study was to verify, using periapical radiographs, whether a partially erupted M3M is a factor in the presence of dental caries on the distal surface of the adjacent 2M	The results indicate that the presence of a partially erupted M3M with an angulation of 31 degrees or more, is a risk factor for caries on the distal surface of the mandibular 2Ms	246 radiographs were taken from the patient records. The average age of the patients was 24.17 years (range 16–57). 126 of the radiographs (52.1%) were of the third left-sided molar and 177 (72%) female The multivariate logistical regression analysis showed that only an angulation greater than 31 degrees (OR=8.5; 95% CI: 1.7 to 43.8) and the patient's sex (OR=3.3; 95% CI: 1.4 to 7.7), had a statistically significant link to distal caries on the 2M, after adjusting for the age variable
McArdle & Renton 2006[218]	Unclear whether all patients pathology-free/trouble-free	DCC in mandibular 2M teeth are responsible for the removal of up to 5% of all M3Ms. Our aim was to identify the clinical features of these patients	DCC is a late phenomenon and has been reported only in association with impacted 3Ms. The early or prophylactic removal of a partially erupted mesioangular 3M could prevent DCC forming in the mandibular 2M	Records of 100 patients who attended the oral surgery department at Guy's Hospital who had M3Ms removed because of the presence of DCC 2M. Data were collected over a 1-year period Dental disease was measured by calculating the DMFT score; 39 patients had a DMFT score of 5 or less; 36 between 6 and 10, and 24 of 11 or more. All 122 3Ms were partially erupted and radiographic examination showed that 119 teeth were in contact with the 2M tooth at, or close to, the amelocemental junction. Mesial angulations of the 3M fell into three groups; 100 (82%) had an angulation of between 40 and 80; 12 (10%) less than 40, and 10 (8%) greater than 80

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
McArdle et al 2014[13]	Unclear whether all patients pathology-free/trouble-free	The aim of this follow-up study was to find out whether the findings in a new group of patients corroborate those of our previous study	The prophylactic removal of a partially erupted mesioangular 3M will prevent distal cervical caries forming in the 2M tooth	239 patients who had M3Ms removed due to DCC 2M during a 24-month period. Sex, age, angulation and eruption status of the 3M, DMFT score, and the proximity of the 3M to the amelocemental junction of the 2M were recorded In 190 patients, a single 2M was affected, and both were affected in 49 (bilateral disease). In total, 288 M3Ms were extracted, 144 from each side. A total of 161 patients (67%) had a DMFT score of 5 or less; 56 (23%) had a score of between 6 and 10, and 22 (9%) had a score of 11 or more. Of note, 50 patients (21%) had a compensated DMFT score of zero as the only lesion was the DCC associated with the 2M tooth
Ozec et al 2009[147]	Not all patients pathology-free/trouble-free	The aim was to evaluate the prevalence of DCC 2M in a Turkish population and to determine the factors that affect it	The results revealed that DCC 2M justifies prophylactic 3M removal and partially erupted 3Ms that have an angulation of 30–90° with a contact point on the amelocemental junction should be removed to prevent DCC 2M	The records of 485 patients with 585 partially erupted M3Ms were examined using panoramic radiographs to determine the prevalence of DCC 2M. The angulation of the 3M, the second and 3M contact point and the patients' age were also recorded The prevalence of 2M distal caries was 20% (n=117). The median age of the group was 25.2 years (range 18–49 years) and a statistically significant relationship between age and 2M distal caries was observed (χ^2=46.78; df=3; p<0.05). The relationship between 3M angulation and 2M distal caries was statistically significant (χ^2=139.28; df=5; p<0.05)
Phillips et al 2007[126]	Not all mandibular and impacted, results unclear	To assess changes over time in 3M position relative to the occlusal plane and in the periodontal probing status of 3Ms in asymptomatic patients who had at least 1 3M below the occlusal plane at baseline and retained all 3Ms to follow-up	The anatomic position of 3Ms was not static over time even if patients were older than 25 years. Thus, unerupted 3Ms should be monitored for changes in position and periodontal pathology as long as the teeth are retained	Data from 146 patients with 4 asymptomatic 3Ms and at least 1 3M below the occlusal plane at baseline were available for analyses. 66% of the patients were under 25 years old, and approximately 75% were Caucasian. Males and females were evenly represented in the older age cohorts; females (57%) predominated in the younger age cohort 68% of the 97 younger patients and 43% of the 49 older patients presented at baseline with all 4 3Ms

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
				not fully erupted. Of 584 3Ms evaluated, 79% were not fully erupted at baseline; of 462 molars, 80% could not be probed at baseline. Eruption to the level of the occlusal plane occurred in all 4 strata although only a third of the unerupted molars reached the occlusal plane even in the younger patients with the longer follow-up. Of 369 molars that could not be probed at baseline, approximately 35% could be probed at follow-up with the highest percentage of change in the older patients with the longer follow-up (46%)
Polat et al 2008[151]	Not pathology-free/trouble-free	To determine the association between commonly found pathological conditions and angulations and impaction depths of lower 3M teeth	Horizontal and mesioangular impactions were found with more pathological situations; especially in class A impaction depth. Angulation and impaction depth of the IM3M should be taken into consideration when making a decision whether or not to extract an IM3M	The sample comprised 1914 panoramic radiographs with 3050 teeth from a population of patients specifically referred for 3M surgery in an 8-year period from 1997 to 2005. There were 1086 women (56.7%) and 828 men (43.3%) who ranged in age from 18 to 60 years (mean 25.91±6.34 years) When evaluating the prevalences of the caries on the second and 3Ms, horizontal and mesioangular impactions had significantly higher scores than others (for 2M: χ^2=298.99; for IM3M: χ^2=69.10). When all of the results were considered together, it could be seen that 73.5% of the all cases were not affected by any of the pathological changes. Therefore, 26.5% of the cases were affected by at least 1 of the 4 pathological changes. Horizontal and mesioangular impactions showed significantly higher prevalence than others
Venta et al 1999[154]	Not all impacted or mandibular or pathology-free or trouble-free, no relevant outcomes reported	The aim of the study was to follow the clinical changes in 3M status during a 12-year period in patients aged 20 to 32 years	3Ms undergo continuous clinical change at least up to the age of 32 years	The study was based on a follow-up of 81 university students (32 men, 49 women). They were clinically examined and panoramic radiographs were taken at baseline (mean age 20.7±0.5 years) and at the end of the study (mean age 32.6±0.6 years) The students had 285 unerupted, partially erupted, or fully erupted 3Ms at the beginning of the study, and 150 at the end. On final examination, 115 teeth were erupted. During the first 6 years from age 20 to 26, various clinical changes took place in the

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
				status of the 3Ms. In the second 6 years, until age 32, the two main changes were either removal or eruption. During the 12-year follow-up, 22% of 3Ms erupted, a few even after 26 years of age; the percentage of 3Ms removed was 42%
Venta et al 2000[156]	Not all impacted and mandibular and no relevant outcomes reported However, details on symptoms are reported	The aim of this study was to evaluate the estimates on need for 3M removals made at age 20 after 12 years	Because need for surgical removal decreases during early adulthood, routine prophylactic extraction of asymptomatic 3Ms in young adults cannot be recommended. Well-defined indications for prophylactic removals are needed	During the follow-up, one or more 3Ms had been removed from 67% of the former students. A total of 155 3M removals had been estimated, but by age 32 years the percentage actually removed was only 59%. Of the 79 3Ms taken out at the Finnish Student Health Service, 77% were initially estimated to need a surgical procedure, but actually 66% were simply extracted. Most were removed at around age 27 years. According to the questionnaire, 67% of the students were asymptomatic in the 3M region during 12 years Of the 54 teeth extracted 33 (61% were symptom-free). Of the 24 teeth retained 19 (79%) were symptom-free
Venta et al 2004[62]	Not all impacted and mandibular or pathology-free or trouble-free, no relevant outcomes reported	The aim of the present study was to follow the clinical changes in 3M status during an 18-year period in patients aged 20 to 38 years	3Ms undergo continuous clinical change on a reduced scale at least up to the age of 38 years	The series consisted of 118 patients (37 men and 81 women). In the beginning of the study, the mean age was 20.2 years (SD 0.6), and at the end, it was 38.6 years (SD 6). Panoramic radiographs were taken at baseline and at age 38. All of the patients were clinically examined at baseline and at the end of the study. A portion of the patients (n=69) were also examined at age 32 Results: Most of the initially unerupted third molars were removed during the follow-up period (73%, maxilla and mandible together). More than half of the initially partially erupted 3Ms were removed during the follow-up period (64%, maxilla and mandible together). The percentage of erupted 3Ms found in the mouth at age 38 increased significantly depending on the initial status. Of the initially unerupted, partially erupted, or erupted 3Ms, 10%, 33% and 50%, respectively, were erupted at age 38 (maxilla and mandible together). Changes in the status of 3Ms continued from age 32 to age 38,

Study	Reason for exclusion	Aims	Conclusions	Summary of study characteristics and results
				although to a lesser extent (8%). The 3 3Ms with advanced eruption were all maxillary teeth in men

2M=second molar; 3M=third molar; DCC=distal cervical caries; DMFT=decayed, missing, filled teeth; IM3M=impacted mandibular third molar; M3M=mandibular third molar; SD=standard deviation; PD=periodontal probing depth; OR=odds ratio; CI=confidence interval;df=degree of freedom

Appendix 7 Transition probabilities used in the model

Age	Mortality rate active	Probability of symptoms	Age	Mortality rate active	Probability of symptoms
20	0.0003165	0.196694	61	0.007057382	0.045694
21	0.000328486	0.19048	62	0.007728454	0.043989
22	0.000324472	0.184418	63	0.008281076	0.042345
23	0.000372943	0.178507	64	0.009066209	0.040778235
24	0.000357425	0.172744	65	0.009661762	0.03926944
25	0.000375412	0.16713	66	0.010460394	0.037816471
26	0.000414361	0.161663	67	0.011719073	0.036417262
27	0.000424342	0.156341	68	0.012927631	0.035069823
28	0.00046136	0.151162	69	0.014311085	0.033772239
29	0.000475787	0.146125	70	0.015800852	0.032522667
30	0.000525243	0.141229	71	0.017563933	0.031319328
31	0.000569221	0.13647	72	0.02002717	0.030160513
32	0.000572207	0.131847	73	0.02188925	0.029044574
33	0.000626161	0.127357	74	0.024206902	0.027969925
34	0.000677156	0.122999	75	0.026799934	0.026935037
35	0.00074904	0.118769	76	0.029680244	0.025938441
36	0.000776518	0.114666	77	0.032715119	0.024978719
37	0.000864864	0.110687	78	0.03680341	0.024054506
38	0.00097521	0.106829	79	0.041100184	0.023164489
39	0.001062676	0.10309	80	0.046894523	0.022307403
40	0.00116042	0.099467	81	0.05270411	0.021482029
41	0.001236812	0.095958	82	0.059299519	0.020687194
42	0.0013093	0.092561	83	0.066956709	0.019921768
43	0.001457008	0.089271	84	0.075685636	0.019184663
44	0.001580834	0.086088	85	0.084829623	0.01847483
45	0.00175737	0.083007	86	0.095257973	0.017791261
46	0.001809657	0.080027	87	0.106315742	0.017132985
47	0.002005622	0.077145	88	0.118288053	0.016499064
48	0.002094736	0.074359	89	0.1331211	0.015888599
49	0.002342629	0.071665	90	0.146901404	0.015300721
50	0.002514115	0.069062	91	0.161803302	0.014734594
51	0.002791667	0.066546	92	0.184076189	0.014189414
52	0.003009129	0.064116	93	0.197660796	0.013664406
53	0.003313748	0.061769	94	0.210945629	0.013158823
54	0.003623468	0.059502	95	0.230126836	0.012671946
55	0.003987477	0.057313	96	0.260778283	0.012203084
56	0.004297595	0.0552	97	0.279505262	0.01175157
57	0.004825849	0.05316	98	0.301488605	0.011316762
58	0.005308646	0.051192	99	0.324712845	0.010898042
59	0.005923238	0.049293	100	0.335866615	0.010494814
60	0.006400301	0.047461			

Appendix 8 Search strategy (I3M3 specific utilities)

1	Pericoronitis/
2	Toothache/
3	exp Dental Caries/
4	Dry Socket/
5	Tooth Extraction/
6	jaw fractures/ or mandibular fractures/ or maxillary fractures/
7	Facial Paralysis/
8	(Pericoronit* or toothache* or dry socket or tooth extract* or jaw fracture*).tw.
9	((tooth or dental) adj1 (decay* or caries)).tw.
10	((mandibular or maxillary) adj2 fracture*).tw.
11	((Facial or face) adj2 nerve* adj2 damage*).tw.
12	((Facial or face) adj2 paralysis*).tw.
13	or/1-12
14	(multiattribute$ or multi attribute$).ti,ab,kf.
15	utility.ab. /freq=2
16	utilities.ti,ab,kf.
17	disutili$.ti,ab,kf.
18	(standard gamble$ or sg).ti,ab,kf.
19	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.
20	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.
21	or/14-20
22	13 and 21